Ontario Health

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Carrier Screening Programs for Cystic Fibrosis, Fragile X Syndrome, Hemoglobinopathies and Thalassemia, and Spinal Muscular Atrophy: A Health Technology Assessment

Key Messages

What Is This Health Technology Assessment About?

Carrier screening tests are used to determine if a person carries a gene variant known to cause a genetic condition, and allows them to determine the risk of passing the condition to their children. The aim of reproductive carrier screening is to help people make informed reproductive decisions.

We looked at carrier screening programs for four genetic health conditions: cystic fibrosis (CF), fragile X syndrome (FXS), hemoglobinopathies and thalassemia, and spinal muscular atrophy (SMA). Cystic fibrosis is a progressive condition that affects the production of mucus, sweat, and digestive enzymes and damages a person's lungs, digestive system, and other organs. Fragile X syndrome causes intellectual and developmental disability. Hemoglobinopathies and thalassemia affect the structure or production of hemoglobin found in red blood cells, and includes conditions such as sickle-cell anemia. Spinal muscular atrophy causes muscles to become weak and waste away.

This health technology assessment looked at how safe, effective, and cost-effective carrier screening programs for CF, FXS, hemoglobinopathies and thalassemia, and SMA are for people who are considering a near-future pregnancy (preconception) or who are pregnant (prenatal). It also looked at the budget impact of publicly funding carrier screening programs and at the experiences, preferences, and values of people for carrier screening.

What Did This Health Technology Assessment Find?

Carrier screening for CF, FXS, hemoglobinopathies and thalassemia, and SMA likely results in the identification of couples with an increased chance of having an affected pregnancy (at-risk couples). Screening may impact reproductive decision-making and may result in lower anxiety among pregnant people.

Our cost-effectiveness analyses showed that, in the short term, compared with no screening, carrier screening programs for the given conditions in the preconception or prenatal period may detect more at-risk couples (or at-risk pregnancies) and are associated with higher costs. In the long term, while the effectiveness was similar

Published August 2023 Volume 23, Number 4

between strategies, carrier screening programs could be associated with cost savings over no screening, when treatment costs for the screened conditions are considered. We estimate that publicly funding a universal carrier screening program in Ontario would cost an additional $128 million to $491 million, and publicly funding a risk-based screening program would cost an additional $0.8 million to $3 million, over the next 5 years.

Studies found that most patients and health care providers supported carrier screening. People we spoke with valued the potential benefits of early detection and treatment and the social benefits of support and preparation for a child with a potential genetic condition. Health care providers had concerns regarding equity of access to testing, limited testing among high-risk populations, psychosocial impacts of a carrier screening program and potential stigmatization of people, and potential impact on people's private insurance, along with test cost and the cost-effectiveness of screening.

A Note About Terminology

As a government agency, Ontario Health can play an active role in ensuring that people of all identities and expressions recognize themselves in what they read and hear from us. We recognize that gender identities are individual and that many people who are pregnant or wish to be pregnant do not identify as women, despite being assigned female sex at birth. Thus, in this health technology assessment, we use gender-inclusive pronouns and terms as much as possible. However, when citing published literature that uses the terms "woman," "women," "female," we also use these terms for consistency with these cited studies.

Ethnic classifications are not clearly defined terms and can mean different things in different contexts; as such, Ontario Health generally avoids references to ethnic groupings in its reporting. Further, we particularly try to avoid terms that, in addition to not having a clear and concise definition, include stigma or problematic history. However, because some genetic conditions are more prevalent in some populations, it is sometimes necessary to examine and discuss particular ethnic groupings. We discuss the results of these studies using the terminology given by the study authors.

In this project, the term "carrier screening" refers to molecular genetic (DNA) testing used to identify individuals who carry pathogenic variants of genes associated with genetic conditions such as cystic fibrosis, fragile X syndrome, hemoglobinopathies and thalassemia, and spinal muscular atrophy. A "carrier" is a person who has a pathogenic variant associated with a genetic condition that can be passed on to their children but who does not have the condition themselves. Carriers typically do not display symptoms of the condition. "At-risk couples" refers to couples with an increased risk of having a pregnancy affected by the screened genetic condition. We define "couple" in this context as two people who contribute their genes to a pregnancy. The phrase "carrier screening programs" refers to studies that offered carrier screening tests as well as more organized carrier screening programs.

Thalassemia is a quantitative hemoglobin abnormality, whereas hemoglobinopathy is a qualitative abnormality. Due to the relationship between the two terms, they are sometimes treated separately. In these cases, we refer to them as "hemoglobinopathies and thalassemia." Of note, in the Primary Economic Analysis and the Budget Impact Analysis, they are treated and analyzed together as a single group of conditions.

In addition, in economic analyses, for simplicity, we assumed no screening for the comparator. This no screening strategy means that carrier screening was not done at all, either at the opportunistic or program level (i.e., testing is not being offered at all in any format).

Acknowledgements

This report was developed by a multidisciplinary team from Ontario Health. The primary clinical epidemiologist was Myra Wang, the secondary clinical epidemiologist was Alexis Schaink, the medical librarian was Corinne Holubowich, the primary health economist was Olga Gajic-Veljanoski, the secondary health economist was Yuan Zhang, and the patient engagement analyst was David Wells.

The medical editor was Tim Maguire. Others involved in the development and production of this report were Merissa Mohamed, Claude Soulodre, Susan Harrison, Elisabeth Smitko, Sarah McDowell, Chunmei Li, David Wells, Isabelle Labeca, Andrée Mitchell, Charles de Mestral, and Nancy Sikich.

To support this report, CADTH, Canada's drug and health technology agency, conducted a rapid qualitative review of patient preferences, published separately.[1] The qualitative review authors at CADTH were Elijah Herington and Jennifer Horton. Jennifer Horton and Melissa Severn provided a peer review of the literature search for our report. In addition, Angel Petropanagos conducted an ethics review, published separately.

We would like to thank the following people and organizations for lending their expertise to the development of this report:

- Christine Armour, Children's Hospital of Eastern Ontario (CHEO)
- Michelle Axford, The Hospital for Sick Children
- June C. Carroll, Sinai Health, University of Toronto
- Pranesh Chakraborty, Children's Hospital of Eastern Ontario (CHEO)
- David Chitayat, Sinai Health, The Hospital for Sick Children, University of Toronto
- Shelley Dougan, Better Outcomes Registry and Network (BORN)
- Elaine Goh, Trillium Health Partners
- Robin Hayeems, The Hospital for Sick Children
- Jennifer Milburn, Children's Hospital of Eastern Ontario (CHEO)
- Martin Somerville, The Hospital for Sick Children
- John S. Waye, Hamilton Regional Laboratory Medicine Program, McMaster University
- Shawn Winsor, Centre for Health Economics and Policy Analysis, McMaster University
- William W. L. Wong, School of Pharmacy, University of Waterloo

We also thank our lived experience participants who generously gave their time to share their stories with us for this report.

The statements, conclusions, and views expressed in this report do not necessarily represent the views of those we consulted.

Citation

Ontario Health. Carrier screening programs for cystic fibrosis, fragile x syndrome, hemoglobinopathies and thalassemia, and spinal muscular atrophy: a health technology assessment. Ont Health Technol Assess Ser [Internet]. 2023 Aug;23(4):1–398. Available from: https://www.hqontario.ca/evidence-to-improve-care/health-technology-assessment/reviews-and-recommendations/carrier-screening-programs-for-cystic-fibrosis-fragile-x-syndrome-hemoglobinopathies-and-thalassemia-and-spinal-muscular-atrophy

Abstract

Background

We conducted a health technology assessment to evaluate the safety, effectiveness, and cost-effectiveness of carrier screening programs for cystic fibrosis (CF), fragile X syndrome (FXS), hemoglobinopathies and thalassemia, and spinal muscular atrophy (SMA) in people who are considering a pregnancy or who are pregnant. We also evaluated the budget impact of publicly funding carrier screening programs, and patient preferences and values.

Methods

We performed a systematic literature search of the clinical evidence. We assessed the risk of bias of each included study using the Cochrane Risk of Bias tool and the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS), and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic economic literature search and conducted cost-effectiveness analyses comparing preconception or prenatal carrier screening programs to no screening. We considered four carrier screening strategies: 1) universal screening with standard panels; 2) universal screening with a hypothetical expanded panel; 3) risk-based screening with standard panels; and 4) risk-based screening with a hypothetical expanded panel. We also estimated the 5-year budget impact of publicly funding preconception or prenatal carrier screening programs for the given conditions in Ontario. To contextualize the potential value of carrier screening, we spoke with 22 people who had sought out carrier screening.

Results

We included 107 studies in the clinical evidence review. Carrier screening for CF, hemoglobinopathies and thalassemia, FXS, and SMA likely results in the identification of couples with an increased chance of having an affected pregnancy (GRADE: Moderate). Screening likely impacts reproductive decision-making (GRADE: Moderate) and may result in lower anxiety among pregnant people, although the evidence is uncertain (GRADE: Very low).

We included 21 studies in the economic evidence review, but none of the study findings were directly applicable to the Ontario context. Our cost-effectiveness analyses showed that in the short term, preconception or prenatal carrier screening programs identified more at-risk pregnancies (i.e., couples that tested positive) and provided more reproductive choice options compared with no screening, but were associated with higher costs. While all screening strategies had similar values for health outcomes, when comparing all strategies together, universal screening with standard panels was the most cost-effective strategy for both preconception and prenatal periods. The incremental cost-effectiveness ratios (ICERs) of universal screening with standard panels compared with no screening in the preconception period were $29,106 per additional at-risk pregnancy detected and $367,731 per affected birth averted; the corresponding ICERs in the prenatal period were about $29,759 per additional at-risk pregnancy detected and $431,807 per affected birth averted.

We estimated that publicly funding a universal carrier screening program in the preconception period over the next 5 years would require between $208 million and $491 million. Publicly funding a risk-based screening program in the preconception period over the next 5 years would require between $1.3 million and $2.7 million. Publicly funding a universal carrier screening program in the

prenatal period over the next 5 years would require between $128 million and $305 million. Publicly funding a risk-based screening program in the prenatal period over the next 5 years would require between $0.8 million and $1.7 million. Accounting for treatment costs of the screened health conditions resulted in a decrease in the budget impact of universally provided carrier screening programs or cost savings for risk-based programs.

Participants value the perceived potential positive impact of carrier screening programs such as medical benefits from early detection and treatment, information for reproductive decision-making, and the social benefit of awareness and preparation. There was a strong preference expressed for thorough, timely, unbiased information to allow for informed reproductive decision-making.

Conclusions

Carrier screening for CF, FXS, hemoglobinopathies and thalassemia, and SMA is effective at identifying at-risk couples, and test results may impact preconception and reproductive decision-making.

The cost-effectiveness and budget impact of carrier screening programs are uncertain for Ontario. Over the short term, carrier screening programs are associated with higher costs, and also higher chances of detecting at-risk pregnancies compared with no screening. The 5-year budget impact of publicly funding universal carrier screening programs is larger than that of risk-based programs. However, accounting for treatment costs of the screened health conditions results in a decrease in the total additional costs for universal carrier screening programs or in cost savings for risk-based programs.

The people we spoke with who had sought out carrier screening valued the potential medical benefits of early detection and treatment, particularly the support and preparation for having a child with a potential genetic condition.

Table of Contents

A Note About Terminology **2**
Objective **19**
Background **19**
Health Condition 19
Cystic Fibrosis *19*
Fragile X Syndrome *21*
Hemoglobinopathies and Thalassemia *22*
Spinal Muscular Atrophy *23*
Clinical Need and Target Population 25
Current Treatment Options 26
Cystic Fibrosis *26*
Fragile X Syndrome *27*
Hemoglobinopathies and Thalassemia *27*
Spinal Muscular Atrophy *27*
Health Technology Under Review 28
Timing and Approach of Carrier Screening *30*
Regulatory Information 31
Ontario, Canadian, and International Context 32
Ontario and Canadian Context *32*
International Context *33*
Expert Consultation 34
PROSPERO Registration 34
Clinical Evidence **35**
Research Question 35
Methods 35
Clinical Literature Search *35*
Eligibility Criteria *35*
Literature Screening *36*
Data Extraction *36*
Statistical Analysis *37*
Critical Appraisal of Evidence *37*
Results 37
Clinical Literature Search *37*

Characteristics of Included Studies *39*
Risk of Bias in the Included Studies *40*
Screening Uptake *40*
Proportion of At-Risk Couples *46*
Impact on Reproductive Decision-Making *53*
Psychological Impact *63*
Downstream Impacts *65*
Ongoing Studies 67
Discussion 67
Strengths and Limitations 68
Conclusions 69
Economic Evidence 70
Research Question 70
Methods 70
Economic Literature Search *70*
Eligibility Criteria *70*
Literature Screening *71*
Data Extraction *71*
Study Applicability and Limitations *71*
Results 72
Economic Literature Search *72*
Overview of Included Economic Studies *73*
Discussion 79
Multiple-Disease Genetic Carrier Screening *80*
Single-Disease Genetic Carrier Screening *80*
Strengths and Limitations *81*
Conclusions 81
Primary Economic Evaluation 82
Research Questions 82
Methods 82
Type of Analysis *82*
Target Population *84*
Perspective *84*
Interventions and Comparators *84*
Time Horizon and Discounting *88*

Main Assumptions *89*
Model Structure *89*
Clinical Outcomes and Utility Parameters *94*
Cost Parameters *100*
Internal Validation *106*
Analysis *106*
Results **110**
Reference Case Analysis 110
Preconception Carrier Screening Programs *110*
Sensitivity Analysis *116*
Discussion 136
Strengths and Limitations 138
Conclusions 139
Budget Impact Analysis **140**
Research Questions 140
Methods 140
Analytic Framework *140*
Key Assumptions *141*
Target Population *142*
Current Intervention Mix *145*
Uptake of the New Intervention and New Intervention Mix *145*
Resources and Costs *145*
Internal Validation *146*
Analysis *146*
Results 148
Reference Case *148*
Sensitivity Analysis *151*
Prenatal Carrier Screening Programs for CF, FXS, Hemoglobinopathies and Thalassemia, and SMA *153*
Discussion 154
Strengths and Limitations 156
Conclusions 156
Preferences and Values Evidence **157**
Objective 157
Background 157

Quantitative Evidence 157
Research Questions *157*
Methods *158*
Results *160*
Discussion *178*
Conclusions *180*
Qualitative Evidence 181
Key Findings *181*
Direct Patient Engagement 181
Methods *181*
Results *182*
Preferences and Values Evidence Discussion 195
Preferences and Values Evidence Conclusions 196
Conclusions of the Health Technology Assessment 197
Abbreviations 199
Glossary 200
Appendices 208
Appendix 1: Clinical Background Information for Cystic Fibrosis, Fragile X Syndrome, Hemoglobinopathies, and Spinal Muscular Atrophy 208
Appendix 2: Literature Search Strategies 213
Clinical Evidence Search *213*
Economic Evidence Search *217*
Search for Intervention-Related Health State Utilities *223*
Quantitative Evidence of Preferences and Values Search *225*
Grey Literature Search *231*
Appendix 3: Characteristics of Included Studies 233
Appendix 4: Critical Appraisal of Clinical Evidence 252
Appendix 5: Selected Excluded Studies—Economic Evidence 258
Appendix 6: Results of Economic Literature Review—Summary 259
Appendix 7: Results of Applicability and Limitation Checklists for Studies Included in the Economic Literature Review 275
Appendix 8: Primary Economic Evaluation Methods: Costing Screening Care Pathways 286
Appendix 9: Primary Economic Evaluation Methods: Costing of Hypothetical Universal and Risk-Based Carrier Screening Programs in Ontario 287
Appendix 10: Reference Case Results, Cost-Effectiveness of Preconception Screening Programs, by Condition 288

Appendix 11: Reference Case Results, Cost-Effectiveness of Prenatal Screening Programs, By Condition 292

Appendix 12: Results of One-Way Cost-Effectiveness Sensitivity Analyses for Clinical and Cost Parameters, Preconception Carrier Screening (All Examined Conditions), Reference Case Model 296

Appendix 13: Results of One-Way Cost-Effectiveness Sensitivity Analyses for Clinical and Cost Parameters, Prenatal Carrier Screening (All Examined Conditions), Reference Case Model 299

Appendix 14: Results of One-Way Sensitivity Cost-Effectiveness Analyses for Carrier Frequency, Preconception and Prenatal Carrier Screening 302

Appendix 15: Results of One-Way Cost-Effectiveness Sensitivity Analyses for Screening Uptake (Participation) in Preconception or in Prenatal Carrier Screening 308

Appendix 16: Results of One-Way Cost-Effectiveness Sensitivity Analyses for Voluntary TOP in Prenatal Carrier Screening 310

Appendix 17: Results of One-Way Cost-Effectiveness Sensitivity Analyses for Probability of Choosing IVF/PGT-M in Preconception Carrier Screening 311

Appendix 18: Results of One-Way Cost-Effectiveness Sensitivity Analyses for Full Coverage of IVF/PGT-M costs (one life birth) in Preconception Carrier Screening 312

Appendix 19: Results of Cost-Effectiveness Scenarios for Various Screening Care Pathways and Hourly Salary Rate of Medical Genetic Counsellor in Preconception Carrier Screening 314

Appendix 20: Results of Cost-Effectiveness Scenarios for Various Screening Care Pathways and Hourly Salary Rate of Medical Genetic Counsellor in Prenatal Carrier Screening 316

Appendix 21: Results of Cost-Effectiveness Scenarios Related To Program Costs of Preconception or Prenatal Carrier Screening 318

Appendix 22: Results of Budget Impact Scenarios, Preconception Carrier Screening Programs 320

Appendix 23: Results of Budget Impact Scenarios, Prenatal Carrier Screening Programs 348

Appendix 24: Characteristics of Included Studies Among Preconception and Prenatal People and Health Care Providers 371

Appendix 25: Characteristics of Partially Relevant Excluded Systematic Reviews 375

Appendix 26: Letter of Information 379

Appendix 27: Interview Guide 380

References 381

List of Tables

Table 1: Classification of Pathogenic Variants of Cystic Fibrosis 20
Table 2: Interpretation and Clinical Significance of *FMR1* CGG Repeats 22
Table 3: Types of Spinal Muscular Atrophy 25
Table 4: Carrier Frequency, Testing Volume, and Incidence of Cystic Fibrosis, Fragile X Syndrome, Hemoglobinopathies, and Spinal Muscular Atrophy 26
Table 5: Cystic Fibrosis Test Kits Approved by Health Canada 32
Table 6: Results for Carrier Screening Uptake Rate 41
Table 7: Results for Proportion of At-Risk Couples Identified By Carrier Screening 47
Table 8: Results for Impact of Carrier Screening on Reproductive Decision-Making 54
Table 9: Results for Psychological Impact of Carrier Screening 64
Table 10: Results for Downstream Impact of Carrier Screening 66
Table 11: Interventions and Comparators to be Evaluated in the Economic Models 86
Table 12: Matrix: Intervention Strategies in the Sequential Carrier Screening Preconception/Prenatal Models 88
Table 13: Natural and Clinical History Inputs to be Used in the Economic Models—Reference Case and Scenario Analyses 96
Table 14: Inputs Related to Carrier Screening: Test Performance, Participation in Carrier Screening (Uptake), and Reproductive Choices 98
Table 15: Utilities Associated With Health States or Outcomes Used in the Cost–Utility Analysis: Long-Term Scenarios 100
Table 16: Per-Person Cost Estimates Used in the Economic Models 103
Table 17A: Sensitivity Analyses for Short-Term Preconception/Prenatal Reference Case: Clinical Parameters 107
Table 17B: Sensitivity Analyses for Short-Term Preconception/Prenatal Reference Case: Cost Parameters 109
Table 18A: Reference Case Analysis Results, Preconception Screening Programs, All Conditions: All Effectiveness Outcomes 111
Table 18B: Reference Case Analysis: Cost-Effectiveness of Preconception Screening Programs for Given Conditions: Cost Per Affected Birth Averted 111
Table 18C: Reference Case Analysis: Cost-Effectiveness of Preconception Screening Programs for Given Conditions (ICER: Cost Per At-Risk Pregnancy Identified) 112
Table 19A: Reference Case Analysis Results, Prenatal Screening Programs, All Conditions: All Effectiveness Outcomes 114
Table 19B: Reference Case Analysis: Cost-Effectiveness of Prenatal Screening Programs for Given Conditions 114
Table 19C: Reference Case Analysis: Cost-Effectiveness of Preconception Screening Programs for Given Conditions (ICER: $ per At-Risk Pregnancy Identified) 115
Table 20A: Long-Term Scenario Analysis (Newborn's Utility and No Use of Novel Therapies): Cost–Utility of Preconception Carrier Screening for the Given Conditions 121
Table 20B: Long-Term Scenario Analysis (Parents' Utility and No Use of Novel Therapies): Cost–Utility of Preconception Carrier Screening for the Given Conditions 122
Table 21A: Long-Term Scenario Analysis (Newborn's Utility, Novel Therapies): Cost–Utility of Preconception Carrier Screening for the Given Conditions 125
Table 21B: Long-Term Scenario Analysis (Parent's Utility, Novel Therapies): Cost–Utility of Preconception Carrier Screening for the Given Conditions 126

Table 22A: Long-Term Scenario Analysis (Newborn's Utility and No Use of Novel Therapies): Cost–Utility of Prenatal Carrier Screening for the Given Conditions 129
Table 22B: Long-Term Scenario Analysis (Parents' Utility and No Use of Novel Therapies): Cost–Utility of Prenatal Carrier Screening for the Given Conditions 130
Table 23A: Long-Term Scenario Analysis (Newborn's Utility, Novel Therapies): Cost–Utility of Prenatal Carrier Screening for the Given Conditions 133
Table 23B: Long-Term Scenario Analysis (Parent's Utility, Novel Therapies): Cost–Utility of Prenatal Carrier Screening for the Given Conditions 134
Table 24: Estimate of Target Populations: Population-Based Preconception and Prenatal Carrier Screening 143
Table 25: Estimation of Target Populations: Risk-Based Preconception and Prenatal Carrier Screening 144
Table 26A: Annual Per-Case Costs Used in Budget Impact Calculations: Reference Case Analysis, Preconception Carrier Screening 146
Table 26B: Annual Per-Case Costs Used in Budget Impact Calculations: Reference Case Analysis, Prenatal Carrier Screening 146
Table 27: Budget Impact Analysis Results—Reference Case, Preconception Carrier Screening Programs for CF, FXS, Hemoglobinopathies and Thalassemia, and SMA 148
Table 28: Budget Impact Analysis Results—Reference Case, Prenatal Carrier Screening Programs for the Given Conditions 150
Table 29: Budget Impact Scenario Results—Sensitivity Analysis; Preconception Carrier Screening Programs for the Given Conditions 152
Table 30: Budget Impact Scenarios Results—Sensitivity Analysis, Prenatal Carrier Screening Programs for the Given Conditions 153
Table 31: Preferences for Carrier Screening Among People During the Preconception or Prenatal Period 162
Table 32: Preferences for Carrier Screening Among Health Care Providers 171
Table 33: Satisfaction for Carrier Screening Among People During the Preconception or Prenatal Period 174
Table 34: Knowledge and Awareness of Carrier Screening Among People During the Preconception or Prenatal Period 175
Table 35: Knowledge and Awareness of Carrier Screening Among Health Care Providers 178
Table A1: Common Types of Hemoglobinopathies and Thalassemia 208
Table A2: Possible Treatment Options for Cystic Fibrosis, Fragile X Syndrome, Hemoglobinopathies, and Spinal Muscular Atrophy 210
Table A3: Characteristics of Included Studies 233
Table A4: Characteristics of Partially Relevant Excluded Systematic Reviews on Carrier Screening 249
Table A5: Risk of Bias[a] Among Nonrandomized Trials (RoBANS Tool) 252
Table A6: GRADE Evidence Profile for Carrier Screening 257
Table A7: Results of Economic Literature Review—Summary: Reproductive Genetic Carrier Screening for Multiple Diseases 259
Table A8: Results of Economic Literature Review—Summary: Reproductive Genetic Carrier Screening for CF 263
Table A9: Results of Economic Literature Review—Summary: Reproductive Genetic Carrier Screening for FXS 269
Table A10: Results of Economic Literature Review—Summary: Reproductive Genetic Carrier Screening for Hemoglobinopathies and Thalassemia 271

Table A11: Results of Economic Literature Review—Summary: Reproductive Genetic Carrier Screening for SMA 274
Table A12: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Reproductive Genetic Carrier Screening for Multiple Diseases 275
Table A13: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Reproductive Genetic Carrier Screening for CF 276
Table A14: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Reproductive Genetic Carrier Screening for FXS 277
Table A15: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Reproductive Genetic Carrier Screening for Hemoglobinopathies and Thalassemia 278
Table A16: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Reproductive Genetic Carrier Screening for SMA 279
Table A17: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of Reproductive Genetic Carrier Screening for Multiple Diseases 280
Table A18: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of Reproductive Genetic Carrier Screening for CF 281
Table A19: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of Reproductive Genetic Carrier Screening for FXS 283
Table A20: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of Reproductive Genetic Carrier Screening for Hemoglobinopathies and Thalassemia 284
Table A21: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of Reproductive Genetic Carrier Screening for SMA 285
Table A22: Costing Screening Care Pathways: Variations in Medical Visits 286
Table A23: Costing of Hypothetical Universal and Risk-Based Carrier Screening Programs in Ontario 287
Table A24: Reference Case Results, Preconception Screening, Cystic Fibrosis—Effectiveness Outcomes 288
Table A25: Reference Case Results: Cost-Effectiveness of Preconception Screening Programs for Cystic Fibrosis 288
Table A26: Reference Case Results, Preconception Screening, Fragile X Syndrome—Effectiveness Outcomes 289
Table A27: Reference Case Results: Cost-Effectiveness of Preconception Screening Programs for Fragile X Syndrome 289
Table A28: Reference Case Results, Preconception Screening, Hemoglobinopathies and Thalassemia—Effectiveness Outcomes 290
Table A29: Reference Case Results, Cost-Effectiveness of Preconception Screening Programs for Hemoglobinopathies and Thalassemia 290
Table A30: Reference Case Results, Preconception Screening, Spinal Muscular Atrophy—Effectiveness Outcomes 291
Table A31: Reference Case Results: Cost-Effectiveness of Preconception Screening Programs for Spinal Muscular Atrophy 291
Table A32: Reference Case Results, Prenatal Screening, Cystic Fibrosis—Effectiveness Outcomes 292
Table A33: Reference Case Results: Cost-Effectiveness of Prenatal Screening Programs for Cystic Fibrosis 292
Table A34: Reference Case Results, Prenatal Screening, Fragile X Syndrome—Effectiveness Outcomes 293
Table A35: Reference Case Results: Cost-Effectiveness of Prenatal Screening Programs for Fragile X Syndrome 293

Table A36: Reference Case Results, Prenatal Screening, Hemoglobinopathies and Thalassemia — Effectiveness Outcomes 294
Table A37: Reference Case Results: Cost-Effectiveness of Prenatal Screening Programs for Hemoglobinopathies and Thalassemia 294
Table A38: Reference Case Results, Prenatal Screening, Spinal Muscular Atrophy— Effectiveness Outcomes 295
Table A39: Reference Case Results: Cost-Effectiveness of Prenatal Screening Programs for Spinal Muscular Atrophy 295
Table A40: Cost-Effectiveness Sensitivity Analysis Results, Preconception Carrier Screening: Coverage of Full IVF/PGT-M Costs ($39,000 Per Life Birth) 312
Table A41: Cost-Effectiveness Sensitivity Analysis Results, Preconception Carrier Screening: Coverage of Full IVF/PGT-M Costs ($29,260 Per Life Birth) 312
Table A42: Cost-Effectiveness Sensitivity Analysis Results, Preconception Carrier Screening: Coverage of Full IVF/PGT-M Costs ($48,767 Per Life Birth) 313
Table A43: Cost-Effectiveness Scenario Results, Preconception Carrier Screening: Genetic Counsellors Involved Only in Follow-Up of Test-Positive Couples 314
Table A44: Cost-Effectiveness Scenario Results, Preconception Carrier Screening: Removal of Primary Care Visits (Initial and Test-Negative) 314
Table A45: Cost-Effectiveness Scenario Results, Preconception Carrier Screening: Genetic Counsellor, Higher Hourly Rate 315
Table A46: Cost-Effectiveness Scenario Results, Prenatal Carrier Screening: Genetic Counsellors Involved Only in Follow-up of Test-Positive Couples 316
Table A47: Cost-Effectiveness Scenario Results, Prenatal Carrier Screening: Removal of Primary Care Visits (Initial and Test-Negative) 316
Table A48: Cost-Effectiveness Scenario Results, Prenatal Carrier Screening: Genetic Counsellor, Higher Hourly Rate 317
Table A49: Cost-Effectiveness Scenario Results, Preconception Carrier Screening: Inclusion of Program Costs 318
Table A50: Cost-Effectiveness Scenario Results, Preconception Carrier Screening: Inclusion of Program Costs and Full Coverage of IVF/PGT-M Costs 318
Table A51: Cost-Effectiveness Scenario Results, Prenatal Carrier Screening: Inclusion of Program Costs 319
Table A52: Budget Impact Scenario Results—Participation (Uptake) in Preconception Carrier Screening: 20% 320
Table A53: Budget Impact Scenario Results—Participation (Uptake) in Preconception Carrier Screening: 35% 321
Table A54: Budget Impact Scenario Results—Participation (Uptake) in Preconception Carrier Screening: 50% 322
Table A55: Budget Impact Scenario Results—Participation (Uptake) in Preconception Carrier Screening: 100% 323
Table A56: Budget Impact Scenario Results—Preconception Carrier Screening: Carrier Frequency Decreased by Half 324
Table A57: Budget Impact Scenario Results—Preconception Carrier Screening: Carrier Frequency Doubled 325
Table A58: Budget Impact Scenario Results—Preconception Carrier Screening: Panel Costs Decreased by Half 326
Table A59: Budget Impact Scenario Results—Preconception Carrier Screening: A Hypothetical Expanded Panel, Costs Decreased by 80% (~$130) 327

Table A60: Budget Impact Scenario Results—Preconception Carrier Screening: Screening Care Pathway, Reducing Encounters (Visits) With a Genetic Counsellor 328
Table A61: Budget Impact Scenario Results—Preconception Carrier Screening: Screening Care Pathway, Reducing Encounters (Visits) With a Primary Care Physician 329
Table A62: Budget Impact Scenario Results—Preconception Carrier Screening: Screening Care Pathway, Higher Hourly Salary Rate, Genetic Counsellors 330
Table A63: Budget Impact Scenario Results—Preconception Carrier Screening: Full Coverage of IVF/PGT 331
Table A64: Budget Impact Scenario Results—Preconception Carrier Screening: Inclusion of Program Costs (Model-Based Outputs) 332
Table A65: Budget Impact Scenario Results—Preconception Carrier Screening: Inclusion of Program Costs (Assuming Initial Cost Inputs) 334
Table A66A: Budget Impact Scenario Results—Preconception Carrier Screening: Inclusion of All Program Costs (Model-Based Cost Outputs) and Full Coverage of IVF/PGT-M 336
Table A66B: Budget Impact Scenario Results—Preconception Carrier Screening: Inclusion of Implementation Program Costs and Full Coverage of IVF/PGT 337
Table A67: Budget Impact Scenario Results—Preconception Carrier Screening, Summary: Long-Term Scenario Including Treatment Costs (Supportive Therapies) and Program Costs (Implementation and On-Going) 338
Table A68A: Long-Term Scenario, Budget Impact Results by Strategy—Preconception Universal Screening With Standard Panels (Supportive Therapies) 339
Table A68B: Long-Term Scenario Budget Impact Results by Strategy—Preconception Universal Screening With Expanded Panel (Supportive Therapies) 340
Table A68C: Long-Term Scenario Budget Impact Results by Strategy—Preconception Risk-Based Screening With Standard Panels (Supportive Therapies) 341
Table A68D: Long-Term Scenario Budget Impact Results by Strategy—Preconception Risk-Based Screening With Expanded Panels (Supportive Therapies) 342
Table A69: Budget Impact Scenario Results—Preconception Carrier Screening, Summary: Long-Term Scenario Including Treatment Costs (Novel and Supportive Therapies) and Program Costs (Implementation and On-Going) 343
Table A70A: Long-Term Scenario BIA Results by Strategy - Preconception Universal Screening with Standard Panels (Novel Therapies) 344
Table A70B: Long-Term Scenario BIA Results by Strategy—Preconception Universal Screening With Expanded Panel (Novel Therapies) 345
Table A70C: Long-Term Scenario BIA Results by Strategy—Preconception Risk-Based Screening With Standard Panels (Novel Therapies) 346
Table A70D: Long-Term Scenario BIA Results by Strategy—Preconception Risk-Based Screening With Expanded Panels (Novel Therapies) 347
Table A71: Budget Impact Scenario Results—Participation (Uptake) in Prenatal Carrier Screening: 20% 348
Table A72: Budget Impact Scenario Results—Participation (Uptake) in Prenatal Carrier Screening: 35% 349
Table A73: Budget Impact Scenario Results—Participation (Uptake) in Prenatal Carrier Screening: 50% 350
Table A74: Budget Impact Scenario Results—Participation (Uptake) in Prenatal Carrier Screening: 100% 351
Table A75: Budget Impact Scenario Results—Prenatal Carrier Screening: Carrier Frequency Decreased by Half 352

Table A76: Budget Impact Scenario Results—Prenatal Carrier Screening: Carrier Frequency Doubled 353
Table A77: Budget Impact Scenario Results—Prenatal Carrier Screening: Panel Costs Decreased by Half 354
Table A78: Budget Impact Scenario Results—Prenatal Carrier Screening: A Hypothetical Expanded Panel, Costs Decreased by 80% (~$130) 355
Table A79: Budget Impact Scenario Results—Prenatal Carrier Screening: Screening Care Pathway, Reducing Encounters (Visits) With a Genetic Counsellor 356
Table A80: Budget Impact Scenario Results—Prenatal Carrier Screening: Screening Care Pathway, Reducing Encounters (Visits) With a Primary Care Physician 357
Table A81: Budget Impact Scenario Results—Prenatal Carrier Screening: Screening Care Pathway, Higher Hourly Salary Rate, Genetic Counsellors 358
Table A82: Budget Impact Scenario Results—Prenatal Carrier Screening: Inclusion of Program Costs (Model-Based Outputs) 359
Table A83: Budget Impact Scenario Results—Prenatal Carrier Screening: Inclusion of Program Costs (Assuming Initial Cost Inputs) 360
Table A84: Budget Impact Scenario Results—Prenatal Carrier Screening, Summary: Long-Term Scenario Including Treatment Costs (Supportive Therapies) and Program Costs (Implementation and On-Going) 361
Table A85A: Long-Term Scenario Budget Impact Results by Strategy—Prenatal Universal Screening With Standard Panels (Supportive Therapies) 362
Table A85B: Long-Term Scenario BI Results by Strategy - Prenatal Universal Screening with Expanded Panel (Supportive Therapies) 363
Table A85C: Long-Term Scenario Budget Impact Results by Strategy—Prenatal Risk-Based Screening With Standard Panels (Supportive Therapies) 364
Table A85D: Long-Term Scenario BI Results by Strategy—Prenatal Risk-Based Screening With Expanded Panels (Supportive Therapies) 365
Table A86: Scenario Results—Prenatal Carrier Screening, Summary: Long-Term Scenario Including Treatment Costs (Novel and Supportive Therapies) and Program Costs (Implementation and On-Going) 366
Table A87A: Long-Term Scenario Budget Impact Results by Strategy—Prenatal Universal Screening With Standard Panels (Novel Therapies) 367
Table A87B: Long-Term Scenario BI Results by Strategy - Prenatal Universal Screening with Expanded Panel (Novel Therapies) 368
Table A87C: Long-Term Scenario Budget Impact Results by Strategy—Prenatal Risk-Based Screening With Standard Panels (Novel Therapies) 369
Table A87D: Long-Term Scenario Budget Impact Results by Strategy—Prenatal Risk-Based Screening With Expanded Panels (Novel Therapies) 370
Table A88: Characteristics of Included Studies Among Preconception and Prenatal People and Health Care Providers 371
Table A89: Characteristics of Excluded Partially Relevant Systematic Reviews 375

List of Figures

Figure 1: PRISMA Flow Diagram—Clinical Search Strategy 38
Figure 2: PRISMA Flow Diagram—Economic Search Strategy 72
Figure 3A: Simplified Model Structure, Sequential Couple Testing in Preconception/Prenatal Carrier Screening: Reference Case (Autosomal-Recessive Conditions) 91
Figure 3B: Simplified Model Structure, Preconception Carrier Screening, cont. 92
Figure 3C: Simplified Model Structure, Prenatal Carrier Screening, cont. 93
Figure 4: Simplified Markov Model Structure, Long-Term Scenario Analysis 94
Figure 5: Costing Pathway, Most Conservative Reference Case: Carrier Screening 101
Figure 6: Changes in Carrier Frequency for Cystic Fibrosis and the ICER: Preconception Carrier Screening 117
Figure 7: Changes in Screening Uptake and the ICER: Preconception Carrier Screening 118
Figure 8: Changes in Condition-Specific Probability of Voluntary TOP and the ICER: Preconception Carrier Screening 119
Figure 9A: Cost-Effectiveness Acceptability Curve, Preconception Carrier Screening: Newborn's Utility and No Use of Novel Therapies 123
Figure 9B: Cost-Effectiveness Acceptability Curve, Preconception Carrier Screening: Parents' Utility and No Use of Novel Therapies 124
Figure 10A: Cost-Effectiveness Acceptability Curve, Preconception Carrier Screening: Newborn's Utility and Use of Novel Therapies 127
Figure 10B: Cost-Effectiveness Acceptability Curve, Preconception Carrier Screening: Parent's Utility and Use of Novel Therapies 128
Figure 11A: Cost-Effectiveness Acceptability Curve, Prenatal Carrier Screening: Newborn's Utility and No Use of Novel Therapies 131
Figure 11B: Cost-Effectiveness Acceptability Curve, Prenatal Carrier Screening: Parents' Utility and No Use of Novel Therapies 132
Figure 12A: Cost-Effectiveness Acceptability Curve, Prenatal Carrier Screening: Newborn's Utility and Use of Novel Therapies 135
Figure 12B: Cost-Effectiveness Acceptability Curve, Prenatal Carrier Screening: Parents' Utility and Use of Novel Therapies 136
Figure 13: Schematic of Budget Impact Models for Preconception and Prenatal Carrier Screening Programs 141
Figure 14: PRISMA Flow Diagram—Quantitative Evidence of Preferences and Values Search Strategy 160
Figure A1: Tornado Diagram, Preconception Carrier Screening: Universal Screening, Standard Panels Versus No Screening 296
Figure A2: Tornado Diagram, Preconception Carrier Screening: Universal Screening, Expanded Panel Versus No Screening 297
Figure A3: Tornado Diagram, Preconception Carrier Screening: Risk-Based Screening, Standard Panels Versus No Screening 298
Figure A4: Tornado Diagram, Prenatal Carrier Screening: Universal Screening, Standard Panels Versus No Screening 299
Figure A5: Tornado Diagram, Prenatal Carrier Screening: Universal Screening, Expanded Panel Versus No Screening 300
Figure A6: Tornado Diagram, Prenatal Carrier Screening: Risk-Based Screening, Standard Panels Versus No Screening 301

Figure A7: Changes in Carrier Frequency for Spinal Muscular Atrophy and the ICER: Preconception Carrier Screening 302
Figure A8: Changes in Carrier Frequency for FXS and the ICER: Preconception Carrier Screening 303
Figure A9: Changes in Carrier Frequency for Hemoglobinopathies and Thalassemia and the ICER: Preconception Carrier Screening 303
Figure A10: Changes in Carrier Frequency for Cystic Fibrosis and the ICER: Prenatal Carrier Screening 304
Figure A11: Changes in Carrier Frequency for Spinal Muscular Atrophy and the ICER: Prenatal Carrier Screening 305
Figure A12: Changes in Carrier Frequency for FXS and the ICER: Prenatal Carrier Screening 306
Figure A13: Changes in Carrier Frequency for Hemoglobinopathies and Thalassemia and the ICER: Prenatal Carrier Screening 307
Figure A14: Changes in Screening Uptake (Participation) and the ICER: Prenatal Carrier Screening 308
Figure A15: Changes in Screening Uptake (Participation) and the ICER: Universal Versus Risk-Based Preconception Carrier Screening 309
Figure A16: Changes in Condition-Specific Probability of Voluntary TOP and the ICER: Prenatal Carrier Screening 310
Figure A17: Probability of Choosing IVF/PGT-M and the ICER: Preconception Carrier Screening 311

Objective

This health technology assessment evaluates the effectiveness, safety, and cost-effectiveness of carrier screening programs for cystic fibrosis, fragile X syndrome, hemoglobinopathies and thalassemia, and spinal muscular atrophy for people who are considering a pregnancy or who are pregnant. It also evaluates the budget impact of publicly funding carrier screening and the experiences, preferences, and values of people for carrier screening.

Background

Health Condition

Pathogenic variants are genetic changes that can cause disease and are sometimes referred to as a traits or mutations. Use of the term "mutation" is generally discouraged since all genetic changes (pathogenic and benign) result from mutations and the word has become stigmatized. One exception (discussed later in this analysis), is in the use of descriptors for fragile X syndrome (FXS) variants, because there is legacy terminology for causative variants. People who carry a single pathogenic variant in a gene associated with an autosomal recessive condition are known as carriers or may also be described as heterozygous (i.e., carrying one pathogenic variant). Carriers do not typically display symptoms of the disease but can pass pathogenic variants on to their children.

Cystic fibrosis (CF), spinal muscular atrophy (SMA), and hemoglobinopathies and thalassemia are autosomal recessive inherited conditions, meaning that a copy of a pathogenic variant must be present in each of the parents for the condition to be passed on to their children. For conditions with autosomal recessive inheritance, each carrier has a 50% chance of passing the pathogenic variant on to their children. If both parents are carriers of the same condition, they have a 25% chance having an affected child with the condition. There is also a 25% chance of having an unaffected child and a 50% chance of having a child who is a carrier (i.e., carries one pathogenic variant of the gene, but does not have the condition). If only one parent is a carrier, none of the children will be affected with the condition, but each child will have a 50% chance of also being a carrier.

Fragile X syndrome (FXS) is inherited through an X-linked dominant pattern. The X chromosome is one of two sex chromosomes. Females have two X chromosomes (XX) and males have one X and one Y chromosome (XY). For X-linked conditions, only one copy of the pathogenic variant on the X chromosome is required to cause the condition. Female carriers and affected females have up to a 50% chance of having a child with FXS. Affected males and premutation carriers can pass the variant only to their female children and not their male children. Being affected depends on the CGG (cytosine–guanine–guanine) repeats. Among males, only people with more than 200 CGG repeats will be affected; among females, about 50% of people with this number of CGG repeats will be affected.

The sections below describe each condition in more detail.

Cystic Fibrosis

Cystic fibrosis is caused by pathogenic variants in the CF transmembrane conductance regulator (*CFTR*) gene. The *CFTR* gene is located at the q31.2 locus of chromosome 7 and leads to the production of the CFTR protein, which functions as an ion channel across cell membranes and helps maintain the balance of salt and water in- and outside of cells. *CFTR* pathogenic variants lead to a buildup of thick mucus because chloride (a component of salt) is trapped inside the cells and water

cannot hydrate the surface. Pathogenic variants affect CFTR protein function differently and can be categorized into five main types (Table 1).[2]

Table 1: Classification of Pathogenic Variants of Cystic Fibrosis

Pathogenic variant class	Description	Approximate prevalence	Typical disease severity
I	No CFTR protein synthesis Ia) mRNA is not synthesized Ib) mRNA is damaged and cannot be made into protein	22%	More severe
II	Reduced protein function CFTR protein is created, but misfolds, preventing it from moving to the cell surface	88%	More severe
III	Reduced ion channel gating CFTR protein is created and moves to the cell surface, but the channel gate does not open properly	6%	More severe
IV	Decreased ion channel conductance CFTR protein is created and moves to the cell surface, but the function of the channel is faulty	6%	Less severe
V	Reduced CFTR protein synthesis Normal CFTR protein is created and moves to the cell surface, but in insufficient quantities	5%	Less severe

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; mRNA, messenger ribonucleic acid.
Source: Cystic Fibrosis Foundation, 2021.[2]

The most common pathogenic variant for CF is a three-nucleotide deletion resulting in the loss of the amino acid phenylalanine (F) at the 508th position of the CFTR protein (denoted as c.1521_1523delCTT or F508del), which is responsible for about 70% of CF cases in most Caucasian populations (92% of patients in the study self-identified as Caucasian).[3] However, about 2,000 CF variants have been identified (about 300 of these variants are pathogenic). Pathogenic variants include missense (a genetic change in which a single base pair substitution results in the incorporation of an amino acid that is different from the usual amino acid at that position), frameshift (insertion or deletion involving a number of base pairs that is not a multiple of three, which consequently disrupts the triplet reading frame of a DNA sequence), splice-site (genetic change in the DNA sequence that occurs at the boundary of an exon and intron [the splice site], which can result in the loss of exons or the inclusion of introns and an altered protein-coding sequence), or nonsense variant (base change that causes the premature termination of a protein).[3] The prevalence and types of CF pathogenic variants vary by geographic and ethnic origins.

Cystic fibrosis is a progressive condition and affects cells that produce mucus, sweat, and digestive enzymes, with the most affected organs being the lungs, pancreas, liver, and intestine. The symptoms of CF vary depending on disease severity, and symptoms may improve or worsen over time. Respiratory symptoms include the production of thick mucus (sputum) associated with persistent cough that produces wheezing, exercise intolerance, repeated lung and sinus infections,

and inflamed nasal passages. Gastrointestinal symptoms are caused by the blocking of digestive enzymes produced by the pancreas from reaching the small intestine, which may result in bulky or greasy stool, malabsorption, poor weight gain and growth, intestinal blockage, chronic or severe constipation, and rectal prolapse (rectum protrudes through the anus). Most people with CF suffer from pancreatic insufficiency, but up to 15% are pancreatic sufficient.[4] Almost all biological males with CF are infertile due to obstructive azoospermia (no sperm in the ejaculate because of obstruction) caused by congenital bilateral absence of the vas deferens (CBAVD). Cystic fibrosis carriers typically do not experience symptoms, but may be at increased risk of CF-related conditions.[5]

Cystic fibrosis is commonly diagnosed using a sweat chloride test that measures the amount of chloride in sweat, or through DNA analysis for pathogenic variants of the *CFTR* gene. About 2% of people with CF have a milder form of CF, referred to as atypical CF, and may or may not have elevated sweat chloride levels.[6] Due to the severity of CF and the need for proactive treatment, the condition is often included in newborn screening programs; however, milder forms of CF may also be diagnosed later during childhood or adulthood.

There is no cure for CF, but many different types of treatments for symptoms and complications exist. In the past, many children with CF would not survive past their teenage years, but with newer available treatments, the average lifespan of an affected person is about 40 years, with respiratory failure being the most common cause of death.[7] In addition to lower life expectancy, this condition has a major impact on the quality of life of affected people.

Fragile X Syndrome

Fragile X syndrome is a condition that causes intellectual and developmental disability. Other symptoms of FXS include autism spectrum disorders, seizures, abnormal speech, and behavioural issues (e.g., hyperactivity, attention difficulties, unusual sensitivity to environmental stimuli). Fragile X syndrome occurs more often in males and results in more severe symptoms compared with females. Males with FXS almost always exhibit intellectual disability and often have characteristic physical features (e.g., large head, long face, loose joints, large testes) and behaviour. Females with FXS tend to have milder intellectual disability and variable physical features.

Fragile X syndrome is caused by an expansion and methylation of more than 200 CGG repeats (known as a full mutation) in the 5' untranslated region (Xq27.3) of the fragile X mental retardation 1 (*FMR1*) gene on the X chromosome. The interpretation and clinical significance of the number of these CGG repeats is outlined in Table 2. In FXS, expansion of the CGG repeats promotes *FMR1* gene methylation (the addition of a methyl group to DNA, which can modify gene function), which turns off the *FMR1* gene and leads to a reduction or absence of the fragile X mental retardation protein (FMRP). The FMRP is essential for normal cognitive development, and its reduction or absence causes the symptoms of FXS. In rare cases, some people with FXS may be partially or fully missing the *FMR1* gene, which also results in absent or defective FMRP.

Table 2: Interpretation and Clinical Significance of *FMR1* CGG Repeats

No. of CGG repeats	Interpretation	Clinical significance
< 45	Normal	Individual is not a carrier
45–54	Intermediate or grey zone	Individual is not a carrier, but repeats may expand to a premutation in their children
55–200	Premutation	Individual is a carrier and is at risk for fragile X–associated disorders
> 200	Full mutation	Individual is affected with FXS

Abbreviations: CGG, cytosine–guanine–guanine; *FMR1*, fragile X mental retardation 1; FXS, fragile X syndrome.

The inheritance pattern of FXS is complex and based on a progressive generational expansion of the CGG repeats in females. Female premutation carriers are at risk of having children with FXS because the number of CGG repeats may increase when the *FMR1* gene is passed on to the next generation. The greater the number of CGG repeats in a premutation carrier, the greater the likelihood that the repeats will increase to become a full mutation. Male premutation carriers do not pass on the premutation to their male children (since they contribute the Y chromosome), but will always pass the premutation in their only X chromosome to their female children. However, these female children are rarely affected with FXS because premutations generally do not expand during spermatogenesis (sperm production).[8]

People with fragile X premutations do not have FXS and generally have normal intellect and appearance, but are at risk of developing fragile X–associated disorders. Two of the most common fragile X–associated disorders are fragile X–associated primary ovarian insufficiency (FXPOI) and fragile X tremor–ataxia syndrome (FXTAS). Approximately 20% to 25% of female premutation carriers develop FXPOI, which may cause irregular menstrual cycles, early menopause (by age 40), elevated follicle-stimulating hormone, and infertility.[9] Fragile X tremor–ataxia syndrome typically affects people 50 years of age or older and is characterized by progressive issues with movement (ataxia), tremor, memory loss, reduced sensation in the lower extremities (peripheral neuropathy), and mental and behavioural changes. The chance of developing FXTAS increases with age for male premutation carriers, from about 17% for those 50 to 59 years old to about 75% for those over 80 years old.[10] In contrast, about 5% to 8% of female premutation carriers develop FXTAS over the age of 50.[10]

Diagnosis of FXS is made through genetic testing using polymerase chain reaction (PCR) amplification or Southern blot analysis, which aims to detect the number of CGG repeats and the methylation status of the *FMR1* gene. Fragile X syndrome is typically diagnosed in the first few years of life due to developmental delay. People affected with FXS typically have a normal life expectancy.

Hemoglobinopathies and Thalassemia

Hemoglobinopathies affect the quality of hemoglobin produced (also referred to as abnormal hemoglobins), and thalassemia (primarily alpha- and beta-thalassemia) affects the quantity of hemoglobin produced. Abnormal hemoglobins are caused by structural defects resulting from an altered amino acid sequence in the alpha or beta globin chains. The most common forms of abnormal hemoglobin are HbS, HbC, and HbE.

Table A1 (Appendix 1) describes common types of hemoglobinopathies and thalassemia and their corresponding genotype and clinical features. Hemoglobinopathies and thalassemia with moderate to severe disease severity can have a major impact on an affected person's quality of life.

Sickle hemoglobin (HbS) is caused by a substitution of thymine for adenine in codon 6 of the *HBB* gene (a condon is a sequence of three nucleotides that correspond to a particular amino acid). Sickle cell disease (SCD) includes manifestations of HbS (Table A1). In SCD, blood cells become hard and misshapen (sickle or C shaped) and cause obstruction of small blood vessels in different parts of the body, leading to episodes of pain (known as sickle cell pain crises or vaso-occlusive crises), frequent infections, swelling of hands and feet, joint pain, nerve pain, vision loss, acute chest syndrome (a serious complication caused by pulmonary obstruction or pneumonia), and stroke. Severe acute pain crises may require hospitalization and blood transfusions. The condition also results in the early death of red blood cells and a need for recurrent blood transfusions. Acute chest syndrome is the leading cause of death for people with SCD.

Hemoglobin C (HbC) is caused by a substitution of glutamic acid for lysine in codon 6 of the *HBB* gene. The symptoms of hemoglobin C disease include mild, chronic hemolytic anemia, splenomegaly (enlarged spleen), and other symptoms related to anemia. Hemoglobin E (HbE) is caused by a substitution of glutamic acid for lysine at codon 26 of the *HBB* gene and is a common variant found throughout southeast Asia. People with hemoglobin E disease may have mild anemia. Common types of hemoglobin C and E disease are described in Table A1.

Diagnosis of hemoglobinopathies requires a red blood cell count and hemoglobin electrophoresis or high-performance liquid chromatography (HPLC), which measure the different types of hemoglobin in the blood and can detect normal and abnormal types. Molecular genetic testing and sequencing to detect pathogenic variants in the *HBB*, *HBA1*, or *HBA2* genes may also be performed if needed. Sickle cell disease (HbSS, HbSC, or HbS-beta thalassemia) may be included in newborn screening programs, and other types of hemoglobinopathies (other abnormal hemoglobins) may be discovered during prenatal care.

Thalassemia limits the production of specific globin chains of the hemoglobin molecule. A normal individual has four alpha globin genes on the short arm of chromosome 16 (two genes per chromosome) and two beta globin genes on the short arm of chromosome 11 (one gene per chromosome). Alpha-thalassemia results from reduced synthesis of one or more of the hemoglobin subunit alpha genes (*HBA1* or *HBA2*) due to partial (α^+) or total (α^0) deletions (and in rare cases mutations). Similarly, beta-thalassemia occurs when there is insufficient (β^+) or no (β^0) production of the beta globin chains, caused by pathogenic variants in the hemoglobin subunit beta (*HBB*) gene. These variants cause symptoms of anemia due to the faster breakdown of red blood cells and the reduced production of red blood cells and hemoglobin. People with beta-thalassemia major or intermedia also usually have an accumulation of iron in the body, either from the disease itself or from the blood transfusions used to treat the condition. Chelation therapy (a procedure to remove heavy metals from the body) may be necessary to prevent iron overload and toxicity. There are four types of alpha-thalassemia and three types of beta-thalassemia, which are described in Table A1.

Spinal Muscular Atrophy

Spinal muscular atrophy is a genetic condition characterized by weakness and wasting in the skeletal muscles used for movement due to a loss of specialized nerve cells known as motor neurons. Motor

neurons transmit signals from the brain and spinal cord to instruct muscles to contract, allowing the body to move. In SMA, muscle weakness tends to be more severe in proximal muscles (those closer to the torso).

Two neighbouring genes on chromosome 5, *SMN1* and *SMN2* (survival motor neurons 1 and 2, respectively), provide instructions for creating the SMN protein. Most functional SMN protein is typically produced from the *SMN1* gene, with a small amount (10%–15%) produced by the *SMN2* gene.[11] Pathogenic variants in the *SMN1* gene cause the four types of SMA (types 1–4), with SMA type 1 being the most severe and type 4 being the least severe (Table 3).[11] Pathogenic variants of the *SMN1* gene result in either no or insufficient production of SMN protein. The most common form of SMA is caused by homologous deletions in exon 7 in the 5q13.2 region in both *SMN1* genes, which accounts for about 94% of all SMA cases.[11] The remaining affected individuals have a deletion in one *SMN1* gene and a point mutation in the other *SMN1* copy. In about 2% of people with SMA, only one parent is a carrier and the other copy was inherited as a *de novo* (new) variant.[11] Rare non-5q pathogenic variants may also occur, but they are genetically and clinically heterogeneous.

People may have multiple copies of the *SMN2* gene, typically from zero to eight copies. People who have more than two copies of the *SMN2* gene typically do not inherit the extra copies from a parent, but they instead arise from random error during DNA replication in the egg or sperm or just after fertilization. The number of *SMN2* copies strongly correlates with SMA severity; additional copies of *SMN2* modify SMA severity and compensate by producing more functional SMN protein. Having three or more copies of *SMN2* is associated with milder severity.[11] Other disease modifiers that do not cause disease, but may affect disease onset and severity of SMN-related SMA, have been identified, such as plastin 3 protein and zinc finger protein 1 (ZPR1).

Spinal muscular atrophy can be diagnosed by genetic tests that look for deletion variants in the *SMN1* gene and the number of copies of the *SMN1* and *SMN2* gene (using multiplex ligation-dependent probe amplification, or MLPA), and sometimes also with muscle biopsy or electromyography (to measure the electrical activity of muscles). Spinal muscular atrophy can also be included in newborn screening programs.[12,13]

Table 3: Types of Spinal Muscular Atrophy

SMA type	Typical age of onset	Maximum function achieved	Typical life expectancy	Typical No. of copies of *SMN2* gene	Approximate prevalence among SMA diagnoses	Other names
0 Prenatal	Prenatal	Do not achieve developmental motor milestones	A few weeks, < 6 mo	1	Rare, limited information is available	Prenatal SMA
1 Severe	0–6 mo	Never sit	If untreated, < 2 y	1–2	12%	Infantile-onset SMA, Werdnig-Hoffmann disease
2 Intermediate	6–18 mo	Sit, never stand	Survival into adulthood	3	52%	Dubowitz disease
3 Mild	18 mo to childhood	Stand and walk, may require assistance	Almost normal lifespan	3–4	36%	Kugelberg-Welander disease
4 Adult	Early adulthood	Normal, with some muscle weakness	Normal lifespan	4+	Rare, limited information is available	Adult-onset SMA

Abbreviations: SMA, spinal muscular atrophy; *SMN*, survival motor neuron.
Sources: Verhaart et al, 2017[14]; Farrar et al, 2017.[15]

Clinical Need and Target Population

Cystic fibrosis is the most common inherited condition among the White population of Northern European descent. Fragile X syndrome is the most common inherited cause of intellectual disabilities and the most common known cause of autism and has been found in all major ethnic groups and races. Sickle cell disease is the most common hemoglobinopathy and is more commonly found among people of African, Mediterranean, Middle Eastern, and Asian descent. Thalassemia, a quantitative abnormality in the formation of hemoglobin, is one of the most common autosomal recessive disorders in the world and is most common in people of Italian, Greek, Turkish, Middle Eastern, Asian, and African descent. If left untreated, SMA is one of the most common genetic causes of infant death. These conditions are also included as recommended conditions for preconception or prenatal carrier screening in Canadian,[16] American,[17] and Australian guidelines.[18,19] Table 4 outlines the carrier frequency of the conditions, annual Ontario carrier test volumes, and disease incidence.

Table 4: Carrier Frequency, Testing Volume, and Incidence of Cystic Fibrosis, Fragile X Syndrome, Hemoglobinopathies, and Spinal Muscular Atrophy

Condition	Estimated carrier frequency	Annual Ontario carrier test volumes	Incidence/prevalence of the condition
Cystic fibrosis	1 in 35–40 1 in 25 in people of Northern European descent	1,200	Incidence: 1 in 3,600
Fragile X syndrome	Premutation carrier (CGG repeat ≥ 55): 1 in 151 females 1 in 468 males	Not available	Prevalence: 1 in 6,000–11,000 females 1 in 4,000–7,000 males
Sickle cell disease	1 in 7 Caribbean Black people[a] 1 in 4–7 West African Black people[a]	350	Incidence: 1 in 400 in some populations Estimated incidence from Newborn Screening Ontario: 1 in 2,400
Spinal muscular atrophy	1 in 40–60 people	150	Incidence: 1 in 6,000–10,000 Estimated spinal muscular atrophy incidence by type, per live birth: • Type 1: 58% • Type 2: 29% • Type 3: 13% • Type 4: rare, limited information is available

[a]The Black population in Ontario is largely composed of people from the Caribbean and West Africa.

Sources: Newborn Screening Ontario, 2021[13,20,21]; Prenatal Screening Ontario and Spinal Muscular Atrophy Foundation, 2012[22]; National Fragile X Foundation, 2021.[23]

Current Treatment Options

Cystic Fibrosis

Managing CF is complex, and close monitoring with early, aggressive intervention is recommended to slow the progression of the condition, which can also prolong life. The goals of CF treatment primarily include prevention and control of recurrent lung infections, loosening and removal of mucus in the lungs, prevention and treatment of intestinal blockage, and provision of adequate nutrition. Table A2 (Appendix 1) outlines possible treatment options for CF. Most CF therapies only relieve CF symptoms. The only targeted treatments for CF are CFTR modulator therapies, which are used to treat specific pathogenic variants of CF. The CFTR modulator therapies Ivacaftor (Kalydeco), lumacaftor/ivacaftor (Orkambi), tezacaftor/ivacaftor (Symdeko), and elexacaftor/tezacaftor/ivacaftor (Trikafta) have been approved by Health Canada.[24]

Fragile X Syndrome

No specific treatments are available for fragile X syndrome. Management of FXS is generally supportive and includes special education and anticipatory management to avoid excessive stimulation and to support behaviour and learning. Medications may be used to help manage behavioural issues. Early educational intervention that is tailored to specific learning difficulties is important, and individual attention and avoidance of sudden change is often needed. Table A2 outlines some treatment options for FXS.

Hemoglobinopathies and Thalassemia

People with alpha-thalassemia minima and minor do not require treatment. Treatment for hemoglobin H (Hb H) depends on clinical severity. Anemia caused by Hb H requires regular folic acid supplementation, but blood transfusions are rarely indicated. For Hb Bart's syndrome, blood transfusions are required in utero and continuously after birth.

People with beta-thalassemia major or beta-thalassemia intermedia require lifelong blood transfusions combined with the appropriate chelation therapy to remove excess iron from their blood. In cases of beta-thalassemia minor with severe anemia, folic acid supplementation may be considered. Table A2 outlines possible treatment options for alpha- and beta-thalassemia.

Sickle cell disease usually requires lifelong treatment, and the general aims of treatment are avoiding pain episodes, relieving symptoms, and preventing complications. People with SCD are also advised to stay hydrated, avoid temperature extremes, exercise, and refrain from smoking, which can increase one's risk of sickle cell pain crises. Table A2 outlines possible treatment options for SCD. Two new therapies for SCD, the monoclonal antibody crizanlizumab (Adakveo) and the hemoglobin oxygen-affinity modulator voxelotor (Oxbryta), have been approved by the US Food and Drug Administration (FDA), but do not currently have Health Canada approval.

The only cure for beta-thalassemia major, Hb Bart's syndrome, and SCD is stem cell or bone marrow transplantation from a matched donor. The procedure is associated with significant risks (e.g., graft versus host disease, where donor cells attack the host's own tissues), and is generally considered only for people who have not responded to other treatments.

There is also ongoing research evaluating gene editing for SCD and beta-thalassemia using CRISPR–Cas9 (clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9).[25]

Spinal Muscular Atrophy

In 2016, nusinersen (Spinraza; approved by Health Canada in 2017), the first targeted treatment for SMA, became available. Nusinersen modulates the alternative splicing of the *SMN2* gene to functionally convert it to *SMN1*, resulting in increased SMN protein levels. Nusinersen is indicated for people with SMA and is administered intrathecally (into the spinal cord fluid) in four initial doses over a 60-day period, with maintenance doses every 4 months thereafter.[26]

In 2019, onasemnogene abeparvovec (Zolgensma) became the first approved gene replacement therapy to treat SMA. It uses an adeno-associated virus vector to deliver a fully functional copy of the *SMN1* gene to target motor cells. A one-time intravenous administration of onasemnogene abeparvovec results in SMN protein expression in children's motor neurons, which improves muscle

movement, muscle function, and survival.[27] Onasemnogene abeparvovec is indicated for children under 2 years of age with SMA and received Health Canada approval in December 2020.

In 2020, risdiplam (Evrysdi) became available for the treatment of SMA in children 2 months and older.[28] Similar to nusinersen, risdiplam targets alternative splicing of the *SMN2* gene to increase SMN protein production. However, unlike nusinersen, risdiplam is an oral solution that is administered once daily after a meal.

Health Technology Under Review

Carrier screening tests are used to determine if a person carries a gene variant known to cause a genetic condition and helps them identify the risk of passing the condition to their children. Carrier screening programs apply tests for specific conditions for a target population. Carrier screening programs were introduced in the 1970s to offer people the opportunity to learn about their likelihood of passing on an autosomal recessive or X-linked inherited condition.[29] For reproductive carrier screening, the aim is to help people make informed reproductive decisions.

Carrier screening is distinct from but complementary to newborn screening, which aims to detect serious treatable disorders in newborns for early treatment and prevention. For some conditions, newborn screening automatically yields carrier status information (for both the screened newborn and their parents) as an unsolicited finding. Since carrier status has no immediate implications for the child, disclosure of carrier status from newborn screening has been debated. Carrier screening would result in earlier information about carrier status for people and help inform earlier reproductive decision-making.

Different carrier screening tests are used depending on the available technologies and the type of pathogenic variants associated with a condition. Blood samples are typically required, but, depending on the analysis method, other tissue or bodily fluid samples may be used. Testing may be performed for a person and their reproductive partner or on donor gametes (egg or sperm) for the purposes of reproductive decision-making.

For CF, a variant detection panel or assay that includes common CF variants is typically used. Commercial test kits are available that include predefined pathogenic variants, but customized panels may also be developed to include the set of pathogenic variants relevant to the population to be tested. The American College of Medical Genetics and Genomics (ACMG) has published a technical standard guideline for *CFTR* variant testing to help provide quality clinical laboratory genetic services. The ACMG recommends a core panel of 23 pathogenic CF variants that are commonly found in the US population.[30] This set of variants is often the basis of many CF variant panels, and additional relevant variants may be added as appropriate for customized panels. Common CF pathogenic variants included in variant panels are usually based on people of European ancestry and account for more than 90% of CF variants among Caucasians living in North America.[31] However, excluded pathogenic variants of CF may be more relevant to other populations. Thus, CF carrier detection rates based on variant panels may vary considerably between ethnic groups.

Next-generation sequencing (NGS), also known as massively parallel or deep sequencing, allows for the sequencing of millions of small fragments of DNA in parallel and can be used to sequence the entire genome (all of an individual's genetic information, including genes), exome (all protein-coding parts, which comprise approximately 11% of the genome), or specific genes. However, there may be

challenges in sequencing specific gene regions using NGS. While deletions and duplications can be analyzed from NGS data, the analytical validity for larger deletions and duplications depends highly on the quality of NGS data produced.[30] Next-generation sequencing for carrier screening allows the testing of a larger number of variants and results in higher detection rates than targeted testing approaches (e.g., variant panels, deletion, or duplication analysis).

Multiplex ligation-probe amplification, also used in carrier screening, is a PCR-based method for quantifying multiple genomic loci in a single reaction. It is able to efficiently detect large deletions and duplications in genes. A limitation of MLPA is that it can result in false-positive carrier results due to issues with probe hybridization.[30] Multiplex ligation-probe amplification is used for SMA carrier testing and may also be used for quantitative testing of the *CFTR* gene to detect larger deletions or duplications. To identify SMA, quantitative testing of exons 7 and 8 of both the *SMN1* and *SMN2* gene is typically performed. This will detect about 95% of SMA carriers who have a deletion in one copy of the *SMN1* gene.[32] About 5% of SMA carriers have pathogenic variants other than *SMN1* gene deletions and would not be detected using the MLPA approach.[32]

Carrier screening for hemoglobinopathies is typically performed through hemoglobin or capillary electrophoresis or HPLC. Hemoglobin electrophoresis uses electrical current to separate normal and abnormal types of hemoglobin in the blood. Since hemoglobin types have different electrical charges and move at different speeds, the amount of each hemoglobin type can be measured. Similarly, HPLC is an analytic technique used to separate, identify, and quantify components in a mixture using absorbent particles. Different types of hemoglobin are separated due to their different degrees of interaction with the absorbent particles. The HPLC method is faster and more accurate than hemoglobin electrophoresis.[33] Capillary electrophoresis and HPLC have comparable accuracy. Molecular genetic testing or sequencing may be performed to confirm the results of hemoglobin electrophoresis, HPLC, or other suspected carriers. Alpha-thalassemia carriers cannot be captured by hemoglobin electrophoresis alone and require molecular genetic testing.

Carrier screening for FXS is primarily based on measuring the length of the region of the *FMR1* gene containing a variable number of CGG repeats and calculating the repeat number. Analysis of the *FMR1* gene's methylation status is often performed simultaneously. Two approaches are used for carrier screening for FXS: PCR and Southern blot. Southern blot identifies full mutations, large premutations, and gene methylation status, while PCR analysis allows for accurate determination of CGG repeat numbers (especially for normal, intermediate, or grey zone, and premutation alleles).

Positive carrier results should be followed up with post-test genetic counselling. If both members of a couple are carriers for a condition and there is an ongoing pregnancy, prenatal diagnostic testing (chronic villus sampling [CVS] or amniocentesis) may be offered to determine if the fetus is affected.

A negative test result for HbS using capillary electrophoresis or HPLC indicates that the person is not a carrier of HbS. Hemoglobin electrophoresis also helps determine other hemoglobinopathies and the beta-thalassemia carrier state. A negative carrier test result for CF, FXS, SMA, and other types of hemoglobinopathies reduces, but does not eliminate, the risk of being a carrier. Residual risk exists due to excluded pathogenic variants that were not tested for. Also, new pathogenic variants are always possible. Since carrier status may impact related family members, positive test results may lead to testing of family members to determine their carrier status. The testing of the genetic relatives of a person with a positive result is known as cascade testing.

There is minimal direct physical harm from carrier screening (since only a blood sample is required), but psychological harm may be associated with testing and test results. Possible psychological harms include anxiety, stress, and decisional conflict (personal uncertainty about which course of action to take when facing a choice that involves risk, regret, or challenge to personal life values for oneself or for someone else).[34] Some pregnant people may be uncomfortable with prenatal diagnostic testing because of its physical discomfort and the small associated risk of procedure-induced spontaneous loss of pregnancy. In addition, people should be prepared for the possibility of an affected pregnancy even when both members of a couple test negative as carriers due to possibility of false negatives from testing. Negative carrier screening results do not completely eliminate the risk of being a carrier.

Expanded carrier screening (ECS) panels typically include many different genetic conditions and are sometimes called pan-ethnic, in contrast to targeted variant panels that may be ethnicity-based. Although there is no ideal threshold to determine which conditions to include in an expanded carrier screening panel, the selection of conditions with a carrier frequency of 1 in 100 or greater, which corresponds with a disease incidence of 1 in 40,000, is a useful threshold that has been recommended by the American College of Obstetricians and Gynecologists.[35] This recommended threshold aims to provide a balance between identifying carriers for more common conditions and minimizing anxiety associated with identifying carriers of extremely rare disorders. Some conditions are so rarely seen outside of a particular ethnic group that a population-wide carrier rate cannot be calculated and their residual risk is unknown.[35]

Commercially available expanded carrier screening panels typically use NGS technology or a combination of different analytic approaches, depending on which conditions are included and the variants to be tested, with some panels claiming a test sensitivity and specificity greater than 99%.[36] These panels may offer couples more information for reproductive decision-making and may be more cost-effective than single-disease-targeted testing. However, considerations for expanded carrier screening panels include people understanding the inheritance pattern of conditions (e.g., recessive, X-linked), time of condition onset (childhood vs. adulthood), condition severity, phenotypic variability, and available treatment or management options for the conditions tested. Expanded carrier screening panels may also discover a genetic condition with health implications and introduce the possibility of insurance discrimination. Variants of uncertain significance may also be reported for some panels, which cause clinical uncertainty. When screening for many genetic conditions, it is likely that there will be at least one positive result. While some commercial expanded carrier screening panels may offer post-testing genetic counselling (either included or with an additional fee), publicly funded genetic counselling may not be possible based only on a private genetic test result for one carrier. This potentially limits the possibility of formal publicly funded genetic counselling for people with a positive test result.

Timing and Approach of Carrier Screening

Carrier screening may be performed during the preconception or prenatal (i.e., during pregnancy) period. The preconception period encompasses stages of life ranging from before the commencement of relationships to near-future pregnancy (e.g., pre-relationships in high school to the decision to become pregnant). Some professional societies have recommended that carrier screening ideally be offered during the preconception period because it allows for the most reproductive options for people and the most time to make decisions, compared with the prenatal period.[35,37] Reproductive options during the preconception period include proceeding with unassisted

conception (also referred to as natural conception), in vitro fertilization (IVF) and preimplantation genetic testing, use of donor egg or sperm, adoption, refraining from having biological children, or choice of a different reproductive partner. In contrast, once the prenatal stage is reached, options are limited to continuing the pregnancy, with or without prenatal diagnostic testing or, in the case of a positive prenatal diagnostic test, voluntary termination of the affected pregnancy. However, implementation of preconception carrier screening may be limited due to a lack of interest, awareness, or knowledge, and may require changes to the way people approach pregnancy planning. Prenatal carrier screening may be considered easier to implement since most pregnant people will likely already be in contact with the health care system through other prenatal screening or care.

The target population for carrier screening may be people at increased risk (targeted carrier screening program) or all people, regardless of risk, through a broader, population-based or universal screening program. In the past, carrier screening programs have been offered to people at increased risk for a condition (e.g., based on personal or family history or ethnicity), but more recently, some professional guidelines have recommended universal preconception or prenatal screening for conditions such as CF, FXS, and SMA.[17-19]

For couples, carrier screening can be performed concurrently (both people are tested at the same time, also known as simultaneously or in parallel) or sequentially (the second member of the couple is tested only after the first member tests positive). Results can be communicated individually (disclosure of each test result) or couple-based with consent from both members of the couple (disclosure of results only when both partners are carriers and offspring are therefore at risk of having the condition tested for). While couple-based result disclosure may reduce time and resources required for post-test counselling (due to the likely lower number of couples in which both partners test positive as carriers), individual result disclosure would allow a member of the couple to use the same result information if they decide to change reproductive partners. In addition, individual test result disclosure would allow for cascade testing for conditions where only one member of a couple tested positive as a carrier. Cascade testing has implications on the rest of the family of an identified carrier, and further genetic counseling is required.

Regulatory Information

At the time of writing, some carrier screening tests are laboratory-developed tests and are therefore outside the regulatory framework of Health Canada and the US FDA. However, some carrier screening tests are manufactured as test kits, which do require Health Canada approval. Table 5 outlines the Health Canada–approved test kits for CF carrier screening.

Table 5: Cystic Fibrosis Test Kits Approved by Health Canada

Manufacturer	Device name	Class, license No.	Description	Indications for use
Luminex Molecular Diagnostics	xTAG Cystic Fibrosis (*CFTR*) 39 Kit V2	Class III 83052	39 pathogenic variants and 4 modifying variants	• Used to simultaneously detect and identify a panel of variants in the *CFTR* gene in human blood specimens • Panel includes variants currently recommended by ACMG/ACOG, plus some of the world's most common and North American–prevalent variants • For carrier testing in adults of reproductive age, as an aid in newborn screening, and in confirmatory diagnostic testing in newborns and children • Not indicated for use in fetal diagnostic or preimplantation testing, or stand-alone diagnostic testing
	xTAG Cystic Fibrosis (*CFTR*) 71 Kit V2	Class III 83051	71 pathogenic variants and 4 modifying variants	
Illumina	MiSeqDx Cystic Fibrosis 139-Variant Assay	Class III 94699	139 clinically relevant CF disease-causing and modifying and variants	• Used to simultaneously detect 139 clinically relevant CF disease-causing and modifying variants of the *CFTR* gene in genomic DNA isolated from human peripheral whole blood specimens • Variants include those recommended in 2004 by the ACMG and in 2011 by the ACOG • Test is intended for carrier screening in adults of reproductive age, in confirmatory diagnostic testing of newborns and children, and as an initial test to aid in the diagnosis of individuals with suspected CF • Not indicated for newborn screening

Abbreviations: ACMG, American College of Medical Genetics; ACOG, American College of Obstetricians and Gynecologists; CF, cystic fibrosis; *CFTR*, cystic fibrosis transmembrane conductance regulator.

Ontario, Canadian, and International Context

Ontario and Canadian Context

Carrier testing is publicly funded for CF, FXS, hemoglobinopathies and thalassemia, and SMA through hospital global budgets based on indications of increased risk (e.g., personal or family history, ethnic background, clinical manifestations of the condition in themselves, or in the fetus during pregnancy). Ordering carrier testing is at the physician's discretion, which may result in inconsistences in the application of testing criteria within the province. There are also system pressures such as increased demand for testing. Guidance is needed on the use of carrier screening in Ontario.

Testing is currently decentralized in Ontario, with some hospitals performing carrier screening for CF, FXS, and/or SMA. For CF, carrier screening may be performed using a CF test kit (see Table 5) or a customized lab-developed panel that includes different CF variants. More comprehensive *CFTR* sequencing analysis is sometimes performed in Ontario for CF carrier testing, but is typically not offered as a first test option. *CFTR* sequencing may be offered in cases where a person tests negative based on a CF variant panel but may still be at increased risk or there may be risk of a familial CF

pathogenic variant based on family history. Multiplex ligation-dependent probe amplification is used for SMA carrier testing. Southern blot and PCR are used for FXS carrier testing.

Carrier screening for hemoglobinopathies and thalassemia using hemoglobin or capillary electrophoresis or HPLC is performed at hospitals around the province, but molecular genetic carrier screening for hemoglobinopathies and thalassemia is performed at only one Ontario hospital. Most laboratories in Ontario use capillary electrophoresis or HPLC, which are automated complementary platforms.

Carrier screening is typically first discussed with the primary health care provider or maternal care provider in the preconception and prenatal context. Family health history–based risk assessment is the standard for initial assessment of heritable genetic conditions, which includes obtaining a three-generation family history of both members of the couple to be tested.[16] A complete blood count is recommended for all pregnant people to assess their risk of anemia and hemoglobinopathy.[16] If red blood cell indices indicate a low mean hemoglobin volume, or if there is suspicion of hemoglobinopathy based on ethnicity, hemoglobin electrophoresis or HPLC should be performed.[16] People at increased carrier risk for CF, FXS, hemoglobinopathies and thalassemia, or SMA are referred for genetic consultation, and carrier testing is often ordered by medical geneticists. Currently, there is inconsistency in the province for testing of next-degree relatives (cascade testing).

According to Canadian guidelines,[16] prenatal diagnostic testing is offered to allow for appropriate diagnostic and recurrence risk counselling after positive carrier test results. People are counselled on the possible options, and they may choose to accept or decline testing. When prenatal diagnostic testing establishes that a pregnancy is affected with a genetic condition, a timely postnatal follow-up should be offered and people should be advised and educated about the estimated genetic recurrence risk in a subsequent pregnancy.[16]

Carrier testing is typically first performed on the person at increased risk, and then on the reproductive partner if test results are positive (i.e., sequential testing). In some cases, concurrent couple-based testing may be performed in the prenatal context to minimize the wait time for results and support timely decision-making based on the results. Genetic information needs to be held with the same confidentiality as other health information.

People may pursue privately paid carrier screening testing if they are not at increased risk or if they wish to gain information about their carrier status for other genetic conditions. In Ontario, LifeLabs Genetics offers Invitae's Comprehensive Carrier Screen for $625 CAD, which tests for 288 genetic conditions, including CF, FXS, hemoglobinopathies (sickle cell disease) and thalassemia, and SMA.[36] Invitae also offers the test at a patient-pay price of $250 USD, with a $100 USD partner-pay option.[38] The test uses NGS technology and can be performed on either one or both members of the couple, with results available within 2 to 3 weeks. According to LifeLabs, 70% of people screen positive for one or more conditions on the expanded panel, with 1 in 40 couples testing positive for the same condition.[36]

International Context

Carrier screening is offered differently across the world. In some countries, carrier screening is offered only to people at increased risk of a condition (e.g., due to family history, ethnicity), while others offer a more universal approach. In some countries in the Mediterranean (e.g., Cyprus, Greece)

and the Middle East (e.g., Jordan, Iran, Saudi Arabia, Turkey, Bahrain, United Arab Emirates), mandatory carrier screening for hemoglobinopathies and beta-thalassemia is offered in premarital clinics due to a higher rate of consanguinity and a higher carrier frequency in these populations (1%–15%).[39] At-risk couples are offered genetic counselling and, where legal, voluntary termination of pregnancy for affected pregnancies is offered. In some of these countries, program success was linked to the provision of free prenatal diagnostic testing, legal choice of voluntary termination of pregnancy, and effective education and counselling.[39]

Expert Consultation

We engaged with experts in the specialty areas of medical genetics, medical biochemistry, pediatrics, laboratory medicine, family medicine, and research to help inform our understanding of aspects of the health technology and our methodologies and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42021255554), available at https://www.crd.york.ac.uk/PROSPERO.

Clinical Evidence

Research Question

What are the effectiveness and safety of carrier screening program(s) for cystic fibrosis (CF), fragile X syndrome (FXS), hemoglobinopathies and thalassemia, and spinal muscular atrophy (SMA) for people who are considering a near-future pregnancy or who are pregnant?

Methods

Clinical Literature Search

We performed a clinical literature search on April 6, 2021, to retrieve studies published from January 1, 2005, until the search date (we limited studies to those published within the last 16 years to identify the most relevant and recent literature on carrier screening). We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Health Technology Assessment database, and the National Health Service Economic Evaluation Database (NHS EED).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.[40]

We created database auto-alerts in MEDLINE and Embase and monitored them until May 30, 2022. We also performed a targeted grey literature search of the International HTA Database, HTA organizations and regulatory agencies websites, clinical trial and systematic review registries, following a standard list of sites developed internally. See Appendix 2 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published since January 1, 2005
- Randomized controlled trials (RCTs), systematic reviews, comparative and noncomparative nonrandomized studies

Exclusion Criteria

- Animal and in vitro studies
- Nonsystematic reviews, narrative reviews, abstracts, editorials, letters, case reports, and commentaries
- Studies where outcomes of interest are not reported or cannot be extracted

PARTICIPANTS

- People at any carrier risk level, with or without their reproductive partner, at the preconception (near-future pregnancy) or prenatal period
- A single participating person (with or without their reproductive partner); may be either an egg or sperm donor
- Including people who are considering or undergoing in vitro fertilization (IVF)
- Excluded: general population (e.g., people not of reproductive age)

INTERVENTIONS

- Targeted or universal (population-based) carrier screening program for pathogenic variants of CF (related to the CFTR gene), FXS (related to the FMR1 gene), hemoglobinopathies and thalassemia (related to the HBB, HBA1, or HBA2 gene), or SMA (related to SMN1 gene) using any testing approach for reproductive decision-making
- Pathogenic variants as defined or stated in the studies
- Different testing approaches related to timing of screening, simultaneous or sequential testing of people, analytic method, method of result disclosure
- Excluded: screening for purposes other than near-future reproductive decision-making (e.g., premarital or pre-relationship testing for relationship/marriage decisions, young adults of reproductive age such as during high school, testing for only individual carrier status knowledge and not for near-future reproductive decision-making); standard protocol screening for donor egg/sperm (i.e., standard protocol testing at donor egg/sperm bank); screening for other genetic conditions or other types of pathogenic variants of CF, FXS, hemoglobinopathies and thalassemia, or SMA
- Comparator: no testing, different test or screening approach (head-to-head comparisons), no comparison

OUTCOME MEASURES

- Screening uptake rate
- Proportion of at-risk couples (couples found to be at increased risk of having a child affected with the condition)
- Impact on reproductive decision-making (current or future reproduction)
- Proportion of affected children born (to parents who were or were not tested)
- Psychological impact of testing or no testing and test results
- Downstream impacts based on test results or decisions made based on test results
- Impact of results of variants of uncertain significance
- Rates and impacts of cascade testing of family members
- Complications from subsequent prenatal diagnostic testing
- Impact of fragile X–associated disorders related to the identification of fragile X premutation carriers
- Excluded: analytical validity, clinical validity (sensitivity, specificity, positive predictive value, negative predictive value), carrier frequency

Literature Screening

Two reviewers conducted dual screening for 20% of titles and abstracts using Covidence.[41] A single reviewer continued screening the remaining titles and abstracts. The second reviewer reviewed all excluded abstracts. We then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion. A single reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and risk-of-bias items using a data form to collect information on the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, study duration and years, participant allocation, allocation sequence concealment, blinding, reporting of missing data, reporting of outcomes, whether the study compared two or more groups)
- Outcomes (e.g., outcomes measured, number of participants for each outcome, number of participants missing for each outcome, outcome definition and source of information, unit of

measurement, upper and lower limits [for scales], time points at which the outcomes were assessed)

Statistical Analysis

We performed a narrative summary of the included studies due to the differences between the study population and testing method among the studies.

Critical Appraisal of Evidence

We assessed risk of bias using the Cochrane Risk of Bias tool[42] for RCTs and the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) tool[43] for nonrandomized studies (Appendix 3).

We evaluated the quality of the body of evidence for each outcome according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*.[44] The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias. The overall rating reflects our certainty in the evidence.

Results

Clinical Literature Search

The search of the clinical literature yielded 3,926 citations published between January 1, 2005 and April 6, 2021, including grey literature searches and after duplicates were removed. We identified five additional eligible studies from other sources, including database alerts (monitored until May 30, 2022). In total, we identified 107 studies that met our inclusion criteria. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search.

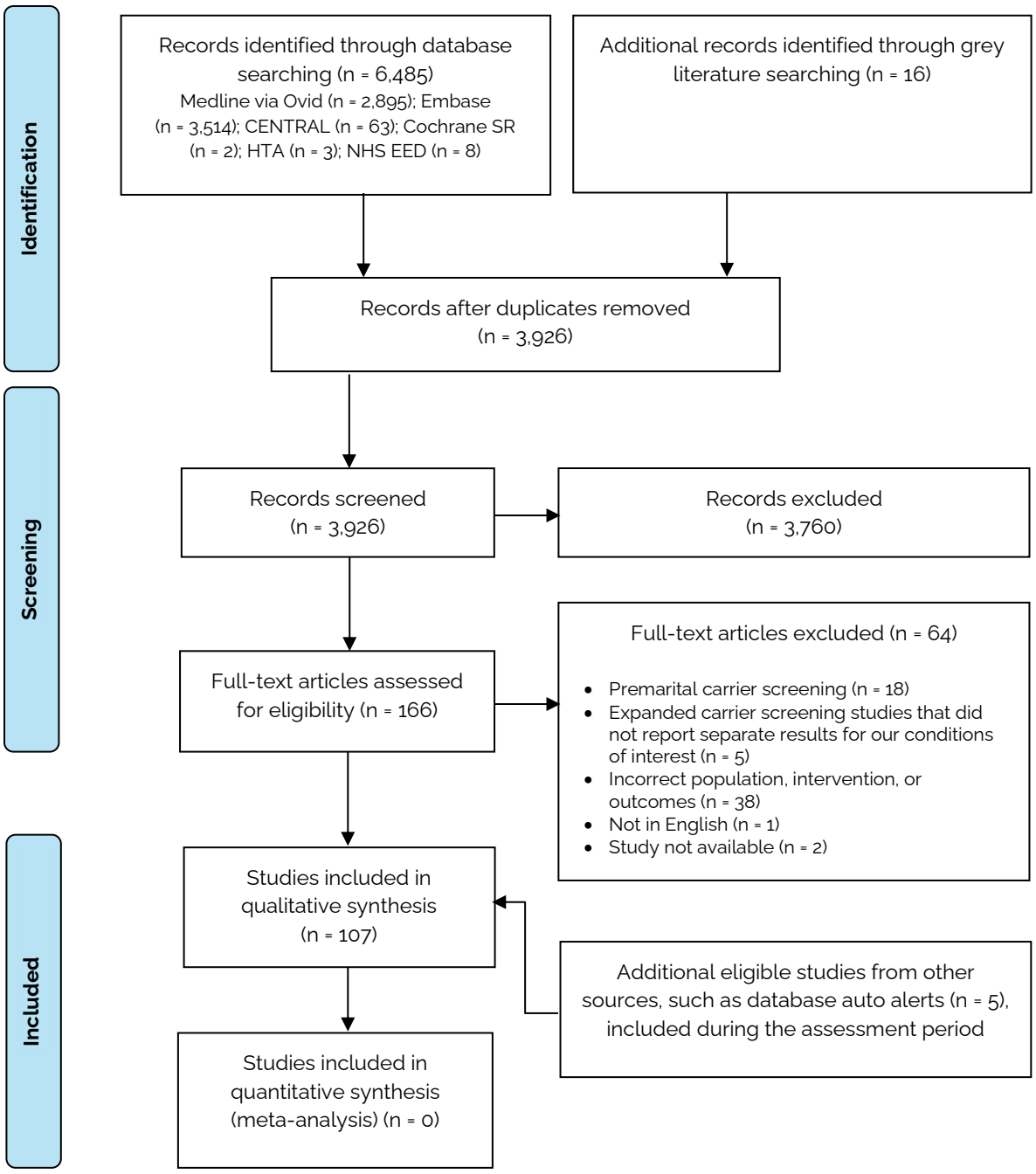

Figure 1: PRISMA Flow Diagram—Clinical Search Strategy

PRISMA flow diagram showing the clinical search strategy. The database search of the clinical literature yielded 6,485 citations published between January 1, 2005, and April 6, 2021. We identified five additional eligible studies from other sources. After removing duplicates, we screened the abstracts of 3,926 studies and excluded 3,744. We assessed the full text of 166 articles and excluded a further 59. In the end, we included 107 articles in the qualitative synthesis.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Page et al.[45]

Characteristics of Included Studies

We included 107 studies in the clinical evidence review. Characteristics of the included studies are presented in Table A2. We found a wide range of studies on preconception and prenatal carrier screening programs (i.e., studies that offered carrier screening testing as well as more formalized carrier screening programs) from countries such as Australia, China, Cuba, Greece, Hong Kong, India, Iran, Israel, Italy, Laos, Mexico, the Netherlands, Pakistan, Spain, United Kingdom, United States, Serbia, South Korea, Switzerland, Taiwan, and Thailand. Almost all studies were noncomparative and retrospective in nature. Three studies compared different types of carrier screening methods or delivery.[46-48] Studies included carrier screening offered only during the preconception or the prenatal period, or a combination of both. Study populations also varied in ethnicity and estimated carrier frequency. The most common hemoglobinopathy or thalassemia evaluated was beta-thalassemia, typically among a population at increased prevalence due to geography or ethnicity.

Most included studies used testing methods for a single condition, while some used expanded carrier screening panels that included our conditions of interest (but also other genetic conditions). Carrier testing methods and the included pathogenic variants also varied between studies, often influenced by factors such as regional laboratory testing capabilities and the most likely pathogenic variants of a condition found within the study population. Almost all studies evaluated sequential carrier screening (i.e., the pregnant person or person considering pregnancy was tested first, and then the partner was tested if the first person was found to be a carrier). For prenatal carrier screening studies, participants were generally recruited from those attending a prenatal clinic or a prenatal visit. Ten studies focused on participants experiencing infertility, typically recruited from infertility clinics or visits.[47,49-57] Information about the participant population was often limited, and few studies reported participants' ethnicity and socioeconomic status.

Information regarding pre- or post-test genetic counselling was not consistently reported within the included studies. Generally, pre-test counselling included information such as clinical information about the tested condition of interest, estimated carrier frequency and inheritance pattern, limitations of testing, test result interpretation, potential benefits and risks of testing, and the option of prenatal diagnostic testing, and reproductive options. The delivery method of pre-test counselling varied from people receiving written information only (e.g., a pamphlet) to discussions with a health care provider. Post-test counselling may include an explanation of the at-risk test results, the residual risk of having an affected pregnancy, and further discussions about the option of prenatal diagnostic testing and subsequent reproductive options.

Study follow-up was sometimes limited to the identification of at-risk couples (i.e., no information about the at-risk couple's prenatal diagnostic testing decision and potential subsequent childbirth). Studies that did report on pregnancy decision-making outcomes mostly included prenatal diagnostic testing acceptance rates and subsequent childbirth (i.e., if a child was born, whether that child was affected or unaffected). We did not find any studies that evaluated the longer-term impacts of carrier screening.

We also found six systematic reviews partially relevant to our research question (Table A3).[58-63] These systematic reviews did not fully address our research question and differed from our review in their conditions of interest (e.g., inclusion of other recessively inherited conditions), timing of screening (e.g., only preconception screening), type of screening method (e.g., only expanded carrier screening panels), outcomes of interest (e.g., only select outcomes of interest), and date of literature captured

(e.g., inclusion of older studies published before our date limit). We examined the reference lists of these systematic reviews to ensure that we also included all relevant studies found within these reviews.

Risk of Bias in the Included Studies

The risk of bias of the included studies was generally low (Table A4). Many studies evaluated people who had already consented to carrier screening, and no information was reported for the population that declined testing. As a result, we do not know if or how the population that declined carrier screening differs from the population that consented. Details on patient characteristics (e.g., ethnicity, socioeconomic status, pregnancy history) were often not reported.

Most studies were noncomparative and retrospective, often evaluating hospital or clinic data of people who chose carrier screening. Studies sometimes lacked information on participants who were lost to follow-up or the rate of follow-up loss or did not report prespecified analyses or subgroups. Retrospective studies are at a higher risk of selection bias, and potentially missing data may also bias outcome reporting. However, information on the carrier test used was often well described within the studies, and there is likely minimal potential bias related to the carrier screening test itself.

Hospital and research grants were the most common funding sources among studies that reported funding information. Studies on expanded carrier screening panels were often associated with the test manufacturer, although some authors noted that study completion was independent from industry.

Screening Uptake

Screening uptake was variably reported within the studies, with some studies reporting only the uptake rate of the pregnant person or person considering pregnancy, while others also included the uptake rate of partners in at-risk couples (Table 6). There was a wide range of reported uptake rates, from about 10% to 100% for the pregnant person or person considering pregnancy, and about 20% to 90% for partner testing.

One found that the main reason for participating in preconception or prenatal carrier screening was the perceived seriousness of the risk of being a carrier and having a child with CF.[64] The uptake rate for screening was also found to potentially differ due to race or ethnicity, parity (number of births [live births and stillbirths] where pregnancies reached viable gestational age), religion, or the genetic counsellors seen.[65,66] Early acceptability was significantly associated with higher education in one study.[56] Fries et al[67] examined the method of counselling delivery and found that there was no significant difference in the overall acceptance of screening for people who were counselled by audiovisual means compared with professional counselling, which was reconfirmed when stratified by ethnicity. When comparing the preconception and prenatal population, Metcalfe et al[68] found a greater percentage of nonpregnant people (70.6%, n = 458) were tested compared with pregnant people (58.8%, n = 298; $P < .001$).

Potential reasons noted within studies for why partners declined testing included a belief that the carrier risk is not high enough for concern, that testing cannot detect all carriers, that testing was a low priority, that test cost was not covered, that testing was against religious or ethical beliefs, and that paternity was questionable or that the partner is no longer involved. Two studies also found that

partner testing was difficult because partners often did not accompany the pregnant person to health care visits[69] or partners did not keep their appointment after counselling.[70]

The GRADE certainty was Very low for screening uptake and was downgraded due to risk of bias, inconsistency, and imprecision (Table A5).

Table 6: Results for Carrier Screening Uptake Rate

Author, year, country	Condition	Timing	Uptake rate for PC/PN person (screened/offered screening)	Uptake rate for partners (screened/offered screening)
Christie et al, 2009[71] Australia	CF	PC, PN	1,000/1,000 (100%)	NR
Coiana et al, 2011[64] Italy	CF	PC, PN	500/505 (99%) Main reason for participating was perceived serious risk of being a carrier and having a child with CF	NR
Dacus et al, 2006[66] United States	CF	PN	2,602/5,616 (46%) Highest among Caucasians: 72% Lowest among Hispanics: 7% (test cost was common reason for declining testing)	19/68 (28%) Possible reasons for declining: carrier testing for partner not paid by Medicaid, partner may believe risk is not high enough for concern, testing cannot detect all carriers, questionable paternity or partner no longer involved, low priority
Fries et al, 2005[67] United States	CF	PN	489/855 (58.2%) of those counselled accepted screening	6/15 (40%) Marital status was the main predictor of uptake of partner testing
Konialis et al, 2007[72] Greece	CF	PN	NR	23/23 (100%)
Massie et al, 2009[73] Australia	CF	PC, PN	NR	106/106 (100%)
Slostad et al, 2007[74] United States	CF	PC	22/1,028 (2.1%) All couples who chose screening were Caucasian	22/22 (100%)
Stuppia et al, 2005[75] Italy	CF	PC	NR	9/9 (100%)
Wei et al, 2007[76] United States	CF	PN	NR	85/143 (59%)

Author, year, country	Condition	Timing	Uptake rate for PC/PN person (screened/offered screening)	Uptake rate for partners (screened/offered screening)
Zlotogora et al, 2009[77] Israel	CF	PC, PN	NR	Most partners were tested after first partner tested positive as a carrier In some localities, up to 70% of partners were not tested
Lakeman et al, 2008[78] Netherlands	CF, HbP	PC	3% (95% CI: 2.2%–3.4%)	NR
Baker et al, 2008[79] United States	CF, HbP, FXS	PC	First cycle: 42/63 (67%) couples accepted FXS testing Second cycle: 4 couples preferred increased testing	NR
Archibald et al, 2018[80] Australia	CF, SMA, FXS	PC, PN	NR	CF and SMA: 552/583 (94.7%) 20/583 (3.4%) could not establish whether partner had been tested 11/583 (1.9%) partner testing not done Reasons for no partner testing: person did not have a partner (6); partner declined testing (2); partner intends to have testing, but has not yet done so (1); couple felt they would not terminate an affected pregnancy (1); partner was of non-Caucasian ancestry and perceived themselves to be at low risk to be a carrier (1)
Simone et al, 2011[81] United States	ECS (CF, HbP)	PC, PN	NR	394/513 (76.8%) Most common reason for no testing: female did not attend post-test follow-up appointment Most common reason for partner declining testing: felt that result would not impact pregnancy outcome Hispanic males were less likely to pursue testing compared with white males, unclear if related to other factors
Chan et al, 2021[82] Hong Kong	ECS (Hb, FXS)	PC	NR	20/69 (29%)
Alfaro Arenas et al, 2016,[83] 2017[84]	FXS	PC, PN	3,371/3,400 (99.1%) agreed to participate Main reasons for declining: lack	NA

Author, year, country	Condition	Timing	Uptake rate for PC/PN person (screened/offered screening)	Uptake rate for partners (screened/offered screening)
Spain			of interest (38%), fear (17%), religious reasons (4%)	
Cronister et al, 2005[85] United States	FXS	PC, PN	2,292/29,103 (7.9%) accepted at time of counselling Highest among patient concern group (95/232; 40.9%) Among people with advanced maternal age: 1,574/16,008 (9.8%) People who accepted PND were almost twice as likely to accept FXS testing (11.4% vs. 6.4%, *P* < .0001)	NA
Metcalfe et al, 2008[86] Australia	FXS	PC	65/338 (19.2%) Reasons for not testing: not currently planning a family, benefits of screening perceived as unimportant, need to return for testing	NA
Metcalfe et al, 2017[68] Australia	FXS	PC, PN	756/961 (78.7%) Nonpregnant women were tested at a greater rate than pregnant women (70.6% [n = 458] vs. 58.8% [n = 298], respectively; *P* < .001)	NA
Xi et al, 2021[54] China	FXS	PN	4,286/7,000 (61.2%)	NA
Borbolla Foster et al, 2021 Australia	HbP	PN	105/643 (16.3%)	14/21 (66.7%)
Choudhuri et al, 2015[70] India	HbP	PN	NR	1,065/2,193 (48.6%) 1,128/2,193 (51.4%) could not be screened because they did not appear at their appointment after counselling
Colah et al, 2008[69] India	HbP	PN	1,033/1,233 (83.8%) carriers attended their counselling appointment	713/1,033 (69%) Only carriers who could bring their partners along for screening Partners often did not accompany pregnant people
Dormandy et al, 2010[48] United Kingdom	HbP	PN	Uptake at < 70 d gestation Midwife care: 9/441 (2%)	Midwife care: 9/21 (44%) Primary care concurrent: 19/47 (40%)

Author, year, country	Condition	Timing	Uptake rate for PC/PN person (screened/offered screening)	Uptake rate for partners (screened/offered screening)
			Primary care concurrent: 161/677 (24%) Primary care sequential: 167/590 (28%) Uptake before 182 d gestation Midwife care: 324/441 (73%) Primary care concurrent: 571/677 (84%) Primary care sequential: 481/590 (82%)	Primary care sequential: 11/25 (44%) No overall difference among groups
Giordano et al, 2006[87] Netherlands	HbP	PN	136/139 (97.8%)	NR
Kaufmann et al, 2011[88] Netherlands	HbP	PN	NR	19/30 (63.3%)
Shukla et al, 2018[89] India	HbP	PN	NR	59/63 (93.7%)
Sorour et al, 2007[90] United Kingdom	Alpha-thal deletions	PN	NR	425/425 (100%)
Baxi et al, 2013[56] India	Beta-thal	PN	1,006/1,320 (76.2%) women Early acceptance significantly associated with higher education level Reasons for not testing: cost, further invasive tests if identified as carriers	28/28 (100%)
Kulkarni et al, 2013[91] India	Beta-thal	PN	NR	9/18 (50%)
Marcheco-Teruel et al, 2019[92] Cuba	SCA	PN	In 1987, screening program reached 79% of pregnant people In 1989, it reached > 90% of pregnant people From 1995 to 2018, screening was performed on 98% of pregnant people in Cuba	143,626 (85.1%) Most common reasons for no partner testing: refusal to accept the possibility of being carriers, failure to acknowledge paternity, living apart from the pregnant person, lack of interest in being diagnosed
Bhukhanvala et al, 2013[93] India	HbP (severe types)	PN	NR	125/148 (84.4%) among partners of pregnant people with beta-thalassemia or sickle cell trait

Author, year, country	Condition	Timing	Uptake rate for PC/PN person (screened/offered screening)	Uptake rate for partners (screened/offered screening)
Gupta et al, 2015[94] India	Thal	PN	NR	80/450 (17.8%)
Li et al, 2006[95] China	Thal	PN	NR	4,890/4,976 (98.3%)
Liao et al, 2005[96] China	Thal	PN	NR	4,503/4,587 (98.2%) Reasons for no partner testing: partner unavailable, pregnant people not ready to disclose details of partner
Qamar et al, 2011[97] Pakistan	Thal	PN	NR	3/17 (17.6%)
Ratanasiri et al, 2006[98] Thailand	Thal	PN	NR	642/996 (64.5%)
Tongsong et al, 2013[99] Thailand	Thal	PN	NR	3,220/3,983 (80.8%)
Wongprachum et al, 2016[100] Laos, Thailand	Thal	PN	NR	17%
Yang et al, 2020[101] China	Thal	PN	NR	213/213 (100%)
Basel-Vanagaite et al, 2008[102] Israel	SMA	PC, PN	NR	13/22 (59.1%)
Prior et al, 2010[103] United States	SMA	PC, PN	About 60% Reasons for accepting: interested in carrier status, worried about pregnancy risk, no additional cost, interest in contributing to SMA knowledge base Reasons for declining: low anxiety about SMA, positive result would not change pregnancy management or would not choose PND, did not wish to know genetic status Adjusting for ethnicity and age, odds of accepting SMA was	14/16 (87.5%) Reason for not testing: not concerned over increased risk of having affected child, elected to have prenatal test for homozygous deletion (had negative result)

Author, year, country	Condition	Timing	Uptake rate for PC/PN person (screened/offered screening)	Uptake rate for partners (screened/offered screening)
			79% lower among African Americans compared with Caucasians ($P < .01$)	
Su et al, 2011[104] Taiwan	SMA	PN	NR	2,038/2,262 (90.1%)
Wood et al, 2016[65] United States	SMA	PN	224/1,158 (19.3%; 95% CI: 17.2%–21.7%) People who accepted screening did not differ in age from those who declined, payer, or marital status, but did differ in race, parity, religion, genetic counsellors seen	3/5 (60%)
Zhang et al, 2020[105] China	SMA	PN	13,069/36,470 (35.8%; 95% CrI: 35.3%–36.3%)	207/231 (89.6%; 95% CI: 85.0%–92.9%)

Abbreviations: CF, cystic fibrosis; CI, confidence interval; CrI, credible interval; ECS, expanded carrier screening; HbP, hemoglobinopathy; FXS, fragile X syndrome; NA, not applicable; NR, not reported; SCA, sickle cell anemia; SMA, spinal muscular atrophy; PC, preconception; PN, prenatal; PND, prenatal diagnosis/diagnostic; thal, thalassemia.

Proportion of At-Risk Couples

The proportion of at-risk couples (couples identified as being at increased risk of having a child with CF, hemoglobinopathy or thalassemia, FXS, or SMA) from carrier screening greatly varied among studies (Table 7). The proportion of at-risk couples detected generally ranged from 0% (no at-risk couples identified) to about 5% for CF, 25% for hemoglobinopathies (depending on the type or severity of the hemoglobinopathy) or thalassemia, 3% for FXS, and 1% for SMA. These results were most likely impacted by the participant population and their risk factors, and the partner's screening uptake rate.

The carrier screening analysis method used within studies also varied. For CF, the most common testing method was a CF variant panel (often defined to include the most common pathogenic variants for the study population), with further testing involving sequencing part of the *CFTR* gene. Similarly, for hemoglobinopathies and thalassemia, a complete blood count with red cell indices was generally performed first and/or capillary electrophoresis or HPLC, and further testing involving potential sequencing of the *HBA*1 or *HBA*2 gene. Carrier testing for FXS was most often done by Southern blot analysis or PCR analysis for CGG repeats. Multiplex ligation-dependent probe amplification was often performed for SMA carrier screening and then potential sequencing of the *SMN1* and *SMN2* genes.

Differences in carrier test analysis methods may also impact the number of at-risk couples identified. One comparative study by Beauchamp et al[46] found that an expanded carrier screening panel would identify more at-risk couples (n = 58) compared with a 23-variant CF panel or NGS (n = 40 and 37,

respectively). In particular, the CF panel would have missed 18 at-risk couples who were diverse in ethnicity.

The GRADE certainty was Moderate for proportion of at-risk couples and was downgraded due to risk of bias and inconsistency, but upgraded due to large magnitude of effect (see Table A5, Appendix 4).

Table 7: Results for Proportion of At-Risk Couples Identified By Carrier Screening

Author, year	Condition	Timing	Testing order	Proportion of at-risk couples
Beauchamp et al, 2019[46]	CF	PC, PN	NR	58/13,080 (0.44%) 18/58 would have been missed with 23-variant CF panel Missed couples ethnically diverse: mixed, other Caucasian, Northern European, South Asian, or Hispanic 37/13,080 (0.8%) identified from NGS
Chamayou et al, 2020[57]	CF	PC	Sequential	10/1,155 (0.86%)
Christie et al, 2009[71]	CF	PC, PN	Sequential	4/1,000 (0.4%) PC:3, PN: 1
Coiana et al, 2011[64]	CF	PC, PN	Concurrent	1/500 (0.2%) Couple was previously identified to be at risk for beta-thal
Dacus et al, 2006[66]	CF	PN	Sequential	0/19 (0%)
Field and Martin, 2011[49]	CF	PC	Sequential	12 couples
Fries et al, 2005[67]	CF	PN	Sequential	0/6 (0%)
Gallati et al, 2009[50]	CF	PC	Sequential	16/70 (22.9%)
Holtkamp et al, 2019[106]	CF	PC	Sequential	0/39 (0%)
Konialis et al, 2007[72]	CF	PN	Sequential	0/1,233 (0%)
Massie et al, 2009[73]	CF	PC, PN	Sequential, concurrent testing for 100 couples	9/3,000 (0.3%)
Picci et al, 2010[107]	CF	PC, PN	Sequential	108/25,104 (0.43%)
Slostad et al, 2007[74]	CF	PC	Sequential	1/22 (4.5%)
Stuppia et al, 2005[75]	CF	PC	Sequential	0/1,195 (0%)
Wei et al, 2007[76]	CF	PN	Sequential	6/6,166 (0.097%)

Author, year	Condition	Timing	Testing order	Proportion of at-risk couples
Lakeman et al, 2008[78]	CF, HbP	PC	Sequential	0/76 (0%)
Baker et al, 2008[79]	CF, HbP, FXS	PC	NA	CF: 3/73 (4.1%) carrier donors Alpha-thal: 1/73 (1.4%) carrier donor FXS: 1/51 (2.0%) carrier donor
Archibald et al, 2018[80]	CF, SMA, FXS	PC, PN	Sequential	CF: 14/319 (4.4%) couples PC: 5/14 (35.7%); PN: 9/14 (64.3%) SMA: 1/233 (0.43%) couples PN:1/1 (100%) FXS: 35/610 (5.7%) PC: 13/35 (37.1%) PN: 22/35 (62.9%)
Franasiak et al, 2015[52]	ECS (CF)	PC	Sequential, concurrent	CF: 3/3,738 (0.80%)
Morgenstern-Kaplan et al, 2022[108]	ECS (CF, FXS)	PC	NR	CF: 3/82 (3.7%) FXS: 1/82 PM (1.2%)
Peyser et al, 2019[51]	ECS (CF, FXS, HbP and thal, SMA)	PC	Sequential, concurrent	1,206 screened couples Beta-thal: 3 (0.25%) CF: 2 (0.17%) SMA: 1 (0.083%) FXS: 73/2,880 (2.5%) females IM:53/73 PM: 17/73 FM: 2/73
Singh et al, 2020[109]	ECS (CF, FXS, HbP and thal, SMA)	PC	Sequential	0/260 (0%)
Capalbo et al, 2021[110]	ECS (CF, FXS, SMA)	PC	NR	CF: 5/766 (0.65%) FXS: 5/766 (0.65%) SMA: 4/766 (0.52%) HBB: 4/766 (0.52%)
Simone et al, 2011[81]	ECS (CF, HbP and thal)	PC, PN	Sequential	CF: 4/513 (0.78%) Silent alpha-thal: 5/513 (0.97%) Sickle beta-beta: 1/513 (0.19%) SCD: 3/513 (0.58%) Alpha-thal trans: 2/513 (0.39%; poses no risk to pregnancy so excluded)
Hernandez-Nieto et al, 2020[53]	ECS (CF, HbP and thal, FXS)	PC	Sequential, concurrent	CF: 3/391 (0.77%) Alpha-thal: 1/391 (0.26%) silent carrier status FXS: 10/391 (2.6%) PM: 6/10 IM: 4/10

Author, year	Condition	Timing	Testing order	Proportion of at-risk couples
Punj et al, 2018[111]	ECS (CF, HbP and thal, FXS, SMA)	PC	Sequential	0/71 (0%) for CF, HbP, FXS, SMA
Bristow et al, 2019[47]	ECS (CF, HbP and thal, SMA)	NR	NR	Panel A (N = 1,206 couples) Beta-chain HbP: 1 (0.083%) CF: 2 (0.17%) SMA: 1 (0.083%) SCA: 1 (0.083%) Panel B (N = 1,186 couples) Beta-chain HbP: 2 (0.17%) CF: 1 (0.084%) SCA: 2 (0.17%) SMA: 1 (0.084%)
Martin et al, 2015[112]	ECS (FXS)	PC	NR	FXS: 1/138 (0.72%) couples undergoing ART using own gametes
Chan et al, 2021[82]	ECS (HbP and thal, FXS)	PC	Sequential and concurrent	FXS: 1/75 (1.3%) PM Alpha-thal: 3/75 (4%)
Hu et al, 2022[113]	ECS (HbP and thal, FXS, SMA)	NR	NR	SMA: 4/1,915 (0.21%) Alpha- or beta-thal: 0/1,915 (0%) FXS: 1/1,195 (0.84%)
Xi et al, 2020[54]	ECS (HbP and thal, SMA)	PC, PN	Sequential	Alpha-thal: 3/1,420 (0.21%) SMA: 5/1,420 (0.35%)
Zhao et al, 2019[114]	ECS (thal)	PC, PN	Concurrent	137/10,476 (1.31%)
Alfaro Arenas et al, 2016,[83] 2017[84]	FXS	PC, PN	NA	PM carriers: 35/3,731 (0.94%; 95% CI: 0.65%–1.30%) IM carriers: 108/3,731 (2.89%; 95% CI: 2.38%–3.45%)
Berkenstadt et al, 2007[115]	FXS	PC, PN	NA	260/40,079 (0.65%) carriers (255 PM, 5 FM) No significant difference in carrier frequency between people with or without family history of mental retardation or developmental abnormalities
Cheng et al, 2017[116]	FXS	PN	NA	Overall: 1/883 (0.11%) or 11 per 10,000 (95% CI: 3–36 per 10,000) PM: 2/2,650 (0.08%) Asymptomatic FM: 1/2,650 (0.04%) IM: 30/2,650 (1.1%)
Cizmeli et al, 2013[117]	FXS	PC	NA	0/62 (0%)

Author, year	Condition	Timing	Testing order	Proportion of at-risk couples
Cronister et al, 2005[85]	FXS	PC, PN	NA	IM: 16/2,292 (0.69%) PM: 6/2,292 (0.26%) FM: 0/2,282 (0%)
Gao et al, 2020[118]	FXS	PC, PN	NA	PM: 16/10,145; 1/634 (95% CI: 1/388–1/1,035) FM: 2/10,145; 1/5,072 (95% CI: 1/1,269–1/20,408)
Hung et al, 2019[119]	FXS	PN	NA	IM: 178/20,188 (0.88%) PM: 26/20,188 (0.13%) FM: 1/20,188 (0.005%)
Jang et al, 2014[120]	FXS	PC, PN	NA	Estimated carrier frequency of 1/788 (95% CI: 1/1 250–1/455) PM: 13/10,241 (0.13%), estimated PM frequency of 0.0006 (95% CI: 0.0003–0.001) IM: 75/10,241 (0.73%), estimated IM frequency of 1/137 (95% CI: 1/172–1/110)
Kim et al, 2013[121]	FXS	PC, PN	NA	IM: 40/5,829 (0.69%) PM: 10/5,829 (0.17%) FM: 1/5,829 (0.017%)
Ma et al, 2019[47]	FXS	PC, PN	NA	IM: 76/11,819 (0.64%); 1/156 (95% CI: 1/199–125) PM: 29/11,819 (0.16%); 1/410 (95% CI: 1/588–286) FM: 3/11,819 (0.025%); 1/3,940 (95% CI: 1/11,765–1,351)
Meraj et al, 2022[122]	FXS	PC	NA	PM: 6/808 (0.74%)
Metcalfe et al, 2008[86]	FXS	PC	NA	PM carrier: 1/65 (1.5%) IM carrier: 3/65 (4.6%)
Metcalfe et al, 2017[68]	FXS	PC, PN	NA	Pregnant people (N = 298) IM: 7/298 (2.3%) PM: 2/298 (0.67%)
Pastore et al, 2008[55]	FXS	PC	NA	PM carrier: 1/20 (5%)
Xi et al, 2021[123]	FXS	PN	NA	IM: 40/4,286 (0.93%) PM: 5/4,286 (0.11%) FM: 3/4,286 (0.07%)
Ai et al, 2020[124]	HbP	PC, PN	Sequentially: 628/729 partners (86%) Concurrently: 102/729 partners (14%)	62/320 (19.4%) recommended for genetic testing 3/40 (7.5%) based on genetic testing 409/729 (56.1%) no partner data for screening 22/62 (35.5%) no partner data for genetic testing

Author, year	Condition	Timing	Testing order	Proportion of at-risk couples
Borbolla Foster et al, 2021[125]	HbP	PN	Unknown	2/99 (2.0%) 6/105 partners were not tested
Choudhuri et al, 2015[70]	HbP	PN	Sequential	119/1,065 (11.2%)
Colah et al, 2008[69]	HbP	PN	Sequential	37/713 (5.2%)
Giordano et al, 2006[87]	HbP	PN	Sequential	0/136 (0%)
Kaufmann et al, 2011[88]	HbP	PN	Sequential	2/1,291 (0.15%)
Shang et al, 2017[126]	HbP	PC, PN	Sequential	186/10,111 (1.8%)
Shukla et al, 2018[89]	HbP	PN	Sequential	2/2,000 (0.1%)
Yin et al, 2014[127]	Alpha- and beta-thal	PN	NR	266/14,300 (1.8%) Alpha-thal: 238/14,300 (1.7%) Beta-thal: 28/14,300 (0.20%)
Sorour et al, 2007[90]	Alpha-thal deletions)	PN	Sequential	0/5,092 (0%)
Baxi et al, 2013[56]	Beta-thal	PN	Sequential	1/28 (3.6%) for beta-thal
Chang et al, 2014[128]	Beta-thal	PN	Sequential	0 couples
Hafezi-Nehad et al, 2014[129]	Beta-thal	PC	NR	449/658 (68.2%) had both beta-thal genotypes 60/658 (9.1%) may have clinically significant HbP in their children (e.g., hydrops fetalis-causing genotypes, certain Hb H genotypes and probable beta-thal intermedia [b-TI] genotypes)
Kulkarni et al, 2013[91]	Beta-thal	PN	Sequential	0/210 (0%)
Miri-Moghaddam et al, 2012[130]	Beta-thal	PN	Sequential	57/106 (53.8%) for beta-thal
Patel et al, 2014[131]	Beta-thal	PN	Sequential	282/111,426 (0.25%)
Suwannakhon et al, 2018[132]	Beta-thal	PN	NR	23/1,115 (2.1%) 20 beta0-thal/Hb E disease 2 beta-thal major 1 beta-thal major or beta0-thal/Hb E disease
Wong et al, 2016[133]	Beta-thal, Hb E	PN	Sequential	23/834 (2.8%) 20 Hb E/beta compound heterozygote Beta-thal homozygote
Suwannakhon et al, 2017[134]	HbP (Hb Bart's)	PN	NR	15/1,235 (1.2%)

Author, year	Condition	Timing	Testing order	Proportion of at-risk couples
Li et al, 2015[135]	Non-deletional beta-thal	PN	Sequential	186/51,105 (0.36%) alpha-thal 168/51,105 (0.33%) Hb Bart's 35/51,105 (0.068%) deletional Hb H
Jiang et al, 2020[136]	HbP, alpha- or beta-thal	PC	Sequential	2/125,661 thal intermedia (0.0016%)
Marcheco-Teruel et al, 2019[92]	HbP (SCA)	PN	Sequential	8,180/4,847,239 (0.17%)
Weil et al, 2020[137]	HbP (SCD), thal	PN	Sequential	8,867/6,608,575 (0.13%)
Ruengdit et al, 2021[138]	Thal (severe)	PC	Sequential	22/306 (7.2%) 3 Hb Bart's affected pregnancies 5 homozygous beta-thal affected pregnancies Hb E/beta0-thal
Yamsri et al, 2010[139]	Thal (severe)	PN	Sequential	1,422 carrier couples identified from initial screening Subsequent Hb analysis found 168/1,422 (11.8%) were false positives; 1,254 true-positive carrier couples were identified Subsequent DNA analysis confirmed 968 true at-risk couples (286 couples confirmed no risk)
Bhukhanvala et al, 2013[93]	Thal (severe)	PN	Sequential	14/148 (9.5%)
Gupta et al, 2015[94]	Thal	PN	Sequential	20/1,500 (1.3%)
Jiang et al, 2017[140]	Thal	PC	Sequential	445/41,531 (1.07%) 0.16% beta-thal 0.39% Hb Bart's 0.46% deletional Hb H disease 0.06% nondeletional Hb H disease
Jiang et al, 2021[141]	Thal	PC	Sequential	0.69% for thal major No carrier couples were misdiagnosed
Li et al, 2006[95]	Thal	PN	Sequential	214/4,4890 (4.4%) alpha-thal 90/4,4890 (1.8%) beta-thal 158/4,4890 (3.2%) alpha/beta-thal
Liao et al, 2005[96]	Thal	PN	Sequential	281/49,221 (6.2%) 198/49,221 (4.4%) alpha-thal 83/49,221 (1.8%) beta-thal major, including E beta-thal
Qamar et al, 2011[97]	Thal	PN	Sequential	3/200 (1.5%)

Author, year	Condition	Timing	Testing order	Proportion of at-risk couples
Ratanasiri et al, 2006[98]	Thal	PN	Sequential	19/1,498 (1.3%) for severe thal conditions 13/19 for beta-thal/Hb E disease, 6/19 Hb Bart's
Theodoridou et al, 2008[142]	Thal	PN	Sequential	148/1,375 (10.7%)
Theodoridou et al, 2018[143]	Thal	PN	Sequential	371/1,598 (23.2%)
Tongsong et al, 2013[99]	Thal	PN	Sequential	281/7,008 couples 151 beta-thal/Hb E 87 Hb Bart's 43 beta-thal major 3 Hb Bart's + beta major 5 Hb Bart's + beta-thal/Hb E Note: some pregnancies were at risk for 2 severe conditions
Wong et al, 2006[144]	Thal	PN	Sequential	18/1,198 (1.5%) 15 compound heterozygous Hb E/beta-thal 3 homozygous alpha-thal 1
Wongprachum et al, 2016	Thal	PN	Sequential	40/71 (56.3%)
Yang et al, 2020[101]	Thal	PN	Sequential	82/2,306 (3.6%) intermediate or severe thal
Khedri et al, 2020[145]	Thal	NR	NR	102/150 (68%) beta-thal
Basel-Vanagaite et al, 2008[102]	SMA	PC, PN	Sequential	0 couples
Prior et al, 2010[103]	SMA	PC, PN	Sequential	0/500 (0%)
Su et al, 2011[104]	SMA	PN	Sequential	47/107,611 (0.043%)
Wood et al, 2016[65]	SMA	PN	Sequential	0/224 (0%)
Zhang et al, 2020[105]	SMA	PN	Sequential	10/36,470 (0.03%)
Zhao et al, 2021[146]	SMA	PC, PN	NR	1/10,309 (0.0097%)

Abbreviations: ART, assisted reproductive therapy; CF, cystic fibrosis; CI, confidence interval; ECS, expanded carrier screening; Hb, hemoglobin; HbP, hemoglobinopathy; FM, full mutation; FXS, fragile X syndrome; IM, intermediate mutation; NA, not applicable; NR, not reported; PC, preconception; PM, premutation; PN, prenatal; SCA, sickle cell anemia; SCD, sickle cell disease; SMA, spinal muscular atrophy; thal, thalassemia.

Impact on Reproductive Decision-Making

Table 8 presents the impact of carrier screening on reproductive decision-making. The most reported pregnancy decision was whether at-risk couples chose prenatal diagnostic testing (chorionic villus sampling or amniocentesis) to confirm if the pregnancy was affected. Fewer studies

reported on the pregnancy outcomes of at-risk couples. In general, we found that most at-risk couples chose prenatal diagnostic testing to confirm whether the pregnancy was affected. Most couples with a confirmed affected pregnancy chose to terminate the pregnancy. Regarding future pregnancies, some people chose to conceive naturally and terminate an affected pregnancy, and some decided to pursue in vitro fertilization with preimplantation genetic testing for their next pregnancy. For preconception carrier screening, few studies evaluated whether couples planned or pursued in vitro fertilization with preimplantation genetic testing, prenatal diagnostic testing, adoption, or avoidance of pregnancy.[46,147]

The type and severity of the hemoglobinopathy condition(s) of interest were also found to affect the decision to undergo prenatal diagnostic testing and thus impact subsequent pregnancy decisions (i.e., pregnant people were less likely to choose pregnancy termination for less severe hemoglobinopathies).[92] One study noted the reasons for new affected births and found factors such as no screening was performed, incorrect test interpretation, couples choosing not to consider the information given, personal preferences or religious beliefs, laboratory error, or lack of gamete donor.[142]

The GRADE certainty was Moderate for reproductive decision-making impact and was downgraded due to risk of bias and indirectness, but upgraded due to large magnitude of effect (see Table A5).

Table 8: Results for Impact of Carrier Screening on Reproductive Decision-Making

Author, year	Condition	Timing	N	Impact on reproductive decision-making
Beauchamp et al, 2019[46]	CF	PC, PN	13,080 couples	PC: 19/37 (51%) screened 17/19 (89%) planned/pursued one of the following actions: 15 (79%) IVF with PGT 3 (16%) PND 1 (5.2%) adoption 1 (5.2%) avoid(ed) pregnancy PN: 18/37 (49%) were screened 10 of those 18 (56%) pursued PND: 3 of those 10 had affected pregnancies 2 of those 3 chose pregnancy termination and 1 chose live birth 8/18 (44%) did not pursue PND All 8 led to live births 7 of those 8 tested postnatally and 2 of those 7 had affected children 19 subsequent pregnancies; 5 (26%) were achieved by IVF and PGT 6 (32%) through PND 2 of those 6 (33%) were affected pregnancies and both couples chose pregnancy termination 13/19 (68%) did not pursue PND 5 (38%) led to live births

Author, year	Condition	Timing	N	Impact on reproductive decision-making
				3 of those 5 tested postnatally with 1 (33%) affected child 7/13 (54%) pregnancies were ongoing at the end of the study and there was 1 (7.7%) spontaneous termination of pregnancy
Christie et al, 2009[71]	CF	PC, PN	1,000	1 PN couple chose PND and had an unaffected child. They plan to have IVF and PGT for next pregnancy 3 PC couples: 1 undergoing IVF, pregnancy not achieved at end of study, 1 became pregnant after carrier testing, chose PND, and then chose to terminate the affected pregnancy, and 1 reported they would choose IVF and PGT-M when ready to conceive
Coiana et al, 2011[64]	CF	PC, PN	1,000 (500 couples)	1/1 chose PND testing for CF and beta-thal
Field and Martin, 2011[49]	CF	PC	5,600	9/12 couples progressed to at least 1 cycle of PGT-M for CF
Fries et al, 2005[67]	CF	PN	855	0 affected children born to pregnant carriers
Massie et al, 2009[73]	CF	PC, PN	3,200 people (3,000 women, 200 men)	6 PN carrier couples: All 6 chose PND 4 were unaffected and continued with the pregnancy There were 2 affected pregnancies, both chose termination (1 couple then opted for IVF with PGT) 3 PC carrier couples; all 3 chose PGT
Picci et al, 2010[107]	CF	PC, PN	25,104 couples	89/108 carrier couples had ongoing pregnancy and chose PND 47/108 pregnancies with variants on 1 CFTR allele 22/89 pregnancies with variants on both alleles Further information about pregnancy decisions after PND were not available
Wei et al, 2007[76]	CF	PN	6,166	5/6 carrier couples chose PND: 1 had an affected pregnancy and chose termination 1 carrier couple declined PND and gave birth to a healthy male, no follow-up information is available 6 female carriers whose partners declined testing chose PND There were no affected pregnancies (negative for variant from female carrier)
Zlotogora et al, 2009[77]	CF	PC, PN	184	CF: 3 carrier couples: 2 couples were PC and pursued IVF and PGT-M (both couples had unaffected children)

Author, year	Condition	Timing	N	Impact on reproductive decision-making
				1 couple was PN and pursued PND (child was unaffected)
Lakeman et al, 2008[78]	CF, HbP	PC	87 (72 couples)	0 carrier couples identified 37/139 (27%) participants would have considered not having (more) children if found to be a carrier couple In case of pregnancy, 124/139 (89%) reported that they would have chosen PND and 84/124 (68%) would consider termination of an affected pregnancy At 3 mo, 112/120 (93%) participants, including carriers, stated that test results had not changed their ideas about having children 6/120 (5%) non-carrier couples reported being more certain about having children
Baker et al, 2008[79]	CF, HbP, FXS	PC	72 oocyte donors, 64 recipients	CF: all recipients proceeded with cycles after the intended fathers were found not to be carriers Alpha-thal: cancelled for unrelated reason (donor noncompliance) FXS: recipient couples decided against proceeding with donor with premutation
Archibald et al, 2018[80]	CF, SMA, FXS	PC, PN	12,000 (at least 69% PN)	CF: 9/9 pregnant couples chose PND testing 4 had affected fetuses 3 of those 4 chose to terminate the pregnancy SMA: 1/1 pregnant couple chose PND testing; they had an affected fetus and chose termination of pregnancy FXS: 22 couples 2 couples declined further testing (presumed unaffected pregnancy) 2 couples experienced spontaneous pregnancy loss 18 couples chose further testing: 2 of the 18 chose NIPT (presumed unaffected pregnancy) while the other 16 chose PND testing 2 of those 16 couples had affected fetuses and both chose termination of pregnancy
Franasiak et al, 2016	ECS (CF)	PC	3,738 couples	1/3 couples planned PGT, but became pregnant on their own; chose PND 2/3 couples scheduled for PGT, but chose not to pursue treatment
Peyser et al, 2019[51]	ECS (CF, FXS, HbP, SMA)	PC	4,232 (1,206 couples)	All CF, beta-thal, SMA carrier couples elected IVF with PGT 1/53 IM carriers pursued PGT 2/17 PM carriers pursued GT 2 FM carriers, did not receive follow-up care at centre

Author, year	Condition	Timing	N	Impact on reproductive decision-making
Capalbo et al, 2021[110]	ECS (CF, FXS, SMA)	PC	766 couples	CF: 3/5 couples pursued PGT 1 couple had an unaffected live birth 1 couple had an ongoing pregnancy FXS: 2/5 couples pursued PGT 1 couple had an unaffected live birth SMA: 4/4 couples pursued PGT 1 couple had an unaffected live birth 1 couple had an ongoing pregnancy Beta-thal/SCA: 4/4 couples pursued PGT
Hernandez-Nieto et al, 2020[53]	ECS (CF, HbP, FXS)	PC	805 (391 couples)	Alpha-thal: decided not to pursue PGT FXS: all PM at risk of passing full mutation to child and all IM carriers pursued PGT before embryo transfer selection
Xi et al, 2020[54]	ECS (HbP, SMA)	PC, PN	2,923 (1,420 couples)	3 alpha-thal carrier couples: 2 couples chose PGT 1 couple took action after ECS was NR 5 SMA carrier couples: 4 couples chose PGT 1 couple took action after ECS was NR
Alfaro Arenas et al, 2016,[83] 2017[84]	FXS	PC, PN	3,731 (3,413 PN, 318 PC)	18/30 PM carriers chose amniocentesis: 12 of the 18 inherited the PM allele; all 12 chose to continue the pregnancy
Berkenstadt et al, 2007[115]	FXS	PC, PN	40,079	370 chose PND (7 FM, 363 PM): 30 had affected pregnancies and all 30 chose termination
Cheng et al, 2017[116]	FXS	PN	2,650	1 FM carrier: did not undergo PND because they were tested in third trimester and termination was not an option. Child was unaffected 2 PM carriers: 1 couple chose PND; the fetus had FM allele and they chose termination and planned for PGT in the future 1 couple chose no PND due to variable phenotype of FM females
Cronister et al, 2005[85]	FXS	PC, PN	29,103	16 IM carriers: 14 offered PND unrelated to FXS 12 of the 14 accepted (7 requested PN FXS analysis—3 had IM expansion the other 4 had no change in transmission of IM) The other 2 declined 6 PM carriers: 3 (50%) accepted FXS PND: 2 had unaffected pregnancies (male child) 1 child was a PM carrier (female child) 3 (50%) declined FXS PND: 2 already chose termination based on information of cytogenetically abnormal fetus results

Author, year	Condition	Timing	N	Impact on reproductive decision-making
				1 declined based on low risk of expansion to FM in pregnancy
Hung et al, 2019[119]	FXS	PN	20,188	26 PM with 30 total pregnancies: 21 of 26 chose PND: Of 17 PM pregnancies, 11 were delivered Of 6 FM pregnancies, 4 chose termination and 2 chose continuation of pregnancy (delivered female babies) 5/26 chose genetic testing after delivery: 1 FM with 2 pregnancies chose PND for both pregnancies 1 continued pregnancy with FM (delivered female baby) 1 terminated pregnancy with partial deletion (male baby)
Jang et al, 2014[120]	FXS	PC, PN	10,241	26 pregnant PM carriers 13/26 affected pregnancies (8 PM, 5 FM)
Johansen Taber et al, 2019[148]	FXS	PC, PN	122	73 PC carrier couples: 34 (47%) were planning or pursuing IVF at time of screening 54 (60%) planned or pursued any of the following: 38 (52%) IVF with PGT 18 (25%) PND 4 (5.5%) use(d) gamete donor 4 (5.5%) avoid(ed) pregnancy 3 (4.1%) adoption 49 PN carrier couples: 20 (41%) pursued PND, of whom 2 (10%) had FM pregnancies (1 had a live birth, the other chose termination) 3 (15%) had PM pregnancies (all 3 had live births) 1 (5%) awaiting result 54 subsequent pregnancies: 15 (28%) achieved by IVF and PGT; all 15 pursued PND 3 (20%) FM pregnancies: 2 live births; 1 couple chose termination 1 (6.7%) PM pregnancy; couple proceeded to live birth 2 (13%) were awaiting results
Kim et al, 2013[121]	FXS	PC, PN	5,829	11 couples: 1 PC carrier and 10 PN carriers All 10 PN carriers chose PND 5 had PM pregnancy 1 had FM pregnancy (female) and chose termination
Ma et al, 2019[47]	FXS	PC, PN	11,891 (6,854 PC, 5,037 PN)	17 pregnant PM or FM carriers: 15 chose PND (13 PM, 2 FM)

Author, year	Condition	Timing	N	Impact on reproductive decision-making
				Of 13 pregnant PM carriers who chose PND there were: 8 FM pregnancies 2 PM pregnancies 3 non-carrier pregnancies Of 2 pregnant FM carriers who chose PND there was: 1 FM pregnancy 1 non-carrier pregnancy 9 FM couples chose termination 6 PM or non-carrier pregnancies continued
Pastore et al, 2008[55]	FXS	PC	20	1 (only) PM carrier declined additional genetic counselling
Xi et al, 2021[123]	FXS	PN	4,286	40 IM carriers: 0 pregnancies where IM expanded to PM 5 PM carriers: 0 affected FXS pregnancies 4 unaffected births 1 carrier chose termination due to trisomy 18 3 FM carriers: 2 unaffected pregnancies 1 FM carrier fetus
Ai et al, 2020[124]	HbP	PC, PN	1,628 women, 729 partners	1/3 couples chose amniocentesis Fetus was compound heterozygous with beta0 variant and a rare beta variant of uncertain significance 2/3 couples declined further testing
Borbolla Foster et al, 2021[125]	HbP	PN	643 (105 screened, 538 screen failure)	1/2 had affected pregnancy with fetal α0, uncomplicated pregnancy 1/2 had affected pregnancy with Hb Barts, resulted in stillbirth at 26 wk 1 infant identified as low-risk pregnancy subsequently underwent Hb screening for neonatal jaundice and probable delta/beta thal was detected Partner screening was not performed in 7 cases, preventing determination of fetal risk, but 1 infant was investigated for anemia at 6 mo and found to be heterozygous HbC with possible co-existing alpha-thal trait
Choudhuri et al, 2015[70]	HbP	PN	20,883	46/119 (38.7%) chose PND; 73/119 (61.3%) had no PND: 5/119 declined testing 68/119 could not be offered PND testing (because the pregnancies were too advanced)

Author, year	Condition	Timing	N	Impact on reproductive decision-making
Colah et al, 2008[69]	HbP	PN	61,935	15/37 (40.5%) chose PND: 4 had affected pregnancies; all 4 chose termination 22/37 (59.5%) did not undergo PND: 16 did not return for PND after counselling 2 experienced a spontaneous termination of pregnancy before PND could be done 4 had advanced pregnancy and were advised to test at birth
Kaufmann et al, 2011[88]	HbP	PN	1,291 (703 included prospectively, 588 included retrospectively)	There were 2 carrier couples; both presented at an advanced stage of pregnancy, where choice of termination was not possible 1 resulted in the birth of a carrier child 1 an affected birth There was no information about future family planning
Shukla et al, 2018[89]	HbP	PN	2,000	2/2 carrier couples were recommended for PND
Baxi et al, 2013[56]	Beta-thal	PN	1,006	1/1 couple chose CVS; the pregnancy was unaffected
Miri-Moghaddam et al, 2012[130]	Beta-thal	PN	106 couples	42 beta-thal couples chose PND (58 PND total, due to multiple pregnancies) 15/58 (25.9%) had affected pregnancies All 15 chose termination
Patel et al, 2014[131]	Beta-thal	PN	282 couples	282 chose PND: 62 had affected pregnancies and all 62 chose termination
Suwannakhon et al, 2018[132]	Beta-thal	PN	1,115	23/23 carrier couples chose PND: 1 had an affected pregnancy with homozygous CD17 5 had affected pregnancies with beta0-thal/Hb E disease
Wong et al, 2016[133]	Beta-thal, Hb E	PN	834	23/23 carrier couples chose PND: 7 had affected pregnancies 6 of the7 had Hb E–beta compound heterozygotes and the 7th had beta thal homozygote
Suwannakhon et al, 2017[134]	HbP (Hb Bart's)	PN	1,235	15/15 carrier couples chose PND: 4 pregnancies were homozygous for alpha0-thal (SEA deletion) 8 had pregnancies with SEA deletion carriers 3 were unaffected pregnancies
Li et al, 2015[135]	Non-deletional beta-thal)	PN	51,105 couples	35 couples were carrier for deletional Hb H: All 35 chose PND 9 had affected pregnancies and 8 of those 9 chose termination

Author, year	Condition	Timing	N	Impact on reproductive decision-making
Marcheco-Teruel et al, 2019[92]	HbP (SCA)	PN	4,847,239	6,475/8,180 (79.2%) carrier couples chose PND testing 1,299 had SCD-associated pregnancies (SS, CC, or SC) Of the couples (or women) facing the most severe forms (SS or SC genotypes), 76.2% chose termination People with CC pregnancies (who develop less severe forms of SCD) rarely chose to terminate
Weil et al, 2020[137]	HbP (SCD), thal	PN	6,608,575	3,941/8,867 (44.4%) carrier couples underwent PND: 964 (24.5%) had affected pregnancies 1,007 (25.6%) had unaffected pregnancies 1,948 (49.4%) had carrier pregnancies 22 (0.6%) had inconclusive or unknown results 964 affected pregnancies: 563 (58.4%) had a known outcome 389 (69.1%) couples terminated their pregnancy 168 (29.8%) couples continued their pregnancy 6 (1.1%) couples had a spontaneous pregnancy loss 401 (41.6%) had an unknown outcome
Yamsri et al, 2010[139]	Thal (severe types)	PN	1,422	756/968 (78.1%) underwent PND
Bhukhanvala et al, 2013[93]	Thal (severe types)	PN	3,009	11/14 (78.6%) chose PND: 3 pregnancies were affected with thal major (all 3 couples chose termination) There were no affected children among continued pregnancies
Gupta et al, 2015[94]	Thal	PN	1,500	17/20 chose PND testing: 2 (11.8%) pregnancies were affected with thal major; both couples chose termination
Jiang et al, 2017[140]	Thal	PC	83,062 (41,531 couples)	66/66 couples with PND indication chose PND: 15 had affected pregnancies; all 15 chose termination The remaining 355 ARC were still preparing for pregnancy
Jiang et al, 2021[141]	Thal	PC	137,222 couples	345 chose to terminate the affected pregnancy No children were born with thal major
Kiani et al, 2022[149]	Thal	PN	241 couples	241 carrier couples 135/241 (56%) underwent PND: 31 (12.8%) had beta-major–affected pregnancies 77 (31.9%) had beta-minor–affected pregnancies 1 (0.4%) had an Hb Bart's–affected pregnancy 1 (0.4%) had an Hb H-affected pregnancy

Author, year	Condition	Timing	N	Impact on reproductive decision-making
Liao et al, 2005[96]	Thal	PN	49,221 pregnant people, 4,502 partners	281 carrier couples: 269 chose PND 12 refused because couple had opposing thoughts about reproductive risk or did not believe the possibility of having a potentially affected child 198 carrier couples of alpha-thal and 187 chose PND: 51 had Hb Bart's pregnancies and all 51 chose termination 3 had Hb H pregnancies and all 3 continued with the pregnancy 83 carrier couples of beta-thal and 82 chose PND: 18 had beta-thal major pregnancies and all 18 chose termination
Ratanasiri et al, 2006[98]	Thal	PN	1,498	10/19 carrier couples chose PND: 6 refused DNA analysis and PND (3 were re-categorized as not at risk based on DNA analysis) 2 had affected pregnancies (1 beta-thal/Hb E disease, 1 Hb Bart's) and both chose termination
Theodoridou et al, 2008[142]	Thal	PN	1,375 couples	100/116 at-risk pregnancies 16 did not have severe clinical disease and PND was not indicated 100 chose PND: 26 pregnancies were affected with clinically significant variants and all 26 chose termination There were no reported cases of misdiagnosed pregnancies
Theodoridou et al, 2018[143]	Thal	PN	1,598 couples	335 carrier couples underwent PND and 76 (22.7%) pregnancies were affected with clinically significant HbP: 73 (96.1%) chose termination Reasons for new affected births: no screening performed, incorrect test interpretation, couples chose not to consider information given, personal or religious beliefs, laboratory error, lack of gamete donor screening in cases of IVF
Tongsong et al, 2013[99]	Thal	PN	12,874	273/281 carrier couples chose PND: 58 pregnancies were affected with severe thal 3 births were affected with severe thal: 2 couples declined PND 1 couple underwent PND, but chose to continue the affected pregnancy There were no cases of severe thal in pregnancies of carrier couples identified as not at risk

Author, year	Condition	Timing	N	Impact on reproductive decision-making
Wong et al, 2006[144]	Thal	PN	2,396 (1,198 couples)	4/18 underwent PND; there were 0 affected pregnancies 14/18 did not undergo PND because of delayed antenatal care
Wongprachum et al, 2016[100]	Thal	PN	411 (71 couples)	5/40 affected pregnancies: 3 Hb Bart's 2 Hb E/beta0-thal
Yang et al, 2020[101]	Thal	PN	2,306	82/82 carrier couples underwent PND: 64 had affected pregnancies (39 alpha-thal, 42 beta-thal, 1 alpha/beta-thal) 29 pregnancies were affected with intermediate or severe thal and all 29 chose termination 35 pregnancies were affected with minor thal and all 35 chose to continue the pregnancy 18 pregnancies were unaffected Neonatal thal genotypes were evaluated after delivery and were consistent with PND results
Su et al, 2011[104]	SMA	PN	107,611	43/47 (91.5%) carrier couples chose PND: 12 (27.9%) had affected pregnancies 11 chose termination, 1 continued to birth but the child died due to respiratory failure at 90 d
Zhang et al, 2020[105]	SMA	PN	13,069 pregnant people and 207 partners	7/10 carrier couples chose PND: 6 had unaffected pregnancies 1 had an affected pregnancy and chose termination 3 carrier couples refused PND due to the risk associated with PND

Abbreviations: ARC, at-risk couple; CF, cystic fibrosis; CVS, chorionic villus sampling; ECS, expanded carrier screening; FXS, fragile X syndrome; Hb, hemoglobin; HbP, hemoglobinopathy; IM, intermediate mutation; IVF, in vitro fertilization; NIPT, noninvasive prenatal testing; NR, not reported; PC, preconception; PGT-M, preimplantation genetic testing for monogenic/single gene defects; PN, prenatal; PND, prenatal diagnosis/diagnostic; SCA, sickle cell anemia; SMA, spinal muscular atrophy; thal, thalassemia.

Psychological Impact

Few studies reported on the psychological impact of carrier screening (Table 9). Only a small minority of studies used a validated tool to evaluate psychological outcomes. Metcalfe et al (2008)[86] found a reduction in anxiety over time among the group of people who accepted carrier screening, and no significant change in the untested group. In comparison, in a subsequent study, the authors found that decisional conflict and regret was generally low, but it was greater in pregnant people compared with non-pregnant people, and in people who were not tested compared with people who were tested.[68]

Pastore et al[55] evaluated FXS carrier screening among people experiencing infertility and found that participants experienced anger and regret that they did not learn sooner that their infertility may be related to their being a carrier. Cizmeli et al[117] found that about 36% of participants reported a favourable emotional response to potentially being a fragile X carrier. The emotions at follow-up

were considerably more positive than at pre-testing. The GRADE certainty was Very low for psychological impact and was downgraded due to risk of bias and inconsistency (see Table A5).

Table 9: Results for Psychological Impact of Carrier Screening

Author, year	Condition	Timing	N	Psychological impact
Lakeman et al, 2008[78]	CF, HbP	PC	87 (72 couples)	Participants reported a low level of anxiety at the start, which decreased further during the study period (*P* = .001) 85/116 (73%) reported that they had not been worried while awaiting their test results 79/116 (68%) felt relieved at 1 wk post-test, with 74/120 (62%) relieved at 3 mo post-test 4 people (including 2 carriers) were disappointed 1 wk post-test, with 0 disappointed at 3 mo post-test
Pastore et al, 2008[55]	FXS	PC	20	Anger that participants did not learn sooner that FXS might be related to infertility: baseline mean 2.16 (SD: ±2.14) vs. 3 mo follow-up projection mean 4.41 (SD: ±2.45), *P* = .02 Regret that participants did not learn sooner that FXS may be related to infertility: baseline mean 3.21 (SD: ±2.88) vs. 3 mo follow-up projection mean 5.41 (SD: ±2.98), *P* = .03
Cizmeli et al, 2013[117]	FXS	PC	62	Emotional response about potentially being FXS carrier (N = 62): 22 (35.5%) favourable or very favourable response 33 (53.2%) ambivalent response 7 (11.3%) unfavourable response Feelings about not being a FXS carrier 3 mo post-test:50/55 (90.9%) favourable or very favourable response 5/55 (9.1%) ambivalent
Alfaro Arenas et al, 2016[83]	FXS	PC, PN	3,731 PN: 3,413 PC: 318	In general, people self-reported low anxiety[a] Anxiety generated by FXS screening: mean 2.9 Anxiety generated by test has been offset by usefulness of results obtained: mean 6.0 Anxiety generated by study has increased anxiety caused by pregnancy itself: mean 2.6
Metcalfe et al, 2008[86]	FXS	PC	31	Reduction in mean anxiety score over time for tested people (*P* = .02) No significant change for untested group (*P* = .5) and no significant change for the untested
Metcalfe et al, 2017[68]	FXS	PC	1,156	Depression Anxiety Stress Scale (DASS): n (%) Depression vs. normal: nonpregnant vs. pregnant: 433 (80.3%) vs. 371 (90.9%), *P* <.001

Author, year	Condition	Timing	N	Psychological impact
				Tested vs. not tested: 627 (84.2%) vs. 177 (87.6%), *P* = .27 Anxiety: normal: Nonpregnant vs. pregnant: 447 (82.5%) vs. 354 (86.8%), *P* = .087 Tested vs. not tested: 626 (83.7%) vs. 153 (75.7%), *P* = .015 Stress vs. normal: Nonpregnant vs. pregnant: 448 (82.2%) vs. 364 (89.7%), *P* = .002 Tested vs. not tested: 636 (84.8%) vs. 176 (87.6%), *P* = .383 Spielberger State-Trait Anxiety Inventory (SATI): mean (SD)[b] Nonpregnant vs. pregnant: 36.7 (12.9) vs. 36.2 (11.2), *P* = .533 Tested vs. not tested: 36.2 (12.5) vs. 37.6 (11.0), *P* = .147
Prior et al, 2010[103]	SMA	PC, PN	500	Among females surveyed who declined screening, 13% stated testing would be associated with increased anxiety 1 person who underwent testing reported negative experience due to added anxiety
Wood et al, 2016[65]	SMA	PN	1,377	25/90 (27.8%) worried screening results would not remain confidential 25/90 (27.8%) worried they would incur discrimination as a carrier

Abbreviations: CF, cystic fibrosis; FXS, fragile X syndrome; HbP, hemoglobinopathy; PC, preconception; PN, prenatal; SD, standard deviation; SATI, Spielberger State-Trait Anxiety Inventory; SMA, spinal muscular atrophy.
[a]Anxiety scale ranges from 0 to 10, higher score indicates greater anxiety.
[b]SATI score ranges from 0 to 80, normal average is 31–49, higher score indicates higher anxiety.

Downstream Impacts

We did not find any studies evaluating the impact of variants of uncertain significance and the impact of fragile X–associated disorders related to the identification of fragile X premutation carriers.

Three studies[94,131,139] reported no fetal loss from prenatal diagnostic testing (chorionic villus sampling or amniocentesis). Two other studies[96,143] did report spontaneous fetal loss related to prenatal diagnostic testing. The results are summarized in Table 10.

Five studies[54,55,84,110,116] reported that cascade testing was either offered or completed for some family members or relatives (Table 10). Pastore et al[55] found that one-third of participants notified parents and/or friends they were undergoing carrier testing, and 17% of participants shared their result information with siblings or extended family members. Two studies reported on cascade screening results.[84,110]

The GRADE certainty was Very low for downstream impact and was downgraded due to risk of bias and inconsistency (see Table A5).

Table 10: Results for Downstream Impact of Carrier Screening

Author, year	Condition	Timing	N	Downstream impacts
Coiana et al, 2011[64]	CF	PC, PN	1,000 (500 couples)	All carriers were invited to inform their relatives about opportunity to be tested for CF
Simone et al, 2011[81]	CF, HbP	PN	513	4 partners were identified as having a VUS, but were excluded from study
Gupta et al, 2015[94]	Thal	PN	1,500	No fetal loss from PND
Patel et al, 2014[131]	Beta-thal	PN	564 (282 couples)	No fetal loss from PND
Yamsri et al, 2010	Beta-thal	PN	1,422	No fetal loss from PND
Theodoridou et al, 2018[143]	Thal	PN	1,598	1 membrane rupture resulting in pregnancy loss due to PND
Liao et al, 2005[96]	Thal	PN	49,221 pregnant people, 4,502 partners	3/269 (1.1%) spontaneous fetal loss due to PND
Pastore et al, 2008[55]	FXS	PC	20	1/3 of participants told parents and/or friends they were undergoing testing 17% shared information with siblings or extended family members
Alfaro Arenas et al, 2017[84]	FXS	PC, PN	3,731 (3,413 pregnant, 318 not pregnant)	Cascade family studies performed: 16/30 (53.3%) were premutation carriers 14/30 (46.7%) were intermediate carriers
Cheng et al, 2017[116]	FXS	PN	2,650	Family of FM carrier declined testing because they were phenotypically normal with no current reproductive plans
Capalbo et al, 2021[110]	ECS (CF, FXS, SMA)	PC	766 couples	1 SMA cascade testing resulted in additional at-risk couple identified in family 1 SMA cascade testing resulted in additional carrier in family 1 CF cascade testing resulted in additional carrier in family
Xi et al, 2021[54]	FXS	PN	4,286	Cascade testing was performed among a few family members of carriers

Abbreviations: CF, cystic fibrosis; CVS, chorionic villus sampling; ECS, expanded carrier screening; FM, full mutation; FXS, fragile X syndrome; HbP, hemoglobinopathy; PC, preconception; PN, prenatal; PND, prenatal diagnosis/diagnostic; SMA, spinal muscular atrophy; thal, thalassemia; VUS, variant of uncertain significance.

Ongoing Studies

We are aware of the following potentially relevant ongoing study on carrier screening at ClinicalTrials.gov: Prenatal Carrier Screening for Spinal Muscular Atrophy Among Thai Pregnant Women (NCT04859179; study still stated to be in recruiting phase with anticipated completion in March 2022).

In PROSPERO, we found four potentially relevant ongoing systematic reviews on carrier screening evaluating:

- Diagnostic Performance and Clinical Validity of Reproductive Carrier Screening Panels: a Systematic Review (CRD42020210784, anticipated completion in August 2020)
- Clinical and Nonclinical Utility of Reproductive Carrier Screening for Recessive Conditions: a Systematic Review (CRD42020186148, anticipated completion in April 2021)
- Comparative Effectiveness of Expanded Carrier Screening With Reproductive Carrier Screening Panels: a Systematic Review (CRD42020209180, anticipated completion in April 2021)
- Psychosocial Impacts of Reproductive Carrier Screening Panels: a Systematic Review (CRD42020210787, anticipated completion in April 2021).

Discussion

Our systematic review found that the uptake of carrier screening can be highly variable among different populations, but carrier screening is effective for the identification of at-risk couples for the purposes of reproductive decision-making. At-risk couples during preconception may choose future pregnancy options, and prenatal at-risk couples may choose whether to terminate an affected pregnancy based on carrier screening results. Informed patient choice is integral to both undergoing carrier screening and the subsequent pregnancy-related decisions.

We found a lack of comparative studies on carrier screening. The included studies were heterogeneous, especially in their study populations and testing methods. Most of the included studies evaluated carrier screening during the prenatal period or a combination of preconception and prenatal timing. While a prenatal carrier screening program is likely more feasible (e.g., could be added to existing prenatal visits), preconception carrier screening allows for the most reproductive options and enhanced reproductive autonomy. Clinical guidelines also recommend that the ideal time to offer carrier screening is during preconception.[16,35,150]

The uptake rate for carrier screening varied considerably among the studies, both for the person to be tested and for their partner. Cultural or personal reasons vary between populations and may influence a person's decision to seek or participate in carrier screening, subsequent prenatal diagnostic testing, and potential voluntary termination of affected pregnancies.[65,66] Therapeutic options have improved over time and can lead to longer life expectancy and improved quality of life for affected people. These treatment advancements may impact a pregnant person's decision to continue or terminate an affected pregnancy.

Differences in study populations and testing methods may contribute to the variability of the results in the proportion of at-risk couples identified. Testing methods may be influenced by a region's laboratory capabilities, and the accuracy of different testing methods may also vary (e.g., common variant panels, gene sequencing, cytogenetic vs. molecular [DNA] genetic testing for

hemoglobinopathies and thalassemia). The included pathogenic variants were typically those most common among the tested participant populations, which in turn may affect the number of identified at-risk couples. However, these variants may not be as common in people who are more racially or ethnically diverse. Canadian and international guidelines support pan-ethnic carrier screening (screening regardless of race or ethnicity), which has been shown to identify carriers and at-risk couples more effectively.[16,35,150] However, a lack of comparative studies makes it difficult to draw conclusions about the relative effectiveness of different types of carrier screening tests or programs.

Studies have noted the importance of both pre- and post-test counselling for carrier screening to achieve informed consent, adequate knowledge and understanding, and help with reproductive decision-making.[16,35,150] Counselling is of particular concern for expanded carrier screening panels that include many conditions, including universal carrier screening. Most studies described some aspects of pre- and post-test counselling, but the level of information given and the delivery of counselling differed among studies, which may impact screening uptake and reproductive decisions.

In recent years, the use of expanded carrier screening panels has increased and now allows for hundreds of genetic conditions to be screened at once. While these panels may provide carrier information for many more genetic conditions, including additional conditions increases the likelihood of a positive test result (for at least one of the conditions tested). There are concerns that positive results may include variants unlikely to cause the genetic condition (low-penetrance variants) or other variants of uncertain significance, which causes uncertainty and difficulty in result interpretation. However, expanded carrier screening panels may identify more at-risk couples compared with predetermined variant panels or NGS-only methods.[46]

Strengths and Limitations

One of the strengths of our review is our broad inclusion criteria, which includes all types of carrier screening tests for CF, hemoglobinopathies and thalassemia, FXS, and SMA for the purposes of pregnancy decision-making. Further, we considered not only the direct clinical outcomes of carrier screening but also the potential psychological and downstream impacts from testing results, although few included studies evaluated the latter outcome.

We found studies on premarital carrier screening, some of which also reported subsequent reproductive decisions and outcomes due to testing. However, we excluded these studies given that the primary purpose of premarital screening is to identify at-risk couples for marriage decisions. These studies were also generally unclear about the number of members of at-risk couples who changed partners due to their carrier status (and then presumably became a member of a lower-risk couple), and the number of at-risk couples who decided to continue with marriage.

Our review aligns with other reviews on carrier screening,[59,61] which have also found a lack of comparative studies and heterogeneity among studies. Unfortunately, due the heterogeneity among studies, we did not perform any further subgroup analyses. This heterogeneity also makes generalization of study results difficult. However, our results show the current variation of carrier screening tests and implementation in different regions and countries in the world.

While our review focused on four specific conditions, our broader results may also apply to the additional similar genetic conditions included in carrier screening programs or expanded carrier screening panels. However, the gene–disease association and clinical validity (accuracy) should be

adequately evaluated for all conditions included in these panels to avoid uncertain results, enable clinical utility, and improve patient-important outcomes.

Conclusions

The uptake rate of carrier screening varied considerably among the included studies. Evidence on the downstream effects of carrier screening was limited.

Carrier screening for CF, hemoglobinopathies and thalassemia, FXS, and SMA:

- Likely results in the identification of couples with an increased risk of having an affected pregnancy
- Likely impacts reproductive decision-making and the decision to continue with the affected pregnancy
- May result in lower anxiety among pregnant people, although the evidence is uncertain

Economic Evidence

Research Question

What is the cost-effectiveness of carrier screening programs for cystic fibrosis (CF), fragile X syndrome (FXS), hemoglobinopathies and thalassemia, and spinal muscular atrophy (SMA) for people who are considering a near-future pregnancy or who are pregnant?

Methods

Economic Literature Search

We performed an economic literature search on April 7, 2021, to retrieve studies published from January 1, 2005, until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE and Embase, and monitored them until July 1, 2022. We also performed a targeted grey literature search of health technology assessment agency websites, systematic review registries, and the Tufts Cost-Effectiveness Analysis Registry. See the Clinical Literature Search section, above, for further details on methods used. See Appendix 2 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published from January 1, 2005
- Cost–utility, cost-effectiveness, cost–benefit, or cost–consequence analyses or systematic reviews of economic analyses

Exclusion Criteria

- Studies where outcomes of interest are not reported or cannot be extracted
- Non-systematic reviews, editorials, commentaries, case reports, conferences abstracts, letters, unpublished studies
- Noncomparative costing studies, feasibility analyses, cost-of-illness studies

POPULATION

Inclusion Criteria

- People at any carrier risk level and/or their reproductive partner at the preconception or prenatal period

Exclusion Criteria

- Members of general population (e.g., people not of reproductive age) or minors (i.e., people of reproductive age, younger than 18 years)

INTERVENTIONS

Inclusion Criteria

- Targeted or universal (population-based) carrier screening program for pathogenic variants of CF (related to the *CFTR* gene), FXS (related to the *FMR1* gene), hemoglobinopathies and thalassemia (related to the *HBB*, *HBA1*, or *HBA2* gene), or SMA (related to *SMN1* gene) using any testing approach for reproductive decision-making

Exclusion Criteria

- Screening for purposes other than near-future reproductive decision-making (e.g., premarital or pre-relationship testing for relationship/marriage decisions, young adults of reproductive age such as during high school, testing for only individual carrier status knowledge and not for near-future reproductive decision-making)
- Standard protocol screening for donor egg/sperm (i.e., standard protocol testing at donor egg/sperm bank)
- Screening for other genetic conditions or other types of pathogenic variants of CF, FXS, hemoglobinopathies and thalassemia, or SMA

COMPARATORS

- No testing (no screening) or different test/screening approach (e.g., screening of embryo, fetus, or child directly)

OUTCOME MEASURES

- Costs
- Health outcomes (e.g., number of detected carriers or at-risk couples [carrier couples], number of affected pregnancies, number of affected births, life-years [LYs], quality-adjusted life-years [QALYs], or disability-adjusted life-years [DALYs])
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios (e.g., incremental cost per identified at-risk couple or per affected pregnancy/birth, or per QALY/DALY) or incremental net benefit

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[41] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. The same reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists for any additional relevant studies not identified through the search.

Data Extraction

We extracted relevant data on study characteristics and outcomes to collect information about the following:

- Source (e.g., citation information, study type)
- Methods (e.g., study design, analytic technique, perspective, time horizon, population, intervention[s], comparator[s])
- Outcomes (e.g., health outcomes, costs, incremental cost-effectiveness ratios)

Study Applicability and Limitations

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom to inform the development of NICE's clinical guidelines.[151] We modified the wording of the questions to remove references to guidelines and to make it specific to Ontario. Next, we separated the checklist into two sections. In the first section, we assessed the applicability of each study to the research question (directly, partially, or not applicable). In the second section, we assessed the limitations (minor, potentially serious, or very serious) of the studies that were included in the review.

Results

Economic Literature Search

The database search of the economic literature yielded 585 citations published from January 1, 2005, until April 7, 2021. We identified 14 additional studies from other sources, for a total of 394 after removing duplicates. In total, we identified 21 economic studies (2 systematic reviews and 19 original research studies) that met our inclusion criteria. See Appendix 5 for a list of selected studies excluded after full-text review. Figure 2 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

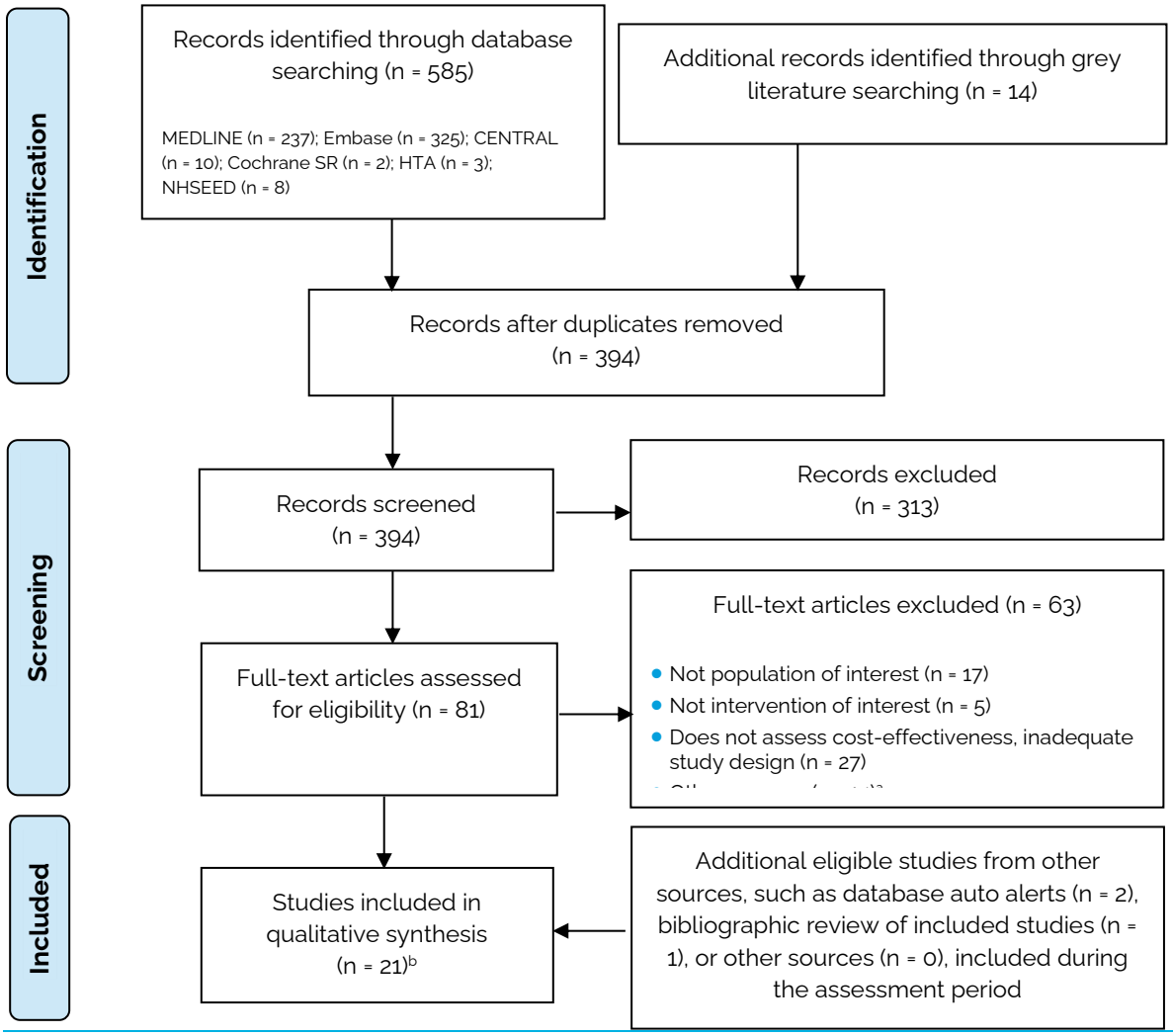

Figure 2: PRISMA Flow Diagram—Economic Search Strategy

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

[a]Other reasons for study exclusion: duplicate findings (n = 9), non-English studies (n = 2) and unable to obtain full text (n = 3).

[b]Two citations present results of the same analysis.[152,153]

PRISMA flow diagram showing the economic search strategy. The database search of the economic literature yielded 585 citations published between January 1, 2005, and April 7, 2021. We identified 14 additional eligible studies from other sources. After removing duplicates, we screened the abstracts of 394 studies and excluded 313. We assessed the full text of 81 articles and excluded a further 63. In the end, we included 21 articles in the qualitative synthesis.

Source: Adapted from Page et al.[45]

Overview of Included Economic Studies

Tables A7–A11 (Appendix 6) describe study design, populations, outcomes, perspectives, time horizons, results, and sensitivity analyses of the included cost-effectiveness analyses. We identified a total of 21 relevant economic studies; of these, eight examined preconception carrier screening, and the remainder examined prenatal carrier screening. Two studies were systematic reviews of the literature; one included all economic analyses published until 2019 for single and multiple conditions,[154] and another included all economic studies published until 2006 for CF only.[155] The remainder of the 19 original evaluations examined multiple conditions (four studies[156-159]) and CF (eight studies[72,76,160-165]), FXS (three studies[166-168]), hemoglobinopathies and thalassemia (three studies[98,153,169]), and SMA (one study[170]) as single conditions. Below, we summarize their findings by looking at preconception and prenatal multiple- and single-condition screening.

COST-EFFECTIVENESS OF PRECONCEPTION CARRIER SCREENING (CARRIER SCREENING IN PEOPLE CONSIDERING A PREGNANCY)

Preconception Screening for Multiple Conditions or Expanded Carrier Screening

Four cost-effectiveness analyses examined preconception carrier screening for multiple conditions (see Table A7).[156-159] All studies were decision-tree models that included multiple pregnancies and assessed various clinical outcomes such as the number of identified carrier couples,[158,159] affected births,[156,157,159] LYs,[156-159] and QALYs or DALYs (of people living with the conditions).[158,159] The studies considered direct medical costs over either a lifetime[156,158,159] or a 3-year[157] time horizon. Two US studies[156,157] were conducted from a private payer (insurance) perspective[156,157] and two Australian studies[158,159] from a health care sector perspective. The two US studies specified the intervention as expanded carrier screening (ECS) with next-generation sequencing (NGS) panels that could detect 176 or 14 genetic conditions (including the conditions of interest to our review) and compared it to minimum screening (two conditions: SMA and CF), targeted genotyping (i.e., non-NGS panels) or no screening. The two Australian studies defined the intervention as universal (population-based) DNA testing for SMA, CF, and FXS, without providing much detail on the panel used for genetic testing, and compared it with targeted screening in a high-risk population[159] or to no screening.[158] The per-person cost of the test was $400 AUD (about $360 adjusted to 2022 CAD) in the Australian analyses and between $500[156,157] and $1,000[157] USD in the US studies (about $657 and $1,314, respectively, adjusted to 2022 CAD).

At a test cost of $500 USD per person, the cost-effectiveness of population-based preconception ECS in the United States compared with targeted screening or no screening was dominant or cost saving.[156,157] At a test cost of $400 AUD per person, population-based preconception multiple-condition screening of SMA, FXS, and CF in Australia was dominant or cost saving compared to no testing,[158] and was cost-effective compared to targeted screening of at-risk populations (an incremental cost-effectiveness ratio [ICER] of $32,145 AUD per DALY)[159]. Zhang et al[159] found that preconception screening was not cost-effective for a single condition (the condition-specific ICERs for CF, SMA, and FXS are $126,630, $468,151, and $130,296 AUD per DALY, respectively). They also showed that multiple-condition screening was dominant (cost saving) over targeted risk-based screening when the test cost decreased from $400 to $200 AUD. In addition to the cost of the test, other factors that influenced the cost-effectiveness of multiple-condition screening were compliance with prenatal testing (given the results of preconception genetic testing), participation of the second (male) partner in the screening,[156-158] carrier frequency rates,[157-159] sensitivity and specificity of genetic tests,[156,158] and treatment costs.[156] Of note, the influence of two factors—the probability of choosing to terminate the pregnancy voluntarily (after being informed of the screening result) and the probability of the first (female) partner participating in the screening—was not clearly reported in the above-

mentioned studies. The probability of voluntary termination of pregnancy was assumed to be relatively high for all examined conditions (between 50%[159] and 75%[156,157]). Only one study reported that an increase in this probability from 75% to 100% would be associated with larger cost savings.[156] No study that examined ECS considered that the probability of voluntary termination of pregnancy could be dependent on the examined condition (i.e., studies assumed the same probability of termination for all examined conditions). In addition, the rate of participation of the first partner seemed to be modeled or was assumed to be high; however, the impact of this parameter on the cost-effectiveness of ECS was not clearly explored or reported.

Wang et al[154] conducted a systematic review of 23 economic studies on reproductive carrier screening published until 2019 (see Table A7). This review included the two above-mentioned US studies,[156,157] but it did not include the two Australian studies,[158,159] which were published too late for inclusion. The main objective of Wang et al[154] was to assess the quality of reporting of the published evidence using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist.[171] The authors did not establish any specific conclusion about the cost-effectiveness of preconception or prenatal screening for multiple or single conditions, based on the published results (see Table S3 in Wang et al[154]). In their conclusion, the authors encouraged future economic studies to establish an expert-validated, clinically plausible, implementable clinical pathway for the reproductive carrier screening strategy that would serve to investigate the country-specific cost-effectiveness of carrier screening for multiple conditions and would also ensure realistic implementation of carrier screening.

Preconception Single-Condition Carrier Screening

Cystic Fibrosis

A few other economic studies, in addition to an evaluation by Zhang et al,[159] examined the cost-effectiveness of preconception carrier screening for CF since 2005 (see Table A8). Norman et al[163] found that, compared to no screening, preconception screening in the first pregnancy was associated with an incremental cost of $150,000 AUD per CF birth averted, but it was cost saving when subsequent pregnancies were accounted in the model.

A systematic economic literature review by Radhakrishnan et al[155] examined 14 decision models published between 1990 and 2006 (Table A8); five of the included studies compared preconception screening of couples or individuals to no screening. One of these studies (Weijers-Poppelaars et al[165]) is reported separately in Table A8, as it met our review criteria as an individual study. For the preconception screening studies in the economic evidence review by Radhakrishnan et al,[155] the most commonly reported outcomes were the cost per at-risk (carrier) couple detected and the cost per birth averted of an individual with CF. All currencies were converted to 2005 USD using purchasing power parity (PPP) exchange rates from Organisation of Economic Co-operation and Development (OECD) tables.[155] Compared with no screening, preconception screening was associated with ICERs ranging from about $394,307 to $572,728 per additional CF birth avoided, $33,504 to $295,121 per additional CF at-risk couple detected, and $4,340 per additional carrier detected. However, the authors concluded that, due to heterogeneity in study design, model inputs, and reporting, comparing and transferring of the economic results across or within countries were difficult to perform. They found that differences in screening participation rates, reproductive choices, test sensitivity, cost of the test, and the lifetime treatment cost of CF could lead to large variations in the ICERs. A systematic review by Wang et al[154] updated the literature to 2019 (Table A7), but it did not include any additional economic studies on CF preconception or prenatal screening. It

also did not provide substantially different conclusions with respect to single-condition screening compared with the Radhakrishnan review.[155]

Next, a study by Weijers-Poppelaars et al[165] examined the cost-effectiveness of a screening program in the Netherlands over 1 year. This study compared two screening approaches for couple testing (single-entry [sequential] and double-entry [simultaneous] testing of couples; testing could be provided either by education counsellors or general practitioners) with doing nothing. The program was evaluated from a societal perspective, and it was found to be associated with cost increases for all screening interventions (see Table A8 for detailed results).

Fragile X Syndrome
No study examined the cost-effectiveness of preconception carrier screening for FXS alone (see Table A9). As mentioned above, a subgroup analysis by Zhang et al[159] found that the population-based preconception screening compared with risk-based (targeted) screening for FXS was not cost-effective at a willingness-to-pay of $50,000 AUD per DALY (ICER: $130,296 AUD per DALY).

Hemoglobinopathies and Thalassemia
We identified one decision-tree analysis by the Medical Services Advisory Committee (MSAC) in 2019 that examined the cost-effectiveness of preconception carrier screening for alpha-thalassemia in couples planning a pregnancy in Australia (see Table A10).[169] The intervention was DNA analysis for a common gene deletion in alpha-thalassemia that continued to usual care hematological testing (i.e., full blood count, ferritin, and thalassemia studies). The cost of the test was $100 AUD for the PCR-GAP analysis (with $85 paid by the ministry and $15 paid by the patient) and $200 AUD for the PCR-GAP analysis followed by Multiplex Ligation-dependent Probe Amplification (MLPA; $170 paid by the ministry). Compared with usual care, the ICERs for preconception genetic screening were $110,266 AUD per additional couple genetically confirmed as being at risk of having a fetus affected by Hb Bart's syndrome (i.e., the most serious, lethal fetal outcome for alpha-thalassemia), and $446 AUD per additional couple with a genetically confirmed carrier status.

Spinal Muscular Atrophy
No study examined the cost-effectiveness of preconception carrier screening for SMA alone (see Table A11). As mentioned above, a subgroup analysis by Zhang et al[159] suggested that this type of single-disease screening did not represent good value for money from the Australian health care system perspective (ICER: $468,151 AUD per DALY).

COST-EFFECTIVENESS OF PRENATAL CARRIER SCREENING (CARRIER SCREENING IN PREGNANT PEOPLE)

Prenatal Screening for Multiple Conditions or Expanded Carrier Screening

In 2020, the MSAC[158] performed an economic analysis to evaluate the lifetime cost-effectiveness of preconception carrier screening. The MSAC reported the lifetime cost-effectiveness of prenatal multiple-condition carrier screening for CF, FXS, and SMA for initial pregnancy (Table A7). Prenatal carrier screening in initial pregnancy only was associated with an increase in per-person costs of about $190 AUD, compared with no testing. It was also associated with an increase in the number of at-risk (carrier) couples detected (from 53 to 660 per 100,000 people tested, depending on the condition) and in QALYs (mean difference, 0.02 QALYs per person). Given a willingness-to-pay value of $50,000 AUD per QALY, this carrier screening approach may be considered cost-effective (ICER: $11,145/QALY).

Prenatal Single-Condition Carrier Screening

Cystic Fibrosis

We identified eight studies—two systematic reviews[154,155] and six individual analyses[72,76,160-162,164]—that examined the cost-effectiveness of prenatal carrier screening for CF alone (Table A8). Avram et al[160] conducted a decision-tree analysis in 2021 from a US societal perspective in pregnant people at general risk of carrying a pathogenic variant for CF. They compared several sequential testing pathways that included NGS in one or in both partners, with sequential testing of both partners, with the currently recommended 23-variant panel (i.e., genotyping). Compared with genotyping of both partners, the sequencing strategies missed fewer carrier couples or CF births and the ICERs were deemed to be large and not cost-effective (> $180,000 USD per QALY).

In another decision-tree analysis published in 2016, the MSAC found ICERs of $1,804 AUD per prenatal CF detected, $1,898 AUD per CF birth averted, and $36,649 AUD per informed CF birth.[161] The carrier testing included two steps: a common pathogenic variant test for parents (at $135 AUD per 10-pathogenic variant panel) and a follow-up confirmation with whole-gene sequencing for a fetus ($1,000 AUD per test).

Maxwell et al[164] conducted a novel economic analysis of a prenatal carrier screening program in Australia (Table A8). The authors compared no screening with interventions related to universal (population-based) carrier genetic testing for pathogenic variants of CF in first (initial) and subsequent pregnancies. Three intervention strategies were considered: 1) one-step expanded screening, where the couple is offered testing simultaneously; 2) two-step screening (i.e., the pregnant person is screened and, if positive, the partner is screened) with simultaneous sample collection (i.e., both partners provide a blood sample at the same time); 3) two-step screening with sequential sample collection (the partner provides a blood sample for testing only after the pregnant person has been identified as a carrier). A decision-tree model was used to estimate costs, outcomes, and net lifetime costs (including the lifetime cost of treatment) for each strategy. The analysis examined commonly used health outcome measures (CF carriers and carrier couples detected, CF pregnancies identified, CF pregnancies terminated, CF-affected births). The program costs included the costs of program management and education, screening, counselling, diagnostic testing and follow-up, and lifetime care for an individual with CF. The considered costs of screening included the cost per sample for specimen collection, DNA extraction, labour and consumables, annual capital, and quality control. Excluding the capital and quality assurance costs, an estimated test cost for a 10-pathogenic variant panel was about $117 AUD. Compared with no screening, the two-step sequential screening program (for 38,000 pregnancies) was associated with the lowest incremental costs per CF couple detected ($253,488 AUD for one-step screening, $159,611 for two-step simultaneous screening, and $139,538 for two-step sequential screening) and the lowest incremental costs per CF pregnancy detected (for the initial pregnancy: $0.695 million AUD vs. $1.26 million [one-step] and $0.795 million [two-step simultaneous]; over two pregnancies, including newborn screening costs: $0.399 million vs. $0.723 million and $0.456 million). The authors estimated the net costs of the program and, once they accounted for the lifetime cost of care for a person with CF, they found a savings of $0.31 million with the two-step sequential screening approach (compared with net cost increases of $1.1 million with the one-step and $0.11 million with the two-step simultaneous approach to carrier screening). These results were sensitive to test sensitivity, diagnostic test uptake, and rate of voluntary termination of pregnancy.

In a systematic review of the economic literature that included published literature until 2006,[155] 10 decision-modelling analyses comparing prenatal screening of couples or individuals with no screening found a large variation in the ICER. The most commonly reported outcomes were cost per carrier couple detected and cost per CF birth averted. Only one study[172] reported cost per QALY gained (where QALYs indicated utility to the person living with CF). The ICER ranged from $75,500 to $134,100 USD per CF carrier couple detected, $739,600 to $1.6 million per CF birth averted, and $110,900 to $159,000 per affected pregnancy. In the cost–utility analysis,[172] the ICER for 2005 was estimated to be $10,086 USD per QALY. Radhakrishnan et al[155] concluded that transferability of this ICER across countries was inappropriate due to the large heterogeneity in study outcomes and study design. In 2021, Wang et al[154] updated this ICER to 2018 USD (i.e., $12,504 USD per QALY) and suggested there was inconclusive cost-effectiveness of CF prenatal screening despite a relatively low value of the ICER (< $50,000 per QALY) due to use of familiar QALYs (of both children with CF and their parents) for estimation of the QALY gain.

The rest of the included economic analyses (Table A8), done in the United Kingdom,[162] Greece,[72] and the United States,[76] also found high incremental costs of prenatal CF carrier screening with health outcomes measured as one CF birth averted[72,76] or one miscarriage averted (where a miscarriage was caused by invasive diagnostic procedures such as chorionic villus sampling [CVS] or amniocentesis).[162]

Fragile X Syndrome

As shown in Table A9, three original economic studies,[166-168] two cost–consequence analyses,[166,167] and a decision-tree cost–utility analysis[168] indicated that prenatal carrier screening for FXS may be cost-effective compared with no screening[167,168] or targeted screening.[166] These studies were also captured by Wang et al[154] in their 2019 systematic review. According to a decision-analytic study conducted from a US societal perspective, FXS carrier screening with PCR and Southern blot (in 20% of the cases) resulted in an ICER of about $14,900 USD/QALY (2004 price), but all outcome measures were poorly reported.[168] Wang et al[154] considered maternal QALYs in the update of this ICER and suggested favorable cost-effectiveness of prenatal FXS carrier screening at a willingness-to-pay of $100,000 USD per QALY (ICER: $19,345 per QALY, 2018 price).

Hemoglobinopathies and Thalassemia

We identified three studies (Table A10)—one cost–consequence and two decision-modelling analyses—that examined prenatal carrier testing for hemoglobinopathies. The decision-tree analysis done in 2019 by the MSAC for preconception carrier screening of alpha-thalassemia also examined DNA testing in pregnant people (Table A10).[169] Prenatal testing compared with no testing was associated with ICERs of $103,179 AUD per additional couple genetically confirmed as being at risk of having a fetus affected by Hb Bart's syndrome, and $417 AUD per additional couple with genetically confirmed carrier status. The UK study by Bryan et al,[153] which was also presented in a 2010 NICE report,[152] examined models of care for carrier testing for sickle cell disease early in primary care compared with testing at the first midwife consultation (usual care model). At the first primary care visit (by 10 weeks' gestation), the following interventions were considered: 1) primary care parallel option (testing offered to both the pregnant person and their partner at the same time) and 2) primary care sequential option (testing the pregnant person, and then testing their partner only after the pregnant person receives a positive result). Compared with usual care with midwife visits and the primary care parallel model, the primary care sequential model was the most efficient and was associated with an ICER of £13 GBP per pregnant person screened. However, based on costing

methods and costs of testing, it is unclear whether this study considered genetic testing in addition to a standard risk-based approach to screening based on hematologic test findings combined with information about family/personal history. Last, in 2006, Ratanasiri et al[98] performed a cost–consequence analysis and found that genetic carrier testing of pregnant couples was associated with a smaller number of severe thalassemia cases and lower costs compared with no testing. Overall, the reviewed studies showed mixed findings, had different study designs, and only considered some types of hemoglobinopathies; thus, it is difficult to infer whether prenatal genetic carrier testing represents good value for all types hemoglobinopathies.

Spinal Muscular Atrophy

An economic study by Little et al[170] examined the cost-effectiveness of universal prenatal DNA carrier testing for SMA for pregnant women and their partners (Table A11). This was a lifetime decision-tree analysis done from the US societal perspective. Compared with no screening, carrier testing (at a per-person test cost of $425 USD) was associated with a smaller number of children born with SMA, QALY gains (eight QALYs), and with substantially larger costs (additional $39.5 million), yielding an ICER of about $4.9 million per QALY (2009 price). At a willingness-to-pay of $100,000 per QALY, carrier screening was cost-effective only 0.03% of the time. The major drivers of the cost-effectiveness results were the prevalence of SMA and the cost of the test (the cost needed to be less than $44 per sample for the ICER to be lower than $100,000 per QALY). The authors found that the prevalence of SMA needed to be increased from 1 in 10,000 (reference case) to 1 in 900 for the ICER to decrease below $50,000 per QALY. In their review, Wang et al [154] indicated that this study considered only maternal QALYs and, similarly to Little et al,[170] reported unfavorable cost-effectiveness of prenatal SMA carrier screening at a willingness-to-pay of $100,000 per QALY based on a very high ICER estimate ($5.7 million per QALY, 2018 price).

Applicability and Limitations of the Included Studies

Appendix 7 presents the results of the applicability and quality appraisal checklists for economic evaluations applied to the included studies. One Australian study, by Zhang et al,[159] examined the cost-effectiveness of population-based preconception carrier screening for SMA, CF, and FXS, but not for hemoglobinopathies and thalassemia, so it was deemed partially applicable to our research question (Table A12). The remaining studies, including the MSAC report[158] and two US studies,[156,157] were deemed not applicable to the Ontario setting or to our research question (Tables A12–A16). Wang et al[154] examined the methodological quality of the 23 studies included in their review using the CHEERS checklist criteria,[171] even though this 24-item guidance statement does not purport to evaluate the methodological quality of economic studies, but to transparently report all elements of economic studies. Nevertheless, the authors conceptualized a complex modelling framework for future economic studies and provided detailed insights on the inputs used for modelling in the published literature. Based on their quality assessment, the overall CHEERS checklist scores ranged from 57% to 96%, with increasing scores over the most recent decade (higher percentages indicate higher quality). Thus, studies published since 2010 had higher overall scores (mean: 95%). We also assessed the methodological quality of the included studies and found that all studies had potentially serious or very serious limitations (see Tables A17–A21, Appendix 7). We found that the majority of studies had partial or unclear reporting or descriptions of model structures, model inputs and study outcomes, sensitivity analyses, funding support, and potential conflicts of interest. Below, we summarize features and potential limitations of the study that was partially applicable to our research question and the Ontario context.

Zhang et al[159] provide a complex analysis of the population-based genomic screening of all young people aged 18 to 25 years for multiple diseases, including pathologic variants for breast, ovarian, and endometrial cancer and carrier screening for CF, FXS, and SMA. Several probabilistic disease-specific decision-tree models accumulated the disease-specific costs and outcomes over the person's lifetime. Given the complex context, a simplified decision-tree simulation modelling technique was appropriate; however, simplifying the disease pathways for the purpose of this generalized genomic modelling resulted in the use of simplifying assumptions for some input parameters (e.g., cost of genetic testing in usual care) and disease model structure, including less sophisticated clinical pathways. In this process, some modelling features that would account for the specifics of genetic testing and clinical course for each examined disease were lost. For instance, the usual care for carrier testing considered the same testing pathway and assumed the same cost of testing for all three conditions, whereas in reality, genetic testing of CF and FXS could be more complex and could require a mix of molecular methods to account for accurate detection of all pathogenic variants. For simplicity of diagnostic test modelling, the intervention strategies assumed 100% accuracy of the genetic panel, leaving unclear how residual disease risk was accounted for. Next, generalization of the health utility input from Down's syndrome was assumed for all models. It is unclear which parts of the program would be funded publicly because the features of the screening program were not clearly defined and the cost components of the genetic test panel were not reported. All of these limitations indicate that the Zhang et al study was more hypothetical than realistic or implementable. Lastly, the authors reported no conflicts of interest, but financial disclosures (including potential grant funding support from the government) were not published, making it difficult to evaluate a potential for bias.

Discussion

Our review identified a total of 21 relevant economic studies published from January 1, 2005 to April 7, 2021. Nineteen studies were original economic evaluations (see Appendix 6), and two were systematic reviews,[154,155] which included published studies up to 2019. The majority of studies used decision-analytic (decision-tree) models to examine the cost-effectiveness of preconception or prenatal genetic carrier screening. Four studies examined the cost-effectiveness of universal (population-based) carrier screening for multiple diseases using the NGS method or customized multi-gene panels to identify the pathogenic genetic variants of interest.[156-159] The remainder examined the cost-effectiveness of universal or risk-based carrier screening for a single disease (CF, FXS, hemoglobinopathies and thalassemia, or SMA). None of the identified studies were directly applicable to our research question with respect to carrier screening timing, detection pathways (including available technologies), or conditions of interest, although a study by Zhang et al[159] was partially applicable because it examined the cost-effectiveness of population-based preconception genetic carrier screening of couples for CF, FXS, and SMA and had an option for further prenatal confirmation of the genetic disorders. However, it did not consider hemoglobinopathies and thalassemia. In addition, none of the included economic studies were conducted using a Canadian or Ontario perspective. Most of the included studies were associated with limitations and were heterogeneous in model structure, study population, outcomes, and model inputs. Given the variability between the studies in model structure, model inputs, testing pathways, and study outcomes, it is difficult to make inferences about generalizability or transferability of the study results across countries.

Multiple-Disease Genetic Carrier Screening

Our review of the four model-based economic studies[156-159] found that population-based preconception and prenatal genetic carrier testing for multiple diseases, including SMA, FXS, and CF, could be cost-effective compared with targeted (risk-based) carrier screening or no screening.

Single-Disease Genetic Carrier Screening

Based on the limited evidence,[159,165] and compared with risk-based screening or no screening, a universal preconception carrier testing program for CF alone is likely associated with a large cost increase and would not be cost-effective at commonly used willingness-to-pay values (estimated ICER of $126,630 AUD per DALY[159]).The economic evidence from seven studies on prenatal carrier screening for CF alone is mixed. A wide variety of screening pathways, comparators, and economic outcomes have been examined, which makes comparability between the studies difficult. While Avram et al[160] suggested that prenatal carrier screening for CF alone with the newest NGS methods may not represent good value for money compared with the genotyping methods used in current practice, a few older studies from 2010[164] and 1999[172] suggested that, compared with no screening, some prenatal carrier screening programs (e.g., those using two-step sequential screening approaches) could be associated with cost savings or could be cost-effective over a lifetime (< $20,000 AUD per QALY). Nevertheless, these study results were sensitive to test accuracy, uptake of screening, and probability of decision to terminate pregnancy informed by the results of genetic testing.

The economic evidence on carrier screening for FXS alone is also very limited, based on the findings of two cost–utility studies.[159,173] In 2019, Zhang et al[159] showed that population-based preconception FXS carrier screening versus risk-based (targeted) screening was not cost-effective at commonly used willingness-to-pay values (ICER: $130,296 AUD per DALY), whereas in 2005, Musci and Moyer[173] found that prenatal FXS carrier screening compared with no screening represented good value ($14,900 USD per QALY). The difference between these two estimates is striking; however, they are not comparable because these two studies were different in model structure, input parameters, comparators, and approaches to carrier testing (in terms of both partner testing and timing of screening).

No economic study examined genetic carrier screening for all types of hemoglobinopathies and thalassemia; therefore, the cost-effectiveness of molecular (genetic) testing, in addition to regular carrier screening using hematological testing (and risk factors), is unknown. The recent MSAC[158] report examined the cost-effectiveness of preconception carrier testing for alpha-thalassemia alone. Since their results were reported in natural units (e.g., ICER: $446 AUD per an additional couple with genetically confirmed carrier status), it is difficult to justify the economic value of the intervention for alpha-thalassemia alone or for hemoglobinopathies and thalassemia altogether.

The economic evidence on carrier screening for SMA alone is very limited, but it was not conflicting.[159,170] Compared with risk-based carrier screening in the preconception stage[159] or with no screening in the prenatal stage,[170] population-based carrier testing for SMA was not cost-effective at commonly used willingness-to-pay values (ICERs: $468,151 AUD per DALY[159] and $4.9 million USD per QALY[170]).

Strengths and Limitations

We conducted a comprehensive review of the economic literature to examine the cost-effectiveness of genetic carrier screening for CF, FXS, hemoglobinopathies and thalassemia, and SMA for people who are considering a pregnancy or who are pregnant. Although we systematically searched electronic databases and grey literature sources, we restricted the search to published studies since 2005. It is possible that we omitted some older economic analyses; however, the genomic field is rapidly developing, and the standard of care is changing alongside these innovations. This suggests that our search was well designed to retrieve all relevant studies. We assessed the limitations and applicability of all studies using modified NICE checklist criteria.[151] The results of our review suggest that the currently published economic evidence is not generalizable to the Ontario context and is not sufficient to address important policy questions related to an introduction of a population-based carrier screening program for CF, FXS, hemoglobinopathies and thalassemia, and SMA for pregnant people or people who are considering a pregnancy.

Conclusions

We found a total of 21 economic studies evaluating the cost-effectiveness of carrier screening. The studies adopted different methodologies, and their results varied. Some found that population-based (universal) preconception or prenatal carrier screening of multiple conditions, including CF, FXS, hemoglobinopathies and thalassemia, and SMA, could be cost-effective compared with risk-based carrier screening or no genetic screening. None of the studies were directly applicable to Ontario, so their findings are not generalizable to Ontario.

Primary Economic Evaluation

We identified several published economic studies evaluating the cost-effectiveness of population-based carrier screening. However, none of the studies were directly applicable to the Ontario context. Therefore, we conducted a primary economic evaluation to examine the cost-effectiveness of preconception and prenatal carrier screening for cystic fibrosis (CF), fragile X syndrome (FXS), hemoglobinopathies and thalassemia, and spinal muscular atrophy (SMA) in Ontario.

Research Questions

1. What is the cost-effectiveness of a universal or risk-based genetic preconception carrier screening program for CF, FXS, hemoglobinopathies and thalassemia, and SMA compared with no screening in people who are considering pregnancy, from the perspective of the Ontario Ministry of Health?

2. What is the cost-effectiveness of a universal or risk-based genetic prenatal carrier screening program for the given conditions compared with no screening in pregnant people, from the perspective of the Ontario Ministry of Health?

The focus of this assessment is the use of genetic (DNA) testing for the given conditions within an organized carrier screening program. In the Primary Economic Analysis and the Budget Impact Analysis (see Terminology Section), hemoglobinopathies and thalassemia were treated and analyzed together as a single group of conditions. Details of the compared strategies and outcomes are discussed in Type of Analysis and Interventions and Comparators, below. Modelling of cascade screening or genetic testing to systematically trace all carriers among family members was beyond of the scope of this analysis.

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[174]

Type of Analysis

For each research question, we conducted a primary cost-effectiveness analysis to evaluate the short-term costs and clinical outcomes of a genetic carrier screening program. This can provide clinicians and decision-makers potentially valuable information about the possible design of a screening program[155] and enable planning and estimation of subsequent resource use or cost impact for Ontario. We also conducted a secondary cost–utility analysis to evaluate the long-term outcomes (i.e., lifetime costs and QALYs), which are more uncertain.

OUTCOMES OF INTEREST

Our primary cost-effectiveness analysis focused on estimating short-term health outcomes related to screening and events during pregnancy. Since timing is the only difference between preconception and prenatal carrier screening, the outcomes are similar for both analyses. An advantage of preconception screening is that couples have a greater number of reproductive options if they are identified as carriers prior to pregnancy (see below). Thus, we estimated the following outcomes:

- The probability of at-risk pregnancy (i.e., couples screening true or false positive; note: for the autosomal recessive disorders, both members of a couple had to test positive, whereas for

FXS, only the pregnant person had to test positive; also, a false positive result was distinguished to indicate the possible use of some procedures and reproductive choice options for couples whose current or future pregnancies are not at risk of affected birth)
- The probability of false negative (indicating at-risk pregnancy and carrier status missed by the screening)
- Reproductive options following the preconception carrier screening, not related to continuing with the natural pregnancy, for instance:
  - Undergoing in vitro fertilization (IVF) with preimplantation genetic testing for monogenic/single gene defects (PGT-M, formerly preimplantation genetic testing, or PGD) procedures to become pregnant (estimated as number of IVF procedures or number of unaffected births), or other choices (e.g., adopting children)
- Reproductive options following preconception or prenatal carrier screening related to the natural pregnancy and prenatal diagnostic testing:
  - Participation in prenatal diagnostic testing (via chorionic villus sampling [CVS] or amniocentesis) to determine the genetic status of the fetus
  - Undergoing voluntary pregnancy termination, informed by prenatal diagnosis results
- The chance of having an affected birth (in at-risk couples who choose against termination of pregnancy in the prenatal stage or in those false negative couples whose carrier risk status was missed by the screening test)

We also estimated total direct medical costs associated with potential preconception and/or prenatal screening (e.g., short-term costs incurred for the genetic testing [currently not publicly funded for all conditions of interest at the population level] and costs associated with procedures during pregnancy, as initiated and informed by the screening results).

For the cost-effectiveness analyses, the incremental cost-effectiveness ratio (ICER) was estimated from the expected mean health outcomes and expected mean total costs and was expressed as additional cost ($) per additional unit of health outcome (e.g., additional cost per at-risk pregnancy [couple] identified or per affected birth).

Our secondary cost–utility analyses estimated the following outcomes:

- QALYs per couple tested (assuming couple's/parents' utility in one analysis and newborn's utility in another analysis for the QALY estimation)
- Total direct medical costs per couple tested (short-term costs associated with carrier screening; e.g., with testing and with health care utilization during the pregnancy, and short and long-term costs associated with health care utilization of a newborn and over the child's lifetime)

The QALY and cost outcomes were used to estimate an incremental cost–utility ratio (ICUR) as an additional cost per QALY gained. The ICUR allows for an explicit comparison across various health care programs or different technologies (vs. ICER, which is expressed in dollars or a natural unit such as an affected birth or an identified at-risk pregnancy), and may be more appropriate to use when making decisions related to resource allocation. Thus, Canadian and other international economic guidelines recommended including an estimated ICUR in economic evaluations.[175] However, we decided to estimate the change in QALYs as a secondary health outcome because research has

suggested many challenges with estimating QALYs for genetic diagnostic technologies.[155,163,176,177] For instance, there are ethical issues related to measuring health-related quality of life and the value of the life of an unborn child.[155] Also, detection of an affected fetus may inform and/or change reproductive choice (e.g., an informed decision to terminate the affected pregnancy). In our prior report,[176] it was suggested that comparing the effectiveness of the two outcomes—newborn with a genetic condition versus termination of pregnancy—may not be sensible in terms of life-year or QALY gains. Last, there is no consensus regarding who the subject in long-term economic evaluations of pregnant people is (i.e., the pregnant person, the couple, or the newborn) or whose preferences (utilities) should be used to estimate the QALY outcome.[177-179] Due to these concerns, we interpreted our cost–utility results with caution.

Target Population

For preconception screening (research question 1), our target population was people (18–49 years old) considering becoming pregnant and, for conditions that are not X-linked, their reproductive partners at any genetic carrier risk level (i.e., universal screening) or at high risk (i.e., risk-based screening based on family or personal medical history, including ethnicity or race, or hematologic test results) for pathogenic variants of CF (on the *CFTR* gene), FXS (on the *FMR1* gene), hemoglobinopathies and thalassemia (on the *HBA1, HBA2,* or *HBB* gene), or SMA (on the *SMN1* gene). Our analyses did not examine any risk-stratification tools based on risk factors (i.e., out of scope of this health technology assessment).

For prenatal screening (research question 2), we considered pregnant people and their reproductive partners (for conditions that are not X-linked) during the prenatal period, at any carrier-risk level or at high risk for the conditions of interest (see Table 11).

Consistent with the inclusion criteria of the Clinical Evidence Review, above, this evaluation did not consider the population not yet at the age of majority (i.e., people of reproductive age who have not yet reached 18 years of age) or people who would use reproductive genetic screening for purposes other than near-future reproductive decision-making (e.g., premarital or pre-relationship testing for relationship/marriage decisions, testing only for individual carrier status knowledge and not for near-future reproductive decision-making, and standard protocol testing at donor egg/sperm banks).

Perspective

We conducted this analysis from the public payer perspective (i.e., that of the Ontario Ministry of Health). The reference case analysis assumed that the costs of genetic testing, procedures, and resource use would be covered by the public payer. While our long-term cost–utility analyses considered a wide range of medical costs related to the treatment of the conditions of interest, we did not consider a societal perspective.

Interventions and Comparators

Consistent with the current Ontario context, we conducted evaluations of different genetic testing approaches to preconception and prenatal carrier screening for CF, FXS, hemoglobinopathies and thalassemia, and SMA.

Table 11 summarizes intervention and control strategies used in the economic models. The strategies differ in terms of the timing of screening (preconception vs. prenatal), population (universal vs. risk-based), and the laboratory methods used for the genetic testing (next-generation sequencing [NGS]

vs. the current targeted testing with available non-NGS molecular methods using single-gene or single-disease panels). We use the term "risk-based carrier screening" (established with input from clinical experts) for genetic reproductive carrier testing of people at high risk based on their family or personal medical history, including their ethnicity or race, or hematologic test results. Risk stratification was not modeled in this analysis. Given that risk-based genetic carrier testing is limited in Ontario, and no organized carrier screening program currently exists in the province for all given conditions, we made a simplifying assumption and included a no-genetic-carrier screening alternative (i.e., the test is not being done at all either at the opportunistic or program level) as a control option for the purpose of comparison and budget impact estimation.

As shown in Tables 11 and 12, we considered a number of possible intervention strategies related to a new genetic laboratory method (i.e., the use of one NGS panel to detect pathogenic variants of the given conditions) and/or a screening approach (i.e., universal, population-based screening), which is not currently publicly funded in Ontario. For example, we proposed a risk-based genetic screening approach with a genetic test that identifies all pathogenic variants of interest. This genetic test is somewhat similar to expanded carrier screening (ECS), but our assumption was that ECS (with one panel) was used for detecting only the genetic conditions examined in this health technology assessment. Currently available ECS panels often cover over 100 conditions with a carrier frequency threshold of at least 1 in 100 (an incidence of 1 in 40,000), as recommended by the American College of Obstetricians and Gynecologists.[17,180] Next-generation sequencing ECS panels are associated with high sensitivity and specificity (> 99%), and assumptions related to good understanding and acceptance of the residual risk. Their costs are potentially greater than the currently publicly funded single-disease genetic tests in Ontario.[156,181-183] In our modelling study, we examined these differences (in the diagnostic performance and cost between various genetic tests), and assessed their trade-offs and cost-effectiveness for carrier screening in Ontario.

Table 11: Interventions and Comparators to be Evaluated in the Economic Models

	Interventions: Preconception/prenatal screening	**Comparators**	**Populations**	**Outcomes**
Universal genetic carrier testing • CF, FXS, hemoglobinopathies and thalassemia, or SMA, screened together (i.e., expanded testing using one genetic NGS panel) • Screening each condition separately (i.e., current practice, standard testing: using different genetic methods and panels) Risk-based genetic carrier testing • Conditions of interest, screened together (expanded testing using one genetic NGS panel) • Screening each condition - separately (i.e., current practice, standard testing: using different genetic tests/methods)	No genetic carrier testing	Preconception: All couples[a] who are considering a pregnancy (preconception) at average or high risk of being a carrier of a condition of interest, based on personal/family history Prenatal: All pregnant couples[a] at average or high risk of being a carrier of a condition of interest, based on personal/family history	Health outcomes: e.g., number (probability) of at-risk couples/affected births/QALYs Total direct medical costs ICER/ICUR[b]	

Abbreviations: CF, cystic fibrosis; FXS, fragile X syndrome; ICER, incremental cost-effectiveness ratio; ICUR, incremental cost–utility ratio; NGS, next-generation sequencing; QALY, quality-adjusted life-year; SMA, spinal muscular atrophy.

[a]Includes people considering a pregnancy or pregnant person and their reproductive partners.

[b]ICER/ICUR will be estimated from cost and health outcomes.

In the current practice (i.e., intervention: standard testing, Table 11), carriers are identified via a risk-based screening approach that considers various currently available genetic tests and panels. For these analyses, blood samples are typically required. The genetic carrier tests used in Ontario are as follows:

- Cystic fibrosis: DNA analysis by the Lumminex panel is often done to test the *CFTR* gene for 39 of the most common pathogenic variants
- Fragile X syndrome: polymerase chain reaction (PCR) amplification or Southern blot analysis, or a combination of both, can be used to analyze trinucleotide (cytosine–guanine–guanine [CGG]) repeats and methylation status in the 5' untranslated region (UTR) of the *FMR1* gene. This genetic testing is done by PCR[184] (e.g., supported by the AmplideX PCR/CE FMR1, or AmplideX Fragile X Dx & Carrier Screen Kit).[185,186] The number of CGG repeats in the *FMR1* gene is used to distinguish a full mutation (i.e., > 200 CGG repeats) from a premutation (i.e., 55–200 CGG repeats). The full mutation confirms diagnosis of FXS, while the premutation indicates a carrier individual who is at risk of expansion of the repeats, and thus of having a child with fragile X syndrome. As adults, some premutation carriers are at risk for fragile X

tremor and ataxia syndrome or at risk of premature ovarian failure, but this is out of scope of our evaluation

- Hemoglobinopathies and thalassemia: carrier testing of hemoglobinopathies is done in two steps; only one involves genetic testing:
    - First tier: routine laboratory testing for hemoglobinopathies and thalassemia typically includes hematologic testing (e.g., red blood cell count with results for hemoglobin (Hb), mean corpuscular volume [MCV] and mean corpuscular hemoglobin) and, in some cases, Hb electrophoresis or high-performance liquid chromatography)
    - Second tier: DNA (genetic) testing is done as a follow-up to routine hematologic screening if both partners are indicated to be carriers, based on hematological testing, for confirmation of carrier status.[187,188] Single deletions in thalassemia, which indicate the carrier status, can rarely be detected by routine screening and need to be confirmed by molecular genotyping. Various molecular genetic methods (e.g., PCR amplification, NGS) are used to identify pathogenic variants in the hemoglobin alpha gene (*HBA1*, *HBA2)* or the hemoglobin beta gene (*HBB*) and confirm the carrier status for hemoglobinopathies. All genetic carrier testing for thalassemia/ hemoglobinopathies in Ontario is performed at one lab[188]
- Spinal muscular atrophy: multiplex ligation-dependent probe amplification (MLPA) is used for DNA deletion and duplication analysis of exons 7 and 8 of the *SMN1* gene to identify the number of gene copies and to confirm carrier status[189]

Carrier Screening: Sequential Testing

In line with current practice in Ontario and the findings of our economic evidence review, we assumed that at-risk couple screening was performed sequentially for autosomal recessive disorders. For FXS, due to lack of data about the contribution of the male partner in the transmission (i.e., expansion of pre-mutation to full mutation), we considered testing of only the female partner in the reference case screening models. The cost of testing of the male partner for FXS was considered in the scenario analysis.

The sequential approach follows two-step testing. The pregnant person or the person considering becoming pregnant is tested first, and the partner is tested only if that person is found to be a carrier with a positive test result. For detecting an at-risk (carrier) couple (where both members of a couple test positive), sequential screening would increase the net specificity (reduce the false positive rate). Concurrent screening (i.e., simultaneous testing of samples from both members of the couple) would increase the net sensitivity, but also the costs due to screening twice as many people (and finding a large number of couples with a single carrier status). Therefore, simultaneous (concurrent) couple screening does not seem to be the optimal approach to carrier testing in universal (population-based) settings[165,190-195]; it was not considered in our analyses. Similarly, as shown in Table 12, in terms of obtaining the blood samples for testing, we made simplifying assumptions on the sequence of blood sampling.

Table 12: Matrix: Intervention Strategies in the Sequential Carrier Screening Preconception/Prenatal Models

	Type of population		Genetic testing method (DNA analysis)		Screening approach: couple testing/ blood sampling couple testing
Intervention strategies	Universal (population-based)	Risk-based (targeted, selective)	Expanded approach NGS DNA analysis, all conditions (expanded panel)	Standard approach DNA analysis, condition-specific (targeted, variant panels)	Sequential (female testing first; if tests positive, partner testing)
Intervention 1: universal, expanded testing approach	X[a]	—	One panel, NGS Sn/Sp: high Cost: high	—	X
Intervention 2: universal, standard testing approach	X	—	—	Single-gene tests Sn/Sp: varies Cost: varies, lower	X
Intervention 3: risk-based, expanded testing approach	—	X	One panel, NGS Sn/Sp: high Cost: high	—	X
Intervention 4 (current practice): risk-based, standard approach	—	X	—	Single-gene tests Sn/Sp: varies Cost: varies, lower	X

Abbreviations: NGS, next-generation sequencing; Sn, sensitivity of the test; Sp, specificity of the test.
[a]Cells marked with an X are applicable; cells marked with a dash are not applicable.

COMPONENTS OF A CARRIER SCREENING PROGRAM

In the reference case, we considered only components and their costs incurred from a public payer perspective. These include the operational (variable) costs of genetic testing (such as screening test consumables and screening test labour costs), initial physician and genetic counselling costs, and post-screening costs or induced health care costs (workup, diagnostic procedures, and follow-up). Other components are related to screening, such as program management (administration, including labour costs), education, and organization of the screening campaign (information and invitations) or quality assurance (control). Given that this is a hypothetical screening program, the program costs and their coverage are uncertain. Therefore, we considered these additional screening program costs in a scenario analysis. For practicality, and due to a lack of knowledge regarding the implementation of this program in the future, we assumed that the program was organized by one centre. We assumed no change in requisition of tests or organization of labs that are currently providing some carrier genetic testing in Ontario, and we assumed there would be no need for additional equipment or infrastructure.

Time Horizon and Discounting

In our reference case cost-effectives analyses, we assumed a short-term time horizon for one (singleton) pregnancy because our most important (primary) outcomes of the genetic carrier preconception and prenatal screening programs occur within a short period of time (i.e., near-future pregnancy and during pregnancy until childbirth). For simplicity, we assumed a 1-year time horizon, and consequently we did not apply an annual discount rate of 1.5% in the reference case analyses.[175]

Our cost–utility analyses evaluated the long-term cost-effectiveness of the screening strategies over a lifetime horizon (assuming health state utilities of the newborn for the QALY calculation in one scenario, and of the parent in another scenario). In accordance with guidelines from the Canadian Agency for Drugs and Technologies in Health (CADTH),[175] we applied an annual discount rate of 1.5% to both costs and QALYs incurred after the first year. All costs were expressed in 2022 CAD.

Main Assumptions

The model's main assumptions were as follows:

- The screening procedure would follow a two-step (sequential) testing approach, with the person considering becoming pregnant or who is pregnant being tested first
- The turnaround time of results (and 1-year time horizon) is sufficient for couples to make informed decisions on screening participation and reproduction choices (assuming no costs or disutility related to waiting for testing results)
- At-risk couples are those where both members of the couple test positive as carriers for the autosomal recessive conditions of interest (SMA, CF, and hemoglobinopathies and thalassemia) or the person considering becoming pregnant or who is pregnant tests positive for as a carrier for FXS (i.e., every pregnancy with a FXS-carrier female would be considered at risk). Based on expert feedback (D. Chitayat, MD, email communication, January 2022) and the literature,[159] only females with a repeat CCG size equal to or more than 60 were considered carriers, with weighted risk of maternal transmission calculated by repeat size
- Couples would use information from preconception genetic carrier screening to make informed decisions on the uptake of prenatal diagnostic testing or future reproductive choice, including informed decisions on voluntary termination of pregnancy or continuation of the affected pregnancy (i.e., the descriptive approach to modelling and policy analysis as opposed to prescriptive modelling[194])
- For simplicity, we modeled one singleton pregnancy and the reproductive choices for that pregnancy
- Reproductive choices and actions:
    - In the reference case, we assumed access to publicly funded usual care procedures (such as IVF with preimplantation genetic testing for monogenic/single gene defects [IVF/PGT-M] with a currently limited coverage for IVF) as this is one possible reproductive choice for at-risk couples in preconception screening. Sensitivity analyses explored full coverage of these procedures in Ontario
- We assumed that a couple is at risk for one of the genetic conditions of interest (i.e., either CF, SMA, hemoglobinopathies and thalassemia, or FXS) because the probability of couples being carriers or at risk for multiple conditions is small.[183] This assumption simplifies modelling complexity. Also, modelling the risks of being a carrier for multiple conditions likely would not impact a couple's decision-making

Model Structure

Based on the Ontario clinical pathways and the published economic literature (see Economic Evidence, above),[155,157-159,161,164,165,169,196] we conceptualized our model structure and the relevant interventions for carrier screening (Tables 11 and 12). We developed probabilistic decision-tree models to estimate the short-term outcomes per couple for preconception and prenatal carrier screening for CF, FXS, hemoglobinopathies and thalassemia, and SMA. In secondary analyses, we combined these decision trees with Markov (state-transition) models to estimate lifetime outcomes (QALYs and costs of treatments), considering two perspectives for assessment of QALYs (newborn and parent QALYs estimated in separate scenarios).

We modeled reproductive decisions and outcomes for one pregnancy and used closed cohort models without population migration. The preconception and prenatal model structures allowed the estimation of the cost-effectiveness outcomes for multiple genetic conditions together and for each condition separately.

DECISION-TREE MODELS

As shown in Figures 3A, B, and C, the decision-tree model structures followed clinical pathways for preconception and prenatal screening and included probability estimates related to the following variables: participation in preconception/prenatal screening, carrier status, a couple's reproductive choices informed by the test results, use of prenatal diagnostic testing, fetal loss caused by prenatal diagnostic testing, voluntary termination of pregnancy, birth of a child affected by the genetic condition of interest (informed vs. not informed by the screening results), and birth of an unaffected child. The model structure flagged certain events to estimate the carrier screening outcomes per couple, decisions made after screening, and outcomes related to informed reproductive decisions such as the birth of an affected child, voluntary termination of pregnancy, or the use of assisted reproductive technology such as IVF with PGT-M.

The interventions are done using a sequential approach to screening, as described previously and in Table 12. At the beginning of the simulation, our target population would be eligible for genetic carrier testing for all conditions of interest (i.e., clinical evaluations including hematologic laboratory testing is completed prior to the genetic screening[187]). All interventions are diagnostic test interventions; thus, the models include a Bayesian approach for estimating carrier status that accounts for the disease-specific carrier prevalence and the corresponding diagnostic performance (sensitivity and specificity) of the genetic test used to detect the pathogenic variants. In the reference case, we used available data to populate the model parameter of carrier frequency given the lack of Ontario-specific estimates. We tested this parameter uncertainty in sensitivity analysis.

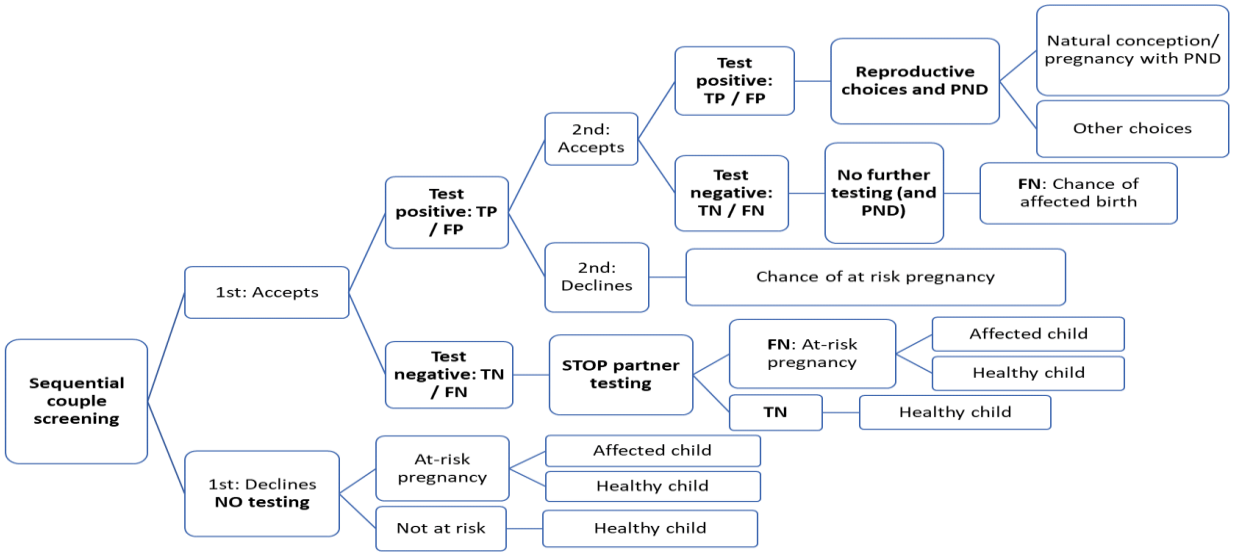

Figure 3A: Simplified Model Structure, Sequential Couple Testing in Preconception/Prenatal Carrier Screening: Reference Case (Autosomal-Recessive Conditions)

Abbreviations: FN, false negative; FP, false positive; PND, prenatal diagnostic testing; TN, true negative; TP, true positive.

This figure describes a decision tree model with sequential testing of a couple and is applicable to the beginning of either prenatal or preconception carrier screening (the reference case). First, the first partner of a couple either accepts or declines genetic testing (carrier screening). If they decline, the model does not account for genetic testing for establishing whether they are at-risk of having an affected child, but it follows a couple till the end of the pregnancy to account for the probability of an affected birth. If the first partner accepts the screening, they may test negative (true or false negative), in which case the second partner is not tested (and, if the result is a true negative, the child is healthy). If the first partner tests positive, then the second partner is offered testing. If they decline, the couple proceeds without a full understanding of their risk status, but the model continues to follow their pregnancy to account for the probability of an affected birth. If both partners accept the carrier testing and they both test positive in preconception, the model continues to follow them through a prenatal period (where they have reproductive choices, including PND, see Figure 3B). If the second partner tests negative at the preconception stage, then the couple continues with the natural pregnancy. PND or other assistive reproductive technology choices are not offered as the couple is assumed to have a healthy child. However, given the possibility of false negative result, the model accounts for the chance of having an affected birth for this situation where the second partner tests negative.

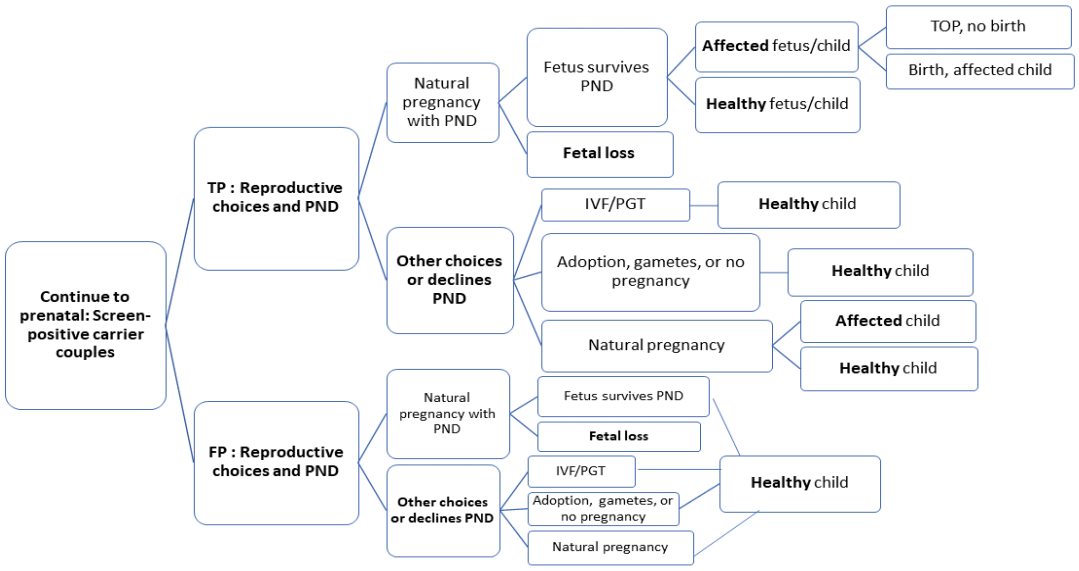

Figure 3B: Simplified Model Structure, Preconception Carrier Screening, cont.

Abbreviations: FP, false positive; IVF/PGT-M, in-vitro fertilization with preimplantation genetic testing for monogenic/single gene defects; PND, prenatal diagnostic testing, including amniocentesis and chorionic villus sampling; TOP, termination of pregnancy; TP, true positive.

This figure describes a decision tree pathway after sequential testing of the couple (Figure 3A). While both true and false negative arms are included in the model, for simplicity, they have not been presented in this figure (see description of Figure 3A for information on the pathway for those who test negative). This diagram represents the preconception carrier testing model applicable to the prenatal or pregnancy period. Thus, after receiving the screening results, a couple in which both partners test positive can make various reproductive choices, including PND. If they do not decide for PND, they may opt for natural pregnancy or other reproductive options such as IVF/PGT-M, adoption, use of gametes, or they may choose to not pursue future pregnancies. If they decide for a natural pregnancy and PND, the couple will find out whether their fetus is affected by the disease and can make an informed choice to keep the affected pregnancy or to voluntarily terminate the pregnancy. For couples who decide to do PND (TP or FP), there is a small chance of pregnancy loss. Of note, outcomes of the FP pathway related to any reproductive option (exception is pregnancy loss because of PND) lead to a healthy child.

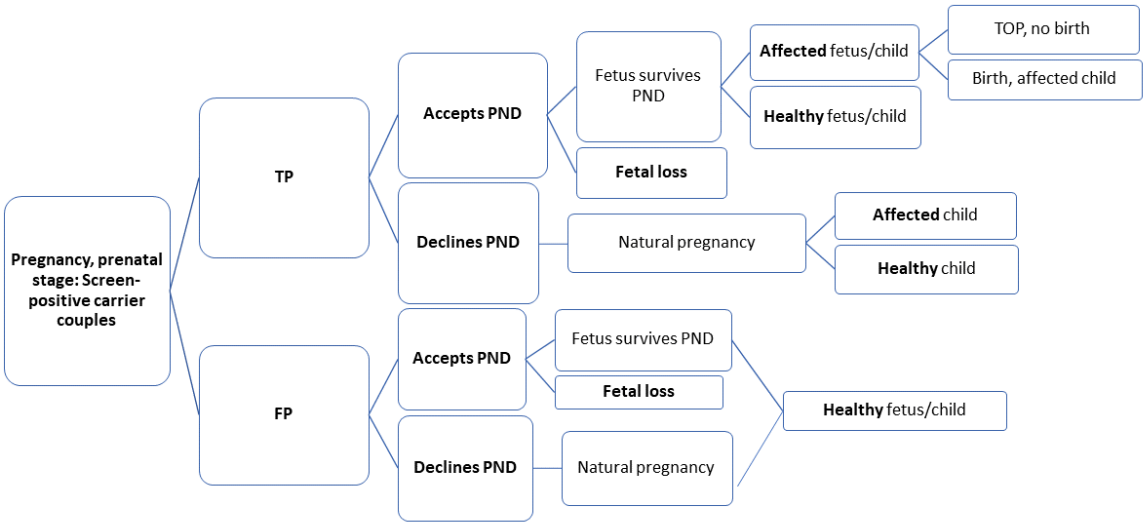

Figure 3C: Simplified Model Structure, Prenatal Carrier Screening, cont.

Abbreviations: FP, false positive; PND, prenatal diagnostic testing, including amniocentesis and chorionic villus sampling; TP, true positive; TOP, termination of pregnancy.

This figure describes a decision tree pathway after sequential testing of the couple (Figure 3A). While both true and false negative arms are included in the model, for simplicity, true negative results have not been presented (see Figure 3A for information on the pathway for those who test negative). This diagram represents reproductive choice options for the prenatal carrier testing model. Thus, after receiving the screening results, a couple in which both partners test positive continue with the pregnancy and is offered PND to determine the genetic carrier status of the fetus. If they decide for PND, they will find out whether their fetus is affected by the disease and can make an informed choice to keep the affected pregnancy or to voluntarily terminate the pregnancy. For couples who decide to do PND (TP or FP), there is a small chance of pregnancy loss. Of note, outcomes of the FP pathway related to any reproductive option (exception is pregnancy loss because of PND) is a healthy child.

MARKOV MODEL: LONG-TERM SCENARIO, COST–UTILITY ANALYSIS

We built a Markov model on the pregnancy outcomes of the decision tree models to accumulate the QALYs and additional costs associated with the given genetic conditions over the person's lifetime. Due to the controversy around the estimation of QALYs for genetic disorders, we explored both the newborn and couple/parents utility perspectives in separate long-term scenarios; the age at the beginning of the simulation was different and assumed to start at 0 years in the newborn utility perspective and at the age of 20 years in the parent utility perspective. In the case of voluntary termination of pregnancy, we made different assumptions to distinguish the difference in accumulation of QALYs that could occur over a lifetime: 1) in the analysis assuming the newborn utility, the utility of death was used after the voluntary termination of pregnancy (i.e., loss of the life) and no accumulation of life-years or QALYs continued to occur over the person's (newborn's) time horizon; 2) in the analysis assuming the couple's (parents') utility, a decrement in the health state utility was accounted for a short time using a disutility value associated with fetal loss,[197] after which the health state utility returned to the pre-pregnancy healthy state and the accumulation of life-years and QALYs continued over the parent lifetime. Given the clinical heterogeneity of the conditions of

interest, our Markov models followed simplified, generalized clinical pathways and used a yearly cycle and a half-cycle correction to balance the distribution of people transitioning between health states. As illustrated in Figure 4, our models included three health states:

- **Healthy, without the condition:** this health state captures QALYs and costs associated with the following: 1) a person born without any of the conditions of interest (i.e., newborn perspective); and 2) a parent (couple) living with a healthy child
- **Living with the condition:** this health state is a simplified general disease state for CF, FXS, hemoglobinopathies and thalassemia, or SMA, in which the health care costs and QALYs of people living with the given conditions associated with the disease are accumulated constantly over time until the affected child dies from the condition of interest or any other cause. Because of the recent development of some novel genetic therapies to treat SMA[198,199] and CF,[200] we considered two additional analyses: 1) one related to the use of standard supportive therapies (assuming no use of novel therapies that could result in improvement of life expectancy; e.g., an average live expectancy is 2 years for people diagnosed with SMA type 1); and 2) another related to use of a novel treatment, which resulted in some improvements in the survival of people diagnosed with SMA or CF. Survival, cost, and utility data associated with CF, FXS, hemoglobinopathies and thalassemia, or SMA are described in the following section
- **Death:** this health state captures the background mortality of people who are born and followed over their lifetime

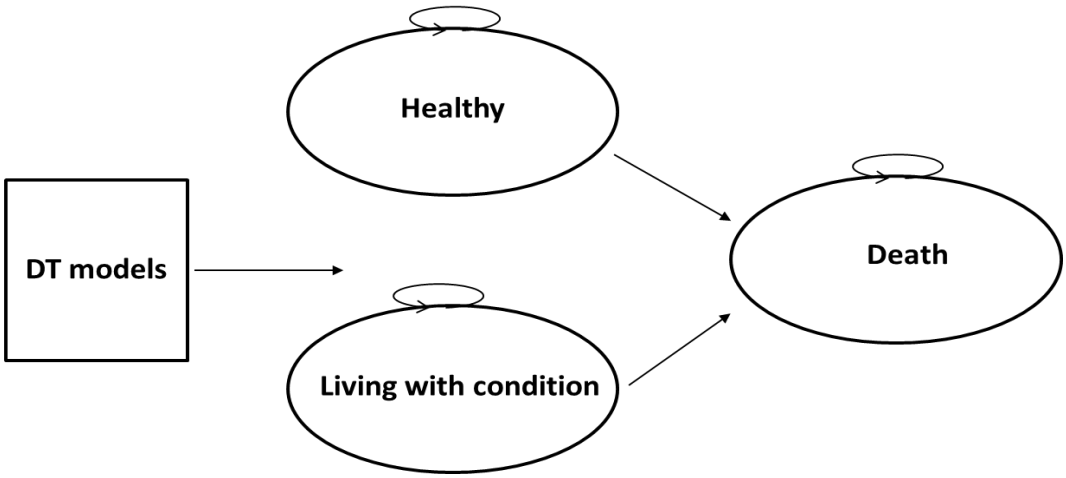

Figure 4: Simplified Markov Model Structure, Long-Term Scenario Analysis

Abbreviation: DT, decision tree.

Model expands decision tree. In this figure we show the progression of Markov health states, from healthy to death or from living with the condition to death.

Clinical Outcomes and Utility Parameters

We populated our short-term models with clinical parameters associated with the carrier status for CF, FXS, hemoglobinopathies and thalassemia, or SMA and pregnancy outcomes. In addition, the

intervention strategies were populated with data related to the diagnostic performance of various genetic tests used for carrier screening (e.g., participation in risk-based and universal genetic carrier screening) and reproductive choices following the screening test. Input parameters that capture consequences and health-related quality of life of people living with the conditions of interest were used in our long-term cost–utility models.

NATURAL AND CLINICAL HISTORY

We identified the model parameters from various published sources such as our clinical evidence review, clinical practice guidelines, and published economic evaluations. As shown in Table 13, natural history parameters are related to carrier frequencies, chance of having an affected child, fetal loss, and life expectancy for the given conditions (used in the long-term scenarios).

We obtained probabilities for carrier frequency for CF, FXS, and SMA from an Australian population-based study by Archibald et al.[80] We estimated carrier frequency for hemoglobinopathies and thalassemia (all combined) based on a study from Ontario;[201] these estimates were in line with the carrier frequency of 0.1198, reported in the 2021 North American guidelines by Gregg et al.[180] Due to the lack of Ontario-specific data for all given conditions, we used sensitivity analyses to explore parameter uncertainty related to the disease-specific carrier frequencies.

We followed the Mendelian inheritance pattern for autosomal recessive disorders such as CF, hemoglobinopathies and thalassemia, and SMA to estimate the probability of affected birth. The weighted probability of affected birth for FXS was estimated from the probabilities of expansion of the *FMR1* gene premutations to a full mutation (by the number of CGG repeats, starting with the sizes ≥ 60 (Dr. D. Chitayat, email communication, January 2022). This estimate was in line with calculations reported by Zhang et al[159] and data reported by Nolan et al.[202]

We accounted for a chance of fetal loss due to alpha-thalassemia (Bart's syndrome) based on one Ontario study.[203] Also, we modeled a small chance of fetal loss due to invasive prenatal diagnostic procedures (i.e., amniocentesis and CVS) using data from a meta-analysis by Akolekar et al.[204] To allow for earlier confirmation of the condition (better timing of the procedures and decisions; Dr. D. Chitayat, email communication, January, 2022), we assumed that CVS would be more likely to be used than amniocentesis (0.7 probability vs. 0.3) and estimated a weighted probability of fetal loss due to prenatal diagnostic procedures (i.e., about 0.0019). We examined the influence of this assumption on the cost-effectiveness estimates in our sensitivity analysis.

Last, in the long-term scenarios, we modeled possible decrements in the life expectancy for CF, SMA, and hemoglobinopathies and thalassemia, compared with the general population and accounted for differences in the life span by disease severity (e.g., SMA type 1).

Table 13: Natural and Clinical History Inputs to be Used in the Economic Models—Reference Case and Scenario Analyses

Model parameters	Mean (±SE)	Distribution[a]	Source
Probabilities: Carrier Frequency	—	—	—
Probability of being a carrier, cystic fibrosis	0.04 (0.004)	Beta	Archibald et al, 2017[80]
Probability of being a carrier, fragile X syndrome (for CGG repeats ≥ 60)	0.0012 (0.00019)	Beta	Estimated, based on the data reported by Archibald, 2017[80]
Probability of being a carrier, hemoglobinopathies and thalassemia (overall)[b]	0.1056 (0.011)	Beta	Estimated[b]
Probability of being a carrier, spinal muscular atrophy	0.025 (0.0025)	Beta	Archibald et al, 2017[80]
Probabilities: Affected Birth	—	—	—
Probability of an affected pregnancy (child): autosomal recessive conditions	0.25	NA	Mendelian inheritance
Fragile X syndrome, weighted probability of expansion to full mutation (for CGG repeats, size ≥ 60) and affected birth	0.6391 (0.064)	Beta	Estimated, based on data from Nolin et al, 2011[202] and Zhang et al, 2019[159]
Probabilities: Fetal Loss	—	—	—
Probability of fetal loss caused by Bart's syndrome (alpha thalassemia)	0.000025	Beta	Zhang et al, 2021[203]
Probability of fetal loss after an invasive prenatal diagnostic test (amniocentesis)	0.0011 (0.00076)	Beta	Akolekar, 2015[204]
Probability of fetal loss after an invasive prenatal diagnostic testing procedure (CVS)	0.0022 (0.0048)	Beta	Akolekar, 2015[204]
Life Expectancy (Long-Term Scenarios)	—	—	—
Annual probability of all-cause mortality	Ontario Life Tables	Age-specific	Ontario Life Tables 2016–2018, Statistics Canada, 2020[205]
Life expectancy in years, cystic fibrosis	53	—	MacKenzie et al, 2014;[7] Zhang et al, 2019[159]
Life expectancy in years, fragile X syndrome or mild form of hemoglobinopathies	Average: 82	—	National Fragile X Foundation, 2021[206]
Life expectancy in years, severe hemoglobinopathies	60	—	Kohne et al, 2011[207]
Life expectancy in years, severe spinal muscular atrophy (type 1)	2	—	Prior, 2008[11]
Life expectancy in years, less severe spinal muscular atrophy	67	—	CADTH HTA, 2020[198,199]

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; CVS, chorionic villus sampling; NA, not applicable; SE, standard error.

[a]Beta distributions were assigned to probability estimates in probabilistic analysis, where applicable.

[b]We estimated the overall prevalence using data from an Ontario-based study[201] (e.g., 0.038, 0.036, and 0.0316 for alpha thalassemia, beta thalassemia, and sickle cell anemia, respectively). Our estimates correspond to the estimate of 0.1198 reported by Gregg et al[180] for these conditions.

IMPACT OF CARRIER SCREENING

Our clinical evidence review provided information on some important parameters related to the impact of and outcomes of preconception and prenatal carrier screening. Table 14 outlines input parameter values used in the models related to the following: performance properties of the diagnostic tests used for genetic carrier screening (i.e., the test's sensitivity and specificity), participation of couples in screening, uptake of prenatal diagnostic testing after testing positive at carrier screening, and reproductive choices after preconception carrier screening and after prenatal diagnostic testing, including voluntary termination of an affected pregnancy.

For standard (currently used) single-disease panels, we assumed the diagnostic test properties from published studies.[186,80,187] Based on evidence from the literature,[182] an expanded (multi-disease) panel was associated with the highest sensitivity and specificity for the detection of a carrier status in examined populations, compared with standard panels.

Our clinical evidence review found no comparative evidence on outcomes such as screening uptake and carrier detection for universal versus risk-based screening interventions. Also, we found a wide range of estimates for the uptake in preconception or prenatal carrier screening, from about 10% to 100%.[71,73] Certainty and quality of the body of evidence related to the this outcome was considered to be very low (GRADE: Very low; see Table 6). Therefore, for the reference case, we assumed uptake in universal preconception carrier screening to correspond to 71%, based on a population-based study from Australia[80] and suggested in the economic model of Zhang et al.[159] We assumed a 68% uptake rate in universal prenatal screening based on evidence from our health technology assessment, supported by the Ontario Newborn Prenatal Screening data.[176] We assumed the same rate of participation for both partners, but tested this assumption in sensitivity analyses in which we used different participation rates for the first and second partner. Using similar assumptions as Zhang et al[159] (with respect to carrier detection with preconception universal screening vs. risk-based screening), we estimated the probabilities of uptake in our preconception and prenatal risk-based screening strategies. To address a substantial lack of evidence and large parameter uncertainty (i.e., there was a wide range of participation levels in preconception carrier screening, and there are some more recent data indicating a slightly lower screening uptake (about 62%) in Ontario newborn prenatal screening[208]), we conducted a number of sensitivity analyses. These analyses examined how changes in the rate of uptake and possible differences in the number of people identified as carriers (in universal screening compared with risk-based screening) would influence the cost-effectiveness results.

Since preconception carrier screening occurs at the pregnancy planning stage, couples involved in it have more reproductive choice options as compared to those who are tested during the prenatal period. Our clinical evidence review suggested that the evidence on the reproductive choice outcome is limited but of moderate quality (see Table 8). In our reference case analysis related to preconception carrier screening for at-risk couples who decided not to continue with prenatal diagnostic testing in the prenatal period, we based our assumption of the probability of having IVF with PGT-M (79%) and of other reproductive choices (e.g., adoption, not planning natural pregnancy anymore) from the data reported by Beauchamp et al.[46] This study examined various reproductive

options chosen by carrier couples who tested positive for CF in preconception screening. Given the limited evidence, we explored parameter uncertainty by varying the reference case input values within the ranges that were reported by Johansen-Taber et al[147] and Cannon et al[58] for profound conditions, including FXS and SMA. In addition, after prenatal diagnostic testing (PND), a chance of voluntary termination of pregnancy was modeled using condition-specific estimates for CF (80%), SMA (67%), and FXS (29%).[147] In sensitivity analyses, we varied the chance of voluntary termination of pregnancy assuming values up to 100% to address a large uncertainty in this parameter estimate.[58,147,209]

Table 14: Inputs Related to Carrier Screening: Test Performance, Participation in Carrier Screening (Uptake), and Reproductive Choices

Model parameters	Mean (±SE)[a,b]	Distribution[a,b]	Source
Test performance	—	—	—
Sensitivity (detection rate)/specificity of a standard (single-disease) genetic carrier panel for:	—	—	—
CF (39-variant panel)	0.90/0.99	Beta	Archibald et al, 2017[80]
FXS (the AmplideX FragileX Dx, Asuragen Inc.)	0.957/0.993	Beta	Berry-Kravis et al, 2021[186] Archibald et al, 2017[80]
Hemoglobinopathies and thalassemia	0.90 /0.99	Beta	Langlois et al, 2008[187]
SMA	0.95 /0.99	Beta	Archibald et al, 2017[80] Committee on Genetics, 2017[210]
Sensitivity/specificity of an expanded (multiple-disease, NGS) panel	0.9988 /0.9999	Beta	Srinivasan et al, 2010[211]; Hogan et al, 2018[182]
Uptake of preconception/prenatal carrier screening	—	—	—
Probability of uptake (both partners) in universal (population-based) preconception carrier screening	0.71 (0.07)	Beta	Zhang et al, 2019[159]
Probability of uptake (both partners) in risk-based preconception carrier screening	0.05 (0.005)	Beta	Archibald et al, 2017[80] Zhang et al, 2019[159]
Ratio, carrier detection (estimated from the uptake): universal vs. risk-based	14.2	—	Estimated from the above data
Probability of uptake in universal prenatal carrier screening (both partners)	0.68 (0.068)	Beta	Health Quality Ontario[176]
Probability of uptake (both partners) in risk-based prenatal carrier screening	0.047 (0.005)	Beta	Estimated

Model parameters	Mean (±SE)[a,b]	Distribution [a,b]	Source
Uptake of prenatal diagnostic testing	—	—	—
Probability of undergoing PND, given a positive result during carrier screening (assumed to be same for preconception and prenatal screening)	0.95 (0.095)	Beta	Health Quality Ontario[176]
Reproductive choices: preconception carrier screening	—	—	—
Probability of use of assisted reproductive technologies: IVF/PGT-M	0.79 (0.004)	Beta	Beauchamp et al, 2019[46]
Probability of other than IVF/PGT-M choice, including adoption, or no future pregnancy	0.16 (0.003)	Beta	Beauchamp et al, 2019[46]
Reproductive choices: prenatal/preconception carrier screening	—	—	—
Probability of voluntary TOP informed by screening test results:	—	—	—
CF	0.80 (0.03)	Beta	Taber et al, 2019[147]
SMA	0.67 (0.04)	—	Taber et al, 2019[147]
FXS/hemoglobinopathies and thalassemia	0.29 (0.04)	Beta	Taber et al, 2019[147]

Abbreviations: CF, cystic fibrosis; FXS, fragile X syndrome; IVF, in vitro fertilization; NGS, next generation sequencing; PGT-M, preimplantation genetic testing for monogenic/single gene defects; PND, prenatal diagnostics; SE, standard error; SMA, spinal muscular atrophy; TOP, termination of pregnancy.

[a]Standard errors were estimated whenever data were available. We assumed 10% around the mean where data were not available.

[b]Beta distributions were assigned to probability estimates in probabilistic analysis.

HEALTH STATE UTILITIES: SCENARIO ANALYSIS

Health state utility describes a person's preference for a certain health state or outcome, such as living with one of the conditions of interest. Utilities are often measured on a scale ranging from 0 (death) to 1 (full health).

We performed a targeted literature search in MEDLINE for health state utility values on June 24, 2021, to retrieve studies published from January 1, 2005, until the search date. We based the search on the population and intervention of the clinical search strategy with a methodologic filter applied to limit retrieval to health state utility values.[212] See Appendix 2 for our literature search strategies, including all search terms. This search did not identify any additional relevant studies. We also examined inputs of the economic studies from our economic evidence review and searched citations in their reference lists to identify potentially valuable scores for our utility estimates.

Table 15 presents utility data used to populate our cost–utility models in the scenario analysis. We used information from a study by Guertin et al[213] to adjust the utility values reported in the literature with the age-specific Canadian (Ontario) utility norms.

Table 15: Utilities Associated With Health States or Outcomes Used in the Cost–Utility Analysis: Long-Term Scenarios

Outcomes or health state	HSU, mean (±SE)[a,b]	Distribution	Source
Fetal loss, parents (spontaneous fetal loss or voluntary termination of pregnancy)	0.92 (0.09)	Beta	Kuppermann et al, 2000[197]
Healthy, living without the condition	Age-specific HSUs	Beta	Guertin et al, 2018[213]
Living with CF	0.70 (0.07)	Beta	Rowley et al. 1998[172]
Living with FXS	0.62 (0.13)	Beta	Chevreul et al, 2016[214]
Living with less severe form of SMA	0.78 (0.08)	Beta	Bach et al, 2003[215]
Living with severe SMA (type 1)	0.16 (0.05)	Gamma	Lopez-Bastida, 2017[216]
Living with severe forms of hemoglobinopathies and thalassemia (corresponding to sickle cell disease)	0.793 (0.08)	Beta	Spackman et al, 2013[217]
Living with non-severe forms of hemoglobinopathies and thalassemia	0.93 (0.09)	Beta	John et al, 2018[218]
Death	0	NA	Assumption

Abbreviations: CF, cystic fibrosis; FXS, fragile X syndrome; HSU, health state utility; NA, not applicable; SE, standard error; SMA, spinal muscular atrophy.

[a]We explored both the newborn and parents utility perspectives in separate long-term scenarios; in the case of voluntary termination of pregnancy, and in the analysis assuming the newborn utility, the utility of death was used after the voluntary termination of pregnancy (i.e., loss of the life). Beta distributions were assigned in probabilistic analysis. Two parameters of the beta distribution (α, β) were derived from the mean and SE (stated for each model parameter). Standard error was assumed to be 10% of the mean where it was not reported. In the analysis assuming the parents' utility, a decrement in the health state utility was accounted for a short time using a disutility value associated with fetal loss (i.e., 1–0.92 = 0.08),[197] after which the health state utility returned to the pre-pregnancy utility value. The rest of the utilities associated with healthy living or living with the conditions were assumed to be the same for both perspectives.

[b]As reported in the original studies. The estimates were adjusted in the models (in the disutility space) using Canadian norms[213] and EQ-5D mapping algorithm. In the newborn perspective, the utility for people younger than 12 years of age were assumed to correspond to the highest utilities of young adults (HUI-3 scores of 0.9).

Cost Parameters

The cost parameters presented in Table 16 were obtained from Ontario sources, through expert consultations, or from the published literature. Figure 5 also describes our approach for costing all components along the screening pathways.

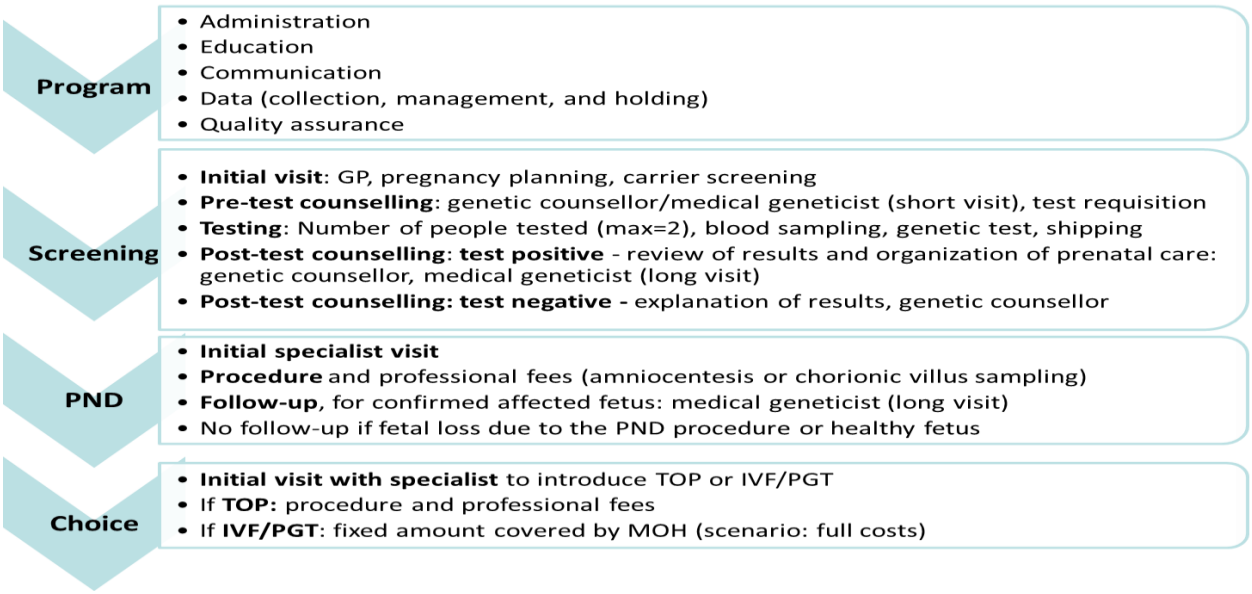

Figure 5: Costing Pathway, Most Conservative Reference Case: Carrier Screening

Abbreviations: GP, general practitioner; IVF/PGT-M, in-vitro fertilization with preimplantation genetic testing with for monogenic/single gene defects; MOH, Ontario Ministry of Health; PND, prenatal diagnostics; TOP, voluntary termination of pregnancy.
Figure showing the costing pathway from program (administration, education, communication, etc.) through screening (initial visit, counselling, testing, etc.), prenatal diagnostics (specialist visit, procedure, follow-up), and ending at patient choice about the course or reproduction (e.g., termination of pregnancy or IVF/PGT-M).

In the reference case, assuming the most conservative (i.e., most expensive) screening pathway, we considered the following costs associated with carrier screening:

- Screening costs of genetic carrier testing
- Screening costs of test visits with health professionals: an additional first visit with a primary care provider, initial (pre-test) and follow-up (post-test) consultation and counselling visits with medical geneticists and genetic counsellors. See Appendix 10 for details on the costing of pre- and post-screening care pathways in the reference case and additional scenarios
- Prenatal screening costs associated with diagnostic services and follow-up care: costs of prenatal diagnostic testing, professional fees, and other additional pregnancy services
- Preconception carrier screening costs: costs of assisted reproductive services (e.g., IVF/PGT-M) that would be incurred in a near-future pregnancy

In our scenario analyses, we also consider the following costs:

- Screening program costs
- Long-term costs of treatment for the conditions of interest

The costing pathway for the reference case is the most conservative option for the current system in Ontario as it costed all medical services (specialist point-of-care) without considering possible human health resource constraints (i.e., regarding the numbers of trained medical geneticists or genetic

counsellors necessary to support population-based screening). An investigation of the most sustainable model of care was out of scope for this assessment, but we conducted sensitivity analyses to explore possible savings (see Appendix 8).

We estimated only the additional costs associated with carrier screening and the conditions of interest. Standard pregnancy care was assumed to be similar between the strategies and was not parsed out for simplicity; consequently, no additional costs would be incurred for the no screening alternative (resulting in the nil cost). Likewise, we did not include standard care costs associated with laboratory tests (e.g., hematologic assessment for hemoglobinopathies) and clinical assessments prior to genetic carrier testing assuming this care is similar between all strategies and would not be impacted by the introduction of genetic carrier screening.

The cost of genetic carrier testing, presented as the cost of the panel in Table 16, was assumed to include all components associated with the cost of testing and follow-up reporting (e.g., labour, consumables, reporting of results); however, we accounted for the cost of sample acquisition (blood sampling) and sample shipping. We solicited the cost estimates on the currently available single-disease genetic tests that are publicly funded from the hospitals. Together with experts (Drs. M. Somerville and M. Axford, email and oral communications, February 2022), we estimated the potential cost of a hospital-based customized one-panel test that would be able to identify the pathogenetic variants of interest using the current NGS technology.

In a scenario analysis, we assumed that currently available commercial NGS carrier screening panels can be used in Ontario. Commercial NGS panel costs were assumed to be the same as those given on the industry websites,[219,220] and implementation, overhead, quality assurance, and transportation of samples costs were included in the cost of the test. These cost estimates may not represent the actual prices of the tests that will be negotiated by the Ministry of Health (and are based on potential volumes and other factors) if carrier screening is publicly funded in the future. Sensitivity threshold analysis was done to explore the impact of the reference case panel costs on the cost-effectiveness of preconception or prenatal carrier screening with different testing interventions (see Table 12).

As mentioned above, we considered additional program costs in a scenario analysis. These costs were estimated by our experts (S. Dougan and J. Milburn, email and oral communications, March 2022), and they included management and administration of a screening program (see Figure 5). In our analyses, program costs were adjusted to per-person costs (which depended on the number of people participating in the preconception or prenatal screening, see Table 16 and Appendix 9).

Another scenario accounted for the long-term outcomes of carrier screening. Direct medical costs used in this scenario analysis included average cost estimates of treatment for CF and hemoglobinopathies and thalassemia, in Ontario published by the Canadian Institute for Health Information.[221] There are no Canadian or Ontario data that specifically address treatment costs of FXS. Consequently, for the purpose of our analyses, we made a simplifying assumption and used the Ontario-based costs estimated by Lunsky et al[222] for people with intellectual and developmental disabilities. The cost estimates of SMA and CF treatment with novel therapies were assumed and based on estimates from relevant CADTH reports.[198,199]

Table 16: Per-Person Cost Estimates Used in the Economic Models

Parameter description	Unit cost, $, Mean (±SE)[a,b]	Frequency	Source
Screening costs: genetic carrier testing (preconception or prenatal screening)	—	—	—
(1) Sample requisition and shipping	—	—	—
Blood sampling	10.76	1	L700, Ontario Schedule of Benefits: Laboratory Services
Sample shipping	6.025 (1.51)	1	Tsiplova et al, 2016[223]
(2A) Single-disease genetic carrier testing (standard approach), per partner	—	—	—
CF, genetic test cost	164 (41.00)	1	Sick Kids Hospital (Somerville and Axford, email communication, February, 2022)
FSX, genetic test cost	203 (50.75)	1	Sick Kids Hospital (Somerville and Axford, email communication, February, 2022)
Hemoglobinopathies and thalassemia, genetic tests' costs (sickle cell disorder, alpha and beta thalassemia, combined)	135 (33.75)	1	Estimated[c]
SMA, genetic test cost	155 (38.75)	1	Sick Kids Hospital (Somerville and Axford, email communication, February, 2022)
(2B) Multi-condition genetic carrier screening panel, per partner (hypothetical customized hospital lab-developed test)	—	—	—
All conditions of interest, customized one-panel (sequencing, NGS) test cost	657 (164.25)	1	Estimated (Somerville and Axford, email communication, February, 2022)
(2C) Multi-condition genetic carrier screening panels, private labs, per partner (sensitivity analysis)	—	—	—
List test price, per partner	625	1	Life Labs Genetics[220]

Parameter description	Unit cost, $, Mean (±SE)[a,b]	Frequency	Source
Preconception or prenatal screening: pre-test and post-test visits	—	—	—
(1A) Pre-test services with primary care physicians	—	—	—
Primary care provider: additional initial screening visit (professional fee)[d]	36.85/67.75[d]	1	P004/A007/K013,[d] OHIP Schedule of Benefits[224]
(1B) Pre-test genetic services	—	—	—
Medical geneticist	38.20	1	K223, OHIP Schedule of Benefits[224]
Genetic counsellor (1 h session)	41.20 (10.30)	1	Ontario Health, 2020[205]
(2A) Post-test genetic services, if test positive (consultation for further prenatal care)	—	—	—
Medical geneticist	75.25	1	K222, OHIP Schedule of Benefits[224]
Primary care provider	67.75	1	K013/K005, OHIP Schedule of Benefits[224]
Genetic counsellor (1 h session)	41.20 (10.30)	1	Ontario Health, 2020[205]
(2B) Post-test genetic services, if test negative	—	—	—
Genetic counsellor (1 h session)	41.20 (10.30)	1	Ontario Health, 2020[205]
Prenatal diagnostic testing and reproductive choice	—	—	—
Initial specialist visit	74.70	1	P002, OHIP Schedule of Benefits[224]
Amniocentesis (professional fee)	102	1	OHIP Schedule of Benefits[224]
Amniocentesis (procedure)	422.31 (130.37)	1	OCC 2016/17, 5AB02HA
CVS (professional fee)	153	1	OHIP Schedule of Benefits[224]
CVS (procedure)	947.12 (236.78)	1	Ontario Health[176]
Physician specialist visit (fee)	161.15	1	A920, OHIP Schedule of Benefits: Medical management (OB-GYN), initial service, professional fee)[224]
Termination of pregnancy (fee)	204.14	1	OHIP Schedule of Benefits: professional fee, surgeon and anesthesiologist[224]

Parameter description	Unit cost, $, Mean (±SE)[a,b]	Frequency	Source
Termination of pregnancy (procedure)	1,450.77 (38.11)	1	5CA89GA, OCCI (2017/18): procedure, day surgery[225]
IVF procedure cost, current coverage	5,000 (1,250)	1	Ministry[226]
IVF/PGT-M, cost per life birth (in sensitivity analysis)	39,013.58 (9,753.40)	1	Lipton et al, 2020[227]
Average cost			
Low cost	29,260.45 (7315.11)	1	—
High cost	48,766.71 (12191.68)	1	—
Additional costs: carrier screening program, scenario analysis	**—**	**—**	**—**
(1) One-time implementation annual costs	**—**	**—**	**—**
Total per person/y, preconception (for a total of 199,625 people), universal	6.01	NA	Estimated, see Appendix 9
Total per person/y, prenatal (for a total of 133,083 people), universal	9.02	NA	Estimated, see Appendix 9
(2) Ongoing operational annual costs	**—**	**—**	**—**
Total per person/y, preconception, universal	3.73	NA	Estimated, see Appendix 9
Total per person/y, prenatal, universal	5.60	NA	Estimated, see Appendix 9
Long-term treatment costs, scenario analysis	**—**	**—**	**—**
CF, without novel therapy	16,512	Annual	CIHI Cost Estimator:[221] Ontario, 2019
CF, novel therapy (eligible patients: > 12 years of age with at least 1 F508del CFTR mutation)	306,000	Annual	CADTH[200]
FXS, major developmental disability	24,613 (6,153)[e]	Annual	Lunsky et al, 2019[222]
Hemoglobinopathies	4,830	Annual	CIHI Cost Estimator: Ontario, 2019 (all age groups)[221]
SMA, without novel therapy, supportive care	31,968	Annual	Estimated, from CADTH, 2020[198,199]

Parameter description	Unit cost, $, Mean (±SE)[a,b]	Frequency	Source
End of life care (the last 30 days), applied for severe forms of SMA and hemoglobinopathy or for CF	74,663	1 month	Widger et al, 2017[228]
SMA, treatment with novel therapy: first and subsequent years	708,000 354,000	Annual	CADTH[198]

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; CF, cystic fibrosis; CIHI, Canadian Institute for Health Information; CVS, chorionic villus sampling; FXS, fragile X syndrome; GP, general practitioner; IVF, in vitro fertilization; PGT-M, preimplantation genetic testing for monogenic/single gene defects; NA, not applicable; NGS, next-generation sequencing; OB-GYN, obstetrician-gynecologist; OCCI, Ontario Case Costing Initiative; OHIP, Ontario Health Insurance Plan; SE, standard error; SMA, spinal muscular atrophy.

[a]All costs in 2022 CAD.

[b]Input parameters presented as the point estimates were treated as fixed (i.e., physician fees or laboratory fees) and were not assigned the gamma distribution. Standard errors were calculated whenever possible; otherwise, SEs were assumed to be 25% of the mean cost. For the inputs with calculated SEs, we assigned the gamma distributions in probabilistic sensitivity analysis. Two parameters of the gamma distribution (α, λ) were derived from the mean and SE. Formulas for these calculations are: α = (Mean^2)/(SE^2); λ = Mean/([Mean × SE]^2).

[c]Cost of testing for hemoglobinopathies and thalassemia is hypothetical and represents a combination (sum) of the costs of genetic carrier tests for thalassemias or sickle cell disorders (a single-disease cost would be approximately one third of the above-reported cost).

[d]Assumed OHIP fee code P004 for the reference case for both research questions for simplicity; OHIP codes related to the initial GP visit for carrier screening in the preconception period could be A007 ($36.85) or K013 ($67.75) (see Appendix 8).

[e]We estimated the costs based on data reported in Table 1 of Lunsky et al.[222] the costs were in 2009/10 CAD ($19,734.72). We converted this cost input to 2022 CAD using the CPI ratio (145.3 [2022]/116.5 [2010])

Internal Validation

Formal internal validation was conducted by the secondary health economist. This included testing the mathematical logic of the model and checking for errors and accuracy of parameter inputs and equations.

Analysis

For each research question, we conducted a reference case analysis and sensitivity analysis. Our reference case and sensitivity analyses adhered to CADTH guidelines[175] when appropriate. The reference case represents the analysis with the most likely set of input parameters and model assumptions. The sensitivity analysis explored how the results are affected by varying input parameters and model assumptions.

We calculated the reference case of this analysis by running 10,000 simulations (probabilistic analysis) to simultaneously capture the uncertainty in all parameters that are expected to vary. Types of distributions assigned to each input parameter that will be used in the probabilistic analysis are presented in the input parameter tables. The probabilistic analysis simultaneously captures the uncertainty in all model parameters. We calculated the mean total costs with 95% credible intervals (95% CrI) and mean effectiveness outcomes (e.g., affected births) with CrIs for each intervention assessed. We also calculated incremental values and estimate incremental cost-effectiveness ratios (ICERs) for preconception and prenatal carrier screening strategies. We used the sequential ICER approach and compared all interventions among themselves and to the no-screening alterative to

ascertain which one represents the optimal carrier screening pathway. Following the CADTH guidelines,[175] we reported the sequential ICERs and an ICER produced from a common comparator (i.e., no screening). We ordered treatments by average total costs, from lowest to highest. For sequential ICERs, after excluding treatments that were either dominated or subject to extended dominance, we calculated the ICER for a less costly comparator compared with the next least costly comparator. For the cost–utility analysis, the results of the probabilistic analysis were also presented on a cost-effectiveness acceptability curve. We present uncertainty quantitatively as the probability that a treatment is cost-effective at various willingness-to-pay values. For each simulation, the treatment with the maximum net monetary benefit at the given willingness-to-pay was considered the most cost-effective among the interventions compared.[229]

SENSITIVITY ANALYSIS

We examined parameter uncertainty in the cost-effectiveness of our screening interventions in one-way sensitivity analyses on more than 30 model parameters (Tables 17 A and B and Appendices 12 and 13). For example:

- Carrier frequency for the conditions of interest (see Appendices 12–14)
- Uptake (participation) in screening (and detection of carriers with universal vs. risk-based screening; see Appendix 15, Figures A14-A15)
- Probability of voluntary termination of pregnancy (ranging from 0% to 100% for all conditions; see Appendix 16, Figure A16)
- Probability of choosing IVF/PGT-M after preconception carrier screening (see Appendix 17, Figure A17)
- Cost of IVF/PGT-M per life birth (see Appendix 18)
- Cost of panels used for carrier screening (i.e., threshold price analysis on the cost estimates of the standard (single-disease) panels and a hypothetical expanded (multi-disease) panel (see Appendices 12 and 13)

Table 17A: Sensitivity Analyses for Short-Term Preconception/Prenatal Reference Case: Clinical Parameters

Clinical parameters	Reference case	Sensitivity analysis
Carrier frequency for the given conditions	—	Range (10 intervals):
CF	0.04	0.02–0.25
SMA	0.025	0.01–0.25
FXS	0.0012	0.0006–0.01
Hemoglobinopathies	0.1056	0.01–0.25
Uptake (Participation) in Screening, Probability	—	Values informed by the clinical evidence review results
Uptake, both partners	0.71	Range (5 intervals): 0.2–1.0
Carrier detection factor ratio, based on participation in screening	14.2 (0.71 [universal] vs. 0.05 [risk-based])	Range in factor ratio from 0.5 to 17, to detect the threshold value and switch between universal and risk-based screening strategies
Test Accuracy, All Conditions	—	Range (4 intervals):

Clinical parameters	Reference case	Sensitivity analysis
CF	Sn = 0.90; Sp = 0.99	Sn/Sp = 0.90–1.00
SMA	Sn = 0.95; Sp = 0.99	Sn/Sp = 0.90–1.00
FXS	Sn = 0.96; Sp = 0.99	Sn/Sp = 0.90–1.00
Hemoglobinopathies	Sn = 0.90; Sp = 0.99	Sn/Sp = 0.90–1.00
Expanded, hypothetical NGS panel (all)	Sn = 0.99; Sp = 0.99	Sn/Sp = 0.90–1.00
Bart's Syndrome (Alpha-Thalassemia), Probability	0.000025	Range (4 intervals): 0.0–0.2
Fetal Loss Due to PND Procedures, weighted probability for amniocentesis and CVS, probability	0.00189	Range (4 intervals): 0.0–0.02
Prenatal Diagnostic Testing	—	—
Uptake, probability	0.95	Range (5 intervals): 0.2–1.0
Use of PND procedures: CVS vs. amniocentesis, probability	0.70 vs. 0.30	Range (5 intervals): 0.2–1.0
Voluntary TOP, probability by condition	—	Range (5 intervals), informed by findings of the clinical evidence review results
CF	0.80	0.2–1.0
SMA	0.67	0.2–1.0
FXS	0.29	0.2–1.0
Hemoglobinopathies	0.29	0.2–1.0
Reproductive Choice: Use of IVF/PGT in Preconception Only, probability	0.79	Range (5 intervals): 0.0–1.0

Abbreviations: CF, cystic fibrosis; CVS, chorionic villus sampling; FXS, fragile X syndrome; SMA, spinal muscular atrophy; SN, sensitivity; SP, specificity; NGS, next generation sequencing; PND, prenatal diagnostics; TOP, voluntary termination of pregnancy; IVF/PGT, in-vitro fertilization with preimplantation genetic testing for monogenic/single gene defects.

Table 17B: Sensitivity Analyses for Short-Term Preconception/Prenatal Reference Case: Cost Parameters

Cost parameters[a]	Reference case	Sensitivity analysis
Standard (single-disease) panel cost	—	Range (5 intervals):
CF	$164	$50–$400
SMA	$155	$50–$400
FXS	$203	$50–$400
Hemoglobinopathies (all types combined)	$135	$50–$400
Hypothetical expanded (multi-disease) NGS panel cost	$657	Range (5 intervals): $100–$800
Cost of blood sampling	$10.76	Range (4 intervals): $0–$20
Cost of blood sample shipping	$6.02	Range (4 intervals): $0–$10
Cost of screening program (per person)	$0	Range (5 intervals): $0–$50
Cost of screening program	—	Additional scenarios related to inclusion of the program cost were informed by data from Table 16 (estimates described in Appendix 9)
Cost of IVF/PGT-M (coverage per life birth)	Applicable only to preconception carrier screening	Applicable only to preconception carrier screening
Ministry coverage per life birth	$5,000	Range (5 intervals): $2,000–$40,000
Full coverage per life birth	NA	Informed by Lipton et al, 2020[227] (Table 16): $39,013 (range: $29,260–$48,766)
Screening care pathway scenarios[b]: hourly rate, medical genetic counsellor	$41.20 (± $10.3)	Higher rate: $50.26 (± $12.6)

Abbreviations: CF, cystic fibrosis; FXS, fragile X syndrome; IVF/PGT-M, in-vitro fertilization with preimplantation genetic testing for monogenic/single gene defects; NGS, next generation sequencing; SMA, spinal muscular atrophy.

[a]All costs are in 2022 CAD.

[b]Other scenarios with structural changes in the care pathway (i.e., initial, pre-test, and post-test visits) are described in Appendix 8.

We also examined structural and methodological uncertainty of the reference case model in the following scenarios:

- **Long-term cost-utility scenarios**: assessment of long-term cost–utility of carrier screening strategies over a person's lifetime for each condition separately and for all conditions combined, using two separate perspectives for estimations of QALYs (the utility perspective of the newborn or people living with the given condition and the parent's perspective). This analysis included costs of lifetime treatment and screening program costs (see Table 16)
- **Scenarios including screening program costs**: inclusion of all costs necessary for running a screening program in a short-term primary analysis (cost inputs presented in Table 16, with more details in Appendix 9)

- **Scenarios including various screening care pathways**: assessment of costs associated with medical professional visits (medical counselors, medical geneticists, and primary care physicians) before and after genetic testing (see Appendix 8 for more details)

All analyses were conducted using TreeAge Pro 2022.[230] Where up-to-date costs were not available, we used the Consumer Price Index to adjust to 2022 CAD.[231]

Results

Our economic evaluation estimated the cost-effectiveness of both preconception and prenatal carrier screening programs. Tables 18 and 19 present the results of our reference case (short-term) cost-effectiveness analyses for all given conditions (combined). Results for each health condition are presented in Appendices 10 and 11.

Reference Case Analysis

Preconception Carrier Screening Programs

COST-EFFECTIVENESS FOR ALL CONDITIONS OF INTEREST

All preconception carrier screening program options were associated with a smaller chance of having an affected birth compared with no screening. Universal screening program options were able to identify more at-risk couples and at-risk pregnancies and, therefore, to offer more choices for future parents. Thus, with these options, higher probabilities of prenatal diagnostic testing, voluntary termination of pregnancy, and in-vitro fertilizations with preimplantation genetic testing were estimated (Table 18A).

In a sequential cost-effectiveness analysis, applying the incremental changes in the health outcome (e.g., affected birth) and incremental costs, we found that, compared with no screening, universal screening with standard panels would cost $367,731 for each affected birth avoided (Table 18B). Compared with no screening, universal screening with standard panels resulted in an ICER of $29,106 per additional at-risk pregnancy identified (Table 18C).

COST-EFFECTIVENESS BY HEALTH CONDITION

In the reference case preconception screening analyses, done for each condition separately, the trend of probabilities of the effectiveness outcomes remained similar to those reported in the main (all given conditions) analyses (Tables A24–A31, Appendix 10).

In sequential preconception screening cost-effectiveness analyses, the universal screening with standard panels strategy remained dominant for CF, hemoglobinopathies and thalassemia, and SMA, while the risk-based screening with standard panels strategy was dominant over other screening options for FXS. However, to avoid one birth affected by either CF, FXS, hemoglobinopathies and thalassemia, or SMA, there is a much higher additional cost (compared to above-mentioned multi-condition analysis), ranging from $0.64 million to $4.8 million, depending on the health condition (see Tables A25, A27, A29, and A31, Appendix 10).

Table 18A: Reference Case Analysis Results, Preconception Screening Programs, All Conditions: All Effectiveness Outcomes

Strategy	Probability: affected birth	Probability: test positive[a]	Probability: test true positive	Probability: test false positive	Probability: test false negative	Probability: PND	Probability: TOP	Probability: IVF/PGT-M
No screening	0.004159338	NA	NA	NA	NA	NA	NA	NA
Risk-based, standard (single-disease) panels	0.004135624	0.000242	0.000131	0.000110	0.000807	0.000230	0.000021	0.000010
Risk-based, expanded (multi-disease) panel	0.004133851	0.000158	0.000142	0.000016	0.000018	0.000150	0.000023	0.000006
Universal, standard panels	0.003431428	0.009196	0.006470	0.002727	0.011793	0.008727	0.000631	0.000371
Universal, expanded panel	0.003369724	0.007823	0.007056	0.000766	0.000799	0.007422	0.000684	0.000316

Abbreviations: IVF/PGT-M, in-vitro fertilization with preimplantation genetic testing; NA, not applicable; PND, prenatal diagnostic testing; TOP, voluntary termination of pregnancy.
[a]At-risk pregnancy (i.e., couples that test positive).

Table 18B: Reference Case Analysis: Cost-Effectiveness of Preconception Screening Programs for Given Conditions: Cost Per Affected Birth Averted

Strategy[a]	Average total costs[a] (95% CrI), $	Average total effects (95% CrI), affected birth	ICER, $/affected birth avoided	
			Versus no screening	Sequential ICER (excluding dominated)
No screening	0	0.004159 (0.0031–0.0054)	—	—
Risk-based, standard panels	17.96 (11–26)	0.004136 (0.0031–0.0054)	757,150.50	Dominated[b]
Risk-based, expanded panel	43.57 (24–70)	0.004134 (0.0031–0.0054)	1,709,520.03	Dominated[b]
Universal, standard panel	267.67 (198–344)	0.003431 (0.0024–0.0046)	367,730.70	367,730.70
Universal, expanded panel	659.87 (407–993)	0.003370 (0.0024–0.0045)	835,688.08	6,356,034.08

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio.
[a]Treatment strategies are ordered by average total costs, from lowest to highest. No screening strategy equals 0 because all have additional costs incurred related to carrier screening.
[b]Extended dominance.

Table 18C: Reference Case Analysis: Cost-Effectiveness of Preconception Screening Programs for Given Conditions (ICER: Cost Per At-Risk Pregnancy Identified)

Strategy[a]	Average total costs[a] (95% CrI), $	Average total effects (95% CrI), at-risk pregnancy identified	ICER, $/at-risk pregnancy identified	
			Versus no screening	Sequential ICER (excluding dominated)
No screening	0	—	—	—
Risk-based, standard panels	17.96 (11–26)	0.000242 (0.0001–0.00058)	74,218.60	Dominated[b]
Risk-based, expanded panel	43.57 (24–70)	0.000158 (0.00009–0.00026)	275,654.96	Dominated[c]
Universal, standard panel	267.67 (198–344)	0.009196 (0.00433–0.01398)	29,106.24	29,106.24
Universal, expanded panel	659.87 (407–993)	0.007823 (0.00435–0.01172)	84,351.05	Dominated[c]

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio.

[a]Treatment strategies are ordered by average total costs, from lowest to highest. No screening strategy equals 0 because all have additional costs incurred related to carrier screening.

[b]Extended dominance.

[c]Strong dominance.

PRENATAL CARRIER SCREENING PROGRAMS

Cost-Effectiveness for All Conditions of Interest

Reference case results for prenatal carrier screening were similar to those reported for preconception carrier screening. As shown in Table 19A, all prenatal carrier screening program options were associated with a smaller chance of having an affected childbirth, compared with no screening. Universal screening program options identified more pregnancies at risk, and had higher probabilities of prenatal diagnostic testing and voluntary terminations of pregnancy.

In a sequential cost-effectiveness analysis applying the incremental changes in the health outcome (affected birth) and incremental costs, we found that compared with no screening, the universal screening with standard panels strategy would cost $431,807 for each affected birth avoided (Table 19B). Compared with no screening, universal screening with standard panels resulted in an ICER of $29,758 per additional at-risk pregnancy identified (Table 19C).

Cost-Effectiveness by Health Condition

For the reference case prenatal carrier screening analyses, which were done for each condition separately, the trends related to the probabilities of the effectiveness outcomes remained similar to those reported in the main analyses (for all given conditions; see Tables A32–A39, Appendix 11).

Similar to the above-mentioned results for preconception carrier screening, the universal screening with standard panels strategy remained dominant for CF, hemoglobinopathies and thalassemia, and SMA in sequential analyses; for FXS, the risk-based screening with standard panels strategy was dominant over other screening strategies. To avoid one birth affected by either CF, FXS, hemoglobinopathies and thalassemia, or SMA, we would have to accept a much higher additional cost, ranging from $0.78 million to $5.4 million, depending on the health condition (see Tables A33, A35, A37, and A39, Appendix 11).

Table 19A: Reference Case Analysis Results, Prenatal Screening Programs, All Conditions: All Effectiveness Outcomes

Strategy	Probability of affected birth	Probability: test positive[a]	Probability: test true positive	Probability: test false positive	Probability: test false negative	Probability: PND	Probability: TOP
No screening	0.004159338	NA	NA	NA	NA	NA	NA
Risk-based, standard panels	0.004139566	0.000228707	0.000123461	0.000105246	0.000774387	0.000217091	1.96803E-05
Risk-based, expanded panel	0.00413807	0.000148117	0.000132966	1.51511E-05	1.72825E-05	0.000140529	2.117E-05
Universal, standard panels	0.003569688	0.008556033	0.005998533	0.0025575	0.011300092	0.008115771	0.000586438
Universal, expanded panel	0.003519759	0.007245256	0.006540015	0.00070524	0.00074329	0.006871914	0.000636098

Abbreviations: NA, not applicable; PND, prenatal diagnostic testing; TOP, voluntary termination of pregnancy.

[a]At-risk pregnancy (i.e., couples that test positive).

Table 19B: Reference Case Analysis: Cost-Effectiveness of Prenatal Screening Programs for Given Conditions

Strategy	Average total costs[a] (95% CrI), $	Average total effects (95% CrI), affected birth	ICER, $/affected birth avoided	
			Versus no screening	Sequential ICER (excluding dominated)
No screening	0	0.004159 (0.0031–0.0054)	—	—
Risk-based, standard panels	17.18 (11–25)	0.00414 (0.0031–0.0054)	869,268.22	Dominated[b]
Risk-based, expanded panel	41.78 (23–67)	0.004138 (0.0031–0.0054)	1,964,533.61	Dominated[b]
Universal, standard panels	254.62 (191–328)	0.00357 (0.0026–0.0047)	431,807.03	431,807.03
Universal, expanded panel	630.07 (386–959)	0.00352 (0.0025–0.0047)	985,126.26	7,519,658.88

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio.

[a]Treatment strategies are ordered by average total costs, from lowest to highest. No screening strategy equals 0 because all additional costs incurred are related to carrier screening.

[b]Extended dominance.

Table 19C: Reference Case Analysis: Cost-Effectiveness of Preconception Screening Programs for Given Conditions (ICER: $ per At-Risk Pregnancy Identified)

Strategy[a]	Average total costs[a] (95% CrI), $	Average total effects (95% CrI), at-risk pregnancy identified	ICER, $/at-risk pregnancy identified	
			Versus no screening	Sequential ICER (excluding dominated)[b]
No screening	0.00	0		
Risk-based, standard panels	17.18 (11–25)	0.000229 (0.00010–0.00055)	75,150.90	Dominated[b]
Risk-based, expanded panel	41.78 (23–67)	0.000148 (0.000087–0.000243)	282,083.27	Dominated[c]
Universal, standard panel	254.62 (191–328)	0.008556 (0.004066–0.01327)	29,758.55	29,758.55
Universal, expanded panel	630.07 (386–959)	0.007245 (0.004056–0.010829)	86,962.65	Dominated[c]

Abbreviation: CrI, credible interval; ICER, incremental cost-effectiveness ratio.

[a]Treatment strategies are ordered by average total costs, from lowest to highest. No screening strategy equals 0 because all additional costs incurred are related to carrier screening.

[b]Extended dominance.

[c]Strong dominance.

Sensitivity Analysis

SENSITIVITY ANALYSES: SHORT-TERM REFERENCE CASE ANALYSES FOR PRECONCEPTION OR PRENATAL CARRIER SCREENING PROGRAMS

We conducted numerous one-way sensitivity analyses, including scenarios to examine parameter and structural uncertainty in the short-term reference case models for preconception and prenatal carrier screening. We reported detailed results of these analyses in Appendices 9 to 18, and discuss several important analyses and their results below.

In the majority of analyses, the effectiveness of interventions (expressed as the probability of having an affected birth) and their total costs changed as the parameter values changed (resulting in changes of the ICER estimate), but the order of strategies remained the same as in the reference case analyses (i.e., universal screening with standard panels as the preferred strategy compared to other strategies, yielding a reference case ICER of $367,731 per affected birth avoided for preconception carrier screening (Table 18B) and a reference case ICER of $431,807 per affected birth avoided for prenatal carrier screening (Table 19B). In none of these analyses, regardless of the ranges of values used, did the ICERs decline below $50,000 per affected birth.

One exception to universal standard panel strategy as the preferred strategy was an analysis examining changes in the carrier detection ratio. In this analysis, the risk-based standard panel strategy became more effective when the probability of participation in risk-based carrier screening became similar to the probability of participation in universal screening (i.e., about 71% for preconception and about 68% for prenatal screening; see Figure A15, Appendix 15, presenting this switch for preconception carrier screening). This was an expected, sensible result because the carrier detection ratio was derived from the participation estimates.

Another exception was an analysis related to the cost of a hypothetical expanded (multi-disease) panel. Assuming a cost about four times lower for this panel (≤ $100 for the preconception and ≤ $170 for prenatal carrier screening) compared with the reference case cost ($657), universal screening with expanded panels was less costly and more effective than universal screening with standard panels; however, the ICER comparing the preconception or prenatal screening option to no screening remained well above $270,000 per affected birth avoided.

Other important parameters that had an impact on the cost-effectiveness were carrier frequency, uptake (participation) in the screening, voluntary termination of pregnancy (TOP), cost of care alongside the carrier screening pathway, cost of IVF with PGT-M (applicable to preconception carrier screening only), and implementation costs of carrier screening programs.

Carrier Frequency

Our analyses showed that if there is a hypothetical (unrealistic) increase in the probability of condition-specific carrier frequency of 2 to 10 times in preconception or prenatal carrier screening (see Table 17A for changes in the disease prevalence), then the ICER of universal screening with standard panels versus no screening would substantially decrease between 2.5 and 6 times (depending on the amount of decrease in the disease prevalence, see Figure 6, below, and Appendix 14). The largest impact on the ICER was seen for the case of CF and SMA in preconception carrier screening, with a decrease in the ICER to $57,261 and $60,604 per affected birth avoided for CF and SMA, respectively (compared with the reference case ICER of $367,731 per affected birth avoided). Although this analysis is hypothetical for some very high carrier frequency input values, it might aid in answering a frequently asked question related to the estimation of a general carrier frequency

threshold (for all rare diseases) at which a decision-maker would consider recommending genetic carrier testing (based on its value for money).

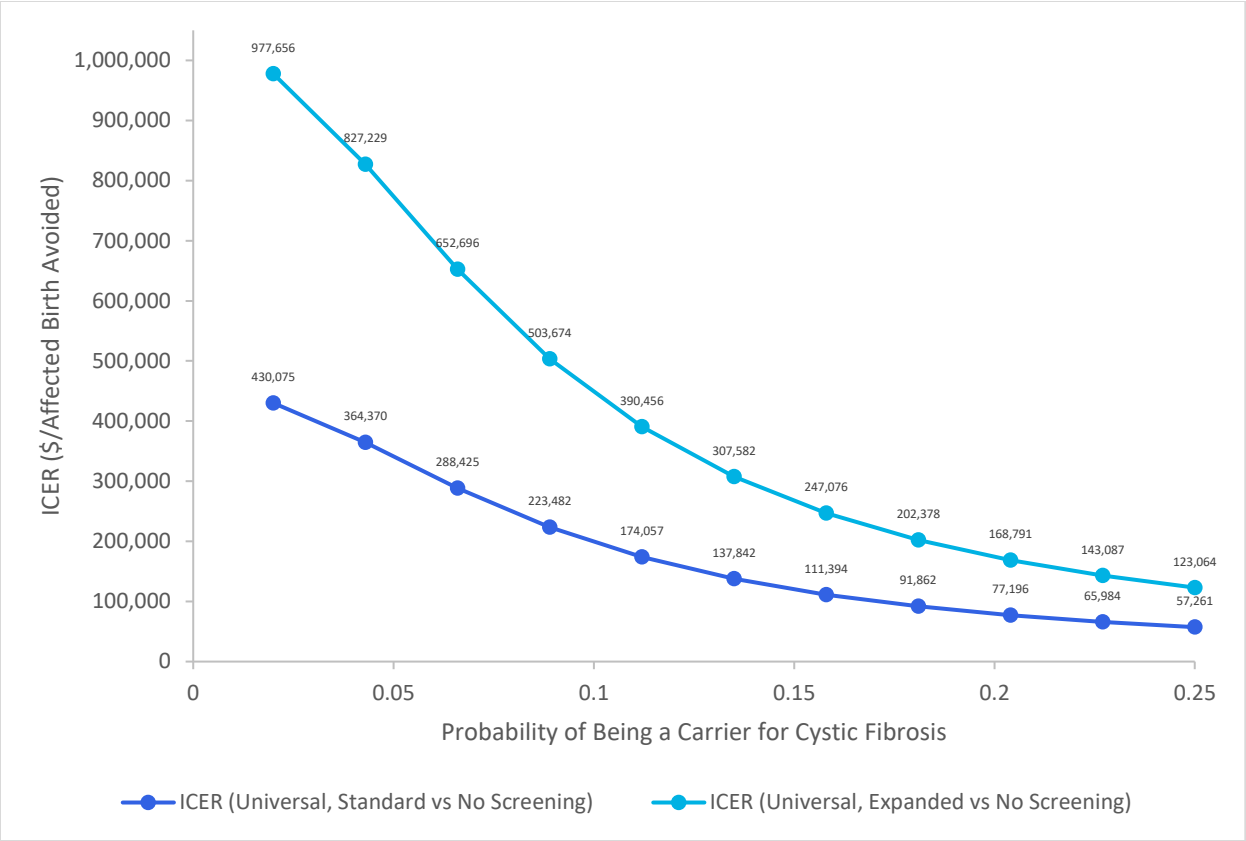

Figure 6: Changes in Carrier Frequency for Cystic Fibrosis and the ICER: Preconception Carrier Screening

Abbreviation: ICER, incremental cost-effectiveness ratio.

Graph showing ICERs for universal standard and expanded panels carrier screening of cystic fibrosis versus no screening, by carrier frequency for cystic fibrosis, with an additional cost per affected birth avoided plotted on the y-axis and probability of being a carrier plotted on the x-axis. Compared with no screening, universal carrier screening with standard panels has an additional cost of $430,075 per affected birth avoided at a carrier probability of 0.025, decreasing to $57,261 per affected birth avoided as the probability of being a carrier increases to 0.25. Universal expanded panel carrier screening has an additional cost of $977,656 per affected birth avoided at a probability of 0.025, decreasing to $123,064 as the probability of being a carrier increases to 0.25.

Participation (Uptake) in Screening

Our clinical evidence review suggested a wide range of estimates related to levels of uptake in carrier screening. Our sensitivity analyses found that the ICER would increase if the rate of participation is smaller than what we assume in the reference case (i.e., 71% and 68% for preconception and prenatal carrier screening, respectively). For instance, with a 20% probability of uptake in carrier screening, the ICER would be 1.6 times higher compared with the reference case (Figure 7 and Appendix 15).

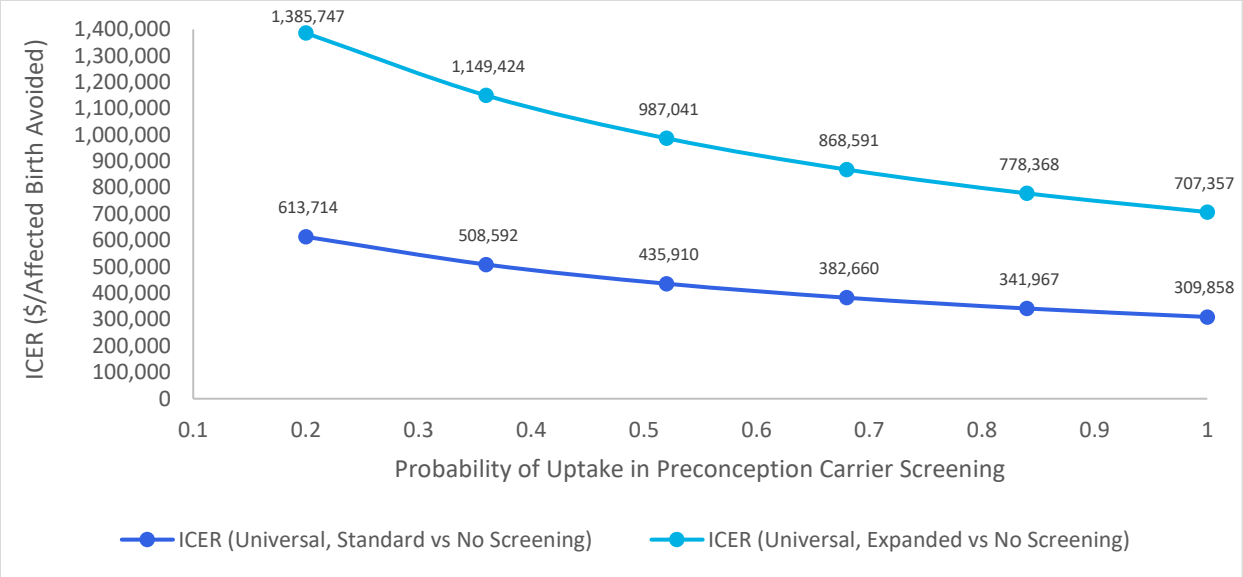

Figure 7: Changes in Screening Uptake and the ICER: Preconception Carrier Screening

Abbreviation: ICER, incremental cost-effectiveness ratio.

Graph showing ICERs for universal standard and expanded panel screening versus no screening by uptake rate in preconception carrier screening, with an additional cost per affected birth avoided plotted on the y-axis and probability of uptake plotted on the x-axis. Universal screening with standard panels has an additional cost of $613,714 per affected birth avoided at a uptake rate of 0.2, decreasing to $309,858 as the rate increases to 1. Universal expanded panel screening has an additional cost of $1,385,747 per affected birth avoided at a probability of 0.2, decreasing to $707,357 as the uptake rate increases to 1.

Voluntary Termination of Pregnancy

The reference case ICERs were sensitive to our assumptions on the condition-specific probability of voluntary TOP in both preconception and prenatal carrier screening (Figure 8 and Appendices 16 and 17). If the chance of choosing TOP as a reproductive option decreased to zero for all conditions of interest, then the ICERs would increase (preconception screening ranging from $399,248 for SMA to $657,736 for hemoglobinopathies and thalassemia, per affected birth; prenatal screening ranging from $472,046 for SMA to $857,536 for hemoglobinopathies and thalassemia, per affected birth). Compared with the reference case, the largest changes in the ICER when increasing the probability of voluntary TOP from 0 to 1 were seen for hemoglobinopathies and thalassemia, and FXS, for two reasons: first, the initially assumed value for these two conditions was much smaller than for CF and SMA (29% for FXS vs. 67% for SMA and 80% for CF), and second, we examined hemoglobinopathies as a group (including all disease types; e.g., sickle cell disorders, alpha and beta thalassemia), resulting in relatively large disease prevalence compared to other examined conditions. However, the ICERs for preconception and prenatal carrier screening remained large even when we assumed a 100% chance of choosing TOP for all conditions in the event of an affected pregnancy (preconception screening ranges from $180,866 for hemoglobinopathies and thalassemia to $362,854 for SMA per affected birth averted, and prenatal screening ranges from $198,215 for hemoglobinopathies and thalassemia to $423,459 for SMA per affected birth averted).

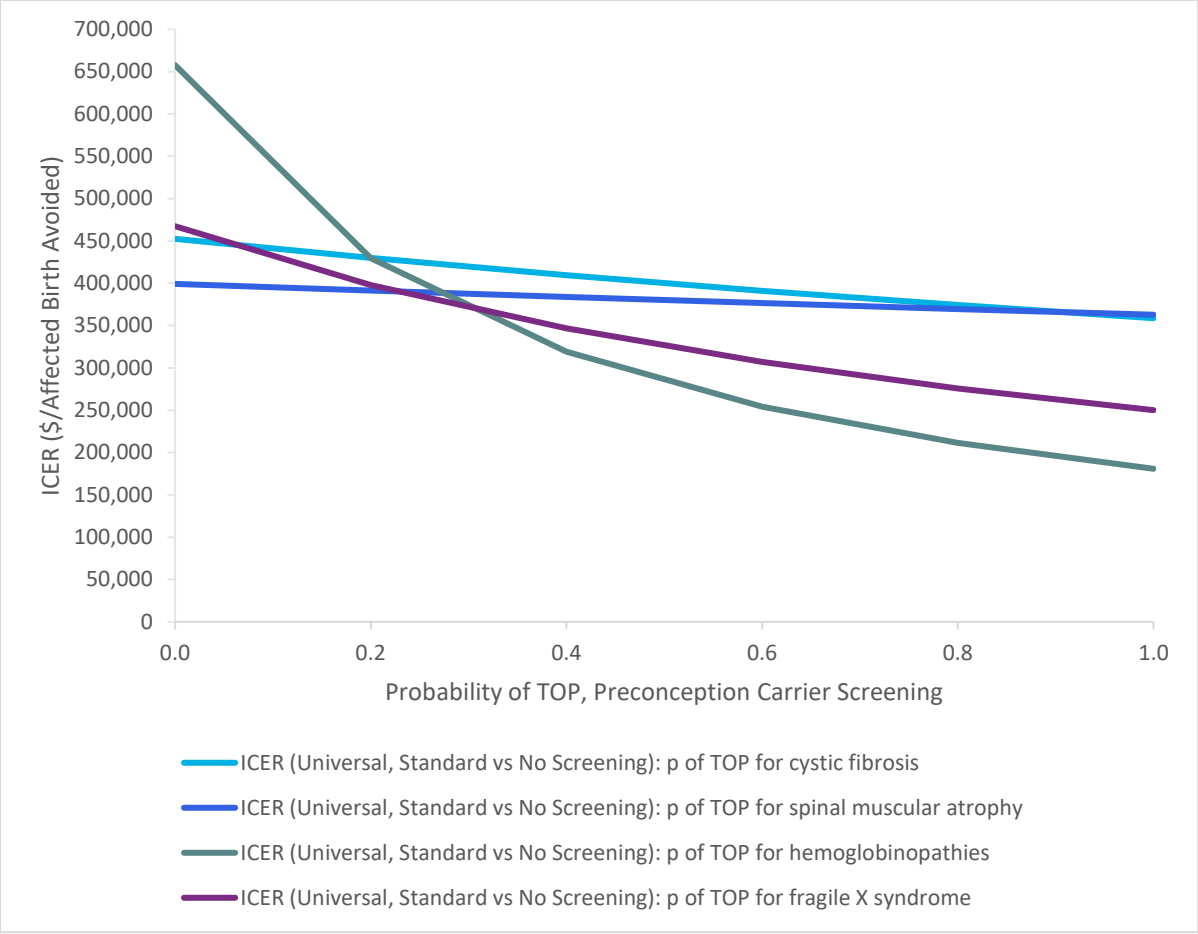

Figure 8: Changes in Condition-Specific Probability of Voluntary TOP and the ICER: Preconception Carrier Screening

Abbreviations: ICER, incremental cost-effectiveness ratio; TOP, voluntary termination of pregnancy.
Graph showing ICERs (universal screening with standard panels versus no screening) for probability of voluntary TOP by condition in preconception carrier screening, with an additional cost per affected birth avoided plotted on the y-axis and probability of TOP plotted on the x-axis. Universal screening for hemoglobinopathies and thalassemia has an additional cost of about $658,000 per affected birth avoided for a TOP of 0, decreasing to about $181,000 as probability of TOP approaches 1. Universal screening for fragile X syndrome has an additional cost of about $467,000 per affected birth avoided for a TOP of 0, decreasing to about $250,000 as probability of TOP approaches 1. Universal screening for cystic fibrosis has a cost of about $450,000 per affected birth avoided for a TOP of 0, decreasing to about $359,000 as probability of TOP approaches 1. Universal screening for spinal muscular atrophy has a cost of about $400,000 per affected birth avoided for a TOP of 0, decreasing to about $363,000 as probability of TOP approaches 1.

IVF and PGT Costs (Preconception Only)

When we considered the full cost of IVF and PGT-M (ranging between $29,000 and $49,000 per life birth; Appendix 18), the ICER would increase an additional $10,000 to $23,000 per affected birth avoided (on the reference case value). For more details on the results of this analysis, see Tables A40-A42, Appendix 18.

Scenario: Screening Care Pathway

The most appropriate model of care for carrier screening is uncertain in Ontario. Our reference case assumed a very conservative, expensive, but possibly ideal case for a screening care pathway in which all necessary medical professionals would be involved and would do follow-up before and after screening tests to provide support and care for all screened couples, regardless of the test results. As the number of people invited to preconception and prenatal carrier screening may be large, we conducted a couple of scenarios that involved fewer follow-up visits with genetic counsellors or less involvement of primary care physicians (considering various assumptions on the Ontario Health Insurance Plan [OHIP] fee codes used to claim an additional carrier screening visit in the preconception or prenatal period). We also explored a situation in which genetic counsellors might be paid more than assumed in the reference case. For example, when we assumed the use of genetic counsellor care for positive test results only, the ICER for the universal, standard panels strategy would decrease to $286,084 and $334,884 per affected birth in preconception and prenatal carrier screening, respectively (compared with the reference case ICERs of $367,731 and $431,807 per affected birth; Appendix 19, Table A43 and Appendix 20, Table A46). In another analysis, we assumed the reference case screening care pathway, but used a higher hourly salary rate for the genetic counsellor (an increase of about $9 compared with the reference case). The ICERs increased to $385,205 and $452,618 per affected birth in preconception and prenatal carrier screening, respectively (Appendix 19 Table A45 and Appendix 20, Table A48). Results of these analyses are presented in Appendices 16 and 17. In summary, the findings of our scenario analyses indicated that the cost-effectiveness, total costs, and overall budget may be considerably influenced by the model of care assumed for carrier screening. The models of care during and after screening depend on many factors and need to be explored carefully in implementation stages because the investigation of the most sustainable and efficient approach was out of scope for this study.

Scenario: Program Costs

Program costs for preconception or prenatal carrier screening programs are highly uncertain. Based on expert suggestions, we roughly estimated a total program cost, which was further adjusted by the number of participants. We presented all calculations of program costs in Appendix 9. In the program cost scenario, we accounted for implementation costs in a short-term analysis used for the reference case (while we accounted for both costs of program implementation and ongoing costs in our long-term models, shown in the following sections). All results are presented in Appendix 21.

After inclusion of the implementation program costs, and compared to the reference case, the ICERs of the universal strategies compared with no screening increased by about 1.7% and 0.7% (universal, standard panels: $373,696; and universal, expanded panel: $841,174 per affected birth; see Appendix 21, Table 49). However, due to a much smaller number of participants in risk-based screening options, and consequently much larger per-person program costs, the ICERs of risk-based strategies increased by 123% compared with the reference case (i.e., $1.7 million vs. $0.8. million per affected birth; Appendix 21, Table A49) for preconception risk-based standard panel strategy, and by 51% for risk-based expanded panel strategy (i.e., $2.6 million vs. $1.71 million per affected birth; Appendix 21). This analysis further showed that substantial program costs could be offset only through population-based screening programs that involve a large number of participants. Risk-based screening programs seem to be even less favorable from an economic standpoint when relatively large per-person program implementation costs are considered.

Scenario: Program Costs and Full Coverage of IVF and PGT-M (Preconception Carrier Screening Only)

In this scenario, we examined changes in the ICERs after accounting for both preconception program costs and full coverage of IVF/PGT-M (see Table A50, Appendix 21). Compared to the reference case, the ICERs of the best universal strategy increased by about 6.35% (universal, standard panels, scenario vs. reference case: $391,085 vs. $367,731 per affected birth; Appendix 21, Table A50).

Long-Term Scenarios: Cost–Utility of Preconception Carrier Screening Programs

Preconception Carrier Screening: Scenarios Without Use of Novel Therapies

As shown in Table 20A, assuming a newborn's utilities for QALY calculation and the costs and benefits of supportive standard therapies (over the lifetime horizon), the no-screening strategy was more expensive but resulted in more QALYs (i.e., the least loss in QALYs) compared with four preconception carrier screening strategies for the given conditions. This is because the accumulation of QALYs in the model stopped after procedure-related fetal loss during the prenatal diagnostic procedures or after choosing termination of pregnancy.

Table 20A: Long-Term Scenario Analysis (Newborn's Utility and No Use of Novel Therapies): Cost–Utility of Preconception Carrier Screening for the Given Conditions

Strategy	Average total costs,[a] $ (95% CrI)	Average total QALYs (95% CrI)	ICER, $/QALY lost	
			Versus no screening[b]	Sequential ICER (excluding dominated)[c]
Universal, standard panels	4,370.21 (3,103.45–6,046.02)	40.0333 (40.004–40.057)	51,851.85	—
Universal, expanded panel	4,690.11 (3,410.99–6,388.98)	40.0322 (40.003–40.056)	27,733.10	Dominated
Risk-based, standard panels	5,073.14 (3,564.29–7,056.81)	40.0468 (40.020–40.067)	48,885.42	Dominated
Risk-based, expanded panel	5,095.91 (3,584.85–7,077.81)	40.0467 (40.020–40.067)	24,976.02	Dominated
No screening	5,123.69 (3,595.02–7,126.61)	40.0478 (40.021–40.068)	—	51,851.85

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

[a]Treatment strategies are ordered by average total costs, from lowest to highest.

[b]Dominant indicates this strategy is less costly and more effective than no screening.

[c]Extended dominance or strong dominance.

As shown in Table 20B, assuming the parent utility for QALY calculation and no use of novel therapies, all preconception screening options were dominant or cost saving (i.e., less expensive and more effective) compared with no screening. In a sequential analysis where all strategies were compared together, risk-based programs and no screening were dominated by universal programs. Compared with universal screening with standard panels, universal screening with expanded (multi-disease) panels was more expensive, but resulted in more QALYs, yielding an ICER of about $507,234

per QALY gained. The price threshold analysis showed that the per-person cost of an expanded panel had to decrease from $657 (price in the reference case) to about $245 for this strategy to become cost saving (compared with the universal screening with standard panels). At the price of about $287, universal screening with expanded panel was cost-effective at a willingness to pay of $50,000 per QALY gained. At the price of about $329, it became cost-effective at a willingness to pay of $100,000 per QALY gained.

Table 20B: Long-Term Scenario Analysis (Parents' Utility and No Use of Novel Therapies): Cost–Utility of Preconception Carrier Screening for the Given Conditions

Strategy	Average total costs,[a] $ (95% CrI)	Average total effects (95% CrI), QALY	ICER, $/QALY gained	
			Versus no screening[b]	Sequential ICER (excluding dominated)[c]
Universal, standard panels	3,874.33 (2,760.84–5,343.02)	33.9149 (33.895–33.929)	Dominant	—
Universal, expanded panel	4,201.23 (3,072.13–5,686.82)	33.9156 (33.896–33.929)	Dominant	507,233.83
Risk-based, standard panels	4,467.16 (3,152.09–6,202.29)	33.9074 (33.885–33.923)	Dominant	Dominated
Risk-based, expanded panel	4,490.42 (3,176.38–6,220.17)	33.9075 (33.885–33.923)	Dominant	Dominated
No screening	4,509.29 (3,178.66–6,266.71)	33.9069 (33.885–33.923)	—	Dominated

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

[a]Treatment strategies are ordered by average total costs, from lowest to highest.

[b]Dominant indicates this strategy is less costly and more effective than no screening.

[c]For analyses with more than two interventions, a sequential analysis of cost-effectiveness is conducted following the CADTH guidelines for economic evaluation. In this analysis, dominated interventions were excluded.

Based on results in Tables 20A and 20B, we could observe that the differences in QALYs between the examined strategies were small (e.g., up to 0.008 in QALYs gained and 0.017 in QALYs lost) as compared to the difference in costs (savings of up to $635 and $754; see Table 20, A and B).

Figure 9A presents the probabilities of cost-effectiveness of all examined strategies for preconception carrier screening (all given conditions), assuming the newborn utility for QALY calculation and no use of novel therapies. Universal screening with standard panels was associated with the highest probability of cost-effectiveness for values below $45,000 per QALY lost (from about 99% at $0 to about 40% at a value of $50,000 per QALY lost). The no screening strategy was more likely to be cost-effective at values of $50,000 and $100,000 per QALY lost (probability of 59% and 89%, respectively). Of note, the willingness-to-pay values for evaluating cost-effectiveness of interventions associated with a loss in the QALY are less researched and may be quite different from the commonly used willingness-to-pay values suggested for interventions associated with a gain in the QALY.

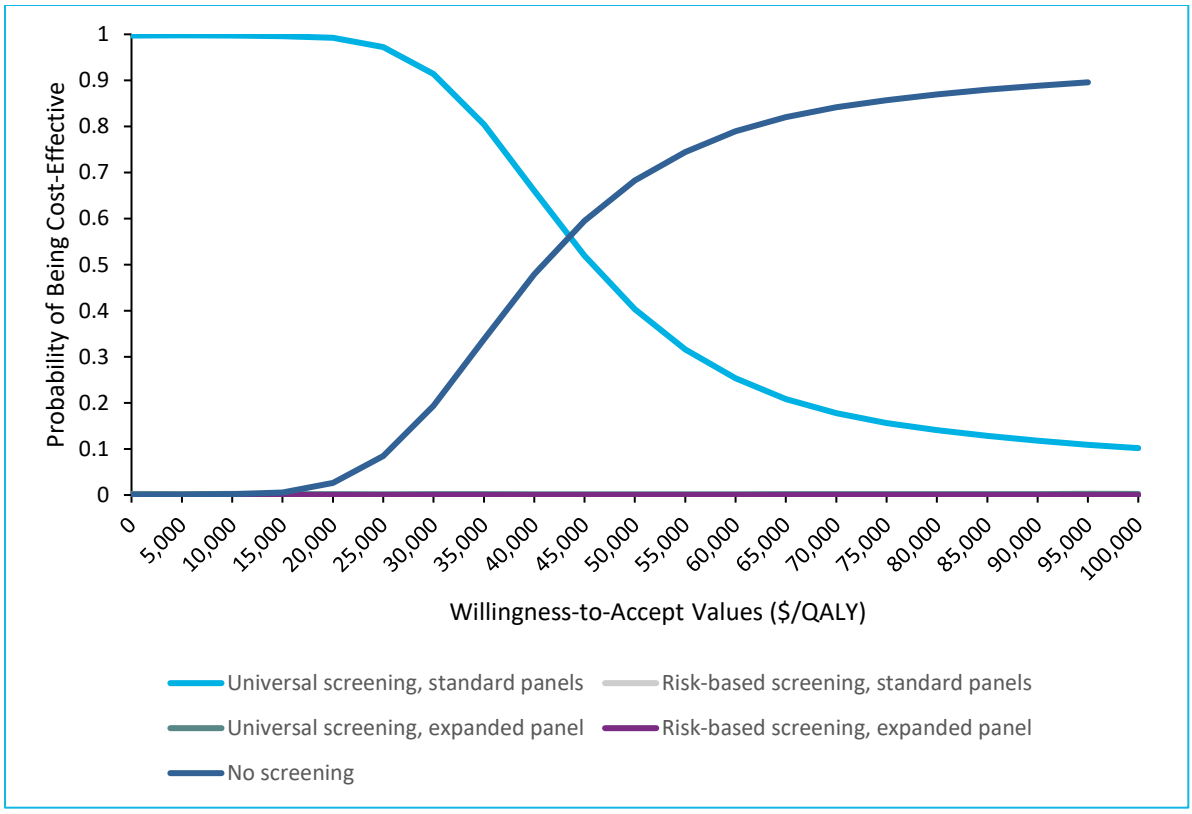

Figure 9A: Cost-Effectiveness Acceptability Curve, Preconception Carrier Screening: Newborn's Utility and No Use of Novel Therapies

Abbreviation: QALY, quality-adjusted life-year.

Graph showing the probability of preconception carrier screening strategies being cost-effective plotted against willingness-to-accept values when the QALYs were estimated using newborn's utility. It is applicable to the long-term analysis in which we accounted for the cost of supportive therapies only. At a value of $0 per QALY lost, universal screening with standard panels has a probability of 1 of being cost-effective, decreasing to near 0.1 as willingness-to-accept value increases to $100,000 per QALY lost. At a value of $0 per QALY lost, no screening has a probability of 0 of being cost-effective, increasing to near 0.9 as willingness-to-accept value increases to $100,000 per QALY lost. All other strategies have a probability of near 0 of being cost-effective for any value below $100,000 per QALY lost.

Figure 9B presents the probabilities of cost-effectiveness of all examined strategies for preconception carrier screening (all given conditions) assuming the parent utility and no use of novel therapies. Universal screening with standard panels was associated with the highest probability of cost-effectiveness, which was about 99% at the value of $50,000 per QALY gained and about 97% at $100,000 per QALY gained. Universal screening with expanded (multi-disease) panel was most likely to become cost-effective at large willingness-to-pay values of over $600,000 per QALY gained.

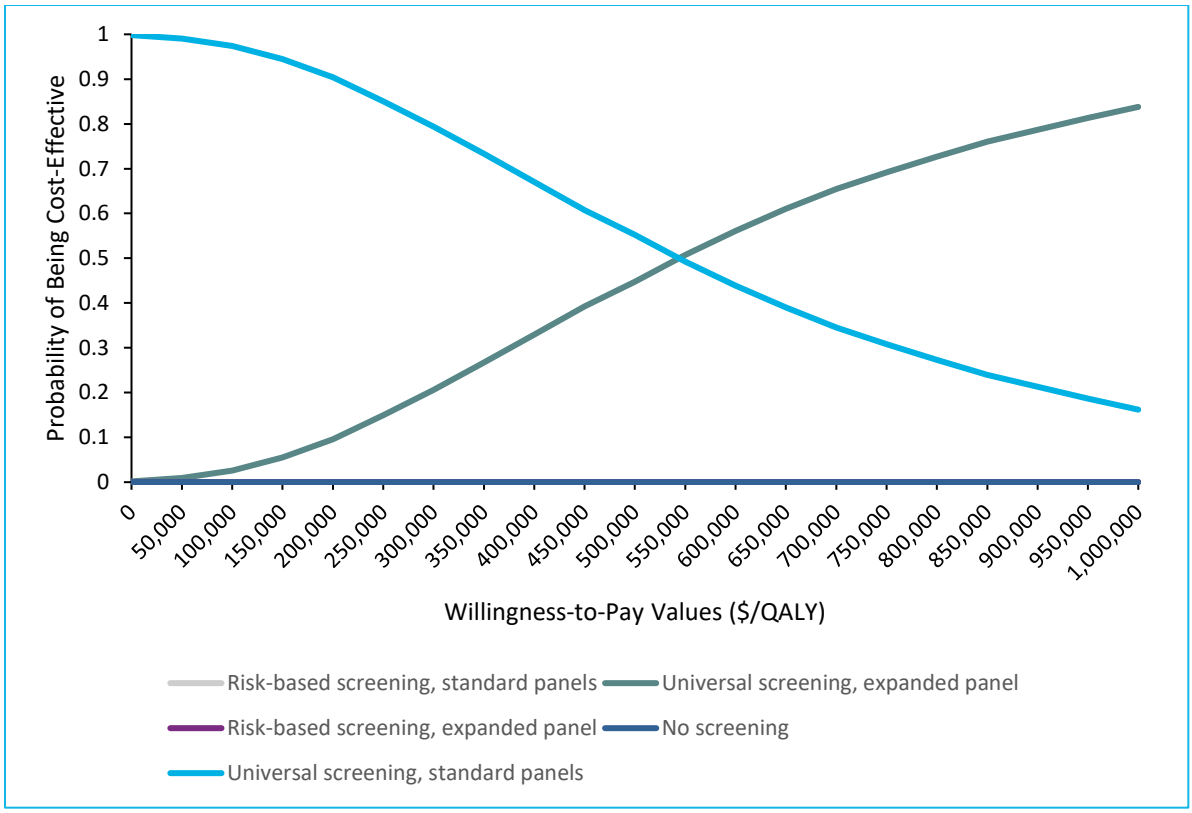

Figure 9B: Cost-Effectiveness Acceptability Curve, Preconception Carrier Screening: Parents' Utility and No Use of Novel Therapies

Abbreviation: QALY, quality-adjusted life-year.

Graph showing the probability of preconception carrier screening strategies being cost-effective plotted against willingness-to-pay values, when the QALYs were estimated using parents' utility. It is applicable to the long-term analysis in which we accounted for the cost of supportive therapies only. At a value of $0 per QALY gained, universal carrier screening with standard panels has a probability of almost 1 of being cost-effective, decreasing to near 0.2 as willingness-to-pay value increases to $1,000,000 per QALY gained. At a value of $0 per QALY gained, universal screening with expanded panel has a probability of 0 of being cost-effective, increasing to near 0.9 as willingness-to-pay value increases to $1,000,000 per QALY gained. All other strategies have a probability of near 0 of being cost-effective for any value below $1,000,000 per QALY gained.

Preconception Carrier Screening: Scenarios With Use of Novel Therapies

In these scenarios, we accounted for additional large costs of novel therapies for CF and SMA and assumed improvements in health outcomes (e.g., survival or utilities). From the newborn utility perspective (all given conditions), the least costly strategy was universal screening with expanded panel (Table 21A); as expected, this strategy was also associated with the largest loss in QALYs. No screening was the most expensive strategy, but also resulted in more QALYs (i.e., the least QALY loss) compared with the preconception carrier screening options.

Table 21A: Long-Term Scenario Analysis (Newborn's Utility, Novel Therapies): Cost–Utility of Preconception Carrier Screening for the Given Conditions

Strategy	Average total costs, $[a] (95% CrI)	Average total effects (95% CrI), QALY	ICER, $/QALY lost	
			Versus no screening	Sequential ICER (excluding dominated)[b]
Universal, expanded panel	14,912.26 (10,280.65–21,258.39)	40.0341 (40.005–40.058)	363,317.52	—
Universal, standard panels	15,072.17 (10,247.42–21,634.243)	40.0352 (40.006–40.058)	380,693.77	135,715.23
Risk-based, expanded panel	20,521.84 (13,976.02–29,267.98)	40.0495 (40.023–40.069)	360,400.44	Dominated
Risk-based, standard panels	20,533.18 (13,970.04–29,329.51)	40.0496 (40.023–40.069)	377,592.16	Dominated
No screening	20,947.84 (14,234.77–29,858.46)	40.0507 (40.024–40.070)	—	380,693.77

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.
[a]Treatment strategies are ordered by average total costs, from lowest to highest.
[b]Extended dominance.

After assuming the parent utility for QALY calculation and use of novel therapies for CF and SMA, all preconception carrier screening options were dominant or cost saving (i.e., less expensive and more effective) compared with no screening (Table 21B). In a sequential analysis, universal screening with expanded panel was the most cost-effective option that dominated all other carrier screening strategies.

Table 21B: Long-Term Scenario Analysis (Parent's Utility, Novel Therapies): Cost–Utility of Preconception Carrier Screening for the Given Conditions

Strategy	Average total costs, $[a] (95% CrI)	Average total effects (95% CrI), QALY	ICER, $/QALY gained	
			Versus no screening[b]	Sequential ICER (excluding dominated)[c]
Universal, expanded panel	13,270.25 (9,146.69–18,854.84)	33.9170 (33.898–33.931)	Dominant	—
Universal, standard panels	13,367.83 (9,085.92–19177.91)	33.9164 (33.897–33.930)	Dominant	Dominated
Risk-based, expanded panel	18,173.15 (12,358.10–25,919.41)	33.9096 (33.888–33.925)	Dominant	Dominated
Risk-based, standard panels	18,180.05 (12,344.96–25,942.626)	33.9095 (33.888–33.925)	Dominant	Dominated
No screening	18,545.06 (12,585.63–26,448.52)	33.9090 (33.887–33.925)	—	Dominated

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

[a]Treatment strategies are ordered by average total costs, from lowest to highest.

[b]Dominant indicates this strategy is less costly and more effective than no screening.

[c]Strong dominance.

Based on results in Tables 21A and 21B, we observe that the differences in QALYs between the examined strategies were relatively small (e.g., up to 0.008 in QALYs gained and 0.017 in QALYs lost) as compared to the difference in costs (savings up to $5,275 and $6,036).

Figure 10A presents the probabilities of cost-effectiveness of all examined strategies for preconception carrier screening (all given conditions) from the newborn utility perspective, including use of novel therapies. Universal screening with expanded panel was associated with the highest probability of cost-effectiveness for willingness-to-accept below $100,000 per QALY lost (from about 74% at $75,000 to about 57% at $100,000 per QALY lost). Universal screening with standard panels and no screening superseded the expanded panel option at higher values (> $175,000 per QALY lost).

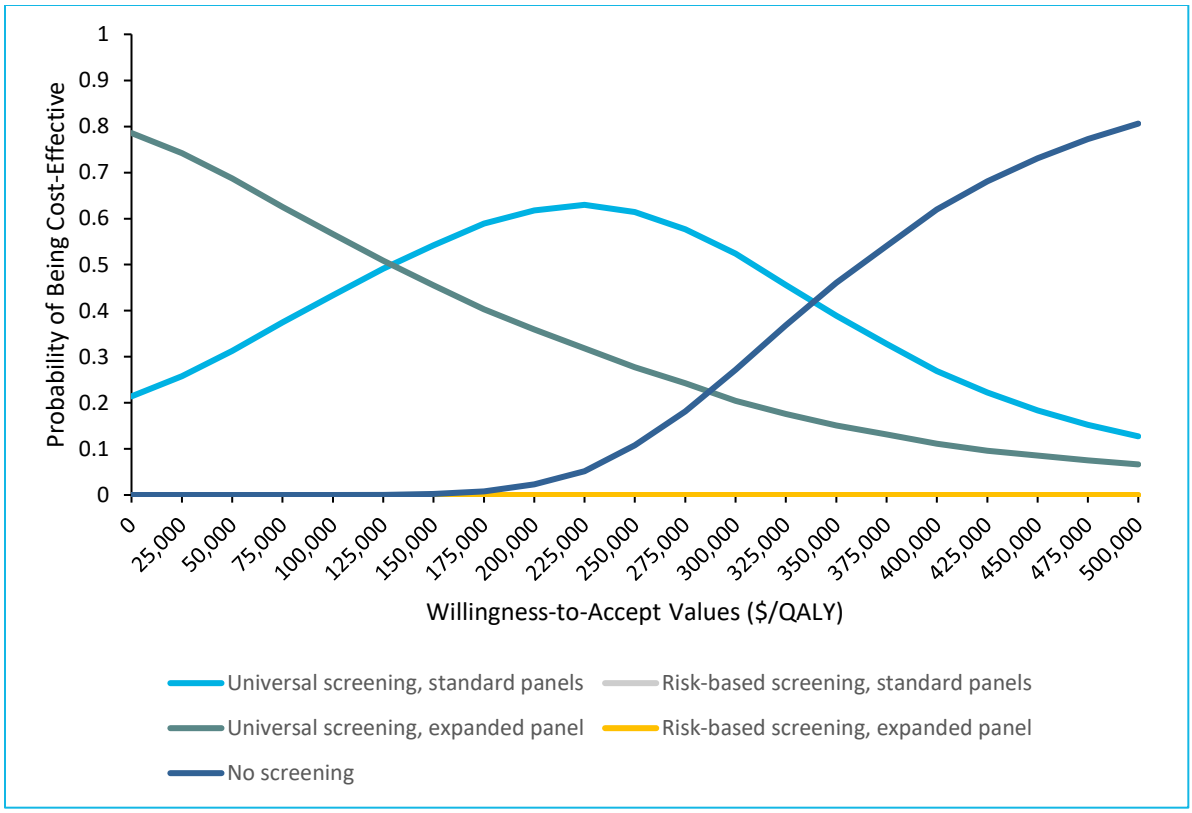

Figure 10A: Cost-Effectiveness Acceptability Curve, Preconception Carrier Screening: Newborn's Utility and Use of Novel Therapies

Abbreviation: QALY, quality-adjusted life-year.

Graph showing the probability of preconception carrier screening strategies being cost-effective plotted against willingness-to-accept values, when the QALYs were estimated using newborn's utility. It is applicable to the long-term analysis in which we accounted for the cost of novel therapies. At a value of $0 per QALY lost, universal screening with expanded panel has a probability of 0.8 of being cost-effective, decreasing to near 0 as willingness-to-accept value increases to $500,000 per QALY lost. At a value of $0 per QALY lost, universal screening with standard panels has a probability of about 0.2 of being cost-effective, initially increasing to about 0.6 as the willingness-to-accept value increases to about $225,000 per QALY lost, before decreasing to about 0.1 as the value approaches $500,000 per QALY lost. All other strategies have a probability of near 0 of being cost-effective for any value below $500,000 per QALY lost.

Figure 10B presents the probabilities of cost-effectiveness for all examined strategies for preconception carrier screening (all given conditions), assuming the parent utility and use of novel therapies. Universal screening with expanded panel was associated with the highest probability of cost-effectiveness, ranging from 75% to 79% at the commonly used willingness-to-pay values of $50,000 and $100,000 per QALY gained.

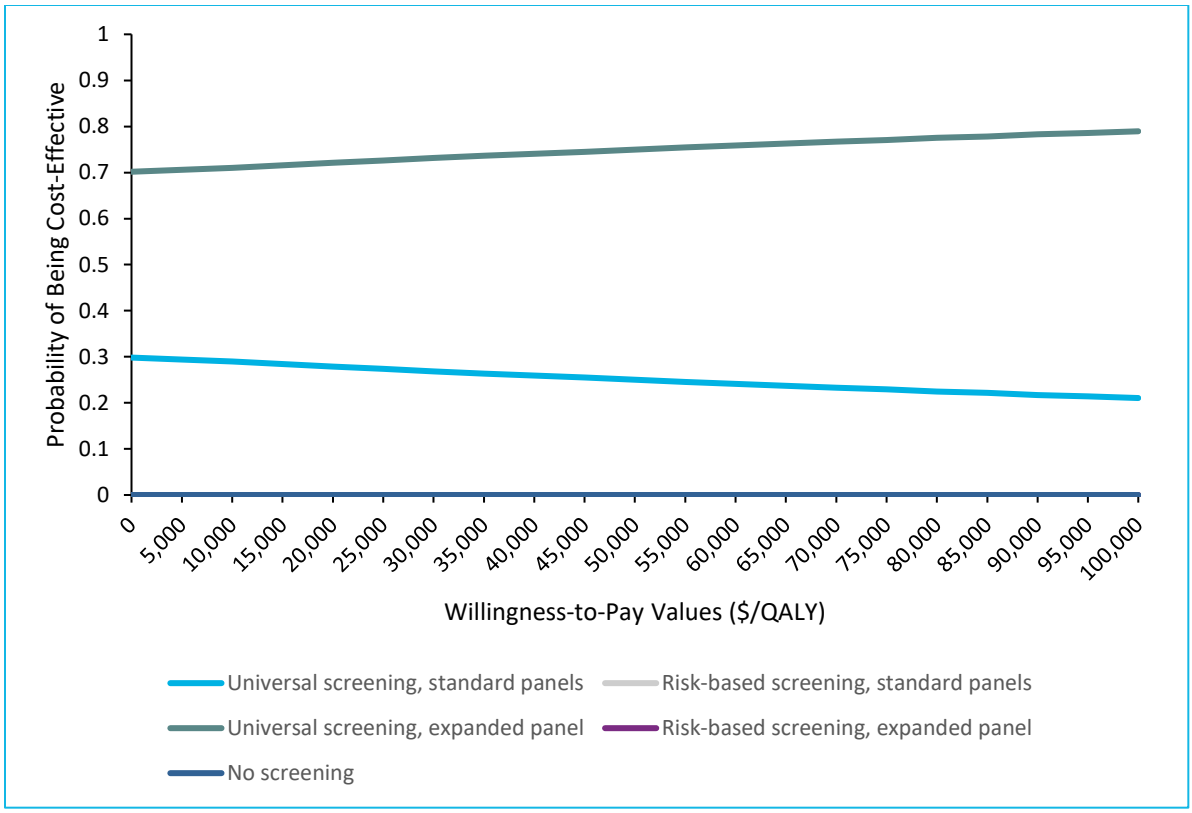

Figure 10B: Cost-Effectiveness Acceptability Curve, Preconception Carrier Screening: Parent's Utility and Use of Novel Therapies

Abbreviation: QALY, quality-adjusted life-year.

Graph showing the probability of preconception carrier screening strategies being cost-effective plotted against willingness-to-pay values when the QALYs were estimated using parents' utility. It is applicable to the long-term analysis in which we accounted for the cost of novel therapies. At a value of $0 per QALY gained, universal screening with expanded panel has a probability of 0.7 of being cost-effective, increasing to about 0.8 as willingness-to-pay increases to $100,000 per QALY gained. At a value of $0 per QALY, universal screening with standard panels has a probability of 0.3 of being cost-effective, decreasing to about 0.2 as the cost-effectiveness willingness-to-pay value approaches $100,000 per QALY gained. All other strategies have a probability of near 0 of being cost-effective for any value below $100,000 per QALY gained.

Long-Term Scenarios: Cost–Utility of Prenatal Carrier Screening Programs

In summary, the results of long-term scenario analyses related to prenatal carrier screening showed similar trends to the corresponding results for preconception carrier screening.

Prenatal Carrier Screening: Scenarios Without Use of Novel Therapies

Over a newborn's lifetime, assuming the use of supportive or standard (no novel) therapies for the given conditions, no screening was more expensive but resulted in more QALYs compared with all four prenatal carrier screening options, but the QALY difference between the strategies was small (Table 22A).

Table 22A: Long-Term Scenario Analysis (Newborn's Utility and No Use of Novel Therapies): Cost–Utility of Prenatal Carrier Screening for the Given Conditions

Strategy	Average total costs, $[a] (95% CrI)	Average total effects (95% CrI), QALY	ICER, $/QALY lost	
			Versus no screening	Sequential ICER (excluding dominated)[b]
Universal, standard panels	4,631.33 (3,333.62–6,399.99)	40.0332 (40.01–40.06)	39,288.32	—
Universal, expanded panel	4,942.89 (3,627.68–6,680.69)	40.0320 (40.00–40.05)	16,787.01	Dominated
Risk-based, standard panels	5,173.92 (3,658.59–7,156.91)	40.0469 (40.02–40.07)	34,978.14	Dominated
Risk-based, expanded panel	5,196.34 (3,681.38–7,178.56)	40.0468 (40.02–40.07)	12,646.87	Dominated
No screening	5,210.61 (3,681.94–7,213.52)	40.0479 (40.02–40.07)	—	39,288.32

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

[a]Treatment strategies are ordered by average total costs, from lowest to highest.

[b]Extended dominance (i.e., risk-based, standard panels) or strong dominance (i.e., universal or risk-based expanded panel).

As shown in Table 22B, assuming the parent utility for the QALY calculation and no use of novel therapies, all carrier screening strategies were less expensive and more effective than the no screening option. In a sequential analysis, universal screening with expanded panel was associated with an ICER of $610,795 per QALY gained, compared with universal screening with standard panels. The price threshold analysis showed that the per-person cost of an expanded (multi-disease) test had to decrease from $657 (reference case) to about $234 for this strategy to become cost saving compared to the universal standard panel strategy. At the panel price of $270 per person, the expanded panel option would become cost-effective at a willingness-to-pay of $50,000 per QALY gained and, at $305 per person, it would become cost-effective at willingness-to-pay of $100,000 per QALY gained.

Table 22B: Long-Term Scenario Analysis (Parents' Utility and No Use of Novel Therapies): Cost–Utility of Prenatal Carrier Screening for the Given Conditions

Strategy	Average total costs, $[a] (95% CrI)	Average total effects (95% CrI), QALY	ICER, $/QALY gained	
			Versus no screening[b]	Sequential ICER (excluding dominated)[c]
Universal, standard panels	4,100.62 (2,963.22–5,628.41)	33.9134 (33.8935–33.9276)	Dominant	—
Universal, expanded panel	4,421.41 (3,265.95–5,955.02)	33.9140 (33.894–33.9280)	Dominant	610,795.20
Risk-based, standard panels	4,553.71 (3,233.03–6,293.34)	33.9073 (33.8853–33.9233)	Dominant	Dominated
Risk-based, expanded panel	4,576.54 (3,260.21–6,314.539)	33.9074 (33.8853–33.9233)	Dominant	Dominated
No screening	4,583.55 (3,252.926–6,340.97)	33.9069 (33.8847–33.9230)	—	Dominated

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

[a]Treatment strategies are ordered by average total costs, from lowest to highest.

[b]Dominant indicates this strategy is less costly and more effective than no screening.

[c]Strong dominance

Figure 11A presents the probabilities of cost-effectiveness of all examined strategies for prenatal carrier screening of all given conditions, assuming the newborn utility for QALY calculation and no use of novel therapies. Universal screening with standard panels was associated with the highest probability of cost-effectiveness for willingness-to-accept values below $40,000 per QALY lost (from about 98% at $0 to about 45% at a value of $40,000 per QALY lost). No screening became more favorable (83% and 99% cost-effective) at values of $50,000 and $100,000 per QALY lost.

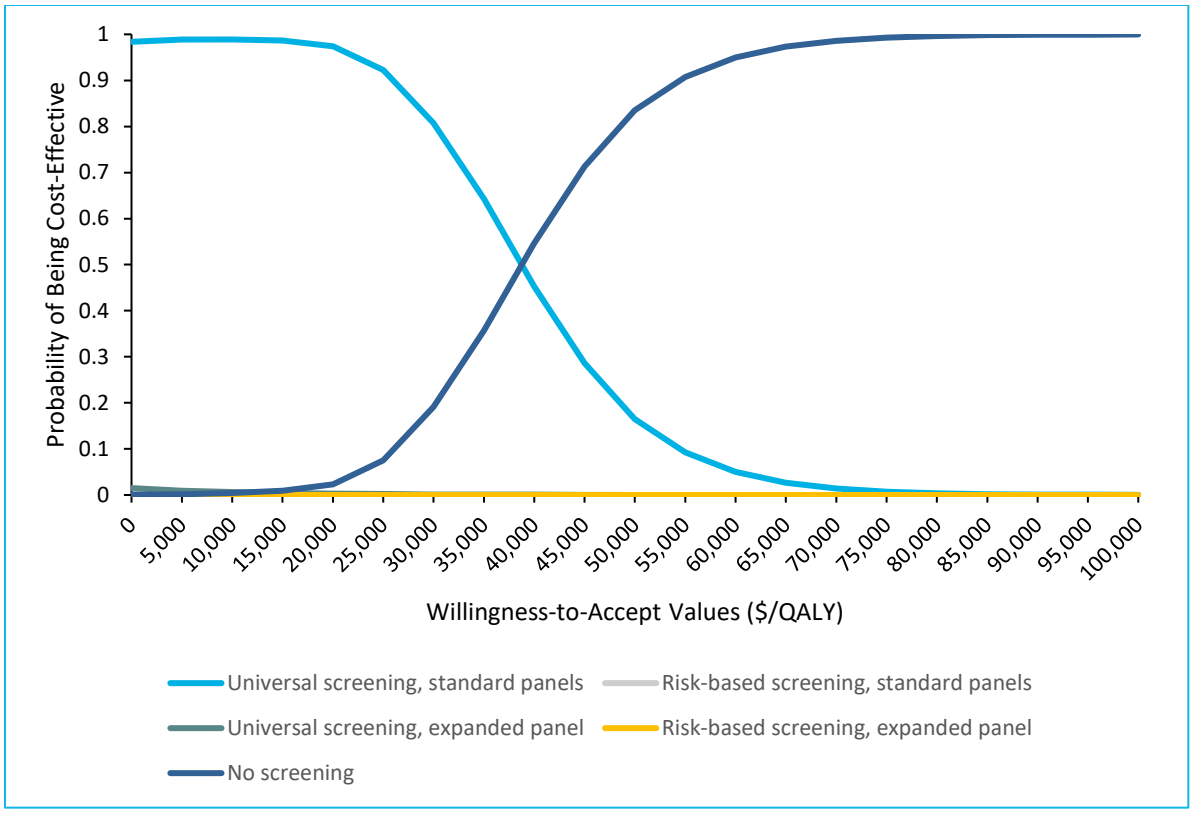

Figure 11A: Cost-Effectiveness Acceptability Curve, Prenatal Carrier Screening: Newborn's Utility and No Use of Novel Therapies

Abbreviation: QALY, quality-adjusted life-year.

Graph showing the probability of prenatal carrier screening strategies being cost-effective plotted against willingness-to-accept values when the QALYs were estimated using newborn's utility. It is applicable to the long-term analysis in which we accounted for the cost of supportive therapies only. At a value of $0 per QALY lost, universal screening with standard panels has a probability of about 1 of being cost-effective, decreasing to about 0 as the value increases to $100,000 per QALY lost. At a value of $0 per QALY lost, no screening has a probability of 0 of being cost-effective, increasing to about 1 as the value approaches $100,000 per QALY lost. All other strategies have a probability of near 0 of being cost-effective for any value below $100,000 per QALY lost.

Figure 11B presents the probabilities of cost-effectiveness of all examined strategies for prenatal carrier screening of the given conditions, assuming the parent utility for QALY calculations and no use of novel therapies. Of all strategies, universal screening with standard panels was most likely to be cost-effective at commonly used willingness-to-pay values of $50,000 and $100,000 per QALY gained (with a probability of about 99%). Over larger cost-effectiveness values, universal screening with expanded panel became more favorable, with the probability of being cost-effective starting from 1% at a value of $100,000 per QALY gained, and rising to 50% at $650,000 and 76% at $1,000,000 per QALY gained.

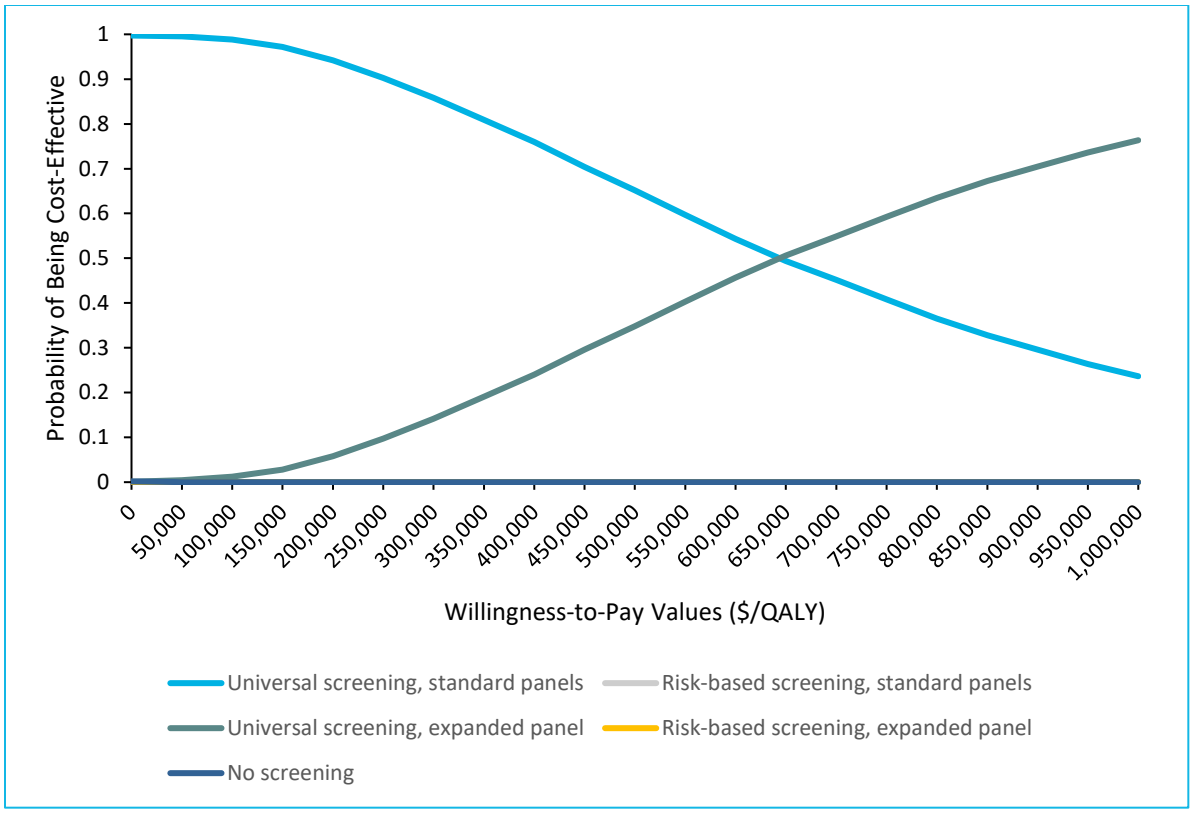

Figure 11B: Cost-Effectiveness Acceptability Curve, Prenatal Carrier Screening: Parents' Utility and No Use of Novel Therapies

Abbreviation: QALY, quality-adjusted life-year.

Graph showing the probability of prenatal carrier screening strategies being cost-effective plotted against willingness-to-pay values when the QALYs were estimated using parents' utility. It is applicable to the long-term analysis in which we accounted for the cost of supportive therapies only. At a value of $0 per QALY gained, universal screening with standard panels has a probability of about 1 of being cost-effective, decreasing to about 0.2 as the value increases to $1,000,000 per QALY gained. At a value of $0 per QALY gained, universal screening with expanded panel has a probability of 0 of being cost-effective, increasing to about 0.7 as the willingness-to-pay value approaches $1,000,000 per QALY gained. All other strategies have a probability of near 0 of being cost effective for any value below $1,000,000 per QALY gained.

Prenatal Carrier Screening: Scenarios With Use of Novel Therapies

After assuming the newborn utility for QALY calculation and accounting for the costs and benefits of novel therapies, we found that the strategy associated with the smallest costs (but the largest loss in QALYs) was universal screening with expanded panel (Table 23A). The no-screening option was the most expensive, but also resulted in more QALYs (i.e., the least QALY loss) compared with the prenatal carrier screening options. In general, the QALY difference between all strategies was quite small.

Table 23A: Long-Term Scenario Analysis (Newborn's Utility, Novel Therapies): Cost–Utility of Prenatal Carrier Screening for the Given Conditions

Strategy	Average total costs, $[a] (95% CrI)	Average total effects (95% CrI), QALY	ICER, $/QALY lost	
			Versus no screening	Sequential ICER (excluding dominated)
Universal, expanded panel	15,854.50 (10,877.40–22,567.27)	40.0340 (40.0053–40.0559)	305,208.95	—
Universal, standard panels	15,953.92 (10,852.68–22,878.97)	40.0352 (40.0064–40.0570)	322,129.73	83,885.49
Risk-based, expanded panel	20,588.53 (13,995.75–29,341.11)	40.0495 (40.0231–40.0692)	302,567.17	Dominated[b]
Risk-based, standard panels	20,595.59 (13,996.84–29,367.25)	40.0496 (40.0232–40.0693)	319,289.15	Dominated[b]
No screening	20,947.84 (14,234.77–29,858.46)	40.0507 (40.0243–40.0704)	—	322,129.73

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

[a]Treatment strategies are ordered by average total costs, from lowest to highest.

[b]This strategy is dominated through extended dominance, which means it would never be the optimal intervention regardless of the willingness-to-pay.

Assuming the parent utility for QALY calculation and after accounting for the use of novel therapies, all prenatal carrier screening options were dominant (i.e., less costly and more effective) compared with no screening (Table 23B). In a sequential analysis where all strategies were compared together, universal screening with expanded panel was the most cost-effective option. However, the difference in QALYs between the screening strategies was very small.

Table 23B: Long-Term Scenario Analysis (Parent's Utility, Novel Therapies): Cost–Utility of Prenatal Carrier Screening for the Given Conditions

Strategy	Average total costs, $[a] (95% CrI)	Average total effects (95% CrI), QALY	ICER, $/QALY gained	
			Versus no screening[b]	Sequential ICER (excluding dominated)[c]
Universal, expanded panel	14,101.15 (9,689.52-20,034.38)	33.9155 (33.8959-33.9295)	Dominant	—
Universal, standard panels	14,147.17 (9,627.19-20,286.39)	33.9150 (33.8951-33.9292)	Dominant	Dominated
Risk-based, expanded panel	18,231.95 (12,398.87-25,985.69)	33.9095 (33.8875-33.9254)	Dominant	Dominated
Risk-based, standard panels	18,235.21 (12,396.40-26,004.75)	33.9094 (33.8875-33.9254)	Dominant	Dominated
No screening	18,545.06 (12,585.63-26,448.52)	33.9090 (33.8870-33.9250)	—	Dominated

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

[a]Treatment strategies are ordered by average total costs, from lowest to highest.

[b]Dominant indicates this strategy is less costly and more effective than no screening.

[c]Strong dominance.

Figure 12A presents the probabilities of cost-effectiveness of all examined strategies for prenatal carrier screening (all given conditions) assuming the newborn utility for QALY calculation and use of novel therapies. Universal screening with expanded panel was associated with the highest probability of being cost-effective for most willingness-to-accept values below $100,000 per QALY lost (from about 58% at $50,000 to about 45% at $100,000 per QALY lost). Universal screening with standard panels and no screening superseded the expanded panel option at values over $100,000 per QALY lost.

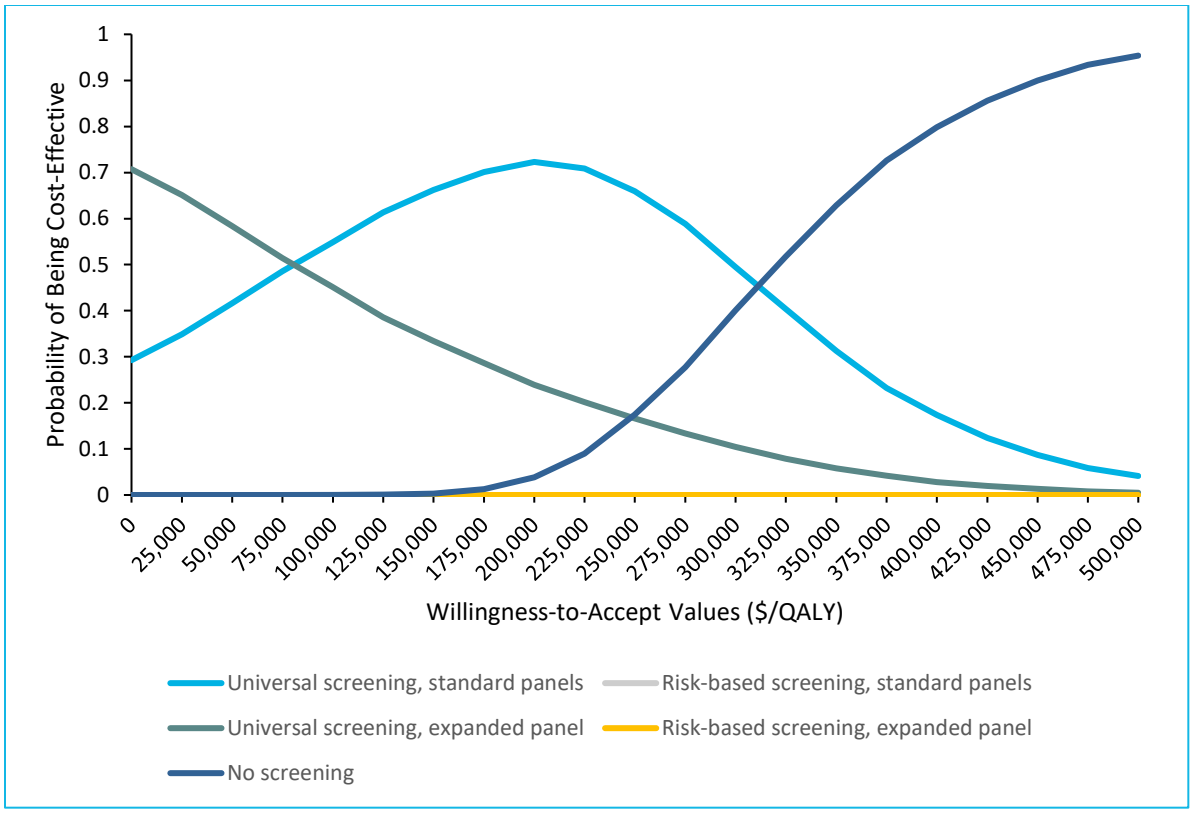

Figure 12A: Cost-Effectiveness Acceptability Curve, Prenatal Carrier Screening: Newborn's Utility and Use of Novel Therapies

Abbreviation: QALY, quality-adjusted life-year.

Graph showing the probability of prenatal carrier screening strategies being cost-effective plotted against willingness-to-accept values when the QALYs were estimated using newborn's utility. It is applicable to the long-term analysis in which we accounted for the cost of novel therapies. At a value of $0 per QALY lost, universal screening with expanded panel has a probability of about 0.75 of being cost-effective, decreasing to about 0 as the value increases to $500,000 per QALY lost. At a value of $0 per QALY lost, universal screening with standard panels has a probability of about 0.29 of being cost- effective, increasing to about 0.72 as cost approaches $220,000 per QALY lost, and then decreasing to about 0.05 as the value approaches $500,000 per QALY lost. At a value of $0 per QALY lost, no screening has a probability of 0 of being cost-effective, increasing to about 1 as the value increases to $500,000 per QALY lost. All other strategies have a probability of near 0 of being cost-effective for any value below $500,000 per QALY lost.

Figure 12B presents the probabilities of cost-effectiveness for all examined strategies for prenatal carrier screening (all given conditions), assuming the parent utility for QALY calculation and use of novel therapies. Universal screening with expanded panel was associated with the highest probability of cost-effectiveness, ranging from 66% to 70% at the commonly used willingness-to-pay values of $50,000 and $100,000 per QALY gained.

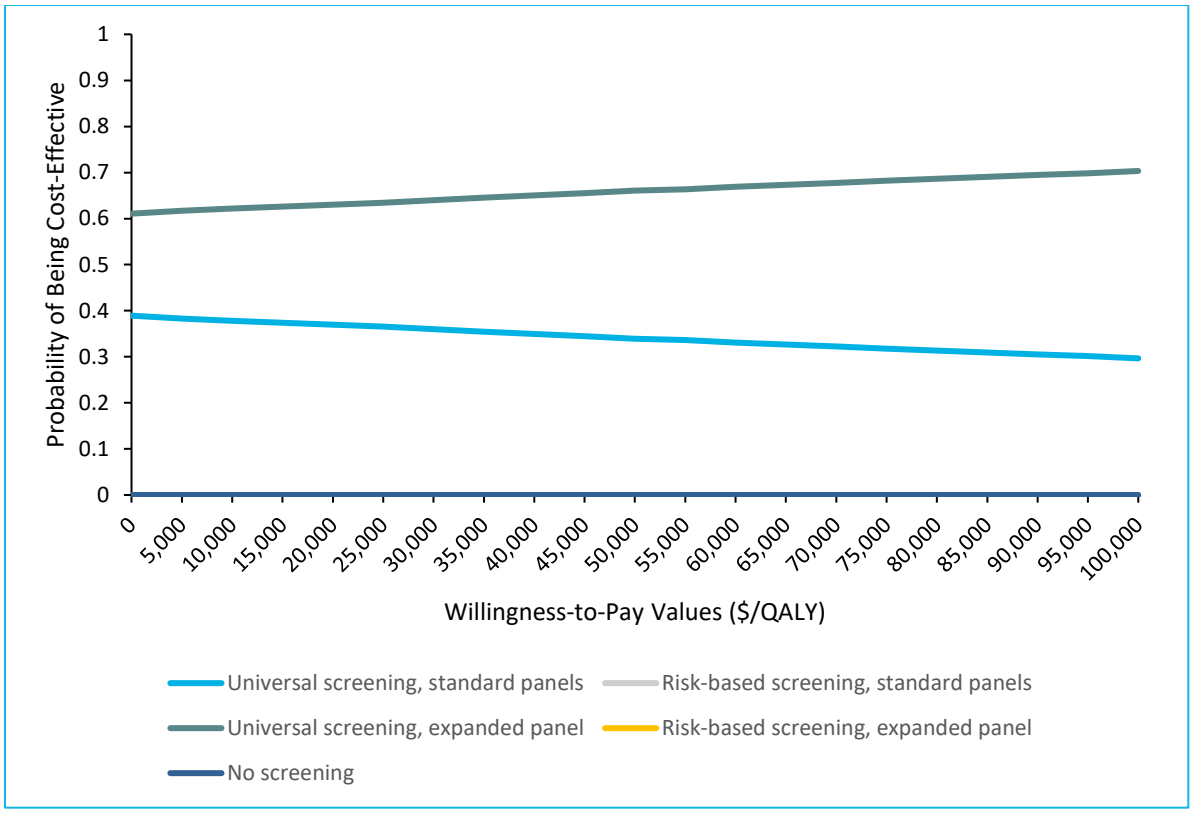

Figure 12B: Cost-Effectiveness Acceptability Curve, Prenatal Carrier Screening: Parents' Utility and Use of Novel Therapies

Abbreviation: QALY, quality-adjusted life-year.

Graph showing the probability of prenatal carrier screening strategies being cost effective plotted against willingness-to-pay values when the QALYs were estimated using parents' utility. It is applicable to the long-term analysis in which we accounted for the cost of novel therapies. At a value of $0 per QALY gained, universal screening with expanded panel has a probability of about 0.6 of being cost-effective, increasing to about 0.7 as the willingness-to-pay value increases to $100,000 per QALY gained. At a value of $0 per QALY gained, universal screening with standard panels has a probability of about 0.4 of being cost-effective, decreasing to about 0.3 as the willingness-to-pay approaches $100,000 per QALY gained. All other strategies have a probability of near 0 of being cost-effective for any value below $100,000 per QALY gained.

Discussion

We conducted a full economic evaluation to determine the cost-effectiveness of universal or risk-based preconception and prenatal carrier screening programs for CF, FXS, hemoglobinopathies and thalassemia, and SMA in Ontario.

Our reference case cost-effectiveness analyses followed health and cost outcomes over the period of one pregnancy (singleton birth) and found that couples who participated in either preconception or prenatal carrier screening programs had a smaller chance of having an affected birth compared to those who chose no screening. Universal carrier screening program options identified more at-risk couples and pregnancies and were associated with higher probabilities of prenatal diagnostic testing or voluntary termination of pregnancy. When the testing was part of the preconception carrier screening, at-risk couples in universal screening options had a greater chance of choosing

reproductive assistive technology options such as IVF/PGT-M or adoption. As expected, all screening program options were associated with additional costs compared to no screening.

When we compared all strategies together, we found that universal screening with standard panels is the most cost-effective screening option for both preconception and prenatal carrier screening programs. Compared to no screening, one would need to pay an additional $367,731 per affected birth avoided, as detected by the preconception carrier screening with standard panels (Table 18B). One would need to pay an additional $431,807 per affected birth avoided, as detected by the prenatal carrier screening pathway with standard panels (Table 19B). The concern with interpretation of these large values of the ICER is related to the value of the lost life. The ICERs associated with other clinical outcomes such as at-risk pregnancy or at-risk couples were smaller. In the preconception period, the ICER was about $29,106 per additional at-risk pregnancy detected and, in the prenatal period, it was about $29,759 per additional at-risk pregnancy detected. To our knowledge, there is no established willingness-to-pay (willingness-to-accept) value that a decision-maker would accept as rational for the health outcomes reported in the natural units (e.g., affected birth, at-risk pregnancy). Therefore, in general, the ICERs estimated in our cost-effectiveness analyses need to be interpreted with caution. Moreover, one could notice overlapping 95% CrIs estimated around the means of above-mentioned effectiveness outcomes for all examined interventions, meaning similar effectiveness of all carrier screening options. Given this, it could be reasonable to focus interpretation of our results on cost differences between the screening strategies and on potential savings shown in the long-term cost-effectiveness and budget impact analyses.

As part of our sensitivity analysis, we examined factors that could change the cost-effectiveness of the short-term reference case analyses. We identified uncertainties and changes in the ICERs with changes in the values of the following parameters: condition-specific carrier frequency, rate of participation in the screening, rate of condition-specific voluntary termination of pregnancy, cost of care alongside the carrier screening pathway, cost of IVF with PGT-M (applicable to preconception carrier screening only), and administrative costs of carrier screening programs. The ICER was most sensitive to changes in the carrier frequency parameter. When the carrier frequency for CF or SMA was assumed to be 10 times higher than that of the reference case, the ICER of universal screening with standard panels versus no screening decreased from about $367,730 per affected birth averted in the reference case to below $65,000 per affected birth averted. Although this analysis is hypothetical, it might help in considering a question related to estimation of a general carrier frequency threshold (for all rare diseases) at which a decision-maker would consider recommending genetic carrier testing (based on its value for money).

It is important to understand that our reference case analysis assumed a conservative screening care pathway associated with the largest costs. The screening pathway was structured according to similar current clinical practice, which occurs mostly in the specialist care setting. However, for a population-based screening program to be more feasible, we would need to consider alternative screening pathways that switch pre-test counselling out of specialist care to front-line and primary care physicians (e.g., Scenario 2, Appendix 8). Our sensitivity analyses suggested that some savings could be achieved with rationalization of medical services provided by genetic counsellors, but feasibility studies are needed to delineate the most sustainable and efficient models of care for future carrier screening programs. In addition to challenges related to having enough health human resources, or more specifically large numbers of genetic counsellors to support universal approaches, we used information on an hourly rate of pay from prior literature (and asked experts to

cross-check our mean and higher estimates of the rate). All our analyses were probabilistic, assuming a standard error around the hourly rate of pay of 25% to capture variation in this cost estimate. Nevertheless, there is a large uncertainty, and the rate of pay could change from year to year, depending on various factors and contract negotiations. Therefore, the number of genetic counsellors needed and their pay for universal carrier screening programs need to be corroborated by future research.

We conducted several long-term cost–utility analyses despite many limitations with using QALY as a measure of health outcomes for genetic conditions. To address some of the limitations, we estimated QALYs from both the newborn's and the couple's perspectives. In these long-term analyses, in addition to previously reported costs of screening (including testing, prenatal diagnostics, and reproductive choice), we accounted for the costs of supportive treatments or novel therapies and the costs of the programs. We found that the QALY changes (the mean QALY loss in the newborn utility perspective or the mean QALY gain in the couple/parent utility perspective) were consistently small between the screening and no-screening options (about or less than 0.01 QALYs). Also, there was a large overlap of the 95% credible intervals around the mean QALY estimate between the strategies, suggesting a large uncertainty and a small difference. Therefore, as mentioned above, the main interpretation of our long-term cost–utility analysis results could be a decrease in total costs with all screening options compared to no screening (i.e., there could be a cost savings). The savings were particularly pronounced with universal carrier screening options used in the preconception or prenatal stage. When we further examined the uncertainty around the ICERs calculated for preconception carrier screening from the couple perspective, assuming no use of novel therapies, we found that universal screening with standard panels was associated with the highest probability of cost-effectiveness: over 97% at values of $50,000 and $100,000 per QALY gained. After the inclusion of expensive novel therapies for CF and SMA, universal screening with expanded panel was associated with the highest probability of cost-effectiveness of all screening options (ranging from 75% to 79% at the commonly used willingness-to-pay values of $50,000 and $100,000 per QALY gained, respectively). This finding indicates that a high cost of a hypothetical expanded multi-disease panel could be offset by the high treatment costs of novel therapies currently approved for CF and SMA. We found similar results in long-term prenatal cost–utility analyses.

Strengths and Limitations

Our modelling study provided some new knowledge regarding the short- and long-term benefits and costs of various preconception or prenatal carrier screening options for Ontario. As with any modelling study, our analyses are limited by parameter and structural model assumptions:

- Given the lack of data available for our analyses, we made a simplifying assumption related to the no-screening comparator, which considered no screening of all given conditions (i.e., no genetic carrier testing). However, currently in Ontario, there is an inconsistent approach to risk-based genetic carrier testing for CF, SMA, and FXS (using standard panels) and somewhat organized risk-based carrier testing for hemoglobinopathies and thalassemia
- The clinical parameters from our clinical evidence review were shown to have a wide range of values; hence, some important factors remain uncertain because no relevant clinical data exist for Ontario. Also, carrier frequencies for all given conditions for Ontario are unknown; thus, we probably overestimated the prevalence and cost of testing for hemoglobinopathies and thalassemia as we examined these diseases together. However, based on the results of our sensitivity analysis, we can deduce that a decrease in carrier frequency of any condition

would result in an increase in the reference case ICER. In addition, overall costs of novel therapies used for treating hemoglobinopathies and thalassemia, could be much higher than the estimates used in our analysis,[232,233] which would further result in additional cost savings over the long-term. All of this implies uncertainty in our estimate of the ICER for preconception or prenatal carrier screening programs and the need for future research

- Our reference case assumed the use of currently available infrastructure and equipment, but we accounted for operational costs, usually paid by the Ministry of Health. We explored the programmatic costs of all carrier screening options in scenario analyses
- One of the main assumptions for sequential carrier testing was that there would be enough time for at-risk couples to make their own reproductive choice as informed by screening/testing. In consultation with experts, a sequential approach to carrier testing was a reasonable assumption and a pragmatic way to proceed with carrier testing in Ontario. However, it is possible that, due to time constraints in a prenatal setting, partners would need to be tested simultaneously (concurrently), which would result in higher costs for prenatal carrier screening.

Therefore, a feasibility study to establish possible screening uptake rates, carrier frequency for the given conditions, genetic laboratory capacities, availability, and number of health care providers needed in universal screening options (e.g., genetic counsellors and geneticists), administrative program structure, and the most sustainable and efficient model of care for the screening pathway will facilitate full-scale implementation of a carrier screening program in Ontario.

Conclusions

In the short-term reference case cost-effectiveness analyses for both preconception and prenatal carrier screening programs, we found that no screening was less costly but associated with the highest chance of having a birth affected by CF, FXS, hemoglobinopathies and thalassemia, or SMA. Our modelling study also suggested that preconception or prenatal carrier screening programs identified more pregnancies at risk and provided more reproductive choice options for future parents. In the long-term lifetime cost–utility analyses, we found a small change in QALYs but important cost savings with universal carrier screening programs in either the preconception or prenatal period.

Budget Impact Analysis

Research Questions

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding a universal or risk-based:

- Preconception carrier screening program for cystic fibrosis (CF), fragile X syndrome (FXS), hemoglobinopathies and thalassemia, and spinal muscular atrophy (SMA) for people who are considering a pregnancy?
- Prenatal carrier screening program for the given conditions for people who are currently pregnant?

Methods

Analytic Framework

In our first analysis, we estimated the budget impact of publicly funding universal or risk-based preconception carrier screening programs for CF, FXS, hemoglobinopathies and thalassemia, and SMA for people who are planning a pregnancy. In our second analysis, we estimated the budget impact of publicly funding universal or risk-based prenatal carrier screening programs for the same conditions for people who are pregnant. In both analyses, we estimated the cost difference between two scenarios: (1) current clinical practice without public funding for organized preconception or prenatal carrier screening for all given conditions (the current "no-screening" scenarios), and (2) anticipated clinical practice with public funding for preconception or prenatal carrier screening programs (the new scenarios). Figure 13 presents the budget impact model schematics.

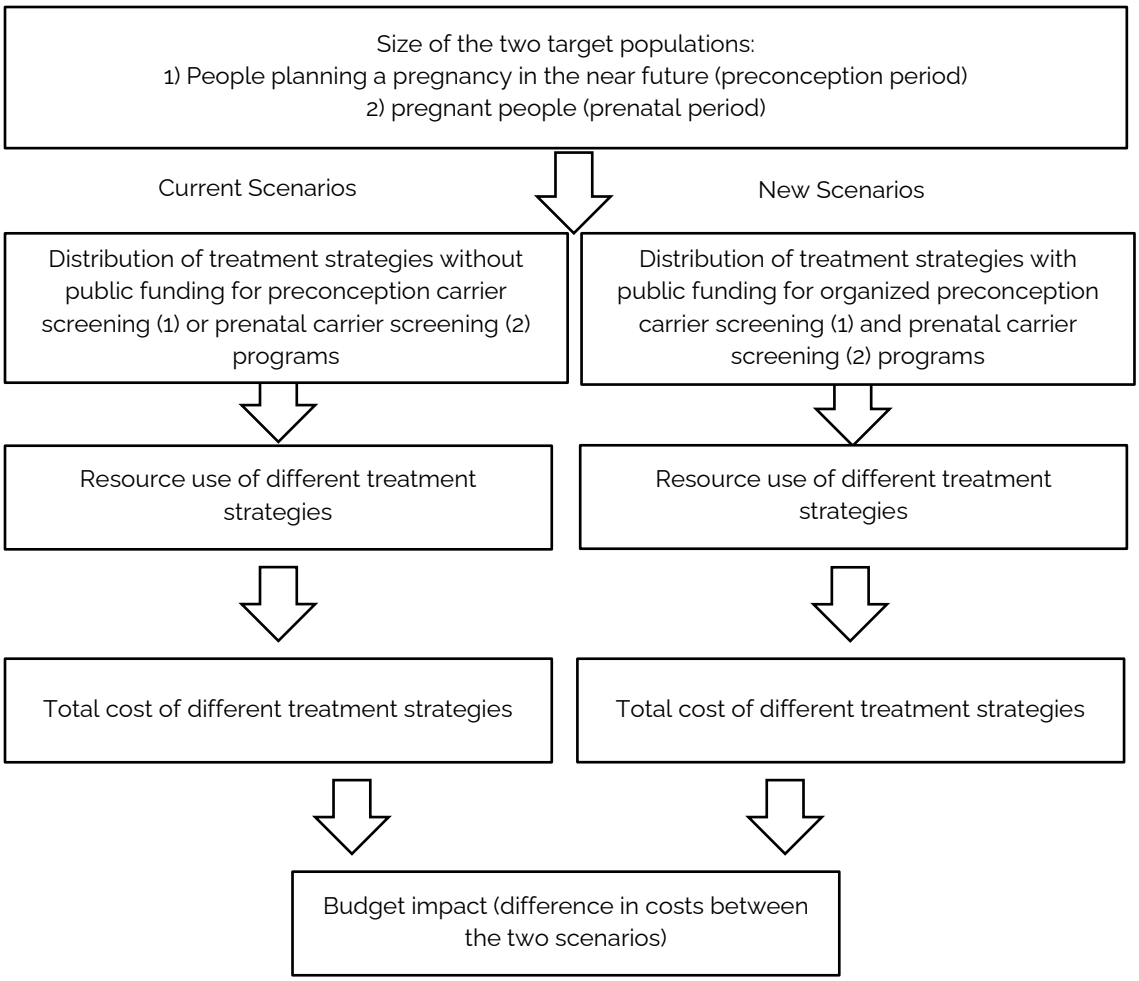

Figure 13: Schematic of Budget Impact Models for Preconception and Prenatal Carrier Screening Programs

Flow chart describing the model for the budget impact analysis. Based on the size of the target population, we created two scenarios: the current scenario, which would explore the distribution of treatment strategies, resource use and total costs without public funding for carrier screening; and the new scenario, which would explore the distribution of treatment strategies, resource use and total costs with public funding for carrier screening. The budget impact would represent the difference in costs between the two scenarios.

Key Assumptions

The assumptions used in our cost-effectiveness analysis also apply to this budget impact analysis. In addition, we considered the following:

- The testing is assumed to be done once and the cost of the test is assumed to remain unchanged over the next 5 years
- Everyone in the estimated target populations is eligible for genetic carrier screening
- Uptake rates are assumed to increase slightly in the first screening year (by 5% between year 1 and year 3) to accommodate a larger interest in the screening and participation of the majority of eligible people; changes in uptake rates over time were tested in sensitivity analyses

- For simplicity, we assumed that eligible couples completed preconception genetic testing and prenatal diagnostic testing within a year (from the beginning of preconception screening)
- One-time implementation and ongoing program costs were not included in the reference case
- We did not make any assumptions about the location or implementation of a potential carrier screening program at the time of this analysis. However, if genetic carrier screening is publicly funded as a province-wide program, then genetic testing would likely be offered in locations with existing equipment and personnel

Target Population

For preconception screening of CF, hemoglobinopathies and thalassemia, and SMA, we considered people who are planning a pregnancy, pregnant people, and their reproductive partners. For prenatal screening of these three conditions, we considered pregnant people and their reproductive partners. We assumed a sequential approach to carrier screening, with genetic testing done in all people who are interested in participating in the screening; consequently, the partners of people who test positive for a genetic condition were assumed to be tested, based on their interest in participating in the screening. For FXS, we considered only people who are considering becoming pregnant or pregnant people in the reference case. For simplicity, we assumed one pregnancy per couple over 5 years (our budget impact timeframe).

For estimation of the expected target populations for years 1 to 5 (2022/23 to 2026/27) in population-based screening, we followed several steps (Table 24):

- We determined the published numbers of live births in Ontario, which ranged between 141,925 in 2016 and 137,813 in 2020.[234] There was no obvious increase in the birth rate over these years (ratios: 1.0003 for 2018/2017, 0.99 for 2019/2018, and 0.97 for 2020/2019). Therefore, we did not assume any substantial increase in the expected number of pregnant people over the next five years
- We estimated the number of singleton births by removing the number of multiple-gestation pregnancies (about 4,730 per year), as suggested by the Better Outcomes Registry & Network (BORN) Ontario data[176]
- We estimated the total number of pregnant people with singleton pregnancies
- For the preconception target population, based on the currently available data, we assumed that 50% of the pregnancies are planned[235]
- Couple participation (uptake) rates in the universal screening programs were assumed to be the same as in our cost-effectiveness analysis (CEA). Thus, for the universal preconception screening, we assumed an uptake rate in genetic carrier testing of 71% for both partners (Tables 24 and 25). For the prenatal screening, we assumed an uptake rate of 68%[176] for the first partner and 95% for the other partner. These rates were tested in sensitivity analyses
- Couple participation rates in the risk-based screening programs were assumed to be the same as in our CEA, and were based on the literature. We assumed an uptake rate in genetic carrier testing of 5% for the first partner and 95% for the other partner (Tables 24 and 25). These rates were tested in sensitivity analyses
- Based on expert feedback, uptake rates in the reference case were assumed to increase slightly in the first screening years (by 5% between years 1 and 3). A larger interest in the screening and participation of the majority of eligible people was tested in sensitivity analysis
- Carrier frequency was estimated from our model outputs (and in line with current research[80,158]). About 10% of people considering becoming pregnant (preconception) or pregnant people (prenatal) were estimated to be carriers of the autosomal recessive conditions of interest. This was used to approximate the number of partners who would be invited for genetic carrier testing for CF, hemoglobinopathies and thalassemia, or SMA in the reference case. Further, based on our models, the carrier rate for FXS was estimated at about 0.6%

As shown in Table 24, over the next 5 years, we estimate that between 152,326 and 167,559 people who are planning a pregnancy and their partners would participate in the universal (population-based) preconception carrier screening annually. Over the next 5 years, between 99,180 and 109,098 pregnant people and their partners would accept universal (population-based) prenatal carrier screening annually.

Table 24: Estimate of Target Populations: Population-Based Preconception and Prenatal Carrier Screening

	Year 1	Year 2	Year 3	Year 4	Year 5
Total No. live births	137,813	137,813	137,813	137,813	137,813
Total No. singleton births[a]	133,083	133,083	133,083	133,083	133,083
Total No. pregnant people	133,083	133,083	133,083	133,083	133,083
Preconception Carrier Screening	—	—	—	—	—
Total No. people planning to become pregnant[b]	66,542	66,542	66,542	66,542	66,542
Total No. people eligible for genetic testing	199,625	199,625	199,625	199,625	199,625
Total No. people participating in genetic testing[c]	141,733	141,733	141,733	141,733	141,733
Total No. partners eligible for genetic testing[d]	14,919	14,919	14,919	14,919	14,919
Total No. partners participating in genetic testing[e]	10,593	10,593	10,593	10,593	10,593
Total target population (No.), preconception carrier screening: no increase in uptake over time	152,326	152,326	152,326	152,326	152,326
Total target population (No.), preconception carrier screening: slight (5%) increase in uptake	**152,326**	**159,943**	**167,559**	**167,559**	**167,559**
Prenatal Carrier Screening	—	—	—	—	—
Total No. pregnant people participating in genetic testing[f]	90,496	90,496	90,496	90,496	90,496
Total No. partners eligible for genetic testing[d]	9,140	9,140	9,140	9,140	9,140
Total No. partners participating in genetic testing[g]	8,683	8,683	8,683	8,683	8,683
Total target population (No.), prenatal carrier screening: No increase in uptake over time	99,180	99,180	99,180	99,180	99,180

	Year 1	Year 2	Year 3	Year 4	Year 5
Total target population (No.), prenatal carrier screening: 5% increase in uptake	**99,180**	**104,139**	**109,098**	**109,098**	**109,098**

[a]For simplicity, we use the number of singleton pregnancies to approximate the budget impact of carrier screening (although multiple-gestation pregnancies would also qualify for carrier screening).
[b]Assumed to be 50% of the number of people who are pregnant.
[c]Assumed to be 71% of the number of people who are eligible.[196]
[d]Assumed to be about 10%, carrier frequency for autosomal recessive conditions of interest, for whom the partner needs to be tested.
[e]Assumed to be about 0.6% of the number of partners who are eligible.
[f]Assumed to be 68% of the number of pregnant people who are eligible.[176]
[g]Assumed to be 95% of the number of partners of the pregnant people who are eligible.[176]

Over the next 5 years, we estimate that between 10,979 and 12,077 people who are planning a pregnancy (including their partners) would participate in the risk-based preconception carrier screening annually. Between 7,293 and 8,022 pregnant people (and their partners) would accept risk-based prenatal carrier screening annually (Table 25).

Table 25: Estimation of Target Populations: Risk-Based Preconception and Prenatal Carrier Screening

	Year 1	Year 2	Year 3	Year 4	Year 5
Total No. live births	137,813	137,813	137,813	137,813	137,813
Total No. singleton births	133,083	133,083	133,083	133,083	133,083
Total No. pregnant people at high risk	133,083	133,083	133,083	133,083	133,083
Preconception Carrier Screening	—	—	—	—	—
Total No. people planning a pregnancy[a]	66,542	66,542	66,542	66,542	66,542
Total No. people eligible for genetic testing	199,625	199,625	199,625	199,625	199,625
Total No. people participating in genetic testing[b]	9,981	9,981	9,981	9,981	9,981
Total No. partners eligible for genetic testing[c]	1,051	1,051	1,051	1,051	1,051
Total No. partners participating in genetic testing[d]	998	998	998	998	998
Total target population (No.), preconception carrier screening: no increase in uptake over time	10,979	10,979	10,979	10,979	10,979

	Year 1	Year 2	Year 3	Year 4	Year 5
Total target population (no.), preconception carrier screening: slight (5%) increase in uptake	**10,979**	**11,528**	**12,077**	**12,077**	**12,077**
Prenatal Carrier Screening	—	—	—	—	—
Total No. pregnant people participating in genetic testing[e]	6,654	6,654	6,654	6,654	6,654
Total No. partners eligible for genetic testing[c]	672	672	672	672	672
Total No. partners participating in genetic testing[f]	638	638	638	638	638
Total target population (No.), prenatal carrier screening: no increase in uptake over time	7,293	7,293	7,293	7,293	7,293
Total target population (No.), prenatal carrier screening: slight (5%) increase in uptake	**7,293**	**7,657**	**8,022**	**8,022**	**8,022**

[a]Assumed to be 50% of the number of people who are pregnant.
[b]Assumed to be 5% of the number of people who are eligible.
[c]Assumed to be 10%, carrier frequency for autosomal recessive conditions of interest, for whom the partner needs to be tested.
[d]Assumed to be 95% of the number of partners who are eligible.
[e]Assumed to be 5% of the number of pregnant people who are eligible.
[f]Assumed to be 95% of the number of partners of the pregnant people who are eligible.[176]

Current Intervention Mix

Given an inconsistent and limited approach to risk-based (targeted) carrier genetic screening in Ontario, we assumed no use of genetic testing for carrier screening in the current scenario.

Uptake of the New Intervention and New Intervention Mix

In the reference cases, we assumed a small increase in uptake rate over 5 years (see Tables 24 and 25). Given the lack of Ontario-specific data, participation in the screening interventions were mostly derived from the literature. We tested assumptions on these parameters in sensitivity analyses.

Resources and Costs

We used inputs on health care resource use and undiscounted costs from our cost-effectiveness analyses, applying them for a period of 1 year. Tables 26A and 26B present total annual per-case costs of the four screening (preconception or prenatal) interventions, and cost components associated with screening, prenatal diagnostic testing and reproductive choice (i.e., voluntary termination of pregnancy or IVF/PGT-M). As mentioned in the CEA, above, no additional costs were incurred for the no screening alternative. The budget impact was analyzed from the perspective of the Ontario Ministry of Health, and all costs were reported in 2022 CAD.

Table 26A: Annual Per-Case Costs Used in Budget Impact Calculations: Reference Case Analysis, Preconception Carrier Screening

Cost components and total costs	Preconception screening, $[a]		Preconception screening, $[a]	
	Universal, standard DNA testing (single-disease panels)	Universal, expanded DNA testing (one multidisease panel)	Risk-based, standard DNA testing (single-disease panels)	Risk-based, expanded DNA testing (one multidisease panel)
Screening	242.39	591.03	17.33	42.14
Prenatal diagnostics	8.95	7.65	0.23	0.16
Reproductive choice	3.17	2.99	0.09	0.08
Total	**254.51**	**601.66**	**17.66**	**42.38**

Note: Results may appear inexact due to rounding.

[a]Costs are per-case (one person tested, per-pregnancy) in 2022 CAD.

Table 26B: Annual Per-Case Costs Used in Budget Impact Calculations: Reference Case Analysis, Prenatal Carrier Screening

Cost components and total costs	Prenatal screening, $[a]		Prenatal screening, $[a]	
	Universal, standard DNA testing (single-disease panels)	Universal, expanded DNA testing (one multidisease panel)	Risk-based, standard DNA testing (single-disease panels)	Risk-based, expanded DNA testing (one multidisease panel)
Screening	232.99	576.36	16.91	40.68
Prenatal diagnostics	8.32	7.08	0.22	0.15
Reproductive choice	1.16	1.26	0.04	0.04
Total	**242.47**	**576.36**	**16.91**	**40.68**

Note: Results may appear inexact due to rounding.

[a]Costs are per-case (one person tested, per-pregnancy) in 2022 CAD.

Internal Validation

The secondary health economist conducted formal internal validation. This process included checking for errors and ensuring the accuracy of parameter inputs and equations in the budget impact analysis.

Analysis

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how the results were affected by varying input parameters and model assumptions. The sensitivity analysis considered several scenarios that could potentially affect the budget impact:

- Change in screening participation (uptake) rates (i.e., by 20%, 35%, 50%, and 100% vs. reference case totals of 71% in preconception and 68% in prenatal carrier screening, resulting in a total of eight additional scenario analyses)
- Change in overall carrier frequency of CF, hemoglobinopathies and thalassemia, FXS, and SMA (i.e., carrier frequency decreased by a half in one scenario and increased two-fold in another, for both preconception and prenatal carrier screening questions; in total, this is four additional analyses)
- Change in costs of carrier genetic standard (currently used) panels and a hypothetical expanded panel (i.e., cost decrease by half for all panels in one scenario and cost of a hypothetical expanded panel decrease by about 80% [from $657 to $130] in another scenario, for both preconception and prenatal carrier screening questions; in total, this is four additional analyses)
- Change in resource use in physician/counselling screening visits pre- and post-genetic testing (i.e., three screening care pathway scenarios for each research question, yielding a total of six additional analyses):
    - Visits provided by genetic counsellors decreased to the minimum and the pre-test visits and post-test follow-ups for couples testing negative became a part of the primary physician's care (see Appendix 8 for details)
    - Visits and follow-ups provided by a primary care physician decreased to minimum, increasing encounters with medical geneticist
    - Increased hourly salary rate for a genetic counsellor (from $41 in the reference case to $50 in this scenario)
- Full coverage of the IVF/PGT-M cost per life birth using a mean estimate from the Lipton study[227] applicable only to the preconception research question (about $39,000 vs. $5,000 in the reference case)
- Inclusion only of screening program costs to both preconception and prenatal carrier screening reference case analyses (i.e., one scenario considered the program implementation and ongoing cost outputs as estimated by the model from the initial cost inputs, accounting for differences in costs based on the participation in screening). Another scenario assumed that the initial model inputs related to the program costs applied to all potential participants (see Appendix 9 for detailed description of inputs); this resulted in four additional analyses
    - Additional scenario applicable to the preconception carrier screening program included both program costs and full IVF/PGT-M costs[227]
- Inclusion of condition-specific health care costs in the budget estimate based on the estimates of the long-term cost–utility analysis:
    - Two scenarios were examined for each research question, one including the cost of supportive therapies and another considering the cost of novel therapies for CF and SMA; both scenarios included the cost of the programs. This resulted in four additional analyses related to the long-term treatment budget impact scenario

All budget impact analyses were based on the estimates of our CEA models and were conducted using Microsoft Excel for Office 365.[236]

Results

Reference Case

PRECONCEPTION CARRIER SCREENING PROGRAMS

Table 27 presents the budget impact of publicly funding universal or risk-based preconception carrier testing interventions for the conditions of interest. Adopting the standard testing strategy at the population level (assuming a high uptake of 71% in year 1, increasing to 81% by year 3 and leveling to year 5), would lead to additional costs of about $38.6 million in year 1 to about $43 million in year 5. The total budget impact for this option was about $208 million for screening about 814,946 people over 5 years. As expected, due to higher costs of testing, the other universal option using one expanded multi-disease panel was associated with the highest budget impact (about $491 million over 5 years). Adopting the standard testing strategy in the high-risk population through a risk-based program (assuming an uptake of 5% in year 1, increasing to 15% by year 3), would lead to additional costs of about $0.24 million in year 1 to about $0.27 million in year 5. The total budget impact for this option was about $1.29 million for screening about 58,738 people over 5 years. The cost of testing was the largest cost component for all screening interventions.

Table 27: Budget Impact Analysis Results—Reference Case, Preconception Carrier Screening Programs for CF, FXS, Hemoglobinopathies and Thalassemia, and SMA

Scenario	Total costs and budget impact, $ million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current (no screening)	—	—	—	—	—	—
Total costs[b]	0	0	0	0	0	0
Universal, standard DNA testing (single-disease panels)	—	—	—	—	—	—
Total costs/Total BI	38.64	40.57	42.60	42.80	43.01	207.62
Costs of screening	36.92	38.77	40.61	40.61	40.61	197.54
Costs associated with prenatal diagnostics	1.27	1.33	1.47	1.61	1.77	7.45
Costs associated with reproductive choice	0.45	0.47	0.52	0.57	0.63	2.64
Universal, expanded DNA testing (one multi-disease panel)	—	—	—	—	—	—
Total costs/Total BI	91.54	96.11	100.77	100.95	101.14	490.51
Costs of screening	90.03	94.53	99.03	99.03	99.03	481.66
Costs associated with prenatal diagnostics	1.08	1.14	1.25	1.38	1.52	6.37
Costs associated with reproductive choice	0.42	0.44	0.49	0.54	0.59	2.49

Scenario	Total costs and budget impact, $ million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Risk-based, standard DNA testing (single-disease panels)	—	—	—	—	—	—
Total costs/Total BI	0.24	0.25	0.26	0.27	0.27	1.29
Costs of screening	0.190	0.200	0.209	0.209	0.209	1.018
Costs associated with prenatal diagnostics	0.0334	0.0350	0.0385	0.0424	0.0466	0.1960
Costs associated with reproductive choice	0.0129	0.0136	0.0150	0.0165	0.0181	0.0761
Risk-based, expanded DNA testing (one multi-disease panel)	—	—	—	—	—	—
Total costs/Total BI	0.50	0.52	0.55	0.55	0.56	2.67
Costs of screening	0.463	0.486	0.509	0.509	0.509	2.475
Costs associated with prenatal diagnostics	0.0221	0.0232	0.0256	0.0281	0.0309	0.1300
Costs associated with reproductive choice	0.0110	0.0115	0.0127	0.0139	0.0153	0.0644

Abbreviation: BI, budget impact.

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]No screening strategy equals 0 because no additional costs were incurred due to carrier screening.

PRENATAL CARRIER SCREENING PROGRAMS

Table 28 presents the budget impact of publicly funding universal or risk-based prenatal carrier testing interventions for the given conditions. Adopting the standard testing strategy at population level (assuming an uptake of 68% in year 1, increasing to 78% by year 3), would lead to additional costs of about $24 million in year 1, increasing to about $27 million in year 5. The total budget impact for this option was about $128 million to screen about 530,613 people over 5 years. As expected, due to higher costs of testing, the other universal option using one expanded multi-disease panel was associated with the highest budget of about $305 million over 5 years. Adopting the standard testing strategy in the high-risk population (assuming an uptake of 5% in year 1, increasing to 15% in year 3), would lead to additional costs of about $0.14 to $0.17 million per year. The total budget impact for this option was about $0.78 million to screen about 39,016 people over 5 years. The cost of testing was again the largest cost component for all screening interventions.

Table 28: Budget Impact Analysis Results—Reference Case, Prenatal Carrier Screening Programs for the Given Conditions

Scenario	Total costs and budget impact, $ million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current (no screening)	—	—	—	—	—	—
Total costs[b]	0	0	0	0	0	0
Universal, standard DNA testing (single-disease panels)	—	—	—	—	—	—
Total costs/Total BI	23.93	25.12	26.37	26.46	26.56	128.44
Costs of screening	23.11	24.26	25.42	25.42	25.42	123.63
Costs associated with prenatal diagnostics	0.72	0.75	0.83	0.91	1.00	4.20
Costs associated with reproductive choice	0.10	0.11	0.12	0.13	0.15	0.62
Universal, expanded DNA testing (one multi-disease panel)	—	—	—	—	—	—
Total costs/Total BI	56.96	59.80	62.69	62.76	62.84	305.04
Costs of screening	56.34	59.15	61.97	61.97	61.97	301.39
Costs associated with prenatal diagnostics	0.61	0.64	0.70	0.77	0.85	3.58
Costs associated with reproductive choice	0.01	0.01	0.01	0.01	0.02	0.06
Risk-based, standard DNA testing (single-disease panels)	—	—	—	—	—	—
Total costs/Total BI	0.144	0.151	0.160	0.162	0.165	0.78
Costs of screening	0.12144	0.12751	0.13358	0.13358	0.13358	0.65
Costs associated with prenatal diagnostics	0.019	0.020	0.022	0.024	0.027	0.11
Costs associated with reproductive choice	0.004	0.004	0.004	0.004	0.005	0.02
Risk-based, expanded DNA testing (one multi-disease panel)	—	—	—	—	—	—
Total costs/Total BI	0.312	0.327	0.344	0.346	0.348	1.68
Costs of screening	0.29528	0.31005	0.32481	0.32481	0.32481	1.58
Costs associated with prenatal diagnostics	0.013	0.013	0.015	0.016	0.018	0.07

Scenario	Total costs and budget impact, $ million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Costs associated with reproductive choice	0.004	0.004	0.004	0.005	0.005	0.02

Abbreviation: BI, budget impact.

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]No screening strategy equals 0 because no additional costs were incurred due to carrier screening.

Sensitivity Analysis

PRECONCEPTION CARRIER SCREENING PROGRAMS FOR CF, FXS, HEMOGLOBINOPATHIES AND THALASSEMIA, AND SMA

Table 29 and Appendix 22 present the results of our sensitivity analyses for the preconception carrier screening programs. The budget impact estimates for each screening strategy had the same trend as compared to the reference case in almost all scenarios. Universal carrier screening with an expanded panel was the strategy associated with the largest budget impact, and risk-based carrier screening with standard panels was the strategy with the smallest budget impact. Substantial changes in the total (5-year) budget impact were driven by the following factors:

- **Participation (uptake) rate:** as expected, with a smaller rate of participation in carrier screening (e.g., 20% for both partners in universal screening and 1.4% in risk-based screening), the total budget impact was more than 10 times smaller than the reference case (assuming the participation rate of 71% for both partners in universal screening and 5% in risk-based screening). In contrast, if participation in universal screening were 100% (i.e., 7% in risk-based screening), the budget impact would have increased more than two times for all strategies
- **Cost of the care (pre- and post-test visits) alongside the screening pathways:** the model of care provided alongside the screening is extremely uncertain for Ontario. Our reference case assumed involvement of all necessary medical professionals and an ideal (most conservative) pre-test and post-test follow-up to assure the best care. There is a capacity limit with respect to some medical professions (e.g., genetic counsellors); so, in real scenarios, it is possible that the post-test care follow-up would be restricted. In turn, this would reduce the number of visits (hours) claimed and would result in a smaller overall budget impact for all strategies (e.g., $170 million vs. $207 million in the reference case)
- **Program costs:** inclusion of the program costs and full coverage of IVF/PGT-M would result in substantial increases in the overall budget impact (up to 12% for universal strategies and 116% for the risk-based strategies, see Appendix 22, Tables A66A and A66B. The largest increase in the budget impact for risk-based strategies was caused by larger per-person program costs for these screening options (i.e., the constant amount assumed for the program cost was spread to a small number of participants)

However, the trend in the amount of estimated budget impact (i.e., the largest budget impact for universal screening with expanded panel) was reversed in two scenarios:

- **Scenarios related to the cost of a hypothetical expanded (multi-disease) panel:** if the cost of a hypothetical expanded panel decreased by 80% or more (from $657 to $130), then the screening strategies with standard panels would be more expensive than those with expanded panels

- **Long-term scenarios that accounted for treatment and all other costs:** as expected, inclusion of the treatment costs reduced the budget impact of carrier screening strategies. Cost savings were observed with risk-based carrier screening programs

Table 29: Budget Impact Scenario Results—Sensitivity Analysis; Preconception Carrier Screening Programs for the Given Conditions

Scenario	Total 5-year budget impact (screening strategy vs. no screening), $ million[a]			
	Universal, standard panels	Universal, expanded panel	Risk-based, standard panels	Risk-based, expanded panel
Reference case	**207.62**	**490.51**	**1.29**	**2.67**
Screening uptake, 20%	16.22	38.83	0.095	0.202
Screening uptake, 35%	52.72	125.87	0.31	0.66
Screening uptake, 50%	113.80	271.04	0.67	1.42
Screening uptake, 100%	500.18	1,187.17	3.21	6.75
Carrier frequency decreased by half (all conditions)	201.23	483.24	1.17	2.54
Carrier frequency doubled (all conditions)	220.71	505.08	1.61	3.02
Panel cost decreased by half	160.14	300.91	1.05	1.70
Expanded panel cost decreased by 80%	207.62	187.15	1.29	1.11
Screening care pathway: reduced genetic counsellor visits to minimum	169.92	489.59	1.06	2.49
Screening care pathway: reduced primary care visits, increased encounter with medical geneticist	197.08	516.67	1.20	2.63
Screening care pathway: increased hourly rate for genetic counsellor	228.72	548.30	1.36	2.79
Inclusion of full IVF/PGT-M costs	218.16	499.46	1.56	2.85
Program costs (implementation only), estimated by the model outputs with current coverage for IVF	218.35	537.94	1.55	2.98
Program costs (implementation and ongoing costs), estimated by the model outputs and full coverage for IVF/PGT-M	231.41	549.41	2.78	4.12

Scenario	Total 5-year budget impact (screening strategy vs. no screening), $ million[a]			
	Universal, standard panels	Universal, expanded panel	Risk-based, standard panels	Risk-based, expanded panel
Long-term treatment costs: supportive therapy for all conditions	169.81	486.90	-4.04	-2.58
Long-term treatment costs: novel therapy for CF and SMA and supportive therapy for hemoglobinopathies and thalassemia, and FXS	144.04	467.00	-16.36	-14.90

Abbreviations: CF, cystic fibrosis; FXS, fragile X syndrome; IVF, in vitro fertilization; PGT-M, preimplantation genetic testing for monogenic/single gene defects; SMA, spinal muscular atrophy.

Note: budget impact for all scenarios except the long-term analysis assumes that the current scenario incurred 0 additional costs. In long-term analyses, the current scenario includes the long-term health care costs (treatment with either supportive or novel therapies). The new scenario includes the long-term health care costs, program, and screening costs. See Tables A16 and A67–A70D in Appendix 22 for more details.

[a]All costs are in 2022 CAD.

Prenatal Carrier Screening Programs for CF, FXS, Hemoglobinopathies and Thalassemia, and SMA

Table 30 and Appendix 23 present the results of our sensitivity analyses for the prenatal carrier screening programs. While the budget impact estimates were smaller in absolute terms in the prenatal carrier screening strategies, the trends and change patterns were similar to those observed for the preconception carrier screening strategies.

Table 30: Budget Impact Scenarios Results—Sensitivity Analysis, Prenatal Carrier Screening Programs for the Given Conditions

Scenario	Total 5-year budget impact (screening strategy vs. no screening), $ million[a]			
	Universal, standard panels	Universal, expanded panel	Risk-based, standard panels	Risk-based, expanded panel
Reference case	**128.44**	**305.04**	**0.783**	**1.676**
Screening uptake, 20%	10.18	24.43	0.058	0.127
Screening uptake, 35%	31.82	76.13	0.18	0.40
Screening uptake, 50%	46.13	110.39	0.27	0.58
Screening uptake, 100%	262.57	622.79	1.69	3.55
Carrier frequency decreased by half (all conditions)	125.22	301.98	0.72	1.61

Scenario	Total 5-year budget impact (screening strategy vs. no screening), $ million[a]			
	Universal, standard panels	Universal, expanded panel	Risk-based, standard panels	Risk-based, expanded panel
Carrier frequency doubled (all conditions)	135.02	312.95	0.94	1.85
Panel cost decreased by half	98.74	187.02	0.63	1.06
Expanded panel cost decreased by 80%	128.44	115.86	0.78	0.68
Screening care pathway: reduced genetic counsellor visits to minimum	104.56	303.86	0.64	1.56
Screening care pathway: reduced primary care visits	121.58	320.83	0.72	1.65
Screening care pathway: increased hourly rate for genetic counsellor	141.40	340.64	0.83	1.75
Program costs (implementation costs) estimated by the model outputs	129.07	306.26	1.00	1.89
Long-term treatment costs: supportive therapy, all conditions	49.70	225.92	-2.28	-1.38
Long-term treatment costs: novel therapy for CF and SMA, and supportive therapy for hemoglobinopathies and thalassemia, and FXS	-43.15	128.31	-10.75	-9.07

Abbreviations: CF, cystic fibrosis; FXS, fragile X syndrome; SMA, spinal muscular atrophy.

Note: budget impact for all scenarios except the long-term analysis assumes that the current scenario incurred 0 additional costs. In the long-term analyses, the current scenario includes the long-term health care costs (treatment with either supportive or novel therapies). The new scenario includes the long-term health care costs, program, and screening costs. See Tables A84–A87D in Appendix 23 for more details.

[a]All costs are in 2022 CAD.

Discussion

We conducted model-based budget impact analyses to estimate the range of investments needed to publicly fund universal or risk-based preconception and prenatal carrier screening programs for CF, FXS, hemoglobinopathies and thalassemia, and SMA in Ontario.

In the case of preconception carrier screening programs for people who are considering pregnancy, the total budget impact was estimated to be $208 million for a universal screening program with standard (single-disease) panels and $491 million for a universal screening program with an expanded (multi-disease) panel, to screen about 815,000 people over 5 years. The corresponding budget impact estimates for the risk-based screening programs using standard and expanded panel

options, used to screen about 59,000 people over 5 years, were $1.2 million (for standard panels) and $2.7 million (for the expanded panel).

In the case of prenatal carrier screening programs for pregnant people, the total budget impact was estimated to be $128 million for a universal screening program with standard panels and $305 million for a universal screening program with an expanded panel, to screen about 531,000 people over 5 years. The corresponding budget impact estimates for the risk-based standard and expanded screening programs, used to screen about 39,000 people over 5 years, were $0.8 million and $1.7 million, respectively.

In sensitivity analyses, we showed that the budget impact estimates (for all examined strategies) were sensitive to the rate of participation, cost of medical care alongside the screening pathway, program costs, coverage of IVF/PGT-M (applicable to the preconception carrier screening program only) and genetic test costs. We showed that the budget impact of carrier screening with a hypothetical expanded panel would be smaller if the cost of this panel decreased more than 80% of the assumed reference case cost ($657). Of note, the expanded panel cost is hypothetical and was established in consultations with experts; this kind of multi-disease panel, which includes only the conditions of interest for this assessment, does not exist in Ontario. Currently, one private lab in Ontario offers a larger multi-disease expanded NGS panel for carrier screening covering over 170 genetic conditions at a cost of about $625 per person tested.[220]

In long-term scenarios, which accounted for the cost of treatments and of the program, the universal screening options seemed more economically viable, but we could observe a larger difference in the overall 5-year budget impact between preconception and prenatal carrier screening. For the universal preconception carrier screening program, the budget impact remained quite large for the strategy with standard panels, ranging from an additional $144 million to $166 million. The budget impact was at least three times higher for the universal program with expanded panel option. The budget impact was substantially offset by the treatment costs of novel therapies in the prenatal universal screening program options, leading to savings of about $43 million over 5 years with the universal screening using standard panels. When it comes to the budget impact of risk-based carrier screening program in the long-term scenarios (accounting for the treatment and program costs), we showed savings with both preconception and prenatal programs. However, the long-term cost-effectiveness models were associated with strong assumptions related to costs and benefits of the treatments for the given conditions; therefore, our findings regarding these savings need to be interpreted with caution.

Based on the results of our short-term reference case CEA, the universal screening program option using standard panels seemed most favorable in economic terms; in the long-term cost–utility analysis, after accounting for the cost of treatments, both universal options represented good value in economic terms. However, our modelling studies were associated with substantial limitations related to a lack of data from Ontario regarding screening participation (uptake) rates, carrier frequency for the given conditions, and the reproductive choices that a couple in Ontario may select after getting results from carrier testing. We assumed the most conservative model of care within the screening pathway, which led to overestimation of the budget impact. Also, our estimate of the target population for a universal preconception carrier screening program was done conservatively, as suggested in prior economic studies,[158,161] so as to include all couples who could be planning a pregnancy in the near future. However, it is possible that the number of people planning a pregnancy may fluctuate over time. If the number decreases, this would result in a decrease in the initial target

population estimate (and a smaller budget impact). In addition, one of the main assumptions for carrier screening program in Ontario is a sequential testing of partners. It is possible that, due to time constraints in the prenatal setting, partners would need to be tested concurrently, which would result in a higher budget impact for prenatal carrier screening. Given these limitations and the large budget impact estimates for both universal screening program options, it is very difficult to justify, using the information in our economic analysis, choosing one screening strategy over another for public funding in Ontario. A feasibility study will help to reduce uncertainty about relevant parameters to determine the budget impact; parameters such as screening participation (uptake) rates, important health human resource constraints, the most sustainable models of care, and the capacity of Ontario-based genetic laboratories to conduct a large-scale carrier genetic testing program yearly for the given conditions (which could potentially include annual testing of over 140,000 people in the preconception or prenatal period).

Strengths and Limitations

Our analyses are restricted by our assumptions and uncertainty in the parameter inputs that informed the model. Our reference case estimate of the budget impact is conservative (i.e., overestimated because some funding is already provided in the province to support risk-based carrier testing), but we conducted several scenario analyses to examine factors that could affect changes in the overall budget, and possibly enable savings.

Conclusions

Based on our short-term reference case analyses, publicly funding universal carrier screening programs for CF, FXS, hemoglobinopathies and thalassemia, and SMA in the preconception stage over the next 5 years (about 815,000 people in Ontario, assuming an initial 71% participation rate) would require an additional $208 million for universal screening with standard (single-disease) panels or an additional $491 million for universal screening with an expanded (multi-disease) panel. Publicly funding risk-based screening programs in the preconception stage over the next 5 years (about 59,000 people) would require an additional $1.2 million for the strategy with standard panels or an additional $2.7 million with the expanded panel.

Based on our short-term reference case analyses, publicly funding universal carrier screening programs for CF, FXS, hemoglobinopathies and thalassemia, and SMA in the prenatal stage over the next 5 years (about 531,000 people in Ontario assuming an initial 68% participation rate) would require an additional $128 million for universal screening with standard panels or an additional $305 million for universal screening with an expanded panel. Publicly funding risk-based screening programs in the prenatal stage over the next 5 years (about 39,020 people) would require an additional $0.8 million for the strategy with standard panels or an additional $1.7 million for the expanded panel.

The long-term scenario analyses, which incorporated the costs of treatment, program administration, and screening over 5 years, indicated a smaller budget impact for all strategies compared with the reference case and cost savings with prenatal universal (standard panels) and prenatal or preconception risk-based (standard or expanded panels) carrier screening programs.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of those who have lived experience of cystic fibrosis (CF), fragile X syndrome (FXS), hemoglobinopathies and thalassemia, or spinal muscular atrophy (SMA), as well as the preferences and perceptions of both patients and providers of carrier screening for these conditions.

Background

Exploring patient preferences and values provides a unique source of information about people's experiences of a health condition and the health technologies or interventions used to manage or treat that health condition. It includes the impact of the condition and its treatment on the person with the health condition, their family and other caregivers, and the person's personal environment. Engagement also provides insights into how a health condition is managed by the province's health system.

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[237-239] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

Because the needs, preferences, priorities, and values of those with lived experience in Ontario are important to consider to understand the impact of the technology in people's lives, we may speak directly with people who live with a given health condition, including those with experience of the technology or intervention we are exploring.

For this analysis, we examined the preferences and values of pregnant people or people considering pregnancy who sought carrier screening for CF, FXS, hemoglobinopathies and thalassemia, and SMA in three ways:

- A review by Ontario Health of the quantitative evidence on patient and provider preferences and values
  - A review by the Canadian Agency for Drugs and Technologies in Health (CADTH) of the published qualitative evidence
- Direct engagement by Ontario Health with people with one or more of these conditions through interviews

Quantitative Evidence

Research Questions

- What is the relative preference of people and health care providers for carrier screening program(s) for CF, FXS, hemoglobinopathies and thalassemia, and SMA compared with no screening or another screening approach?
- What is the relative importance of key attributes of carrier screening for CF, FXS, hemoglobinopathies and thalassemia, and SMA and what trade-offs between attributes are people and health care providers willing to make?
- How satisfied are people and health care providers with carrier screening for CF, FXS, hemoglobinopathies and thalassemia, and SMA?
- What are people and health care providers' awareness, knowledge, and understanding of carrier screening for CF, FXS, hemoglobinopathies and thalassemia, and SMA?

Methods

LITERATURE SEARCH

We performed a literature search for quantitative evidence of preferences and values on April 9, 2021, to retrieve studies published from January 1, 2010, until the search date. We used the Ovid interface to search MEDLINE and the EBSCOhost interface to search the Cumulative Index to Nursing & Allied Health Literature (CINAHL).

The search was based on the population and intervention of the clinical search strategy with a methodological filter applied to limit retrieval to quantitative evidence of preferences and values (modified from Selva et al[240]). The final search strategy was peer reviewed using the PRESS Checklist.[40]

See Appendix 2 for our literature search strategies, including all search terms.

ELIGIBILITY CRITERIA

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published since January 1, 2010
- Studies on patient and provider preferences for carrier screening tests that use quantitative measure
- Systematic reviews, meta-analyses, randomized controlled trials, cohort studies, surveys, questionnaires

Exclusion Criteria

- Animal and in vitro studies
- Nonsystematic reviews, narrative reviews, abstracts, editorials, letters, case reports, commentaries, and qualitative studies
- Studies where outcomes of interest cannot be extracted

Participants

Inclusion Criteria

- Person at any carrier risk level with or without a reproductive partner at the preconception (near-future pregnancy) or prenatal period
- Either/both members of a couple may be egg/sperm donors
- Includes people who are considering or undergoing in vitro fertilization (IVF)
- Health care providers who offer carrier screening tests or consult on the use or results of carrier screening tests
- People affected with the conditions of interest or who know someone who is affected
- Related family members of people who have been or may be tested

Exclusion Criteria

- General population not of reproductive age and not otherwise meeting inclusion criteria

Interventions

Inclusion Criteria

- Targeted or universal (population-based) carrier screening program for CF, FXS, hemoglobinopathies and thalassemia, or SMA using any testing approach for reproductive decision-making
- Different testing approaches related to timing of screening, concurrent or sequential testing of people, analytic method, method of result disclosure

Exclusion Criteria

- Screening for purposes other than near-future reproductive decision-making (e.g., premarital or pre-relationship testing for relationship/marriage decisions, young adults of reproductive age [e.g., people in high school], testing for only individual carrier status knowledge and not for near-future reproductive decision-making)
- Standard protocol screening for donor egg/sperm (i.e., standard protocol testing at donor egg/sperm bank)
- Screening for other genetic conditions

Outcome Measures

- Preferences for carrier screening, test characteristics, and trade-offs
- Preferences for screening approach or delivery
- Satisfaction
- Awareness, knowledge, and understanding of carrier screening

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[41] and then obtained the full text of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion.

Data Extraction

We extracted relevant data on study characteristics using a data form to collect information about the following:

- Source (e.g., citation information, contact details, study type)
- Methods (e.g., study design, study duration, participant recruitment)
- Outcomes (e.g., outcomes measured, outcome definition and source of information, unit of measurement, upper and lower limits [for scales], time points at which the outcomes were assessed)

STATISTICAL ANALYSIS

Results are summarized narratively. No additional statistical analyses were conducted beyond those reported in the primary studies.

CRITICAL APPRAISAL OF EVIDENCE

We did not undertake a formal critical appraisal of the included studies.

Results

LITERATURE SEARCH

The literature search of the quantitative evidence of preferences and values yielded 529 citations published between January 1, 2010, and April 9, 2021, after duplicates were removed. We identified three additional studies from other sources. In total, we identified 29 studies that met our inclusion criteria. Figure 14 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the literature search for quantitative evidence of preferences and values.

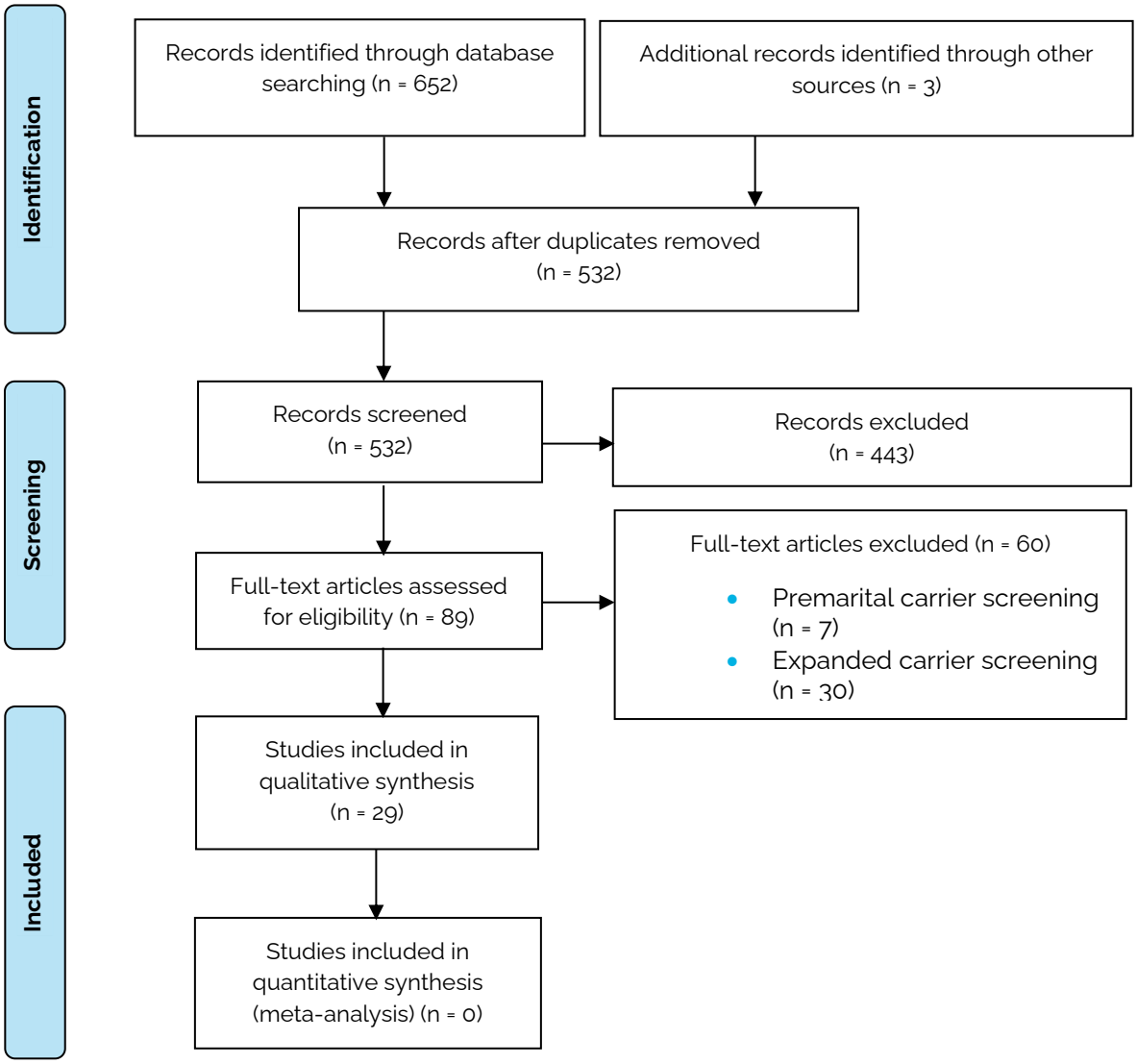

Figure 14: PRISMA Flow Diagram—Quantitative Evidence of Preferences and Values Search Strategy

PRISMA flow diagram showing the clinical search strategy. The database search of the clinical literature yielded 652 citations published between January 1, 2010, and April 9, 2021. We identified 3 additional eligible studies from other sources. After removing duplicates, we screened the abstracts of 532 studies and excluded 443. We assessed the full text of 89 articles and excluded a further 60. In the end, we included 29 articles in the qualitative synthesis.
Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Page et al.[45]

CHARACTERISTICS OF INCLUDED STUDIES

The characteristics of the 29 included studies are presented in Table A88 (Appendix 24). We found studies preference studies related to carrier screening programs (offering of carrier screening testing as well as more organized carrier screening programs) from Australia, Belgium, Ghana, Iran, Israel, Netherlands, Pakistan, Spain, Thailand, the United Kingdom, and the United States. We found a combination of studies examining preferences among people during the preconception and prenatal periods. The health care providers ranged from medical geneticists, genetic counsellors, obstetricians and gynaecologists, reproductive endocrinology and infertility specialists, neonatal and perinatal specialists, primary care providers, midwives, nurses, and other health care providers or workers in a health care centre. In prenatal carrier screening studies, pregnant people were generally recruited from antenatal care centres. Some studies also evaluated people affected with the condition or families with children affected with the condition.

Studies often did not report on how participants were recruited, but generally reported the survey response rate. Studies evaluated a range of screening-related concerns, including: attitudes and support for carrier screening, reasons for accepting or declining screening, preferences for test results, satisfaction with screening, and knowledge and awareness of carrier screening among people and health care providers. Most of the included studies used self-developed surveys and questions to assess preference outcomes.

We also found eight systematic reviews that were partially relevant to our research question (Table A89, Appendix 25).[59,61,63,196,241-244] These systematic reviews did not fully address our research questions and differed from our review in their included conditions of interest (e.g., expanded screening panels), outcomes of interest (e.g., only select outcomes of interest), and date of literature captured (e.g., inclusion of older studies published before our date limit). We examined the reference lists to ensure that we also included all relevant studies found within these reviews. We also found numerous studies on expanded carrier screening panels; however, we excluded these studies since it was not possible to analyze the results based on condition. We are also aware of one ongoing systematic review on the psychosocial impacts of carrier screening panels, which may potentially be relevant to our review (registered in PROSPERO; CRD 42020210787).

PREFERENCES FOR CARRIER SCREENING

During the Preconception or Prenatal Period

Table 31 presents the results on people's preferences for carrier screening during the preconception or prenatal period. Most were supportive of carrier screening, with more support for preconception screening compared with prenatal screening. People found that carrier screening provided more information for the person or pregnancy that would help inform reproductive choices and decision-making. In addition, some felt that carrier screening would contribute to increasing the knowledge base of the condition. People noted that carrier screening prior to conception may lead to fewer voluntary terminations of affected pregnancies and fewer affected children born.

Some studies also evaluated the reasons for accepting or declining screening, which included personal or religious reasons, a desire to know their carrier status, fear or anxiety of testing or test results, test cost, believed test results would not affect decision-making, family history of the condition, perceived risk of being a potential carrier, desire to contribute to the knowledge base of the condition, and time. For SMA screening, the type of SMA identified among affected people or affected families may also impact their preferences for carrier screening. Some people also reported

that carrier results would have altered their reproductive choices if they had been aware of their carrier status earlier.

Concerns about carrier screening include potential stigmatization of identified carriers, potential difficulty for identified carriers to get married or have children, the effect of carrier identification on choice of reproductive partner, possible tension between partners, worries that screening may lead to less investment in the development of new treatments for the condition, difficulty in accessing insurance or increased insurance for identified carriers, and confidentiality of test results. However, in general, people believed that the potential benefits of carrier screening were greater than the potential disadvantages.

Two studies[245,246] also reported on people's preferences for the location of carrier screening and the type of health care provider to offer screening, Most people preferred the location to be a general provincial hospital and thought that a gynaecologist, clinical geneticist, primary care provider, or midwife should offer carrier screening. People also generally thought that the test cost should be free or low, or that it should be supported by government.

Table 31: Preferences for Carrier Screening Among People During the Preconception or Prenatal Period

Author, year	Condition	Timing	N	Preferences for characteristics or approach to carrier screening
Alfaro Arenas et al, 2017[84]	FXS	PC, PN	3,731 PC: 318 PN: 3,413	Reasons for not accepting carrier screening • 38% lack of interest • 17% fear • 4% religious concerns
Ames et al, 2015[247]	FXS	PC	241	169 (70%) had positive attitudes toward FXS carrier screening
Bailey et al, 2012[248]	FXS	PC, PN	1,099	Most people agreed or strongly agreed that free, voluntary screening should be offered at all times • 83% for PC carrier screening • 68% for PN maternal carrier screening Parents were significantly less likely to endorse PN screening of either pregnant person or fetus compared with other screening options ($P < .0001$) When forced to select one screening option, 76% preferred PC carrier screening • 89% said that PC screening would inform reproductive decisions (more reproductive control and options) Most parents indicated they would like to be informed about carrier status • Desire to have any/all relevant health information about child • Feeling of right to know this information • Potential utility in preparing child for future

Author, year	Condition	Timing	N	Preferences for characteristics or approach to carrier screening
				Parents who did not want to know their carrier information or were uncertain mostly questioned whether the information had any real utility and whether knowing would cause unnecessary worry
Boardman et al, 2017,[249] 2018[250]	SMA	PC, PN	337 Families: 255 Individual adults: 82	77.2% in favour of PC screening (no difference between families and adults with SMA) • More support from type 1 SMA families compared with type 2 or type 3 SMA families (88% vs. 72%, *P* = .002) • Lowest level of support from adults with type 2 SMA (63%), significantly lower than adults with type 3 SMA (94%, *P* = .008) Concerns with PC screening • 42% of adults with SMA thought screening would result in stigmatization vs. 17% for families with SMA (*P* < .0001) • 44% of adults with SMA thought screening was a form of social engineering vs. 20% for families with SMA (*P* < .0001) 76.3% supported prenatal screening • No difference between adults and families with SMA (78.4% vs. 69.5%, respectively; *P* = .25) • Families with type 1 SMA showed greatest support (88%), compared with families with type 2 (72%) and type 3 (68%) • Adults with type 3 SMA showed greater support than adults with type 2 (81% vs. 52%, respectively) Concerns with PN screening • Leads to fewer people with SMA who could have lived fulfilling lives • Potential loss to society to have fewer people with SMA Reasons for supporting PC/PN screening • Raise awareness of SMA in general population • Help with informed decision-making • Reduction in SMA-associated voluntary terminations of pregnancy
Boardman et al, 2020[251]	Thal	PC	80	73% (92) support PC screening program for thal • Some participants thought identifying carriers would lead to carriers feeling stigmatization or different, would be more difficult for carriers to get married/have children once their carrier status is known, PC identification of carriers will affect choice of reproductive partner

Author, year	Condition	Timing	N	Preferences for characteristics or approach to carrier screening
Brown et al, 2011[252]	SCD, thal	PN	484	90.7% had positive attitude toward prenatal sickle cell trait screening
Hanprasertpong et al, 2018[245]	Thal	PN	1,006	90.4% agreed screening is useful and should be done for all 69.6% thought cost should not influence screening decision 84.5% thought screening should be done PC or as early as possible Reasons for accepting screening • 818 (81.3%) reported anxiety about fetal abnormality • 742 (73.8%) cited opportunities for Down syndrome risk assessment • 455 (45.2%) cited opportunities for fetal sex determination Reasons for declining screening • 592 (58.8%): cost concern • 352 (35.0%): fear of venipuncture pain • 36 (3.6%): family suggestion Preferred places for screening • 745 (74.1%): general provincial hospital • 400 (39.8%): public health centre • 344 (34.2%): primary community public hospital • 238 (23.7%): private hospital • 194 (19.3%): tertiary or university hospital • 189 (18.8%): private clinic Economic support preference • 885 (88.0%): total cost support from government • 121 (12.0%): self-pay
Ioannou et al, 2014[253]	CF	PN	158	80.5% thought CF screening should be offered by the public health system 36.9% thought screening should be free 49.7% would have liked to have been offered screening during current pregnancy Most common potential factors influencing choice to screen • 59.5%: partner's opinion • 46.3%: lack of family history • 38.7%: would not consider a termination of an affected pregnancy • 36.9%: thought physician's recommendation would not influence decision • 61.4%: thought test cost would not influence decision

Author, year	Condition	Timing	N	Preferences for characteristics or approach to carrier screening
				3 factors were significantly more influential for people who did not undergo screening: family history of CF, family history of other genetic conditions, and perceived susceptibility of being a CF carrier
Ioannou et al, 2014[254]	CF	PN	54	24% wished to be offered screening at another time. Of these, 72% would have liked PC screening 95% believed that screening should be available for those who wish to have it Factors influencing decision to decline screening • 58%: no family history of CF • 54%: no family history of other genetic conditions • 45%: believed they would not terminate an affected pregnancy • 61%: stated doctor's recommendation did not influence decision • 84%: stated that lack of time did not influence decision Physician recommendation was more of an influencing factor for people who accepted versus those who declined screening Test cost • 37% declined screening because they believed a reasonable price to pay for CF screening is $50–$100 AUD • 32% thought test should be free • 16.7% thought > $100 AUD was a reasonable price
Janssens et al, 2016[246]	CF	PC, PN	111 Parents of children with CF: 64 People with CF: 47	94.5% believed aim of screening programs should be informing carrier couples of their reproductive risks 60.9% believed aim of screening programs should be avoiding births of children affected with CF 80.0% believed benefits of screening program are greater than the potential disadvantages More than 90% believed that everyone should be free to decide whether to accept screening 86.2% believed test should be offered to all couples during PC 72.9% thought screening during pregnancy was acceptable • 96.3% thought tests should not be limited to people with a family history of CF Attitudes on which HCPs should offer screening

Author, year	Condition	Timing	N	Preferences for characteristics or approach to carrier screening
				• 93.2%: gynecologists • 93.1%: clinical geneticists • 78.4%: GPs • 76.3%: PC consultation providers • 61.4%: midwives 82.5% of parents would have accepted carrier screening if the test had been provided to them before 68.7% would have altered their reproductive choices if they had been aware of their carrier status 44.5% agreed that screening would lead to more terminations of pregnancy 40.9% believed identification of carrier couples may cause tension between partners 31.8% were worried that screening may lead to less investment in the development of new treatments for CF 23.1% agreed that identified carriers may have difficulty accessing insurance
Maxwell et al, 2011[255]	CF	NA	149	Attitudes on universal PC screening • Over 90% thought PC screening provides couples with choice, that it should be offered in Western Australia, and that it should be available for all couples planning a pregnancy • 90% of family members and 85% of people with CF support screening • Most people agreed that screening has many benefits and reduces suffering associated with CF • 63% of families and 41% of people with CF thought screening will not take important resources away from CF services Attitudes on universal PN screening • 93% of families and 85% of people with CF thought screening provides couples with choice • Over 80% thought screening should be offered in Western Australia and should be made available for all pregnant couples • Compared with people with CF, more families personally support screening and think it has many benefits (70% vs. 81% and 63% vs. 80%, respectively) • 21% of families and 41% of people with CF thought screening would reduce the motivation to find a cure or improve treatments for CF

Author, year	Condition	Timing	N	Preferences for characteristics or approach to carrier screening
				In general, people had more positive attitudes toward PC screening compared with PN screening There was no significant association between acceptability of termination of an affected pregnancy and having different views on PN or PC screening
Mayo-Gamble et al, 2018[256]	SCD	PC	300	Factors underlying intention to go to physician to ask for sickle cell trait screening: age, education, perceived threat, attitude, perceived norm, and perceived behavioural control
Metcalfe et al, 2017[68]	FXS	PC, PN	961	72.9% (95% CI: 69.9%–75.7%) had positive attitudes towards screening • No difference between pregnant and nonpregnant people, adjusting for sociodemographic differences between groups (OR: 0.9; 95% CI: 0.67–1.22, P = .506) • People who had been tested had a significantly more positive attitude towards screening than people who had not been tested (86.9% vs. 20.5%, P < .001) 74.0% (95% CI: 71.0%–76.8%) made an informed choice • Tested people were significantly more likely to report having made an informed choice compared with not-tested people (76.0% vs 66.7%, P = .012) • Poor knowledge accounted for half of people who were reported to have not made an informed choice, while mismatched attitudes and behaviour accounted for the other half • 87.9% of people deliberated on their decision to be tested, with no difference between groups
Prior et al, 2010[257]	SMA	PN	392	Reasons for declining testing • 58.7%: low anxiety about SMA • 38.0%: a positive result would not change pregnancy management or they would not choose PND if the result was positive • 27.3%: did not wish to know their genetic status • 13%: testing would be associated with increased anxiety Reasons for pursuing testing • 74.5% were interested in their carrier status • 57.3% worried about risk of having an affected pregnancy • 45% because of no additional cost for testing • 47% expressed interest in contributing to SMA knowledge base

Author, year	Condition	Timing	N	Preferences for characteristics or approach to carrier screening
				• 96.9% would pursue screening if testing was covered by insurance • 29% would still pursue testing at a cost of $500 if insurance would not cover testing
van Elderen et al, 2010[258]	HbP	PC	109	91 people (83.5%) reported they intended to participate in PC screening if it is offered • None of the socio-demographic characteristics evaluated had a significant relationship to people's intention to participate in screening • Authors found a relationship between people's wish to reduce uncertainty and the intention to participate in screening • Knowledge about HbP and their hereditary characteristics did not have a significant relationship to people's intention to participate
Vuthiwong et al, 2012[259]	Thal	PN	100	Partner's attitudes toward screening • 93% agreed/highly agreed that test results would be beneficial to family • 83% agreed/highly agreed that test results would be beneficial to themselves • 74% agreed/highly agreed that they wished to know whether pregnancy was affected • 46% agreed/highly agreed that they clearly knew the possibility of having an affected child Most common reasons for declining testing • 57%: inconvenient to go to hospital • 49%: certain that child is not affected by thal • 27%: lack of understanding of condition and testing • 21%: high cost of testing • 20%: not advised of testing by anyone • 17%: concern that test results may be disclosed to unauthorized people • 6%: fear that people will hate them Occupation was found to be correlated with attitudes towards testing • Labourers or business owners were less likely to have positive attitudes compared with those who were in government or unemployed
Widayanti et al, 2011[260]	Thal	PC	180 74 had affected child 106 did not have an	• Attitudes toward carrier screening were not significantly different between females with or without an affected child (P = .2) • Females with lower education had a significantly more positive attitude toward receiving information about thal compared with average or higher educated females (P = .03)

Author, year	Condition	Timing	N	Preferences for characteristics or approach to carrier screening
			affected child	• Females with lower education were not more likely to report positive attitudes toward carrier testing compared with average or higher educated females (*P* = .03) People did not report experiencing social influence from others in their social circle (partners, family, and friends, GPs) for carrier testing • Females with an affected child experienced significantly more social influence from GP compared with those who did not have an affected child (*P* < .001) Lack of money and time were the most important reported barriers to screening People with an affected child perceived significantly more control over screening compared with people who did not have an affected child (*P* = .05) • People with higher education perceived significantly less control over testing compared with those with average or lower education (*P* = .004) People reported anticipated feelings of stigmatization toward thal carriers and fear of discrimination if they were found to be carriers People with an affected child reported significantly stronger feelings of anticipated stigmatization compared with people who did not have an affected child (*P* < .001) Predictors of future reproductive planning • Attitudes toward testing was a strong predictor of future reproductive plans (*P* = .005) • Other predictors included potential stigmatization if identified as a carrier (*P* = .003), education level (*P* = .001), and age (*P* = .001)
Wood et al, 2016[65]	SMA	PN	90	76.4% believed that prenatal carrier screening for SMA in addition to CF and FXS should be universally offered to people 87.6% thought screening for CF, FXS, and SMA should be covered by insurance 84.3% agreed that people should receive pre-test counselling on all conditions to be screened 100% agreed that people should receive post-test counselling if test is positive 24.4% agreed that religion would influence their participation in screening 12.4% agreed that their views on pregnancy termination would limit the value of screening

Author, year	Condition	Timing	N	Preferences for characteristics or approach to carrier screening
				56.2% agreed that carrier screening is socially responsible behaviour 28.4% reported worrying that screening results would not remain confidential 28.1% reported worrying that they would experience discrimination as a carrier 43.8% though that screening may increase insurance rates 57.3% would prefer people be screened for a larger number of conditions if costs were the same
Zafari et al, 2016[261]	Thal	PC	327 carrier couples	Most common attitudes • Belief that people should be aware if they are carriers • Will pursue PND if expecting a child • Before marriage, had hoped to have many children, but since identified as carrier, 1 or 2 children would be enough 58% had positive attitude toward genetic counselling No significant relationship between place of residence, knowledge, and attitudes No significant relationship between age, knowledge, attitude, and SES

Abbreviations: CF, cystic fibrosis; CI, confidence interval; FXS, fragile X syndrome; GP, general practitioner; HbP, hemoglobinopathy; HCP, health care professional; NA, not applicable; OR, odds ratio; PC, preconception; PN, prenatal; PND, prenatal diagnosis/diagnostic; SCD, sickle cell disease; SES, socioeconomic status; SMA, spinal muscular atrophy; thal, thalassemia.

Health Care Providers

We found six studies[262-267] that evaluated preferences for carrier screening among health care providers (Table 32). In general, most providers were in favour of carrier screening because of the potential to identify carriers and the potential impact on patients' reproductive choices and decision-making. Factors influencing providers' decision to support or not support carrier screening included clinical picture and prognosis of the condition, quality of life of people affected with the condition, carrier frequency, personal beliefs, and fear of litigation.

Most providers offered carrier screening either to all people or to people based on certain clinical situations (e.g., personal or family history of the condition). Providers who were less likely to refer people for genetic testing also perceived more barriers to offering carrier screening. Some health care providers also identified concerns about offering carrier screening, including equity of access, limited testing in high-risk populations, potential increase in anxiety for people, targeting of preconception or prenatal couples, potential for stigmatization for identified carriers, perception of impact on insurance for identified carriers, and the lack of cost–benefit analysis on carrier screening. Some providers also noted the lack of community knowledge and awareness of carrier screening and the potential test cost for people.

Table 32: Preferences for Carrier Screening Among Health Care Providers

Author, year	Condition	N	Preferences for characteristics or approach to carrier screening
Cunningham et al, 2014[262]	CF	51 physicians, 19 clinic coordinators	56.3% were in favour of population-based screening, 36.6% were not in favour, 7.0% were unsure • Important factors influencing the decision to support or not support screening: clinical picture and prognosis of CF (67.6%), quality of life for people with CF (59.2%), carrier risk being 1/25 (58.5%), daily treatment regimen for CF (52.1%) • Least important factors: fear of litigation (2.8%), beliefs about termination of pregnancy (5.6%) Primary benefits of screening • 73.2%: identification of people and couples at risk of having child with CF • 59.2%: reduce number of children born with CF • 43.7%: increase awareness of CF in the community Potential disadvantages of screening • 87.3%: potential anxiety of identified carriers • 56.3%: discrimination and stigmatization of carriers Potential barriers to screening • 67.1%: inability to accurately predict clinical outcomes associated with some CF alleles • 58.6%: insufficient time and resources • 31.3%: CF screening not cost-effective • 50.7%: having to pay for screening
Darcy et al, 2011[264]	CF	143 HCPs (39% private, 32% hospital-based, 16% clinic-based, 13% mixed)	88.2% (95% CI: 84.2%–92.8%) offered screening per ACOG guidelines • No differences based on practice type of HCP Reasons for not offering screening • 16.5% of HCPs experienced barriers to offering screening (95% CI: 10.5%–22.6%) • No significant difference based on affiliation with academia or practice type Potential factors in decision to not offer screening: lack of universal insurance coverage for screening, patient population was not at high enough risk, CF screening would not make difference for their patients, patients would not be interested in screening, not enough resources to be able to offer screening, screening was not standard of care in practice No respondents cited lack of support from superiors or thought ACOG guidelines were unclear
Jans et al, 2012[265]	Hemoglobinopathy	1,346 Midwives: 795 GPs: 511	Analysis of current behaviour showed that both GPs and midwives almost never offer ethnicity-based testing

Author, year	Condition	N	Preferences for characteristics or approach to carrier screening
			On average, GPs had a fairly positive attitude toward offering ethnicity-based testing, regardless of family history; midwives had more positive attitude than GPs 45% of respondents (significantly fewer GPs than midwives) thought that offering ethnicity-based screening should become national policy If ethnicity-based screening were to become national policy, most respondents (significantly more midwives than GPs) expressed the intention to offer testing to their patients The intention to offer testing was mainly due to 3 factors: attitude toward offering ethnicity-based testing, perceived opinions of colleagues, control over ability to effectuate the test
Lieberman et al, 2011[266]	FXS	80 Physicians: 13 Genetic counsellors: 20 Not given: 1	Pre-screening counselling • Divided opinion on informing people of their risk of FXPOI and FXTAS • 70% of people who thought FXPOI should be mentioned in counselling had same opinion for FXTAS • Only 25% informed people about these risks, resulting in a significant difference between the desired and actual genetic counselling (P = .001) Counselling risk in carrier fetus • 38% thought counselling regarding FXTAS for the fetus should be performed • 32% thought counselling regarding FXPOI in female fetuses should be performed • Only 17% inform people about the risk of FXTAS and FXPOI in fetuses Counselling after PND • 79% agreed that complete information including number of CGG repeats should be given to people • 62% thought people should not be informed about risk of FXTAS in carrier fetuses 80% felt there is need for uniform policy for FXS counselling; 47% thought public opinion should be taken into account
Stark et al, 2013[263]	CF, thal, FXS, SMA	156 obstetricians	152 (97%) and 130 (83%) supported PN carrier screening for beta-thal and CF, respectively 32 (20%) and 12 (8%) offered screening for beta-thal and CF, respectively, to all patients • 113 (72%) and 128 (82%) offered screening for beta-thal and CF, respectively, to some patients • 109 (70%) offered screening for thal and 123 (79%) for CF based on personal or family history • 85 (55%) offered screening for thal and 123 (79%) for CF based on ethnicity risk • 75 (48%) offered screening for thal and 88 (56%) for CF in response to patient request

Author, year	Condition	N	Preferences for characteristics or approach to carrier screening
			• -11 (7%) and 16 (10%) did not offer screening for thal or CF, respectively, to any patients 8 (5%) and 3 (2%) routinely offered screening for FXS and SMA, respectively Providers reported moderate levels of concern for potential psychological harms to the patient due to increased anxiety Minor level of concern for: • Increased number of pregnancy terminations if additional conditions are screened • Rarity of inherited conditions compared with other pregnancy issues • Liability from not offering screening if the person has an affected child for whom screening is available • Availability of supporting services to help with result interpretation and patient counselling • Time spent on arranging screening, patient education, and result follow-up Mean rating for practical aspects of beta-thal and CF screening (from 1: very poor, to 5: excellent) • Ease of test access: 4.0 for thal, 3.7 for CF • Test cost: 3.4 for thal, 2.9 for CF • Accuracy of test: 3.7 for thal, 3.6 for CF • Availability of lab and counselling support to help with interpretation and results follow-up: 3.6 for thal, 3.6 for CF • Availability of educational materials to help counsel people: 2.8 for thal, 3.3 for CF • Community awareness of condition: 2.3 for thal, 2.5 for CF Other concerns about carrier screening • Equity of access and distributive justice from the perspective of disadvantaged or multicultural populations • Limiting testing to high-risk populations • Targeting PC/PN couples • Potential harm through creating perception of eugenics • Potential for stigmatization • Raising questions regarding paternity • Impact on life insurance • Lack of cost–benefit evidence • Need for policy-driven screening
Valente et al, 2020[267]	CF	87	31 (35.6%) reported offering CF carrier screening to all people they see for PC and early PN appointments 36 (42.4%) only offered screening in certain clinical situations (most common reason for screening was personal or family history of CF) • 20 (23.0%) did not offer CF carrier screening to patients • Low referrers were more likely to agree that there is a lack of awareness of screening among HCPs (P = .001) • High referrers were more likely to perceive screening as a routine test (P = .022) and agree that screening options would increase in the future (P = .002)

Author, year	Condition	N	Preferences for characteristics or approach to carrier screening
			83 (95.4%) agreed that people should have information on the availability of screening 76 (87.4%) agreed that screening is a patient choice 80 (92.0%) agreed there is lack of community awareness for screening Low referrers perceived more barriers to offering screening compared with high referrers (*P* = .037) 89% of low referrers and of 69% high referrers reported testing cost as a barrier 73% of low referrers and 58% of high referrers reported people's assigning a low priority to CF testing in PC or early PN as a barrier 80.3% of high referrers and 45.9% of low referrers considered time constraint as a barrier (*P* = .031)

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; CF, cystic fibrosis; FXPOI, fragile X–associated primary ovarian insufficiency; FXTAS, fragile X–associated tremor/ataxia syndrome; FXS, fragile X syndrome; GP, general practitioner; HCP, health care professional; PC, preconception; PN, prenatal; SMA, spinal muscular atrophy; thal, thalassemia.

SATISFACTION FOR CARRIER SCREENING

During the Preconception or Prenatal Period

Three studies[84,268] reported on satisfaction for carrier screening among people in the preconception or prenatal stage (Table 33). In general, participants were satisfied with the carrier screening process and their decision to accept or decline screening.

Table 33: Satisfaction for Carrier Screening Among People During the Preconception or Prenatal Period

Author, year, country	Condition	N	Reported satisfaction for carrier screening
Alfaro Arenas et al, 2017[84] Spain	FXS	607	Mean satisfaction scores[a] • Information provided on FXS: 8.4 • Care provided during carrier screening process (from offering to result delivery): 8.6 • Care received after test results: 8.6 • Time between blood collection and receipt of results: 8.2
Ioannou et al, 2014[254] Australia	CF	54	Satisfaction with reason to decline • 72% felt they had made the right decision • 58% felt decision was wise • 72% would make the same choice if they had to choose again • 14% felt decision did them a lot of harm • 9% regretted their screening choice Satisfaction with pre-test information

Author, year, country	Condition	N	Reported satisfaction for carrier screening
			• 76% believed they had enough information to make their decision to decline screening • 80% were satisfied with information provided • 20% sought further information
Prior et al, 2010[257] United States	SMA	392	After result disclosure, 98.7% were glad they pursued screening

Abbreviations: CF, cystic fibrosis; FXS, fragile X syndrome; SMA, spinal muscular atrophy.
[a]Scale of 1–10, where higher score indicates greater satisfaction.

Health Care Providers

We did not find any studies on the satisfaction of carrier screening for health care providers.

KNOWLEDGE AND AWARENESS OF CARRIER SCREENING

People in the Preconception or Prenatal Period

Table 34 presents the results for knowledge and awareness of carrier screening among people who are in the preconception or prenatal stage. Knowledge and awareness varied among the study participants (i.e., reported knowledge levels ranged from low to good). Possible predictors for increased knowledge within the studies included older age, more education, family history of the condition, positive attitude toward screening, people without an affected child, and multigravida (pregnant for at least a second time). Knowledge was also lower among people who were not offered carrier screening compared with those who were.

Of the studies that reported on informed choice, possible predictors of low informed choice included being a non-native speaker (i.e., the questionnaire had to be translated for the person) or being from a high-risk ethnicity.

Table 34: Knowledge and Awareness of Carrier Screening Among People During the Preconception or Prenatal Period

Author, Year	Condition	N	Knowledge and awareness of carrier screening
Alfaro Arenas et al, 2017[84]	FXS	3,731 PC: 318 PN: 3,413	950 (25%) had heard about FXS before testing
Ames et al, 2015[247]	FXS	241	Knowledge score: of 10 questions, mean 6.6 (SD: 2.0), median 7 (IQR: 5–8, range: 0–9) 172 (71%) had good knowledge of FXS (score ≥ 6)
Brown et al, 2011[252]	SCD, thal	464	30.6% thought they made an informed choice to accept or decline screening • Predictors of making an informed choice: more education, older age • Predictors of making an uninformed choice: having questionnaire translated, being from high-risk ethnicity

Author, Year	Condition	N	Knowledge and awareness of carrier screening
			34.7% had good knowledge of screening • Predictors of good knowledge: older age, more education, telephone questionnaire completion • Predictor of poor knowledge: having questionnaire translated
Ghoreyshyzadeh et al, 2017[269]	Thal	282	Respondents had low to average knowledge • Knowledge of how thal couples are referred for genetic tests: mean 3.11 (SD ±1.09) • Intensive care of carrier couples: mean 3.31 (SD ±1.02)
Hanprasertpong et al, 2018[245]	Thal	1,006	81.7% correctly responded that carrier status could be determined by blood test 68.2% correctly responded that an affected child may inherit the pathogenic variant from both parents • Statistically significant factors associated with knowledge score: older age, more education, family history of thal, positive attitude toward screening, not first pregnancy
Ioannou et al, 2014[253]	CF	158	Fewer than 50% of participants answered all knowledge questions correctly More than 50% of participants selected "unsure" to all knowledge questions • Knowledge was significantly lower in people who were not offered screening compared with those who were offered ($P < .01$) • People who were not offered screening more often chose the "unsure" response option
Ioannou et al, 2014[268]	CF	54	25 (47%) correctly answered ≥ 10 of 15 knowledge questions Fewer than 25% correctly answered knowledge questions related to residual risk after carrier testing • Knowledge was significantly lower in people who declined screening vs. people who accepted it ($P < .01$)
Ishaq et al, 2012[270]	Thal	115 families	33% knew that a test was available for detecting carrier status 12.2% were able to name the test used for detecting carrier status
Mayo-Gamble et al, 2018[256]	SCD	300	42.6% had partially or completely correct responses to sickle cell trait screening knowledge questions
Metcalfe et al, 2017[68]	FXS	961	85.0% (95% CI: 82.5%–87.1%) had good knowledge of carrier screening • No significant difference between pregnant vs. nonpregnant people (83.5% vs. 86.9%, respectively, $P = .145$) • Significant difference between tested and not tested people (85.6% vs. 67.2%, respectively, $P < .001$)

Author, Year	Condition	N	Knowledge and awareness of carrier screening
Prior et al, 2010[257]	SMA	392	Among people who accepted testing, 76.4% knew nothing about SMA prior to their pre-test counselling session • 74% thought the patient education material provided to them was very helpful, 26% thought it somewhat helpful
Vuthiwong et al, 2012[259]	Thal	100	71% agreed/highly agreed that they clearly understood the reason for carrier screening 52% agreed/highly agreed that they distinctly understood about thal 53% agreed/highly agreed they had enough information about thal from their physician
Widayanti et al, 2011[260]	Thal	180 (74 had affected child, 106 did not have an affected child)	18% of people had heard of carrier screening for thal People without an affected child were significantly more likely to have heard about carrier status of thal before compared with people with an affected child ($P < .001$) 91% of people without an affected child either did or may know a person with thal
Wood et al, 2016[65]	SMA	90	More than 90% of respondents correctly answered 8 of 9 knowledge questions
Zafari et al, 2016[261]	Thal	327 carrier couples	74% had acceptable knowledge of carrier screening (≥ 6 of 11 correct answers)

Abbreviations: CF, cystic fibrosis; CI, confidence interval; FXS, fragile X syndrome; PC, preconception; PN, prenatal; SCD, sickle cell disease; SD, standard deviation; SMA, spinal muscular atrophy; thal, thalassemia.

Health Care Providers

Table 35 presents the results of knowledge and awareness of carrier screening among health care providers. Knowledge and awareness varied among the study population but were generally high among providers. Most providers felt comfortable offering and interpreting carrier screening results, although some preferred to have additional training. Different types of providers may be more knowledgeable about screening or comfortable with offering carrier screening (e.g., increased knowledge among general practitioners compared with midwives, and providers with high referrals for screening compared with those with low referrals). In addition, providers who were associated with academia were found to be more knowledgeable than those who were not.

Table 35: Knowledge and Awareness of Carrier Screening Among Health Care Providers

Author, year, country	Condition	N	Knowledge and awareness of carrier screening
Darcy et al, 2011[264] United States	CF	143 obstetricians, perinatologists, and their equivalent (e.g., GPs who provide obstetric services)	87.7% (95% CI: 81.5%–92.0%) were ware of ACOG guidelines for CF screening • No differences based on practice type of HCP • 81.7% (95% CI: 76.8%–86.6%) knew basic information about CF carrier rates • 82.3% (95% CI: 78.2%–86.9%) could accurately interpret and explain example CF screening results • HCPs associated with academia were somewhat more likely to interpret and explain CF screening results correctly vs. those who were not (86.3% vs. 77.8%, respectively, *P* = .056) • 83.2% (95% CI: 77.7%–89.0%) were comfortable interpreting and explaining CF test results • 57.0% (95% CI: 50.7%–63.8%) indicated they had information about CF carrier rates, screening sensitivities, and residual risks • HCPs associated with academia had significantly more access to this information than those without academic ties (64.9% and 48.6%, respectively, *P* = .014)
Jans et al, 2012[265] Netherlands	HbP	1,346 Midwives: 795 GPs: 511	GPs felt somewhat more able to perform carrier testing compared with midwives
Stark et al, 2013[263] Australia	CF, thal, FXS, SMA	156 obstetricians	Minor concern regarding: level of comfort at discussing genetics with patients, level of familiarity with genetic and clinical aspects of conditions screened 93 respondents (60%) would like more training on population-based screening
Valente et al, 2020[267] Australia	CF	87 HCPs with Victorian Clinical Genetics Services	32 (36.8%) answered all 7 knowledge questions correctly 64 (73.5%) answered at least 5 of 7 questions correctly High referrers had greater knowledge of CF and carrier screening compared with low referrers (*P* ≤ .001) Most common incorrect questions were about the presence of residual risk after testing Patient and provider knowledge of CF and screening were more likely to be considered barriers by low referrers (*P* = .031 and .001, respectively)

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; CF, cystic fibrosis; CI, confidence interval; FXS, fragile X syndrome; GP, general practitioner; HbP, hemoglobinopathy; HCP, health care provider; SMA, spinal muscular atrophy; thal, thalassemia.

Discussion

Our review found that most people who are considering pregnancy or who are pregnant and most health care providers were supportive of carrier screening programs. Most study participants preferred preconception compared with prenatal carrier screening because of the greater

reproductive options and time for decision-making at this earlier stage. People were generally satisfied with carrier screening.

We found a wide range of patient preferences and factors influencing people's decision to accept or decline carrier screening programs (e.g., personal or religious beliefs, desire to know their carrier status, psychological impact of testing or test results, test cost, perceived risk of being a potential carrier, and time). Some factors were more influential in certain populations, indicating the possible range of preferences and attitudes on carrier screening. Whether to be screened for carrier status is a personal choice, and testing information should be presented clearly for the person or couple to make their best-informed decision.

We also found variability in the knowledge and awareness of carrier screening among patients and health care providers, which was likely due to the geographic heterogeneity of the included studies and the different types of health care providers surveyed. People's knowledge was found to be low or poor in some studies, which highlights the importance of consistent education about carrier screening and the conditions that are tested. In general, we found that most providers had good knowledge of carrier screening and were comfortable with offering carrier screening to people. Providers who specialize in pregnancy or genetics or are affiliated with academia may have increased knowledge compared with more general health care providers.

Due to study heterogeneity, it was difficult to compare results between studies. For example, personal and religious factors that influence preferences may differ among people. There are also differences in people's views on termination of pregnancy and having a child affected with a particular condition. Study authors often developed their own questionnaires and surveys, which makes direct comparison between studies difficult. There was often no mention of testing or validation of the questionnaires and surveys used in the studies.

The importance of test cost and equitable access was noted by people who are considering pregnancy or who are pregnant and by health care providers. Test cost was an influencing factor, and those with higher incomes were willing and able to pay more for screening. A willingness-to-pay study on expanded carrier screening panels found similar results—that people value test results, but high test costs could result in health care disparities.[271] People willing to pay nothing or only a small amount cited financial resource issues, while those who were willing to pay higher amounts were motivated by "peace of mind" from the test results.[271] Similarly, some studies found that people supported publicly funded carrier screening programs.

We also found that health care providers may experience barriers to offering or implementing carrier screening. Our results aligned with reviews on health care providers' perceptions of carrier screening programs. The main themes were the use and potential impact of carrier screening programs (e.g., equitable access to screening, potential psychosocial impact on the tested person), the providers' beliefs and expectations (including perceived ability to deliver screening, knowledge and support required to deliver screening, expectations and potential external circumstances influencing views), and the available resources (e.g., provision of genetic counselling, variation in potential service models, and nonclinical resource barriers such as responsibility and time).[241,242]

One of the limitations of our review is our exclusion of studies on expanded carrier screening panels that did not report separate analyses for one of our conditions of interest. People's preferences for expanded carrier screening panels may be different since panels typically include a large number of

conditions, which may vary in clinical severity and clinical presentation. However, the overall conclusions of studies align with our results.[59,61,63,196,243,244] Studies found overall support for carrier screening, that counselling and educational strategies are essential, and for the importance of supporting the possible psychosocial impact of testing. While our review focused on four specific conditions, our broader results may also apply to additional similar genetic conditions included in some carrier screening programs or expanded carrier screening panels.

Conclusions

- Most people who are considering pregnancy or who are pregnant and health care providers supported carrier screening programs because of the potential to identify carriers and the potential impact of the information on people's reproductive choices and decision-making
- There are a wide range of factors that may affect a person's preferences for carrier screening, such as personal or religious beliefs, desire to know their carrier status, psychological impact of testing or test results, test cost, perceived risk of being a potential carrier, and the time required for the carrier screening process
- There was concern from people that identified carriers may experience an impact on partner relationships, stigmatization, and private insurance eligibility or cost, along with issues of privacy and confidentiality
- Health care providers had concerns regarding equity of access to testing, limited testing among high-risk populations, psychosocial impacts and potential stigmatization of people, and potential impact on people's private insurance, along with test cost and the cost-effectiveness of screening
- People were generally satisfied with the carrier screening process and their decisions on screening
- Knowledge and awareness of carrier screening varied among people who are considering pregnancy or who are pregnant and health care providers, but providers generally had good knowledge and awareness

Qualitative Evidence

Ontario Health collaborated with CADTH to conduct this health technology assessment. CADTH conducted a review of the qualitative literature on the expectations, experiences, and perspectives on preconception and prenatal genetic carrier testing programs of adults and their reproductive partners, related family members, and health care providers.[175] We have summarized the key findings of this review below.

Key Findings

- The rapid qualitative evidence synthesis included 11 primary studies
- People in all included studies described wanting access to genetic carrier screening as they felt knowing about genetic risk could support their desire to be prepared
- Supporting informed decision making may involve both providing descriptive information on possible screening results and facilitating conversations on potential ramifications to people's lives
- People across studies universally wanted access to preconception, as opposed to prenatal, carrier screening
- If prenatal carrier screening is the only option, accessing it as early in the pregnancy as possible is desirable
- People felt that sequential carrier screening of reproductive partners may place undue anxiety on the prospective parents if there was a long waiting period for the second set of results
- The opportunity to engage with genetic counselors in the event of a positive result was considered valuable

Direct Patient Engagement

Methods

PARTNERSHIP PLAN

The partnership plan for this health technology assessment focused on consultation to examine the experiences of people with a positive carrier status for certain genetic conditions and those of their families. We engaged people via phone interviews.

We used a qualitative interview, as this method of engagement allowed us to explore the meaning of central themes in the experiences of people who sought genetic carrier screening as well as those of their families and caregivers.[272] The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that support our choice of an interview methodology.

PARTICIPANT OUTREACH

We used an approach called purposive sampling,[273-276] which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We approached a variety of partner organizations to spread the word about this engagement activity and to contact people with experience with genetic carrier screening and their family members and caregivers.

Inclusion Criteria
Adults with lived experience of positive carrier status for certain genetic conditions or their family members or who had sought genetic carrier screening. Participants did not have to have direct experience with any of the four genetic conditions or have received carrier screening to participate.

Exclusion Criteria
We did not set exclusion criteria.

Participants
For this project, we spoke with 22 people who had sought out genetic carrier testing who are living in Ontario. Seventeen were positive carriers for one of the four identified genetics conditions of this assessment. We spoke with people who had experience with one or more of these genetic conditions as well as people who were carriers of one of the genetic conditions.

APPROACH
At the beginning of the interview, we explained the role of our organization, the purpose of this health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants both verbally and in a letter of information (Appendix 26), if requested. We then obtained participants' verbal consent before starting the interview. With participants' consent, we audio-recorded and then transcribed the interviews.

Interviews lasted approximately 20 to 40 minutes. The interview was loosely structured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.[277] Questions focused on discovery of carrier status, the impact of this diagnosis for both the participant and their family members, their experience with genetic carrier testing, and their perceptions of the benefits or limitations of a potential carrier screening program in Ontario. See Appendix 27 for our interview guide.

DATA EXTRACTION AND ANALYSIS
We used a modified version of a grounded-theory methodology to analyze interview transcripts. The grounded-theory approach allowed us to organize and compare information on experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[278,279] We used the qualitative data analysis software program NVivo to identify and interpret patterns in the data. The patterns we identified allowed us to highlight the impact of genetic carrier testing on patients and family members we interviewed.

Results
CARRIER TESTING—AWARENESS AND PROMPTING
The people we interviewed came from diverse backgrounds and had varied initial familiarity with genetic carrier screening. However, due to the nature of our recruitment methods, most participants were positive carriers of one of four genetic conditions (SMA, fragile X syndrome, sickle cell anemia, or cystic fibrosis) or had the condition. Therefore, participants generally reported retroactively on carrier testing and its impact on their decision-making and family planning. Few participants were currently seeking carrier testing for decision-making or family planning. The results below are less indicative of the potential knowledge of the general population, who may be less familiar with these genetic conditions or the potential implications of carrier screening.

Participants generally reported that carrier testing was not something that they sought out unprompted prior to marriage or discussions with their partner around family planning. Some people acknowledged knowing very little about genetic testing or believing that it was not something that would impact them or their children. Many other participants commented that, while they were perhaps aware that genetic testing for carrier status existed, they were unaware of existing familial genetic conditions that would necessitate testing. Therefore, this was not something that they would have pursued prior to pregnancy without prompting.

> *To be honest, it wasn't on my radar. It was the first child on my side of the family to ever be affected by this disease…. I was very young. You know, "Oh, it will never happen to me. I'm healthy; I'm this, I'm that. This is never gonna happen to me."*

> *I feel like if we had any in our immediate family [with] known genetic conditions, I probably would have thought about it, but because [people] on both sides were generally healthy. And I mean I was happy to do the regular prenatal [testing], like the Down syndrome…. But no, we didn't think in advance that we should have any preventative type screening.*

> *And that time, we decided not to [get carrier screening] before we had kids. So we talked about that because we knew about CF. But we never talked about having carrier testing done for SMA because we didn't know anybody related to us or even know anybody who had SMA at that time.*

Most participants reported not seeking out genetic carrier testing unprompted; instead, there was typically a precipitating incident or new information that caused them to seek out carrier testing. This trigger to undergo carrier testing could come from various sources and circumstances; for example, a medical incident, the development of symptoms, or because they were starting to think about having children. Two participants reported being adopted and expressed a desire to know their carrier status in preparation for any future health concerns or family planning.

> *I'm adopted, so there's that side of it as well. By which I mean, I researched…because I wanted to know.*

> *In 2011, I stopped menstruating for no apparent reason. So I went to several different doctors…to figure out why I was no longer menstruating, because in 2011 I was 30 years old. So that's not typical. They did a ton of tests and finally, about a year and a half later, I got the results back that I have Fragile X. I'm a carrier.*

> *I did have screening as part of getting a marriage certificate and so I was a carrier. So then my husband had to get tested as well to make sure that we weren't both carriers.*

More frequently, participants reported seeking out carrier testing after being informed by family members of the birth of a child with a genetic condition or a close family member discovering that they themselves were a carrier. In some cases, there could be a precipitating medical event in the family, or an existing genetic condition could prompt a sibling to check their carrier status. Prompted by family members, participants reported that seeking out their own carrier status could be done for their own health reasons, for their own family planning, or simply for the value in knowing if they were carriers and may need to inform or test their own children in the future.

> *So, interestingly, on my dad's side, he had a sickle cell sister, but they never [told us], there was no warning. So I was not aware that I was a carrier until one of my sisters got pregnant and the doctor [who] was following her was more exposed to sickle cell and its impact in the African population.*
>
> *And it was a little form, it kind of looked like a requisition form and there was a letter attached that indicated that my biological family member, an aunt, had almost died because of [this condition]. So they decided to test the family or somebody said the entire family should be tested because my aunt was one of five sisters on my mother's side.*
>
> *My brother has CF and he was born in 1990, and then I was born a few years after that. So he was diagnosed around 6 months old. And then my parents knew that I didn't have CF, but they didn't do carrier testing when I was younger. So then fast forward, I got married in 2019 and then we started talking about what we would want to do for family planning. So I got carrier screening.*

Other participants reported that they were prompted to conduct carrier genetic testing once their newborn child had been diagnosed with a genetic condition, either through a newborn screening program or when they were further along in their development.

> *So my husband and I didn't…we had no idea, no one in our families has CF, no one was identified as a carrier. Our little guy was born in September, 2020, and [on] October 15th, we got a call from the newborn screening program.*
>
> *My spouse and I didn't do genetic testing or anything like that. When we were trying for children, we talked about it because…I was 34 when I got pregnant. And my spouse was pushing 40. So as older first-time parents, we thought maybe we would need fertility treatments and maybe we would get some testing done as a result of that in our process. But we actually became pregnant quite quickly. So we didn't get any sort of testing and so it wasn't until she was nine days old and the results came back from her newborn screening as positive for CF that we realized that we must be carriers. And we later confirmed that.*

A few participants faced the tragic circumstances of learning of their carrier status following investigation into the death of a newborn. In these circumstances, it was only after the tragic events that the parents learned of the cause of their child's death and their status as carriers of the genetic condition.

> *It wasn't until after we got his blood panel back with his SMN1 proteins that they figured out that we should be tested, my husband and I, and that's how we found out that we were carriers and what [our son] had actually had.*

ACCESS TO CARRIER TESTING AND SUPPORT

Overall, participants generally reported mixed access to carrier testing, with some commenting that they did not experience any exceptional wait-times or challenges in access. There could be an expected wait time as samples were analyzed, and some participants commented that genetic carrier testing could be added onto other tests for medical reasons, occasionally.

> *If it was quick, took maybe six weeks for the blood to come back from [hospital]. At the time it felt like a lifetime. But in reality, not that long.*
>
> *My husband has low hemoglobin. So as he was going in to do that test, he just asked for a full screening at the same time. It wasn't [a difficult process] because he was dealing with other health issues.*

Other people we spoke with felt that there could be barriers when it came to the logistics and bureaucracy necessary to obtain a referral for genetic carrier testing. Often this referral would need to come from a family doctor and there could be challenges in knowing where and how to access testing.

> *I have a great family doctor, but when I approached her around October, she actually wasn't really sure what to do and she said, "oh, let me get back to you and I'll look into it." So I think even at the family doctor level there probably isn't too much knowledge on how to get these types of things done. She did look into it, which was great, but I think obviously it's a specialty and they just don't have that kind of knowledge.*
>
> *We had the conversation [about carrier testing], but the doctor was also much, much older, on the brink of retirement…. So he may have just not been aware, I don't know.*

Additionally, there could be challenges in obtaining genetic carrier screening for the spouse/partner of participants. Often, genetic carrier screening is not done at the same time for both partners, but rather is done sequentially based on the results of the first screening test. This could cause frustration and delays for people who are anxious to know the results.

> *I got the results back and I actually am a carrier, so at that point, obviously, my husband needs to get tested as well. And that's the part where it gets even more complicated because the geneticist said, "OK, so now your husband needs to go to his family doctor and get a referral." And then I said "oh, so that will that take another five months?" because obviously you don't get into contact with your family doctor that quickly. And then they have to make their referral and then it kind of goes into a black hole for several months and you don't know where it is. So that was a bit frustrating.*
>
> *And then my husband is Filipino, so they said they wouldn't test him until mine came back because he wouldn't likely be CF carrier…. So they had me do the blood work, but I found it odd that they did test both of us for sickle cell and something else, so he was already doing blood work that day for other screening. So I thought it was weird that they wouldn't just add this CF test in with it.*

Conversely, participants reported that access to carrier testing could ease once one family member had obtained access; often the genetic counselor or a clinician would be able to write a referral for other family members to have access to genetic carrier testing, based on the initial positive test. This cascade testing allowed other family members to learn their carrier status relatively quickly and at little or no cost. This result may reflect the participant sample in our recruited population rather than a reflection of the status of cascade carrier testing in Ontario.

> *Once my son's blood test came back, the geneticist offered up a letter to anyone in my family to get that test. So once I was able to get somebody to get my son tested, my family was then able to access the test. It was getting my son tested that was the struggle.*
>
> *Now the benefit to having [an] appointment with [a genetic counselor] was that when my mom and my brother and my daughter and I think my aunt wanted to get tested, they could go to [the same counselor]. They didn't have to go searching around for whatever doctor would do this test, right?*
>
> *It is very difficult to get tested unless someone else in your family has already been diagnosed. And even then, they don't really want to do the testing. I imagine it's rather expensive to do genetic testing, but it's very useful.*

While the people we interviewed generally reported that access to carrier testing was not overly burdensome, many commented that this would perhaps not be the case throughout Ontario. Many raised concerns about the potential cost of carrier testing if it was to be paid out of pocket, or the necessity of traveling to have the testing done if not available locally. These potential barriers to access could impact decision-making and family planning for many in Ontario.

> *Because of my family history, I think we would have paid for [carrier testing]. But we did choose not to pay for all of the other [genetic conditions] that they would have tested for.*
>
> *So I found it more affordable for me. But I could mention it to my children and they would say "I'm not paying for that!" Do you know what I mean? It would be something that they wouldn't consider to do for themselves. So it's each individual. For me it was worthwhile because I felt like it's something I really wanted to be aware of, what health issues there might be.*
>
> *My brother and sister-in-law live in southern Ontario. They drove down to McMaster [and] had the test. But what does that look like if you live somewhere else in Ontario? What does that look like if you live in Northern Ontario and there's enough expenses getting places, let alone if the test isn't covered, right?*
>
> *Well, luckily, they paid for everything when we were there. Thank God. Because we never would have been able to afford it.*

Beyond simply getting access to carrier testing and receiving the results, participants reflected on the value of receiving information about their genetic condition from an informed source, such as a genetic counselor. The ability to speak about the impacts and potential consequences of results of carrier testing was seen as a highly valuable aspect of testing and helpful in decision-making. This was especially true as some participants reported that their family doctors were not particularly informed about certain genetic conditions and the potential impact of a positive carrier screening test.

> *We did meet with the genetic counselor there and she explained the chances of having a child with CF…or passing on the gene if one or both of us were carriers and a little bit more about the math behind it.*

> *So my family doctor had fully admitted…he is great…he had reached his maximum of his general practitioner knowledge. So he was willing to make any referrals I needed.*
>
> *Those are the things that I like to know then from a genetic counselor; identifying it is one thing, [but] where do we go from there is my sort of question right now.*

IMPACT OF POSITIVE CARRIER TEST—SELF

Obtaining carrier testing and receiving a positive result could have an enormous impact on people, their families, and their partners. Whether the positive result was expected or a complete surprise, participants reflected on the significant effects on themselves and the emotional repercussions that could occur. One of the more immediate impacts for some people was related to their own health; for some genetic conditions, being a carrier had health implications, and identifying the causes of these health concerns allowed some people we spoke with to learn to manage and treat their symptoms.

> *Based on my numbers and based on me being followed, I have different medical profiles. So I can have maybe some bone challenges or muscle issues. I can have psychosomatic things like depression and more susceptibility. I could have early ovarian failure and early menopause. There [are] multiple areas of the carrier [status] that will impact my medical health.*
>
> *But if I had known I was a carrier and maybe I'm more susceptible, maybe I would have pushed my doctors a bit further to get on a medication. There's so many layers to that conversation.*
>
> *With that [positive carrier result], I guess that also opened up my world for, "OK, that explains maybe in my pregnancy that was a bit more faced with postpartum depression" and [the doctor felt that it] could have been related to me being a carrier.*

However, beyond the immediate health impact for the carrier, there were the emotional implications of a positive test result. A number of participants spoke of the initial shock at learning of their carrier status and, for some, the shock of learning that their offspring had a full mutation of a genetic condition. This could especially be true if there were no previous indication of a genetic condition in the family. In some cases, participants were informed that their child had a genetic condition many months or years into their diagnostic journey. Participants spoke of this shock, but also of other emotions such as guilt and regret, knowing that they had passed on their genetic mutation to their children.

> *That was obviously a shock, right? Not knowing anything about this before and, again, I'm a mom [who] has already had three other children. And so it was definitely something,… it's not easy to accept.*
>
> *It's a very emotional journey…I fell into a deep depression finding out the diagnosis because my world was just changed dramatically. I didn't know anything about it.*
>
> *I work closely with a mom who has a story where she's the carrier. And I remember thinking like, "Oh, how do you deal with that guilt? How do you deal with it?" But now I know you don't.*
>
> *In our case, and me specifically, when I learned that my son was sick with sickle cell, although we decided to pursue [a family] at the very beginning, there was that guilt part. Because it's*

always you have one chance out of; it's as if you are just taking a chance. I took a chance and now my son will live with this for his entire life.

Despite these challenging circumstances, some people we spoke with reported being relieved to know about their carrier status. Overall, they acknowledged how the experience could be both positive and negative from the patient perspective. Many perceived that learning their carrier status could be positive by allowing for a greater degree of control in decision-making and input for future planning. Additionally, some participants reflected that learning of their carrier status allowed for them to make more informed decisions when it came to family planning, which they viewed as beneficial despite how challenging it could be to act on those decisions..

It's a double-edged sword. We're happy to know, and also it was the worst day of our entire lives.

I like to know because I'm just more that way; I want to know if I can do something. If I have a health condition, I'd like to know that I can do something preventative-wise instead of just ignoring things. So I thought, "Hey it wouldn't hurt. Let's do it." That's why I decided I'm just going to do [carrier testing].

I think in time in terms of moving forward, the best thing to do is to get tested because, obviously, if my husband and I are both carriers, then we probably would look at IVF, which is another long process to undertake. Especially I think at this age, being in our early to almost mid-thirties, that it's really kind of top of mind. So I did want to get tested, but I can see it could be an awkward conversation for families where maybe they aren't as close or they don't fully understand how CF works in terms of genetics.

IMPACT OF POSITIVE CARRIER TEST—FAMILY

Receiving a positive carrier test result not only impacted the health and emotional status of individuals, but also their family members and partners. Some people we spoke to reflected on this impact from their experience as the positive carrier, while others reflected on it as a family member of a positive genetic carrier. Many participants spoke of the downstream effect of a positive test result: specifically, how it can place a burden on family members and cause anxiety and stress, affecting family dynamics and partnerships.

He got tested [and] he doesn't have the gene. So thank God for that, yes. So now that is a huge help to his mental health.

Mom didn't get tested. So I was like, whatever, I'm not gonna push it. It's not a big deal. I also didn't want any guilt to go with this because there's also a big level of guilt when it comes to carriers. There's a level of emotional processing of passing something down to a child. And it was generational there.

Yes, it was [hard emotionally]. For my mom it was really hard. I could feel just in her voice how bad she felt. Like it's not her fault but she felt very guilty for being a carrier, right. And I think more importantly for not knowing that she was a carrier.

It's, of course, nobody's fault. But it put a massive amount of stress on our relationship because it didn't really bug my brother that much when it was me and my baby [who were] impacted. But all of a sudden, when it was his first baby to be, it became an entirely different story. So if they

> *had been screened and both of them were fine and we already knew that we could have avoided the entire situation, [that] would have been good.*

Other impacts of a positive carrier test result were of a more practical nature; the necessity of talking with extended family members and informing them of the positive test result and potentially helping to guide them into getting their own testing done. For some people, this was a relatively straight-forward process; however, others found resistance to testing among family members or resistance to receiving carrier information.

> *No, they never did [show interest in getting tested]. But I don't think that they realized the magnitude of what I have because I'm not that close with them. So they see that I walk a bit different and I've told them what I have, but they've never really been interested in taking it any further.*

> *They offered to test my husband at the time to see if he had a gene in his family so we would know more about the kids, but he didn't want to be tested.*

> *It was a mixed bag…. Some of my family members, like my mom for instance, were like, "Yeah, that explains a lot of things. And I probably do have that." So she was pretty game to get tested. Other family members were not on board with it. They didn't really believe it was a thing and there was resistance there, they didn't want to accept it, I guess.*

Some participants reflected that discussing a positive carrier status and informing partners could be an emotional and complicated process. For family planning purposes, having both partners carrier tested was seen as practical; however, there could be resistance from partners for cultural or emotional reasons.

> *That's more of the belief that we have…. It was like…because he's chubby and a well healthy man, he was like, "Me? No." And me, I'm so small and tiny and usually people will go, "Oh of course she has the [carrier] trait because she's tiny and stuff." So he was like, "Me? No never," so we never tested [him] because he was almost never sick.*

> *My husband [is] from a very [cultural] background and I think a lot of disclosing personal information, there comes a certain shame aspect to it and embarrassment. So I think that the family didn't want to talk about any of that because they were embarrassed, or they were ashamed that they had this genetic mutation and it caused harm to their baby and they didn't want to answer any of the tough questions. But it wasn't until we started asking questions that the information actually came out.*

Additionally, some people we spoke with reflected on the burden of whether to inform their children that they might also be carriers. Participants felt that it was a difficult decision and they reported giving consideration to different factors, such as the child's age and whether the child's carrier status may have implications for their health or quality of life going forward. Some participants felt that the children should be allowed to make that decision for themselves when they became adults, while other parents wanted to have their children aware of their carrier status as early as possible. One individual who was a carrier reported that she wished her parents had made the decision for her as a child, rather than go through testing herself as a young adult.

It was recommended that we test our kids, [but] we weren't ready to do that right away. The doctor definitely said we should, …but we weren't ready emotionally. We said it's certainly something we want to look into, but not yet.

To actually have a sit-down conversation with [my son] and say, "Mom has this. You could have it in the future," I haven't had to parse with him. And I think it might be something…he's a pretty intuitive little dude. I think it would be something he would be very interested in knowing proceeding forward…heaven forbid that he should be dating sometime….

The valuable thing for us at this age is then we can guide her, right? So she's not finding out when she's 25 and then she's like, "I never knew about this," which is kind of where I was at. So I think now we can actually help her, guide her through that conversation as parents. I think that's a really big thing.

Personally, I would have preferred if [my parents] just did it when I was born. Just to know. Because it adds that extra layer of conversations. Either way, we would have wanted to get my husband tested, but it would have been nice to just know from the beginning.

CARRIER SCREENING PROGRAM

We asked the participants to reflect on the potential of a hypothetical Ontario-wide carrier screening program for the four genetic conditions included in our analysis. Participants were encouraged to consider their preferences and values when it came to what would be included in such a program and what would be important, based on their experiences with carrier testing and its impact on themselves and their family members. Timing, access to information and patient education, and perceived benefits, as well as implications were all discussed by the participants.

Timing

In general, participants had a strong preference for the availability of carrier screening for the four genetic conditions through a provincial program. One aspect of the program that participants emphasized was the timing of the testing. Most participants felt that the earlier testing would be better than later testing as it would allow them to make informed reproductive decisions with their partners. Many commented that a positive carrier test would not have resulted in a different decision regarding having children, though this may be a bias due to the method of finding and contacting people for our interviews. Participants acknowledged that other individuals may make different reproductive decisions based on carrier status, but felt that having that information as soon as possible allowed for the most flexibility and informed decision-making.

I personally think that a carrier screening program is important, especially for people planning to have a family. Now, I would not have changed my decision to have family, but I'm sure that there are people who would have changed their decision to have a family if they knew ahead of time that they were a carrier and that their child could have problems because it is difficult to raise [a] child who is not typical.

I would have liked to know that [earlier] because it would be…obviously if I was a carrier and my spouse was a carrier, we would know before planning to have children what [the] percentages were and do testing that way. To me it would be important.

> *"When?" is the question. When do you have the screening? I think as early as possible, and if it's like one of those things where you know your blood type, you also know if you're a carrier or not because once you get…once you're in a relationship or once you're thinking about conceiving, you need to have that information available to you.*

Another timing issue mentioned by people we spoke to concerns the testing of both the individual and their partner. Often, participants reported that this process was done sequentially, with gaps of weeks or even months between results from the first to the second test. For family planning, this time lag between the first and second test could have negative consequences and emotional impacts. It was felt that having both partners tested at the same time would be of great value and could reduce anxiety caused by the delay.

> *I didn't understand why they wouldn't do both together, especially since they were testing me for things like sickle cell. And he was doing blood work already that day.*

> *It does add that; "OK, I got mine. But now we have to go through [the anxiety] all over again with his." So I would have loved if it [were] both of them together.*

> *If they were all a part of the same screening experience, I think that would just be easier for everyone. And yeah, doing them together would have made it a lot less stressful [instead of] two separate experiences.*

Information and Education

People we spoke with also commented on the essential need of a carrier screening program to provide information and guidance on carrier testing and the consequences of a positive result. As shown previously, the information provided by carrier testing could have an enormous impact on individuals and families, and many people reflected on the value they felt in the ability to discuss all potential ramifications.

Within their strong preference that the carrier screening program include education, participants also reflected on many nuances of how and when this information could be provided. For example, there were differing preferences on the timing of sharing testing results, particularly in the case of children, whose testing is arranged by their parents—whether it is more effective to provide the information earlier, while not overwhelming an individual who is not prepared to understand it.

> *I think you can have information overload; like we're saying [my son] at 11. He can't comprehend all the information he'd be getting, but my biological family was 15 when they conceived with me. So, I think teenagers even need to be made aware because unfortunately, teen pregnancies happen and that kind of thing. I think they need to be made aware of the possibility [that] their kids could have these diseases or disabilities or whatever that will have implications for the rest of their lives.*

Participants also reflected on the nuances of where the information comes from and how it is presented. While receiving this type of information from a trusted source such as a family doctor was seen as valuable by some people, others acknowledged that the expertise to convey all the intricacies of a positive genetic carrier result may best come from a genetic specialist counselor. People also reflected on the need for this information and discussion to be fulsome, but unbiased, to

provide individuals and partners who may be planning families support in making their own decisions without judgement.

> *I would say probably your family doctor level—even just the introduction of it at that level. I know they probably are bombarded with stuff that they already are responsible for, but I think they've got the family history for the most part, so they may pick up on something at that level and be able to say, "you should speak with a geneticist, you should speak with this person. Here's the literature or the information if you want to take it forward."*
>
> *We wouldn't have made a different decision, but I think there's a responsibility from the medical community to not just give the information and then say, "You're on your own" or to sway a decision, right?*
>
> *I think it has to be multi-pronged because there's so many different levels of people and their understanding. So it actually isn't my family doctor that I'm super comfortable with. It was the specialist who diagnosed [my son].*

Drawing from their own experiences, those who we spoke with reflected on the emotional impact of their positive carrier test and they emphasized the potential value of a carrier screening program to help mitigate this impact through supportive discussions with experts.

> *I think there's always trying to find that balance between education and creating fear. And I would have no suggestions on that, but providing a program that highlights this could be beneficial, [while] also trying not to scare people.*
>
> *I think that this screening program, while helpful, would need to be followed up with education and resources…. Just giving screening alone and "Oh, hey, you might have a child with a disability," I think that information by itself can be very scary for a young family. I think that it would need to be followed up with some sort of research or…counseling education. Where they know that, "What are the options, and what can we do?" as opposed to just making decisions based in prevention.*
>
> *Not even just the screening program being important, but having follow up to it would be the biggest thing, right? Like it not being just, "Here's your results," but having meaningful follow-up.*

Potential Medical Benefits

When considering the possibility of a provincial carrier screening program, participants reported that the potential medical benefits would be of great value. Participants stated that, for some of the genetic conditions in question, early intervention and treatment can make a significant impact on the well-being of the affected individual even if the carrier status did not alter the family planning of the parents. Knowing their carrier status could allow parents and medical staff to monitor closely for the genetic condition in the offspring and begin treatments or interventions earlier, potentially having an enormous medical benefit over the lifetime of the child. A number of participants reflected that if they had known their carrier status and begun treatment of their child earlier, it could have reduced their medical needs and improved their quality of life. It was felt that a provincial program that allowed for earlier treatment at a population level would increase the impact.

> *Especially with my daughter, because she's full mutation, it would have been so much nicer had we found out earlier, because early intervention is a big deal, right? I think the screening would be incredibly beneficial to parents.*
>
> *At least if there was screening, you would know to put extra scrutiny on those sorts of things and to watch for [clinical indicators]. That's just something that the screening is [good for], setting aside the idea of what do you do with that information? Well, one of the things you do with that information is, you know what to look for. And there could be a CF team or a genetic specialist in place during the pregnancy to make sure to catch that and to intervene if needed.*
>
> *I imagine early detection…and then for the carriers, they may or they may not decide to have children, but if they do decide to have a child and the child has the disease, the earlier interventions in the course of most diseases, the better.*
>
> *The gene therapies are amazing. When he got access to them, it certainly changed…like when you talk about the kind of cost analysis you do, he's a super expensive kid versus if there was screening for us or screening for him earlier that could have made a huge, huge difference.*

Some participants reported feeling that the potential medical benefits would not be limited to those individuals with full mutations, but would extend to the carriers themselves. With some genetic conditions, the carriers also experience symptoms. With a carrier screening program, these individuals may also obtain treatments or interventions.

> *I just think that it would be so wonderful if people could learn about this just for the amount of things that it branches out into…. All of the symptoms that carriers feel, I just think it's important and would love to see it happen that it be more common.*
>
> *What should be done for this specific illness is, if you were somebody [who is] a carrier, depending on whether it was single banded or double banded, you can prevent a person from possibly having some cancers and different expensive illnesses down the road. So it would be looking at the cost versus prevention.*
>
> *The other situation is, [what if] I have a question mark about a condition and I believe genetic testing would allow me to get proper medical care? Right now I just don't see any options for having that genetic testing.*

Other Benefits

Beyond the potential medical benefits, some participants identified other benefits that they perceived from a carrier screening program. Many people we spoke with had direct experience with family members with full genetic mutations and reflected on the support sometimes required to care for these family members. Even if a carrier screening program could not provide any direct medical benefit, it was felt that the awareness and information could allow families and communities to prepare themselves for this responsibility and the impact on their lives. Additionally, earlier identification of genetic conditions may open access to social programs and support. Access to carrier screening could allow earlier identification of a full-mutation in children and therefore earlier access to these types of programs.

That's the whole point; knowing is good. But now, let's approach it as a community, as a family, how can we support this child, how can we support this community, the disabled community?

I think it helps families to be able to know what limitations, what they can expect, because there's a lot of costs involved. There's a lot of everything. They have to be ready to handle [it].

I think I would have liked to have known. It would have still been hard, obviously, but it wouldn't have been like 100% out of the blue. It maybe would have been…at least it would have been on my radar and I would have been like, "OK, if this happens, then we can think about this, talk about this." As opposed to…getting that call and being like, "Do you know what cystic fibrosis is?"

Ethics and Equity

Though unprompted, a number of participants commented on ethical and health equity aspects of a provincial carrier screening program. While many participants commented specifically on the value of the information that carrier screening could provide, it was acknowledged that this raises ethical issues of family planning when choosing to potentially terminate a pregnancy. Many participants acknowledged this as a potential ethical concern, but emphasized that carrier screening information would be valuable in preparation to support a child, and not exclusively for terminating a pregnancy. This could be an emotionally challenging aspect of a carrier screening program, with strong sentiments, even among family members.

Can we support these children? Can we support them as adults? I think that's so powerful and so important out of this carrier screening and not just an emergency response; we're not identifying this to freak out and fret and abort. Personally, for me it's identifying it so we can make decisions to provide our society and our community and those children, those adults with the right support and services.

I hope that wouldn't be Ontario's goal, to eliminate these genetic syndromes or genetic conditions. So the goal here is to identify, support the individual, support the parents [who] are having these children and the story that goes around…the community and the family. So I think that's the end goal.

My parents knew that we were getting the testing and, similar to the fertility doctor, it was kind of polarizing just among that small group…. We were getting a lot of strong opinions from different people about family planning if we had come back positive [and I] wasn't fully expecting that.

The concern with prenatal screening or pre pregnancy screening is the choices to terminate the pregnancy or the choice not to have children. So of course, from my perspective, being an adult with a disability who has lived for 40 years and had many successes and obviously impacted the world in my own way. The thought of that concept where parents would say, "Oh well, I guess I'm a carrier, so I guess I won't have children then," that's obviously a little frightening and certainly goes down a rabbit hole of some pretty dark things.

A few participants commented on the potential for a false-positive or false-negative in the test results and the challenges of making an informed decision when the information is potentially inaccurate. The principle of autonomy and informed decision-making can be obscured if the carrier information provided is not delivered in a way that is accessible for the individual patient. Language barriers and issues related to access can impede decision-making and prevent the affected individual from fully understanding all the implications of a carrier test result.

> *There's a lot of false negatives, there's a lot of ethical quandaries around that…I have a lot of concerns about testing and making decisions when you're pregnant, but I think the big thing is; if we had known we were carriers, we would have known what the symptoms of SMA were, and we would have probably been able to access treatment a lot faster. Or if we had known we were carriers, they would have tested our children for SMA when they were born or maybe in utero. Or maybe I would feel different about testing in utero if I knew I was a carrier of that condition and [my partner] was, right? So I think carrier testing has a huge value.*

> *For those families that have language barriers or intellectual barriers—that's where I think how you build into the support, how you plan to know that people are going to need additional supports after they receive the first boat of information. It's probably more important.*

> *I know that now, after 6 years of understanding this disease better, but I wouldn't have necessarily known that as a potential first-time parent, pregnant and scared, and not really sure what I was going to be dealing with. So I don't know. I don't know if I would have wanted to know to be honest, because there's nothing else you can do with that other than [be] prepared to have a child with CF or make the decision to terminate. There's no real other third option there, right? You either live with that knowledge or you make a very serious decision and live with that decision.*

Lastly, one person mentioned a concern around privacy and the potential for carrier testing to inadvertently identify parentage in certain circumstances.

> *If a child has a trait and the parents…say the mom doesn't have the [carrier trait] [and] the father [also] doesn't have the trait…. That means that somebody else [is the father].*

Preferences and Values Evidence Discussion

Participants provided diverse perspectives on carrier testing and the potential of an Ontario carrier screening program for CF, FXS, hemoglobinopathies and thalassemia, and SMA. The robust engagement allowed for a thorough examination of the implications and impact of carrier screening programs on the health, emotional well-being, and decision-making processes of individuals and family members.

Due to our outreach methodologies, participants were almost exclusively either positive carriers of one of the genetic conditions of interest for this HTA or had full mutations. Additionally, participants were typically no longer actively engaged in the family planning and decision-making stage of their journey, and so they were reflective in their discussions, rather than anticipating any potential future

impacts of carrier screening. Their reflections may not capture all those of the general population or those who will be considering pregnancy in the future.

Despite this limitation, the focused experiences and preferences of participants and family members who had experienced carrier testing directly provided perspective on a potential Ontario carrier screening program. They were able to comment on many aspects of this potential program, including some health equity and ethical implications. In this way, direct engagement through interviews generated a thematic analysis of diverse perspectives and values when it comes to carrier screening testing.

Preferences and Values Evidence Conclusions

Carrier testing has the potential to substantially impact individuals and their families through the disclosure of certain genetic traits. To capture this impact, OH conducted direct patient engagement and a quantitative evidence analysis on patient and provider preferences and values. Additionally, a review by CADTH of the published qualitative evidence was also included.

The quantitative evidence results found that most patients and health care providers supported carrier screening because of the potential to identify carriers and the potential impact of test results on people's reproductive choices and decision-making. There are a wide range of factors that may affect a person's preferences for carrier screening, such as personal or religious beliefs, desire to know, the psychological impact of testing, cost, perceived risk of being a carrier**,** impact on partner relationships, potential stigmatization, private insurance eligibility, privacy, and confidentiality.

Results from the qualitative evidence align with the direct patient engagement findings. People we spoke with valued the potential benefits of a carrier screening program in Ontario, focusing on the potential medical benefits to early detection and treatment and the social benefits of support and preparation for a child with a potential genetic condition. They emphasized that implementation requires thorough, unbiased education and information surrounding carrier testing and acknowledged the ethical and health equity concerns surrounding this topic.

Conclusions of the Health Technology Assessment

The uptake rate of carrier screening programs varied considerably among the included studies. Evidence on the downstream effects of carrier screening programs was limited. Carrier screening for CF, hemoglobinopathies and thalassemia, FXS, and SMA likely results in the identification of couples with an increased risk of having an affected pregnancy and likely impacts reproductive decision-making in terms of whether to continue with an affected pregnancy. Carrier screening programs may result in lower anxiety among pregnant people, although the evidence is uncertain.

Short-term cost-effectiveness analyses for preconception or prenatal carrier screening programs for CF, FXS, hemoglobinopathies and thalassemia, and SMA identified more pregnancies or couples at risk and offered more reproductive choice options. We found similar effectiveness of compared carrier screening strategies with respect to the number of affected births and the number of at-risk pregnancies detected; nevertheless, all carrier screening program strategies were more costly than no screening over the short term. Lifetime cost–utility analyses suggested small differences in quality-adjusted life-years between the carrier screening program strategies. Compared with no screening, we found cost savings with preconception or prenatal carrier screening programs, which were the largest with the universal programs.

Publicly funding preconception carrier screening programs over the next 5 years would require between $1.3 million and $2.7 million for risk-based screening or between $208 million and $491 million for universal screening. Similarly, publicly funding prenatal carrier screening programs over the next 5 years would require between $0.8 million and $1.7 million for risk-based screening programs or between $128 million and $305 million for universal screening programs. After incorporating the costs of treatment, program administration, and screening, we found a decrease of the 5-year budget impact for universal carrier screening programs (e.g., preconception universal carrier screening program with standard and expanded panels would result in additional 5-year costs of $170 million and $487 million, respectively), or cost savings for risk-based programs (e.g., preconception risk-based carrier screening program would result in total 5-year savings of about $4 million and $2.6 million with standard and expanded panels, respectively).

The quantitative evidence results found that most patients and health care providers supported carrier screening testing because of the potential to identify carriers and the potential impact of test results on people's reproductive choices and decision-making. There are a wide range of factors that may affect a person's preferences for carrier screening testing, such as personal or religious beliefs, desire to know, the psychological impact of testing, cost, perceived risk of being a carrier**,** impact on partner relationships, potential stigmatization, private insurance eligibility, privacy, and confidentiality.

Studies also found that people were generally satisfied with the carrier screening process and their decisions on screening, and that knowledge and awareness of carrier screening may vary among people who are considering pregnancy or who are pregnant and also health care providers.

Results from the qualitative literature review aligned with direct patient engagement findings. People we spoke with valued the potential benefits of a carrier screening program in Ontario, focusing on the perceived medical benefits to early detection and treatment and the social benefits of support and

preparation for a child with a potential genetic condition. They emphasized that implementation requires thorough, unbiased education and information surrounding carrier testing and acknowledged the ethical and health equity concerns surrounding this topic.

Abbreviations

CADTH: Canadian Agency for Drugs and Technologies in Health

CEA: cost-effectiveness analysis

CF: cystic fibrosis

CFTR: cystic fibrosis transmembrane conductance regulator

CHEERS: Consolidated Health Economic Evaluation Reporting Standards

CrI: credible interval

CVS: chronic villus sampling

DALY: disability-adjusted life-year

ECS: expanded carrier screening

FXS: fragile X syndrome

GRADE: Grading of Recommendations Assessment, Development, and Evaluation

Hb: hemoglobin

HbP: hemoglobinopathy

HPLC: high-performance liquid chromatography

ICER: incremental cost-effectiveness ratio

IVF: in vitro fertilization

MLPA: multiplex ligation-dependent probe amplification

MSAC: Medical Services Advisory Committee

NICE: National Institute for Health and Care Excellence

NGS: next-generation sequencing

PCR: polymerase chain reaction

PGD: preimplantation genetic diagnosis/diagnostic testing

PGT-M: preimplantation genetic testing for monogenic disorders, previously known as PGD

QALY: quality-adjusted life-year

RCT: randomized controlled trial

SCD: sickle cell disease

SMA: spinal muscular atrophy

TOP: termination of pregnancy

Glossary

Adverse event: An adverse event is an unexpected medical problem that happens during treatment for a health condition. Adverse events may be caused by something other than the treatment.

At-risk carrier: In genetics, a person is at-risk if they carry a gene that increases the probability of developing or passing on a particular condition (they have a genetic predisposition).

Base case: In economic evaluations, the base case is the "best guess" scenario, including any assumptions, considered most likely to be accurate. In health technology assessments conducted by Ontario Health, the reference case is used as the base case.

Budget impact analysis: A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).

Cohort model: In economic evaluations, a cohort model is used to simulate what happens to a homogeneous cohort (group) of patients after receiving a specific health care intervention. The proportion of the cohort who experiences certain health outcomes or events is estimated, along with the relevant costs and benefits. In contrast, a microsimulation model follows the course of individual patients.

Cost–consequence analysis: A cost–consequence analysis is a type of economic evaluation that estimates the costs and consequences (i.e., the health outcomes) of two or more health care interventions. In this type of analysis, the costs are presented separately from the consequences.

Cost-effective: A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.
Cost-effectiveness acceptability curve: In economic evaluations, a cost-effectiveness acceptability curve is a graphical representation of the results of a probabilistic analysis. It illustrates the probability of health care interventions being cost-effective over a range of willingness-to-pay values. Willingness-to-pay values are plotted on the horizontal axis of the graph, and the probability of the intervention of interest and its comparator(s) being cost-effective at corresponding willingness-to-pay values is plotted on the vertical axis.

Cost-effectiveness acceptability frontier: In economic evaluations, a cost-effectiveness acceptability frontier is a graph summarizing the probability of a number of health care interventions being cost-effective over a range of willingness-to-pay values. Like cost-effectiveness acceptability curves, cost-effectiveness acceptability frontiers plot willingness-to-pay values on the horizontal axis and the probability of the interventions being cost-effective at particular willingness-to-pay values on the vertical axis.

Cost-effectiveness analysis: Used broadly, "cost-effectiveness analysis" may refer to an economic evaluation used to compare the benefits of two or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used more specifically, "cost-effectiveness analysis" may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.

Cost-effectiveness plane: In economic evaluations, a cost-effectiveness plane is a graph used to show the differences in cost and effectiveness between a health care intervention and its comparator(s). Differences in effects are plotted on the horizontal axis, and differences in costs are plotted on the vertical axis.

Cost-minimization analysis: In economic evaluations, a cost-minimization analysis compares the costs of two or more health care interventions. It is used when the intervention of interest and its relevant alternative(s) are determined to be equally effective.

Cost–utility analysis: A cost–utility analysis is a type of economic evaluation used to compare the benefits of two or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years, which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.

Decision tree: A decision tree is a type of economic model used to assess the costs and benefits of two or more alternative health care interventions. Each intervention may be associated with different outcomes, which are represented by distinct branches in the tree. Each outcome may have a different probability of occurring and may lead to different costs and benefits.

Deterministic sensitivity analysis: Deterministic sensitivity analysis is an approach used to explore uncertainty in the results of an economic evaluation by varying parameter values to observe the potential impact on the cost-effectiveness of the health care intervention of interest. One-way sensitivity analysis accounts for uncertainty in parameter values one at a time, whereas multiway sensitivity analysis accounts for uncertainty in a combination of parameter values simultaneously.

Disability-adjusted life-year (DALY): The disability-adjusted life-year (DALY) is a health-related quality-of-life measure used to quantify the burden of disease from ill health, disability, or premature death. One disability-adjusted life-year represents the loss of one year of full health. Disability-adjusted life-years enable comparisons across different diseases, such that a disease that may cause premature death (e.g., measles) can be compared with a disease that may cause disability (e.g., cataracts).

Discounting: Discounting is a method used in economic evaluations to adjust for the differential timing of the costs incurred and the benefits generated by a health care intervention over time. Discounting reflects the concept of positive time preference, whereby future costs and benefits are reduced to reflect their present value. The health technology assessments conducted by Ontario Health use an annual discount rate of 1.5% for both future costs and future benefits.

Disease-specific preference-based measures: Disease-specific preference-based measures are instruments used to obtain the quality-adjusted weight (i.e., the utility value) of being in a particular health state or having a specific health condition. Disease-specific preference-based measures are

often thought to be more sensitive than generic preference-based measures in capturing condition-specific health effects. Like generic preference-based measures, disease-specific preference-based measures typically consist of a self-completed questionnaire, a health-state classification system, and a scoring formula that calculates the utility value. The key difference is that health states in disease-specific preference-based measures are important for the health condition of interest but may not apply to all patient populations. Examples of disease-specific preference-based measures include the Diabetes Utility Index (DUI) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30).

Disutility: A disutility is a decrease in utility (i.e., a decrease in preference for a particular health outcome) typically resulting from a particular health condition (e.g., experiencing a symptom or complication).

Dominant: A health care intervention is considered dominant when it is more effective and less costly than its comparator(s).

EQ-5D: The EQ-5D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The EQ-5D questionnaire consists of five questions relating to different domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, there are three response options: no problems, some problems, or severe problems. A newer instrument, the EQ-5D-5L, includes five response options for each domain. A scoring table is used to convert EQ-5D scores to utility values.

Extended dominance: A health care intervention is considered to be extendedly dominated when it has an incremental cost-effectiveness ratio higher than that of the next most costly or effective comparator. Interventions that are extendedly dominated are ruled out.

Gene: Genes are segments of DNA that contain instructions for building the molecules that make the body work. Health conditions that are caused by genes are referred to as genetic conditions because they can be passed from parent to child (genetic inheritance).

Generic preference-based measures: Generic preference-based measures are generic (i.e., not disease specific) instruments used to obtain the quality-adjusted weight (i.e., the utility value) of being in a given health state. Generic preference-based measures typically consist of a self-completed questionnaire, a health-state classification system, and a scoring formula that calculates the utility value. Examples include the Health Utilities Index Mark 3 (HUI3), the EQ-5D, and the Short Form–Six Dimensions (SF-6D). The quality-adjusted weights are obtained from the public or from patients, who are provided with a descriptive profile of each predefined health state and asked to fill out a questionnaire. The benefit of using a generic instrument is the ability to obtain utility values that are comparable across different health care interventions and diseases.

Health-related quality of life: Health-related quality of life is a measure of the impact of a health care intervention on a person's health. It includes the dimensions of physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception, and general life satisfaction.

Health state: A health state is a particular status of health (e.g., sick, well, dead). A health state is associated with some amount of benefit and may be associated with specific costs. Benefit is captured through individual or societal preferences for the time spent in each health state and is expressed in quality-adjusted weights called utility values. In a Markov model, a finite number of mutually exclusive health states are used to represent discrete states of health.

Health Utilities Index Mark 3 (HUI3): The HUI3 is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The HUI3 was developed in Canada and is used in major Canadian population health surveys. The HUI3 comprises eight attributes: vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain and discomfort. Each attribute is associated with five or six defined functional levels, thus producing a total of 972,000 unique health states. A predefined scoring formula is used to convert HUI3 scores to utility values.

Human capital approach: In economic evaluations, the human capital approach is used to estimate a monetary value that represents a person's loss of productivity due to disability, illness, or premature death.

Incremental cost: The incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.

Incremental cost-effectiveness ratio (ICER): The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.

Incremental net benefit: Incremental net benefit is a summary measure of cost-effectiveness. It incorporates the differences in cost and effect between two health care interventions and the willingness-to-pay value. Net health benefit is calculated as the difference in effect minus the difference in cost divided by the willingness-to-pay value. Net monetary benefit is calculated as the willingness-to-pay value multiplied by the difference in effect minus the difference in cost. An intervention can be considered cost-effective if either the net health or net monetary benefit is greater than zero.

Market distribution: When evaluating more than two technologies, the market distribution is the proportion of the population that uses each technology.

Markov model: A Markov model is a type of decision-analytic model used in economic evaluations to estimate the costs and health outcomes (e.g., quality-adjusted life-years gained) associated with using a particular health care intervention. Markov models are useful for clinical problems that involve events of interest that may recur over time (e.g., stroke). A Markov model consists of mutually exclusive, exhaustive health states. Patients remain in a given health state for a certain period of time before moving to another health state based on transition probabilities. The health states and events modelled may be associated with specific costs and health outcomes.

Microsimulation model: In economic evaluations, a microsimulation model (e.g., an individual-level or patient-level model) is used to simulate the health outcomes for a heterogeneous group of patients (e.g., patients of different ages or with different sets of risk factors) after receiving a particular health care intervention. The health outcomes and health events of each patient are modelled, and the outcomes of several patients are combined to estimate the average costs and benefits accrued by a group of patients. In contrast, a cohort model follows a homogeneous cohort of patients (e.g., patients of the same age or with the same set of risk factors) through the model and estimates the proportion of the cohort who will experience specific health events.

Ministry of Health perspective: The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).

Monte Carlo simulation: Monte Carlo simulation is an economic modelling method that derives parameter values from distributions rather than fixed values. The model is run several times, and in each iteration, parameter values are drawn from specified distributions. This method is used in microsimulation models and probabilistic analysis.

Multiway sensitivity analysis: A multiway sensitivity analysis is used to explore uncertainty in the results of an economic evaluation. It is done by varying a combination of model input (i.e., parameter) values simultaneously between plausible extremes to observe the potential impact on the cost-effectiveness of the health care intervention of interest.

Natural history of a disease: The natural history of a disease is the progression of a disease over time in the absence of any health care intervention.

One-way sensitivity analysis: A one-way sensitivity analysis is used to explore uncertainty in the results of an economic evaluation. It is done by varying one model input (i.e., a parameter) at a time between its minimum and maximum values to observe the potential impact on the cost-effectiveness of the health care intervention of interest.

PGT-M: Preimplantation genetic testing – mutation is a genetic test performed on embryos created through in vitro fertilization (IVF) that is designed for individuals who know they are at an increased risk of having a child with a specific genetic disorder. PGT-M was formerly known as PGD or preimplantation genetic diagnosis.

Probabilistic analysis: A probabilistic analysis (also known as a probabilistic sensitivity analysis) is used in economic models to explore uncertainty in several parameters simultaneously and is done using Monte Carlo simulation. Model inputs are defined as a distribution of possible values. In each iteration, model inputs are obtained by randomly sampling from each distribution, and a single estimate of cost and effectiveness is generated. This process is repeated many times (e.g., 10,000 times) to estimate the number of times (i.e., the probability) that the health care intervention of interest is cost-effective.

Quality-adjusted life-year (QALY): The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.

Reference case: The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.

Return on investment: Return on investment is a type of economic evaluation that values the financial return, or benefits, of a health care intervention against the total costs of its delivery. Return on investment is the benefit minus the cost, expressed as a proportion of the cost.

Risk-based screening: Risk-based screening is an approach that targets people who may be at increased risk of being a carrier (e.g., due to personal or family history, ethnicity, etc.; see Universal (population-wide) screening for alternative approach.)

Risk difference: Risk difference is the difference in the risk of an outcome occurring between one health care intervention and an alternative intervention.

Scenario analysis: A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.

Sensitivity analysis: Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.

Short-Form–Six Dimensions (SF-6D): The SF-6D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The classification system consists of six attributes (physical functioning, role limitations, social functioning, pain, mental health, and vitality), each associated with four to six levels, thus producing a total of 18,000 possible unique health states. A scoring table is used to convert SF-6D scores to health state values.

Societal perspective: The perspective adopted in an economic evaluation determines the types of costs and health benefits to include. The societal perspective reflects the broader economy and is the aggregation of all perspectives (e.g., health care payer and patient perspectives). It considers the full effect of a health condition on society, including all costs (regardless of who pays) and all benefits (regardless of who benefits).

Standard gamble: In economic evaluations, standard gamble is a direct method of measuring people's preferences for various health states. In a standard gamble, respondents are asked about their preference for either (a) remaining in a certain health state for the rest of their life, or (b) a

gamble scenario in which there is a chance of having optimal health for the rest of one's life but also a chance of dying immediately. Respondents are surveyed repeatedly, with the risk of immediate death varying each time (e.g., 75% chance of optimal health, 25% chance of immediate death) until they are indifferent about their choice. The standard gamble is considered the gold standard for eliciting preferences as it incorporates individual risk attitudes, unlike other methods of eliciting preferences.

Time horizon: In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.

Time trade-off: In economic evaluations, time trade-off is a direct method of measuring people's preferences for various health states. In a time-trade off, respondents are asked about their preference for either (a) living with a chronic health condition for a certain amount of time, followed by death, or (b) living in optimal health but for less time than in scenario (a). That is, respondents decide how much time in good health they would be willing to "trade off" for more time spent in poorer health. Respondents are surveyed repeatedly, with the amount of time spent in optimal health varying each time until they are indifferent about their choice.

Tornado diagram: In economic evaluations, a tornado diagram is used to determine which model parameters have the greatest influence on results. Tornado diagrams present the results of multiple one-way sensitivity analyses in a single graph.

Universal (population-wide) screening: Universal screening represents one of two approaches to identifying carriers of a condition within a population (see risk-based screening for alternative approach). Universal screening tests the entire population of interest.

Uptake rate: In instances where two technologies are being compared, the uptake rate is the rate at which a new technology is adopted. When a new technology is adopted, it may be used in addition to an existing technology, or it may replace an existing technology.

Utility: A utility is a value that represents a person's preference for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.

Value-of-information analysis: In economic evaluations, value-of-information analysis is used to estimate the value of investing in future research to minimize uncertainty in input parameters.

Visual analogue scale (VAS): The visual analogue scale (VAS) is a direct method of measuring people's preferences for various health states. Respondents are first asked to rank a series of health states from least to most preferable. Then, they are asked to place the health states on a scale with intervals reflecting the differences in preference among the given health states. The scale ranges from 0 (worst imaginable health) to 100 (best imaginable health). The value of a respondent's preference for each health state is given by their placement of each health state on the scale.

Willingness-to-pay value: A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

Appendices

Appendix 1: Clinical Background Information for Cystic Fibrosis, Fragile X Syndrome, Hemoglobinopathies, and Spinal Muscular Atrophy

Table A1: Common Types of Hemoglobinopathies and Thalassemia

Name	Genotype	Clinical features	Estimated life expectancy
Alpha-thalassemia			
Alpha-thalassemia minima (alpha-thalassemia silent carrier)	– α/α α	Asymptomatic, slight changes to blood count	Normal
Alpha-thalassemia minor (alpha-thalassemia trait)	– –/α α – α/– α	Asymptomatic, mild microcytic anemia	Normal
Hb H disease	– –/– α	Moderate to severe microcytic anemia, splenomegaly (enlarged spleen)	May be reduced
Hb Bart's hydrops fetalis (thalassemia major)	– –/– –	Life-threatening fetal anemia, hydrops fetalis (abnormal accumulation of fluid in at least two fetal compartments)	Usually lethal *in utero*
Beta-thalassemia			
Beta-thalassemia minor (beta-thalassemia trait)	β++ β+ β	Asymptomatic, mild microcytic anemia	Normal
Beta-thalassemia intermedia	β+/β+ β+/β++ β+/β0 β0/β0 + influential factors	Moderate to severe anemia, iron overload	May be reduced
Beta-thalassemia major (Cooley's anemia)	β+/β+ β0/β0 β+/β0	Severe anemia, poor growth, skeletal abnormalities, iron overload, splenomegaly	Decreased mostly due to complications from chronic transfusions
Sickle cell disease (HbS)			
Sickle cell trait (HbS heterozygosity)	HbAS	Asymptomatic In rare cases: muscle breakdown, reduced blood supply to the spleen, glaucoma (increased pressure in the eye), and hematuria (blood in the urine) during heavy physical exertion	Normal

Name	Genotype	Clinical features	Estimated life expectancy
		Factors such as increased atmospheric pressure, low oxygen levels, dehydration, or high altitude may induce symptoms	
Sickle cell anemia	HbSS	Severe disease	Median: 40–50 y old[280]
Sickle C disease	HbSC	May or may not be severe than HbSS	Median: 60–70 y old[280]
Sickle β+ thalassemia	HbSβ+	Mild disease	Normal
Sickle β0 thalassemia	HbSβ0	Severe, similar symptoms to HbSS	May be reduced
Sickle D, E, O	HbSD, SE, SO	Generally severe for Hb SD and Hb SO-Arab, and mild for Hb SE	May vary depending on type of Hb variant
Hb C disease			
Hb C heterozygosity	HbAC	Asymptomatic	Normal
Hb C disease	HbCC	Pain crises, chronic hemolytic anemia	Normal
Hb E disease			
Hb E heterozygosity	HbAE	Mild anemia	Normal
HbE β+ thalassemia	HbE β+	Variable, moderate microcytic anemia	Normal
HbE β0 thalassemia	HbE β0	Similar to beta-thalassemia major	May be reduced
Hb E disease	HbEE	Mild anemia, hemolysis caused by infections or medications	Normal

Abbreviation: Hb, hemoglobin.
Sources: Kohne et al, 2011[207]; US Centers for Disease Control and Prevention[281].

Table A2: Possible Treatment Options for Cystic Fibrosis, Fragile X Syndrome, Hemoglobinopathies, and Spinal Muscular Atrophy

Treatment category	Treatment description
Cystic fibrosis	
Nutritional therapy	Aid in nutritional absorption (e.g., diet changes, vitamin supplements, pancreatic enzyme supplements)
Antibiotics	Treat and prevent lung infections
Anti-inflammatory medications	Reduce swelling in lung airways
Mucolytics (mucus thinners)	Help cough up mucus to improve lung function
Bronchodilators	Relax airway muscles
Airway clearance techniques	Loosen and remove mucus to reduce infection and inflammation in lung airways (e.g., breathing and coughing techniques, mechanical devices)
Pulmonary rehabilitation	Program to improve lung function and overall well-being, which may include physical exercise, breathing techniques, counselling and support, and education
Oxygen therapy	For low blood oxygen levels to prevent pulmonary hypertension
Noninvasive ventilation	Use of a nose or mouth mask to provide positive pressure in the airways and lungs when breathing in; typically used when sleeping and often in combination with oxygen therapy
CFTR modulator therapy	To correct malfunctioning CFTR protein, used in people with specific *CFTR* pathogenic variants • Ivacaftor (Kalydeco) • Lumacaftor/ivacaftor (Orkambi) • Tezacaftor/ivacaftor (Symdeko) • Elexacaftor/tezacaftor/ivacaftor (Trikafta)
Surgical procedures	Nasal and sinus surgery to remove nasal polyps that obstruct breathing, bowel surgery to remove bowel blockages, liver transplant for severe CF-related liver disease, lung transplant for severe breathing difficulties or life-threatening lung complications
Fragile X syndrome	
Early intervention services and special education	Teach language, learning, and social skills
Augmentative and alternative communication systems	Tools to supplement or replace speech
Occupational and speech language therapy	Develop appropriate use of mouth and oral cavity
Cognitive behavioural therapy	For behavioural or mood disorders, such as ADHD, anxiety
Medical therapy	For behavioural or mood disorders, such as ADHD, anxiety
Thalassemia	
Folic acid supplements	To treat anemia

Treatment category	Treatment description
Blood transfusions	Donor red blood cells are transfused to increase the number of normal red blood cells, for beta-thalassemia major/intermedia and required in utero for Hb Bart's syndrome
Chelation therapy	Remove excess iron from the blood, for beta-thalassemia major/intermedia
Bone marrow or stem cell transplantation	Stem cells from a matched donor replace the affected person's thalassemia cells, for beta-thalassemia major and Hb Bart's syndrome
Sickle cell disease	
Nutritional therapy	Provide appropriate nutrition to help prevent the likelihood of disease exacerbation (e.g., omega-3 fatty acid supplements, folic acid supplements)
Pain medications	Pain relief during sickle cell pain crises
Antibiotics	Infection prevention, especially for young children (e.g., penicillin)
Hydroxyurea	Increases total and fetal hemoglobin, reduces frequency of painful crises, and may reduce need for blood transfusions and hospitalizations
L-glutamine	Reduces oxidative stress in red blood cells and reduces frequency of pain crises
Monoclonal antibody	Binds to P-selectin (adhesion molecule) and reduces frequency of pain crises • Crizanlizumab (Adakveo)[a]
Hemoglobin oxygen-affinity modulator	Increases hemoglobin's affinity for oxygen and improves anemia • Voxelotor (Oxbryta)[a]
Blood transfusions	Donor red blood cells are transfused to increase the number of normal red blood cells to reduce symptoms and complications
Bone marrow or stem cell transplantation	Stem cells from a matched donor replace the affected person's sickle cells
Spinal muscular atrophy	
Muscle relaxants	Ease spasticity when muscles become stiff and tense
Assistive devices	Assist with balance, increase mobility (e.g., splints, braces, orthotics, standers, walkers, wheelchairs)
Physical therapy	Improve posture, prevent joint immobility, slow muscle weakness and atrophy
Breathing aids	Ventilation (noninvasive or invasive) to support breathing when there is a lack of oxygen
SMN2 gene splicing modifier	Modulates alternative splicing of *SMN2* gene to functionally convert it into *SMN1* gene, increases SMN protein levels • Nusinersen (Spinraza) • Risdiplam (Evrysdi)
Gene replacement therapy	Delivers new, working copy of the *SMN1* gene to motor neuron cells in the body • Onasemnogene abeparvovec (Zolgensma)

Abbreviations: ADHD, attention-deficit hyperactivity disorder; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; Hb, hemoglobinopathy; SMN1, survival motor neuron 1; SMN2, survival motor neuron 2.
[a]Not approved by Health Canada, but has been approved by the US Food and Drug Administration.

Sources: US Centers for Disease Control and Prevention,[281] Cystic Fibrosis Foundation,[282] Genetic and Rare Diseases Information Center.[283]

Appendix 2: Literature Search Strategies

Clinical Evidence Search

Search date: April 6, 2021

Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CRD Health Technology Assessment Database, and NHS Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <February 2021>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to March 31, 2021>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2021 Week 13>, Ovid MEDLINE(R) ALL <1946 to April 05, 2021>

Search Strategy:

---

1 Cystic Fibrosis/ (110294)

2 Cystic Fibrosis Transmembrane Conductance Regulator/ (16935)

3 ((cystic adj2 fibrosis) or fibrocystic disease* or mucoviscidosis or CFTR).ti,ab,kf. (128665)

4 CF.ti. (10842)

5 Muscular Atrophy, Spinal/ (9734)

6 "Spinal Muscular Atrophies of Childhood"/ (2068)

7 ((atroph* adj2 (spinal muscular or progressive muscular or myelopathic muscular)) or spinal amyotroph* or (neuropath* adj2 hereditary motor)).ti,ab,kf. (15343)

8 ((survival adj2 (motor neuron* 1 or motor neuron* 2)) or SMN1 or SMN2).ti,ab,kf. (3769)

9 ((werdnig hoffmann or dubowitz or kugelberg welander) adj2 disease*).ti,ab,kf. (604)

10 SMA.ti. (2960)

11 exp Hemoglobinopathies/ (115340)

12 (sickle adj3 (disease* or an?emia* or disorder* or trait* or h?emoglobin*)).ti,ab,kf. (59095)

13 (h?emoglobinopath* or h?emoglobulinopath* or hbp or hbps).ti,ab,kf. (21183)

14 (thalass?emia* or alphathalass?emia* or betathalass?emia* or deltathalass?emia* or (beta adj3 microcyt?emia*) or (an?emia* adj3 (cooley* or erythroblast* or mediterranean)) or target cell an?emia* or alpha thal or beta thal or delta thal).ti,ab,kf. (53001)

15 exp Hemoglobins, Abnormal/ (30462)

16 (h?emoglobin s or h?emoglobin c or h?emoglobin d or h?emoglobin e or h?emoglobin o or h?emoglobin h or h?emoglobin bart*).ti,ab,kf. (8569)

17 ((hbs or hb s or hgbs or hgb s or hbc or hb c or hgbc or hgb c or hbd or hb d or hgbd or hgb d or hbe or hb e or hgbe or hgb e or hbo or hb o or hgbo or hgb o or hbh or hb h or hgbh or hgb h or hb Bart* or hgb Bart*) adj5 (variant* or mutat* or abnormal* or anomal* or sickle or disease* or disorder* or trait*)).ti,ab,kf. (7453)

18 (hbas or hbac or hb ac or hbad or hb ad or hbae or hb ae or hbao or hb ao).ti,ab,kf. (1193)

19 (((h?emoglobin* or hb or hgb) adj3 (variant* or mutat* or abnormal* or anomal* or sickle or disease* or disorder* or trait* or subunit* or alpha* or beta*)) or hbb or hba1 or hba2 or alpha globin* or beta globin* or delta globin*).ti,ab,kf. (61248)

20 Fragile X Syndrome/ (14158)

21 Fragile X Mental Retardation Protein/ (6614)

22 (fragile x* or fraxa or frax a or fra x or mar x or marker x or martin bell or martinbell or FXS or FXTAS or FXPOI or FXAND or FXAD or FX associat*).ti,ab,kf. (17650)

23 (FMRP* or FMR1* or ((x linked or xlinked) adj3 (fragile or mental retard*))).ti,ab,kf. (11227)

24 or/1-23 (376883)
25 Genetic Carrier Screening/ (14806)
26 (carrier* adj3 (screen* or test* or panel* or counsel* or assess* or detect* or diagnos* or analys* or inform* or status or rate* or risk* or mother* or father* or parent or parents or couple* or marriage* or married or program*)).ti,ab,kf. (50650)
27 (massive* parallel sequenc* or ((sequential or parallel or panethnic or pan ethnic or multigene* or multi gene*) adj2 (screen* or panel*))).ti,ab,kf. (12045)
28 ((Preconception* or Pre-conception* or Prepregnan* or Pre-pregnan* or ((pregnan* or reproduct*) adj4 (future or decision* or before or plan*))) adj4 (screen* or test* or panel* or diagnos* or assess*)).ti,ab,kf. (6911)
29 or/25-28 (78795)
30 24 and 29 (7606)
31 carrier*.ti,ab,kf. (484060)
32 Preconception Care/ (4478)
33 (preconception* or pre-conception* or prepregnan* or pre-pregnan* or ((pregnan* or reproduct*) adj4 (future or decision* or before or plan*))).ti,ab,kf. (99463)
34 Prenatal Care/ (71166)
35 (prenatal* or pre-natal* or antenatal* or ante-natal*).ti,ab,kf. (329460)
36 Family Planning Services/ (55992)
37 ((pregnan* or conception* or family) adj3 plan*).ti,ab,kf. (83248)
38 Genetic Counseling/ (46919)
39 (counsel* adj4 genetic*).ti,ab,kf. (49478)
40 (couple* adj3 risk*).ti,ab,kf. (3910)
41 or/31-40 (1051645)
42 exp Genetic Testing/ (141771)
43 ((genetic* or genomic* or gene or genes) adj3 (screen* or test* or panel* or diagnos* or assess*)).ti,ab,kf. (325761)
44 High-Throughput Nucleotide Sequencing/ (74505)
45 (((high throughput or high through put) adj2 (sequenc* or analys*)) or deep sequenc*).ti,ab,kf. (74981)
46 (((next gen or nextgen or next generation) adj2 sequenc*) or NGS).ti,ab,kf. (119338)
47 Sequence Analysis, DNA/ (166681)
48 ((DNA or parallel or target*) adj1 sequenc*).ti,ab,kf. (245029)
49 Heterozygote/ (111944)
50 Heterozygote Detection/ (14770)
51 ((heterozygot* or heterozygous*) adj3 (screen* or test* or panel* or counsel* or assess* or detect* or diagnos* or analy*)).ti,ab,kf. (11120)
52 ((target* or universal or population or variant* or mutation* or recessive) adj2 (screen* or test* or panel* or assay* or analysis)).ti,ab,kf. (276913)
53 Chromatography, High Pressure Liquid/ (447997)
54 (high performance liquid chromatograph* or high pressure liquid chromatograph* or high speed liquid chromatograph* or HPLC).ti,ab,kf. (473871)
55 Blood protein electrophoresis/ (18981)
56 (((h?emoglobin or capillar*) adj2 electrophores#s) or southern blot*).ti,ab,kf. (100304)
57 exp Polymerase Chain Reaction/ (1445357)
58 ((multiplex ligation* adj2 probe amplification*) or polymerase chain reaction* or PCR or MLPA).ti,ab,kf. (1614831)
59 or/42-58 (3843314)

60 41 and 59 (172022)
61 24 and 60 (14453)
62 ((expanded adj3 carrier* adj3 (screen* or test* or panel*)) or (carrier screen* adj3 (program* or service*))).ti,ab,kf. (828)
63 30 or 61 or 62 (17143)
64 exp Animals/ not Humans/ (18066097)
65 63 not 64 (13358)
66 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (5782804)
67 65 not 66 (12007)
68 limit 67 to english language [Limit not valid in CDSR; records were retained] (10796)
69 limit 68 to yr="2005 -Current" (5767)
70 69 use medall,cctr,coch,clhta,cleed (2971)
71 cystic fibrosis/ (110294)
72 cystic fibrosis transmembrane conductance regulator/ (16935)
73 ((cystic adj2 fibrosis) or fibrocystic disease* or mucoviscidosis or CFTR).tw,kw. (129638)
74 CF.ti. (10842)
75 spinal muscular atrophy/ (11722)
76 exp hereditary spinal muscular atrophy/ (3383)
77 ((atroph* adj2 (spinal muscular or progressive muscular or myelopathic muscular)) or spinal amyotroph* or (neuropath* adj2 hereditary motor)).tw,kw. (15482)
78 ((survival adj2 (motor neuron* 1 or motor neuron* 2)) or SMN1 or SMN2).tw,kw. (3795)
79 ((werdnig hoffmann or dubowitz or kugelberg welander) adj2 disease*).tw,kw. (652)
80 SMA.ti. (2960)
81 exp hemoglobinopathy/ (115284)
82 (sickle adj3 (disease* or an?emia* or disorder* or trait* or h?emoglobin*)).tw,kw. (59034)
83 (h?emoglobinopath* or h?emoglobulinopath* or hbp or hbps).tw,kw. (21958)
84 (thalass?emia* or alphathalass?emia* or betathalass?emia* or deltathalass?emia* or (beta adj3 microcyt?emia*) or (an?emia* adj3 (cooley* or erythroblast* or mediterranean)) or target cell an?emia* or alpha thal or beta thal or delta thal).tw,kw. (53505)
85 exp hemoglobin variant/ (18968)
86 (h?emoglobin s or h?emoglobin c or h?emoglobin d or h?emoglobin e or h?emoglobin o or h?emoglobin h or h?emoglobin bart*).tw,kw. (8826)
87 ((hbs or hb s or hgbs or hgb s or hbc or hb c or hgbc or hgb c or hbd or hb d or hgbd or hgb d or hbe or hb e or hgbe or hgb e or hbo or hb o or hgbo or hgb o or hbh or hb h or hgbh or hgb h or hb Bart* or hgb Bart*) adj5 (variant* or mutat* or abnormal* or anomal* or sickle or disease* or disorder* or trait*)).tw,kw. (7530)
88 (hbas or hbac or hb ac or hbad or hb ad or hbae or hb ae or hbao or hb ao).tw,kw. (1208)
89 (((h?emoglobin* or hb or hgb) adj3 (variant* or mutat* or abnormal* or anomal* or sickle or disease* or disorder* or trait* or subunit* or alpha* or beta*)) or hbb or hba1 or hba2 or alpha globin* or beta globin* or delta globin*).tw,kw. (61571)
90 fragile X syndrome/ (14158)
91 fragile X mental retardation protein/ (6614)
92 (fragile x* or fraxa or frax a or fra x or mar x or marker x or martin bell or martinbell or FXS or FXTAS or FXPOI or FXAND or FXAD or FX associat*).tw,kw. (17918)
93 (FMRP* or FMR1* or ((x linked or xlinked) adj3 (fragile or mental retard*))).tw,kw. (11553)
94 or/71-93 (378507)
95 heterozygote detection/ (14770)

96 (carrier* adj3 (screen* or test* or panel* or counsel* or assess* or detect* or diagnos* or analys* or inform* or status or rate* or risk* or mother* or father* or parent or parents or couple* or marriage* or married or program*)).tw,kw,dv. (51006)
97 (massive* parallel sequenc* or ((sequential or parallel or panethnic or pan ethnic or multigene* or multi gene*) adj2 (screen* or panel*))).tw,kw,dv. (12363)
98 ((Preconception* or Pre-conception* or Prepregnan* or Pre-pregnan* or ((pregnan* or reproduct*) adj4 (future or decision* or before or plan*))) adj4 (screen* or test* or panel* or diagnos* or assess*)).tw,kw,dv. (7000)
99 or/95-98 (79492)
100 94 and 99 (7692)
101 carrier*.tw,kw,dv. (486742)
102 prepregnancy care/ (2011)
103 (preconception* or pre-conception* or prepregnan* or pre-pregnan* or ((pregnan* or reproduct*) adj4 (future or decision* or before or plan*))).tw,kw,dv. (100911)
104 prenatal care/ (71166)
105 (prenatal* or pre-natal* or antenatal* or ante-natal*).tw,kw,dv. (336408)
106 family planning/ (57129)
107 ((pregnan* or conception* or family) adj3 plan*).tw,kw,dv. (64644)
108 genetic counseling/ (46919)
109 (counsel* adj4 genetic*).tw,kw,dv. (50466)
110 (couple* adj3 risk*).tw,kw,dv. (3955)
111 or/101-110 (1048756)
112 genetic screening/ (132264)
113 ((genetic* or genomic* or gene or genes) adj3 (screen* or test* or panel* or diagnos* or assess*)).tw,kw,dv. (329885)
114 high throughput sequencing/ (80690)
115 massively parallel signature sequencing/ (43)
116 (((high throughput or high through put) adj2 (sequenc* or analys*)) or deep sequenc*).tw,kw,dv. (75615)
117 (((next gen or nextgen or next generation) adj2 sequenc*) or NGS).tw,kw,dv. (120710)
118 sequence analysis/ (171474)
119 ((DNA or parallel or target*) adj1 sequenc*).tw,kw,dv. (247203)
120 heterozygote/ (111944)
121 ((heterozygot* or heterozygous*) adj3 (screen* or test* or panel* or counsel* or assess* or detect* or diagnos* or analy*)).tw,kw,dv. (11221)
122 ((target* or universal or population or variant* or mutation* or recessive) adj2 (screen* or test* or panel* or assay* or analysis)).tw,kw,dv. (281373)
123 high performance liquid chromatography/ (470678)
124 (high performance liquid chromatograph* or high pressure liquid chromatograph* or high speed liquid chromatograph* or HPLC).tw,kw,dv. (480243)
125 protein electrophoresis/ (18981)
126 capillary electrophoresis/ (43662)
127 (((h?emoglobin or capillar*) adj2 electrophores#s) or southern blot*).tw,kw,dv. (101689)
128 exp polymerase chain reaction/ (1445357)
129 multiplex ligation dependent probe amplification/ (12164)
130 ((multiplex ligation* adj2 probe amplification*) or polymerase chain reaction* or PCR or MLPA).tw,kw,dv. (1627670)
131 or/112-130 (3877878)

132 111 and 131 (170322)
133 94 and 132 (14017)
134 ((expanded adj3 carrier* adj3 (screen* or test* or panel*)) or (carrier screen* adj3 (program* or service*))).tw,kw,dv. (833)
135 100 or 133 or 134 (17402)
136 (exp animal/ or nonhuman/) not exp human/ (11026265)
137 135 not 136 (17247)
138 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (11857355)
139 137 not 138 (12833)
140 limit 139 to english language [Limit not valid in CDSR; records were retained] (11506)
141 limit 140 to yr="2005 -Current" (6491)
142 141 use emez (3514)
143 70 or 142 (6485)
144 143 use medall (2895)
145 143 use emez (3514)
146 143 use cctr (63)
147 143 use coch (2)
148 143 use clhta (3)
149 143 use cleed (8)
150 limit 143 to yr="2015 -Current" (2797)
151 remove duplicates from 150 (1726)
152 limit 143 to yr="2005 - 2014" (3688)
153 remove duplicates from 152 (2311)
154 151 or 153 (4037)

Economic Evidence Search

Search date: April 7, 2021
Databases searched: Ovid MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database, and National Health Service (NHS) Economic Evaluation Database

Database segments: EBM Reviews - Cochrane Central Register of Controlled Trials <March 2021>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to March 31, 2021>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2021 Week 13>, Ovid MEDLINE(R) ALL <1946 to April 06, 2021>
Search Strategy:
---
1 Cystic Fibrosis/ (110305)
2 Cystic Fibrosis Transmembrane Conductance Regulator/ (16938)
3 ((cystic adj2 fibrosis) or fibrocystic disease* or mucoviscidosis or CFTR).ti,ab,kf. (128714)
4 CF.ti. (10850)
5 Muscular Atrophy, Spinal/ (9735)
6 "Spinal Muscular Atrophies of Childhood"/ (2069)

7 ((atroph* adj2 (spinal muscular or progressive muscular or myelopathic muscular)) or spinal amyotroph* or (neuropath* adj2 hereditary motor)).ti,ab,kf. (15349)
8 ((survival adj2 (motor neuron* 1 or motor neuron* 2)) or SMN1 or SMN2).ti,ab,kf. (3771)
9 ((werdnig hoffmann or dubowitz or kugelberg welander) adj2 disease*).ti,ab,kf. (604)
10 SMA.ti. (2961)
11 exp Hemoglobinopathies/ (115358)
12 (sickle adj3 (disease* or an?emia* or disorder* or trait* or h?emoglobin*)).ti,ab,kf. (59110)
13 (h?emoglobinopath* or h?emoglobulinopath* or hbp or hbps).ti,ab,kf. (21192)
14 (thalass?emia* or alphathalass?emia* or betathalass?emia* or deltathalass?emia* or (beta adj3 microcyt?emia*) or (an?emia* adj3 (cooley* or erythroblast* or mediterranean)) or target cell an?emia* or alpha thal or beta thal or delta thal).ti,ab,kf. (53024)
15 exp Hemoglobins, Abnormal/ (30462)
16 (h?emoglobin s or h?emoglobin c or h?emoglobin d or h?emoglobin e or h?emoglobin o or h?emoglobin h or h?emoglobin bart*).ti,ab,kf. (8571)
17 ((hbs or hb s or hgbs or hgb s or hbc or hb c or hgbc or hgb c or hbd or hb d or hgbd or hgb d or hbe or hb e or hgbe or hgb e or hbo or hb o or hgbo or hgb o or hbh or hb h or hgbh or hgb h or hb Bart* or hgb Bart*) adj5 (variant* or mutat* or abnormal* or anomal* or sickle or disease* or disorder* or trait*)).ti,ab,kf. (7457)
18 (hbas or hbac or hb ac or hbad or hb ad or hbae or hb ae or hbao or hb ao).ti,ab,kf. (1194)
19 (((h?emoglobin* or hb or hgb) adj3 (variant* or mutat* or abnormal* or anomal* or sickle or disease* or disorder* or trait* or subunit* or alpha* or beta*)) or hbb or hba1 or hba2 or alpha globin* or beta globin* or delta globin*).ti,ab,kf. (61261)
20 Fragile X Syndrome/ (14158)
21 Fragile X Mental Retardation Protein/ (6614)
22 (fragile x* or fraxa or frax a or fra x or mar x or marker x or martin bell or martinbell or FXS or FXTAS or FXPOI or FXAND or FXAD or FX associat*).ti,ab,kf. (17656)
23 (FMRP* or FMR1* or ((x linked or xlinked) adj3 (fragile or mental retard*))).ti,ab,kf. (11228)
24 or/1-23 (377001)
25 Genetic Carrier Screening/ (14806)
26 (carrier* adj3 (screen* or test* or panel* or counsel* or assess* or detect* or diagnos* or analys* or inform* or status or rate* or risk* or mother* or father* or parent or parents or couple* or marriage* or married or program*)).ti,ab,kf. (50658)
27 (massive* parallel sequenc* or ((sequential or parallel or panethnic or pan ethnic or multigene* or multi gene*) adj2 (screen* or panel*))).ti,ab,kf. (12048)
28 ((Preconception* or Pre-conception* or Prepregnan* or Pre-pregnan* or ((pregnan* or reproduct*) adj4 (future or decision* or before or plan*))) adj4 (screen* or test* or panel* or diagnos* or assess*)).ti,ab,kf. (6919)
29 or/25-28 (78814)
30 24 and 29 (7607)
31 carrier*.ti,ab,kf. (484149)
32 Preconception Care/ (4480)
33 (preconception* or pre-conception* or prepregnan* or pre-pregnan* or ((pregnan* or reproduct*) adj4 (future or decision* or before or plan*))).ti,ab,kf. (99528)
34 Prenatal Care/ (71180)
35 (prenatal* or pre-natal* or antenatal* or ante-natal*).ti,ab,kf. (329598)
36 Family Planning Services/ (55998)
37 ((pregnan* or conception* or family) adj3 plan*).ti,ab,kf. (83306)
38 Genetic Counseling/ (46924)

39 (counsel* adj4 genetic*).ti,ab,kf. (49492)
40 (couple* adj3 risk*).ti,ab,kf. (3912)
41 or/31-40 (1051974)
42 exp Genetic Testing/ (141786)
43 ((genetic* or genomic* or gene or genes) adj3 (screen* or test* or panel* or diagnos* or assess*)).ti,ab,kf. (325839)
44 High-Throughput Nucleotide Sequencing/ (74536)
45 (((high throughput or high through put) adj2 (sequenc* or analys*)) or deep sequenc*).ti,ab,kf. (75000)
46 (((next gen or nextgen or next generation) adj2 sequenc*) or NGS).ti,ab,kf. (119387)
47 Sequence Analysis, DNA/ (166694)
48 ((DNA or parallel or target*) adj1 sequenc*).ti,ab,kf. (245050)
49 Heterozygote/ (111952)
50 Heterozygote Detection/ (14770)
51 ((heterozygot* or heterozygous*) adj3 (screen* or test* or panel* or counsel* or assess* or detect* or diagnos* or analy*)).ti,ab,kf. (11122)
52 ((target* or universal or population or variant* or mutation* or recessive) adj2 (screen* or test* or panel* or assay* or analysis)).ti,ab,kf. (277032)
53 Chromatography, High Pressure Liquid/ (448032)
54 (high performance liquid chromatograph* or high pressure liquid chromatograph* or high speed liquid chromatograph* or HPLC).ti,ab,kf. (473933)
55 Blood protein electrophoresis/ (18981)
56 (((h?emoglobin or capillar*) adj2 electrophores#s) or southern blot*).ti,ab,kf. (100306)
57 exp Polymerase Chain Reaction/ (1445400)
58 ((multiplex ligation* adj2 probe amplification*) or polymerase chain reaction* or PCR or MLPA).ti,ab,kf. (1615264)
59 or/42-58 (3844092)
60 41 and 59 (172052)
61 24 and 60 (14455)
62 ((expanded adj3 carrier* adj3 (screen* or test* or panel*)) or (carrier screen* adj3 (program* or service*))).ti,ab,kf. (829)
63 30 or 61 or 62 (17145)
64 exp Animals/ not Humans/ (18066712)
65 63 not 64 (13360)
66 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (5783422)
67 65 not 66 (12009)
68 limit 67 to english language [Limit not valid in CDSR; records were retained] (10798)
69 limit 68 to yr="2005 -Current" (5769)
70 69 use coch,clhta,cleed (13)
71 economics/ (261962)
72 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (907941)
73 economics.fs. (446112)
74 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (1037390)
75 exp "costs and cost analysis"/ (624064)
76 (cost or costs or costing or costly).ti. (294428)

77 cost effective*.ti,ab,kf. (378623)
78 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kf. (247069)
79 models, economic/ (14460)
80 markov chains/ or monte carlo method/ (92468)
81 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (50745)
82 (markov or markow or monte carlo).ti,ab,kf. (149046)
83 quality-adjusted life years/ (46337)
84 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (89574)
85 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (147950)
86 or/71-85 (2872412)
87 69 and 86 (485)
88 87 use medall,cctr (247)
89 70 or 88 (260)
90 cystic fibrosis/ (110305)
91 cystic fibrosis transmembrane conductance regulator/ (16938)
92 ((cystic adj2 fibrosis) or fibrocystic disease* or mucoviscidosis or CFTR).tw,kw. (129687)
93 CF.ti. (10850)
94 spinal muscular atrophy/ (11723)
95 exp hereditary spinal muscular atrophy/ (3383)
96 ((atroph* adj2 (spinal muscular or progressive muscular or myelopathic muscular)) or spinal amyotroph* or (neuropath* adj2 hereditary motor)).tw,kw. (15489)
97 ((survival adj2 (motor neuron* 1 or motor neuron* 2)) or SMN1 or SMN2).tw,kw. (3797)
98 ((werdnig hoffmann or dubowitz or kugelberg welander) adj2 disease*).tw,kw. (653)
99 SMA.ti. (2961)
100 exp hemoglobinopathy/ (115302)
101 (sickle adj3 (disease* or an?emia* or disorder* or trait* or h?emoglobin*)).tw,kw. (59050)
102 (h?emoglobinopath* or h?emoglobulinopath* or hbp or hbps).tw,kw. (21967)
103 (thalass?emia* or alphathalass?emia* or betathalass?emia* or deltathalass?emia* or (beta adj3 microcyt?emia*) or (an?emia* adj3 (cooley* or erythroblast* or mediterranean)) or target cell an?emia* or alpha thal or beta thal or delta thal).tw,kw. (53530)
104 exp hemoglobin variant/ (18968)
105 (h?emoglobin s or h?emoglobin c or h?emoglobin d or h?emoglobin e or h?emoglobin o or h?emoglobin h or h?emoglobin bart*).tw,kw. (8829)
106 ((hbs or hb s or hgbs or hgb s or hbc or hb c or hgbc or hgb c or hbd or hb d or hgbd or hgb d or hbe or hb e or hgbe or hgb e or hbo or hb o or hgbo or hgb o or hbh or hb h or hgbh or hgb h or hb Bart* or hgb Bart*) adj5 (variant* or mutat* or abnormal* or anomal* or sickle or disease* or disorder* or trait*)).tw,kw. (7534)
107 (hbas or hbac or hb ac or hbad or hb ad or hbae or hb ae or hbao or hb ao).tw,kw. (1209)
108 (((h?emoglobin* or hb or hgb) adj3 (variant* or mutat* or abnormal* or anomal* or sickle or disease* or disorder* or trait* or subunit* or alpha* or beta*)) or hbb or hba1 or hba2 or alpha globin* or beta globin* or delta globin*).tw,kw. (61586)
109 fragile X syndrome/ (14158)
110 fragile X mental retardation protein/ (6614)
111 (fragile x* or fraxa or frax a or fra x or mar x or marker x or martin bell or martinbell or FXS or FXTAS or FXPOI or FXAND or FXAD or FX associat*).tw,kw. (17924)
112 (FMRP* or FMR1* or ((x linked or xlinked) adj3 (fragile or mental retard*))).tw,kw. (11554)
113 or/90-112 (378629)

114 heterozygote detection/ (14770)
115 (carrier* adj3 (screen* or test* or panel* or counsel* or assess* or detect* or diagnos* or analys* or inform* or status or rate* or risk* or mother* or father* or parent or parents or couple* or marriage* or married or program*)).tw,kw,dv. (51014)
116 (massive* parallel sequenc* or ((sequential or parallel or panethnic or pan ethnic or multigene* or multi gene*) adj2 (screen* or panel*))).tw,kw,dv. (12366)
117 ((Preconception* or Pre-conception* or Prepregnan* or Pre-pregnan* or ((pregnan* or reproduct*) adj4 (future or decision* or before or plan*))) adj4 (screen* or test* or panel* or diagnos* or assess*)).tw,kw,dv. (7011)
118 or/114-117 (79514)
119 113 and 118 (7693)
120 carrier*.tw,kw,dv. (486831)
121 prepregnancy care/ (2011)
122 (preconception* or pre-conception* or prepregnan* or pre-pregnan* or ((pregnan* or reproduct*) adj4 (future or decision* or before or plan*))).tw,kw,dv. (100978)
123 prenatal care/ (71180)
124 (prenatal* or pre-natal* or antenatal* or ante-natal*).tw,kw,dv. (336550)
125 family planning/ (57135)
126 ((pregnan* or conception* or family) adj3 plan*).tw,kw,dv. (64707)
127 genetic counseling/ (46924)
128 (counsel* adj4 genetic*).tw,kw,dv. (50483)
129 (couple* adj3 risk*).tw,kw,dv. (3957)
130 or/120-129 (1049095)
131 genetic screening/ (132278)
132 ((genetic* or genomic* or gene or genes) adj3 (screen* or test* or panel* or diagnos* or assess*)).tw,kw,dv. (329975)
133 high throughput sequencing/ (80721)
134 massively parallel signature sequencing/ (43)
135 (((high throughput or high through put) adj2 (sequenc* or analys*)) or deep sequenc*).tw,kw,dv. (75648)
136 (((next gen or nextgen or next generation) adj2 sequenc*) or NGS).tw,kw,dv. (120758)
137 sequence analysis/ (171475)
138 ((DNA or parallel or target*) adj1 sequenc*).tw,kw,dv. (247226)
139 heterozygote/ (111952)
140 ((heterozygot* or heterozygous*) adj3 (screen* or test* or panel* or counsel* or assess* or detect* or diagnos* or analy*)).tw,kw,dv. (11224)
141 ((target* or universal or population or variant* or mutation* or recessive) adj2 (screen* or test* or panel* or assay* or analysis)).tw,kw,dv. (281497)
142 high performance liquid chromatography/ (470710)
143 (high performance liquid chromatograph* or high pressure liquid chromatograph* or high speed liquid chromatograph* or HPLC).tw,kw,dv. (480310)
144 protein electrophoresis/ (18981)
145 capillary electrophoresis/ (43663)
146 (((h?emoglobin or capillar*) adj2 electrophores#s) or southern blot*).tw,kw,dv. (101692)
147 exp polymerase chain reaction/ (1445400)
148 multiplex ligation dependent probe amplification/ (12169)
149 ((multiplex ligation* adj2 probe amplification*) or polymerase chain reaction* or PCR or MLPA).tw,kw,dv. (1628123)

150 or/131-149 (3878686)
151 130 and 150 (170353)
152 113 and 151 (14019)
153 ((expanded adj3 carrier* adj3 (screen* or test* or panel*)) or (carrier screen* adj3 (program* or service*))).tw,kw,dv. (834)
154 119 or 152 or 153 (17404)
155 (exp animal/ or nonhuman/) not exp human/ (11026880)
156 154 not 155 (17249)
157 Case Report/ or Comment/ or Editorial/ or (letter.pt. not (letter.pt. and randomized controlled trial/)) or conference abstract.pt. or conference review.pt. (11857987)
158 156 not 157 (12835)
159 limit 158 to english language [Limit not valid in CDSR; records were retained] (11508)
160 limit 159 to yr="2005 -Current" (6493)
161 Economics/ (261962)
162 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (136699)
163 Economic Aspect/ or exp Economic Evaluation/ (492050)
164 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw. (1064584)
165 exp "Cost"/ (624064)
166 (cost or costs or costing or costly).ti. (294428)
167 cost effective*.tw,kw. (391568)
168 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kw. (259780)
169 Monte Carlo Method/ (72491)
170 (decision adj1 (tree* or analy* or model*)).tw,kw. (54645)
171 (markov or markow or monte carlo).tw,kw. (154143)
172 Quality-Adjusted Life Years/ (46337)
173 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw. (93514)
174 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw. (169371)
175 or/161-174 (2475335)
176 160 and 175 (605)
177 176 use emez (325)
178 89 or 177 (585)
179 178 use medall (237)
180 178 use emez (325)
181 178 use cctr (10)
182 178 use coch (2)
183 178 use cleed (8)
184 178 use clhta (3)
185 remove duplicates from 178 (386)

Search for Intervention-Related Health State Utilities

Health State Utilities Search

Search date: June 24, 2021

Databases searched: Ovid MEDLINE

Database segment: Ovid MEDLINE(R) ALL <1946 to June 23, 2021>
Search Strategy:

---

1 Cystic Fibrosis/ (36526)
2 Cystic Fibrosis Transmembrane Conductance Regulator/ (9521)
3 ((cystic adj2 fibrosis) or fibrocystic disease* or mucoviscidosis or CFTR).ti,ab,kf. (50182)
4 CF.ti. (2457)
5 Muscular Atrophy, Spinal/ (4044)
6 "Spinal Muscular Atrophies of Childhood"/ (1416)
7 ((atroph* adj2 (spinal muscular or progressive muscular or myelopathic muscular)) or spinal amyotroph* or (neuropath* adj2 hereditary motor)).ti,ab,kf. (6595)
8 ((survival adj2 (motor neuron* 1 or motor neuron* 2)) or SMN1 or SMN2).ti,ab,kf. (1473)
9 ((werdnig hoffmann or dubowitz or kugelberg welander) adj2 disease*).ti,ab,kf. (331)
10 SMA.ti. (1146)
11 exp Hemoglobinopathies/ (46721)
12 (sickle adj3 (disease* or an?emia* or disorder* or trait* or h?emoglobin*)).ti,ab,kf. (25046)
13 (h?emoglobinopath* or h?emoglobulinopath* or hbp or hbps).ti,ab,kf. (8655)
14 (thalass?emia* or alphathalass?emia* or betathalass?emia* or deltathalass?emia* or (beta adj3 microcyt?emia*) or (an?emia* adj3 (cooley* or erythroblast* or mediterranean)) or target cell an?emia* or alpha thal or beta thal or delta thal).ti,ab,kf. (23057)
15 exp Hemoglobins, Abnormal/ (11519)
16 (h?emoglobin s or h?emoglobin c or h?emoglobin d or h?emoglobin e or h?emoglobin o or h?emoglobin h or h?emoglobin bart*).ti,ab,kf. (4212)
17 ((hbs or hb s or hgbs or hgb s or hbc or hb c or hgbc or hgb c or hbd or hb d or hgbd or hgb d or hbe or hb e or hgbe or hgb e or hbo or hb o or hgbo or hgb o or hbh or hb h or hgbh or hgb h or hb Bart* or hgb Bart*) adj5 (variant* or mutat* or abnormal* or anomal* or sickle or disease* or disorder* or trait*)).ti,ab,kf. (3073)
18 (hbas or hbac or hb ac or hbad or hb ad or hbae or hb ae or hbao or hb ao).ti,ab,kf. (483)
19 (((h?emoglobin* or hb or hgb) adj3 (variant* or mutat* or abnormal* or anomal* or sickle or disease* or disorder* or trait* or subunit* or alpha* or beta*)) or hbb or hba1 or hba2 or alpha globin* or beta globin* or delta globin*).ti,ab,kf. (28049)
20 Fragile X Syndrome/ (5225)
21 Fragile X Mental Retardation Protein/ (2983)
22 (fragile x* or fraxa or frax a or fra x or mar x or marker x or martin bell or martinbell or FXS or FXTAS or FXPOI or FXAND or FXAD or FX associat*).ti,ab,kf. (7808)
23 (FMRP* or FMR1* or ((x linked or xlinked) adj3 (fragile or mental retard*))).ti,ab,kf. (5061)
24 or/1-23 (152990)
25 Genetic Carrier Screening/ (8682)
26 (carrier* adj3 (screen* or test* or panel* or counsel* or assess* or detect* or diagnos* or analys* or inform* or status or rate* or risk* or mother* or father* or parent or parents or couple* or marriage* or married or program*)).ti,ab,kf. (21841)

27 (massive* parallel sequenc* or ((sequential or parallel or panethnic or pan ethnic or multigene* or multi gene*) adj2 (screen* or panel*))).ti,ab,kf. (4646)
28 ((Preconception* or Pre-conception* or Prepregnan* or Pre-pregnan* or ((pregnan* or reproduct*) adj4 (future or decision* or before or plan*))) adj4 (screen* or test* or panel* or diagnos* or assess*)).ti,ab,kf. (2714)
29 or/25-28 (35141)
30 24 and 29 (3455)
31 carrier*.ti,ab,kf. (224067)
32 Preconception Care/ (2458)
33 (preconception* or pre-conception* or prepregnan* or pre-pregnan* or ((pregnan* or reproduct*) adj4 (future or decision* or before or plan*))).ti,ab,kf. (41769)
34 Prenatal Care/ (29397)
35 (prenatal* or pre-natal* or antenatal* or ante-natal*).ti,ab,kf. (144272)
36 Family Planning Services/ (25317)
37 ((pregnan* or conception* or family) adj3 plan*).ti,ab,kf. (51251)
38 Genetic Counseling/ (14724)
39 (counsel* adj4 genetic*).ti,ab,kf. (21336)
40 (couple* adj3 risk*).ti,ab,kf. (1608)
41 or/31-40 (481695)
42 exp Genetic Testing/ (48681)
43 ((genetic* or genomic* or gene or genes) adj3 (screen* or test* or panel* or diagnos* or assess*)).ti,ab,kf. (132254)
44 High-Throughput Nucleotide Sequencing/ (36823)
45 (((high throughput or high through put) adj2 (sequenc* or analys*)) or deep sequenc*).ti,ab,kf. (34900)
46 (((next gen or nextgen or next generation) adj2 sequenc*) or NGS).ti,ab,kf. (47345)
47 Sequence Analysis, DNA/ (163249)
48 ((DNA or parallel or target*) adj1 sequenc*).ti,ab,kf. (114810)
49 Heterozygote/ (47533)
50 Heterozygote Detection/ (8682)
51 ((heterozygot* or heterozygous*) adj3 (screen* or test* or panel* or counsel* or assess* or detect* or diagnos* or analy*)).ti,ab,kf. (4581)
52 ((target* or universal or population or variant* or mutation* or recessive) adj2 (screen* or test* or panel* or assay* or analysis)).ti,ab,kf. (113482)
53 Chromatography, High Pressure Liquid/ (189908)
54 (high performance liquid chromatograph* or high pressure liquid chromatograph* or high speed liquid chromatograph* or HPLC).ti,ab,kf. (205413)
55 Blood protein electrophoresis/ (12408)
56 (((h?emoglobin or capillar*) adj2 electrophores#s) or southern blot*).ti,ab,kf. (46901)
57 exp Polymerase Chain Reaction/ (456076)
58 ((multiplex ligation* adj2 probe amplification*) or polymerase chain reaction* or PCR or MLPA).ti,ab,kf. (685757)
59 or/42-58 (1683670)
60 41 and 59 (69538)
61 24 and 60 (6096)
62 ((expanded adj3 carrier* adj3 (screen* or test* or panel*)) or (carrier screen* adj3 (program* or service*))).ti,ab,kf. (321)
63 30 or 61 or 62 (7358)

64 Quality-Adjusted Life Years/ (13407)
65 (quality adjusted or adjusted life year*).ti,ab,kf. (18845)
66 (qaly* or qald* or qale* or qtime*).ti,ab,kf. (11982)
67 (illness state$1 or health state$1).ti,ab,kf. (7102)
68 (hui or hui1 or hui2 or hui3).ti,ab,kf. (1663)
69 (multiattribute* or multi attribute*).ti,ab,kf. (1004)
70 (utility adj3 (score$1 or valu* or health* or cost* or measure* or disease* or mean or gain or gains or index*)).ti,ab,kf. (16130)
71 utilities.ti,ab,kf. (7819)
72 (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eurqol5d or euro?qul or eur?qul5d or euro* quality of life or European qol).ti,ab,kf. (13300)
73 (euro* adj3 (5 d or 5d or 5 dimension* or 5dimension* or 5 domain* or 5domain*)).ti,ab,kf. (4657)
74 (sf36* or sf 36* or sf thirtysix or sf thirty six).ti,ab,kf. (23612)
75 (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kf. (2034)
76 ((qol or hrqol or quality of life).ti. or *quality of life/) and ((qol or hrqol* or quality of life) adj2 (increas* or decreas* or improve* or declin* or reduc* or high* or low* or effect or effects of worse or score or scores or change$1 or impact$1 or impacted or deteriorate$)).ab. (35904)
77 Cost-Benefit Analysis/ and (cost effectiveness ratio* and (perspective* or life expectanc*)).ti,ab,kf. (4003)
78 *quality of life/ and (quality of life or qol).ti. (57786)
79 quality of life/ and ((quality of life or qol) adj3 (improve* or chang*)).ti,ab,kf. (27879)
80 quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kf. (12744)
81 quality of life/ and health-related quality of life.ti,ab,kf. (35691)
82 quality of life/ and ec.fs. (10597)
83 quality of life/ and (health adj3 status).ti,ab,kf. (9780)
84 (quality of life or qol).ti,ab,kf. and cost-benefit analysis/ (14006)
85 models, economic/ (10627)
86 or/64-85 (177222)
87 63 and 86 (24)
88 limit 87 to english language (24)

Quantitative Evidence of Preferences and Values Search

Search date: April 9, 2021
Databases searched: Ovid MEDLINE, Cumulative Index to Nursing & Allied Health Literature (CINAHL)
Search filter used: Quantitative preference evidence filter, modified from Selva et al[240]

Database segment: Ovid MEDLINE(R) ALL <1946 to April 08, 2021>
Search Strategy:
---

1 Cystic Fibrosis/ (36171)
2 Cystic Fibrosis Transmembrane Conductance Regulator/ (9401)
3 ((cystic adj2 fibrosis) or fibrocystic disease* or mucoviscidosis or CFTR).ti,ab,kf. (49687)
4 CF.ti. (2443)
5 Muscular Atrophy, Spinal/ (3944)

6 "Spinal Muscular Atrophies of Childhood"/ (1379)
7 ((atroph* adj2 (spinal muscular or progressive muscular or myelopathic muscular)) or spinal amyotroph* or (neuropath* adj2 hereditary motor)).ti,ab,kf. (6496)
8 ((survival adj2 (motor neuron* 1 or motor neuron* 2)) or SMN1 or SMN2).ti,ab,kf. (1456)
9 ((werdnig hoffmann or dubowitz or kugelberg welander) adj2 disease*).ti,ab,kf. (331)
10 SMA.ti. (1120)
11 exp Hemoglobinopathies/ (46171)
12 (sickle adj3 (disease* or an?emia* or disorder* or trait* or h?emoglobin*)).ti,ab,kf. (24772)
13 (h?emoglobinopath* or h?emoglobulinopath* or hbp or hbps).ti,ab,kf. (8531)
14 (thalass?emia* or alphathalass?emia* or betathalass?emia* or deltathalass?emia* or (beta adj3 microcyt?emia*) or (an?emia* adj3 (cooley* or erythroblast* or mediterranean)) or target cell an?emia* or alpha thal or beta thal or delta thal).ti,ab,kf. (22858)
15 exp Hemoglobins, Abnormal/ (11451)
16 (h?emoglobin s or h?emoglobin c or h?emoglobin d or h?emoglobin e or h?emoglobin o or h?emoglobin h or h?emoglobin bart*).ti,ab,kf. (4183)
17 ((hbs or hb s or hgbs or hgb s or hbc or hb c or hgbc or hgb c or hbd or hb d or hgbd or hgb d or hbe or hb e or hgbe or hgb e or hbo or hb o or hgbo or hgb o or hbh or hb h or hgbh or hgb h or hb Bart* or hgb Bart*) adj5 (variant* or mutat* or abnormal* or anomal* or sickle or disease* or disorder* or trait*)).ti,ab,kf. (3052)
18 (hbas or hbac or hb ac or hbad or hb ad or hbae or hb ae or hbao or hb ao).ti,ab,kf. (476)
19 (((h?emoglobin* or hb or hgb) adj3 (variant* or mutat* or abnormal* or anomal* or sickle or disease* or disorder* or trait* or subunit* or alpha* or beta*)) or hbb or hba1 or hba2 or alpha globin* or beta globin* or delta globin*).ti,ab,kf. (27859)
20 Fragile X Syndrome/ (5168)
21 Fragile X Mental Retardation Protein/ (2927)
22 (fragile x* or fraxa or frax a or fra x or mar x or marker x or martin bell or martinbell or FXS or FXTAS or FXPOI or FXAND or FXAD or FX associat*).ti,ab,kf. (7730)
23 (FMRP* or FMR1* or ((x linked or xlinked) adj3 (fragile or mental retard*))).ti,ab,kf. (5004)
24 or/1-23 (151589)
25 Genetic Carrier Screening/ (8651)
26 (carrier* adj3 (screen* or test* or panel* or counsel* or assess* or detect* or diagnos* or analys* or inform* or status or rate* or risk* or mother* or father* or parent or parents or couple* or marriage* or married or program*)).ti,ab,kf. (21615)
27 (massive* parallel sequenc* or ((sequential or parallel or panethnic or pan ethnic or multigene* or multi gene*) adj2 (screen* or panel*))).ti,ab,kf. (4559)
28 ((Preconception* or Pre-conception* or Prepregnan* or Pre-pregnan* or ((pregnan* or reproduct*) adj4 (future or decision* or before or plan*))) adj4 (screen* or test* or panel* or diagnos* or assess*)).ti,ab,kf. (2676)
29 or/25-28 (34786)
30 24 and 29 (3438)
31 carrier*.ti,ab,kf. (221138)
32 Preconception Care/ (2416)
33 (preconception* or pre-conception* or prepregnan* or pre-pregnan* or ((pregnan* or reproduct*) adj4 (future or decision* or before or plan*))).ti,ab,kf. (41004)
34 Prenatal Care/ (28911)
35 (prenatal* or pre-natal* or antenatal* or ante-natal*).ti,ab,kf. (142438)
36 Family Planning Services/ (25127)
37 ((pregnan* or conception* or family) adj3 plan*).ti,ab,kf. (50861)

38 Genetic Counseling/ (14561)
39 (counsel* adj4 genetic*).ti,ab,kf. (21033)
40 (couple* adj3 risk*).ti,ab,kf. (1590)
41 or/31-40 (475647)
42 exp Genetic Testing/ (47813)
43 ((genetic* or genomic* or gene or genes) adj3 (screen* or test* or panel* or diagnos* or assess*)).ti,ab,kf. (129829)
44 High-Throughput Nucleotide Sequencing/ (35346)
45 (((high throughput or high through put) adj2 (sequenc* or analys*)) or deep sequenc*).ti,ab,kf. (33930)
46 (((next gen or nextgen or next generation) adj2 sequenc*) or NGS).ti,ab,kf. (45725)
47 Sequence Analysis, DNA/ (162140)
48 ((DNA or parallel or target*) adj1 sequenc*).ti,ab,kf. (113866)
49 Heterozygote/ (47052)
50 Heterozygote Detection/ (8651)
51 ((heterozygot* or heterozygous*) adj3 (screen* or test* or panel* or counsel* or assess* or detect* or diagnos* or analy*)).ti,ab,kf. (4535)
52 ((target* or universal or population or variant* or mutation* or recessive) adj2 (screen* or test* or panel* or assay* or analysis)).ti,ab,kf. (111598)
53 Chromatography, High Pressure Liquid/ (188218)
54 (high performance liquid chromatograph* or high pressure liquid chromatograph* or high speed liquid chromatograph* or HPLC).ti,ab,kf. (203851)
55 Blood protein electrophoresis/ (12394)
56 (((h?emoglobin or capillar*) adj2 electrophores#s) or southern blot*).ti,ab,kf. (46718)
57 exp Polymerase Chain Reaction/ (454179)
58 ((multiplex ligation* adj2 probe amplification*) or polymerase chain reaction* or PCR or MLPA).ti,ab,kf. (676674)
59 or/42-58 (1664266)
60 41 and 59 (68642)
61 24 and 60 (6054)
62 ((expanded adj3 carrier* adj3 (screen* or test* or panel*)) or (carrier screen* adj3 (program* or service*))).ti,ab,kf. (311)
63 30 or 61 or 62 (7304)
64 Attitude to Health/ (84565)
65 Health Knowledge, Attitudes, Practice/ (116188)
66 Patient Participation/ (26866)
67 Patient Preference/ (9237)
68 Attitude of Health Personnel/ (124923)
69 *Professional-Patient Relations/ (12013)
70 *Physician-Patient Relations/ (36280)
71 Choice Behavior/ (33272)
72 (choice or choices or value* or valuation* or knowledg*).ti. (277929)
73 (preference* or expectation* or attitude* or acceptab* or point of view).ti,ab,kf. (624481)
74 ((patient*1 or user*1 or men or women or personal or provider* or practitioner* or professional*1 or (health* adj2 worker*) or clinician* or physician* or doctor* or geneticist* or genetic counselor*) adj2 (participation or perspective* or perception* or misperception* or perceiv* or view* or understand* or misunderstand* or value*1 or knowledg*)).ti,ab,kf. (152652)
75 health perception*.ti,ab,kf. (2902)

76 *Decision Making/ (43867)
77 (patient*1 or user*1 or men or women or personal or provider* or practitioner* or professional*1 or (health* adj2 worker*) or clinician* or physician* or doctor* or geneticist* or genetic counselor*).ti. (2586065)
78 76 and 77 (8107)
79 (decision* and mak*).ti. (31144)
80 (decision mak* or decisions mak*).ti,ab,kf. (163500)
81 79 or 80 (165032)
82 (patient*1 or user*1 or men or women or personal or provider* or practitioner* or professional*1 or (health* adj2 worker*) or clinician* or physician* or doctor* or geneticist* or genetic counselor*).ti,ab,kf. (8590414)
83 81 and 82 (103531)
84 (discrete choice* or decision board* or decision analy* or decision-support or decision tool* or decision aid* or latent class* or decision* conflict* or decision* regret*).ti,ab,kf. (39834)
85 Decision Support Techniques/ (21054)
86 (health and utilit*).ti. (1598)
87 (gamble* or prospect theory or health utilit* or utility value* or utility score* or utility estimate* or health state or feeling thermometer* or best-worst scaling or time trade-off or TTO or probability trade-off).ti,ab,kf. (14300)
88 (preference based or preference score* or preference elicitation or multiattribute or multi attribute).ti,ab,kf. (3061)
89 or/64-75,78,83-88 (1363719)
90 63 and 89 (650)
91 Case Reports/ or Comment.pt. or Editorial.pt. or (Letter not (Letter and Randomized Controlled Trial)).pt. or Congress.pt. (3956583)
92 90 not 91 (626)
93 limit 92 to english language (596)
94 limit 93 to yr="2010 -Current" (300)

CINAHL

#	Query	Results
S1	(MH "Cystic Fibrosis")	8,160
S2	((cystic N2 fibrosis) or fibrocystic disease* or mucoviscidosis or CFTR)	10,551
S3	TI CF	413
S4	(MH "Muscular Atrophy, Spinal")	681
S5	((atroph* N2 (spinal muscular or progressive muscular or myelopathic muscular)) or spinal amyotroph* or (neuropath* N2 hereditary motor))	1,805
S6	((survival N2 (motor neuron* 1 or motor neuron* 2)) or SMN1 or SMN2)	162
S7	((werdnig hoffmann or dubowitz or kugelberg welander) N2 disease*)	10
S8	TI SMA	159
S9	(MH "Hemoglobinopathies+")	8,676
S10	(sickle N3 (disease* or anaemia* or anemia* or disorder* or trait* or haemoglobin* or hemoglobin*))	6,871
S11	(haemoglobinopath* or hemoglobinopath* or haemoglobulinopath* or hemoglobulinopath* or hbp or hbps)	1,585
S12	(thalassaemia* or thalassemia* or alphathalassaemia* or alphathalassemia* or betathalassaemia* or betathalassemia* or deltathalassaemia* or deltathalassemia* or (beta N3 (microcytaemia or microcytemia*)) or ((anaemia* or anemia*) N3 (cooley* or erythroblast* or	

mediterranean)) or target cell anaemia* or target cell anemia* or alpha thal or beta thal or delta thal) 3,543
S13 (haemoglobin s or hemoglobin s or haemoglobin c or hemoglobin c or haemoglobin d or hemoglobin d or haemoglobin e or hemoglobin e or haemoglobin o or hemoglobin o or haemoglobin h or hemoglobin h or haemoglobin bart* or hemoglobin bart*) 628
S14 ((hbs or hb s or hgbs or hgb s or hbc or hb c or hgbc or hgb c or hbd or hb d or hgbd or hgb d or hbe or hb e or hgbe or hgb e or hbo or hb o or hgbo or hgb o or hbh or hb h or hgbh or hgb h or hb Bart* or hgb Bart*) N5 (variant* or mutat* or abnormal* or anomal* or sickle or disease* or disorder* or trait*)) 296
S15 (hbas or hbac or hb ac or hbad or hb ad or hbae or hb ae or hbao or hb ao) 2,192
S16 (((haemoglobin* or hemoglobin* or hb or hgb) N3 (variant* or mutat* or abnormal* or anomal* or sickle or disease* or disorder* or trait* or subunit* or alpha* or beta*)) or hbb or hba1 or hba2 or alpha globin* or beta globin* or delta globin*) 23,856
S17 (MH "Fragile X Syndrome") 1,009
S18 (fragile x* or fraxa or frax a or fra x or mar x or marker x or martin bell or martinbell or FXS or FXTAS or FXPOI or FXAND or FXAD or FX associat*) 5,706
S19 (FMRP* or FMR1* or ((x linked or xlinked) N3 (fragile or mental retard*))) 383
S20 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 52,340
S21 (carrier* N3 (screen* or test* or panel* or counsel* or assess* or detect* or diagnos* or analys* or inform* or status or rate* or risk* or mother* or father* or parent or parents or couple* or marriage* or married or program*)) 4,524
S22 (massive* parallel sequenc* or ((sequential or parallel or panethnic or pan ethnic or multigene* or multi gene*) N2 (screen* or panel*))) 719
S23 ((preconception* or pre-conception* or prepregnan* or pre-pregnan* or ((pregnan* or reproduct*) N4 (future or decision* or before or plan*))) N4 (screen* or test* or panel* or diagnos* or assess*)) 9,695
S24 S21 OR S22 OR S23 14,762
S25 S20 AND S24 630
S26 carrier* 42,485
S27 (MH "Prepregnancy Care") 2,046
S28 (preconception* or pre-conception* or prepregnan* or pre-pregnan* or ((pregnan* or reproduct*) N4 (future or decision* or before or plan*))) 19,196
S29 (MH "Prenatal Care") 17,900
S30 (prenatal* or pre-natal* or antenatal* or ante-natal*) 65,818
S31 (MH "Family Planning") 7,030
S32 ((pregnan* or conception* or family) N3 plan*) 47,090
S33 (MH "Genetic Counseling") 4,413
S34 (counsel* N4 genetic*) 6,519
S35 (couple* N3 risk*) 577
S36 S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 167,994
S37 (MH "Genetic Screening") 14,202
S38 ((genetic* or genomic* or gene or genes) N3 (screen* or test* or panel* or diagnos* or assess*)) 143,687
S39 (((high throughput or high through put) N2 (sequenc* or analys*)) or deep sequenc*) 1,430
S40 (((next gen or nextgen or next generation) N2 sequenc*) or NGS) 5,013
S41 ((DNA or parallel or target*) N1 sequenc*) 21,199
S42 (MH "Heterozygote") 3,573

S43 ((heterozygot* or heterozygous*) N3 (screen* or test* or panel* or counsel* or assess* or detect* or diagnos* or analy*)) 596
S44 ((target* or universal or population or variant* or mutation* or recessive) N2 (screen* or test* or panel* or assay* or analysis)) 411,023
S45 (MH "Chromatography, High Pressure Liquid") 10,401
S46 (high performance liquid chromatograph* or high pressure liquid chromatograph* or high speed liquid chromatograph* or HPLC) 14,936
S47 Blood protein electrophoresis 155
S48 (MH "Blood Protein Electrophoresis") 155
S49 (((haemoglobin or hemoglobin or capillar*) N2 electrophores*) or southern blot*) 1,437
S50 (MH "Polymerase Chain Reaction+") 48,118
S51 ((multiplex ligation* N2 probe amplification*) or polymerase chain reaction* or PCR or MLPA) 74,669
S52 S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 565,524
S53 S36 AND S52 39,291
S54 S20 AND S53 1,721
S55 ((expanded N3 carrier* N3 (screen* or test* or panel*)) or (carrier screen* N3 (program* or service*))) 124
S56 S25 OR S54 OR S55 1,986
S57 (MH "Attitude to Health") 45,604
S58 (MH "Health Knowledge") 31,760
S59 (MH "Consumer Participation") Display
S60 (MH "Patient Preference") 1,141
S61 (MH "Attitude of Health Personnel") 46,628
S62 (MM "Professional-Patient Relations") Display
S63 (MM "Physician-Patient Relations") 16,595
S64 (MM "Nurse-Patient Relations") Display
S65 TI (choice or choices or value* or valuation* or knowledg*) 101,027
S66 (preference* or expectation* or attitude* or acceptab* or point of view) Display
S67 ((patient or patients or user or users or men or women or personal or provider* or practitioner* or professional or professionals or (health* N2 worker*) or clinician* or physician* or doctor* or nurse or nurses or practitioner* or geneticist* or genetic counselor*) N2 (participation or perspective* or perception* or misperception* or perceiv* or view* or understand* or misunderstand* or value or values or knowledg*)) 846,194
S68 health perception* Display
S69 (MH "Decision Making, Shared") Display
S70 (MH "Decision Making, Patient") 15,291
S71 (MH "Decision Making, Family") Display
S72 (MM "Decision Making") 23,631
S73 TI (patient or patients or user or users or men or women or personal or provider* or professional or professionals or (health* N2 worker*) or clinician* or physician* or doctor* or nurse or nurses or practitioner* or geneticist* or genetic counselor*) Display
S74 S72 AND S73 4,554
S75 TI (decision* and mak*) Display
S76 (decision mak* or decisions mak*) 159,208
S77 S75 OR S76 Display

S78 (patient or patients or user or users or men or women or personal or provider* or professional or professionals or (health* N2 worker*) or clinician* or physician* or doctor* or nurse or nurses or practitioner* or geneticist* or genetic counselor*) 3,414,632
S79 S77 AND S78 Display
S80 (discrete choice* or decision board* or decision analy* or decision support or decision tool* or decision aid* or latent class* or decision* conflict* or decision* regret*) 29,959
S81 (MH "Decision Support Techniques") 7,032
S82 TI (health and utilit*) 951
S83 (gamble* or prospect theory or health utilit* or utility value* or utility score* or utility estimate* or health state or feeling thermometer* or best worst scaling or time trade off or TTO or probability trade off) 18,617
S84 (preference based or preference score* or preference elicitation or multiattribute or multi attribute) 1,553
S85 S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S74 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 1,294,604
S86 S56 AND S85 582
S87 PT (Case Study or Commentary or Editorial or Letter or Proceedings) 1,260,824
S88 S86 NOT S87 554
S89 S86 NOT S87
Limiters - English Language 550
S90 S86 NOT S87
Limiters - Published Date: 20100101-20211231; English Language 352

Grey Literature Search

Performed on:
April 12-15, 2021

Websites searched:
Alberta Health Evidence Reviews, Alberta Health Services, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Universite de Quebec-Universite Laval, International HTA Database, Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Centers for Medicare & Medicaid Services Technology Assessments, Veterans Affairs Health Services Research and Development, Institute for Clinical and Economic Review, Oregon Health Authority Health Evidence Review Commission, Washington State Health Care Authority Health Technology Reviews, National Institute for Health and Care Excellence (NICE), Healthcare Improvement Scotland, Health Technology Wales, Ireland Health Information and Quality Authority Health Technology Assessments, Australian Government Medical Services Advisory Committee, Council of Australian Governments Health Technologies, Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S), Italian National Agency for Regional Health Services (AGENAS), Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment, Swedish Agency for Health Technology Assessment and Assessment of Social Services, Ministry of Health Malaysia Health Technology Assessment Section, Tuft's Cost-Effectiveness Analysis Registry, Sick Kids PEDE Database, PROSPERO, EUnetHTA, clinicaltrials.gov

Keywords used:

carrier, carrier screening, carrier testing, carrier panel, carrier program, carrier service, expanded carrier, preconception, family planning, genetic testing, genetic screening, genetic counseling, deep sequencing, sequence analysis, next generation sequencing, heterozygote, target screening, universal screening, HPLC, electrophoresis, polymerase chain reaction, PCR, MLPA, cystic fibrosis, CF, spinal muscular atrophy, SMA, spinal muscular, progressive muscular, survival motor neuron, SMN1, SMN2, sickle cell, sickle cell anemia, sickle cell anaemia, sickle cell disease, hemoglobinopathy, haemoglobinopathy, hemoglobin, haemoglobin, abnormal hemoglobin, abnormal haemoglobin, thalassemia, thalassaemia, fragile x, FMRP, dépistage des porteurs, test des porteurs, électrophorèse, mucoviscidose, atarophie musculaire spinale, drépanocytaire, syndromes drépanocytaires, hémoglobinopathie, thalassémie

Clinical results (included in PRISMA): 16
Economic results (included in PRISMA): 14
Ongoing HTAs (PROSPERO/EUnetHTA/): 8
Ongoing RCTs (clinicaltrials.gov): 34

Appendix 3: Characteristics of Included Studies

Table A3: Characteristics of Included Studies

Author, year	Country	Study type	Study period	Cond	Timing	Population	N	Testing order	Test method
Ai et al, 2020[124]	Australia	Noncomparative, retrospective	January 2015 to December 2017 (3 y)	HbP	PC, PN	Women attending antenatal clinics at feeder hospitals	1,628 women, 729 partners	Sequential, concurrent 628/729 partners (86%) screened simultaneously 102/729 partners (14%) screened sequentially	HPLC, MLPA, DNA Sanger sequencing
Alfaro Arenas et al, 2016[83], 2017[84]	Spain	Noncomparative, prospective	November 2012 to March 2014 (~1.5 y)	FXS	PC, PN	PC: consultation for women planning pregnancy PN: women at 10–12 wk routine antenatal visit	3,731 (3,413 PN, 318 PC)	NA	TP-PCR
Archibald et al, 2018[80]	Australia	Noncomparative, retrospective	Starting late 2012	CF, SMA, FXS	PC, PN	First 12,000 people screened by Victorian Clinical Genetics Services Women prior to pregnancy or early in pregnancy (recommended ≤ 12 wk gestation)	12,000 (at least 69% PN)	Sequential	38 CFTR variant panel accounting for ~90% of CF carriers in Australian population Sanger sequencing FXS TP-PCR and CE SBA SMA qRT-PCR
Baker et al, 2008[79]	United States	Noncomparative, retrospective	June 2005 to December 2006	CF, HbP, FXS	PC	Recipient couples of oocyte donors	72 oocyte donors, 64 recipients	NA	CF: CFTR variant analysis (initially 86 variant assay, later 97 variant assay for higher detection rate in Hispanics and African-Americans), CBC and Hb electrophoresis FXS: SBA and PCR
Basel-Vanagaite et al, 2008[102]	Israel	Noncomparative, retrospective	January 2006 to January 2007 (1 y)	SMA	PC, PN	Women for routine pregnancy monitoring or examination of their child	168 PC/PN, 11 partners	Sequential	Fluorescent multiplex PCR assay
Baxi et al, 2013[56]	India	Noncomparative, retrospective	June 2007 to May	Beta-thal	PN	Pregnant people and partners at Disha Fertility and Surgical Centre	1,006	Sequential	HPLC, ARMS-PCR

Author, year	Country	Study type	Study period	Cond	Timing	Population	N	Testing order	Test method
			2009 (~2 y)						
Beauchamp et al, 2019[46]	United States	Comparative (CF panel, NGS, NGS + CNV), retrospective	July 2017 to May 2018 (~1 y)	CF	PC, PN	People tested with Foresight ECS as part of routine screening	13,080 couples	Unknown	23-variant CF panel, NGS-based ECS for CFTR gene Did not report VUS or benign variants (determined by Foresight)
Berkenstadt et al, 2007[115]	Israel	Noncomparative, retrospective	January 1994 to June 2004 (~10 y)	FXS	PC, PN	Women with no known family history of FXS or PM/FM carriers 31% PC, 69% PN	40,079	NA	PCR and SBA
Bhukhanvala et al, 2013[93]	India	Noncomparative, retrospective	NR	HbP (severe types)	PN	Pregnant people visiting different maternity hospitals in Surat city	3,009	Sequential	HPLC
Borbolla Foster et al, 2021[125]	Australia	Noncomparative, retrospective	January 2014 to December 2016 (3 y)	HbP	PN	All women attending for public antenatal care at single tertiary centre with expected delivery date between January 2014 and December 2016 Exclusion: patients where certain data parameters could not be ascertained from detailed medical records and pathology review	643 (105 screened, 538 screen failure)	Unknown	HPLC
Bristow et al, 2019[47]	United States	Comparative (2 ECS panels), retrospective	June 2013 to July 2015 (2 y)	ECS (CF, HbP, SMA)	NR	People seen at Northwell Health Fertility	7,700 Panel A: 4,232 (55.0%) Panel B: 3,468 (45.0%)	NR	Panel A: 401 variants in 102 genetic diseases Panel B: 2,717 variants in 307 genetic diseases Both panels commercially available, use microarray, and additional testing for FMR1 and SMN1
Capalbo et al, 2021[110]	Italy	Noncomparative, retrospective	January 2017 to January 2020 (3 y)	ECS (CF, FXS, SMA)	PC	People planning to conceive naturally, from obstetrics and gynecology general practices People planning IVF and	766 couples	NR	qPCR and NGS

Author, year	Country	Study type	Study period	Cond	Timing	Population	N	Testing order	Test method
						gamete donors, from reproductive clinics			
Chamayou et al, 2020[57]	Italy	Noncomparative, retrospective	July 2014 to June 2019 (5 y)	CF	PC	Couples in Sicily attending infertility counselling	1,279 (1,055 males, 224 females)	Sequential	NGS
Chan et al, 2021[82]	Hong Kong	Noncomparative, retrospective	March 2016 to March 2017 (1 y)	ECS (Hb, FXS)	PC	People who attended subfertility clinic and pre-pregnancy counselling clinic, screening for possible carrier status before contemplating pregnancy	123	Sequential and concurrent	NGS-based ECS with 104 conditions (Family Prep Screen 2.0, Counsyl)
Chang et al, 2014[128]	Pakistan	Noncomparative, retrospective	February 2013 to February 2014 (1 y)	Beta-thal	PN	Pregnant people from rural districts of Shaheed Benazirabad and other neighboring districts Exclusion: people with liver diseases or other types of HbP	461 women	Sequential	NESTROFT, Hb electrophoresis
Cheng et al, 2017[116]	China	Noncomparative, prospective	August 2014 to April 2015 (~1 y)	FXS	PN	Pregnant Chinese women 4–41 wk gestation, ≥ 18 y old, who could understand English or Chinese and give informed consent Exclusion: people with known family history of FXS	2,650	NA	PCR, fragment sizing with microfluidic capillary electrophoresis
Choudhuri et al, 2015[70]	India	Noncomparative, retrospective	4 y: February 2009 to November 2012	HbP	PN	People attending PN clinic (any gravida or pregnancy duration)	20,883	Sequential	HPLC
Christie et al, 2009[71]	Australia	Noncomparative, retrospective	January 2003 to December 2007 (5 y)	CF	PC, PN	Couples considering pregnancy People in early pregnancy (< 14 wk) + partners	1,000	Sequential	Initial test for p.F508del If pregnant person was a carrier, partner was tested for p.F508del and another 28 CFTR pathogenic variants
Cizmeli et al, 2013[117]	United States	Noncomparative, retrospective	March 2005 to September 2011 (~6 y)	FXS	PC	People diagnosed with DOR ≤ 42 y, regular menstrual cycles for the preceding 6 mo Exclusion: known cause of elevated FSH for one's age unrelated to FXS, family history of FXS, or PM	62	NA	Capillary electrophoresis, SBA

Author, year	Country	Study type	Study period	Cond	Timing	Population	N	Testing order	Test method
Coiana et al, 2011[64]	Italy	Noncomparative, prospective	NR	CF	PC, PN	Couples of Sardinian descent, either planning pregnancy or in early stage of pregnancy (3–10 wk) with no family history of CF of CFTR-related disorders Enrolled from group of people requesting voluntary hematological screening for beta-thal	1,000 (500 couples)	Concurrent	Reverse dot-blot assay, PAGE analysis, MLPA
Colah et al, 2008[69]	India	Noncomparative, retrospective	1997–2003 (7 y)	HbP	PN	Pregnant people registered for first antenatal checkup at Wadia Maternity Hospital in Mumbai city catering to women from low SES group	61,935	Sequential	NESTROFT, HPLC
Cronister et al, 2005[85]	United States	Noncomparative, retrospective	2001–2002 (2 y)	FXS	PC, PN	People seeking PN genetic counselling services on voluntary basis, referred for variety of reasons Exclusion: people referred for/found to have suspected/known family history of FXS	29,103	NA	SBA and PCR
Dacus et al, 2006[66]	United States	Noncomparative, retrospective	July 2002 to December 2004 (2.5 y)	CF	PN	People at initial PN visit	5,616	Sequential	33-variant CF panel
Dormandy et al, 2010[152]	United Kingdom	Comparative, prospective	June 2005 to August 2007 (~2 y)	HbP	PN	Primary care: pregnant people during initial pregnancy consultation visit Secondary (midwife) care: pregnant people at first antenatal check by community midwife Eligible for inclusion in analysis if: people wanted to continue pregnancy, pregnancy ≤ 19 wk, and 6 d gestation at first visit to primary care, no written record of their sickle cell and thal carrier status in primary care, estimates of gestational age based on date of last menstrual period were	1,441	Sequential vs. concurrent	NR

Author, year	Country	Study type	Study period	Cond	Timing	Population	N	Testing order	Test method
						considered by them to be certain Exclusion: people who confirmed their pregnancy at later gestation			
Field and Martin, 2011[49]	Australia	Noncomparative, retrospective	NR	CF	PC	People presenting for infertility treatment Female or male could opt for CFTR testing, all egg/sperm donors also tested	5,600	Sequential testing Individual results disclosure	30-variant CF panel
Franasiak et al, 2015[52]f	United States	Noncomparative, retrospective	2011 to 2014 (3 y)	ECS (CF)	PC	People at infertility clinic	3,738 couples	Sequential, concurrent	Inheritest (97 conditions and additional 20 ordered on the Ashkenazi Jewish descent panel) Counsyl 1.0 test (102 conditions) Counsyl 2.0 (includes targeted variant testing for the same 102 conditions as 1.0 test plus sequencing to maximize coverage across genes)
Fries et al, 2005[67]	United States	Noncomparative, prospective	October 2001 to November 2002 (1 y)	CF	PN	PN patients attending Air Force Medical Genetics Center at Keesler Air Force Base, MS	855	Sequential	Multiplex PCR and reverse dot blot (20 variants initially, but in September 2002 expanded to ACOG's recommended 25 variant panel)
Gallati et al, 2009[50]	Switzerland	Noncomparative, prospective	NR	CF	PC	Men 27–57 y who consulted for primary couple infertility, referred for severe oligozoospermia or azoospermia with or without CAVD	310 men	Sequential	Screening of the entire coding sequence of the CFTR gene
Gao et al, 2020[118]	China	Noncomparative, retrospective	NR	FXS	PC, PN	Chinese women of child-bearing age (PN and planning pregnancy)	10,145	NA	PCR and SBA
Giordano et al, 2006[87]	Netherlands	Noncomparative, prospective	NR	HbP	PN	Random population consisting of people in early pregnancy and visiting OB/GYN outpatient department at the general	139	Sequential	HPLC, molecular analysis of HBA and HBB genes

Author, year	Country	Study type	Study period	Cond	Timing	Population	N	Testing order	Test method
						hospital Groene Hart in the city of Gouda			
Gupta et al, 2015[94]	India	Noncomparative, retrospective	18 mo	Thal	PN	Pregnant people in first or early second trimester (< 16 wk) willing to undergo carrier screening Exclusion: people who attended antenatal clinics in late second/third trimester, people who did not consent	1,500	Sequential	HPLC, ARMS-PCR
Hafezi-Nehad et al, 2014[129]	Iran	Noncomparative, retrospective	14 y	Beta-thal)	PC	People with normal Hb electrophoresis who have had genetic counselling	658 couples	NR	HPLC, PCR followed by reverse hybridization, DNA sequencing of alpha1 and beta1 genes, MLPA
Hernandez-Nieto et al, 2020[53]	Mexico	Noncomparative, retrospective	2012–2018 (6 y)	ECS (CF, HbP, FXS)	PC	People who underwent ART treatment from January 2015 to January 2019 and received primary care at Mexico City facility	805 (391 couples)	Sequential, concurrent	Sema4-Expanded Carrier Screen (283 conditions) NGS, genotyping with PCR amplification, MLPA, array CGH, long-range PCR qPCR, microarray, Sanger sequencing used as confirmation methods when appropriate FXS: SBA
Holtkamp et al, 2019[106]	Netherlands	Noncomparative, retrospective	2010–2016 (6 y)	CF	PC	PC people who requested online direct-to-consumer CF testing through hospital website	44 (39 couples, 5 individuals, due to donor gamete procedures)	Sequential	35 variant CF panel
Hu et al, 2022[113]	China	Noncomparative, retrospective	NR	ECS (HbP, FXS, SMA)	NR	People who underwent carrier screening for SMA at Department of PND, Nanjing Maternity and Child Care Hospital	1,915 couples	NR	Capillary electrophoresis-based multiplex PCR assay (CEBMPA) that analyzes 448 variants among 24 genes associated with 20 conditions, which covers the most common variants in

Author, year	Country	Study type	Study period	Cond	Timing	Population	N	Testing order	Test method
									the Chinese population Sanger sequencing, MLPA, or Gap-PCR used to confirm detected variants
Hung et al, 2019[119]	China	Noncomparative, retrospective	September 2014 to May 2017 (~3 y)	FXS	PN	Pregnant people age ≥ 20 y Excluded: people with known family history of FXS	20,188	NA	PCR, capillary electrophoresis, SBA
Jang et al, 2014[120]	Korea	Noncomparative, retrospective	December 2011 to December 2012 (1 y)	FXS	PC, PN	PC or PN women tested on their own initiative or on advice of physician	10,241	NA	PCR and SBA
Jiang et al, 2017[140]	China	Noncomparative, retrospective	2015–2017 (2 y)	Thal	PC	PC couples who chose to participate in Guangzhou Health Authority's pre-gestational thal screening program	83,062 (41,531 couples)	Sequential	Beta-thal: PCR-reverse dot blot assay for 17 known beta-globin variants in Chinese population, direct DNA sequencing of beta-globin gene and MLPA Alpha-thal: Gap-PCR and reverse dot-blot methods for common alpha-thal variants in southern China
Jiang et al, 2020[136]	China	Noncomparative, retrospective	January 2016 to December 2018 (3 y)	HbP (PFH/ alpha or beta-thal)	PC	PC couples who chose to participate in Guangzhou Health Authority's pre-gestational thal screening program	125,661 couples	Sequential	Gap-PCR for common alpha-thal deletions Reverse-dot hybridization for 3 nondeletional alpha-thal variants and 17 beta-globin gene variants
Jiang et al, 2021[141]	China	Noncomparative, retrospective	2016–2019 (4 y)	Thal	PC	PC couples who chose to participate in Guangzhou Health Authority's pre-gestational thal screening program	137,222 couples	Sequential	Gap-PCR, reverse-dot blot, Sanger sequencing Includes 4 common deletional alpha-thal, 3 common nondeletional alpha-

Author, year	Country	Study type	Study period	Cond	Timing	Population	N	Testing order	Test method
									thal, 17 common variants of beta-thal
Johansen Taber et al, 2019[148]	United States	Noncomparative, retrospective	September 2015 to December 2017 (~2 y)	FXS	PC, PN	Couples who had received carrier screening by Foresight, consented to be involved in research, were found to be at risk for current or future pregnancies affected by at least one of 176 autosomal recessive or X-linked conditions Couple where female partner was FMR1 PM carrier	122	NR	Foresight ECS
Kaufmann et al, 2011[88]	Netherlands	Noncomparative, mixed prospective and retrospective	January 2007 to January 2010 (3 y)	HbP	PN	Age 18+ y pregnant women at prenatal visit	1,291 (703 included prospectively, 588 included retrospectively)	Sequential	HPLC, capillary electrophoresis, molecular analyses with MLPA and direct sequencing
Khedri et al, 2020[145]	Iran	Noncomparative, prospective	2015 to 2018 (3 y)	Thal	NR	Randomly selected couples from Izeh health centres	150	NR	Capillary electrophoresis, sequencing of *HBB* gene, ARMS-PCR
Kiani et al, 2022[149]	Israel	Noncomparative, retrospective	March 2018 to March 2020 (2 y)	Thal	PN	Randomly selected couples who were suspected of thal, no age or gender restriction Exclusion: couples with incomplete information	241 couples	Sequential	Multiplex cap PCR, ARMS-PCR, sequencing, and MLPA-PCR
Kim et al, 2013[121]	South Korea	Noncomparative, retrospective	September 2003 to December 2011 (~8 y)	FXS	PC, PN	PC or PN women screened at Department of Medical Genetics, Cheil General Hospital and Women's Healthcare Centre Applied for testing on their own initiative or on the advice of their physician	5,829	NA	PCR, SBA
Konialis et al, 2007[72]	Greece	Noncomparative, retrospective	March 2004 to July 2005 (~1 y)	CF	PN	Pregnant people presenting for Down syndrome biochemical marker testing were offered CF carrier screening		Sequential	Multiplex reaction using DNA sequencer for ΔF508 testing Partners of carriers tested with 36-variant or 33-variant CF panel

Author, year	Country	Study type	Study period	Cond	Timing	Population	N	Testing order	Test method
Kulkarni et al, 2013[91]	India	Noncomparative, retrospective	June to August 2010 (3 mo)	Beta-thal	PN	Pregnant women who attended antenatal care clinic for the first time and their partners	210	Sequential	NESTROFT, Hb electrophoresis
Lakeman et al, 2008[78]	Netherlands	Noncomparative, retrospective	January to December 2005 (1 y)	CF, HbP	PC	PC with partner who were planning a pregnancy (near future or at a later date), recruited from people's own GP, or was a selected name from the practice register of the Municipal Health Service Exclusion: pregnancy, inability to read and write Dutch, positive family history of CF/HbPs	87 (72 couples)	Sequential	CF: 33 variant CF panel HbP: NR
Li et al, 2006[95]	China	Noncomparative, retrospective	January 1993 to December 2004 (12 y)	Thal	PN	Pregnant people at first presentation for prenatal care	53,495	Sequential	Hb electrophoresis, molecular testing for couples with discordant thal carrier status, Gap-PCR
Li et al, 2015[135]	China	Noncomparative, retrospective	January 2009 to December 2013 (5 y)	HbP (nondeletional beta-thal)	PN	Couples screened for thal at Guangzhou Maternal & Neonatal Hospital	51,105 couples	Sequential	Gap-PCR, PCR reverse dot-blot
Liao et al, 2005[96]	China	Noncomparative, prospective	January 1993 to December 2003 (10 y)	Thal	PN	All pregnant women evaluated at GZMNH (biggest birth size hospital in Guangdong province) by their regular obstetrical health care professionals in the first or second trimester	49,221 pregnant people, 4,502 partners	Sequential	Hb analysis, confirmatory testing with DNA analysis
Ma et al, 2019[284]	China	Noncomparative, retrospective	January 2015 to September 2017 (~2 y)	FXS	PC, PN	PC or PN women from obstetrics or family planning department who were tested after education and genetic counselling from physicians	11,891 (6,854 PC, 5,037 PN)	NA	TRP-PCR
Marcheco-Teruel et al, 2019[92]	Cuba	Noncomparative, retrospective	1982 to 2018 (36 y)	HbP (SCA)	PN	Pregnant people at first antenatal appointment	4,847,239	Sequential	Hb electrophoresis
Martin et al, 2005[112]	United Kingdom	Noncomparative, retrospective	NR	ECS (FXS)	PC	People undergoing PC ECS carrier screening in fertility centres for ART	138 couples undergoing ART using their own gametes	NR	NGS-based ECS with 549 genes implicated in 623 disease phenotypes

Author, year	Country	Study type	Study period	Cond	Timing	Population	N	Testing order	Test method
Massie et al, 2009[73]	Australia	Noncomparative, prospective	January 2006 to December 2008 (3 y)	CF	PC, PN	Women or couples attending obstetrician or GP who are PC or in early pregnancy stages (recommended to be < 14 completed weeks gestation)	3,200 people (3,000 women, 200 men)	Sequential, concurrent testing for 100 couples	12 variant CF panel, with most frequent variants in the study population
Meraj et al, 2022[122]	Pakistan	Noncomparative, retrospective	April 2018 to December 2020 (~2.5 y)	FXS	PC	Women of reproductive age consulting primary care in Khyber Pakhtunkhwa region of Pakistan for PC care, fulfilled ACOG screening criteria	808	NA	PCR, SBA, capillary electrophoresis
Metcalfe et al, 2008[86]	Australia	Noncomparative, prospective	NR	FXS	PC	Women ≥ 18, not pregnant at the time of recruitment and who could read, write, and speak English	31 (at Phase 2)	NA	PCR, SBA
Metcalfe et al, 2017[68]	Australia	Noncomparative, prospective	July 2009 to April 2013 (~4 y)	FXS	PC, PN	PC women or women up to 13-wk pregnant from family practice, public and private obstetric practice, and private obstetric ultrasound clinics in 2 cities (Melbourne and Perth)	961 (551 PC, 410 PN)	NA	PCR
Miri-Moghaddam et al, 2012[130]	Iran	Noncomparative, retrospective	June 2002 to June 2011 (9 y)	Beta-thal	PN	Couples at risk for beta-thal referred by primary health centre; low MCV (< 8 0fL), low MCH (< 27 pg), HbA2 high (> 3.0%), or normal; ruled out iron deficiency	106 couples	Sequential	Gap-PCR and ARMS-PCR first, if no variant found then subsequent complete sequencing of HBA1/2 genes
Morgenstern-Kaplan et al, 2022[108]	Mexico	Noncomparative, retrospective	June 2020 to April 2021	ECS (CF, FXS)	PC	PC couples and individuals who were members of the Mexican Jewish population Exclusion: pregnant people	208 (82 couples)	NR	NGS-based ECS panel TRP-PCR and CE for FXS
Pastore et al, 2008[55]	United States	Noncomparative, prospective and retrospective	NR	FXS	PC	Females diagnosed with DOR, mentally capable of making informed decisions Either self-nominated after participation in previous FXS PM study or physician referral from local private reproductive endocrinology practice Exclusion: family history of FXS (FM)	20	NA	NR

Author, year	Country	Study type	Study period	Cond	Timing	Population	N	Testing order	Test method
Patel et al, 2014[131]	India	Noncomparative, retrospective	April 2009 to June 2013 (~4 y)	Beta-thal	PN	Pregnant people with gestational age < 20 wk Exclusion: pregnant people with > 20-wk gestation because termination is not legally allowed after 20 wk in India	282 couples	Sequential	HPLC Genetic variant analysis performed when CBC and HPLC were negative, if: • Couple with previous child affected by homozygous HbP • 1 parent with heterozygous HbP and other with borderline Hb A2 value • 1 parent with heterozygous HbP and other with low MCV and/or MCH
Peyser et al, 2019[51]	United States	Noncomparative, retrospective	June 2013 to July 2015 (2 y)	ECS (CF, FXS, HbP, SMA)	PC	Individuals or couples seen at fertility centre during initial visit	4,232 (1,206 couples)	Sequential and concurrent	NGS-based Counsyl ECS (400 variants of 102 genes)
Picci et al, 2010[107]	Italy	Noncomparative, retrospective	1996–2006 (10 y)	CF	PC, PN	Adults enrolled in CF carrier screening program from University of Padova Pediatrics Department	25,104 couples	Sequential	47-variant CF panel based on common variants in northern and southern Italy Multiplex PCR and reverse-dot blot, further analysis with DGGE and HPLC in couples where one partner has CFTR pathogenic variant
Prior et al, 2010[103]	United States	Noncomparative, retrospective	October 2007 to June 2009 (~2 y)	SMA	PC, PN	PC or PN people seeking prenatal counselling during initial visit	500	Sequential	SMN1 gene dosage analysis
Punj et al, 2018[111]	United States	Noncomparative, prospective	NR	ECS (CF, HbP, FXS, SMA)	PC	Females planning pregnancy in near future, had CF screening test ordered by a clinician that was complete with results, not pregnant at time of consent	202 (71 couples)	Sequential	ECS with 728 gene–disorder pairs

Author, year	Country	Study type	Study period	Cond	Timing	Population	N	Testing order	Test method
						Females were members of Kaiser Permanente Northwest integrated health care delivery health management system			
Qamar et al, 2011[97]	Pakistan	Noncomparative, prospective	June 2004 to June 2005 (1 y)	Thal	PN	Randomly selected pregnant people attending outpatient department and labour ward of Department of Obstetrics and Gynaecology at Liaquat University Hospital (tertiary care hospital) Hyderabad	200	Sequential	Hb electrophoresis
Ratanasiri et al, 2006[98]	Thailand	Noncomparative, retrospective	February 2002 to February 2005 (3 y)	Thal	PN	Screened pregnant women with gestation age < 17 wk, first presenting at the antenatal care clinic in the Department of Obstetrics and Gynecology, Srinagarind Hospital, Khon Kaen University	1,498	Sequential	HPLC, PCR
Ruengdit et al, 2021[138]	Thailand	Noncomparative, retrospective	June 2020 to July 2021 (1 y)	HbP (severe thal)	PC	Pregnant people and spouses from 15 district hospitals in 6 provinces in northern Thailand	306 couples	Sequential	qPCR and HRM
Shang et al, 2017[126]	China	Comparative, prospective	NR	HbP	PC, PN	PC or PN randomly selected couples from 5 provinces in Southern China	10,111 couples	Sequential	NGS-based ECS Traditional methods: Gap-PCR and MLPA, reverse-dot blot, high-resolution melting analysis, Sanger sequencing
Shukla et al, 2018[89]	India	Noncomparative, retrospective	2010–2013 (3 y)	HbP	PN	People with microcytic hypochromic anemia attending hospital antenatal clinic	2,000	Sequential	HPLC
Simone et al, 2011[81]	United States	Noncomparative, retrospective	January 2017 to March 2018 (~1 y)	ECS (CF, HbP)	PC, PN	Women identified as carriers for autosomal recessive conditions through perinatal genetics practices ECS offered to all women who present for genetics consultation, regardless of referral indication Exclusion: people < 18 y	513 (505 PN, 8 PC)	Sequential	When appropriate, given opportunity of either genotyping, sequencing, or CBC/Hb electrophoresis 64% of partners had genotyping testing
Singh et al, 2020[109]	India	Noncomparative, retrospective	October 2016 to	ECS (CF,	PC	Unrelated people visiting medical genetics and	200 (160 couples)	Sequential	NGS-based ECS

Author, year	Country	Study type	Study period	Cond	Timing	Population	N	Testing order	Test method
			June 2018 (~2 y)	FXS, HbP, SMA)		OB/GYN outpatient clinic at Sir Ganga Ram Hospital for various reasons unrelated to genetic disorders Exclusion: people known to be carriers of any genetic disease or with history of chronic medical disorder or familial genetic disorder			
Slostad et la, 2007[74]	United States	Noncomparative, retrospective	October 2001 to October 2006 (5 y)	CF	PC	Couples evaluated for primary and secondary infertility at fertility centre	1,028 couples	Sequential	NR
Sorour et al, 2007[90]	United Kingdom	Noncomparative, retrospective	August 2001 to August 2002 (1 y)	HbP (alpha-Thal deletions)	PN	Female people who attended antenatal clinic at Sheffield Teaching Hospitals who underwent routine HbP screening	5,092	Sequential	Multiplex PCR
Stuppia et al, 2005[75]	Italy	Noncomparative, retrospective	January 2000 to May 2004 (~ 3.5 y)	CF	PC	Consecutive couples who underwent genetic counselling for IVF in 4 centres in Italy Exclusion: couples with family history of CF	1,195 couples	Sequential	Reverse dot blot, identifies 29 most common variants in Italy and polyT polymorphism
Su et al, 2011[104]	Taiwan	Noncomparative, prospective	January 2005 to June 2009 (4.5 y)	SMA	PN	Pregnant people recruited from primary clinics located in 25 countries around Taiwan (northern, central, southern, and eastern regions)	107,611	Sequential	Multiplex PCR and DHPLC analysis, MLPA to confirm genotypes of SMN genes
Suwannakhon et al, 2017[134]	Thailand	Noncomparative, prospective	January 2015 to August 2016 (~1 y)	HbP (Hb Bart's)	PN	Pregnant people and partners from antenatal care clinic at Phayao Provincial Hospital	1,235	NR	Multiplex RT-PCR
Suwannakhon et al, 2018[132]	Thailand	Noncomparative, prospective	2015–2016 (1 y)	Beta-thal	PN	Pregnant people and partners from antenatal care clinic at Phayao Provincial Hospital	1,115	NR	Micro-column chromatography and CE, high-resolution DNA melting analysis
Theodoridou et al, 2008[142]	Greece	Noncomparative, retrospective	2002–2006 (5 y)	Thal	PN	Pregnant people screened through National Programme for Prevention of Thalassemia in northern Greece	1,375 couples	Sequential	HPLC, column microchromatography, electrophoresis

Author, year	Country	Study type	Study period	Cond	Timing	Population	N	Testing order	Test method
Theodoridou et al, 2018[143]	Greece	Noncomparative, retrospective	2001–2015 (15 y)	Thal	PN	Pregnant people screened through National Programme for Prevention of Thalassemia in northern Greece	1,598 couples	Sequential	HPLC and electrophoresis, column microchromatography, NESTROFT DNA analysis: DGGE, ASO analysis, high-resolution melting point analysis, ARMS- and Gap-PCR, DNA sequencing
Tongsong et al, 2013[99]	Thailand	Noncomparative, prospective	August 2009 to December 2011 (~2 y)	Thal	PN	Pregnant people attending antenatal care clinic in first half of pregnancy, not anemic (Hb > 10 gm/dL) Exclusion: known thal carrier, any hematological disease, loss to follow-up or not following protocol, data for final PN/fetal diagnosis could not be obtained	12,874	Sequential	MCV or CMU-E screen, HbA2/HbE microcolumn and IC-strip/PCR, HPLC
Wei et al, 2007[76]	United States	Noncomparative, retrospective	May 2001 to March 2005 (~4 y)	CF	PN	Pregnant people from Henry Ford Health System who underwent CF screening	6,166	Sequential	May–December 2001: combination of 2 lab-developed methods (heteroduplex analysis and RFLP) January–September 2002: CF OLA to test 31 + 3 variants From October 2002: CF OLA to test 25 variants recommended by ACMG + 7 other variants
Weil et al, 2020[137]	United Kingdom	Noncomparative, retrospective	April 2007 to March 2017 (10 y)	HbP (SCD and thal)	PN	Pregnant people screened through NHS Sickle Cell and Thalassemia screening programme	6,608,575	Sequential	NR
Wong et al, 2006[144]	Thailand	Noncomparative, retrospective	December 2002 to June 2003 (6 mo)	Thal	PN	Pregnant people who attended antenatal clinic at Buddhachinaraj Provincial Hospital and 8 community hospitals	2,396 (1,198 couples)	Sequential	HPLC, PCR, microcolumn chromatography

Author, year	Country	Study type	Study period	Cond	Timing	Population	N	Testing order	Test method
Wong et al, 2016[133]	Thailand	Noncomparative, retrospective	January 2015 to January 2016 (1 y)	Beta-thal, HbP (Hb E)	PN	Consecutive couples and partners attending antenatal care unit at Phayao Hospital	834	Sequential	Micro-column chromatography, HPLC, RT-PCR, HRDM, direct DNA sequencing
Wongprachum et al, 2016[100]	Laos, Thailand	Noncomparative, retrospective	NR	Thal	PN	Pregnant people attending antenatal care service for the first time at Maria Teresa Hospital, gestational age < 16wk	411 (71 couples)	Sequential	HPLC, allele-specific PCR, direct DNA sequencing
Wood et al, 2016[65]	United States	Noncomparative, retrospective	August 2014 to March 2015 (~1 y)	SMA	PN	People receiving PN genetic counselling who have a reported family history of SMA or other indications (e.g., advanced maternal age, abnormal aneuploidy screening, family or personal history of another genetic disorder or malformation, etc.) are offered genetic counseling	1,377	Sequential	NR
Xi et al, 2020[54]	China	Noncomparative, prospective	May 2017 to July 2019 (~2 y)	ECS (HbP, SMA)	PC, PN	People seeking ART at single genetics and IVF clinic who chose ECS	2,923 (1,420 couples)	Sequential	NBGS-based ECS that covers 201 genes implicated in 135 single-gene recessive conditions For SMA and HbP: SMA and HBA MLPA kits and CE
Xi et al, 2021[123]	China	Noncomparative, prospective	August 2017 to September 2019 (2 y)	FXS	PN	Pregnant people who would receive PND because of various indications	4,286	NA	PCR and SBA
Yamsri et al, 2010[139]	Thailand	Noncomparative, retrospective	January 1993 to December 2008 (16 y)	HbP (severe thal)	PN	At-risk couples referred to regional reference centre for PND and extensive genetic counselling, originally screened at community hospital	1,422	Sequential	Initial screening with OF and DCIP Next HPLC and CE, PCR, direct DNA sequencing
Yang et al, 2020[101]	China	Noncomparative, prospective	May 2014 to May 2020 (6 y)	Thal	PN	Pregnant people with anemia receiving PND in Guiyang Maternity and Child Health Care Hospital and Guiyang Children's Hospital	2,306	Sequential	Hb analysis, PCR

Author, year	Country	Study type	Study period	Cond	Timing	Population	N	Testing order	Test method
						Exclusion: pregnant people with iron deficiency anemia			
Yin et al, 2014[127]	China	Noncomparative, prospective	May to August 2012 (3 mo)	HbP (alpha- and beta-thal)	PN	Pregnant people going to deliver between May and August 2012 and their partners, both members of couple were of Guangdong ancestry Exclusion: couples not of Guangdong ancestry, unqualified samples	14,332	NR	CE, molecular analysis for 23 common variants, Gap-PCR
Zhang et al, 2020[105]	China	Noncomparative, prospective	July 2017 to June 2019 (2 y)	SMA	PN	Pregnant people with no family history of SMA	13,069 and 207 partners	Sequential	qPCR and MPLA
Zhao et al, 2019[114]	China	Noncomparative, retrospective	NR	ECS (thal)	PC, PN	Couples without self-identified family history of inherited conditions selected from 5 provinces in southern China, underwent ECS	10,476 couples	Concurrent	NGS-based ECS
Zhao et al, 2021[146]	China	Noncomparative, prospective	May 2014 to December 2017 (~3.5 y)	SMA	PC, PN	PC or PN randomly selected couples from 5 provinces in Southern China	10,309	NR	NGS, TaqMan PCR, MLPA
Zlotogora et al, 2009[77]	Israel	Noncomparative, retrospective	2002–2007 (5 y)	CF	PC, PN	Mostly married couples in reproductive years	184	Sequential, concurrent	NR

Abbreviations: ACMG, American College of Medical Genetics; ARMS, amplification-refractory mutation system; ACOG, American College of Obstetricians and Gynecologists; ART, assisted reproductive therapy; CAVD, congenital absence of the vas deferens; CBC, complete blood count; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CNV, copy number variation; DGGE, denaturing gradient gel electrophoresis; DOR, diminished ovarian reserve; ECS, expanded carrier screen/screening; FM, full mutation; FMR1, fragile X mental retardation 1; FXS, fragile X syndrome; FSH, follicle-stimulating hormone; Hb, hemoglobin; HbP, hemoglobinopathy; HPLC, high-performance liquid chromatography; IVF, in vitro fertilization; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; MLPA, multiplex-ligation dependent probe amplification, NA, not applicable; NESTROFT, naked eye single tube red cell osmotic fragility test; NGS, next-generation sequencing; NR, not reported; OB/GYN, obstetrician gynecologist; OLA, oligonucleotide ligation assay; PAGE, polyacrylamide gel electrophoresis; PC, preconception; PM, premutation; PN, prenatal; PND, prenatal diagnosis/diagnostic; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; RT-PCR, reverse transcription PCR; SBA, Southern blot analysis; SES, socioeconomic status; SMA, spinal muscular atrophy; SMN1, survival motor neuron 1; thal, thalassemia; TP-PCR, triplet repeat primed PCR; VUS, variant of unknown significance.

Table A4: Characteristics of Partially Relevant Excluded Systematic Reviews on Carrier Screening

Author, year	Included conditions	Inclusion criteria	Literature search information	No. of included studies	Main conclusions
Kornman et al, 2009[62]	FXS	RCTs comparing females being tested regardless of family history, compared with females tested only where there is family history of FXS or other undiagnosed mental illness/impairment	Search up to October 2008 Databases: Cochrane Pregnancy and Childbirth Group's Trials Register	0	• Studies are needed comparing preconception or prenatal FXS screening for all females with screening only of females at increased risk
Hill et al, 2010[59]	FXS	Studies in which population-based screening had been offered to participants from the general population Molecular (DNA) testing for FXS Inclusion criteria for psychosocial outcomes were broad, with no limitations on study participants or study design Exclusion: studies that only had participants with intellectual disability, FXTAS, FXPOI, other clinical populations; only had participants with a family history of FXS; FXS status based only on cytogenetic testing and clinical assessments; cost-effectiveness studies unless FXS was offered	January 1991 to November 2009 Databases: Medline, CINAHL, Cochrane library, Embase, PsycInfo, National Research Register, Clinical Evidence	11 (10 carrier screening, 1 newborn screening)	• Health professionals and families of people with FXS seem to view that offering FXS carrier screening during the preconception period is most appropriate • Majority of studies are on prenatal carrier screening • People value making their own choice whether or not to undergo carrier screening
Ioannou et al, 2014[61]	CF	Studies in which participants were offered CF carrier screening or were asked to consider a hypothetical offer of	Search up to October 12, 2012 Databases: Medline, Embase,	85	• CF carrier screening was generally associated with relatively high uptake, positive attitudes, correct recall and understanding of carrier status, no long-term psychological harm

Author, year	Included conditions	Inclusion criteria	Literature search information	No. of included studies	Main conclusions
		screening, or their views of CF carrier screening were sought Exclusion: non-English studies, non-original research (e.g., editorials, opinions, commentaries, reviews); newborn screening studies; focus on laboratory aspects of carrier screening	CINAHL, PsycINFO, Cochrane library		• There was considerable heterogeneity among included studies • Need large real-world studies of population-based carrier screening
Hussein et al, 2018[60]	Thalassemia, sickle cell disease, CF, Tay-Sachs	RCT or quasi-RCT (published or unpublished) comparing preconception genetic risk assessment with usual care	1970 to November 16, 2017 Databases: CF and Genetic Disorders Groups' Trials Registers, Medline, Embase, CINAHL, PsycINFO	0	• Research is currently limited to nonrandomized studies • Recommendation for well-designed and adequately powered RCTs
Cannon et al, 2019[58]	Autosomal recessive and X-linked recessive disorders	Original research articles on carrier screening reporting the reproductive decisions of people/couples at risk of having an affected child	Search undertaken in January 2019 Databases: PubMed, Web of Science, CINAHL, Cochrane library	17 distinct studies in 19 peer-reviewed publications	• Most at-risk couples tend to act on their carrier status information • Post-test genetic counselling and psychological support for at-risk couples is important • Expanded carrier screening panels are becoming more common
Van Steijvoort et al, 2020[63]	Conditions included on an expanded carrier screening panel	Quantitative studies assessing the intention to take a hypothetical carrier screening test and/or actual uptake of a carrier screening offer; population is a priori not at risk based on personal or family history	January 2009 to January 2019 Databases: PubMed, Web of Science, CINAHL, Cochrane library	9	• Considerable interest in ECS among people of reproductive age in the general population • Actual uptake of ECS is substantially lower than people's reported intentions to undergo ECS • There is a generally higher overall uptake among pregnant people, compared with lower rates for people in the preconception stage • Results may not be generalizable to a broader population

Author, year	Included conditions	Inclusion criteria	Literature search information	No. of included studies	Main conclusions
		Exclusion: studies assessing interest in or uptake of genetic tests for non-reproductive medical information; studies focused on targeting dominant genetic disorders; studies within specific communities; non-original research (e.g., reviews, opinion articles); non-English studies			

Abbreviations: CF, cystic fibrosis; CINAHL, Cumulative Index to Nursing and Allied Health Literature; ECS, expanded carrier screening; FXS, fragile X syndrome; FXPOI, fragile X-associated primary ovarian insufficiency; FXTAS, fragile X-associated tremor/ataxia syndrome RCT, randomized controlled trial.

Appendix 4: Critical Appraisal of Clinical Evidence

Table A5: Risk of Bias[a] Among Nonrandomized Trials (RoBANS Tool)

Author, year	Selection of participants	Confounding variables	Intervention measurement	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
Ai et al, 2020[124]	High[b]	High[b]	Low	Low	Low	High[c]
Alfaro Arenas et al, 2016[83]	Low	Low	Low	Low	Low	Low
Alfaro Arenas et al, 2017[84]	Low	Low	Low	Low	Low	Low
Archibald et al, 2018[80]	Low	Low	Low	Low	Low	Low
Baker et al, 2008[79]	High[b,d]	Low	Low	Low	High[e]	Low
Basel-Vanagaite et al, 2008[102]	Low	Low	Low	Low	High[e]	Low
Baxi et al, 2013[56]	High[b]	High[f]	Low	Low	Low	High[c]
Beauchamp et al, 2019[46]	Low	High[f]	Low	Low	Low	Low
Berkenstadt et al, 2007[115]	Low	Low	Low	Low	Low	High[c]
Bhukhanvala et al, 2013[93]	Low	Low	Low	Low	Low	High[c]
Borbolla Foster et al, 2021[125]	High[b]	High[f]	Low	Low	High[e]	High[c]
Bristow et al, 2019[47]	High[b]	Low	Low	Low	Low	Low
Capalbo et al, 2021[110]	Low	High[f,g]	Low	Low	Low	High[c]
Chamayou et al, 2020[57]	Low	High[f,g]	Low	Low	High[e]	High[c]
Chan et al, 2021[82]	High[b,d]	Low	Low	Low	Low	Low
Chang et al, 2014[128]	Low	Low	Low	Low	Low	Low
Cheng et al, 2017[116]	Low	High[f]	Low	Low	Low	Low
Choudhuri et al, 2015[70]	Low	Low	Low	Low	Low	Low
Christie et al, 2009[71]	Low	High[f]	Low	Low	High[e]	Low
Cizmeli et al, 2013[117]	High[b]	High[g]	Low	Low	High[e]	Low
Coiana et al, 2011[64]	Low	High[f]	Low	Low	Low	Low

Author, year	Selection of participants	Confounding variables	Intervention measurement	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
Colah et al, 2008[69]	Low	Low	Low	Low	High[e]	Low
Cronister et al, 2005[85]	Low	High[f]	Low	Low	High[e]	Low
Dacus et al, 2006[66]	High[b,d]	High[f,g]	Low	Low	High[e]	Low
Dormandy et al, 2010[152]	Low	Low	Low	Low	High[e]	Low
Eissa et al, 2022[285]	High[b]	High	Low	Low	High	High
Field and Martin, 2011[49]	Low	High[f]	Low	Low	High[e]	Low
Franasiak et al, 2015[52]	Low	High[g]	Low	Low	Low	Low
Fries et al, 2005[67]	High[b]	Low	Low	Low	Low	Low
Gallati et al, 2009[50]	High[b]	Low	Low	Low	Low	Low
Gao et al, 2020[118]	Low	High[f]	Low	Low	Low	Low
Ghiossi et al, 2018[286]	High[b]	Low	Low	Low	Low	Low
Giordano et al, 2006[87]	Low	Low	Low	Low	High[e]	High[c]
Guo et al, 2019[166]	Low	High[f]	Low	Low	Low	Low
Gupta et al, 2015[94]	Low	Low	Low	Low	Low	Low
Hafezi-Nehad et al, 2014[129]	High[b]	Low	Low	Low	Low	High[c]
Hernandez-Nieto et al, 2020[53]	Low	High[f]	Low	Low	High[e]	Low
Holtkamp et al, 2019[106]	Low	Low	Low	Low	High[e]	High[c]
Hu et al, 2022[113]	High[b]	High[f]	Low	Low	High[e]	High[c]
Hung et al, 2019[119]	Low	Low	Low	Low	Low	Low
Jang et al, 2014[120]	High[b]	High[f,g]	Low	Low	Low	Low
Jiang et al, 2017[140]	Low	Low	Low	Low	Low	Low
Jiang et al, 2020[136]	High[b]	Low	Low	Low	High[e]	Low
Jiang et al, 2021[141]	Low	High[f]	Low	Low	Low	High[c]
Johansen Taber et al, 2019[148]	Low	Low	Low	Low	High[e]	High[c]

Author, year	Selection of participants	Confounding variables	Intervention measurement	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
Kaufmann et al, 2011[88]	High[b]	High[f,g]	Low	Low	Low	Low
Khedri et al, 2020[145]	High[b]	High[f]	Low	Low	High[e]	Low
Kiani et al, 2022[149]	High[b]	Low	Low	Low	High[e]	High[c]
Kim et al, 2013[121]	Low	High[g]	Low	Low	Low	High[c]
Konialis et al, 2007[72]	High[b]	Low	Low	Low	Low	High[c]
Kulkarni et al, 2013[91]	Low	High[f]	Low	Low	Low	Low
Lakeman et al, 2008[78]	Low	Low	Low	Low	High[e]	Low
Li et al, 2006[95]	High[b]	High[g]	Low	Low	High[e]	Low
Li et al, 2015[135]	Low	Low	Low	Low	High[e]	Low
Liao et al, 2005[96]	High[b,d]	High[f]	Low	Low	High[e]	Low
Ma et al, 2019[284]	Low	Low	Low	Low	High[e]	High[c]
Marcheco-Teruel et al, 2019[92]	High[b]	Low	Low	Low	High[e]	High[c]
Martin et al, 2005[112]	Low	Low	Low	Low	Low	High[c]
Massie et al, 2009[73]	High[b]	High	Low	Low	Low	Low
Meraj et al, 2022[122]	High[b]	Low	Low	Low	Low	High[c]
Metcalfe et al, 2008[86]	Low	High[f]	Low	Low	Low	Low
Metcalfe et al, 2017[68]	Low	High[f,g]	Low	Low	Low	Low
Miri-Moghaddam et al, 2012[130]	High[b]	High[f]	Low	Low	High[e]	Low
Morgenstern-Kaplan et al, 2022[108]	High[b]	Low	Low	Low	High[e]	High[c]
Pastore et al, 2008[55]	Low	High[f,g]	Low	Low	High[e]	High[c]
Patel et al, 2014[131]	Low	High[f,g]	Low	Low	Low	Low
Peyser et al, 2019[51]	High[b,d]	Low	Low	Low	High[e]	High
Picci et al, 2010[107]	High[b]	High[f]	Low	Low	High[e]	Low
Prior et al, 2010[103]	Low	Low	Low	Low	High[e]	Low

Author, year	Selection of participants	Confounding variables	Intervention measurement	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
Punj et al, 2018[111]	High[b]	High[f]	Low	Low	High[e]	Low
Koren et al, 2009[287]	High[b]	Low	Low	Low	High[e]	Low
Qamar et al, 2011[97]	Low	Low	Low	Low	Low	Low
Ratanasiri et al, 2006[98]	Low	High[f]	Low	Low	Low	High[c]
Ruengdit et al, 2021[138]	Low	Low	Low	Low	High[e]	Low
Shi et al, 2021[288]	Low	High[g,f]	Low	Low	High[e]	Low
Shang et al, 2017[126]	High[b]	High[f]	Low	Low	High[e]	Low
Shukla et al, 2018[89]	High[b]	Low	Low	Low	Low	Low
Simone et al, 2011[81]	Low	High[f,g]	Low	Low	Low	Low
Singh et al, 2020[109]	Low	High[f]	Low	Low	High[e]	Low
Singer et al, 2021[289]	High[b]	High[f]	Low	Low	High[e]	Low
Slostad et la, 2007[74]	Low	High[f]	Low	Low	Low	High[c]
Sorour et al, 2007[90]	Low	Low	Low	Low	Low	Low
Stuppia et al, 2005[75]	Low	High[f]	Low	Low	High[e]	Low
Su et al, 2011[104]	Low	Low	Low	Low	Low	Low
Suwannakhon et al, 2017[134]	High[b]	Low	Low	Low	Low	Low
Suwannakhon et al, 2018[132]	Low	High[f]	Low	Low	Low	Low
Theodoridou et al, 2008[142]	Low	Low	Low	Low	Low	High[c]
Theodoridou et al, 2018[143]	High[b]	Low	Low	Low	Low	Low
Tongsong et al, 2013[99]	Low	High[f]	Low	Low	Low	Low
Wei et al, 2007[76]	Low	Low	Low	Low	High[e]	Low
Weil et al, 2020[137]	High[b,d]	High[f,g]	Low	Low	High[e]	High[c]
Wong et al, 2006[144]	High[b]	High[f,g]	Low	Low	High[e]	Low
Wong et al, 2016[133]	Low	Low	Low	Low	High[e]	Low

Author, year	Selection of participants	Confounding variables	Intervention measurement	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting
Wongprachum et al, 2016[100]	Low	High[f]	Low	Low	High[e]	Low
Wood et al, 2016[65]	High[b]	Low	Low	Low	High[e]	Low
Xi et al, 2020[54]	Low	Low	Low	Low	Low	High[c]
Xi et al, 2021[123]	High[b]	Low	Low	Low	High[e]	Low
Yamsri et al, 2010[139]	High[b]	High[f]	Low	Low	High[e]	Low
Yang et al, 2020[101]	High	Low	Low	Low	Low	High[c]
Yin et al, 2014[127]	High	Low	Low	Low	Low	Low
Zhang et al, 2020[105]	Low	High[f]	Low	Low	High	High
Zhao et al, 2019[114]	Low	Low	Low	Low	Low	Low
Zlotogora et al, 2009[77]	Low	Low	Low	Low	High[e]	Low

[a]Possible risk-of-bias levels: low, high, unclear.
[b]Method of patient recruitment was unclear or not reported.
[c]Incomplete or unclear reporting of prespecified analyses or subgroups.
[d]Selection or recruitment process for other centres or sources was unclear or not reported.
[e]Incomplete or no information on patients lost to follow-up or the loss rate.
[f]Limited or no information on genetic counselling process.
[g]Limited information on patient characteristics.
Note: Carrier screening test methods were generally well-described among studies and thus evaluated as low for intervention measurement. Blinding was not explicitly reported in any of the studies, but was evaluated as low due to the genetic testing process.

Table A6: GRADE Evidence Profile for Carrier Screening

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Screening uptake							
45 (observational)	Serious limitations (−1)[a]	Serious limitations (−1)[b]	No serious limitations	Serious limitations (−1)[c]	Undetected	None	⨁ Very Low
Proportion of at-risk couples							
93 (observational)	Serious limitations (−1)[a]	Serious limitations (−1)[c]	No serious limitations	No serious limitations	Undetected	Large magnitude of effect (+2)[d]	⨁⨁⨁ Moderate
Reproductive decision-making impact							
59 (observational)	Serious limitations (−1)[a]	No serious limitations	Serious limitations (−1)[e]	No serious limitations	Undetected	Large magnitude of effect (+2)[f]	⨁⨁⨁ Moderate
Psychological impact							
8 (observational)	Serious limitations (−1)[a]	Serious limitations (−1)[g]	No serious limitations	No serious limitations	Undetected	None	⨁ Very low
Downstream impact							
12 (observational)	Serious limitations (−1)[a]	Serious limitations (−1)[h]	No serious limitations	No serious limitations	Undetected	None	⨁ Very Low

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

[a]Majority of studies were retrospective. Limited or no information on patient selection/characteristics among some studies.

[b]Some studies included all people who accepted carrier screening.

[c]Differences in populations and testing methods among studies.

[d]Study participants would otherwise not likely have been identified as carriers.

[e]Reported anticipated decisions may differ from actual decisions made.

[f]Carrier screening test results affected/changed people's reproductive decisions.

[g]Most studies did not use a validated tool for evaluation.

[h]Differences in data collection and unclear duration of data collection for the outcome.

Appendix 5: Selected Excluded Studies—Economic Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Wiwanitkit V. A cost utility analysis of the right method for screening hemoglobin E among Thai pregnant women. Arch Gynecol Obstet. 2006;274(2):88-90.	Intervention: not genetic testing of carriers
Koren A, Profeta L, Zalman L, Palmor H, Levin C, Zamir RB. Prevention of β-thalassemia in Northern Israel - a cost-benefit analysis. Mediterr J Hematol Infect Dis, 2014: 6(1).	Intervention: not genetic testing of carriers
Andrade E, Diaz J. Cost-effectiveness of the CFTR gene-sequencing test for asymptomatic carriers in the Colombian population. Biomedica. 2020;40(2):283-95.	Language: non-English full text
van den Akker-van Marle ME, Dankert HM, Verkerk PH, Dankert-Roelse JE. Cost-effectiveness of 4 neonatal screening strategies for cystic fibrosis. Pediatrics. 2006;118(3):896-905.	Population: newborn screening
Warren E, Anderson R, Proos AL, Burnett LB, Barlow-Stewart K, Hall J. Cost-effectiveness of a school-based Tay-Sachs and cystic fibrosis genetic carrier screening program. Genet Med. 2005;7(7):484-94.	Population: school-based screening program
Davis LB, Champion SJ, Fair SO, Baker VL, Garber AM. A cost-benefit analysis of preimplantation genetic diagnosis for carrier couples of cystic fibrosis. Fertil Steril. 2010;93(6):1793-804.	Intervention: IVF/PGD and population: genetically confirmed carriers
Al-Allawi NA, Al-Doski AA, Markous RS, Mohamad Amin KA, Eissa AA, Badi AI, et al. Premarital screening for hemoglobinopathies: experience of a single center in Kurdistan, Iraq. Public Health Genomics. 2015;18(2):97-103.	Population and intervention: premarital screening
Massie J, Delatycki MB. Cystic fibrosis carrier screening. Paediatr Respir Rev. 2013;14(4):270-5.	Study design: not CEA, policy review

Appendix 6: Results of Economic Literature Review—Summary

Table A7: Results of Economic Literature Review—Summary: Reproductive Genetic Carrier Screening for Multiple Diseases

Author, year, country	Study design, analytic technique, perspective, time horizon, discount rate	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
Wang et al, 2021[154] Australia	Study design: SR of 23 modeling studies (published between 1990 and 2019) Types of studies: cost-effectiveness, cost–utility, and cost-benefit analyses Analytic technique: decision models Perspective: health care sector, private (insurance), third-party payer, societal Time horizon: short term (1–4 y) or lifetime Discount rate: 3%–5% (> 1 y horizon)	People planning a pregnancy: 13% of studies Pregnant people: 61% Both: 22%	Intervention: genetic carrier screening, prenatal or preconception Comparator: no screening or standard care Conditions: autosomal recessive (CF, SMA, sickle cell disease and thalassemia), FXS, both (multiple) Majority of studies are for a single condition	No. of women screened, carriers identified, affected pregnancies, or fetuses identified, affected birth averted, LYs, and QALYs Mean difference (various outcomes), screening vs. no screening: NR	Currency: 2018 USD (using PPP) Total costs, mean difference, screening vs. no screening: NR Mean test cost per person: NR	Authors considered only results as reported in the original studies and did not provide any firm summarized conclusions on the cost-effectiveness of reproductive carrier screening Authors concluded that establishing a validated and practical clinical strategy of reproductive carrier screening and investigating the cost-effectiveness of multiple conditions in one economic evaluation are critical for implementing reproductive carrier screening in the future
MSAC, 2020[158] Australia	Study design: cost-effectiveness analysis Analytic technique: decision tree model Perspective: health care sector Time horizon:· lifetime Discount rate:·5%	Pregnant person or person planning a pregnancy, including their reproductive partners where the pregnant person is found to be a carrier and the condition is not X-linked	Intervention: universal screening, genetic (DNA) carrier testing for a pathogenic variant for CF, SMA, or FXS in all people planning a pregnancy or who are pregnant Comparator: no genetic testing Targeted screening (DNA testing) in people at risk (e.g., family history, or a GP referral), was not a suitable comparator	Carrier couples detected for CF and SMA, carriers detected for FXS, and QALYs, for initial pregnancy and for multiple pregnancies· Carrier couples or carriers detected per 100,000 screened (mean), preconception or prenatal testing vs. no testing, one pregnancy: 121.82 (CF),53.022 (SMA),660 (FXS) vs. 0 Mean difference (carriers), preconception or prenatal testing vs. no testing: 121.82 (CF), 53.022 (SMA), 660 (FXS)	Currency: AUD, 2020 Total costs (mean), preconception testing vs. no testing, and prenatal testing vs. no testing, one pregnancy: $575.89 vs. $595.07, and $785.57 vs. $595.07 Mean cost difference, preconception or prenatal testing and no testing: -$19.19 or $190.50	Base-case analysis: compared with no testing, combined preconception and prenatal carrier testing over multiple pregnancies is dominant Reporting of methods and results of sensitivity analysis limited. It is unclear if PA was conducted at all. The following factors influenced CEA results: the sensitivity of the CF test, the cost of the test, the CF carrier rate in the partner

Author, year, country	Study design, analytic technique, perspective, time horizon, discount rate	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
				QALYs (mean), preconception or prenatal testing vs. no testing, one pregnancy: 17.94 or 17.91 vs. 17.89 Mean QALY difference, preconception or prenatal testing vs. no testing: 0.04 or 0.02 Carrier couples or carriers detected per 100,000 screened (mean), combined testing vs. no testing, multiple pregnancies: 841.61 (CF, SMA, and FXS) vs. 0 Mean difference for carrier couples/carriers identified, combined testing vs. no testing: 841.61 QALYs (mean), combined testing vs. no testing, multiple pregnancies: 17.93 (CF, SMA, and FXS) vs. 17.91 Mean QALY difference, combined testing vs. no testing: 0.02	Total costs (mean), combined testing vs. no testing, multiple pregnancies: $391.25 vs. $651.16 Mean cost difference, combined testing vs. no testing, multiple pregnancies: -$259.91 Test cost per person over lifetime: $400	population, the participation rate of partners, the specificity of the test for CF, SMA, or FXS
Beauchamp et al, 2019[157] United States	Study design: Cost-effectiveness analysis Analytic technique: decision tree model Perspective: private (commercial) payer Time horizon: 1 and 3 y Discount rate: 3% (3 y)	Couples planning a pregnancy, at risk or not at risk for 176 panel-related conditions including CF, SMA, and FXS	Intervention: genetic carrier testing using a 176-condition ECS panel in couples planning a pregnancy Comparators: minimal screening (CF and SMA only) or no screening Both partners concurrently tested with ECS panel, followed by an optional intervention to avoid an affected birth (adoption, IVF with PGD, PND, or TOP)	Life-years gained, the number of affected births, and number of reproductive interventions At-risk carrier couples detected, affected births averted (per 100,000) and LYs (mean), population impact ECS vs. minimal screen: 1,160 couples detected and 290 births averted and 0.0161 LYs vs. 127 couples detected and	Currency: USD, 2018 Total 3-year costs (mean), population impact ECS vs. minimal screen: $500 (test) - $405.66 (disease) + $159.77 (intervention) vs. $693 - $127.03 + $17.46 Total costs for population impact, 77% intervention ECS	Base-case analysis: compared with minimal screen, population impact ECS is cost saving at a test cost of $500 and cost-effective at a test cost of $1,000 (ICER: $14,292/LY). ICER at a test cost of $2,000: $98,328/LY. Similar trends of increases in the ICER with increases in the test cost were seen with other strategies[d]

Author, year, country	Study design, analytic technique, perspective, time horizon, discount rate	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
			7 strategies compared, including: no screening, population impact, minimal screen (CF23, SMA). Population impact-ECS[b]	31.7 births averted and 0.00415 LYs Mean difference for LYs, population impact ECS vs. minimal screen: 0.0119	and 50% intervention[c]	PA: Done, did not present results for all health outcomes One-way deterministic analyses: population carrier frequency for couples at risk and test cost; compliance with screening not clearly evaluated
Zhang et al, 2019[159] Australia	Study design: Cost-effectiveness analysis Analytic technique: decision tree model Perspective: health care sector Time horizon: lifetime Discount rate: 5%	Young adults participating in prevention genomic screening for 7 conditions, including SMA, CF, and FXS	Intervention: universal preconception carrier screening, genetic carrier testing for pathogenic variants of CF, SMA, or FXS, assuming uptake rate of 71% Comparator: targeted testing in people at risk with uptake rate of 5% 3 independent decision tree models for each disease, combined to estimate the carrier frequency for a closed population (no migration)	Health outcomes: DALY, the number of disease cases (affected births) Mean difference, disease cases (affected births) averted (mean), universal screening vs. targeted (for 2.7 million screened): 169 (CF), 70 (SMA), 240 (FXS), and 491 (all combined) Mean difference for DALYs: 4,339 (CF), 1,490 (SMA), 3,586 (FXS), 9,702 (all combined)	Currency: AUD 2017[a] Total costs (mean in millions), universal screening vs. targeted: $14,124 (95% CrI: 10,703–17,630) and $14,659 (95% CrI: 10,384–19,275) Direct medical costs (mean, in millions), intervention and comparator: $10,530 (95% CrI: 7,487–13,600) and $10,323 (95% CrI: 6,568–14,433) Total costs, mean difference (in millions): $544 (CF), $707 (SMA), $465 (FXS), $317 (combined) Mean test cost per person: $400	Base-case analysis: compared with targeted screening, population-based preconception screening for all 3 diseases is cost-effective (ICER (combined): $32,145/DALY; disease-specific ICERs: $126,630/DALY (CF), $468,151/DALY (SMA), $130,296/DALY (FXS) PA and one-way sensitivity analyses: results remained robust, but were sensitive to cost of the test: at $200 per sample, combined screening is cost saving; at $800 and $1,200 per test sample, the ICER = $104,610/DALY and $177, 568/DALY, respectively
Azimi et al, 2016[156] United States	Study design: Cost-effectiveness analysis Analytic Technique: decision tree model	Couples planning a pregnancy, at risk or not for 14 genetic	Intervention: genetic (NGS) carrier testing using a 14-condition ECS panel, including CF in couples planning a pregnancy: preconception and prenatal arms	Life-years gained, and the number of affected births and affected births averted Affected births, number of affected births averted, and Lys (mean, 1 million screened	Currency: USD, 2014 Total costs (mean), ECS vs. genotyping vs. no screen: $670 million vs. $683	Base-case analysis: compared with no screen, ECS (NGS), ICER = $29,498/LY gained; genotyping ICER: $33,812/LY gained; NGS vs. genotyping: cost saving

Author, year, country	Study design, analytic technique, perspective, time horizon, discount rate	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
	Perspective: US health plan (private insurance) Time horizon: lifetime Discount rate: 3%	diseases, including CF	Comparators: targeted screen with genotyping (preconception and prenatal) or no screening Both partners concurrently tested with ECS panel (test price per couple), followed by an optional intervention to avoid an affected birth	couples): NGS: 141 affected births, 223 affected births avoided, and 8,636 Lys Genotyping: 162 affected births, 202 affected births avoided, and 7,918 LYs No screening: 364 affected births, 0 affected births avoided, and 0 LYs Mean difference for Lys, NGS vs. no screen and vs. genotyping: 8,636 and 7,918	million, vs. $415 million ECS panel test cost/genotyping test cost per couple: $500	PA: done, 98% chance that NGS screening associated with an increase in the number of affected births averted and a decrease in costs One-way deterministic analyses, NGS vs. genotyping remains cost saving, but influential parameters: CF carrier frequencies, CF mutation detection rate, treatment costs, use of screening, and probability of screening the partner and fetus after a positive test

Abbreviations: CEA, cost-effectiveness analysis; CF, cystic fibrosis; CrI, credible interval; DALY; disability-adjusted life-year; ECS, expanded carrier screening; FXS, fragile X syndrome; GP, general practitioner; ICER, incremental cost-effectiveness ratio; IVF, in vitro fertilization; LY, life-year; MSAC, Medical Advisory Service Committee; NGS, next-generation sequencing; NR, not reported; PA, probabilistic analysis; PGD, prenatal genetic diagnosis; PND, prenatal diagnostic testing; PPP, purchasing power parity; QALY, quality-adjusted life-year; SMA, spinal muscular atrophy; SR, systemic review; TOP, termination of pregnancy.

[a]Study authors did not include a currency year. 2017 is estimated based on publication date.

[b]Seven interventions included: 1) no screening; 2) population impact, minimal screen (CF23, SMA). couples screened for SMA and CF23 variants (all at-risk couples intervened to avoid an affected birth; residual risk remains for other conditions); 3) population impact-ECS: 176 conditions screened (all at-risk couples intervened); 4) 77% intervention CF23 and SMA (~77% intervened); 5) 77% intervention ECS (~77% intervened); 6) 50% intervention CF23 and SMA (~50% intervened); 7) 50% intervention ECS (~50% intervened).

[c]Total costs for population impact, 77% intervention ECS and 50% intervention ECS (cost of $500), mean difference: population impact: −$193.60 + (−$278.63) + $142.31 = −$329.92; 77% intervention ECS: −$128.80; and 50% intervention ECS: −$261.70.

[d]Results: 77% and 50% intervention ECS vs. 77% or 50% intervention minimal screen (cost saving, ICERs: $22,107 per LY [77%]/$40,889 per LY [50%] and $131,556 per LY [77%]/$207,836 per LY [50%]).

Table A8: Results of Economic Literature Review—Summary: Reproductive Genetic Carrier Screening for CF

Author, year, country	Study design analytic technique perspective time horizon discount rate	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
Avram et al, 2021[160] United States	Study design: cost-effectiveness analysis Analytic technique: decision tree model Perspective: societal Time horizon: lifetime Discount Rate: 3%	Pregnant people and their partners with no prior knowledge of CF carrier risk	Intervention: prenatal genetic carrier testing for CFTR mutations using sequential screening pathways: **1) genotyping/sequencing**: genotyping one partner followed by NGS for the second partner if the first partner was positive); **2) sequencing/ sequencing (both):** sequencing one partner followed by NGS for the second partner if the first partner was positive Comparator (control): carrier screening by **3) genotyping/ genotyping (both;** sequential testing) using the standard 23-variant panel recommended by ACMG/ACOG Test sensitivity and carrier frequency analyzed for pan-ethnic US population (reference case) and also by ethnicities (sensitivity analyses)	Missed CF carrier couples, CF newborns, CF births missed by prenatal diagnosis, CF-related pregnancy terminations (births averted), procedure-related losses, spontaneous fetal losses, unaffected births, and QALYs **1) Genotyping/sequencing**, missed CF carrier couples, CF newborns, CF births missed by prenatal diagnosis, CF-related pregnancy terminations, and QALYs for 4 million pan-ethnic pregnant people (mean): 669, 392, 166, 282, and 106,935,168, respectively **2) Sequencing/sequencing (both),** missed CF carrier couples, CF newborns, CF births missed by prenatal diagnosis, CF-related pregnancy terminations, and QALYs (mean): 47, 306, 12, 368, and 106,935,590, respectively **3) Genotyping/genotyping (both)**, missed CF carrier couples, CF newborns, CF births missed by prenatal diagnosis, CF-related pregnancy terminations and QALYs (mean): 1,146, 458, 285, 216, and 106,934,725, respectively	Currency: USD, 2020 **Genotyping/sequencing**, total costs (mean): $17.6 billion **Sequencing/sequencing** (both), total costs (mean): $25.0 billion **Genotyping/genotyping** (both), total costs (mean): $17.5billion Test cost per person, over lifetime: $293 (genotyping: common 23-mutation panel test), $2,174 (NGS for CFTR)	Base-case analysis: compared to genotyping/genotyping (both), fewer couples missed or CF births missed or more CF births averted with inclusion of sequencing ICER of sequencing/sequencing (both) vs. control: $17.6 million/QALY; ICER of genotyping/sequencing vs. control: $180,000/QALY PA, genotyping both partners vs. genotyping/sequencing was 63% cost-effective at $100,000/QALY Cost of testing influenced the CEA results: sequencing/sequencing was cost-effective at the cost of testing of $339, and genotyping/ sequencing was cost-effective when the cost of testing was between $340 and $1,840; other factors: sensitivity of NGS and genotyping, termination rate, and lifetime medical cost of CF
MSAC, 2016[161]	Study design: cost-effectiveness analysis	Pregnant couples at high risk of CF and	Intervention: prenatal genetic carrier testing for	Prenatal CF cases detected, CF births averted, pre-informed CF	Currency: AUD, 2014	Base-case analysis compared to no testing

Author, year, country	Study design analytic technique perspective time horizon discount rate	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
Australia	Analytic technique: decision tree model Perspective: health care sector Time horizon: pregnancy & birth (< 1 y) Discount rate: ·NA	two cohorts (two models) for two distinct fetal populations: Model 1: fetuses at risk because of parents being CF carriers (known carriers or had previous child diagnosed with CF) Model 2: fetus at risk because of diagnosis of echogenic bowel on the second-trimester ultrasound	CFTR mutations (two models) Comparator: no prenatal CFTR mutation testing (no prenatal diagnosis of CF), followed by newborn screening (CF diagnosed by screening or clinical diagnosis after birth)	births, CF birth total per 100 pregnancies Model 1: Prenatal CF case detected, CF birth averted, pre-informed CF birth, CF birth total (mean), prenatal testing vs. no testing:24.94, 23.72, 1.23, and 1.23 vs. 0, 0, 0, and 24.59, respectively Model 1: mean difference for prenatal CF cases detected , CF births averted, pre-informed CF births, CF birth total, prenatal testing vs. no testing: 24.94 (benefit), 23.72 (benefit), 1.23 (benefit), and -23.36, respectively Model 2: prenatal CF cases detected, CF births averted, pre-informed CF births, CF births total (mean), prenatal testing vs. no testing: 3.58, 2.34, 1.24, and 2.13 vs. 0, 0, 0, 4.44, respectively Model 2, mean difference for prenatal CF cases detected, CF births averted, pre-informed CF births, CF births total, prenatal testing vs. no testing: 3.58 (benefit), 2.34 (benefit), 1.24 (benefit), -2.31, respectively	Model 1: total costs per pregnancy (mean), prenatal testing vs. no testing: $4,521.66 vs. $4,071.61 Model 1: mean cost difference per pregnancy, prenatal testing and no testing: $450.05 Model 2: total costs per pregnancy (mean), prenatal testing vs. no testing: $4,410.45 vs. $3,866.92 Model 2: mean cost difference per pregnancy, prenatal testing and no testing: $543.54 Test cost per person, over lifetime: $135 (common 10-variant panel test, parents), $200 (common 32-variant test, parents in scenario), $80 (single variant test for F508del, fetus), $99 (known variant test, fetus), and $1,000 (whole genome sequencing Sanger, fetus)	Base-case analysis compared with no testing, prenatal testing in parents whose fetus has echogenic bowel (model 2) associated with ICERs: $15,182, prenatal CF detected, $23,254, CF birth averted, $43,727, pre-informed CF birth PA was not conducted. The following factors influenced the CEA results: Model 1: uptake of termination of affected pregnancy, clinical sensitivity of the common variant carrier CF test, the cost of whole genome sequencing, cost of newborn screening Model 2: incidence of CF in fetuses at risk, uptake of invasive testing when one parent is a carrier; uptake of termination of affected pregnancy, clinical sensitivity of the common variant carrier CF test
Hill et al, 2015[162] United Kingdom	Study design: cost-effectiveness analysis Analytic technique:· decision tree model Perspective: NR Time horizon: Pregnancy, < 1 y Discount rate: NA	Prenatal screening in pregnant people undergoing invasive prenatal diagnostic testing because of risk of CF (carriers)	Intervention: 1) NIPD testing using a 10-variant NGS panel for direct diagnosis of CF without pathway to IPD 2) paternal NIPD for exclusion of CF with inclusion of IPD (CVS) Comparators: prenatal diagnosis with IPD (CVS),	Number of pregnant people undergoing NIPD, number undergoing IPD, number of procedure-related miscarriages Number of pregnant people undergoing NIPD, number undergoing IPD, and number of procedure-related miscarriages (mean) per 100 pregnancies,	Currency: GBP, 2015 Total costs (mean), NIPD direct vs. NIPD paternal vs. no testing: £74,670 vs. £57,185 vs. £48,160 NIPD NGS panel test cost: for direct diagnosis of CF: £750; for exclusion of paternal carrier variant: £550	Base-case analysis: compared to no testing, prenatal NIPD testing prevents miscarriages (due to smaller number of pregnant people choosing IPD) but is more costly PA: not done, one-way not done

Author, year, country	Study design analytic technique perspective time horizon discount rate	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
			no mutation testing of carriers (no migration)	NIPD direct vs. NIPD paternal vs. no testing: 95.0, 0, 0 vs. 28.8, 36.3, 0.18 vs. 0, 43, 0.22		
Norman et al, 2012[163] Australia	Study design: cost-effectiveness analysis Analytic technique: decision tree model Perspective: health care sector Time horizon: lifetime Discount rate: 5%	Couples planning a first pregnancy	Intervention: universal preconception carrier genetic testing for pathogenic variants of CF in initial pregnancy (base case), in subsequent pregnancy, and all pregnancies (scenarios) Comparator: No screening	Number of disease cases (affected births) Affected CF infants per 100,000 births (mean), initial pregnancy, subsequent pregnancy, all pregnancies vs. no screen: 18.79, 10.81, 14.02 vs. 40.0, 30.0, 34.03 Mean difference in affected births per 100,000, screening vs. no screening: 21.21 averted CF births (initial pregnancy), 19.19 averted CF births (subsequent pregnancy), and 20.01 (all pregnancies)	Currency: AUD, 2010 Total costs (mean), initial pregnancy, subsequent pregnancy, all pregnancies vs. no screen: 16.6 million, 13.4 million, 3.6 million, 10.1 million, and 9 million, 11.5 million Total costs, mean difference ($ million): screening vs. no screening: $3.2 million (initial pregnancy), -6.5 million (subsequent pregnancy) and -2.5 million (all pregnancies) Mean test cost per person (10-variant panel): $116.77	Base-case analysis: compared with no screening, preconception screening in initial pregnancy is associated with incremental cost of $150,000 per CF birth averted and was cost saving for subsequent or both pregnancies PA was not done; one-way sensitivity analyses found that reduction in lifetime cost of CF by 50% would increase ICER across all pregnancies to $49,000 per averted birth; if the carrier rate was 2% instead of 4%, ICER would be $498,000 per averted birth; also cost of the test and probability of termination after positive IPD (CVS) test
Maxwell et al, 2010[164] Australia	Study design: cost-effectiveness analysis Analytic technique: decision tree model Perspective: health care sector Time horizon: lifetime Discount rate: 3.5% (costs)	Pregnant women and their partners	Intervention: universal prenatal carrier genetic program of couples, for pathogenic variants of CF in first and subsequent pregnancies (initial round with 38,000 pregnancies and established program with additional 16,720 pregnancies), 3 strategies: 1) one-step expanded (couples tested simultaneously, carrier status reported	CF carriers, CF carrier couples, CF pregnancies identified, CF births avoided, CF carrier couples with healthy child, CF-affected births CF carriers, CF carrier couples, CF pregnancies identified, avoided, CF births (mean), one-step, two-step simultaneous, two-step sequential: 1,996, 21, 4–5, 3–4, 9–10 Mean difference in CF carriers, CF carrier couples, CF	Currency: AUD, 2008 Total costs (mean), one-vs. two-step simultaneous vs. two-step sequential (initial and established rounds): 7.72 million vs. 4.89 million vs. 4.28 million Total costs, mean difference ($ million): screening vs. no screening: 7.72 million vs. 4.89 million vs. 4.28 million	Base-case analysis: compared with no screening, prenatal screening associated with incremental cost of $253,488 per CF carrier couple identified in one-step screening, $159,611 per couple in two-step simultaneous and $139,538 in two-step sequential screening

Author, year, country	Study design analytic technique perspective time horizon discount rate	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
			individually and for both) 2) two-step screening (pregnant person first and partner screened if pregnant person is positive) with simultaneous sample collection 3) two-step screening with sequential sample collection (partner provides sample only if pregnant person is positive) Comparator: no screening	pregnancies identified, terminated, CF births (mean), screening vs. no screening: 1,996, 21, 4–5, 3–4, 9–10	Mean test cost per person (10-variant panel): $116.77	Base-case analysis: compared with no screening in initial pregnancy, prenatal screening associated with incremental cost of $1,2 million per CF pregnancy identified in one-step screening, $0,795 million per couple in two-step simultaneous and $0.695 million in two-step sequential screening. Reduction of ICER by about $0.5 million was found for two pregnancies including newborn screening Base-case analysis: compared with no screening in initial pregnancy, prenatal screening over two pregnancies including newborn screening was associated with net costs of $2.08 million per CF pregnancy identified in one-step screening, $0.11 million per couple in two-step simultaneous and savings of $0.3 million in two-step sequential. Net cost accounted for decrease in lifetime cost of care for CF and was reduced in case of termination PA was not done; one-way sensitivity analyses found that test sensitivity for carrier detection,

Author, year, country	Study design analytic technique perspective time horizon discount rate	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
						diagnostic test uptake, and rate of termination influenced the results
Radhakrishnan et al, 2008[155] Australia	Study design: cost-effectiveness analysis Analytic technique: systematic review of 14 modeling studies Perspective: health care sector and societal Time horizon: short term or long term Discount rate: 3%–5% (> 1 y)	People planning a pregnancy or pregnant people and their partners	Intervention: prenatal carrier genetic screening or preconception carrier screening Comparator: no screening	CF carriers, CF carrier couples, CF births Mean difference in CF carriers, CF carrier couples, CF births (mean), screening vs. no screening: NR	Currency: USD (PPP), 2005 Total costs, mean difference ($ million): screening vs. no screening: NR Mean test cost per person: $28–$240	Base-case analysis: compared with no screening, prenatal screening associated with ICERs ranging from $739,000 to $1.6 million per CF birth averted, $10,086 per QALY, $110,000–$159,000 per affected pregnancy, and $75,000–$134,000 per CF carrier couple detected Compared with no screening, preconception screening associated with ICERs ranging from $394,000 to $573,000 per CF birth avoided, $33,000 to $295,000 per CF carrier couple detected, and $4,000 per carrier detected
Konialis et al, 2007[72] Greece	Study design: cost-consequence analysis Analytic technique: estimated benefits and costs Perspective: health care sector Time horizon: < 1 y Discount rate: NA	Pregnant people (n = 1,233) and their partners	Intervention: prenatal carrier genetic screening for pathogenic variants of CF (ΔF508 in pregnant people and 36 CFTR mutations in partners of pregnant people tested were positive) Comparator: no screening	CF carriers CF carriers, CF carrier couples (recalculated: test sensitivity × prevalence = 0.78 × 1/30): 1.8% or 1,620 of 90,000 screened, 42 couples CF affected births (calculated as 1/4): 11	Currency: Euro , 2007 Total costs (mean), screening (per 90,000 tested): €1.08 million Mean test cost per pregnant person (1 variant): €10, (€100 per partner)	Base-case analysis: compared with no screening, prenatal screening associated with incremental cost of €1.08 million per CF affected birth PA was not done, nor one-way sensitivity analysis
Wei et al, 2007[76] United States	Study design: cost-consequence analysis Analytic technique: retrospective analysis of hospital data	Pregnant people (n = 6,166) and their partners	Intervention: prenatal carrier couple sequential screening Comparator: no screening	CF carriers, CF carrier couples, CF affected births CF carriers, CF carrier couples, CF births (mean), screening: 143	Currency: USD, 2005 Total costs (mean), screening: $334,400 Mean test cost per person: $50	Base-case analysis: compared with no screening, prenatal screening associated with incremental cost of

Author, year, country	Study design analytic technique perspective time horizon discount rate	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
	Perspective: hospital Time horizon: < 1 y Discount rate: NA			(of 6,166 screened), 6 carrier couples, 1 CF affected birth		$334,000 per CF-affected birth PA was not done nor one-way sensitivity analysis
Weijers-Poppelaars et al, 2005[165] Netherlands	Study design: cost-effectiveness analysis Analytic technique: simulation Perspective: societal Time horizon: 1 y and lifetime Discount rate: 4% (lifetime, costs)	Couples planning a pregnancy	Intervention: preconception carrier screening program provided by a GP or education group counseling, with DNA sample taken at the same time from a couple, but they were tested either sequentially (SETS, one partner first, the second only if the first tests positive) or at the same time (DETS) Comparator: no screening	CF carrier couples, CF affected births (for 106,635 screened couples) CF carrier couples (mean), group counseling (SETS, DETS) and GP (SETS, DETS): 22, 23 and 39, 40 CF births (mean), group counseling (SETS, DETS) and GP (SETS, DETS): 6, 6 and 11, 11	Currency: USD, 2005 Total costs of the program (mean, 106,635 couples), group counseling (SETS, DETS) and GP (SETS, DETS): $3.46 million, $4.15 million and $4.72 million, $5.92 million Mean test cost per person: $27 and $96 (second test has larger number of variants)	Base-case analysis (average CER, ACER): compared with no screening (assuming 0 cases), preconception screening by education counseling associated with incremental cost of $157,000 (SETS) or $182,000 (DETS) per CF carrier couple detected or $563,000 and $655,000 per CF birth; preconception screening by GP associated with IC of $122,000 (SETS) or $148,000 (DETS) per CF carrier couple detected or $438,000 and $534,000 per CF birth avoided No screening was associated with savings after accounting for terminated pregnancies and lifetime costs of CF PA was not done. One-way sensitivity analysis showed costs of information (invitations) and of care for CF were important factors

Abbreviations: ACER, average cost-effectiveness ratio; ACMG, American College of Medical Genetics; ACOG, American College of Obstetricians and Gynecologists; CEA, cost-effectiveness analysis; CER, cost-effectiveness ratio; CF, cystic fibrosis, CFTR, cystic fibrosis transmembrane conductance regulator; CVS, chorionic villus sampling; DETS, double-entry two-step; GP, general practitioner; IC, incremental cost; ICER, incremental cost-effectiveness ratio; IPD, invasive prenatal diagnosis; MSAC, Medical Advisory Service Committee; NA, not applicable; NIPD, noninvasive prenatal diagnosis; NR, not reported; NGS, next-generation sequencing; PA, probabilistic analysis; PPP, purchasing power parity; SETS, single-entry two-step; QALY, quality-adjusted life-year.

Table A9: Results of Economic Literature Review—Summary: Reproductive Genetic Carrier Screening for FXS

Author, year, country	Study design Analytic technique Perspective Time horizon Discount rate	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
Guo et al, 2021,[166] China	Study design: cost-consequence analysis Analytic technique: calculation of costs and consequences using decision analytic model and retrospective cohort data Perspective: NR Time horizon: NR (costs over he lifetime of person with FXS) Discount rate: NR	Adult women, East Asian population (n = 39,458 screened)	Intervention: universal genetic carrier testing for FXS of adult women (including prenatal diagnosis) Comparator: targeted genetic testing, based on family history (with prenatal diagnosis)	Identified carriers, identified fetuses with FXS Mean number of identified carriers, population-based testing vs. targeted testing: 1 in 556 (71 identified) vs. 1 in 1,793 (22 identified) 69% of carriers missed in targeted testing Mean number of identified affected fetuses, population-based testing vs. targeted testing: 13 vs. 4	Currency: USD, 2020 or 2021 (unclear) Total cost, population-based testing (screening costs for 39,458 screened women) vs. targeted testing (screening costs for 157 screened women and treatment costs for 4 children born with FXS): $3,974,200 (screening) + 0 (treatment costs) vs. $24,500 (screening) + $2.5 million (treatment costs) Mean cost difference, calculated: $1,449,700 Test cost per person: NR	Authors conclusion: compared to targeted testing, population-based carrier testing is dominant as it identifies more carriers of FXS and avoids birth of affected children ICER, calculated ($1.45 million/9): $161,078 per additional affected child ICER, calculated from our model, reproduced based on data: > $67,000 per additional carrier identified
Hollingsworth, 2005[167] Australia	Study design: cost-consequence analysis Analytic technique: calculation of costs and consequences Perspective: societal Time horizon: lifetime Discount rate: 5%	Pregnant people	Intervention: universal prenatal genetic carrier testing for FXS in pregnant people Comparator: no genetic testing	Affected children Mean difference in affected cases, prenatal testing vs. no testing: 31 affected cases	Currency: USD, 2005[a] Mean cost difference, prenatal testing and no testing: -$366,000 Test cost per person: $240	Base-case analysis: compared with no testing, prenatal carrier testing is associated with cost savings, and FXS cases avoided PA: not done
Musci et al, 2005[168] United States	Study design: cost-effectiveness analysis Analytic technique: decision tree model Perspective: societal Time horizon: lifetime Discount rate: 3%	Pregnant people, assuming 87% accept participation in screening program	Intervention: genetic testing for FXS mutation using PCR in all, followed by Southern blot in 20% Comparator: no screening	QALYs gained, number of affected births, number of reproductive interventions Mean difference for cases affected and QALYs, prenatal screen vs. no screen: NR	Currency: USD, 2004 Total costs (mean), prenatal screen vs. no screening: NR PCR test cost: $95.33 and Southern blot test cost: $143.80	Base-case analysis: compared with no screening, prenatal screening associated with ICER of $14,858 per QALY PA: results not presented for all health outcomes

Author, year, country	Study design Analytic technique Perspective Time horizon Discount rate	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
						One-way deterministic analyses: test cost (if $140, the ICER is $99,367 per QALY)

Abbreviations: FXS, fragile X syndrome; ICER, incremental cost-effectiveness ratio; NR, not reported; PA, probabilistic analysis; PCR, polymerase chain reaction; QALY, quality-adjusted life-year.

[a]Study authors did not include a currency year. 2005 is estimated based on publication date.

Table A10: Results of Economic Literature Review—Summary: Reproductive Genetic Carrier Screening for Hemoglobinopathies and Thalassemia

Author, year, country	Study design analytic technique perspective time horizon discount rate	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
MSAC, 2019[169] Australia	Study design: cost-effectiveness analysis Analytic treatment:· decision tree model Perspective: Health care plan (including direct cost and patient co-payment) Time horizon: < 1 y Discount rate: NA	Couples planning a pregnancy (or pregnant people with abnormal red cell indices and, when necessary, their reproductive partners)	Intervention: genetic (DNA) carrier testing for a common gene deletion in alpha-thalassemia that follows prior usual care hematological testing Comparator: no genetic testing, usual care testing includes full blood count, ferritin, and thalassemia studies	Preconception: carrier couples correctly confirmed, couples genetically confirmed at risk of having a fetus affected by Hb Bart's (with fetal outcome), carrier couples identified at risk of having a fetus affected by Hb Bart's Prenatal: carrier couples detected, carrier couples detected at risk of having a fetus affected by Hb Bart's, and affected cases (Hb Bart's) Mean difference, preconception testing vs. no testing: 99.98% carrier couples properly detected, 0.4% genetically confirmed at risk, and 0.1% carrier couples identified at risk (0.4% by DNA screen vs. 0.3% by usual care) Mean difference, prenatal vs. no testing: 99.98% carrier couples properly detected, 0.4% genetically confirmed at risk, 0.1% carrier couples identified at risk, and 0.1% avoided	Currency: AUD, 2019? Total costs (mean), preconception testing vs. no testing: $585 vs. $139 Mean cost difference, preconception testing vs no testing: $445 Total costs (mean), prenatal testing vs. no testing: $8,273 vs. $7,856 Mean cost difference, prenatal testing vs. no testing: $417 Test cost per person, over lifetime: $100 for PCR-GAP ($85 paid by ministry and $15 paid by patient); $200 for gap-PCR followed by MLPA ($170 paid by ministry)	Base-case analysis: preconception testing, ICERs: $110,266 per additional couple genetically confirmed as being at risk of having a fetus affected by Hb Bart's; $426,499 per additional couple identified as being at risk of having a fetus affected by Hb Bart's; $446 per additional couple with genetically confirmed status Base-case analysis: prenatal testing, ICERs: $103,179 per additional couple genetically confirmed as being at risk of having a fetus affected by Hb Bart's; $399,086 per additional couple identified as being at risk of having a fetus affected by Hb Bart's; $417 per additional couple with genetically confirmed

Author, year, country	Study design analytic technique perspective time horizon discount rate	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
				cases of Hb Bart's (0.01 vs. 0.1)		status; $419,612 per avoided case of Hb Bart's Reporting of methods and results of sensitivity analysis limited. It is unclear if PA was conducted at all. The following factors influenced CEA results: prevalence of variants, cost of test, need for further testing, approach to testing (simultaneous vs. sequential). If both parents require abnormal results before they enter genetic testing (i.e., simultaneous testing), then the ICERs are 3× lower (and incremental benefit is higher, e.g., 0.2% vs. 0.4%)
Bryan et al, 2011[153] (duplicate findings by Dormandy et al, 2010[152]) United Kingdom	Study design: cost-effectiveness analysis Analytic technique: probabilistic decision-tree model utilizing the SHIFT trial data Perspective: health care sector	Pregnant people and partners of those who test positive on carrier screening for SCD	Interventions: models of care for genetic carrier testing for SCD early in primary care: 1) primary care parallel (testing offered to both pregnant person and partner	Proportion of pregnant people screened by 70 days, affected births Number of screened and affected births (mean), primary care parallel vs. primary care sequential vs. midwife care: 2,556 screened and 27.83	Currency: GBP, 2010 Total costs (mean), primary care parallel vs. primary care sequential vs. midwife care: £201,000 vs. £178,000 vs £145,000, respectively	Base-case analysis: primary care sequential dominated primary care parallel and is associated with an ICER of £13 per person screened by 70 d, compared with midwife care

Author, year, country	Study design analytic technique perspective time horizon discount rate	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
	Time horizon: pregnancy (< 1 yr) Discount rate: NA		at the same time) at the first primary care visit by 10 weeks' gestation, and 2) primary care sequential (testing pregnant person, and then testing partner if the pregnant person tests positive) Comparators: usual care: sequential screening at the first midwife consultation	affected births vs. 2,887 and 27.17 vs. 264 and 27.83, respectively Mean difference for number of pregnant people screened, primary care parallel vs. primary care sequential: -331	Mean cost difference, primary care parallel vs. midwife care: £56,000; primary care sequential vs. midwife care: £33,000 Mean cost difference, primary care parallel vs. primary care sequential: £23,000	
Ratanasiri et al, 2006[98] Thailand	Study design: Cost-consequence analysis, retrospective analysis of medical registry data Analytic technique: estimation of costs and benefits Perspective: NR Time horizon: NR Discount rate: NR	Pregnant people (n = 1,498), participants of a prenatal prevention program for severe thalassemia	Intervention: genetic (PCR) carrier testing of pregnant people and their partners for hemoglobinopathies Comparators: no genetic testing	Affected cases (severe thalassemia) Mean difference, testing vs. no testing: 2 cases avoided by testing	Currency: Bahts, 2006[a] Total costs (mean), testing vs. no testing: -$1,142,600 Bahts	Base-case analysis: compared with no testing, prenatal screening program was more effective and less costly PA or other sensitivity analyses not done

Abbreviations: CEA, cost-effectiveness analysis; ICER, incremental cost-effectiveness ratio; MSAC, Medical Advisory Service Committee; MLPA, Multiplex Ligation-dependent Probe Amplification; NA, not applicable; NR, not reported; PA, probabilistic analysis; gap-PCR, gap polymerase chain reaction; SCD, sickle cell disorders.

[a]Study authors did not include a currency year. 2006 is estimated based on publication date.

Table A11: Results of Economic Literature Review—Summary: Reproductive Genetic Carrier Screening for SMA

Author, year, country	Study design analytic technique perspective time horizon discount rate	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
Little et al, 2010[170] United States	Study design: cost–effectiveness analysis Analytic technique: decision tree model Perspective: societal Time horizon: lifetime Discount rate: 3%	Pregnant people and their partners	Intervention: universal prenatal genetic (DNA) carrier testing for a pathogenic variant for SMA of pregnant people and their partners (in case of a positive result) Comparator: no genetic testing	Affected children with SMA detected and QALYs Number of affected children and QALYs (mean per 100,000 women), prenatal testing vs. no testing: 2 vs. 10 affected, 2,575,954 vs. 2,572,946 Mean difference in affected cases and QALYs, prenatal testing vs. no testing: 8 affected cases and 8 QALYs	Currency: USD, 2009 Total costs (mean per 100,000 women), prenatal testing vs. no testing: $44,295,289 vs. $4,714,165 Mean cost difference, prenatal testing and no testing: $39,581,124 Test cost per person: $425	Base-case analysis: compared with no testing, prenatal carrier testing is associated with ICER of $4,985,028 per case averted and ICER of $4,889,685 per QALY PA: prenatal testing not cost-effective 99.7% of the time at WTP of $100,000 per QALY One-way sensitivity analysis identified 2 major parameters: 1) prevalence of SMA needed to be increased from 1 in 10,000 (base case) to 1 in 900 for ICER to be < $50,000 per QALY. Screening is dominant if disease prevalence is > 1 in 800; 2) test cost of $44 per test for ICER to be < $100,000 per QALY

Abbreviations: ICER, incremental cost-effectiveness ratio; PA, probabilistic analysis; SMA, spinal muscular atrophy; QALY, quality-adjusted life-year; WTP, willingness-to-pay.

Appendix 7: Results of Applicability and Limitation Checklists for Studies Included in the Economic Literature Review

Table A12: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Reproductive Genetic Carrier Screening for Multiple Diseases

Author, year, country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall Judgment[a]
Wang et al, 2021,[154] Australia	Partially, SR	Partially	NA	Yes, majority of studies	Unclear	Yes, majority of the studies	Yes, few studies	Unclear	Not applicable, SR - does not include all EE studies
MSAC, 2020,[158] Australia	Partially	Partially	No	Unclear, summary published	Unclear	Yes, 5%	Yes	Unclear	Not applicable
Beauchamp et al, 2019,[157] United States	Partially	Partially	No	Yes, private sector	Yes	Yes, 3%	No	No	Not applicable
Zhang et al, 2019,[159] Australia	Partially	Partially	No	Yes, health care sector	Yes	Yes	Yes	Unclear	Partially applicable
Azimi et al, 2016,[156] United States	No	Partially	No	Yes, US health plan	Yes	Yes	No	Unclear	Not applicable

Abbreviations: EE, economic evaluation; NA, not applicable; SR, systematic review.

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA.".

[a]Overall judgment may be "directly applicable," "partially applicable," or "not applicable."

Table A13: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Reproductive Genetic Carrier Screening for CF

Author, year, country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall Judgment[a]
Avram et al, 2021,[160] United States	Partially	Partially	No	Yes, societal	Yes	Yes	Yes	Unclear	Not applicable
MSAC, 2016,[161] Australia	Partially, only CF and prenatal	Partially	No	Yes, health care sector	Yes	NA	No	No	Not applicable
Hill et al, 2015,[162] United Kingdom	No	No	No	Unclear	No	NA	No	No	Not applicable
Norman et al, 2012,[163] Australia	Partially	Partially	No	Yes, health care sector	Yes	Yes, 5%	No	No	Not applicable
Maxwell et al, 2010,[164] Australia	Partially	Partially	No	Yes, health care sector	Yes	Yes, 3.5%	No	No	Not applicable
Radhakrishnan et al, 2008,[155] Australia	Partially, CF and SR	Partially	No	Yes	Unclear	NA	NA	NA	Not applicable
Konialis et al, 2007,[72] Greece	Partially	No	No	No	No	No	No	No	Not applicable
Wei et al, 2007,[76] United States	Partially	No	No	No	Partially	No	No	No	Not applicable

Weijers-Poppelaars et al, 2005,[165] Netherlands	Partially	Partially	No	Unclear	Unclear	Partially, 4%	No	Unclear	Not applicable

Abbreviations: CF, cystic fibrosis; MSAC, Medical Advisory Service Committee; NA, not applicable; SR, systematic review.
Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA."
[a]Overall judgment may be "directly applicable," "partially applicable," or "not applicable."

Table A14: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Reproductive Genetic Carrier Screening for FXS

Author, year, country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall Judgment[a]
Guo et al, 2021,[166] China	Unclear	Unclear	No	Unclear	Unclear	No	No	No	Not applicable
Hollingsworth, 2005,[167] Australia	Partially, only FXS	No	No	No	No	Yes, 5%	No	Unclear	Not applicable
Musci et al, 2005,[173] United States	Partially, only FXS	No	No	Yes, societal	Yes	Yes, 3%	Yes	Unclear	Not applicable

Abbreviations FXS, fragile X syndrome.
Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).
[a]Overall judgment may be "directly applicable," "partially applicable," or "not applicable."

Table A15: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Reproductive Genetic Carrier Screening for Hemoglobinopathies and Thalassemia

Author, year, country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall Judgment[a]
MSAC, 2019,[169] Australia	Partially, only alpha-thalassemia	Partially	No	Unclear	Unclear	NA	No	Unclear	Not applicable
Bryan et al, 2011,[152,153] United Kingdom	Partially, only SCD	No	No	Yes, health care sector	Yes	NA	No	Yes	Not applicable
Ratanasiri et al, 2006,[98] Thailand	Partially, only thalassemia	No	No	No	No	No	No	No	Not applicable

Abbreviations: NA, not applicable; MSAC, Medical Advisory Service Committee; SCD, sickle-cell disease.

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA."

[a]Overall judgment may be "directly applicable," "partially applicable," or "not applicable."

Table A16: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of Reproductive Genetic Carrier Screening for SMA

Author, year, country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall Judgment[a]
Little et al, 2010,[170] United States	Partially, only SMA	No	No	Yes	Partially	Yes, 3%	Yes	Unclear	Not applicable

Abbreviation: SMA, spinal muscular atrophy.

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

[a]Overall judgment may be "directly applicable," "partially applicable," or "not applicable."

Table A17: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of Reproductive Genetic Carrier Screening for Multiple Diseases

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs[a] obtained from the best available sources?	Do the clinical inputs[a] match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall Judgment[b]
Wang et al, 2021,[154] Australia	Partially, SR	Yes	Partially, summarized	Yes, summarized	Unclear	Unclear, summarized	Unclear	Unclear	Partially	Unclear	Unclear	NA, SR
MSAC, 2020,[158] Australia	Partially	Yes	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	No	Unclear	Potentially or very serious limitations due to partial reporting of study methods
Beauchamp et al, 2019,[157] United States	Yes	Partially	Partially	Unclear	Unclear	Yes	Unclear	Unclear	Partially	Partially	Yes	Potentially serious limitations
Zhang et al, 2019,[159] Australia	Yes	Yes	Partially	Unclear	Unclear	Partially	Yes	Yes	Yes	Yes	Unclear	Potentially serious limitations
Azimi et al, 2016,[156] United States	Partially	Yes	Partially	Unclear	Unclear	Yes	Unclear	Unclear	Partially	Partially	Yes	Potentially serious limitations

Abbreviations: NA, not applicable; SR, systematic review.

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA."

[a]Clinical inputs include relative treatment effects, natural history, and utilities.

[b]Overall judgment may be "minor limitations," "potentially serious limitations," or "very serious limitations."

Table A18: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of Reproductive Genetic Carrier Screening for CF

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs[a] obtained from the best available sources?	Do the clinical inputs[a] match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall Judgment[b]
Avram et al, 2021,[160] United States	Partially	Yes	Yes	Yes	Unclear	Yes	Unclear	Unclear	Yes	Partially	No	Potentially serious limitations
MSAC, 2016,[161] Australia	Partially	No	Partially	Yes	Yes	Partially	Yes	Yes	Partially	Partially	Unclear	Potentially serious limitations
Hill et al, 2015,[162] United Kingdom	No	No	No	No	No	Partially	Unclear	Unclear	Partially	No	Unclear	Very serious limitations
Norman et al, 2012,[163] Australia	Partially	Yes	No	No	Unclear	Yes	Unclear	Unclear	Partially	No	Unclear	Potentially serious limitations
Maxwell et al, 2010,[164] Australia	Partially	Yes	No	Unclear	Unclear	Yes	Yes	Yes	Yes	Partially	No	Potentially serious limitations
Radhakrishnan et al, 2008,[155] Australia	Partially	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	NR	NR	Unclear	NA, SR
Konialis et al, 2007,[72] Greece	No	No	No	No	No	Partially	Partially	No	No	No	Unclear	Very serious limitations
Wei et al, 2007,[76] United States	No	No	No	No	No	Partially	Partially	Unclear	No	No	Unclear	Very serious limitations

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs[a] obtained from the best available sources?	Do the clinical inputs[a] match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall Judgment[b]
Weijers-Poppelaars et al, 2005,[165] Netherlands	No	Partially	No	Unclear	Unclear	Yes	Yes	Unclear	No	No	Unclear	Potentially serious limitations

Abbreviations: CF, cystic fibrosis; NA, not applicable; NR, not reported; SR, systematic review.

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA."

[a]Clinical inputs include relative treatment effects, natural history, and utilities.

[b]Overall judgment may be "minor limitations," "potentially serious limitations," or "very serious limitations."

Table A19: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of Reproductive Genetic Carrier Screening for FXS

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs[a] obtained from the best available sources?	Do the clinical inputs[a] match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall Judgment[b]
Guo et al, 2021,[166] China	No	Unclear	Unclear	Partially	Unclear	No	Unclear	Unclear	No	No	Unclear	Very serious limitations
Hollingsworth, 2005,[167] Australia	No	Yes	No	No	Unclear	Unclear	Unclear	Unclear	No	No	Unclear	Very serious limitations
Musci et al, 2005,[173] United States	Partially	Yes	Unclear	Yes	Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear	Very serious limitations

Abbreviation: FXS, fragile X syndrome.

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

[a]Clinical inputs include relative treatment effects, natural history, and utilities.

[b]Overall judgment may be "minor limitations," "potentially serious limitations," or "very serious limitations."

Table A20: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of Reproductive Genetic Carrier Screening for Hemoglobinopathies and Thalassemia

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs[a] obtained from the best available sources?	Do the clinical inputs[a] match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall Judgment[b]
MSAC, 2019,[169] Australia	Partially	No	Partially	Unclear	Unclear	Unclear	Unclear	Unclear	Partially	Unclear	Unclear	Very serious limitations, due to limited published information
Bryan et al, 2011,[152,153] United Kingdom	Partially	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Potentially serious limitations
Ratanasiri et al, 2006,[98] Thailand	Partially	No	No	No	No	No	No	No	No	No	Unclear	Very serious limitations

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

[a]Clinical inputs include relative treatment effects, natural history, and utilities.

[b]Overall judgment may be "minor limitations," "potentially serious limitations," or "very serious limitations."

Table A21: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of Reproductive Genetic Carrier Screening for SMA

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs[a] obtained from the best available sources?	Do the clinical inputs[a] match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall Judgment[b]
Little et al, 2010,[170] United States	Partially	Yes	Partially	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Partially	Unclear	Potentially very serious limitations

Abbreviation: SMA, spinal muscular atrophy.

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

[a]Clinical inputs include relative treatment effects, natural history, and utilities.

[b]Overall judgment may be "minor limitations," "potentially serious limitations," or "very serious limitations."

Appendix 8: Primary Economic Evaluation Methods: Costing Screening Care Pathways

Table A22: Costing Screening Care Pathways: Variations in Medical Visits

	Pre-test visit	Pre-test screening visit		Post-test visit screen positive			Post-test visit screen negative	
Analyses	**GP**	**MG**	**GC**	**MG**	**GC**	**GP**	**GP**	**GC**
Reference case (the most conservative option)	1[a]	1[b]	1 hour	1[c]	1 hour	1[d]	None	1 hour
Scenario 1: Fewer visits with GP	None	1[b]	1 hour	2[e]	None	1[a]	None	1 hour
Scenario 2: Fewer visits with GC	1[a]	None	None	1[c]	1 hour	1[a]	1[a]	None
Scenario 3: High hourly rate for GC[f]	1[a]	1[b]	1 hour	1[c]	1 hour	1[d]	None	1 hour

Abbreviations: GC, genetic counsellor; GP, general practitioner; ICER, incremental cost-effectives ratio; MG, medical geneticist; OHIP, Ontario Health Insurance Plan.

Notes: OHIP codes and fees are explained in Table 6 for cost parameters. This presents several scenarios only as examples of the influence of the cost of screening pathway on the ICER. Investigation of the most efficient and sustainable screening care pathway was out of scope for this assessment.

[a]One additional visit; for reference case, we simplified and assumed that the OHIP code P004 was billed in both preconception and prenatal carrier screening. In a scenario analysis (data not shown), we distinguished OHIP code A007 (preconception carrier screening) from P004 (prenatal carrier screening). Also, for preconception screening, the code K013 could be used instead of A007. The model of care for carrier screening with GP (with respect to additional number of visits and associated billing codes) is uncertain.

[b]One visit with a medical geneticist, assumed to be billed under OHIP code K223.

[c]One visit with medical geneticist, assumed to be billed under OHIP code K222.

[d]One visit with a GP, assumed to be billed under either OHIP code K013 or code K005, depending on the time of screening (associated with the same cost).

[e]Two visits with a medical geneticist, assumed to be billed under OHIP code K222.

[f]One hour with a genetic counsellor assumed to be $50.26, compared with the reference case of about $41.20.

Appendix 9: Primary Economic Evaluation Methods: Costing of Hypothetical Universal and Risk-Based Carrier Screening Programs in Ontario

Table A23: Costing of Hypothetical Universal and Risk-Based Carrier Screening Programs in Ontario

Strategies	Total implementation program cost[a]	Total on-going program cost[b]	Total communication cost[c]	No. eligible participants[d]	Program cost, $ per person[e]		
					One-time (implementation)	On-going	Communication
Preconception: universal	$1,200,000	$745,000	$175,000	199,625	6.01	3.73	0.88
Prenatal: universal	$1,200,000	$745,000	$175,000	133,083	9.02	5.60	1.31
Preconception: risk-based	$1,200,000	$745,000	$175,000	9,981[e]	120.23	74.64	17.53
Prenatal: risk-based	$1,200,000	$745,000	$175,000	6,654[e]	180.34	111.96	26.30

[a]Implementation: one-time program costs were calculated based on expert consultation (S. Dougan and J. Milburn, email communications, March 2022). The cost components included in this calculation were: a) cost of human resources, and b) cost of data collection and information management.
[b]On-going program costs were also based on expert consultation (email communication, S. Dougan and J. Milburn, March 2022). The cost components included in this calculation are: a) cost of human resources: b) cost of data collection and information management:
[c]Program communication costs were assumed to include the following cost components: a) cost of human resources: 1) communication/marketing; 2) website development, communication planning.
[d]Target population estimated for universal programs correspond to the number of people in our Budget Impact Assessment. Five percent of people were assumed to participate in risk-based programs, based on our CEA models and literature.
[e]We estimated per-person program cost by dividing total costs by the number of eligible people for each strategy

Appendix 10: Reference Case Results, Cost-Effectiveness of Preconception Screening Programs, by Condition

Table A24: Reference Case Results, Preconception Screening, Cystic Fibrosis—Effectiveness Outcomes

Strategy	Probability of affected birth	Probability: test positive[a]	Probability: test true positive	Probability: test false positive	Probability: test false negative	Probability		
						PND	TOP	IVF/PGT-M
No screening	0.000405477	NA	NA	NA	NA	NA	NA	NA
Risk-based, standard panels	0.000395974	0.000077	0.000047	0.000030	0.000208	0.000073	0.000009	0.000003
Risk-based, expanded panel	0.00039493	0.000066	0.000052	0.000013	0.000008	0.000062	0.000010	0.000003
Universal, standard panels	0.00027189	0.001088	0.000661	0.000427	0.002917	0.001033	0.000125	0.000044
Universal, expanded panel	0.000257224	0.000923	0.000734	0.000189	0.000112	0.000876	0.000139	0.000037

Abbreviations: IVF/PGT-M, in-vitro fertilization with preimplantation genetic testing; NA, not applicable; PND, prenatal diagnostic testing; TOP, voluntary termination of pregnancy.

[a]At-risk pregnancy as detected via screening (i.e., the couple tests positive).

Table A25: Reference Case Results: Cost-Effectiveness of Preconception Screening Programs for Cystic Fibrosis

Strategy[a]	Average total costs[a] $	Average total effects, affected birth	ICER, $/affected birth avoided	
			Versus no screening	Sequential ICER (excluding dominated)
No screening	0	0.000405477	—	—
Risk-based, standard panels	17.49	0.000395974	1,840,832.94	Dominated[b]
Risk-based, expanded panel	42.98	0.00039493	4,074,889.48	Dominated[b]
Universal, standard panels	245.82	0.00027189	1,840,105.25	1,840,105.25
Universal, expanded panel	604.06	0.000257224	4,074,509.86	24,426,728.76

Abbreviation: ICER, incremental cost-effectiveness ratio.

[a]Treatment strategies are ordered by average total costs, from lowest to highest.

[b]Extended dominance.

Table A26: Reference Case Results, Preconception Screening, Fragile X Syndrome—Effectiveness Outcomes

	Probability							
Strategy	Affected birth	Test Positive[a]	Test true positive	Test false positive	Test false negative	PND	TOP	IVF/PGT-M
No screening	0.000774686	NA	NA	NA	NA	NA	NA	NA
Risk-based, standard panels	0.000762675	0.000411	0.000059	0.000353	0.000003	0.000391	0.000010	0.000016
Risk-based, expanded panel	0.00076215	0.000061	0.000061	0.000000	0.000000	0.000058	0.000011	0.000002
Universal, standard panels	0.000605923	0.005781	0.000823	0.004958	0.000037	0.005493	0.000142	0.000228
Universal, expanded panel	0.000598536	0.000860	0.000860	0.000000	0.000001	0.000816	0.000149	0.000035

Abbreviations: IVF/PGT-M, in-vitro fertilization with preimplantation genetic testing; NA, not applicable; PND, prenatal diagnostic testing; TOP, voluntary termination of pregnancy.

[a]At-risk pregnancy as detected via screening (i.e., couple tests positive).

Table A27: Reference Case Results: Cost-Effectiveness of Preconception Screening Programs for Fragile X Syndrome

			ICER, $/affected birth avoided	
Strategy[a]	Average total costs,[a] $	Average total effects, affected birth	Versus no screening	Sequential ICER (excluding dominated)
No screening	0	0.000774686	—	—
Risk-based, standard panels	19.62	0.000762675	1,633,510.53	1,633,510.53
Risk-based, expanded panel	41.99	0.00076215	3,349,482.87	Dominated[b]
Universal, standard panels	275.69	0.000605923	1,633,622.26	1,633,630.82
Universal, expanded panel	590.20	0.000598536	3,350,548.60	42,574,623.55

Abbreviation: ICER, incremental cost-effectiveness ratio.

[a]Treatment strategies are ordered by average total costs, from lowest to highest.

[b]Extended dominance

Table A28: Reference Case Results, Preconception Screening, Hemoglobinopathies and Thalassemia—Effectiveness Outcomes

Strategy	Probability							
	Affected birth	Test positive[a]	Test true positive	Test false positive	Test false negative	PND	TOP	IVF/PGT-M
No screening	0.002821532	NA	NA	NA	NA	NA	NA	NA
Risk-based, standard panels	0.002819587	0.000048	0.000024	0.000024	0.000534	0.000046	0.000004	0.000002
Risk-based, expanded panel	0.002819395	0.000029	0.000027	0.000002	0.000009	0.000028	0.000005	0.000001
Universal, standard panels	0.002445258	0.009379	0.004696	0.004683	0.007938	0.008893	0.000835	0.000293
Universal, expanded panel	0.002408139	0.005615	0.005159	0.000456	0.000651	0.005327	0.000918	0.000173

Abbreviations: IVF/PGT-M, in-vitro fertilization with preimplantation genetic testing; NA, not applicable; PND, prenatal diagnostic testing; TOP, voluntary termination of pregnancy.

[a]At-risk pregnancy as detected via screening (i.e., couple tests positive).

Table A29: Reference Case Results, Cost-Effectiveness of Preconception Screening Programs for Hemoglobinopathies and Thalassemia

Strategy[a]	Average total costs,[a] $	Average total effects, affected birth	ICER, $/affected birth avoided	
			Versus no screening	Sequential ICER (excluding dominated)
No screening	0	0.002821532		
Risk-based, standard panels	15.87	0.002819587	8,160,272.99	Dominated[b]
Risk-based, expanded panel	42.29	0.002819395	19,796,671.95	Dominated[b]
Universal, standard panels	240.87	0.002445258	640,135.72	640,135.72
Universal, expanded panel	633.71	0.002408139	1,532,951.92	10,583,253.73

Abbreviation: ICER, incremental cost-effectiveness ratio.

[a]Treatment strategies are ordered by average total costs, from lowest to highest.

[b]Extended dominance.

Table A30: Reference Case Results, Preconception Screening, Spinal Muscular Atrophy—Effectiveness Outcomes

Strategy	Probability							
	Affected birth	Test positive[a]	Test true positive	Test false positive	Test false negative	PND	TOP	IVF/PGT-M
No screening	0.000157643	NA	NA	NA	NA	NA	NA	NA
Risk-based, standard panels	0.000157388	0.00000316	0.00000149	0.00000167	0.00006309	0.00000300	0.00000024	0.00000013
Risk-based, expanded panel	0.000157375	0.00000220	0.00000157	0.00000063	0.00000147	0.00000209	0.00000025	0.00000009
Universal, standard panels	0.000108357	0.00061275	0.00028918	0.00032357	0.00090111	0.00058176	0.00004569	0.00002447
Universal, expanded panel	0.000105825	0.00042553	0.00030403	0.00012150	0.00003535	0.00040401	0.00004803	0.00001699

Abbreviations: IVF/PGT, in-vitro fertilization with preimplantation genetic testing-M; NA, not applicable; PND, prenatal diagnostic testing; TOP, voluntary termination of pregnancy.

[a]At-risk pregnancy as detected via screening (i.e., couple tests positive).

Table A31: Reference Case Results: Cost-Effectiveness of Preconception Screening Programs for Spinal Muscular Atrophy

Strategy[a]	Average total costs,[a] $	Average total effects, affected birth	ICER, $/affected birth avoided	
			Versus no screening	Sequential ICER (excluding dominated)
No screening	0	0.000157643	—	—
Risk-based, standard panels	16.67	0.000157388	65,449,243.73	Dominated[b]
Risk-based, expanded panel	41.98	0.000157375	1,935,169,163.53	Dominated[b]
Universal, standard panels	237.27	0.000108357	4,814,133.27	4,814,133.27
Universal, expanded panel	598.09	0.000105825	142,519,641.41	142,519,641.41

Abbreviation: ICER, incremental cost-effectiveness ratio.

[a]Treatment strategies are ordered by average total costs, from lowest to highest.

[b]Extended dominance.

Appendix 11: Reference Case Results, Cost-Effectiveness of Prenatal Screening Programs, By Condition

Table A32: Reference Case Results, Prenatal Screening, Cystic Fibrosis—Effectiveness Outcomes

	Probability						
Strategy	Affected birth	Test positive[a]	Test true positive	Test false positive	Test false negative	PND	TOP
No screening	0.000405477	NA	NA	NA	NA	NA	NA
Risk-based, standard panels	0.00039724	0.000071	0.000043	0.000028	0.000199	0.000068	0.000008
Risk-based, expanded panel	0.000396335	0.000061	0.000048	0.000012	0.000008	0.000057	0.000009
Universal, standard panels	0.000289689	0.001004	0.000610	0.000395	0.002798	0.000952	0.000116
Universal, expanded panel	0.000276978	0.000851	0.000676	0.000174	0.000105	0.000807	0.000128

Abbreviations: NA, not applicable; PND, prenatal diagnostic testing; TOP, voluntary termination of pregnancy.

[a]At-risk pregnancy as detected via screening (i.e., couple tests positive).

Table A33: Reference Case Results: Cost-Effectiveness of Prenatal Screening Programs for Cystic Fibrosis

			ICER, $/affected birth avoided	
Strategy[a]	Average total costs,[a] $	Average total effects, affected birth	Versus no screening	Sequential ICER (excluding dominated)
No screening	0	0.000405477	—	—
Risk-based, standard panels	16.78	0.00039724	2,037,213.97	Dominated[b]
Risk-based, expanded panel	41.24	0.000396335	4,510,974.28	Dominated[b]
Universal, standard panels	235.85	0.000289689	2,036,910.60	2,036,910.60
Universal, expanded panel	579.74	0.000276978	4,511,595.75	27,052,894.84

Abbreviation: ICER, incremental cost-effectiveness ratio.

[a]Treatment strategies are ordered by average total costs, from lowest to highest.

[b]Extended dominance.

Table A34: Reference Case Results, Prenatal Screening, Fragile X Syndrome—Effectiveness Outcomes

Strategy	Probability						
	Affected birth	Test positive[a]	Test true positive	Test false positive	Test false negative	PND	TOP
No screening	0.000774686	NA	NA	NA	NA	NA	NA
Risk-based, standard panels	0.000764888	0.000395	0.000056	0.000339	0.000003	0.000375	0.000010
Risk-based, expanded panel	0.000764458	0.000059	0.000059	0.000000	0.000000	0.000056	0.000010
Universal, standard panels	0.000637027	0.005553	0.000791	0.004762	0.000036	0.005275	0.000137
Universal, expanded panel	0.000630982	0.000826	0.000826	0.000000	0.000001	0.000783	0.000143

Abbreviations:; NA, not applicable; PND, prenatal diagnostic testing; TOP, voluntary termination of pregnancy.
[a]At-risk pregnancy as detected via screening (i.e., couple tests positive).

Table A35: Reference Case Results: Cost-Effectiveness of Prenatal Screening Programs for Fragile X Syndrome

Strategy[a]	Average total costs,[a] $	Average total effects, affected birth	ICER, $/affected birth avoided	
			Versus no screening	Sequential ICER (excluding dominated)
No screening	0	0.000774686	—	—
Risk-based, standard panels	18.77	0.000764888	1,915,395.11	1,915,395.11
Risk-based, expanded panel	40.33	0.000764458	3,943,220.93	Dominated[b]
Universal, standard panels	263.76	0.000637027	1,916,010.03	1,916,057.15
Universal, expanded panel	566.98	0.000630982	3,945,442.80	50,164,204.08

Abbreviation: ICER, incremental cost-effectiveness ratio.
[a]Treatment strategies are ordered by average total costs, from lowest to highest.
[b]Extended dominance.

Table A36: Reference Case Results, Prenatal Screening, Hemoglobinopathies and Thalassemia — Effectiveness Outcomes

	Probability						
Strategy	Affected birth	Test positive[a]	Test true positive	Test false positive	Test false negative	PND	TOP
No screening	0.002821531	NA	NA	NA	NA	NA	NA
Risk-based, standard panels	0.002820013	0.000000	0.000000	0.000000	0.000000	0.000000	0.000000
Risk-based, expanded panel	0.002819863	0.000045	0.000022	0.000022	0.000512	0.000042	0.000002
Universal, standard panels	0.002527556	0.000027	0.000025	0.000002	0.000008	0.000025	0.000002
Universal, expanded panel	0.002498547	0.008632	0.004331	0.004301	0.007601	0.008175	0.000292

Abbreviations: NA, not applicable; PND, prenatal diagnostic testing; TOP, voluntary termination of pregnancy.

[a]At-risk pregnancy as detected via screening (i.e., couple tests positive).

Table A37: Reference Case Results: Cost-Effectiveness of Prenatal Screening Programs for Hemoglobinopathies and Thalassemia

			ICER, $/affected birth avoided	
Strategy[a]	Average total costs,[a] $	Average total effects, affected birth	Versus no screening	Sequential ICER (excluding dominated)
No screening	0	0.002821531	—	—
Risk-based, standard panels	15.23	0.002820013	10,030,332.58	Dominated[b]
Risk-based, expanded panel	40.61	0.002819863	24,344,277.57	Dominated[b]
Universal, standard panels	228.83	0.002527556	778,386.80	778,386.80
Universal, expanded panel	606.24	0.002498547	1,877,000.86	13,010,076.60

Abbreviation: ICER, incremental cost-effectiveness ratio.

[a]Treatment strategies are ordered by average total costs, from lowest to highest.

[b]Extended dominance.

Table A38: Reference Case Results, Prenatal Screening, Spinal Muscular Atrophy—Effectiveness Outcomes

	Probability						
Strategy	Affected birth	Test positive[a]	Test true positive	Test false positive	Test false negative	PND	TOP
No screening	0.000157643	NA	NA	NA	NA	NA	NA
Risk-based, standard panels	0.000157425	0.0000029	0.0000014	0.0000015	0.0000606	0.0000028	0.0000002
Risk-based, expanded panel	0.000157413	0.0000020	0.0000014	0.0000006	0.0000014	0.0000019	0.0000002
Universal, standard panels	0.000115415	0.0005645	0.0002669	0.0002976	0.0008647	0.0005358	0.0000421
Universal, expanded panel	0.000113252	0.0003923	0.0002805	0.0001117	0.0000337	0.0003724	0.0000443

Abbreviations: NA, not applicable; PND, prenatal diagnostic testing; TOP, voluntary termination of pregnancy.
[a]At-risk pregnancy as detected via screening (i.e., couple tests positive).

Table A39: Reference Case Results: Cost-Effectiveness of Prenatal Screening Programs for Spinal Muscular Atrophy

			ICER, $/affected birth avoided	
Strategy[a]	Average total costs,[a] $	Average total effects, affected birth	Versus no screening	Sequential ICER (excluding dominated)
No screening	0	0.000157643	—	—
Risk-based, standard panels	16.02	0.000157425	73,403,572.44	Dominated[b]
Risk-based, expanded panel	40.33	0.000157413	175,808,122.43	Dominated[b]
Universal, standard panels	227.74	0.000115415	5,393,190.74	5,393,190.74
Universal, expanded panel	574.32	0.000113252	12,937,765.05	160,191,671.45

Abbreviation: ICER, incremental cost-effectiveness ratio.
[a]Treatment strategies are ordered by average total costs, from lowest to highest.
[b]Extended dominance.

Appendix 12: Results of One-Way Cost-Effectiveness Sensitivity Analyses for Clinical and Cost Parameters, Preconception Carrier Screening (All Examined Conditions), Reference Case Model

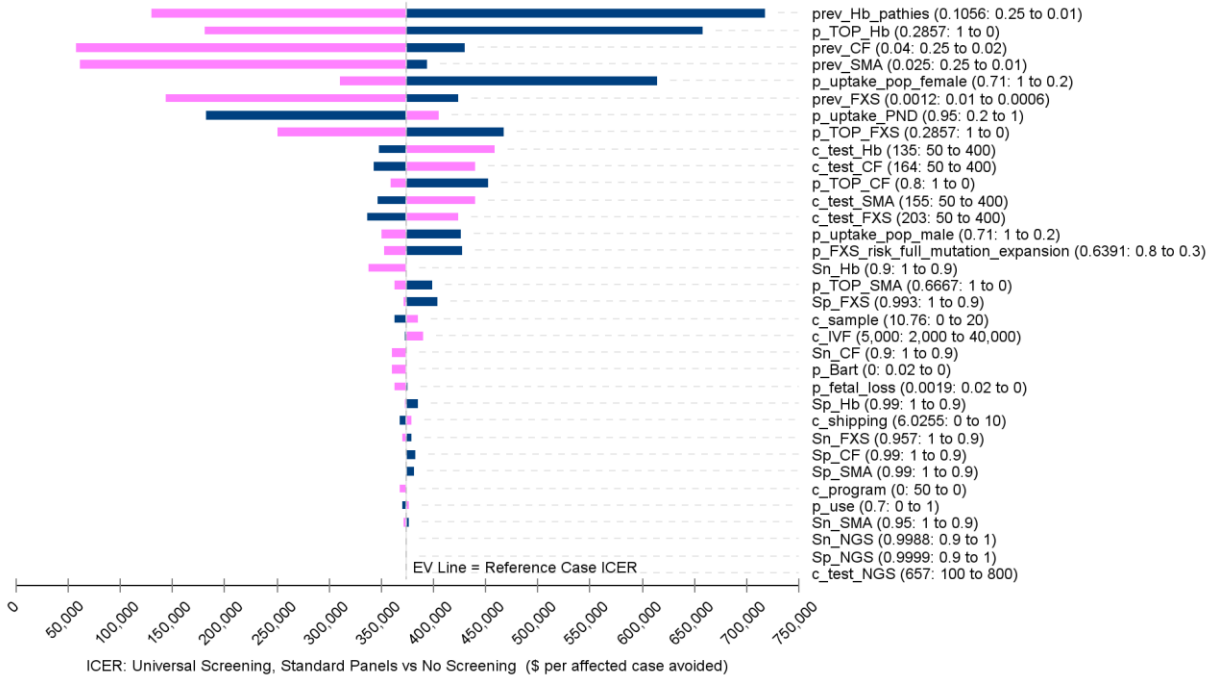

Figure A1: Tornado Diagram, Preconception Carrier Screening: Universal Screening, Standard Panels Versus No Screening

Abbreviations: c_, cost of; c_IVF, cost of IVF with PGT-M; c_program, cost of screening program; c_sample, cost of blood sampling; c_shipping, cost of blood sample shipping; c_test_CF, cost of genetic testing for CF; c_test_FXS, cost of genetic testing for FXS; c_test_Hb, cost of genetic testing for hemoglobinopathies and thalassemia; c_test_NGS, cost of NGS panel; c_test_SMA, cost of genetic testing for SMA; CF, cystic fibrosis; FXS, fragile X syndrome; Hb, hemoglobinopathies and thalassemia; ICER, incremental cost-effectiveness ratio; IVF, in vitro fertilization; NGS, next-generation sequencing; p_, probability of; p_Bart, probability of the Bart syndrome; p_fetal_loss; probability of fetal loss with PND procedures; p_FXS_risk_full_mutation_expansion, probability of premutaion expansion to full mutation for FXS; p_TOP_CF, probability of voluntary TOP for CF; p_TOP_FXS, probability of voluntary TOP for FXS; p_TOP_Hb, probability of voluntary TOP for hemoglobinopathies and thalassemia; p_uptake_PND, uptake of PND; p_uptake_pop_female, screening uptake by a female partner; p_uptake_pop_male, screening uptake by a male partner; p_use, probability of use of PND procedure (CVS vs, amniocentesis); PND, prenatal diagnostic testing; pop, population; prev_, prevalence (carrier frequency) of; prev_CF, prevalence (carrier frequency) for CF; prev_FXS, prevalence (carrier frequency) for FXS; prev_Hb_pathies, prevalence (carrier frequency) for hemoglobinopathies and thalassemia; prev_SMA, prevalence (carrier frequency) for SMA; SMA, spinal muscular atrophy; Sn, sensitivity; Sn_CF, test sensitivity for CF panel; Sn_FXS, test sensitivity for FXS panel; Sn_Hb, test sensitivity for hemoglobinopathies and thalassemia panel; Sn_NGS, test sensitivity for NGS panel; Sn_SMA, test sensitivity for SMA panel; Sp, specificity; Sp_CF, test specificity for CF panel; Sp_FXS, test specificity for FXS panel; Sp_Hb, test specificity for hemoglobinopathies and thalassemia panel; Sp_NGS, test specificity for NGS panel; Sp_SMA, test specificity for SMA panel; TOP, voluntary termination of pregnancy.

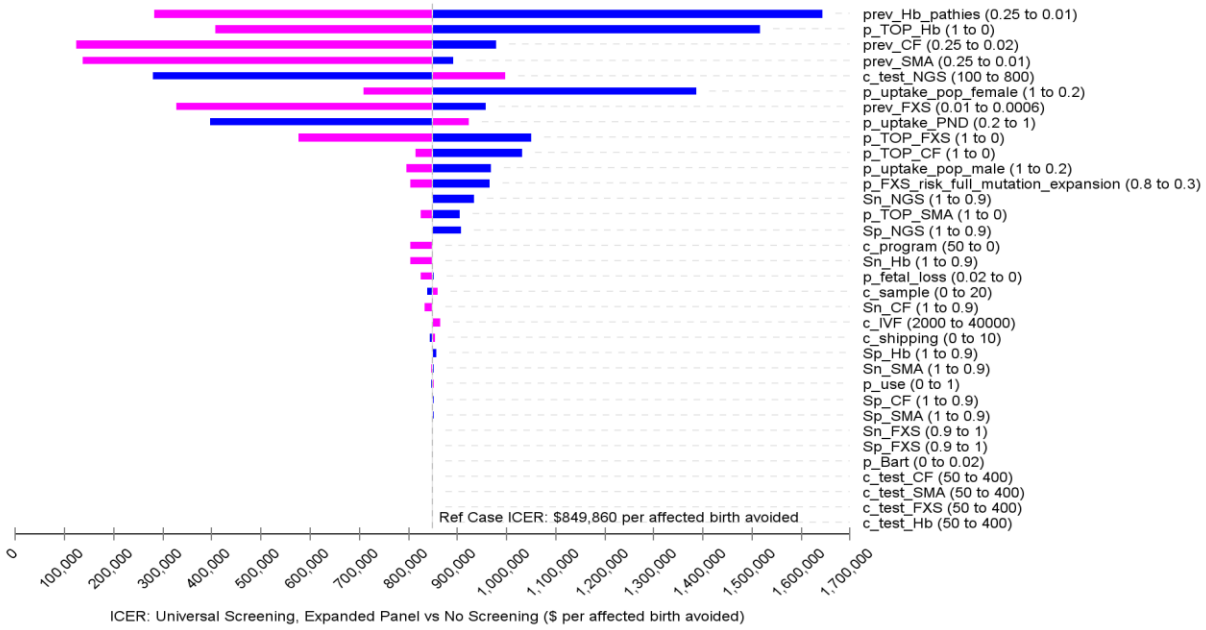

Figure A2: Tornado Diagram, Preconception Carrier Screening: Universal Screening, Expanded Panel Versus No Screening

Abbreviations: c_, cost of; c_IVF, cost of IVF with PGT-M; c_program, cost of screening program; c_sample, cost of blood sampling; c_shipping, cost of blood sample shipping; c_test_CF, cost of genetic testing for CF; c_test_FXS, cost of genetic testing for FXS; c_test_Hb, cost of genetic testing for hemoglobinopathies and thalassemia; c_test_NGS, cost of NGS panel; c_test_SMA, cost of genetic testing for SMA; CF, cystic fibrosis; FXS, fragile X syndrome; Hb, hemoglobinopathies and thalassemia; ICER, incremental cost-effectiveness ratio; IVF, in vitro fertilization; NGS, next-generation sequencing; p_, probability of; p_Bart, probability of the Bart syndrome; p_fetal_loss; probability of fetal loss with PND procedures; p_FXS_risk_full_mutation_expansion, probability of premutaion expansion to full mutation for FXS; p_TOP_CF, probability of voluntary TOP for CF; p_TOP_FXS, probability of voluntary TOP for FXS; p_TOP_Hb, probability of voluntary TOP for hemoglobinopathies and thalassemia; p_uptake_PND, uptake of PND; p_uptake_pop_female, screening uptake by a female partner; p_uptake_pop_male, screening uptake by a male partner; p_use, probability of use of PND procedure (CVS vs, amniocentesis); PND, prenatal diagnostic testing; pop, population; prev_, prevalence (carrier frequency) of; prev_CF, prevalence (carrier frequency) for CF; prev_FXS, prevalence (carrier frequency) for FXS; prev_Hb_pathies, prevalence (carrier frequency) for hemoglobinopathies and thalassemia; prev_SMA, prevalence (carrier frequency) for SMA; SMA, spinal muscular atrophy; Sn, sensitivity; Sn_CF, test sensitivity for CF panel; Sn_FXS, test sensitivity for FXS panel; Sn_Hb, test sensitivity for hemoglobinopathies and thalassemia panel; Sn_NGS, test sensitivity for NGS panel; Sn_SMA, test sensitivity for SMA panel; Sp, specificity; Sp_CF, test specificity for CF panel; Sp_FXS, test specificity for FXS panel; Sp_Hb, test specificity for hemoglobinopathies and thalassemia panel; Sp_NGS, test specificity for NGS panel; Sp_SMA, test specificity for SMA panel; TOP, voluntary termination of pregnancy.

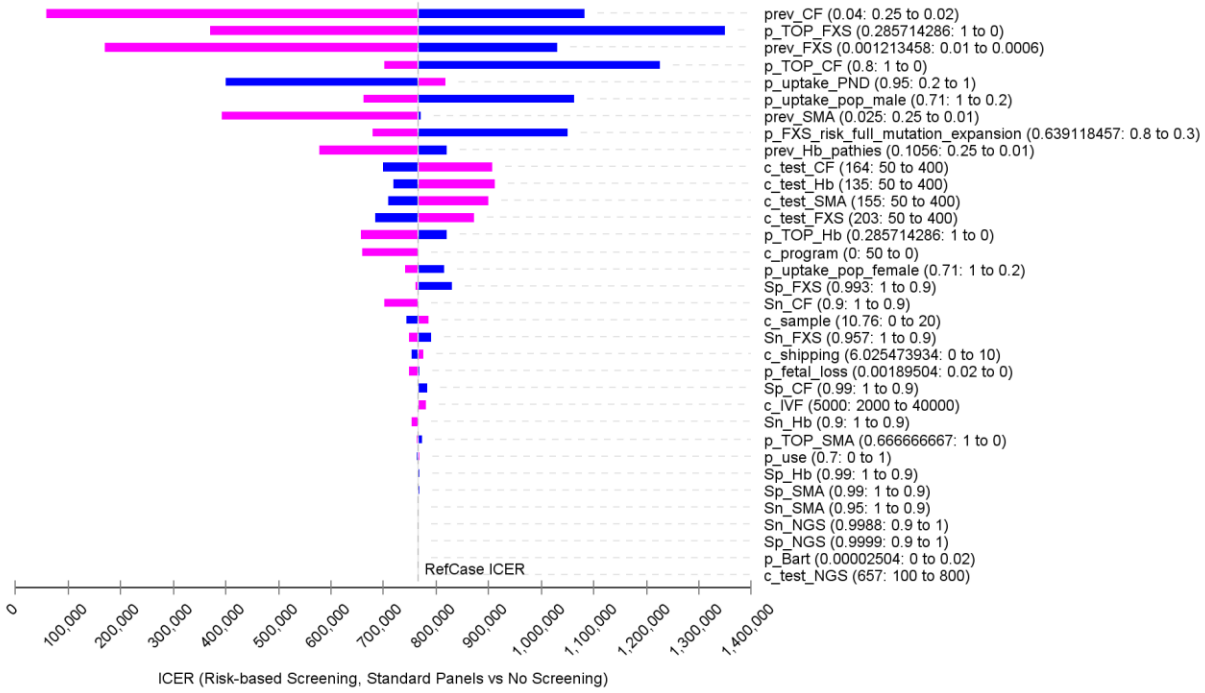

Figure A3: Tornado Diagram, Preconception Carrier Screening: Risk-Based Screening, Standard Panels Versus No Screening

Abbreviations: c_, cost of; c_IVF, cost of IVF with PGT-M; c_program, cost of screening program; c_sample, cost of blood sampling; c_shipping, cost of blood sample shipping; c_test_CF, cost of genetic testing for CF; c_test_FXS, cost of genetic testing for FXS; c_test_Hb, cost of genetic testing for hemoglobinopathies and thalassemia; c_test_NGS, cost of NGS panel; c_test_SMA, cost of genetic testing for SMA; CF, cystic fibrosis; FXS, fragile X syndrome; Hb, hemoglobinopathies and thalassemia; ICER, incremental cost-effectiveness ratio; IVF, in vitro fertilization; NGS, next-generation sequencing; p_, probability of; p_Bart, probability of the Bart syndrome; p_fetal_loss; probability of fetal loss with PND procedures; p_FXS_risk_full_mutation_expansion, probability of premutaion expansion to full mutation for FXS; p_TOP_CF, probability of voluntary TOP for CF; p_TOP_FXS, probability of voluntary TOP for FXS; p_TOP_Hb, probability of voluntary TOP for hemoglobinopathies and thalassemia; p_uptake_PND, uptake of PND; p_uptake_pop_female, screening uptake by a female partner; p_uptake_pop_male, screening uptake by a male partner; p_use, probability of use of PND procedure (CVS vs, amniocentesis); PND, prenatal diagnostic testing; pop, population; prev_, prevalence (carrier frequency) of; prev_CF, prevalence (carrier frequency) for CF; prev_FXS, prevalence (carrier frequency) for FXS; prev_Hb_pathies, prevalence (carrier frequency) for hemoglobinopathies and thalassemia; prev_SMA, prevalence (carrier frequency) for SMA; SMA, spinal muscular atrophy; Sn, sensitivity; Sn_CF, test sensitivity for CF panel; Sn_FXS, test sensitivity for FXS panel; Sn_Hb, test sensitivity for hemoglobinopathies and thalassemia panel; Sn_NGS, test sensitivity for NGS panel; Sn_SMA, test sensitivity for SMA panel; Sp, specificity; Sp_CF, test specificity for CF panel; Sp_FXS, test specificity for FXS panel; Sp_Hb, test specificity for hemoglobinopathies and thalassemia panel; Sp_NGS, test specificity for NGS panel; Sp_SMA, test specificity for SMA panel; TOP, voluntary termination of pregnancy.

Appendix 13: Results of One-Way Cost-Effectiveness Sensitivity Analyses for Clinical and Cost Parameters, Prenatal Carrier Screening (All Examined Conditions), Reference Case Model

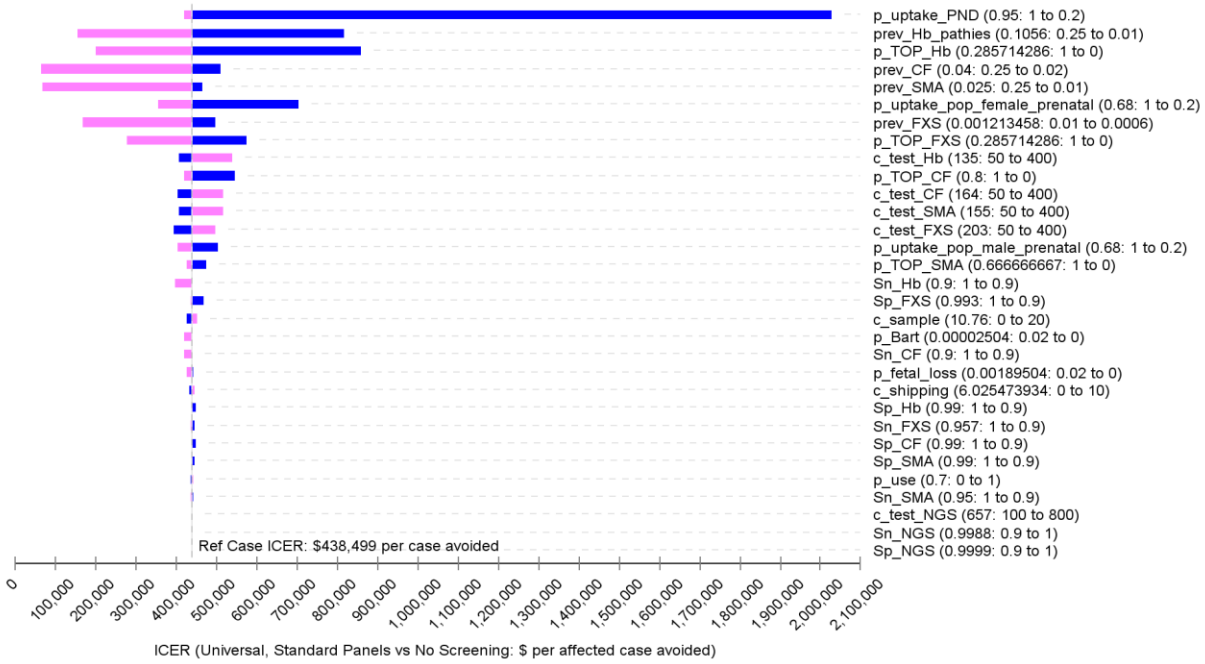

Figure A4: Tornado Diagram, Prenatal Carrier Screening: Universal Screening, Standard Panels Versus No Screening

Abbreviations: c_, cost of; c_IVF, cost of IVF with PGT-M; c_program, cost of screening program; c_sample, cost of blood sampling; c_shipping, cost of blood sample shipping; c_test_CF, cost of genetic testing for CF; c_test_FXS, cost of genetic testing for FXS; c_test_Hb, cost of genetic testing for hemoglobinopathies and thalassemia; c_test_NGS, cost of NGS panel; c_test_SMA, cost of genetic testing for SMA; CF, cystic fibrosis; FXS, fragile X syndrome; Hb, hemoglobinopathies and thalassemia; ICER, incremental cost-effectiveness ratio; IVF, in vitro fertilization; NGS, next-generation sequencing; p_, probability of; p_Bart, probability of the Bart syndrome; p_fetal_loss; probability of fetal loss with PND procedures; p_FXS_risk_full_mutation_expansion, probability of premutaion expansion to full mutation for FXS; p_TOP_CF, probability of voluntary TOP for CF; p_TOP_FXS, probability of voluntary TOP for FXS; p_TOP_Hb, probability of voluntary TOP for hemoglobinopathies and thalassemia; p_uptake_PND, uptake of PND; p_uptake_pop_female, screening uptake by a female partner; p_uptake_pop_male, screening uptake by a male partner; p_use, probability of use of PND procedure (CVS vs, amniocentesis); PND, prenatal diagnostic testing; pop, population; prev_, prevalence (carrier frequency) of; prev_CF, prevalence (carrier frequency) for CF; prev_FXS, prevalence (carrier frequency) for FXS; prev_Hb_pathies, prevalence (carrier frequency) for hemoglobinopathies and thalassemia; prev_SMA, prevalence (carrier frequency) for SMA; SMA, spinal muscular atrophy; Sn, sensitivity; Sn_CF, test sensitivity for CF panel; Sn_FXS, test sensitivity for FXS panel; Sn_Hb, test sensitivity for hemoglobinopathies and thalassemia panel; Sn_NGS, test sensitivity for NGS panel; Sn_SMA, test sensitivity for SMA panel; Sp, specificity; Sp_CF, test specificity for CF panel; Sp_FXS, test specificity for FXS panel; Sp_Hb, test specificity for hemoglobinopathies and thalassemia panel; Sp_NGS, test specificity for NGS panel; Sp_SMA, test specificity for SMA panel; TOP, voluntary termination of pregnancy.

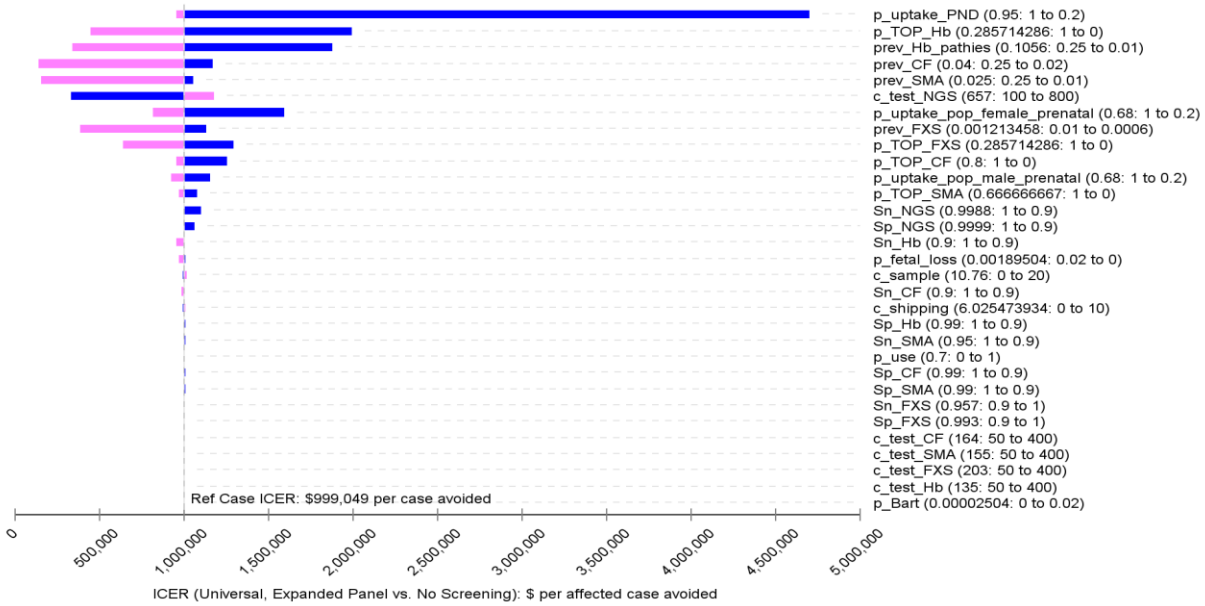

Figure A5: Tornado Diagram, Prenatal Carrier Screening: Universal Screening, Expanded Panel Versus No Screening

Abbreviations: c_, cost of; c_IVF, cost of IVF with PGT-M; c_program, cost of screening program; c_sample, cost of blood sampling; c_shipping, cost of blood sample shipping; c_test_CF, cost of genetic testing for CF; c_test_FXS, cost of genetic testing for FXS; c_test_Hb, cost of genetic testing for hemoglobinopathies and thalassemia; c_test_NGS, cost of NGS panel; c_test_SMA, cost of genetic testing for SMA; CF, cystic fibrosis; FXS, fragile X syndrome; Hb, hemoglobinopathies and thalassemia; ICER, incremental cost-effectiveness ratio; IVF, in vitro fertilization; NGS, next-generation sequencing; p_, probability of; p_Bart, probability of the Bart syndrome; p_fetal_loss; probability of fetal loss with PND procedures; p_FXS_risk_full_mutation_expansion, probability of premutaion expansion to full mutation for FXS; p_TOP_CF, probability of voluntary TOP for CF; p_TOP_FXS, probability of voluntary TOP for FXS; p_TOP_Hb, probability of voluntary TOP for hemoglobinopathies and thalassemia; p_uptake_PND, uptake of PND; p_uptake_pop_female, screening uptake by a female partner; p_uptake_pop_male, screening uptake by a male partner; p_use, probability of use of PND procedure (CVS vs, amniocentesis); PND, prenatal diagnostic testing; pop, population; prev_, prevalence (carrier frequency) of; prev_CF, prevalence (carrier frequency) for CF; prev_FXS, prevalence (carrier frequency) for FXS; prev_Hb_pathies, prevalence (carrier frequency) for hemoglobinopathies and thalassemia; prev_SMA, prevalence (carrier frequency) for SMA; SMA, spinal muscular atrophy; Sn, sensitivity; Sn_CF, test sensitivity for CF panel; Sn_FXS, test sensitivity for FXS panel; Sn_Hb, test sensitivity for hemoglobinopathies and thalassemia panel; Sn_NGS, test sensitivity for NGS panel; Sn_SMA, test sensitivity for SMA panel; Sp, specificity; Sp_CF, test specificity for CF panel; Sp_FXS, test specificity for FXS panel; Sp_Hb, test specificity for hemoglobinopathies and thalassemia panel; Sp_NGS, test specificity for NGS panel; Sp_SMA, test specificity for SMA panel; TOP, voluntary termination of pregnancy.

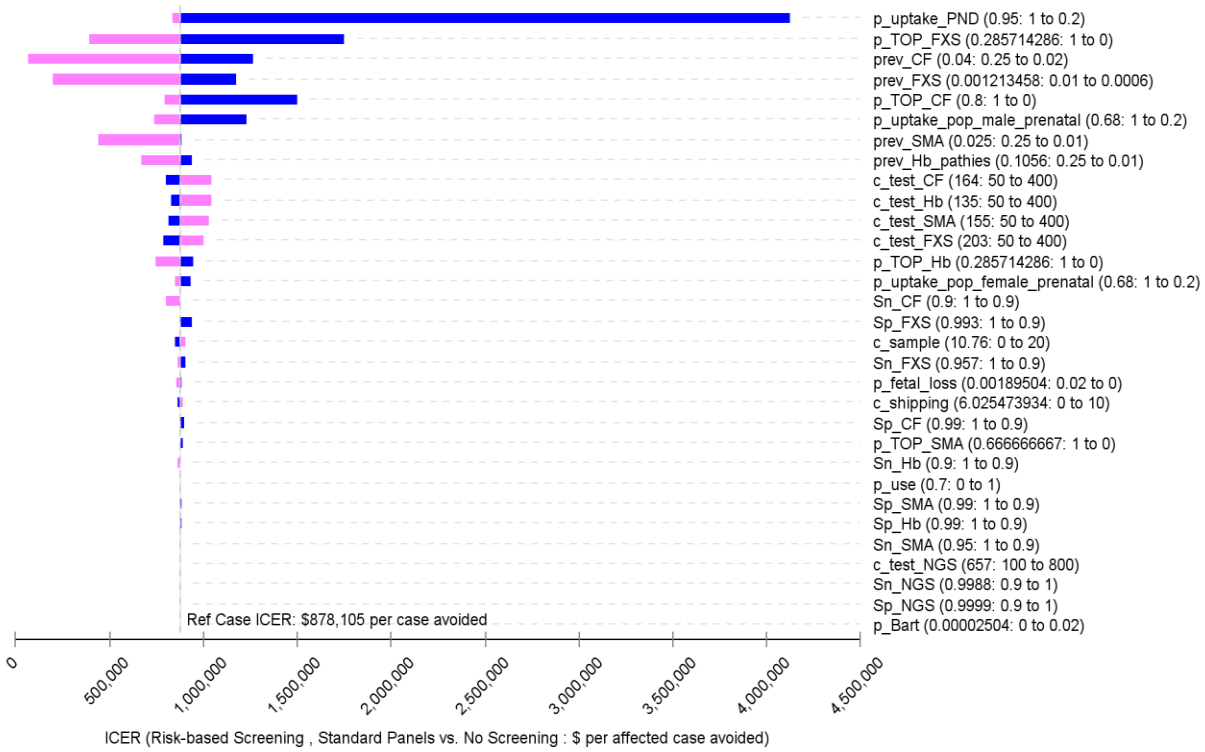

Figure A6: Tornado Diagram, Prenatal Carrier Screening: Risk-Based Screening, Standard Panels Versus No Screening

Abbreviations: c_, cost of; c_IVF, cost of IVF with PGT-M; c_program, cost of screening program; c_sample, cost of blood sampling; c_shipping, cost of blood sample shipping; c_test_CF, cost of genetic testing for CF; c_test_FXS, cost of genetic testing for FXS; c_test_Hb, cost of genetic testing for hemoglobinopathies and thalassemia; c_test_NGS, cost of NGS panel; c_test_SMA, cost of genetic testing for SMA; CF, cystic fibrosis; FXS, fragile X syndrome; Hb, hemoglobinopathies and thalassemia; ICER, incremental cost-effectiveness ratio; IVF, in vitro fertilization; NGS, next-generation sequencing; p_, probability of; p_Bart, probability of the Bart syndrome; p_fetal_loss; probability of fetal loss with PND procedures; p_FXS_risk_full_mutation_expansion, probability of premutaion expansion to full mutation for FXS; p_TOP_CF, probability of voluntary TOP for CF; p_TOP_FXS, probability of voluntary TOP for FXS; p_TOP_Hb, probability of voluntary TOP for hemoglobinopathies and thalassemia; p_uptake_PND, uptake of PND; p_uptake_pop_female, screening uptake by a female partner; p_uptake_pop_male, screening uptake by a male partner; p_use, probability of use of PND procedure (CVS vs, amniocentesis); PND, prenatal diagnostic testing; pop, population; prev_, prevalence (carrier frequency) of; prev_CF, prevalence (carrier frequency) for CF; prev_FXS, prevalence (carrier frequency) for FXS; prev_Hb_pathies, prevalence (carrier frequency) for hemoglobinopathies and thalassemia; prev_SMA, prevalence (carrier frequency) for SMA; SMA, spinal muscular atrophy; Sn, sensitivity; Sn_CF, test sensitivity for CF panel; Sn_FXS, test sensitivity for FXS panel; Sn_Hb, test sensitivity for hemoglobinopathies and thalassemia panel; Sn_NGS, test sensitivity for NGS panel; Sn_SMA, test sensitivity for SMA panel; Sp, specificity; Sp_CF, test specificity for CF panel; Sp_FXS, test specificity for FXS panel; Sp_Hb, test specificity for hemoglobinopathies and thalassemia panel; Sp_NGS, test specificity for NGS panel; Sp_SMA, test specificity for SMA panel; TOP, voluntary termination of pregnancy.

Appendix 14: Results of One-Way Sensitivity Cost-Effectiveness Analyses for Carrier Frequency, Preconception and Prenatal Carrier Screening

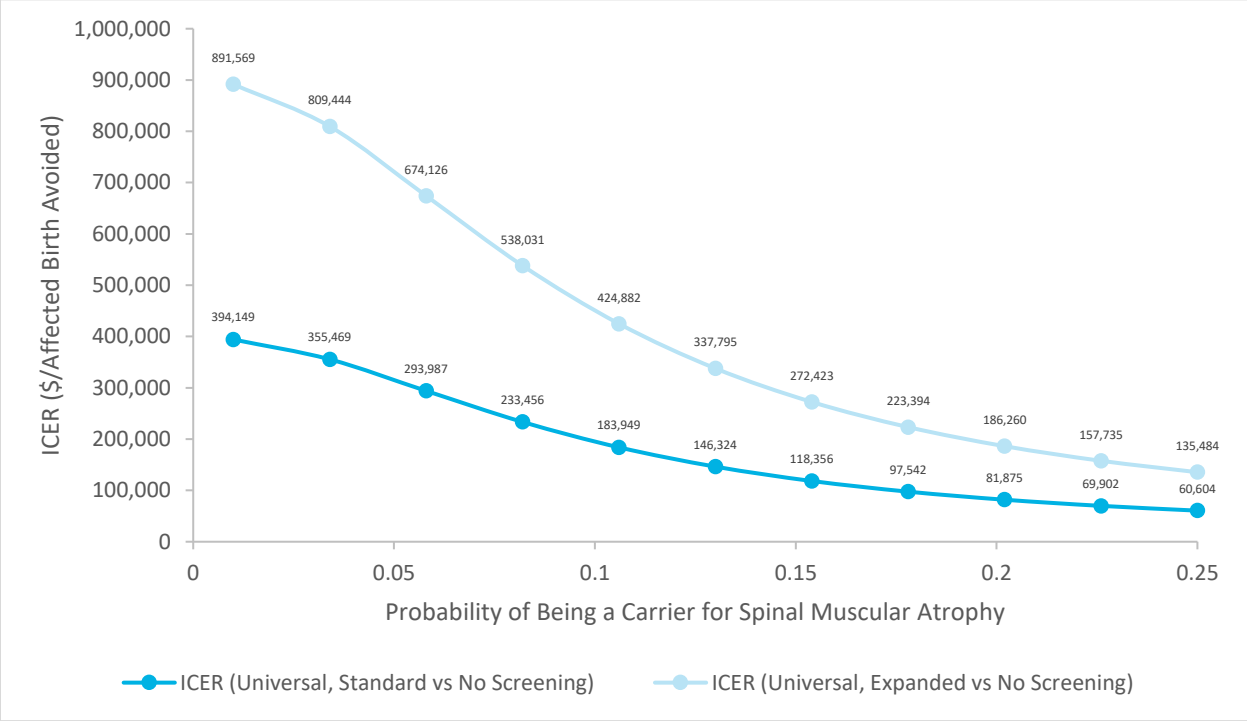

Figure A7: Changes in Carrier Frequency for Spinal Muscular Atrophy and the ICER: Preconception Carrier Screening

Abbreviation: ICER, incremental cost-effectiveness ratio.

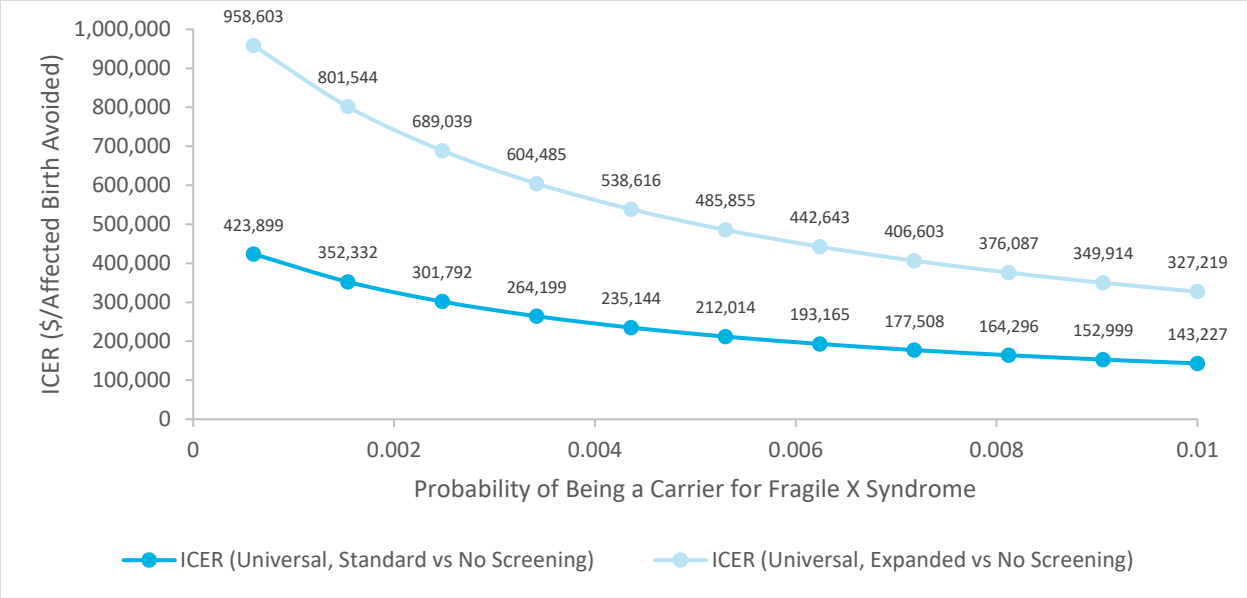

Figure A8: Changes in Carrier Frequency for FXS and the ICER: Preconception Carrier Screening

Abbreviation: ICER, incremental cost-effectiveness ratio.

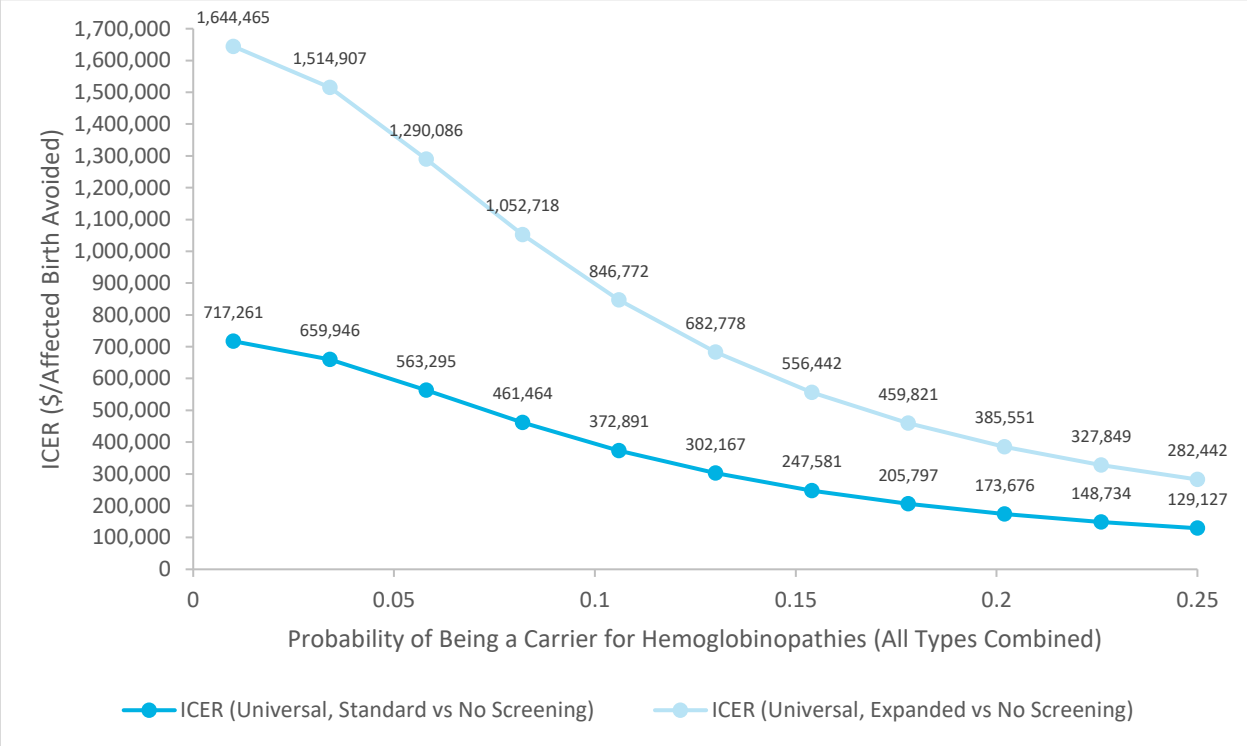

Figure A9: Changes in Carrier Frequency for Hemoglobinopathies and Thalassemia and the ICER: Preconception Carrier Screening

Abbreviation: ICER, incremental cost-effectiveness ratio.

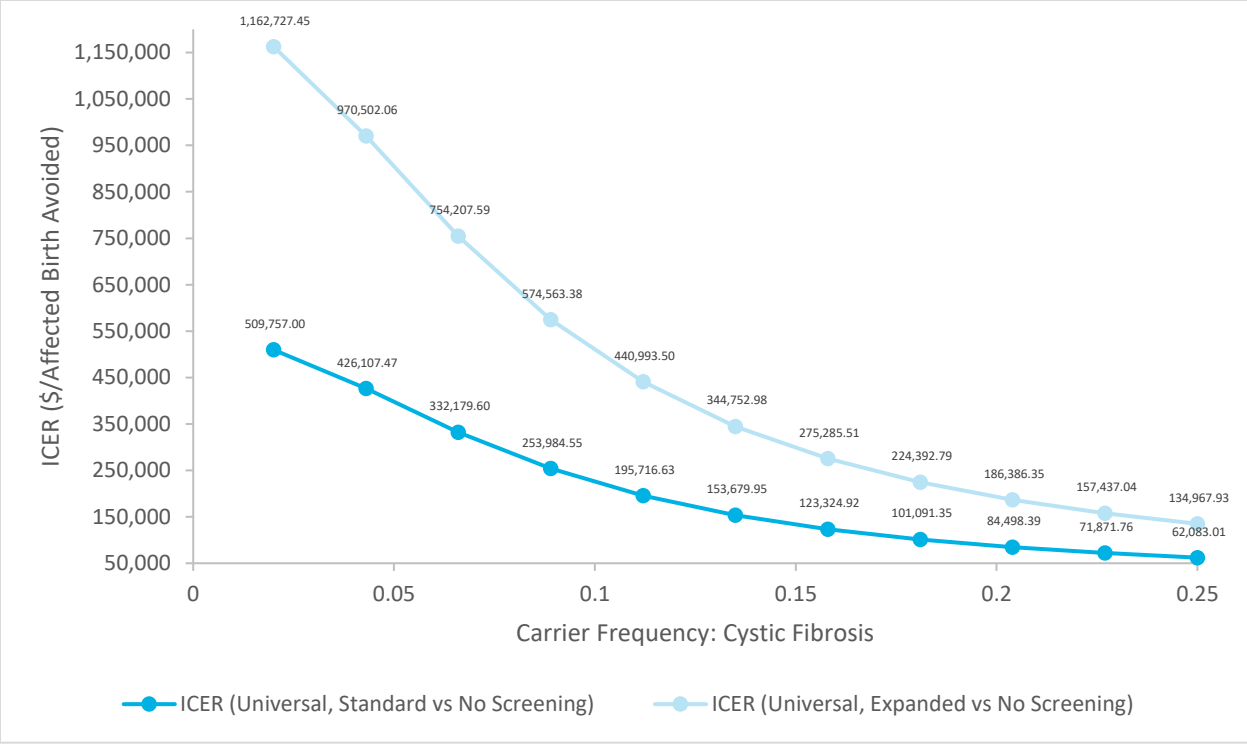

Figure A10: Changes in Carrier Frequency for Cystic Fibrosis and the ICER: Prenatal Carrier Screening

Abbreviation: ICER, incremental cost-effectiveness ratio.

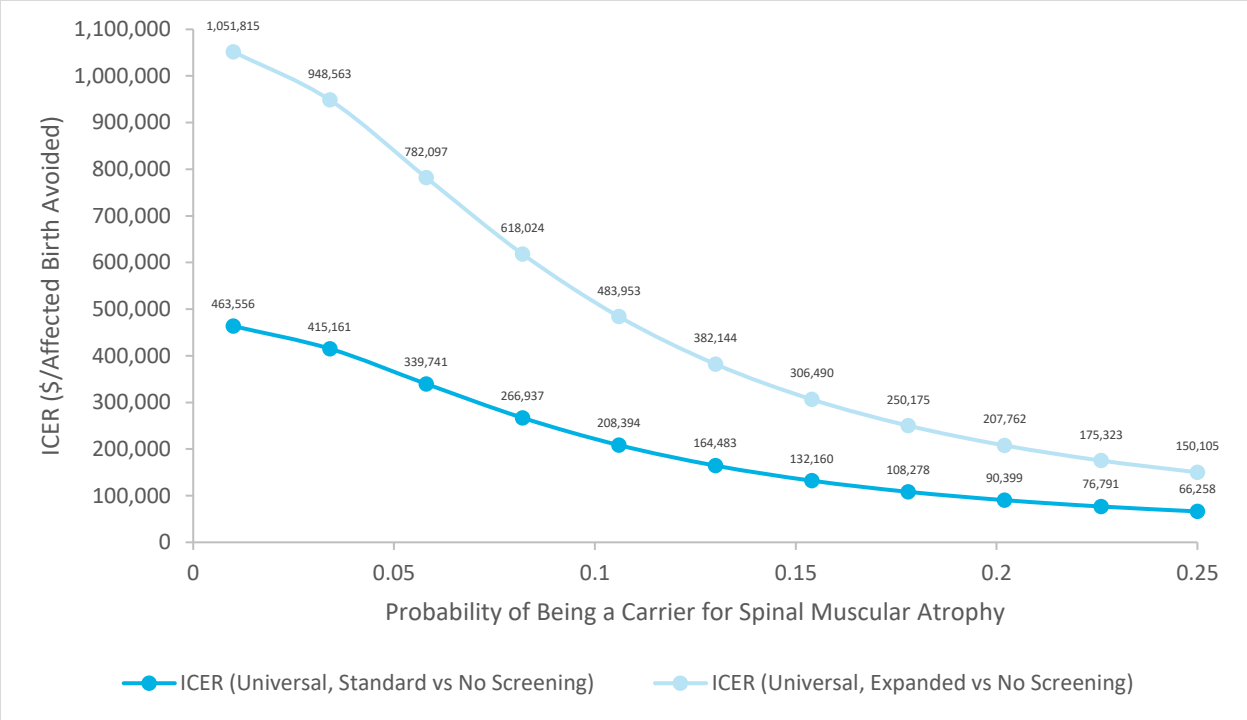

Figure A11: Changes in Carrier Frequency for Spinal Muscular Atrophy and the ICER: Prenatal Carrier Screening

Abbreviation: ICER, incremental cost-effectiveness ratio.

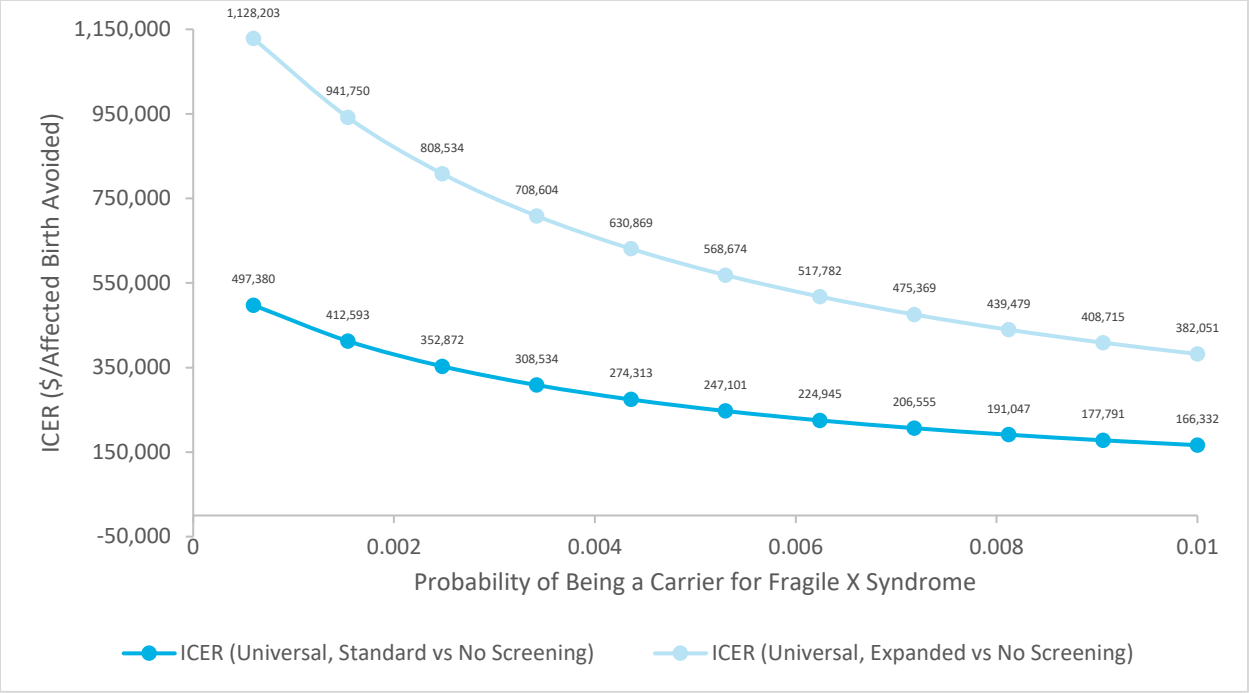

Figure A12: Changes in Carrier Frequency for FXS and the ICER: Prenatal Carrier Screening

Abbreviation: ICER, incremental cost-effectiveness ratio.

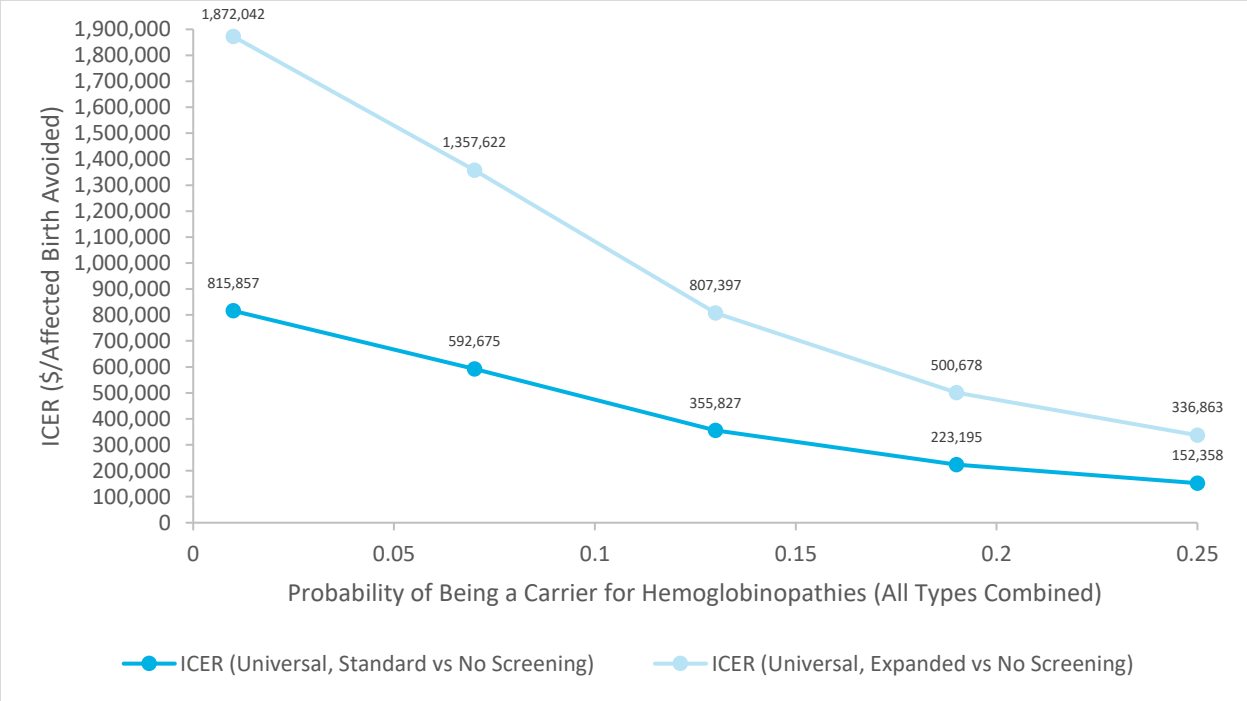

Figure A13: Changes in Carrier Frequency for Hemoglobinopathies and Thalassemia and the ICER: Prenatal Carrier Screening

Abbreviation: ICER, incremental cost-effectiveness ratio.

Appendix 15: Results of One-Way Cost-Effectiveness Sensitivity Analyses for Screening Uptake (Participation) in Preconception or in Prenatal Carrier Screening

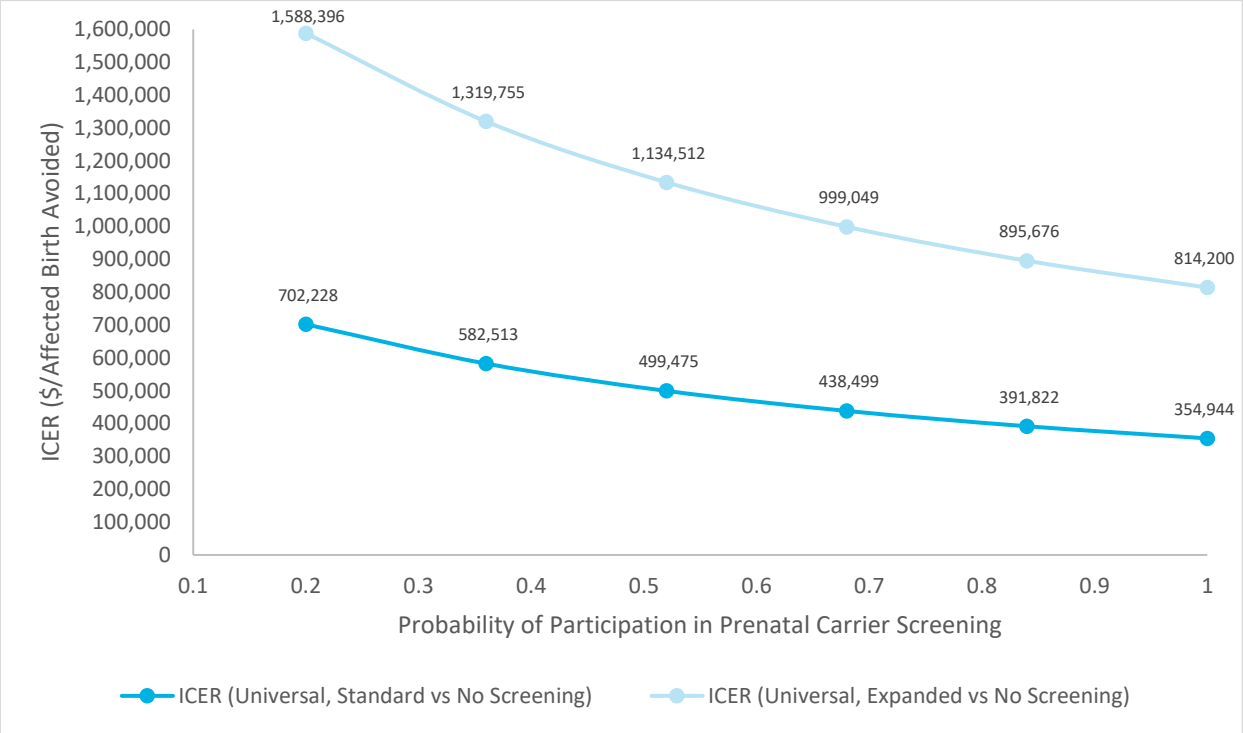

Figure A14: Changes in Screening Uptake (Participation) and the ICER: Prenatal Carrier Screening

Abbreviation: ICER, incremental cost-effectiveness ratio.

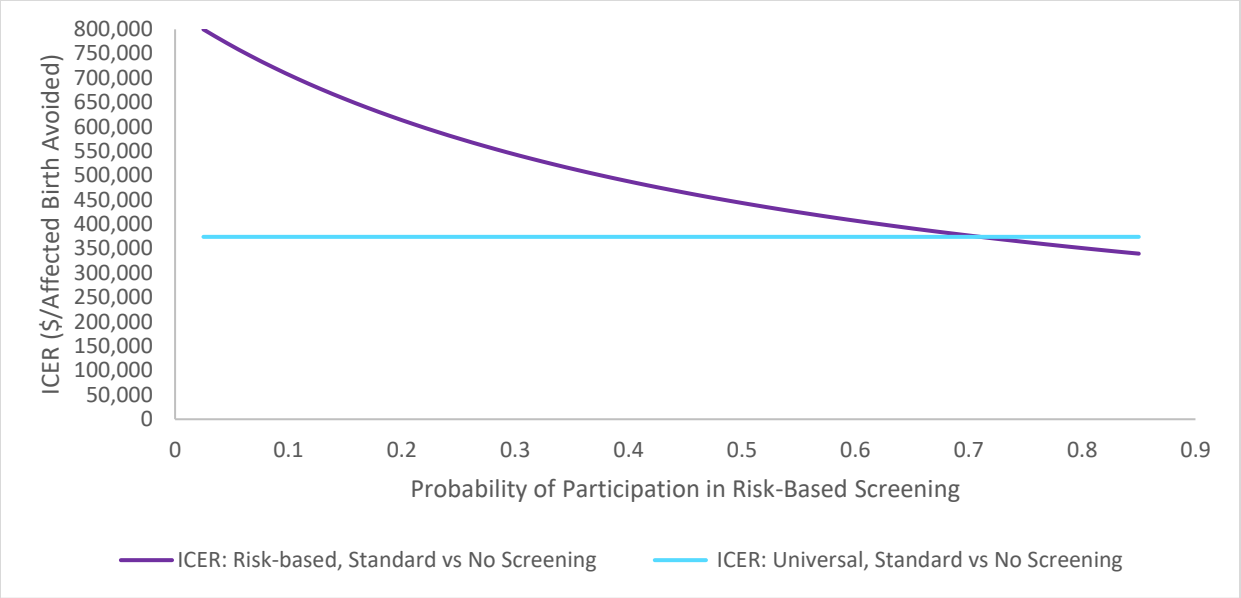

Figure A15: Changes in Screening Uptake (Participation) and the ICER: Universal Versus Risk-Based Preconception Carrier Screening

Abbreviation: ICER, incremental cost-effectiveness ratio.

Appendix 16: Results of One-Way Cost-Effectiveness Sensitivity Analyses for Voluntary TOP in Prenatal Carrier Screening

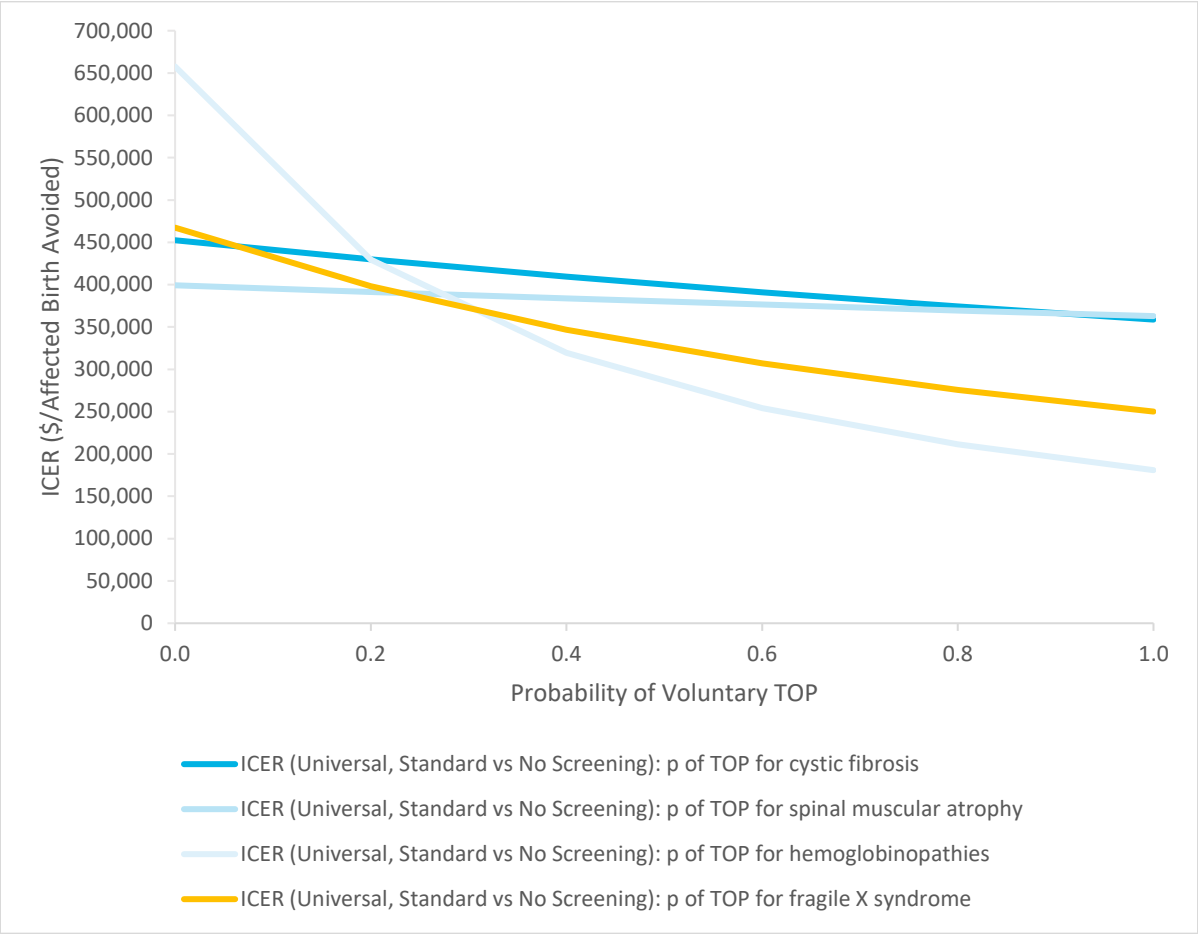

Figure A16: Changes in Condition-Specific Probability of Voluntary TOP and the ICER: Prenatal Carrier Screening

Abbreviations: ICER, incremental cost-effectiveness ratio; TOP, termination of pregnancy.

Appendix 17: Results of One-Way Cost-Effectiveness Sensitivity Analyses for Probability of Choosing IVF/PGT-M in Preconception Carrier Screening

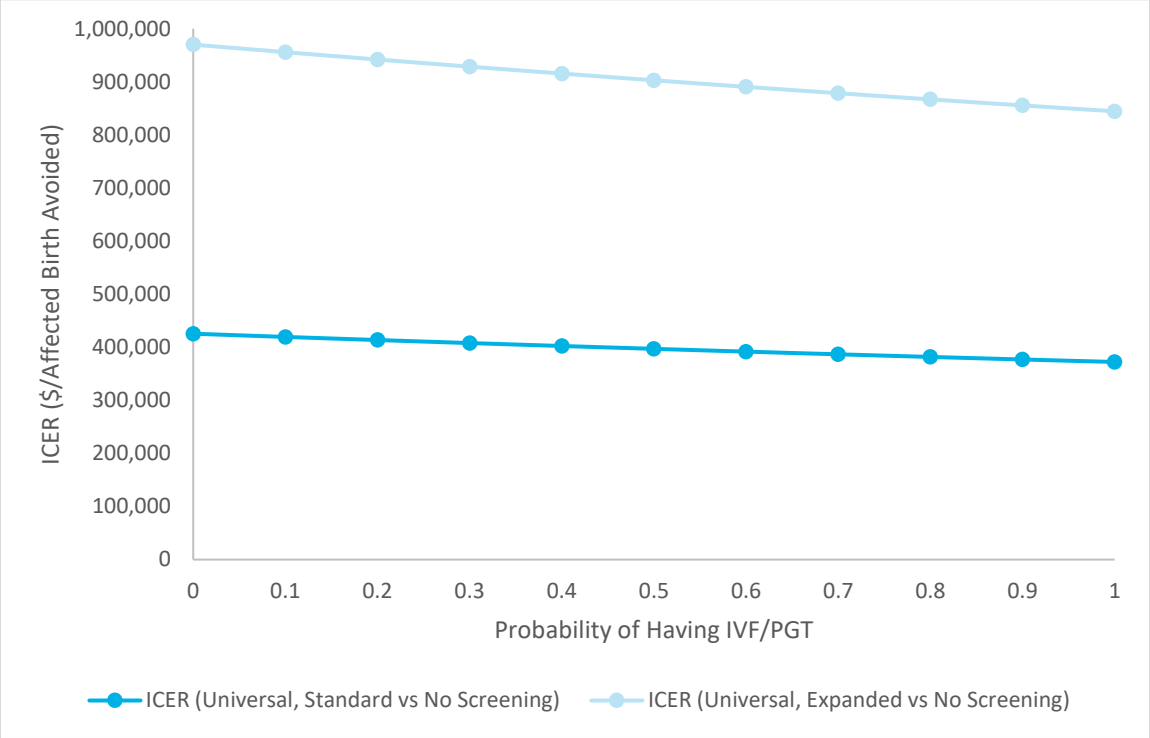

Figure A17: Probability of Choosing IVF/PGT-M and the ICER: Preconception Carrier Screening

Abbreviations: ICER, incremental cost-effectiveness ratio; IVF/PGT-M, in-vitro fertilization with preimplantation genetic testing.

Appendix 18: Results of One-Way Cost-Effectiveness Sensitivity Analyses for Full Coverage of IVF/PGT-M costs (one life birth) in Preconception Carrier Screening

Table A40: Cost-Effectiveness Sensitivity Analysis Results, Preconception Carrier Screening: Coverage of Full IVF/PGT-M Costs ($39,000 Per Life Birth)

Strategy[a]	Average total costs,[a] $	Average total effects, affected birth	ICER, $/affected birth avoided	
			Versus no screening	Sequential ICER (excluding dominated)
No screening	0	0.004159	—	—
Risk-based, standard panels	18.28	0.004136	770,993.81	Dominated[b]
Risk-based, expanded panel	43.79	0.004134	1,718,010.25	Dominated[b]
Universal, standard panels	280.33	0.003431	385,119.02	**385,119.02**
Universal, expanded panel	670.63	0.003370	849,309.42	6,325,217.65

Abbreviations: ICER, incremental cost-effectiveness ratio; IVF/PGT-M, in-vitro fertilization with preimplantation genetic testing.
[a]Treatment strategies are ordered by average total costs, from lowest to highest. The cost of IVF/PGT was assumed to be $39,014 (mean estimate; Linton et al[227]) compared with $5,000 in the reference case.
[b]Extended or strong dominance.

Table A41: Cost-Effectiveness Sensitivity Analysis Results, Preconception Carrier Screening: Coverage of Full IVF/PGT-M Costs ($29,260 Per Life Birth)

Strategy[a]	Average total costs,[a] $	Average total effects, affected birth	ICER, $/affected birth avoided	
			Versus no screening	Sequential ICER (excluding dominated)
No screening	0	0.004159	—	—
Risk-based, standard panels	18.19	0.004136	767,013.13	Dominated[b]
Risk-based, expanded panel	43.73	0.004134	1,715,562.61	Dominated[b]
Universal, standard panels	276.70	0.003431	380,136.12	**380,136.12**
Universal, expanded panel	667.54	0.003370	845,395.64	6,333,915.83

Abbreviations: ICER, incremental cost-effectiveness ratio; IVF/PGT-M, in-vitro fertilization with preimplantation genetic testing.
[a]Treatment strategies are ordered by average total costs, from lowest to highest. The cost of IVF/PGT was assumed to be $29,260 (lower range estimate, Linton et al, 2020)[227] compared with $5,000 in the reference case.
[b]Extended or strong dominance.

Table A42: Cost-Effectiveness Sensitivity Analysis Results, Preconception Carrier Screening: Coverage of Full IVF/PGT-M Costs ($48,767 Per Life Birth)

Strategy[a]	Average total costs,[a] $	Average total effects, affected birth	ICER, $/affected birth avoided	
			Versus no screening	Sequential ICER (excluding dominated)
No screening	0	0.004159	—	—
Risk-based, standard panels	18.38	0.004136	774,948.84	Dominated[b]
Risk-based, expanded panel	43.85	0.004134	1,720,452.09	Dominated[b]
Universal, standard panels	283.99	0.003431	390,128.22	**390,128.22**
Universal, expanded panel	673.75	0.003370	853,264.93	6,316,743.04

Abbreviations: ICER, incremental cost-effectiveness ratio; IVF/PGT-M, in-vitro fertilization with preimplantation genetic testing.
[a]Treatment strategies are ordered by average total costs, from lowest to highest. The cost of IVF/PGT was assumed to be $48,767 (upper range estimate, Linton et al, 2020)[227] compared with $5,000 in the reference case
[b]Extended or strong dominance.

Appendix 19: Results of Cost-Effectiveness Scenarios for Various Screening Care Pathways and Hourly Salary Rate of Medical Genetic Counsellor in Preconception Carrier Screening

Table A43: Cost-Effectiveness Scenario Results, Preconception Carrier Screening: Genetic Counsellors Involved Only in Follow-Up of Test-Positive Couples

Strategy[a]	Average total costs,[a] $	Average total effects, affected birth	ICER, $/Affected birth avoided	
			Versus no screening	Sequential ICER (excluding dominated)
No screening	0.00	0.004159	—	—
Risk-based, standard panels	13.75	0.004136	579,754.91	Dominated[b]
Risk-based, expanded panel	39.38	0.004134	1,544,937.58	Dominated[b]
Universal, standard panels	208.24	0.003431	286,084.59	**286,084.59**
Universal, expanded panel	600.53	0.003370	760,538.46	6,357,521.45

Abbreviation: ICER, incremental cost-effectiveness ratio.

[a]Treatment strategies are ordered by average total costs, from lowest to highest. The screening care pathway described for Scenario 2 (Appendix 8, Table A22).

[b]Extended or strong dominance.

Table A44: Cost-Effectiveness Scenario Results, Preconception Carrier Screening: Removal of Primary Care Visits (Initial and Test-Negative)

Strategy[a]	Average total costs,[a] $	Average total effects, affected birth	ICER, $/affected birth avoided	
			Versus no screening	Sequential ICER (excluding dominated)
No screening	0.00	0.004159	—	—
Risk-based, standard panels	16.10	0.004136	678,756.77	Dominated[b]
Risk-based, expanded panel	41.71	0.004134	1,636,570.17	Dominated[b]
Universal, standard panels	241.57	0.003431	331,868.85	**331,868.85**
Universal, expanded panel	633.76	0.003370	802,620.90	6,355,934.82

Abbreviation: ICER, incremental cost-effectiveness ratio.

[a]Treatment strategies are ordered by average total costs, from lowest to highest.

[b]Extended or strong dominance.

Table A45: Cost-Effectiveness Scenario Results, Preconception Carrier Screening: Genetic Counsellor, Higher Hourly Rate

Strategy[a]	Average total costs,[a] $	Average total effects, affected birth	ICER, $/affected birth avoided	
			Versus no screening	Sequential ICER (excluding dominated)
No screening	0.00	0.004159	—	—
Risk-based, standard panels	18.82	0.004136	793,726.73	Dominated[b]
Risk-based, expanded panel	44.44	0.004134	1,743,412.00	Dominated[b]
Universal, standard panels	280.39	0.003431	385,205.34	385,205.34
Universal, expanded panel	672.57	0.003370	851,775.12	6,355,752.15

Abbreviation: ICER, incremental cost-effectiveness ratio.

[a]Treatment strategies are ordered by average total costs, from lowest to highest. The hourly rate was assumed to be $50.26, compared with $41.2 in the reference case (see Appendix 8, Table A22, Scenario 3).

[b]Extended or strong dominance.

Appendix 20: Results of Cost-Effectiveness Scenarios for Various Screening Care Pathways and Hourly Salary Rate of Medical Genetic Counsellor in Prenatal Carrier Screening

Table A46: Cost-Effectiveness Scenario Results, Prenatal Carrier Screening: Genetic Counsellors Involved Only in Follow-up of Test-Positive Couples

Strategy[a]	Average total costs,[a] $	Average total effects, affected birth	ICER, $/affected birth avoided	
			Versus no screening	Sequential ICER (excluding dominated)
No screening	0.00	0.004159	—	—
Risk-based, standard panels	13.14	0.0041396	664,748.44	Dominated[b]
Risk-based, expanded panel	37.75	0.0041381	1,774,938.72	Dominated[b]
Universal, standard panels	197.46	0.00356969	334,883.62	**334,883.62**
Universal, expanded panel	573.01	0.0035198	895,913.69	7,521,509.09

Abbreviation: ICER, incremental cost-effectiveness ratio.

[a]Treatment strategies are ordered by average total costs, from lowest to highest. The screening care pathway described for Scenario 2 (Appendix 8, Table A22).

[b]Extended or strong dominance.

Table A47: Cost-Effectiveness Scenario Results, Prenatal Carrier Screening: Removal of Primary Care Visits (Initial and Test-Negative)

Strategy[a]	Average total costs,[a] $	Average total effects, affected birth	ICER, $/affected birth avoided	
			Versus no screening	Sequential ICER (excluding dominated)
No organized screening	0.00	0.004159	—	—
Risk-based, standard panels	15.40	0.0041396	778,962.84	Dominated[b]
Risk-based, expanded panel	40.00	0.0041381	1,880,564.83	Dominated[b]
Universal, standard panels	229.54	0.00356969	389,279.55	**389,279.55**
Universal, expanded panel	604.98	0.0035198	945,910.35	7,519,551.62

Abbreviation: ICER, incremental cost-effectiveness ratio.

[a]Treatment strategies are ordered by average total costs, from lowest to highest. The screening care pathway described for Scenario 1 (Appendix 8, Table A22).

[b]Extended or strong dominance.

Table A48: Cost-Effectiveness Scenario Results, Prenatal Carrier Screening: Genetic Counsellor, Higher Hourly Rate

Strategy[a]	Average total costs,[a] $	Average total effects, affected birth	ICER, $/affected birth avoided	
			Versus no screening	Sequential ICER (excluding dominated)
No screening	0.00	0.004159	—	—
Risk-based, standard panels	18.03	0.0041396	911,660.69	Dominated[b]
Risk-based, expanded panel	42.62	0.0041381	2,003,774.13	Dominated[b]
Universal, standard panels	266.89	0.00356969	452,618.44	452,618.44
Universal, expanded panel	642.32	0.0035198	1,004,282.98	7,519,274.30

Abbreviation: ICER, incremental cost-effectiveness ratio.

[a]Treatment strategies are ordered by average total costs, from lowest to highest. The hourly rate was assumed to be $50.26 compared with $41.2 in the reference case (see Appendix 8, Table A22, Scenario 3)

[b]Extended or strong dominance.

Appendix 21: Results of Cost-Effectiveness Scenarios Related To Program Costs of Preconception or Prenatal Carrier Screening

Table A49: Cost-Effectiveness Scenario Results, Preconception Carrier Screening: Inclusion of Program Costs

Strategy[a]	Average total costs,[a] $	Average total effects, affected birth	ICER, $/affected birth avoided	
			Versus no screening	Sequential ICER (excluding dominated)
No screening	0.00	0.004159	—	—
Risk-based, standard panels	40.01	0.004136	1,687,162.20	Dominated[b]
Risk-based, expanded panel	65.58	0.004134	2,573,161.31	Dominated[b]
Universal, standard panels	272.02	0.003431	373,696.27	**373,696.27**
Universal, expanded panel	664.20	0.003370	841,174.34	6,355,866.08

Abbreviations: ICER, incremental cost-effectiveness ratio; IVF/PGT-M, in-vitro fertilization with preimplantation genetic testing;
[a]Treatment strategies are ordered by average total costs, from lowest to highest. The cost of a program includes the cost of implementation only as this is a 1-year model. No full cost of IVF/PGT-M was assumed (i.e., same cost in the reference case—$5,000).
[b]Extended or strong dominance.

Table A50: Cost-Effectiveness Scenario Results, Preconception Carrier Screening: Inclusion of Program Costs and Full Coverage of IVF/PGT-M Costs

Strategy[a]	Average total costs,[a] $	Average total effects, affected birth	ICER, $/affected birth avoided	
			Versus no screening	Sequential ICER (excluding dominated)
No screening	0.00	0.004159	—	—
Risk-based, standard panels	40.34	0.004136	1,701,005.51	Dominated[b]
Risk-based, expanded panel	65.80	0.004134	2,581,651.53	Dominated[b]
Universal, standard panels	284.67	0.003431	A504.58	**391,084.58**
Universal, expanded panel	674.96	0.003370	854,795.68	6,325,049.65

Abbreviations: ICER, incremental cost-effectiveness ratio; IVF/PGT-M, in-vitro fertilization with preimplantation genetic testing.
[a]Treatment strategies are ordered by average total costs, from lowest to highest. The cost of a program includes the cost of implementation only as this is a 1-year model. The cost of IVF/PGT-M was assumed to be about $39,000 per life birth.
[b]Extended or strong dominance.

Table A51: Cost-Effectiveness Scenario Results, Prenatal Carrier Screening: Inclusion of Program Costs

Strategy[a]	Average total costs,[a] $	Average total effects, affected birth	ICER, $/affected birth avoided	
			Versus no screening	Sequential ICER (excluding dominated)
No screening	0.00	0.004159	—	—
Risk-based, standard panels	49.94	0.0041396	2,525,591.26	Dominated[b]
Risk-based, expanded panel	74.47	0.0041381	3,501,491.98	Dominated[b]
Universal, standard panels	260.93	0.00356969	442,517.62	**442,517.62**
Universal, expanded panel	636.37	0.0035198	994,975.01	7,519,329.50

Abbreviation: ICER, incremental cost-effectiveness ratio.

[a]Treatment strategies are ordered by average total costs, from lowest to highest. The cost of a program includes the cost of implementation only as this is a 1-year model.

[b]Extended or strong dominance.

Appendix 22: Results of Budget Impact Scenarios, Preconception Carrier Screening Programs

Table A52: Budget Impact Scenario Results—Participation (Uptake) in Preconception Carrier Screening: 20%

Type of cost	Future scenario costs and budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Universal, standard DNA testing (single-disease panels)						
Total	**3.03**	**3.18**	**3.33**	**3.34**	**3.35**	**16.22**
Costs of screening	2.97	3.11	3.26	3.26	3.26	15.86
Costs associated with prenatal diagnostics	0.04	0.05	0.05	0.06	0.06	0.26
Costs associated with reproductive choice	0.02	0.02	0.02	0.02	0.02	0.09
Universal, expanded DNA testing (one multi-disease panel)						
Total	**7.25**	**7.62**	**7.98**	**7.99**	**7.99**	**38.83**
Costs of screening	7.21	7.57	7.93	7.93	7.93	38.57
Costs associated with prenatal diagnostics	0.03	0.03	0.04	0.04	0.04	0.18
Costs associated with reproductive choice	0.01	0.01	0.02	0.02	0.02	0.08
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.017**	**0.018**	**0.019**	**0.020**	**0.020**	**0.095**
Costs of screening	0.015	0.016	0.016	0.016	0.016	0.080
Costs associated with prenatal diagnostics	0.002	0.002	0.002	0.002	0.003	0.011
Costs associated with reproductive choice	0.001	0.001	0.001	0.001	0.001	0.004
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.038**	**0.040**	**0.042**	**0.042**	**0.042**	**0.202**
Costs of screening	0.036	0.038	0.040	0.040	0.040	0.193
Costs associated with prenatal diagnostics	0.001	0.001	0.001	0.001	0.001	0.006
Costs associated with reproductive choice	0.001	0.001	0.001	0.001	0.001	0.003

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A53: Budget Impact Scenario Results—Participation (Uptake) in Preconception Carrier Screening: 35%

Type of cost	Future scenario costs and budget impact, $ million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Universal, standard DNA testing (single-disease panels)						
Total	**9.83**	**10.32**	**10.83**	**10.85**	**10.89**	**52.72**
Costs of screening	9.58	10.06	10.53	10.53	10.53	51.23
Costs associated with prenatal diagnostics	0.19	0.20	0.22	0.24	0.26	1.09
Costs associated with reproductive choice	0.07	0.07	0.08	0.08	0.09	0.39
Universal, expanded DNA testing (one multi-disease panel)						
Total	**23.51**	**24.68**	**25.87**	**25.89**	**25.92**	**125.87**
Costs of screening	23.30	24.47	25.63	25.63	25.63	124.68
Costs associated with prenatal diagnostics	0.14	0.15	0.17	0.18	0.20	0.85
Costs associated with reproductive choice	0.06	0.06	0.07	0.07	0.08	0.35
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.06**	**0.06**	**0.06**	**0.06**	**0.07**	**0.31**
Costs of screening	0.05	0.05	0.05	0.05	0.05	0.26
Costs associated with prenatal diagnostics	0.01	0.01	0.01	0.01	0.01	0.04
Costs associated with reproductive choice	0.00	0.00	0.00	0.00	0.00	0.01
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.12**	**0.13**	**0.14**	**0.14**	**0.14**	**0.66**
Costs of screening	0.12	0.12	0.13	0.13	0.13	0.63
Costs associated with prenatal diagnostics	0.00	0.00	0.00	0.00	0.01	0.02
Costs associated with reproductive choice	0.00	0.00	0.00	0.00	0.00	0.01

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A54: Budget Impact Scenario Results—Participation (Uptake) in Preconception Carrier Screening: 50%

Type of cost	Future scenario costs and budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Universal, standard DNA testing (single-disease panels)						
Total	**21.21**	**22.27**	**23.36**	**23.44**	**23.52**	**113.80**
Costs of screening	20.55	21.58	22.61	22.61	22.61	109.96
Costs associated with prenatal diagnostics	0.48	0.51	0.56	0.61	0.67	2.84
Costs associated with reproductive choice	0.17	0.18	0.20	0.22	0.24	1.01
Universal, expanded DNA testing (one multi-disease panel)						
Total	**50.61**	**53.14**	**55.70**	**55.76**	**55.83**	**271.04**
Costs of screening	50.06	52.56	55.06	55.06	55.06	267.80
Costs associated with prenatal diagnostics	0.39	0.41	0.46	0.50	0.55	2.32
Costs associated with reproductive choice	0.16	0.17	0.18	0.20	0.22	0.93
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.12**	**0.13**	**0.14**	**0.14**	**0.14**	**0.67**
Costs of screening	0.10	0.11	0.11	0.11	0.11	0.55
Costs associated with prenatal diagnostics	0.01	0.02	0.02	0.02	0.02	0.09
Costs associated with reproductive choice	0.01	0.01	0.01	0.01	0.01	0.03
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.26**	**0.28**	**0.29**	**0.29**	**0.30**	**1.42**
Costs of screening	0.25	0.26	0.28	0.28	0.28	1.34
Costs associated with prenatal diagnostics	0.01	0.01	0.01	0.01	0.01	0.05
Costs associated with reproductive choice	0.00	0.00	0.01	0.01	0.01	0.03

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A55: Budget Impact Scenario Results—Participation (Uptake) in Preconception Carrier Screening: 100%

Type of cost	Future scenario costs and budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Universal, standard DNA testing (single-disease panels)						
Total	**100.04**	**100.04**	**100.04**	**100.04**	**100.04**	**500.18**
Costs of screening	95.56	95.56	95.56	95.56	95.56	477.82
Costs associated with prenatal diagnostics	3.30	3.30	3.30	3.30	3.30	16.48
Costs associated with reproductive choice	1.17	1.17	1.17	1.17	1.17	5.87
Universal, expanded DNA testing (one multi-disease panel)						
Total	**237.43**	**237.43**	**237.43**	**237.43**	**237.43**	**1,187.17**
Costs of screening	233.40	233.40	233.40	233.40	233.40	1166.98
Costs associated with prenatal diagnostics	2.91	2.91	2.91	2.91	2.91	14.56
Costs associated with reproductive choice	1.13	1.13	1.13	1.13	1.13	5.63
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.59**	**0.62**	**0.65**	**0.67**	**0.68**	**3.21**
Costs of screening	0.48	0.51	0.53	0.53	0.53	2.58
Costs associated with prenatal diagnostics	0.08	0.08	0.09	0.10	0.11	0.45
Costs associated with reproductive choice	0.03	0.03	0.04	0.04	0.04	0.18
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**1.25**	**1.32**	**1.38**	**1.39**	**1.40**	**6.75**
Costs of screening	1.17	1.23	1.29	1.29	1.29	6.28
Costs associated with prenatal diagnostics	0.05	0.06	0.06	0.07	0.08	0.32
Costs associated with reproductive choice	0.03	0.03	0.03	0.03	0.04	0.16

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 Canadian dollars.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A56: Budget Impact Scenario Results—Preconception Carrier Screening: Carrier Frequency Decreased by Half

Type of cost	Future scenario costs and budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Universal, standard DNA testing (single-disease panels)						
Total	**37.54**	**39.41**	**41.33**	**41.43**	**41.53**	**201.23**
Costs of screening	36.74	38.58	40.41	40.41	40.41	196.55
Costs associated with prenatal diagnostics	0.61	0.64	0.71	0.78	0.85	3.59
Costs associated with reproductive choice	0.19	0.20	0.22	0.24	0.26	1.10
Universal, expanded DNA testing (one multi-disease panel)						
Total	**90.28**	**94.79**	**99.33**	**99.39**	**99.44**	**483.24**
Costs of screening	89.82	94.31	98.80	98.80	98.80	480.54
Costs associated with prenatal diagnostics	0.33	0.35	0.38	0.42	0.46	1.94
Costs associated with reproductive choice	0.13	0.14	0.15	0.16	0.18	0.76
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.22**	**0.23**	**0.24**	**0.24**	**0.25**	**1.17**
Costs of screening	0.19	0.20	0.21	0.21	0.21	1.01
Costs associated with prenatal diagnostics	0.02	0.02	0.02	0.03	0.03	0.12
Costs associated with reproductive choice	0.01	0.01	0.01	0.01	0.01	0.04
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.47**	**0.50**	**0.52**	**0.52**	**0.52**	**2.54**
Costs of screening	0.46	0.48	0.51	0.51	0.51	2.47
Costs associated with prenatal diagnostics	0.01	0.01	0.01	0.01	0.01	0.05
Costs associated with reproductive choice	0.00	0.00	0.00	0.01	0.01	0.02

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A57: Budget Impact Scenario Results—Preconception Carrier Screening: Carrier Frequency Doubled

Type of cost	Future scenario costs and budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Universal, standard DNA testing (single-disease panels)						
Total	**40.90**	**42.94**	**45.19**	**45.61**	**46.07**	**220.71**
Costs of screening	37.25	39.11	40.97	40.97	40.97	199.27
Costs associated with prenatal diagnostics	2.62	2.75	3.03	3.33	3.66	15.39
Costs associated with reproductive choice	1.03	1.08	1.19	1.31	1.44	6.05
Universal, expanded DNA testing (one multi-disease panel)						
Total	**94.05**	**98.75**	**103.66**	**104.08**	**104.54**	**505.08**
Costs of screening	90.39	94.91	99.43	99.43	99.43	483.59
Costs associated with prenatal diagnostics	2.59	2.72	3.00	3.30	3.63	15.23
Costs associated with reproductive choice	1.07	1.12	1.23	1.35	1.49	6.26
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.29**	**0.31**	**0.33**	**0.34**	**0.35**	**1.61**
Costs of screening	0.19	0.20	0.21	0.21	0.21	1.03
Costs associated with prenatal diagnostics	0.07	0.07	0.08	0.09	0.09	0.40
Costs associated with reproductive choice	0.03	0.03	0.04	0.04	0.04	0.18
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.56**	**0.58**	**0.62**	**0.63**	**0.64**	**3.02**
Costs of screening	0.46	0.49	0.51	0.51	0.51	2.49
Costs associated with prenatal diagnostics	0.06	0.06	0.07	0.08	0.08	0.35
Costs associated with reproductive choice	0.03	0.03	0.04	0.04	0.04	0.18

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A58: Budget Impact Scenario Results—Preconception Carrier Screening: Panel Costs Decreased by Half

	Future scenario costs and Budget Impact, $ Million[a,b]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Universal, standard DNA testing (single-disease panels)						
Total	**29.76**	**31.25**	**32.84**	**33.03**	**33.25**	**160.14**
Costs of screening	28.05	29.45	30.85	30.85	30.85	150.05
Costs associated with prenatal diagnostics	1.27	1.33	1.47	1.61	1.77	7.45
Costs associated with reproductive choice	0.45	0.47	0.52	0.57	0.63	2.64
Universal, expanded DNA testing (one multi-disease panel)						
Total	**56.10**	**58.90**	**61.79**	**61.96**	**62.16**	**300.91**
Costs of screening	54.59	57.32	60.05	60.05	60.05	292.06
Costs associated with prenatal diagnostics	1.08	1.14	1.25	1.38	1.52	6.37
Costs associated with reproductive choice	0.42	0.44	0.49	0.54	0.59	2.49
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.19**	**0.20**	**0.21**	**0.22**	**0.22**	**1.05**
Costs of screening	0.14	0.15	0.16	0.16	0.16	0.77
Costs associated with prenatal diagnostics	0.03	0.04	0.04	0.04	0.05	0.20
Costs associated with reproductive choice	0.01	0.01	0.01	0.02	0.02	0.08
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.31**	**0.33**	**0.35**	**0.35**	**0.36**	**1.70**
Costs of screening	0.28	0.30	0.31	0.31	0.31	1.50
Costs associated with prenatal diagnostics	0.02	0.02	0.03	0.03	0.03	0.13
Costs associated with reproductive choice	0.01	0.01	0.01	0.01	0.02	0.06

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A59: Budget Impact Scenario Results—Preconception Carrier Screening: A Hypothetical Expanded Panel, Costs Decreased by 80% (~$130)

	Future scenario costs and budget impact, $ million[a,b]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Universal, standard DNA testing (single-disease panels)						
Total	**38.64**	**40.57**	**42.60**	**42.80**	**43.01**	**207.62**
Costs of screening	36.92	38.77	40.61	40.61	40.61	197.54
Costs associated with prenatal diagnostics	1.27	1.33	1.47	1.61	1.77	7.45
Costs associated with reproductive choice	0.45	0.47	0.52	0.57	0.63	2.64
Universal, expanded DNA testing (one multi-disease panel)						
Total	**34.83**	**36.58**	**38.40**	**38.58**	**38.77**	**187.15**
Costs of screening	33.33	34.99	36.66	36.66	36.66	178.30
Costs associated with prenatal diagnostics	1.08	1.14	1.25	1.38	1.52	6.37
Costs associated with reproductive choice	0.42	0.44	0.49	0.54	0.59	2.49
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.24**	**0.25**	**0.26**	**0.27**	**0.27**	**1.29**
Costs of screening	0.19	0.20	0.21	0.21	0.21	1.02
Costs associated with prenatal diagnostics	0.03	0.04	0.04	0.04	0.05	0.20
Costs associated with reproductive choice	0.01	0.01	0.01	0.02	0.02	0.08
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.21**	**0.22**	**0.23**	**0.23**	**0.24**	**1.11**
Costs of screening	0.17	0.18	0.19	0.19	0.19	0.92
Costs associated with prenatal diagnostics	0.02	0.02	0.03	0.03	0.03	0.13
Costs associated with reproductive choice	0.01	0.01	0.01	0.01	0.02	0.06

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A60: Budget Impact Scenario Results—Preconception Carrier Screening: Screening Care Pathway, Reducing Encounters (Visits) With a Genetic Counsellor

	Future scenario costs and budget impact, $ million[a,b]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Universal, standard DNA testing (single-disease panels)						
Total	**31.59**	**33.17**	**34.85**	**35.04**	**35.26**	**169.92**
Costs of screening	29.88	31.37	32.86	32.86	32.86	159.83
Costs associated with prenatal diagnostics	1.27	1.33	1.47	1.61	1.77	7.45
Costs associated with reproductive choice	0.45	0.47	0.52	0.57	0.63	2.64
Universal, expanded DNA testing (one multi-disease panel)						
Total	**91.36**	**95.93**	**100.58**	**100.76**	**100.95**	**489.59**
Costs of screening	89.86	94.35	98.84	98.84	98.84	480.73
Costs associated with prenatal diagnostics	1.08	1.14	1.25	1.38	1.52	6.37
Costs associated with reproductive choice	0.42	0.44	0.49	0.54	0.59	2.49
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.19**	**0.20**	**0.22**	**0.22**	**0.23**	**1.06**
Costs of screening	0.15	0.15	0.16	0.16	0.16	0.79
Costs associated with prenatal diagnostics	0.03	0.04	0.04	0.04	0.05	0.20
Costs associated with reproductive choice	0.01	0.01	0.01	0.02	0.02	0.08
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.46**	**0.49**	**0.51**	**0.51**	**0.52**	**2.49**
Costs of screening	0.43	0.45	0.47	0.47	0.47	2.30
Costs associated with prenatal diagnostics	0.02	0.02	0.03	0.03	0.03	0.13
Costs associated with reproductive choice	0.01	0.01	0.01	0.01	0.02	0.06

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars. The screening care pathway described for Scenario 2 (Appendix 8, Table A22).

Table A61: Budget Impact Scenario Results—Preconception Carrier Screening: Screening Care Pathway, Reducing Encounters (Visits) With a Primary Care Physician

	Future scenario costs and budget impact, $ million[a,b]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Universal, standard DNA testing (single-disease panels)						
Total	**36.67**	**38.50**	**40.43**	**40.63**	**40.85**	**197.08**
Costs of screening	34.95	36.70	38.45	38.45	38.45	186.99
Costs associated with prenatal diagnostics	1.27	1.33	1.47	1.61	1.77	7.45
Costs associated with reproductive choice	0.45	0.47	0.52	0.57	0.63	2.64
Universal, expanded DNA testing (one multi-disease panel)						
Total	**96.43**	**101.25**	**106.15**	**106.33**	**106.52**	**516.67**
Costs of screening	94.92	99.66	104.41	104.41	104.41	507.81
Costs associated with prenatal diagnostics	1.08	1.14	1.25	1.38	1.52	6.37
Costs associated with reproductive choice	0.42	0.44	0.49	0.54	0.59	2.49
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.22**	**0.23**	**0.24**	**0.25**	**0.26**	**1.20**
Costs of screening	0.17	0.18	0.19	0.19	0.19	0.93
Costs associated with prenatal diagnostics	0.03	0.04	0.04	0.04	0.05	0.20
Costs associated with reproductive choice	0.01	0.01	0.01	0.02	0.02	0.08
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.49**	**0.51**	**0.54**	**0.54**	**0.55**	**2.63**
Costs of screening	0.46	0.48	0.50	0.50	0.50	2.44
Costs associated with prenatal diagnostics	0.02	0.02	0.03	0.03	0.03	0.13
Costs associated with reproductive choice	0.01	0.01	0.01	0.01	0.02	0.06

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars. The screening care pathway described for Scenario 1 (Appendix 8, Table A22).

Table A62: Budget Impact Scenario Results—Preconception Carrier Screening: Screening Care Pathway, Higher Hourly Salary Rate, Genetic Counsellors

	Future scenario costs and budget impact, $ million[a,b]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Universal, standard DNA testing (single-disease panels)						
Total	**42.58**	**44.71**	**46.94**	**47.13**	**47.35**	**228.72**
Costs of screening	40.87	42.91	44.95	44.95	44.95	218.63
Costs associated with prenatal diagnostics	1.27	1.33	1.47	1.61	1.77	7.45
Costs associated with reproductive choice	0.45	0.47	0.52	0.57	0.63	2.64
Universal, expanded DNA testing (one multi-disease panel)						
Total	**102.34**	**107.45**	**112.65**	**112.83**	**113.02**	**548.30**
Costs of screening	100.83	105.87	110.91	110.91	110.91	539.44
Costs associated with prenatal diagnostics	1.08	1.14	1.25	1.38	1.52	6.37
Costs associated with reproductive choice	0.42	0.44	0.49	0.54	0.59	2.49
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.25**	**0.26**	**0.28**	**0.28**	**0.29**	**1.36**
Costs of screening	0.20	0.21	0.22	0.22	0.22	1.09
Costs associated with prenatal diagnostics	0.03	0.04	0.04	0.04	0.05	0.20
Costs associated with reproductive choice	0.01	0.01	0.01	0.02	0.02	0.08
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.52**	**0.54**	**0.57**	**0.58**	**0.58**	**2.79**
Costs of screening	0.49	0.51	0.53	0.53	0.53	2.60
Costs associated with prenatal diagnostics	0.02	0.02	0.03	0.03	0.03	0.13
Costs associated with reproductive choice	0.01	0.01	0.01	0.01	0.02	0.06

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars. The screening care pathway described for Scenario 3 (Appendix 8, Table A22).

Table A63: Budget Impact Scenario Results—Preconception Carrier Screening: Full Coverage of IVF/PGT

Type of cost	Future scenario costs and budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Universal, standard DNA testing (single-disease panels)						
Total	**40.43**	**42.46**	**44.67**	**45.08**	**45.52**	**218.16**
Costs of screening	36.92	38.77	40.61	40.61	40.61	197.54
Costs associated with prenatal diagnostics	1.27	1.33	1.47	1.61	1.77	7.45
Costs associated with reproductive choice	2.24	2.35	2.59	2.85	3.13	13.17
Universal, expanded DNA testing (one multi-disease panel)						
Total	**93.06**	**97.71**	**102.53**	**102.88**	**103.27**	**499.46**
Costs of screening	90.03	94.53	99.03	99.03	99.03	481.66
Costs associated with prenatal diagnostics	1.08	1.14	1.25	1.38	1.52	6.37
Costs associated with reproductive choice	1.95	2.04	2.25	2.47	2.72	11.44
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.28**	**0.30**	**0.32**	**0.33**	**0.34**	**1.56**
Costs of screening	0.19	0.20	0.21	0.21	0.21	1.02
Costs associated with prenatal diagnostics	0.03	0.04	0.04	0.04	0.05	0.20
Costs associated with reproductive choice	0.06	0.06	0.07	0.08	0.08	0.35
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.53**	**0.55**	**0.58**	**0.59**	**0.60**	**2.85**
Costs of screening	0.46	0.49	0.51	0.51	0.51	2.48
Costs associated with prenatal diagnostics	0.02	0.02	0.03	0.030	0.03	0.13
Costs associated with reproductive choice	0.04	0.04	0.05	0.05	0.06	0.24

Abbreviation: IVF/PGT, in-vitro fertilization with preimplantation genetic testing.

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A64: Budget Impact Scenario Results—Preconception Carrier Screening: Inclusion of Program Costs (Model-Based Outputs)

	Future scenario costs and budget impact, $ million[a,b]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Universal, standard DNA testing (single-disease panels)						
Total (all program costs)	**41.31**	**43.13**	**45.27**	**45.47**	**45.69**	**220.87**
Total (implementation costs only)	**41.31**	**42.68**	**44.80**	**45.00**	**45.22**	**218.35**
Costs of program (implementation and on-going)	0.66	0.45	0.47	0.47	0.47	2.52
Costs of screening	38.93	40.87	42.82	42.82	42.82	208.27
Costs associated with prenatal diagnostics	1.27	1.33	1.47	1.61	1.77	7.45
Costs associated with reproductive choice	0.45	0.47	0.52	0.57	0.63	2.64
Universal, expanded DNA testing (one multi-disease panel)						
Total (all program costs)	**101.06**	**105.87**	**111.00**	**111.17**	**111.36**	**540.46**
Total (implementation costs only)	**101.06**	**105.42**	**110.53**	**110.70**	**110.89**	**537.94**
Costs of program (implementation and on-going)	0.66	0.45	0.47	0.47	0.47	2.52
Costs of screening	98.90	103.84	108.79	108.79	108.79	529.09
Costs associated with prenatal diagnostics	1.08	1.14	1.25	1.38	1.52	6.37
Costs associated with reproductive choice	0.42	0.44	0.49	0.54	0.59	2.49
Risk-based, standard DNA testing (single-disease panels)						
Total (all program costs)	**0.48**	**0.48**	**0.51**	**0.51**	**0.52**	**2.51**
Total (implementation costs only)	**0.48**	**0.25**	**0.27**	**0.27**	**0.28**	**1.55**
Costs of program (implementation and on-going)	0.24	0.23	0.24	0.24	0.24	1.20
Costs of screening	0.19	0.20	0.21	0.21	0.21	1.04
Costs associated with prenatal diagnostics	0.03	0.04	0.04	0.04	0.05	0.20
Costs associated with reproductive choice	0.01	0.01	0.01	0.02	0.02	0.08

Type of cost	Future scenario costs and budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Risk-based, expanded DNA testing (one multi-disease panel)						
Total (all program costs)	**0.75**	**0.77**	**0.80**	**0.81**	**0.81**	**3.94**
Total (implementation costs only)	**0.75**	**0.53**	**0.56**	**0.57**	**0.57**	**2.98**
Costs of program (implementation and on-going)	0.24	0.23	0.24	0.24	0.24	1.20
Costs of screening	0.48	0.50	0.52	0.52	0.52	2.55
Costs associated with prenatal diagnostics	0.02	0.02	0.03	0.03	0.03	0.13
Costs associated with reproductive choice	0.01	0.01	0.01	0.01	0.02	0.06

Note: Results may appear inexact due to rounding. Model-based output costs were estimated in simulation of the implementation costs over the first year: $4.34 (universal, standard panels), $4.33 (universal, expanded panels), $22.05 (risk-based, standard panels), $22.01 (risk-based expanded panels). Estimated model outputs for the program ongoing costs (years 2–5): $2.81 (universal, standard panels), $2.80 (universal, expanded panels), $20.05 (risk-based, standard panels), $20.02 (risk-based expanded panels)

[a]All costs are in 2022 CAD. Implementation costs are 1st year, one-time costs. On-going costs are costs for the rest of follow-up (see Appendix 9).

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A65: Budget Impact Scenario Results—Preconception Carrier Screening: Inclusion of Program Costs (Assuming Initial Cost Inputs)

	Future scenario costs and budget impact, $ million[a,b]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Universal, standard DNA testing (single-disease panels)						
Total (all program costs)	**41.56**	**43.27**	**45.43**	**45.63**	**45.85**	**221.74**
Total (implementation costs only)	**41.56**	**42.68**	**44.80**	**45.00**	**45.22**	**219.27**
Costs of program (implementation and on-going)	0.92	0.60	0.63	0.63	0.63	3.39
Costs of screening	38.93	40.87	42.82	42.82	42.82	208.27
Costs associated with prenatal diagnostics	1.27	1.33	1.47	1.61	1.77	7.45
Costs associated with reproductive choice	0.45	0.47	0.52	0.57	0.63	2.64
Universal, expanded DNA testing (one multi-disease panel)						
Total (all program costs)	**101.32**	**106.02**	**111.15**	**111.33**	**111.52**	**541.33**
Total (implementation costs only)	**101.32**	**105.42**	**110.53**	**110.70**	**110.89**	**538.86**
Costs of program (implementation and on-going)	0.92	0.60	0.63	0.63	0.63	3.39
Costs of screening	98.90	103.84	108.79	108.79	108.79	529.09
Costs associated with prenatal diagnostics	1.08	1.14	1.25	1.38	1.52	6.37
Costs associated with reproductive choice	0.42	0.44	0.49	0.54	0.59	2.49
Risk-based, standard DNA testing (single-disease panels)						
Total (all program costs)	**1.56**	**1.11**	**1.17**	**1.17**	**1.18**	**6.19**
Total (implementation costs only)	**1.56**	**0.25**	**0.27**	**0.27**	**0.28**	**2.63**
Costs of program (implementation and on-going)	1.32	0.86	0.90	0.90	0.90	4.88
Costs of screening	0.19	0.20	0.21	0.21	0.21	1.04
Costs associated with prenatal diagnostics	0.03	0.04	0.04	0.04	0.05	0.20
Costs associated with reproductive choice	0.01	0.01	0.01	0.02	0.02	0.08

Type of cost	Future scenario costs and budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Risk-based, expanded DNA testing (one multi-disease panel)						
Total (all program costs)	**1.83**	**1.39**	**1.46**	**1.47**	**1.47**	**7.62**
Total (implementation costs only)	**1.83**	**0.53**	**0.56**	**0.57**	**0.57**	**4.06**
Costs of program (implementation and on-going)	1.32	0.86	0.90	0.90	0.90	4.88
Costs of screening	0.48	0.50	0.52	0.52	0.52	2.55
Costs associated with prenatal diagnostics	0.02	0.02	0.03	0.03	0.03	0.13
Costs associated with reproductive choice	0.01	0.01	0.01	0.01	0.02	0.06

Note: Results may appear inexact due to rounding. Input costs presented in Appendix 9.

[a]All costs are in 2022 CAD. Implementation costs are 1st year, one-time costs. On-going costs are costs for the rest of follow-up. Total program costs (all program costs) include both implementation and on-going costs (see Appendix 9 for the cost inputs).

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A66A: Budget Impact Scenario Results—Preconception Carrier Screening: Inclusion of All Program Costs (Model-Based Cost Outputs) and Full Coverage of IVF/PGT-M

Type of cost	Future scenario costs and budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Universal, standard DNA testing (single-disease panels)						
Total	**43.10**	**45.01**	**47.35**	**47.75**	**48.20**	**231.41**
Costs of program (implementation and on-going)	0.66	0.45	0.47	0.47	0.47	2.52
Costs of screening	38.93	40.87	42.82	42.82	42.82	208.27
Costs associated with prenatal diagnostics	1.27	1.33	1.47	1.61	1.77	7.45
Costs associated with reproductive choice	2.24	2.35	2.59	2.85	3.13	13.17
Universal, expanded DNA testing (one multi-disease panel)						
Total	**102.59**	**107.47**	**112.76**	**113.11**	**113.49**	**549.41**
Costs of program (implementation and on-going)	0.66	0.45	0.47	0.47	0.47	2.52
Costs of screening	98.90	103.84	108.79	108.79	108.79	529.09
Costs associated with prenatal diagnostics	1.08	1.14	1.25	1.38	1.52	6.37
Costs associated with reproductive choice	1.95	2.04	2.25	2.47	2.72	11.44
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.53**	**0.53**	**0.56**	**0.57**	**0.58**	**2.78**
Costs of program (implementation and on-going)	0.24	0.23	0.24	0.24	0.24	1.20
Costs of screening	0.19	0.20	0.21	0.21	0.21	1.04
Costs associated with prenatal diagnostics	0.03	0.04	0.04	0.04	0.05	0.20
Costs associated with reproductive choice	0.06	0.06	0.07	0.08	0.08	0.35
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.78**	**0.80**	**0.84**	**0.85**	**0.85**	**4.12**
Costs of program (implementation and on-going)	0.24	0.23	0.24	0.24	0.24	1.20
Costs of screening	0.48	0.50	0.52	0.52	0.52	2.55
Costs associated with prenatal diagnostics	0.02	0.02	0.03	0.03	0.03	0.13
Costs associated with reproductive choice	0.04	0.04	0.05	0.05	0.06	0.24

Abbreviation: IVF/PGT-M, in-vitro fertilization with preimplantation genetic testing.

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A66B: Budget Impact Scenario Results—Preconception Carrier Screening: Inclusion of Implementation Program Costs and Full Coverage of IVF/PGT

Future scenario costs and budget impact, $ million[a,b]						
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Universal, standard DNA testing (single-disease panels)						
Total	**43.10**	**44.56**	**46.88**	**47.28**	**47.73**	**229.55**
Costs of program (implementation)	0.66	0.00	0.00	0.00	0.00	0.66
Costs of screening	38.93	40.87	42.82	42.82	42.82	208.27
Costs associated with prenatal diagnostics	1.27	1.33	1.47	1.61	1.77	7.45
Costs associated with reproductive choice	2.24	2.35	2.59	2.85	3.13	13.17
Universal, expanded DNA testing (one multi-disease panel)						
Total	**102.59**	**107.02**	**112.29**	**112.64**	**113.02**	**547.56**
Costs of program (implementation)	0.66	0.00	0.00	0.00	0.00	0.66
Costs of screening	98.90	103.84	108.79	108.79	108.79	529.09
Costs associated with prenatal diagnostics	1.08	1.14	1.25	1.38	1.52	6.37
Costs associated with reproductive choice	1.95	2.04	2.25	2.47	2.72	11.44
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.53**	**0.30**	**0.32**	**0.33**	**0.34**	**1.82**
Costs of program (implementation)	0.24	0.00	0.00	0.00	0.00	0.24
Costs of screening	0.19	0.20	0.21	0.21	0.21	1.04
Costs associated with prenatal diagnostics	0.03	0.04	0.04	0.04	0.05	0.20
Costs associated with reproductive choice	0.06	0.06	0.07	0.08	0.08	0.35
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.78**	**0.57**	**0.60**	**0.60**	**0.61**	**3.16**
Costs of program (implementation)	0.24	0.00	0.00	0.00	0.00	0.24
Costs of screening	0.48	0.50	0.52	0.52	0.52	2.55
Costs associated with prenatal diagnostics	0.02	0.02	0.03	0.03	0.03	0.13
Costs associated with reproductive choice	0.04	0.04	0.05	0.05	0.06	0.24

Abbreviation: IVF/PGT, in-vitro fertilization with preimplantation genetic testing.

Note: Results may appear inexact due to rounding. Implementation costs are 1st year, one-time costs.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A67: Budget Impact Scenario Results—Preconception Carrier Screening, Summary: Long-Term Scenario Including Treatment Costs (Supportive Therapies) and Program Costs (Implementation and On-Going)

	Budget impact, $ million[a]					
Table summary	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Table A68A: universal, standard DNA testing (single-disease panels)						
Total	**39.10**	**36.65**	**34.89**	**31.36**	**27.80**	**169.81**
Costs of screening, PND and choice (e.g., IVF)	40.65	42.68	44.80	45.00	45.22	218.35
Costs of treatment	-2.21	-6.48	-10.38	-14.11	-17.89	-51.07
Costs of program	0.66	0.45	0.47	0.47	0.47	2.52
Table A68B: universal, expanded DNA testing (one multi-disease panel)						
Total	**98.78**	**99.16**	**100.16**	**96.33**	**92.47**	**486.90**
Costs of screening, PND and choice (e.g., IVF)	100.40	105.42	110.53	110.70	110.89	537.94
Costs of treatment	-2.29	-6.71	-10.83	-14.84	-18.89	-53.56
Costs of program	0.66	0.45	0.47	0.47	0.47	2.52
Table A68C: risk-based, standard DNA testing (single-disease panels)						
Total	**0.21**	**-0.34**	**-0.83**	**-1.31**	**-1.78**	**-4.04**
Costs of screening, PND and choice (e.g., IVF)	0.24	0.25	0.27	0.27	0.28	1.31
Costs of treatment	-0.27	-0.82	-1.34	-1.82	-2.30	-6.55
Costs of program	0.24	0.23	0.24	0.24	0.24	1.20
Table A68C: risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.48**	**-0.05**	**-0.53**	**-1.01**	**-1.47**	**-2.58**
Costs of screening, PND and choice (e.g., IVF)	0.51	0.53	0.56	0.57	0.57	2.74
Costs of treatment	-0.27	-0.82	-1.34	-1.81	-2.29	-6.52
Costs of program	0.24	0.23	0.24	0.24	0.24	1.20

Abbreviations: IVF, in-vitro fertilization; PND, prenatal diagnostic testing.

Note: Results may appear inexact due to rounding. Implementation costs are 1st year, one-time costs. On-going costs are costs for the rest of follow-up. Total program costs (all program costs) include both implementation and on-going costs (see Appendix 9 for cost inputs).

[a]All costs are in 2022 CAD. Negative costs indicate savings.

Table A68A: Long-Term Scenario, Budget Impact Results by Strategy—Preconception Universal Screening With Standard Panels (Supportive Therapies)

	Total costs and budget impact, $ million[a]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current scenario						
Total	**5.34**	**16.02**	**26.18**	**35.81**	**45.45**	**128.81**
Costs of screening, PND and choice (e.g., IVF)	0.00	0.00	0.00	0.00	0.00	0.00
Costs of treatment	5.34	16.02	26.18	35.81	45.45	128.81
Costs of program	0.00	0.00	0.00	0.00	0.00	0.00
New scenario (universal, standard panels)						
Total	**44.44**	**52.68**	**61.07**	**67.18**	**73.25**	**298.61**
Costs of screening, PND and choice (e.g., IVF)	40.65	42.68	44.80	45.00	45.22	218.35
Costs of treatment	3.13	9.55	15.80	21.70	27.56	77.74
Costs of program	0.66	0.45	0.47	0.47	0.47	2.52
Budget impact (universal, standard panels)						
Total	**39.10**	**36.65**	**34.89**	**31.36**	**27.80**	**169.81**
Screening, PND and choice (e.g., IVF)	40.65	42.68	44.80	45.00	45.22	218.35
Treatment	-2.21	-6.48	-10.38	-14.11	-17.89	-51.07
Program	0.66	0.45	0.47	0.47	0.47	2.52

Abbreviations: IVF, in-vitro fertilization; PND, prenatal diagnostic testing.

Note: Results may appear inexact due to rounding. Costs expressed in 2022 CAD.

[a]Budget impact: New scenario minus the current scenario. Negative costs indicate savings.

Table A68B: Long-Term Scenario Budget Impact Results by Strategy—Preconception Universal Screening With Expanded Panel (Supportive Therapies)

	Total costs and budget impact, $ million[a]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current scenario						
Total	**5.34**	**16.02**	**26.18**	**35.81**	**45.45**	**128.81**
Costs of screening, PND and choice (e.g., IVF)	0.00	0.00	0.00	0.00	0.00	0.00
Costs of treatment	5.34	16.02	26.18	35.81	45.45	128.81
Costs of program	0.00	0.00	0.00	0.00	0.00	0.00
New scenario (universal, standard panels)						
Total	**104.12**	**115.19**	**126.35**	**132.15**	**137.91**	**615.71**
Costs of screening, PND and choice (e.g., IVF)	100.40	105.42	110.53	110.70	110.89	537.94
Costs of treatment	3.05	9.32	15.35	20.98	26.55	75.25
Costs of program	0.66	0.45	0.47	0.47	0.47	2.52
Budget impact (universal, standard panels)						
Total	**98.78**	**99.16**	**100.16**	**96.33**	**92.47**	**486.90**
Screening, PND and choice (e.g., IVF)	100.40	105.42	110.53	110.70	110.89	537.94
Treatment	-2.29	-6.71	-10.83	-14.84	-18.89	-53.56
Program	0.66	0.45	0.47	0.47	0.47	2.52

Abbreviations: IVF, in-vitro fertilization; PND, prenatal diagnostic testing.

Note: Results may appear inexact due to rounding. Costs expressed in 2022 CAD.

[a]Budget impact: New scenario minus the current scenario. Negative costs indicate savings.

Table A68C: Long-Term Scenario Budget Impact Results by Strategy—Preconception Risk-Based Screening With Standard Panels (Supportive Therapies)

	Total costs and budget impact, $ million[a]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current scenario						
Total	**5.34**	**16.02**	**26.18**	**35.81**	**45.45**	**128.81**
Costs of screening, PND and choice (e.g., IVF)	0.00	0.00	0.00	0.00	0.00	0.00
Costs of treatment	5.34	16.02	26.18	35.81	45.45	128.81
Costs of program	0.00	0.00	0.00	0.00	0.00	0.00
New scenario (universal, standard panels)						
Total	**5.56**	**15.69**	**25.35**	**34.50**	**43.67**	**124.76**
Costs of screening, PND and choice (e.g., IVF)	0.24	0.25	0.27	0.27	0.28	1.31
Costs of treatment	5.07	15.21	24.84	33.99	43.15	122.26
Costs of program	0.24	0.23	0.24	0.24	0.24	1.20
Budget impact (universal, standard panels)						
Total	**0.21**	**-0.34**	**-0.83**	**-1.31**	**-1.78**	**-4.04**
Screening, PND and choice (e.g., IVF)	0.24	0.25	0.27	0.27	0.28	1.31
Treatment	-0.27	-0.82	-1.34	-1.82	-2.30	-6.55
Program	0.24	0.23	0.24	0.24	0.24	1.20

Abbreviations: IVF, in-vitro fertilization; PND, prenatal diagnostic testing.

Note: Results may appear inexact due to rounding. Costs expressed in 2022 CAD.

[a]Budget impact: New scenario minus the current scenario. Negative costs indicate savings.

Table A68D: Long-Term Scenario Budget Impact Results by Strategy—Preconception Risk-Based Screening With Expanded Panels (Supportive Therapies)

	Total costs and budget impact, $ million[a]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current scenario						
Total	**5.34**	**16.02**	**26.18**	**35.81**	**45.45**	**128.81**
Costs of screening, PND and choice (e.g., IVF)	0.00	0.00	0.00	0.00	0.00	0.00
Costs of treatment	5.34	16.02	26.18	35.81	45.45	128.81
Costs of program	0.00	0.00	0.00	0.00	0.00	0.00
New scenario (universal, standard panels)						
Total	**5.82**	**15.97**	**25.65**	**34.81**	**43.97**	**126.23**
Costs of screening, PND and choice (e.g., IVF)	0.51	0.53	0.56	0.57	0.57	2.74
Costs of treatment	5.07	15.21	24.85	34.00	43.16	122.29
Costs of program	0.24	0.23	0.24	0.24	0.24	1.20
Budget impact (universal, standard panels)						
Total	**0.48**	**-0.05**	**-0.53**	**-1.01**	**-1.47**	**-2.58**
Screening, PND and choice (e.g., IVF)	0.51	0.53	0.56	0.57	0.57	2.74
Treatment	-0.27	-0.82	-1.34	-1.81	-2.29	-6.52
Program	0.24	0.23	0.24	0.24	0.24	1.20

Abbreviations: IVF, in-vitro fertilization; PND, prenatal diagnostic testing.

Note: Results may appear inexact due to rounding. Costs expressed in 2022 CAD.

[a]Budget impact: New scenario minus the current scenario. Negative costs indicate savings.

Table A69: Budget Impact Scenario Results—Preconception Carrier Screening, Summary: Long-Term Scenario Including Treatment Costs (Novel and Supportive Therapies) and Program Costs (Implementation and On-Going)

	Budget impact, $ million[a]					
Table summary	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Table A70A: universal, standard DNA testing (single-disease panels)						
Total	**37.23**	**32.35**	**29.55**	**24.94**	**19.98**	**144.04**
Costs of screening, PND and choice (e.g., IVF)	40.65	42.68	44.80	45.00	45.22	218.35
Costs of treatment	-4.07	-10.78	-15.73	-20.54	-25.71	-76.83
Costs of program	0.66	0.45	0.47	0.47	0.47	2.52
Table A70B: universal, expanded DNA testing (one multi-disease panel)						
Total	**97.23**	**95.65**	**95.98**	**91.49**	**86.65**	**467.00**
Costs of screening, PND and choice (e.g., IVF)	100.40	105.42	110.53	110.70	110.89	537.94
Costs of treatment	-3.83	-10.22	-15.02	-19.68	-24.71	-73.46
Costs of program	0.66	0.45	0.47	0.47	0.47	2.52
Table A70C: risk-based, standard DNA testing (single-disease panels)						
Total	**-0.46**	**-2.04**	**-3.32**	**-4.62**	**-5.91**	**-16.36**
Costs of screening, PND and choice (e.g., IVF)	0.24	0.25	0.27	0.27	0.28	1.31
Costs of treatment	-0.95	-2.53	-3.83	-5.14	-6.43	-18.86
Costs of program	0.24	0.23	0.24	0.24	0.24	1.20
Table A70D: risk-based, expanded DNA testing (one multi-disease panel)						
Total	**-0.19**	**-1.76**	**-3.02**	**-4.32**	**-5.61**	**-14.90**
Costs of screening, PND and choice (e.g., IVF)	0.51	0.53	0.56	0.57	0.57	2.74
Costs of treatment	-0.94	-2.52	-3.82	-5.13	-6.42	-18.83
Costs of program	0.24	0.23	0.24	0.24	0.24	1.20

Abbreviations: IVF, in-vitro fertilization; PND, prenatal diagnostic testing.

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD. Negative costs indicate savings.

Table A70A: Long-Term Scenario BIA Results by Strategy - Preconception Universal Screening with Standard Panels (Novel Therapies)

	Total costs and budget impact, $ million[a]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current scenario						
Total	**13.95**	**37.36**	**56.28**	**75.20**	**94.12**	**276.91**
Costs of screening, PND and choice (e.g., IVF)	0.00	0.00	0.00	0.00	0.00	0.00
Costs of treatment	13.95	37.36	56.28	75.20	94.12	276.91
Costs of program	0.00	0.00	0.00	0.00	0.00	0.00
New scenario (universal, standard panels)						
Total	**51.18**	**69.70**	**85.83**	**100.14**	**114.10**	**420.95**
Costs of screening, PND and choice (e.g., IVF)	40.65	42.68	44.80	45.00	45.22	218.35
Costs of treatment	9.87	26.58	40.55	54.66	68.41	200.07
Costs of program	0.66	0.45	0.47	0.47	0.47	2.52
Budget impact (universal, standard panels)						
Total	**37.23**	**32.35**	**29.55**	**24.94**	**19.98**	**144.04**
Screening, PND and choice (e.g., IVF)	40.65	42.68	44.80	45.00	45.22	218.35
Treatment	-4.07	-10.78	-15.73	-20.54	-25.71	-76.83
Program	0.66	0.45	0.47	0.47	0.47	2.52

Abbreviations: IVF, in-vitro fertilization; PND, prenatal diagnostic testing.

Note: Results may appear inexact due to rounding. Costs expressed in 2022 CAD.

[a]Budget impact: New scenario minus the current scenario. Negative costs indicate savings.

Table A70B: Long-Term Scenario BIA Results by Strategy—Preconception Universal Screening With Expanded Panel (Novel Therapies)

	Total costs and budget impact, $ million[a]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current scenario						
Total	**13.95**	**37.36**	**56.28**	**75.20**	**94.12**	**276.91**
Costs of screening, PND and choice (e.g., IVF)	0.00	0.00	0.00	0.00	0.00	0.00
Costs of treatment	13.95	37.36	56.28	75.20	94.12	276.91
Costs of program	0.00	0.00	0.00	0.00	0.00	0.00
New scenario (universal, standard panels)						
Total	**111.18**	**133.01**	**152.26**	**166.69**	**180.77**	**743.90**
Costs of screening, PND and choice (e.g., IVF)	100.40	105.42	110.53	110.70	110.89	537.94
Costs of treatment	10.12	27.13	41.26	55.52	69.41	203.44
Costs of program	0.66	0.45	0.47	0.47	0.47	2.52
Budget impact (universal, standard panels)						
Total	**97.23**	**95.65**	**95.98**	**91.49**	**86.65**	**467.00**
Screening, PND and choice (e.g., IVF)	100.40	105.42	110.53	110.70	110.89	537.94
Treatment	-3.83	-10.22	-15.02	-19.68	-24.71	-73.46
Program	0.66	0.45	0.47	0.47	0.47	2.52

Abbreviations: IVF, in-vitro fertilization; PND, prenatal diagnostic testing.

Note: Results may appear inexact due to rounding. Costs expressed in 2022 CAD.

[a]Budget impact: New scenario minus the current scenario. Negative costs indicate savings.

Table A70C: Long-Term Scenario BIA Results by Strategy—Preconception Risk-Based Screening With Standard Panels (Novel Therapies)

	Total costs and budget impact, $ million[a]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current scenario						
Total	**13.95**	**37.36**	**56.28**	**75.20**	**94.12**	**276.91**
Costs of screening, PND and choice (e.g., IVF)	0.00	0.00	0.00	0.00	0.00	0.00
Costs of treatment	13.95	37.36	56.28	75.20	94.12	276.91
Costs of program	0.00	0.00	0.00	0.00	0.00	0.00
New scenario (universal, standard panels)						
Total	**13.48**	**35.31**	**52.96**	**70.58**	**88.21**	**260.55**
Costs of screening, PND and choice (e.g., IVF)	0.24	0.25	0.27	0.27	0.28	1.31
Costs of treatment	13.00	34.83	52.45	70.06	87.69	258.04
Costs of program	0.24	0.23	0.24	0.24	0.24	1.20
Budget impact (universal, standard panels)						
Total	**-0.46**	**-2.04**	**-3.32**	**-4.62**	**-5.91**	**-16.36**
Screening, PND and choice (e.g., IVF)	0.24	0.25	0.27	0.27	0.28	1.31
Treatment	-0.95	-2.53	-3.83	-5.14	-6.43	-18.86
Program	0.24	0.23	0.24	0.24	0.24	1.20

Abbreviations: IVF, in-vitro fertilization; PND, prenatal diagnostic testing.

Note: Results may appear inexact due to rounding. Costs expressed in 2022 CAD.

[a]Budget impact: New scenario minus the current scenario. Negative costs indicate savings.

Table A70D: Long-Term Scenario BIA Results by Strategy—Preconception Risk-Based Screening With Expanded Panels (Novel Therapies)

	Total costs and budget impact, $ million[a]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current scenario						
Total	**13.95**	**37.36**	**56.28**	**75.20**	**94.12**	**276.91**
Costs of screening, PND and choice (e.g., IVF)	0.00	0.00	0.00	0.00	0.00	0.00
Costs of treatment	13.95	37.36	56.28	75.20	94.12	276.91
Costs of program	0.00	0.00	0.00	0.00	0.00	0.00
New scenario (universal, standard panels)						
Total	**13.75**	**35.60**	**53.26**	**70.88**	**88.51**	**262.01**
Costs of screening, PND and choice (e.g., IVF)	0.51	0.53	0.56	0.57	0.57	2.74
Costs of treatment	13.00	34.83	52.46	70.07	87.70	258.07
Costs of program	0.24	0.23	0.24	0.24	0.24	1.20
Budget impact (universal, standard panels)						
Total	**-0.19**	**-1.76**	**-3.02**	**-4.32**	**-5.61**	**-14.90**
Screening, PND and choice (e.g., IVF)	0.51	0.53	0.56	0.57	0.57	2.74
Treatment	-0.94	-2.52	-3.82	-5.13	-6.42	-18.83
Program	0.24	0.23	0.24	0.24	0.24	1.20

Abbreviations: BIA, budget impact analysis; IVF, in-vitro fertilization; PND, prenatal diagnostic testing.

Note: Results may appear inexact due to rounding. Costs expressed in 2022 CAD.

[a]Budget impact: New scenario minus the current scenario. Negative costs indicate savings.

Appendix 23: Results of Budget Impact Scenarios, Prenatal Carrier Screening Programs

Table A71: Budget Impact Scenario Results—Participation (Uptake) in Prenatal Carrier Screening: 20%

	Future scenario costs and budget impact, $ million[a,b]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Universal, standard DNA testing (single-disease panels)						
Total	**1.90**	**1.99**	**2.09**	**2.10**	**2.10**	**10.18**
Costs of screening	1.87	1.96	2.05	2.05	2.05	9.99
Costs associated with prenatal diagnostics	0.03	0.03	0.03	0.04	0.04	0.17
Costs associated with reproductive choice	0.00	0.00	0.00	0.01	0.01	0.02
Universal, expanded DNA testing (one multi-disease panel)						
Total	**4.56**	**4.79**	**5.02**	**5.02**	**5.03**	**24.43**
Costs of screening	4.54	4.77	4.99	4.99	4.99	24.29
Costs associated with prenatal diagnostics	0.02	0.02	0.02	0.03	0.03	0.12
Costs associated with reproductive choice	0.00	0.00	0.01	0.01	0.01	0.03
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.011**	**0.011**	**0.012**	**0.012**	**0.012**	**0.058**
Costs of screening	0.009	0.010	0.010	0.010	0.010	0.050
Costs associated with prenatal diagnostics	0.001	0.001	0.001	0.002	0.002	0.007
Costs associated with reproductive choice	0.000	0.000	0.000	0.000	0.000	0.001
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.024**	**0.025**	**0.026**	**0.026**	**0.026**	**0.127**
Costs of screening	0.023	0.024	0.025	0.025	0.025	0.122
Costs associated with prenatal diagnostics	0.001	0.001	0.001	0.001	0.001	0.004
Costs associated with reproductive choice	0.000	0.000	0.000	0.000	0.000	0.001

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A72: Budget Impact Scenario Results—Participation (Uptake) in Prenatal Carrier Screening: 35%

Type of cost	Future scenario costs and budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Universal, standard DNA testing (single-disease panels)						
Total	**5.93**	**6.23**	**6.54**	**6.55**	**6.57**	**31.82**
Costs of screening	5.80	6.09	6.38	6.38	6.38	31.02
Costs associated with prenatal diagnostics	0.12	0.12	0.14	0.15	0.16	0.69
Costs associated with reproductive choice	0.02	0.02	0.02	0.02	0.02	0.10
Universal, expanded DNA testing (one multi-disease panel)						
Total	**14.22**	**14.93**	**15.65**	**15.66**	**15.67**	**76.13**
Costs of screening	14.11	14.81	15.52	15.52	15.52	75.48
Costs associated with prenatal diagnostics	0.09	0.10	0.11	0.12	0.13	0.54
Costs associated with reproductive choice	0.02	0.02	0.02	0.02	0.03	0.11
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.03**	**0.04**	**0.04**	**0.04**	**0.04**	**0.18**
Costs of screening	0.03	0.03	0.03	0.03	0.03	0.16
Costs associated with prenatal diagnostics	0.004	0.004	0.005	0.005	0.006	0.024
Costs associated with reproductive choice	0.001	0.001	0.001	0.001	0.001	0.004
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.07**	**0.08**	**0.08**	**0.08**	**0.08**	**0.40**
Costs of screening	0.07	0.07	0.08	0.08	0.08	0.38
Costs associated with prenatal diagnostics	0.002	0.002	0.003	0.003	0.003	0.014
Costs associated with reproductive choice	0.001	0.001	0.001	0.001	0.001	0.004

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A73: Budget Impact Scenario Results—Participation (Uptake) in Prenatal Carrier Screening: 50%

Type of cost	Future scenario costs and budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Universal, standard DNA testing (single-disease panels)						
Total	**8.60**	**9.03**	**9.47**	**9.50**	**9.52**	**46.13**
Costs of screening	8.41	8.83	9.25	9.25	9.25	44.99
Costs associated with prenatal diagnostics	0.17	0.18	0.19	0.21	0.24	0.99
Costs associated with reproductive choice	0.02	0.03	0.03	0.03	0.03	0.15
Universal, expanded DNA testing (one multi-disease panel)						
Total	**20.62**	**21.65**	**22.69**	**22.71**	**22.73**	**110.39**
Costs of screening	20.46	21.48	22.51	22.51	22.51	109.47
Costs associated with prenatal diagnostics	0.13	0.14	0.15	0.17	0.18	0.77
Costs associated with reproductive choice	0.03	0.03	0.03	0.03	0.04	0.16
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.05**	**0.05**	**0.05**	**0.06**	**0.06**	**0.27**
Costs of screening	0.04	0.04	0.05	0.05	0.05	0.23
Costs associated with prenatal diagnostics	0.01	0.01	0.01	0.01	0.01	0.03
Costs associated with reproductive choice	0.00	0.00	0.00	0.00	0.00	0.01
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.11**	**0.11**	**0.12**	**0.12**	**0.12**	**0.58**
Costs of screening	0.10	0.11	0.11	0.11	0.11	0.55
Costs associated with prenatal diagnostics	0.00	0.00	0.00	0.00	0.00	0.02
Costs associated with reproductive choice	0.00	0.00	0.00	0.00	0.00	0.01

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A74: Budget Impact Scenario Results—Participation (Uptake) in Prenatal Carrier Screening: 100%

Type of cost	Future scenario costs and budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Universal, standard DNA testing (single-disease panels)						
Total	**52.51**	**52.51**	**52.51**	**52.51**	**52.51**	**262.57**
Costs of screening	50.12	50.12	50.12	50.12	50.12	250.60
Costs associated with prenatal diagnostics	2.09	2.09	2.09	2.09	2.09	10.44
Costs associated with reproductive choice	0.31	0.31	0.31	0.31	0.31	1.53
Universal, expanded DNA testing (one multi-disease panel)						
Total	**124.56**	**124.56**	**124.56**	**124.56**	**124.56**	**622.79**
Costs of screening	122.38	122.38	122.38	122.38	122.38	611.91
Costs associated with prenatal diagnostics	1.84	1.84	1.84	1.84	1.84	9.22
Costs associated with reproductive choice	0.33	0.33	0.33	0.33	0.33	1.66
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.31**	**0.33**	**0.35**	**0.35**	**0.36**	**1.69**
Costs of screening	0.25	0.27	0.28	0.28	0.28	1.35
Costs associated with prenatal diagnostics	0.05	0.05	0.06	0.06	0.07	0.29
Costs associated with reproductive choice	0.01	0.01	0.01	0.01	0.01	0.06
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.66**	**0.69**	**0.73**	**0.73**	**0.74**	**3.55**
Costs of screening	0.62	0.65	0.68	0.68	0.68	3.29
Costs associated with prenatal diagnostics	0.03	0.04	0.04	0.04	0.05	0.20
Costs associated with reproductive choice	0.01	0.01	0.01	0.01	0.01	0.06

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A75: Budget Impact Scenario Results—Prenatal Carrier Screening: Carrier Frequency Decreased by Half

Type of cost	Future scenario costs and budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Universal, standard DNA testing (single-disease panels)						
Total	**23.37**	**24.54**	**25.73**	**25.77**	**25.82**	**125.22**
Costs of screening	22.99	24.14	25.29	25.29	25.29	123.00
Costs associated with prenatal diagnostics	0.35	0.36	0.40	0.44	0.48	2.03
Costs associated with reproductive choice	0.03	0.03	0.04	0.04	0.05	0.19
Universal, expanded DNA testing (one multi-disease panel)						
Total	**56.42**	**59.24**	**62.08**	**62.10**	**62.13**	**301.98**
Costs of screening	56.20	59.01	61.82	61.82	61.82	300.68
Costs associated with prenatal diagnostics	0.19	0.20	0.21	0.24	0.26	1.09
Costs associated with reproductive choice	0.03	0.04	0.04	0.04	0.05	0.20
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.13**	**0.14**	**0.15**	**0.15**	**0.15**	**0.72**
Costs of screening	0.12	0.13	0.13	0.13	0.13	0.65
Costs associated with prenatal diagnostics	0.012	0.013	0.014	0.015	0.017	0.070
Costs associated with reproductive choice	0.001	0.001	0.002	0.002	0.002	0.008
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.30**	**0.32**	**0.33**	**0.33**	**0.33**	**1.61**
Costs of screening	0.29	0.31	0.32	0.32	0.32	1.57
Costs associated with prenatal diagnostics	0.005	0.005	0.005	0.006	0.007	0.028
Costs associated with reproductive choice	0.001	0.001	0.002	0.002	0.002	0.008

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A76: Budget Impact Scenario Results—Prenatal Carrier Screening: Carrier Frequency Doubled

Type of cost	Future scenario costs and budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Universal, standard DNA testing (single-disease panels)						
Total	**25.07**	**26.32**	**27.67**	**27.87**	**28.10**	**135.02**
Costs of screening	23.31	24.48	25.64	25.64	25.64	124.72
Costs associated with prenatal diagnostics	1.47	1.55	1.70	1.87	2.06	8.66
Costs associated with reproductive choice	0.28	0.29	0.32	0.35	0.39	1.64
Universal, expanded DNA testing (one multi-disease panel)						
Total	**58.32**	**61.24**	**64.25**	**64.46**	**64.68**	**312.95**
Costs of screening	56.56	59.39	62.22	62.22	62.22	302.62
Costs associated with prenatal diagnostics	1.46	1.53	1.68	1.85	2.04	8.55
Costs associated with reproductive choice	0.30	0.32	0.35	0.39	0.42	1.78
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.17**	**0.18**	**0.19**	**0.20**	**0.20**	**0.94**
Costs of screening	0.12	0.13	0.13	0.13	0.13	0.66
Costs associated with prenatal diagnostics	0.04	0.04	0.04	0.05	0.05	0.23
Costs associated with reproductive choice	0.01	0.01	0.01	0.01	0.01	0.06
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.34**	**0.36**	**0.38**	**0.38**	**0.39**	**1.85**
Costs of screening	0.30	0.31	0.33	0.33	0.33	1.59
Costs associated with prenatal diagnostics	0.03	0.04	0.04	0.04	0.05	0.20
Costs associated with reproductive choice	0.01	0.01	0.01	0.01	0.02	0.06

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A77: Budget Impact Scenario Results—Prenatal Carrier Screening: Panel Costs Decreased by Half

Type of cost	Future scenario costs and budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Universal, standard DNA testing (single-disease panels)						
Total	**18.38**	**19.30**	**20.26**	**20.35**	**20.46**	**98.74**
Costs of screening	17.56	18.43	19.31	19.31	19.31	93.93
Costs associated with prenatal diagnostics	0.72	0.75	0.83	0.91	1.00	4.20
Costs associated with reproductive choice	0.10	0.11	0.12	0.13	0.15	0.62
Universal, expanded DNA testing (one multi-disease panel)						
Total	**34.89**	**36.63**	**38.42**	**38.50**	**38.59**	**187.02**
Costs of screening	34.16	35.87	37.58	37.58	37.58	182.78
Costs associated with prenatal diagnostics	0.61	0.64	0.70	0.77	0.85	3.58
Costs associated with reproductive choice	0.11	0.12	0.13	0.14	0.16	0.67
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.12**	**0.12**	**0.13**	**0.13**	**0.13**	**0.63**
Costs of screening	0.09	0.10	0.10	0.10	0.10	0.49
Costs associated with prenatal diagnostics	0.019	0.020	0.022	0.024	0.027	0.112
Costs associated with reproductive choice	0.004	0.004	0.004	0.004	0.005	0.021
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.20**	**0.21**	**0.22**	**0.22**	**0.22**	**1.06**
Costs of screening	0.18	0.19	0.20	0.20	0.20	0.96
Costs associated with prenatal diagnostics	0.013	0.013	0.015	0.016	0.018	0.074
Costs associated with reproductive choice	0.004	0.004	0.004	0.005	0.005	0.022

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A78: Budget Impact Scenario Results—Prenatal Carrier Screening: A Hypothetical Expanded Panel, Costs Decreased by 80% (~$130)

	Future scenario costs and budget impact, $ million[a,b]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Universal, standard DNA testing (single-disease panels)						
Total	**23.93**	**25.12**	**26.37**	**26.46**	**26.56**	**128.44**
Costs of screening	23.11	24.26	25.42	25.42	25.42	123.63
Costs associated with prenatal diagnostics	0.72	0.75	0.83	0.91	1.00	4.20
Costs associated with reproductive choice	0.10	0.11	0.12	0.13	0.15	0.62
Universal, expanded DNA testing (one multi-disease panel)						
Total	**21.58**	**22.66**	**23.78**	**23.87**	**23.96**	**115.86**
Costs of screening	20.86	21.90	22.95	22.95	22.95	111.61
Costs associated with prenatal diagnostics	0.61	0.64	0.70	0.77	0.85	3.58
Costs associated with reproductive choice	0.11	0.12	0.13	0.14	0.16	0.67
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.14**	**0.15**	**0.16**	**0.16**	**0.17**	**0.78**
Costs of screening	0.12	0.13	0.13	0.13	0.13	0.65
Costs associated with prenatal diagnostics	0.019	0.020	0.022	0.024	0.027	0.112
Costs associated with reproductive choice	0.004	0.004	0.004	0.004	0.005	0.021
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.13**	**0.13**	**0.14**	**0.14**	**0.14**	**0.68**
Costs of screening	0.11	0.12	0.12	0.12	0.12	0.59
Costs associated with prenatal diagnostics	0.013	0.013	0.015	0.016	0.018	0.074
Costs associated with reproductive choice	0.004	0.004	0.004	0.005	0.005	0.022

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A79: Budget Impact Scenario Results—Prenatal Carrier Screening: Screening Care Pathway, Reducing Encounters (Visits) With a Genetic Counsellor

	Future scenario costs and budget impact, $ million[a,b]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Universal, standard DNA testing (single-disease panels)						
Total	**19.46**	**20.44**	**21.46**	**21.55**	**21.65**	**104.56**
Costs of screening	18.64	19.58	20.51	20.51	20.51	99.75
Costs associated with prenatal diagnostics	0.72	0.75	0.83	0.91	1.00	4.20
Costs associated with reproductive choice	0.10	0.11	0.12	0.13	0.15	0.62
Universal, expanded DNA testing (one multi-disease panel)						
Total	**56.73**	**59.56**	**62.44**	**62.52**	**62.61**	**303.86**
Costs of screening	56.00	58.80	61.60	61.60	61.60	299.62
Costs associated with prenatal diagnostics	0.61	0.64	0.70	0.77	0.85	3.58
Costs associated with reproductive choice	0.11	0.12	0.13	0.14	0.16	0.67
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.12**	**0.12**	**0.13**	**0.13**	**0.14**	**0.64**
Costs of screening	0.09	0.10	0.10	0.10	0.10	0.50
Costs associated with prenatal diagnostics	0.02	0.02	0.02	0.02	0.03	0.11
Costs associated with reproductive choice	0.004	0.004	0.004	0.004	0.005	0.021
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.29**	**0.30**	**0.32**	**0.32**	**0.32**	**1.56**
Costs of screening	0.27	0.29	0.30	0.30	0.30	1.47
Costs associated with prenatal diagnostics	0.01	0.01	0.01	0.02	0.02	0.07
Costs associated with reproductive choice	0.004	0.004	0.004	0.005	0.005	0.022

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 Canadian dollars. Screening care pathway described in Scenario 2 (see Appendix 8).

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A80: Budget Impact Scenario Results—Prenatal Carrier Screening: Screening Care Pathway, Reducing Encounters (Visits) With a Primary Care Physician

Type of cost	Future scenario costs and budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Universal, standard DNA testing (single-disease panels)						
Total	**22.65**	**23.78**	**24.96**	**25.05**	**25.15**	**121.58**
Costs of screening	21.83	22.92	24.01	24.01	24.01	116.76
Costs associated with prenatal diagnostics	0.72	0.75	0.83	0.91	1.00	4.20
Costs associated with reproductive choice	0.10	0.11	0.12	0.13	0.15	0.62
Universal, expanded DNA testing (one multi-disease panel)						
Total	**59.90**	**62.89**	**65.93**	**66.01**	**66.10**	**320.83**
Costs of screening	59.17	62.13	65.09	65.09	65.09	316.59
Costs associated with prenatal diagnostics	0.61	0.64	0.70	0.77	0.85	3.58
Costs associated with reproductive choice	0.11	0.12	0.13	0.14	0.16	0.67
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.13**	**0.14**	**0.15**	**0.15**	**0.15**	**0.72**
Costs of screening	0.11	0.12	0.12	0.12	0.12	0.59
Costs associated with prenatal diagnostics	0.02	0.02	0.02	0.02	0.03	0.11
Costs associated with reproductive choice	0.004	0.004	0.004	0.004	0.005	0.021
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.31**	**0.32**	**0.34**	**0.34**	**0.34**	**1.65**
Costs of screening	0.29	0.30	0.32	0.32	0.32	1.55
Costs associated with prenatal diagnostics	0.01	0.01	0.01	0.02	0.02	0.07
Costs associated with reproductive choice	0.004	0.004	0.004	0.005	0.005	0.022

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD. Screening care pathway described in Scenario 1 (see Appendix 8).

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A81: Budget Impact Scenario Results—Prenatal Carrier Screening: Screening Care Pathway, Higher Hourly Salary Rate, Genetic Counsellors

Type of cost	Future scenario costs and budget impact, $ million[a,b]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Universal, standard DNA testing (single-disease panels)						
Total	**26.35**	**27.67**	**29.03**	**29.12**	**29.23**	**141.40**
Costs of screening	25.53	26.81	28.08	28.08	28.08	136.58
Costs associated with prenatal diagnostics	0.72	0.75	0.83	0.91	1.00	4.20
Costs associated with reproductive choice	0.10	0.11	0.12	0.13	0.15	0.62
Universal, expanded DNA testing (one multi-disease panel)						
Total	**63.60**	**66.78**	**70.00**	**70.08**	**70.18**	**340.64**
Costs of screening	62.88	66.02	69.17	69.17	69.17	336.40
Costs associated with prenatal diagnostics	0.61	0.64	0.70	0.77	0.85	3.58
Costs associated with reproductive choice	0.11	0.12	0.13	0.14	0.16	0.67
Risk-based, standard DNA testing (single-disease panels)						
Total	**0.15**	**0.16**	**0.17**	**0.17**	**0.17**	**0.83**
Costs of screening	0.13	0.14	0.14	0.14	0.14	0.69
Costs associated with prenatal diagnostics	0.02	0.02	0.02	0.02	0.03	0.11
Costs associated with reproductive choice	0.004	0.004	0.004	0.004	0.005	0.021
Risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.33**	**0.34**	**0.36**	**0.36**	**0.36**	**1.75**
Costs of screening	0.31	0.32	0.34	0.34	0.34	1.66
Costs associated with prenatal diagnostics	0.01	0.01	0.01	0.02	0.02	0.07
Costs associated with reproductive choice	0.004	0.004	0.004	0.005	0.005	0.022

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 Canadian dollars. Screening care pathway described in Scenario 3 (see Appendix 8)

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A82: Budget Impact Scenario Results—Prenatal Carrier Screening: Inclusion of Program Costs (Model-Based Outputs)

	Future scenario costs and budget impact, $ million[a,b]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Universal, standard DNA testing (single-disease panels)						
Total (all program costs)	**24.55**	**25.55**	**26.81**	**26.91**	**27.01**	**130.83**
Total (implementation costs only)	**24.55**	**25.12**	**26.37**	**26.46**	**26.56**	**129.07**
Costs of program (implementation and on-going costs)	0.62	0.43	0.45	0.45	0.45	2.39
Costs of screening	23.11	24.26	25.42	25.42	25.42	123.63
Costs associated with prenatal diagnostics	0.72	0.75	0.83	0.91	1.00	4.20
Costs associated with reproductive choice	0.10	0.11	0.12	0.13	0.15	0.62
Universal, expanded DNA testing (one multi-disease panel)						
Total (all program costs)	**57.68**	**60.34**	**63.25**	**63.33**	**63.42**	**308.02**
Total (implementation costs only)	**57.68**	**59.91**	**62.80**	**62.89**	**62.98**	**306.26**
Costs of program (implementation and on-going)	0.62	0.42	0.44	0.44	0.44	2.38
Costs of screening	56.34	59.15	61.97	61.97	61.97	301.39
Costs associated with prenatal diagnostics	0.61	0.64	0.70	0.77	0.85	3.58
Costs associated with reproductive choice	0.11	0.12	0.13	0.14	0.16	0.67
Risk-based, standard DNA testing (single-disease panels)						
Total (all program costs)	**0.36**	**0.40**	**0.42**	**0.43**	**0.43**	**2.04**
Total (implementation costs only)	**0.36**	**0.15**	**0.16**	**0.16**	**0.17**	**1.00**
Costs of program (implementation and on-going)	0.22	0.25	0.26	0.26	0.26	1.26
Costs of screening	0.12	0.13	0.13	0.13	0.13	0.65
Costs associated with prenatal diagnostics	0.02	0.02	0.02	0.02	0.03	0.11
Costs associated with reproductive choice	0.004	0.004	0.004	0.004	0.005	0.021
Risk-based, expanded DNA testing (one multi-disease panel)						
Total (all program costs)	**0.53**	**0.58**	**0.61**	**0.61**	**0.61**	**2.93**
Total (implementation costs only)	**0.53**	**0.33**	**0.34**	**0.35**	**0.35**	**1.89**
Costs of program (implementation and on-going)	0.22	0.25	0.26	0.26	0.26	1.25
Costs of screening	0.30	0.31	0.32	0.32	0.32	1.58
Costs associated with prenatal diagnostics	0.01	0.01	0.01	0.02	0.02	0.07
Costs associated with reproductive choice	0.004	0.004	0.004	0.005	0.005	0.022

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD.. Implementation costs are 1st year, one-time costs. On-going costs are costs for the rest of follow-up. Total program costs (all program costs) include both implementation and on-going costs.

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A83: Budget Impact Scenario Results—Prenatal Carrier Screening: Inclusion of Program Costs (Assuming Initial Cost Inputs)

	Future scenario costs and budget impact, $ million[a,b]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Universal, standard DNA testing (single-disease panels)						
Total (all program costs)	**24.82**	**25.71**	**26.98**	**27.07**	**27.18**	**131.75**
Total (implementation costs only)	**24.82**	**25.12**	**26.37**	**26.46**	**26.56**	**129.34**
Costs of program (implementation and on-going)	0.89	0.58	0.61	0.61	0.61	3.31
Costs of screening	23.11	24.26	25.42	25.42	25.42	123.63
Costs associated with prenatal diagnostics	0.72	0.75	0.83	0.91	1.00	4.20
Costs associated with reproductive choice	0.10	0.11	0.12	0.13	0.15	0.62
Universal, expanded DNA testing (one multi-disease panel)						
Total (all program costs)	**57.95**	**60.49**	**63.41**	**63.50**	**63.59**	**308.95**
Total (implementation costs only)	**57.95**	**59.91**	**62.80**	**62.89**	**62.98**	**306.53**
Costs of program (implementation and on-going)	0.89	0.58	0.61	0.61	0.61	3.31
Costs of screening	56.34	59.15	61.97	61.97	61.97	301.39
Costs associated with prenatal diagnostics	0.61	0.64	0.70	0.77	0.85	3.58
Costs associated with reproductive choice	0.11	0.12	0.13	0.14	0.16	0.67
Risk-based, standard DNA testing (single-disease panels)						
Total (all program costs)	**1.46**	**1.01**	**1.06**	**1.06**	**1.06**	**5.65**
Total (implementation costs only)	**1.46**	**0.15**	**0.16**	**0.16**	**0.16**	**2.08**
Costs of program (implementation and on-going)	1.32	0.86	0.90	0.90	0.90	4.87
Costs of screening	0.12	0.13	0.13	0.13	0.13	0.65
Costs associated with prenatal diagnostics	0.02	0.02	0.02	0.02	0.03	0.11
Costs associated with reproductive choice	0.004	0.004	0.004	0.004	0.005	0.021
Risk-based, expanded DNA testing (one multi-disease panel)						
Total (all program costs)	**1.63**	**1.18**	**1.24**	**1.24**	**1.25**	**6.54**
Total (implementation costs only)	**1.63**	**0.33**	**0.34**	**0.35**	**0.35**	**2.99**
Costs of program (implementation and on-going)	1.32	0.86	0.90	0.90	0.90	4.87
Costs of screening	0.30	0.31	0.32	0.32	0.32	1.58
Costs associated with prenatal diagnostics	0.01	0.01	0.01	0.02	0.02	0.07
Costs associated with reproductive choice	0.004	0.004	0.004	0.005	0.005	0.022

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD. . Implementation costs are 1st year, one-time costs. On-going costs are costs for the rest of follow-up. Total program costs (all program costs) include both implementation and on-going costs (see Appendix 9 for cost inputs).

[b]Budget Impact and total costs of the future scenario are the same because the current scenario (no screening) is assumed to be zero dollars.

Table A84: Budget Impact Scenario Results—Prenatal Carrier Screening, Summary: Long-Term Scenario Including Treatment Costs (Supportive Therapies) and Program Costs (Implementation and On-Going)

	Budget impact, $ million[a]					
Table summary	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Table A85A: universal, standard DNA testing (single-disease panels)						
Total	**21.07**	**15.21**	**10.20**	**4.48**	**-1.25**	**49.70**
Costs of screening, PND and choice (e.g., TOP)	23.93	25.12	26.37	26.46	26.56	128.44
Costs of treatment	-3.48	-10.34	-16.62	-22.42	-28.26	-81.13
Costs of program	0.62	0.43	0.45	0.45	0.45	2.39
Table A85B: universal, expanded DNA testing (one multi-disease panel)						
Total	**54.18**	**49.94**	**46.49**	**40.61**	**34.71**	**225.92**
Costs of screening, PND and choice (e.g., TOP)	57.06	59.91	62.80	62.89	62.98	305.64
Costs of treatment	-3.50	-10.40	-16.76	-22.72	-28.71	-82.10
Costs of program	0.62	0.42	0.44	0.44	0.44	2.38
Table A85C: risk-based, standard DNA testing (single-disease panels)						
Total	**0.18**	**-0.15**	**-0.47**	**-0.77**	**-1.07**	**-2.28**
Costs of screening, PND and choice (e.g., TOP)	0.14	0.15	0.16	0.16	0.17	0.78
Costs of treatment	-0.18	-0.55	-0.89	-1.20	-1.50	-4.32
Costs of program	0.22	0.25	0.26	0.26	0.26	1.26
Table A85D: risk-based, expanded DNA testing (one multi-disease panel)						
Total	**0.35**	**0.03**	**-0.28**	**-0.59**	**-0.89**	**-1.38**
Costs of screening, PND and choice (e.g., TOP)	0.31	0.33	0.34	0.35	0.35	1.68
Costs of treatment	-0.18	-0.55	-0.89	-1.20	-1.50	-4.31
Costs of program	0.22	0.25	0.26	0.26	0.26	1.25

Abbreviations: PND, prenatal diagnostic testing; TOP, voluntary termination of pregnancy.

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 Canadian dollars.

Table A85A: Long-Term Scenario Budget Impact Results by Strategy—Prenatal Universal Screening With Standard Panels (Supportive Therapies)

Type of cost	Total costs and budget impact, $ million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario						
Total	**5.64**	**16.92**	**27.51**	**37.41**	**47.31**	**134.79**
Costs of screening, PND and choice (e.g., IVF)	0.00	0.00	0.00	0.00	0.00	0.00
Costs of treatment	5.64	16.92	27.51	37.41	47.31	134.79
Costs of program	0.00	0.00	0.00	0.00	0.00	0.00
New scenario (universal, standard panels)						
Total	**26.71**	**32.13**	**37.71**	**41.89**	**46.05**	**184.49**
Costs of screening, PND and choice (e.g., IVF)	23.93	25.12	26.37	26.46	26.56	128.44
Costs of treatment	2.16	6.58	10.90	14.99	19.04	53.66
Costs of program	0.62	0.43	0.45	0.45	0.45	2.39
Budget impact (universal, standard panels)						
Total	**21.07**	**15.21**	**10.20**	**4.48**	**-1.25**	**49.70**
Screening, PND and choice (e.g., IVF)	23.93	25.12	26.37	26.46	26.56	128.44
Treatment	-3.48	-10.34	-16.62	-22.42	-28.26	-81.13
Program	0.62	0.43	0.45	0.45	0.45	2.39

Abbreviations: IVF, in-vitro fertilization; PND, prenatal diagnostic testing.

Note: Results may appear inexact due to rounding. Costs expressed in 2022 CAD.

[a]Budget impact: New scenario minus the current scenario. Negative costs indicate savings.

Table A85B: Long-Term Scenario BI Results by Strategy - Prenatal Universal Screening with Expanded Panel (Supportive Therapies)

	Total costs and budget impact, $ million[a]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current scenario						
Total	**5.64**	**16.92**	**27.51**	**37.41**	**47.31**	**134.79**
Costs of screening, PND and choice (e.g., IVF)	0.00	0.00	0.00	0.00	0.00	0.00
Costs of treatment	5.64	16.92	27.51	37.41	47.31	134.79
Costs of program	0.00	0.00	0.00	0.00	0.00	0.00
New scenario (universal, standard panels)						
Total	**59.82**	**66.86**	**74.00**	**78.02**	**82.02**	**360.72**
Costs of screening, PND and choice (e.g., IVF)	57.06	59.91	62.80	62.89	62.98	305.64
Costs of treatment	2.14	6.52	10.75	14.69	18.59	52.70
Costs of program	0.62	0.42	0.44	0.44	0.44	2.38
Budget impact (universal, standard panels)						
Total	**54.18**	**49.94**	**46.49**	**40.61**	**34.71**	**225.92**
Screening, PND and choice (e.g., IVF)	57.06	59.91	62.80	62.89	62.98	305.64
Treatment	-3.50	-10.40	-16.76	-22.72	-28.71	-82.10
Program	0.62	0.42	0.44	0.44	0.44	2.38

Abbreviations: IVF, in-vitro fertilization; PND, prenatal diagnostic testing.

Note: Results may appear inexact due to rounding. Costs expressed in 2022 CAD.

[a]Budget impact: New scenario minus the current scenario. Negative costs indicate savings.

Table A85C: Long-Term Scenario Budget Impact Results by Strategy—Prenatal Risk-Based Screening With Standard Panels (Supportive Therapies)

	Total costs and budget impact, $ million[a]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current scenario						
Total	**5.64**	**16.92**	**27.51**	**37.41**	**47.31**	**134.79**
Costs of screening, PND and choice (e.g., IVF)	0.00	0.00	0.00	0.00	0.00	0.00
Costs of treatment	5.64	16.92	27.51	37.41	47.31	134.79
Costs of program	0.00	0.00	0.00	0.00	0.00	0.00
New scenario (universal, standard panels)						
Total	**5.82**	**16.78**	**27.04**	**36.64**	**46.24**	**132.52**
Costs of screening, PND and choice (e.g., IVF)	0.14	0.15	0.16	0.16	0.17	0.78
Costs of treatment	5.46	16.37	26.62	36.21	45.81	130.48
Costs of program	0.18	0.55	0.89	1.20	1.50	4.32
Budget impact (universal, standard panels)						
Total	**0.18**	**-0.15**	**-0.47**	**-0.77**	**-1.07**	**-2.28**
Screening, PND and choice (e.g., IVF)	0.14	0.15	0.16	0.16	0.17	0.78
Treatment	-0.18	-0.55	-0.89	-1.20	-1.50	-4.32
Program	0.22	0.25	0.26	0.26	0.26	1.26

Abbreviations: IVF, in-vitro fertilization; PND, prenatal diagnostic testing.

Note: Results may appear inexact due to rounding. Costs expressed in 2022 CAD.

[a]Budget impact: New scenario minus the current scenario. Negative costs indicate savings.

Table A85D: Long-Term Scenario BI Results by Strategy—Prenatal Risk-Based Screening With Expanded Panels (Supportive Therapies)

	Total costs and budget impact, $ million[a]					
Type of cost	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Current scenario						
Total	**5.64**	**16.92**	**27.51**	**37.41**	**47.31**	**134.79**
Costs of screening, PND and choice (e.g., IVF)	0.00	0.00	0.00	0.00	0.00	0.00
Costs of treatment	5.64	16.92	27.51	37.41	47.31	134.79
Costs of program	0.00	0.00	0.00	0.00	0.00	0.00
New scenario (universal, standard panels)						
Total	**5.99**	**16.95**	**27.23**	**36.82**	**46.42**	**133.41**
Costs of screening, PND and choice (e.g., IVF)	0.31	0.33	0.34	0.35	0.35	1.68
Costs of treatment	5.46	16.38	26.62	36.21	45.81	130.48
Costs of program	0.22	0.25	0.26	0.26	0.26	1.25
Budget impact (universal, standard panels)						
Total	**0.35**	**0.03**	**-0.28**	**-0.59**	**-0.89**	**-1.38**
Screening, PND and choice (e.g., IVF)	0.31	0.33	0.34	0.35	0.35	1.68
Treatment	-0.18	-0.55	-0.89	-1.20	-1.50	-4.31
Program	0.22	0.25	0.26	0.26	0.26	1.25

Abbreviations: IVF, in-vitro fertilization; PND, prenatal diagnostic testing.

Note: Results may appear inexact due to rounding. Costs expressed in 2022 CAD.

[a]Budget impact: New scenario minus the current scenario. Negative costs indicate savings.

Table A86: Scenario Results—Prenatal Carrier Screening, Summary: Long-Term Scenario Including Treatment Costs (Novel and Supportive Therapies) and Program Costs (Implementation and On-Going)

	Budget impact, $ million[a]					
Table summary	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total**
Table A87A: universal, standard DNA testing (single-disease panels)						
Total	**14.80**	**-0.10**	**-10.91**	**-22.78**	**-24.16**	**-43.15**
Costs of screening, PND and choice (e.g., TOP)	23.93	25.12	26.37	26.46	26.56	128.44
Costs of treatment	-9.75	-25.65	-37.72	-49.69	-51.17	-173.99
Costs of program	0.62	0.43	0.45	0.45	0.45	2.39
Table A87B: universal, expanded DNA testing (one multi-disease panel)						
Total	**48.23**	**35.42**	**26.54**	**14.93**	**3.20**	**128.31**
Costs of screening, PND and choice (e.g., TOP)	57.06	59.91	62.80	62.89	62.98	305.64
Costs of treatment	-9.46	-24.92	-36.71	-48.40	-60.23	-179.71
Costs of program	0.62	0.42	0.44	0.44	0.44	2.38
Table A87C: risk-based, standard DNA testing (single-disease panels)						
Total	**-0.28**	**-1.32**	**-2.17**	**-3.06**	**-3.93**	**-10.75**
Costs of screening, PND and choice (e.g., TOP)	0.14	0.15	0.16	0.16	0.17	0.78
Costs of treatment	-0.64	-1.72	-2.59	-3.48	-4.35	-12.79
Costs of program	0.22	0.25	0.26	0.26	0.26	1.26
Table A87D: risk-based, expanded DNA testing (one multi-disease panel)						
Total	**-0.11**	**-1.14**	**-1.99**	**-2.87**	**-2.96**	**-9.07**
Costs of screening, PND and choice (e.g., TOP)	0.31	0.33	0.34	0.35	0.35	1.68
Costs of treatment	-0.64	-1.72	-2.59	-3.48	-3.57	-12.00
Costs of program	0.22	0.25	0.26	0.26	0.26	1.25

Abbreviations: PND, prenatal diagnostic testing; TOP, voluntary termination of pregnancy.

Note: Results may appear inexact due to rounding.

[a]All costs are in 2022 CAD. Negative costs indicate savings.

Table A87A: Long-Term Scenario Budget Impact Results by Strategy—Prenatal Universal Screening With Standard Panels (Novel Therapies)

Type of cost	Total costs and budget impact, $ million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario						
Total	**16.64**	**44.19**	**65.98**	**87.78**	**109.58**	**324.18**
Costs of screening, PND and choice (e.g., IVF)	0.00	0.00	0.00	0.00	0.00	0.00
Costs of treatment	16.64	44.19	65.98	87.78	109.58	324.18
Costs of program	0.00	0.00	0.00	0.00	0.00	0.00
New scenario (universal, standard panels)						
Total	**31.44**	**44.08**	**55.08**	**65.00**	**85.42**	**281.03**
Costs of screening, PND and choice (e.g., IVF)	23.93	25.12	26.37	26.46	26.56	128.44
Costs of treatment	6.89	18.53	28.26	38.09	58.41	150.19
Costs of program	0.62	0.43	0.45	0.45	0.45	2.39
Budget impact (universal, standard panels)						
Total	**14.80**	**-0.10**	**-10.91**	**-22.78**	**-24.16**	**-43.15**
Screening, PND and choice (e.g., IVF)	23.93	25.12	26.37	26.46	26.56	128.44
Treatment	-9.75	-25.65	-37.72	-49.69	-51.17	-173.99
Program	0.62	0.43	0.45	0.45	0.45	2.39

Abbreviations: IVF, in-vitro fertilization; PND, prenatal diagnostic testing.

Note: Results may appear inexact due to rounding. Costs expressed in 2022 CAD.

[a]Budget impact: New scenario minus the current scenario. Negative costs indicate savings.

Table A87B: Long-Term Scenario BI Results by Strategy - Prenatal Universal Screening with Expanded Panel (Novel Therapies)

Type of cost	Total costs and budget impact, $ million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario						
Total	**16.64**	**44.19**	**65.98**	**87.78**	**109.58**	**324.18**
Costs of screening, PND and choice (e.g., IVF)	0.00	0.00	0.00	0.00	0.00	0.00
Costs of treatment	16.64	44.19	65.98	87.78	109.58	324.18
Costs of program	0.00	0.00	0.00	0.00	0.00	0.00
New scenario (universal, standard panels)						
Total	**64.87**	**79.60**	**92.53**	**102.71**	**112.78**	**452.49**
Costs of screening, PND and choice (e.g., IVF)	57.06	59.91	62.80	62.89	62.98	305.64
Costs of treatment	7.19	19.27	29.28	39.38	49.35	144.47
Costs of program	0.62	0.42	0.44	0.44	0.44	2.38
Budget impact (universal, standard panels)						
Total	**48.23**	**35.42**	**26.54**	**14.93**	**3.20**	**128.31**
Screening, PND and choice (e.g., IVF)	57.06	59.91	62.80	62.89	62.98	305.64
Treatment	-9.46	-24.92	-36.71	-48.40	-60.23	-179.71
Program	0.62	0.42	0.44	0.44	0.44	2.38

Abbreviations: IVF, in-vitro fertilization; PND, prenatal diagnostic testing.

Note: Results may appear inexact due to rounding. Costs expressed in 2022 CAD.

[a]Budget impact: New scenario minus the current scenario. Negative costs indicate savings.

Table A87C: Long-Term Scenario Budget Impact Results by Strategy—Prenatal Risk-Based Screening With Standard Panels (Novel Therapies)

Type of cost	Total Costs and Budget Impact, $ Million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario						
Total	**16.64**	**44.19**	**65.98**	**87.78**	**109.58**	**324.18**
Costs of screening, PND and choice (e.g., IVF)	0.00	0.00	0.00	0.00	0.00	0.00
Costs of treatment	16.64	44.19	65.98	87.78	109.58	324.18
Costs of program	0.00	0.00	0.00	0.00	0.00	0.00
New scenario (universal, standard panels)						
Total	**16.36**	**42.87**	**63.81**	**84.73**	**105.66**	**313.43**
Costs of screening, PND and choice (e.g., IVF)	0.14	0.15	0.16	0.16	0.17	0.78
Costs of treatment	16.00	42.47	63.39	84.30	105.23	311.39
Costs of program	0.22	0.25	0.26	0.26	0.26	1.26
Budget impact (universal, standard panels)						
Total	**-0.28**	**-1.32**	**-2.17**	**-3.06**	**-3.93**	**-10.75**
Screening, PND and choice (e.g., IVF)	0.14	0.15	0.16	0.16	0.17	0.78
Treatment	-0.64	-1.72	-2.59	-3.48	-4.35	-12.79
Program	0.22	0.25	0.26	0.26	0.26	1.26

Abbreviations: IVF, in-vitro fertilization; PND, prenatal diagnostic testing.

Note: Results may appear inexact due to rounding. Costs expressed in 2022 CAD.

[a]Budget impact: New scenario minus the current scenario.. Negative costs indicate savings.

Table A87D: Long-Term Scenario Budget Impact Results by Strategy—Prenatal Risk-Based Screening With Expanded Panels (Novel Therapies)

Type of cost	Total costs and budget impact, $ million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total
Current scenario						
Total	**16.64**	**44.19**	**65.98**	**87.78**	**109.58**	**324.18**
Costs of screening, PND and choice (e.g., IVF)	0.00	0.00	0.00	0.00	0.00	0.00
Costs of treatment	16.64	44.19	65.98	87.78	109.58	324.18
Costs of program	0.00	0.00	0.00	0.00	0.00	0.00
New scenario (universal, standard panels)						
Total	**16.53**	**43.05**	**64.00**	**84.91**	**106.62**	**315.11**
Costs of screening, PND and choice (e.g., IVF)	0.31	0.33	0.34	0.35	0.35	1.68
Costs of treatment	16.00	42.47	63.39	84.30	106.01	312.18
Costs of program	0.22	0.25	0.26	0.26	0.26	1.25
Budget impact (universal, standard panels)						
Total	**-0.11**	**-1.14**	**-1.99**	**-2.87**	**-2.96**	**-9.07**
Screening, PND and choice (e.g., IVF)	0.31	0.33	0.34	0.35	0.35	1.68
Treatment	-0.64	-1.72	-2.59	-3.48	-3.57	-12.00
Program	0.22	0.25	0.26	0.26	0.26	1.25

Abbreviations: IVF, in-vitro fertilization; PND, prenatal diagnostic testing.

Note: Results may appear inexact due to rounding. Costs expressed in 2022 CAD.

[a]Budget impact: New scenario minus the current scenario. Negative costs indicate savings.

Appendix 24: Characteristics of Included Studies Among Preconception and Prenatal People and Health Care Providers

Table A88: Characteristics of Included Studies Among Preconception and Prenatal People and Health Care Providers

Author, Year	Country	Condition	Timing	N	Population
Aboagye et al, 2019[290]	Ghana	SCD	NA	351	Consultants, residents, house officers, midwives, and nurses directly involved in antenatal care at main tertiary hospital in Accra, Ghana
Alfaro Arenas et al, 2017[84]	Spain	FXS	PC, PN	3,731 (318 PC, 3,413 PN)	People at 10–12 wk of pregnancy attending antenatal consultation with gynecologist People attending PC consultation with midwife
Ames et al, 2015[247]	Australia	FXS	PC	241	Women attending family planning drop-in clinic in Melbourne, age ≥ 18 y, not pregnant; could read, write, and speak English Exclusion: people attending clinic in crisis or emergency situations
Bailey Jr et al, 2012[248]	United States	FXS	NA	1,099	Parents or other caregivers from families of children with FXS
Boardman et al, 2017,[249] 2018[291]	United Kingdom	SMA	PC, PN	337 (255 families, 82 individuals)	People affected with SMA or at least one dx of SMA in family, > 18 y
Boardman et al, 2020[251]	United Kingdom	Thalassemia	PC	80	People and families with thalassemia
Brown et al, 2011[252]	United Kingdom	SCD, thalassemia	PN	464	Pregnant people who attended general practice and planned to continue pregnancy, ≤ 18 wk and 6 d gestation, no written record of sickle cell and thalassemia carrier status in primary care, age ≥ 18 y, agreed to be contacted by research team Excluded: people who had spontaneous pregnancy loss before being contacted by research team

Author, Year	Country	Condition	Timing	N	Population
Cunningham et al, 2014[262]	Australia	CF	NA	51 physicians, 19 clinic coordinators	Physicians from CF special interest group of the Thoracic Society of Australia and New Zealand, Clinic coordinators from CF Nurses Network
Darcy et al, 2011[264]	United States	CF	NA	—	Practicing obstetricians, perinatologists, and their equivalent, such as GPs who provide obstetric services
Ghoreyshyzadeh et al, 2017[269]	Iran	Thalassemia	NA	282	Employees in urban family health units of Tabriz health centers, and managers and senior officials of the same centres
Hanprasertpong et al, 2018[245]	Thailand	Thalassemia	PN	1,006	Pregnant people who attended antenatal care at Maha Chakri Sirindhorn Medical Center
Ioannou et al, 2014[268]	Australia	CF	PN	158	Pregnant people < 16 wk gestation from antenatal clinics at 2 public hospitals in Melbourne, Australia Excluded: people unable to read/write English or required an interpreter
Ioannou et al, 2014[254]	Australia	CF	PN	54	Pregnant people at 2 private obstetric ultrasound clinics in Melbourne, Australia; people who received offer of CF screening and declined screening
Ishaq et al, 2012[270]	Pakistan	Thalassemia	NA	115 families	Parents of people with beta-thalassemia major Excluded: parents of people with other blood disorders such as alpha-thalassemia, thalassemia intermedia, congenital dyserythropoietic anemia, hereditary spherocytosis, etc.
Jans et al, 2012[265]	Netherlands	Hemoglobinopathy	NA	1,346 (795 midwives, 511 GPs)	GPs randomly selected from Netherlands Institute of Health Services Research, Primary care midwives
Janssens et al, 2016[246]	Belgium	CF	NA	111 (64 parents of children with CF, 47 people with CF)	People with CF and parents of children with CF from the Department of Pneumology at University of Ghent
Lieberman et al, 2011[266]	Israel	FXS	NA	80 (13 physicians, 20 genetic counsellors, 1 NA)	Clinical geneticists and genetic counsellors actively performing genetic counselling for FXS

Author, Year	Country	Condition	Timing	N	Population
Maxwell et al, 2011[255]	Australia	CF	NA	149	Members of Cystic Fibrosis Western Australia, people affected with CF or family member of someone with CF
Mayo-Gamble et al, 2018	United States	SCD	PC	300	People aged 18–35 y, self-identified as Black/African-American or mixed race including Black/African-American, did not know sickle cell carrier status
Metcalfe et al, 2017[68]	Australia	FXS	PC, PN	961	People aged 18–70 y who were not pregnant or were up to 13 wk pregnant from general practice, public and private obstetric, and private obstetric ultrasound clinics in Melbourne and Perth, Western Australia
Prior et al, 2010[257]	United States	SMA	PN	392	Individuals or couples referred to 2 perinatal centres in Columbus, Ohio for genetic counselling and consultation with maternal fetal medicine specialist
Stark et al, 2013[263]	Australia	CF, thalassemia, FXS, SMA	NA	156	Australian Fellows of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists
Valente et al, 2020[267]	Australia	CF	NA	87	Health care providers within the Maternal Serum Screening database at the Victorian Clinical Genetics Services
van Elderen et al, 2010[258]	Netherlands	Hemoglobinopathy	PC	109	Turkish female immigrants, aged 18–35 y planning to become pregnant
Vuthiwong et al, 2012[259]	Thailand	Thalassemia	PN	100	Partners of pregnant people who tested as carriers, partners who declined screening
Widayanti et al, 2011[260]	Indonesia	Thalassemia	PC	74	Females who were not affected, but with children who were affected
Wood et al, 2016[65]	United States	SMA	PN	90	Maternal fetal medicine specialists, obstetrician-gynecologists, reproductive endocrinology and infertility specialists, neonatal and perinatal medicine specialists, pediatricians, medical geneticists, and genetic counselling at University of Alabama at Birmingham Prenatal Genetics Clinic and First Trimester Screening Clinic

Author, Year	Country	Condition	Timing	N	Population
Zafari et al, 2016[261]	Iran	Thalassemia	PC	327 carrier couples	Carrier couples who had been married for at least 1 y, from 3 health care centres in the province of Mazandaran, Iran

Abbreviations: CF, cystic fibrosis; FXS, fragile X syndrome; GP, general practitioner; NA, not applicable; PC, preconception; PN, prenatal; SCD, sickle cell disease; SMA, spinal muscular atrophy

Appendix 25: Characteristics of Partially Relevant Excluded Systematic Reviews

Table A89: Characteristics of Excluded Partially Relevant Systematic Reviews

Author, year	Included conditions	Inclusion criteria	Literature search information	No. of included studies	Main conclusions
Best et al, 2021[241]	No specific conditions	HCP attitudes on enablers and barriers to implementation of reproductive carrier screening, HCPs engaged with reproductive carrier screening, implementation or pre-implementation of screening programs in real-world context, peer-reviewed research	September 2020 Databases: Medline, EMBASE, Scopus, PsycINFO, Web of Science, PubMed, CINAHL	26	Main themes identified: • Use and potential impact of reproductive genetic carrier screening • HCP beliefs and expectations on the process of delivering screening • Available resources for carrier screening
Hill et al, 2010[59]	FXS	Offering FXS screening in the general population, psychosocial issues associated with screening Exclusion: participants with only intellectual disability, FXTAS, FXPOI, or other clinical populations; studies; screening based only on cytogenic tests or clinical assessments, cost-effectiveness of FXS screening, unless screening was offered	January 1991 to November 2009 Databases: Medline, CINAHL, Cochrane library, EMBASE, PsycINFO, National Research Register, clinical evidence	11	• Studies offered PC and PN screening • Potential anxiety among people to be tested or who have been tested • Targeted counselling and education strategies are essential to support screening of the general population for FXS • Crucial that future studies offering FXS screening explore a range of psychosocial aspects in addition to evaluating uptake rate and carrier frequency
Ioannou et al, 2014	CF	People offered CF screening or who were asked to consider a hypothetical screening offer, people's views on carrier screening, peer-reviewed original research	Latest search date: October 31, 2012 Databases: Medline, EMBASE, CINAHL, PsycINFO, Cochrane library	85	• Generally positive attitude and support for carrier screening • Preference for offer of screening from GP • Preference for offer of screening to be in person, rather than via letter or brochure

Author, year	Included conditions	Inclusion criteria	Literature search information	No. of included studies	Main conclusions
					• Main information people wanted to receive was information about CF and screening, specifically for the risk of being a carrier and having an affected child • Factors influencing accepting screening: gender, ethnicity, parity, future reproductive plans, income, level of education • Factors influencing declining screening: low perceived susceptibility, lack of family history, lack of intention to terminate pregnancy, opposition to PND, no further reproductive plans, lack of time, partner's opinion, anxiety, test cost, lack of interest • Possible psychosocial impact: anxiety, mainly before testing; feelings of surprise, shock, worry after receiving positive test results
Janssens et al, 2014[242]	CF	Attitudes of HCPs toward carrier screening on a population-based perspective, qualitative or quantitative studies, published in peer-reviewed journals English language	1990–2011 Databases: PubMed, Web of Science, Google Scholar	14	• HCPs generally had positive attitudes toward carrier screening and were willing to be involved in carrier screening • Main concerns and barriers toward carrier screening: time commitment, need for education for possible providers, possible psychological consequences for carriers
Massie et al, 2014[196]	CF	Focus on original research from Australia and New Zealand regarding PC and PN screening, current methods of offering screening, attitudes toward screening, health economic evaluation	December 20, 2013 Databases: Medline, EMBASE	22	• Study participants thought PC and PN carrier screening should be available • Health economic analyses support carrier screening (can be cost-effective) • There are small carrier screening programs in Victoria, New South Wales, and Queensland in Australia • Human Genetics Society of Australasia specifically recommends screening be offered

Author, year	Included conditions	Inclusion criteria	Literature search information	No. of included studies	Main conclusions
					to people and couples planning pregnancy and in early stages of pregnancy • Other professional bodies endorse availability of carrier screening • Barriers to screening: not being offered screening, testing cost, inequity of access, incorrect perception that not having a family history lowers CF risk
Moultrie et al, 2016[243]	SMA	Awareness, knowledge, attitudes held by public and non-geneticist clinicians about various aspects of SMA, including carrier and newborn screening, peer-reviewed articles, English language	January 2000 to January 2015 Databases: PubMed, CINAHL, PsycINFO, ERIC, Cochrane library	9	• Public is generally unfamiliar with SMA, but had favourable views of carrier screening • HCPs had limited understanding of SMA, but generally supported carrier screening • Barriers to patient education: time constraints, language and cultural barriers, potential psychological impact on people
Van Steijvoort et al, 2020[63]	ECS	Quantitative assessment of intention to undergo a (hypothetical) carrier screening test, uptake of carrier screening offer, or both Exclusion: assessment of interest or uptake of genetic tests aimed at obtaining non-reproductive medical information, focused on genetic tests targeting dominant genetic conditions, assessment of interest or uptake within specific communities, non-original publications, non-English	January 2015 to January 2019 Databases: PubMed, Web of Science, CINAHL, Cochrane library	12	• 32%–76% of respondents interested in a (hypothetical) ECS test • 8%–50% uptake rates for actual ECS offers • Highest overall uptake was observed among pregnant people (50%) • 8%–34% overall uptake rate among PC population, except for 1 study where people were counselled PC in preparation for IVF (68.7%)

Author, year	Included conditions	Inclusion criteria	Literature search information	No. of included studies	Main conclusions
Yu et al, 2012[244]	No specific conditions	Primarily people of Asian descent who lived in a western country, primary research and audits, English language Exclusion: literature review or discussion articles, focus on HCPs or Asian community members rather than Asian people, did not provide separate breakdown of results by ethnic group	1995–2010 Databases: Medline, CINAHL, ASSIA, PsycINFO	22	• Asian people have difficulty accessing antenatal and PND testing, have poor knowledge of testing, less able to make informed choices around test uptake • Asian people in the United Kingdom and Australia tend to be less likely than white people to undergo antenatal screening and PND • Antenatal services need to consider social and cultural appropriateness for population served

Abbreviations: ASSIA, Applied Social Sciences Index & Abstracts; CF, cystic fibrosis; CINAHL, Cumulative Index to Nursing and Allied Health Literature; ECS, expanded carrier screening; ERIC, Education Resources Information Center; FXPOI, fragile X–associated primary ovarian insufficiency; FXS, fragile X syndrome; FXTAS, fragile X–associated tremor/ataxia syndrome; GP, general practitioner; HCP, health care provider; IVF, in vitro fertilization; PC, preconception; PN, prenatal; PND, prenatal diagnosis/diagnostic; SMA, spinal muscular atrophy.

Appendix 26: Letter of Information

Ontario Health

LETTER OF INFORMATION

Ontario Health is conducting a review of a **Carrier Screening program for genetic conditions Fragile X, Cystic Fibrosis, Spinal Muscular Atrophy and Hemoglobinopathies (such as sickle cell disease).** The purpose is to understand whether this program should be more broadly funded in Ontario.

An important part of this review involves speaking to patients and family members of those who may have experience with carrier testing, or who may have attempted to access it. Our goal is always to make sure the lived-experience of individuals and families are considered in the funding recommendations for this test.

WHAT DO YOU NEED FROM PARTICIPANTS?

- ✓ 20-40 minutes of time for a phone or in-person interview to hear about their experiences
- ✓ Permission to audio- (not video-) record the interview

WHAT PARTICIPATION INVOLVES

If a participant agrees to share their experiences, they will be asked to have an interview with Ontario Health staff. The interview will likely last 20-40 minutes. It will be held in a private location or over the telephone. With consent, the interview will be audio-recorded. The interviewer will ask questions about perspectives of carrier status, access, information, decision-making and more general thoughts about carrier genetic testing and program options in Ontario.

Participation is voluntary. Those who volunteer may decide not to participate, refuse to answer any questions or withdraw before the interview. Withdrawal will in no way affect the care received.

CONFIDENTIALITY

All information collected for the review will be kept confidential and privacy will be protected except as required by law. The results of this review will be published, however no identifying information will be released or published. Any records containing information from the interview will be stored securely.

RISKS TO PARTICIPATION:

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their lived experience. If this is the case, participants can speak to our staff.

If you have any questions, please contact Ontario Health staff:

Appendix 27: Interview Guide

Interview for Carrier Screening HTA

What are the preferences and values of patients who may seek out carrier screening for these four genetic conditions? What are their preferences and values in considering this testing and its impact on the care of themselves or their loved ones?

Intro
Explain OH(Q) purpose, HTA process, and purpose of interview

Lived- Experience with Genetic Carrier Testing (if applicable)
What led to genetic carrier testing?
Information provided regarding testing
Impact of genetic carrier testing
- On self
- On family members/others

Info/Supports for Screening Program
To make an informed decision about carrier/screening testing, what information do you (or did you) want to know?
- Where do you want this info to come from? (ex fam doc, specialist, own research, family, etc)

Carrier Screening Program
If a Carrier Screening program (x4 conditions) was to exist, is there a time when you think it would be best to test?
- (Prompts: in early family planning? Pre-conceptions? Prenatal?)
- Do you have any concerns or thoughts around the timing of the test?

Broadly, do you see any downsides/concerns to a carrier screening program for these four conditions?
What (if anything) would make you hesitate about getting genetic testing? Procedure? Cost?

References

(1) Canadian Agency for Drugs and Technologies in Health. Genetic carrier screening for cystic fibrosis, fragile X syndrome, hemoglobinopathies, and spinal muscular atrophy [Internet]. Ottawa (ON): The Agency; (c)2023 [cited 2023 Jan 12]. Available from: https://www.cadth.ca/genetic-carrier-screening-cystic-fibrosis-fragile-x-syndrome-hemoglobinopathies-and-spinal-muscular

(2) Cystic Fibrosis Foundation. Types of CFTR mutations [Internet]. Bethesda (MD): Cystic Fibrosis Foundation; 2021 [cited 2021 Jan 11]. Available from: https://www.cff.org/What-is-CF/Genetics/Types-of-CFTR-Mutations

(3) Pereira SV, Ribeiro JD, Ribeiro AF, Bertuzzo CS, Marson FAL. Novel, rare and common pathogenic variants in the CFTR gene screened by high-throughput sequencing technology and predicted by in silico tools. Sci Rep. 2019;9(1):6234.

(4) Wilschanski M, Durie PR. Pathology of pancreatic and intestinal disorders in cystic fibrosis. J R Soc Med. 1998;91 Suppl 34:40-9.

(5) Miller AC, Comellas AP, Hornick DB, Stoltz DA, Cavanaugh JE, Gerke AK, et al. Cystic fibrosis carriers are at increased risk for a wide range of cystic fibrosis-related conditions. Proc Natl Acad Sci U S A. 2020;117(3):1621-7.

(6) Paranjape SM, Zeitlin PL. Atypical cystic fibrosis and CFTR-related diseases. Clin Rev Allergy Immunol. 2008;35(3):116-23.

(7) MacKenzie T, Gifford AH, Sabadosa KA, Quinton HB, Knapp EA, Goss CH, et al. Longevity of patients with cystic fibrosis in 2000 to 2010 and beyond: survival analysis of the Cystic Fibrosis Foundation patient registry. Ann Intern Med. 2014;161(4):233-41.

(8) Rare disease database: fragile X syndrome [Internet]. Danbury (CT): National Organization for Rare Disorders; 2021 [cited 2021 Apr 7]. Available from: https://rarediseases.org/rare-diseases/fragile-x-syndrome

(9) National Fragile X Foundation. Fragile X-associated primary ovarian insufficiency [Internet]. McLean (VA): National Fragile X Foundation; 2021 [cited 2021 Apr 7]. Available from: https://fragilex.org/understanding-fragile-x/fxpoi-primary-ovarian-insufficiency

(10) National Fragile X Foundation. Fragile X-associated tremor/ataxia syndrome [Internet]. McLean (VA): National Fragile X Foundation; 2021 [cited 2021 Apr 7]. Available from: https://fragilex.org/understanding-fragile-x/tremor-ataxia-syndrome-fxtas

(11) Prior TW, Professional Practice and Guidelines Committee. Carrier screening for spinal muscular atrophy. Genet Med. 2008;10(11):840-2.

(12) Kariyawasam DST, Russell JS, Wiley V, Alexander IE, Farrar MA. The implementation of newborn screening for spinal muscular atrophy: the Australian experience. Genet Med. 2020;22(3):557-65.

(13) Screening results: spinal muscular atrophy (SMA) [Internet]. Ottawa (ON): Newborn Screening Ontario; 2021 [cited 2021 Jan 7]. Available from: https://www.newbornscreening.on.ca/en/disease/spinal-muscular-atrophy-sma

(14) Verhaart IEC, Robertson A, Wilson IJ, Aartsma-Rus A, Cameron S, Jones CC, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy - a literature review. Orphanet J Rare Dis. 2017;12(1):124.

(15) Farrar MA, Park SB, Vucic S, Carey KA, Turner BJ, Gillingwater TH, et al. Emerging therapies and challenges in spinal muscular atrophy. Ann Neurol. 2017;81(3):355-68.

(16) Wilson RD, De Bie I, Armour CM, Brown RN, Campagnolo C, Carroll JC, et al. Joint SOGC-CCMG opinion for reproductive genetic carrier screening: an update for all Canadian providers of maternity and reproductive healthcare in the era of direct-to-consumer testing. J Obstet Gynaecol Can. 2016;38(8):742-62 e3.

(17) Grody WW, Thompson BH, Gregg AR, Bean LH, Monaghan KG, Schneider A, et al. ACMG position statement on prenatal/preconception expanded carrier screening. Genet Med. 2013;15(6):482-3.

(18) Genetic carrier screening [Internet]. East Melbourne (Australia): Royal Australian and New Zealand College of Obstetricians and Gynaecologists; 2019 [cited 2021 Jan 11]. Available from:

https://ranzcog.edu.au/wp-content/uploads/2022/05/Genetic-carrier-screeningC-Obs-63New-March-2019_1.pdf
(19) Genomics in general practice [Internet]. East Melbourne (Australia): Royal Australian College of General Practitioners; 2020 [cited 2021 Jan 11]. Available from: https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/genomics
(20) Screening results: sickle cell disease (hemoglobin SS) [Internet]. Ottawa (ON): Newborn Screening Ontario; 2021 [cited 2021 Jan 7]. Available from: https://www.newbornscreening.on.ca/en/disease/sickle-cell-disease-hemoglobin-ss
(21) Screening results: cystic fibrosis (CF) [Internet]. Ottawa (ON): Newborn Screening Ontario; 2021 [cited 2021 Jan 7]. Available from: https://www.newbornscreening.on.ca/en/disease/cystic-fibrosis-cf
(22) SMA overview [Internet]. Jackson (WY): Spinal Muscular Atrophy Foundation; 2012 [cited 2021 Jan 7]. Available from: https://www.smafoundation.org/wp-content/uploads/2012/03/SMA-Overview.pdf
(23) National Fragile X Foundation. Prevalence [Internet]. McLean (VA): National Fragile X Foundation; 2021 [cited 2021 Apr 7]. Available from: https://fragilex.org/understanding-fragile-x/fragile-x-101/prevalence
(24) Cystic Fibrosis Canada. Trikafta can't wait [Internet]. Toronto (ON): Cystic Fibrosis Canada; 2021 [cited 2021 Jan 22]. Available from: https://www.cysticfibrosis.ca/our-programs/advocacy/how-to-take-action/trikafta-cant-wait
(25) Frangoul H, Altshuler D, Cappellini MD, Chen YS, Domm J, Eustace BK, et al. CRISPR-Cas9 gene editing for sickle cell disease and beta-thalassemia. N Engl J Med. 2021;384(3):252-60.
(26) Biogen Canada. Product monograph including patient medication information: Spinraza (nusinersen injection) [Internet]. Mississauga (ON): Biogen Canada; 2020 [cited 2021 Jan 11]. Available from: https://www.biogen.ca/content/dam/corporate/en_CA/pdfs/products/SPINRAZA/SPINRAZAProduct_Monograph_EN.pdf
(27) Novartis Gene Therapies. Highlights of prescribing information [Internet]. Bannockburn (IL): Novartis Gene Therapies; 2019 [cited 2021 Jan 11]. Available from: https://www.avexis.com/content/pdf/prescribing_information.pdf
(28) Genentech. Highlights of prescribing information [Internet]. South San Francisco (CA): Genentech; 2020 [cited 2021 Jan 11]. Available from: https://www.gene.com/download/pdf/evrysdi_prescribing.pdf
(29) Kraft SA, Duenas D, Wilfond BS, Goddard KAB. The evolving landscape of expanded carrier screening: challenges and opportunities. Genet Med. 2019;21(4):790-7.
(30) Deignan JL, Astbury C, Cutting GR, Del Gaudio D, Gregg AR, Grody WW, et al. CFTR variant testing: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2020;22(8):1288-95.
(31) Hospital for Sick Children. Cystic fibrosis and CFTR-related disorders [Internet]. Toronto (ON): Hospital for Sick Children; 2021 [cited 2021 Jan 12]. Available from: https://wapps.sickkids.ca/PDFs/Paediatric%20Laboratory%20Medicine/info-sheets/56255-CF_OMG1620P_03.pdf
(32) Hospital for Sick Children. Spinal muscular atrophy (type 1, 2, & 3) [Internet]. Toronto (ON): Hospital for Sick Children; 2021 [cited 2021 Jan 12]. Available from: https://wapps.sickkids.ca/PDFs/Paediatric%20Laboratory%20Medicine/info-sheets/56280-SMA_OMG1620AK_04.pdf
(33) US Centers for Disease Control and Prevention. Hemoglobinopathies: current practices for screening, confirmation and follow-up [Internet]. Silver Spring (MD): Association of Public Health Laboratories; 2015 [cited 2021 Jan 12]. Available from: https://www.cdc.gov/ncbddd/sicklecell/documents/nbs_hemoglobinopathy-testing_122015.pdf
(34) LeBlanc A, Kenny DA, O'Connor AM, Legare F. Decisional conflict in patients and their physicians: a dyadic approach to shared decision making. Med Decis Making. 2009;29(1):61-8.

(35) American College of Obstetricians and Gynecologists' Committee on Genetics. Committee opinion no. 690: carrier screening in the age of genomic medicine. Obstet Gynecol. 2017;129(3):e35-e40.
(36) LifeLabs Genetics. Expanded carrier screening for informed family planning [Internet]. Etobicoke (ON): LifeLabs Genetics; 2021 [cited 2021 Jan 11]. Available from: https://www.lifelabsgenetics.com/product/expanded-carrier-screening
(37) Henneman L, Borry P, Chokoshvili D, Cornel MC, van El CG, Forzano F, et al. Responsible implementation of expanded carrier screening. Eur J Hum Genet. 2016;24(6):e1-e12.
(38) High-quality testing, easily accessible [Internet]. San Francisco (CA): Invitae Corp.; 2021 [cited 2021 Apr 7]. Available from: https://www.invitae.com/en/billing
(39) Saffi M, Howard N. Exploring the effectiveness of mandatory premarital screening and genetic counselling programmes for beta-thalassaemia in the middle east: a scoping review. Public Health Genomics. 2015;18(4):193-203.
(40) McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. J Clin Epidemiol. 2016;75:40-6.
(41) Covidence (systematic review software) [Computer program]. Veritas Health Innovation. Melbourne (Australia). Available at: https://www.covidence.org/home.
(42) Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Br Med J. 2011;343:d5928.
(43) Kim SY, Park JE, Lee YJ, Seo HJ, Sheen SS, Hahn S, et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. J Clin Epidemiol. 2013;66(4):408-14.
(44) Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook [Internet]. Hamilton (ON): Grade Working Group; 2013 [cited 2017 Dec]. Available from http://gdt.guidelinedevelopment.org/app/handbook/handbook.html.
(45) Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. J Clin Epidemiol. 2021;134:178-89.
(46) Beauchamp KA, Johansen Taber KA, Grauman PV, Spurka L, Lim-Harashima J, Svenson A, et al. Sequencing as a first-line methodology for cystic fibrosis carrier screening. Genet Med. 2019;21(11):2569-76.
(47) Bristow SL, Morris JM, Peyser A, Gamma A, Singer T, Mullin C, et al. Choosing an expanded carrier screening panel: comparing two panels at a single fertility centre. Reprod Biomed Online. 2019;38(2):225-32.
(48) Dormandy E, Gulliford M, Bryan S, Roberts TE, Calnan M, Atkin K, et al. Effectiveness of earlier antenatal screening for sickle cell disease and thalassaemia in primary care: cluster randomised trial. BMJ. 2010;341:c5132.
(49) Field PD, Martin NJ. CFTR mutation screening in an assisted reproductive clinic. Aust N Z J Obstet Gynaecol. 2011;51(6):536-9.
(50) Gallati S, Hess S, Galie-Wunder D, Berger-Menz E, Bohlen D. Cystic fibrosis transmembrane conductance regulator mutations in azoospermic and oligospermic men and their partners. Reprod Biomed Online. 2009;19(5):685-94.
(51) Peyser A, Singer T, Mullin C, Bristow SL, Gamma A, Onel K, et al. Comparing ethnicity-based and expanded carrier screening methods at a single fertility center reveals significant differences in carrier rates and carrier couple rates. Genet Med. 2019;21(6):1400-6.
(52) Franasiak JM, Olcha M, Bergh PA, Hong KH, Werner MD, Forman EJ, et al. Expanded carrier screening in an infertile population: how often is clinical decision making affected? Genet Med. 2016;18(11):1097-101.
(53) Hernandez-Nieto C, Alkon-Meadows T, Lee J, Cacchione T, Iyune-Cojab E, Garza-Galvan M, et al. Expanded carrier screening for preconception reproductive risk assessment: prevalence of carrier status in a Mexican population. Prenat Diagn. 2020;40(5):635-43.
(54) Xi Y, Chen G, Lei C, Wu J, Zhang S, Xiao M, et al. Expanded carrier screening in Chinese patients seeking the help of assisted reproductive technology. Mol Genet Genomic Med. 2020;8(9):e1340.

(55) Pastore LM, Morris WL, Karns LB. Emotional reaction to fragile X premutation carrier tests among infertile women. J Genet Couns. 2008;17(1):84-91.
(56) Baxi A, Manila K, Kadhi P, Heena B. Carrier screening for beta thalassemia in pregnant Indian women: experience at a single center in Madhya Pradesh. Indian J Hematol Blood Transfus. 2013;29(2):71-4.
(57) Chamayou S, Sicali M, Lombardo D, Maglia E, Liprino A, Cardea C, et al. The true panel of cystic fibrosis mutations in the Sicilian population. BMC Med Genet. 2020;21(1):89.
(58) Cannon J, Van Steijvoort E, Borry P, Chokoshvili D. How does carrier status for recessive disorders influence reproductive decisions? A systematic review of the literature. Expert Rev Mol Diagn. 2019;19(12):1117-29.
(59) Hill MK, Archibald AD, Cohen J, Metcalfe SA. A systematic review of population screening for fragile X syndrome. Genet Med. 2010;12(7):396-410.
(60) Hussein N, Weng SF, Kai J, Kleijnen J, Qureshi N. Preconception risk assessment for thalassaemia, sickle cell disease, cystic fibrosis and Tay-Sachs disease. Cochrane Database Syst Rev. 2018;3:CD010849.
(61) Ioannou L, McClaren BJ, Massie J, Lewis S, Metcalfe SA, Forrest L, et al. Population-based carrier screening for cystic fibrosis: a systematic review of 23 years of research. Genet Med. 2014;16(3):207-16.
(62) Kornman LH, Nisbet DL, Liebelt J. Preconception and antenatal screening for the fragile site on the X-chromosome. Cochrane Database Syst Rev. 2009(4).
(63) Van Steijvoort E, Chokoshvili D, J WC, Peeters H, Peeraer K, Matthijs G, et al. Interest in expanded carrier screening among individuals and couples in the general population: systematic review of the literature. Hum Reprod Update. 2020;26(3):335-55.
(64) Coiana A, Faa V, Carta D, Puddu R, Cao A, Rosatelli MC. Preconceptional identification of cystic fibrosis carriers in the Sardinian population: a pilot screening program. J Cyst Fibros. 2011;10(3):207-11.
(65) Wood SL, Brewer F, Ellison R, Biggio JR, Edwards RK. Prenatal carrier screening for spinal muscular atrophy. Am J Perinatol. 2016;33(12):1211-7.
(66) Dacus J, Mabie B, Gailey T, Rogers C, Likes C, Metcalf L. Cystic fibrosis screening at the Greenville Hospital System. J S C Med Assoc. 2006;102(1):14-6.
(67) Fries MH, Bashford M, Nunes M. Implementing prenatal screening for cystic fibrosis in routine obstetric practice. Am J Obstet Gynecol. 2005;192(2):527-34.
(68) Metcalfe SA, Martyn M, Ames A, Anderson V, Archibald AD, Couns GDG, et al. Informed decision making and psychosocial outcomes in pregnant and nonpregnant women offered population fragile X carrier screening. Genet Med. 2017;19(12):1346-55.
(69) Colah R, Surve R, Wadia M, Solanki P, Mayekar P, Thomas M, et al. Carrier screening for beta-thalassemia during pregnancy in India: a 7-year evaluation. Genet Test. 2008;12(2):181-5.
(70) Choudhuri S, Sen A, Ghosh MK, Misra S, Bhattacharyya M. Effectiveness of prenatal screening for hemoglobinopathies in a developing country. Hemoglobin. 2015;39(6):380-3.
(71) Christie LM, Ingrey AJ, Turner GM, Proos AL, Watts GE. Outcomes of a cystic fibrosis carrier testing clinic for couples. Med J Aust. 2009;191(9):499-501.
(72) Konialis CP, Hagnefelt B, Kazamia C, Karapanou S, Pangalos C. CFTR DeltaF508 mutation detection from dried blood samples in the first trimester of pregnancy: a possible routine prenatal screening strategy for cystic fibrosis? Fetal Diagn Ther. 2007;22(1):41-4.
(73) Massie J, Petrou V, Forbes R, Curnow L, Ioannou L, Dusart D, et al. Population-based carrier screening for cystic fibrosis in Victoria: the first three years experience. Aust N Z J Obstet Gynaecol. 2009;49(5):484-9.
(74) Slostad J, Stein QP, Flanagan JD, Hansen KA. Screening for mutations in the cystic fibrosis transmembrane regulator gene in an infertility clinic. Fertil Steril. 2007;88(6):1687-8.
(75) Stuppia L, Antonucci I, Binni F, Brandi A, Grifone N, Colosimo A, et al. Screening of mutations in the CFTR gene in 1195 couples entering assisted reproduction technique programs. Eur J Hum Genet. 2005;13(8):959-64.
(76) Wei S, Quigg MH, Monaghan KG. Is cystic fibrosis carrier screening cost effective? Community Genetics. 2007;10(2):103-9.

(77) Zlotogora J, Carmi R, Lev B, Shalev SA. A targeted population carrier screening program for severe and frequent genetic diseases in Israel. Eur J Hum Genet. 2009;17(5):591-7.
(78) Lakeman P, Plass AM, Henneman L, Bezemer PD, Cornel MC, ten Kate LP. Three-month follow-up of Western and non-Western participants in a study on preconceptional ancestry-based carrier couple screening for cystic fibrosis and hemoglobinopathies in the Netherlands. Genet Med. 2008;10(11):820-30.
(79) Baker VL, Rone HM, Adamson GD. Genetic evaluation of oocyte donors: recipient couple preferences and outcome of testing. Fertil Steril. 2008;90(6):2091-8.
(80) Archibald AD, Smith MJ, Burgess T, Scarff KL, Elliott J, Hunt CE, et al. Reproductive genetic carrier screening for cystic fibrosis, fragile X syndrome, and spinal muscular atrophy in Australia: outcomes of 12,000 tests. Genet Med. 2018;20(5):513-23.
(81) Simone L, Khan S, Ciarlariello M, Lin J, Trackman S, Heiman GA, et al. Reproductive male partner testing when the female is identified to be a genetic disease carrier. Prenat Diagn. 2021;41(1):21-7.
(82) Chan OYM, Leung TY, Cao Y, Shi MM, Kwan AHW, Chung JPW, et al. Expanded carrier screening using next-generation sequencing of 123 Hong Kong Chinese families: a pilot study. Hong Kong Med. 2021;18:18.
(83) Alfaro Arenas R, Rosell Andreo J, Heine Suner D, Group for the study of F. X. S. in the Balearic Islands. Fragile X syndrome screening in pregnant women and women planning pregnancy shows a remarkably high FMR1 premutation prevalence in the Balearic Islands. Am J Med Genet B Neuropsychiatr Genet. 2016;171(8):1023-31.
(84) Alfaro Arenas R, Rosell Andreo J, Heine Suner D, Group for the study of FXSitBI. A pilot study of fragile X yndrome screening in pregnant women and women planning pregnancy: implementation, acceptance, awareness, and geographic factors. J Genet Couns. 2017;26(3):501-10.
(85) Cronister A, DiMaio M, Mahoney MJ, Donnenfeld AE, Hallam S. Fragile X syndrome carrier screening in the prenatal genetic counseling setting. Genet Med. 2005;7(4):246-50.
(86) Metcalfe S, Jacques A, Archibald A, Burgess T, Collins V, Henry A, et al. A model for offering carrier screening for fragile X syndrome to nonpregnant women: results from a pilot study. Genet Med. 2008;10(7):525-35.
(87) Giordano PC, Plancke A, Van Meir CA, Janssen CA, Kok PJ, Van Rooijen-Nijdam IH, et al. Carrier diagnostics and prevention of hemoglobinopathies in early pregnancy in the Netherlands: a pilot study. Prenat Diagn. 2006;26(8):719-24.
(88) Kaufmann JO, Demirel-Gungor G, Selles A, Hudig C, Steen G, Ponjee G, et al. Feasibility of nonselective testing for hemoglobinopathies in early pregnancy in the Netherlands. Prenat Diagn. 2011;31(13):1259-63.
(89) Shukla S, Singh D, Dewan K, Sharma S, Trivedi SS. Antenatal carrier screening for thalassemia and related hemoglobinopathies: a hospital-based study. J Med Soc. 2018;32(2):118-22.
(90) Sorour Y, Heppinstall S, Porter N, Wilson GA, Goodeve AC, Rees D, et al. Is routine molecular screening for common alpha-thalassaemia deletions necessary as part of an antenatal screening programme? J Med Screen. 2007;14(2):60-1.
(91) Kulkarni P, Masthi NR, Niveditha S, Suvarna R. The prevalence of the beta thalassemia trait among the pregnant women who attended the ANC clinic in a PHC, by using the NESTROF test in Bangalore, Karnataka. J Clin Diagn Res. 2013;7(7):1414-7.
(92) Marcheco-Teruel B. Sickle cell anemia in Cuba: prevention and management, 1982-2018. MEDICC Rev. 2019;21(4):34-8.
(93) Bhukhanvala DS, Sorathiya SM, Sawant P, Colah R, Ghosh K, Gupte SC. Antenatal screening for identification of couples for prenatal diagnosis of severe hemoglobinopathies in surat, South Gujarat. J Obstet Gynaecol India. 2013;63(2):123-7.
(94) Gupta V, Sharma P, Jora R, Amandeep M, Kumar A. Screening for thalassemia carrier status in pregnancy and pre-natal diagnosis. Indian Pediatr. 2015;52(9):808-9.
(95) Li D, Liao C, Li J, Xie X, Huang Y, Zhong H. Detection of alpha-thalassemia in beta-thalassemia carriers and prevention of Hb Bart's hydrops fetalis through prenatal screening. Haematologica. 2006;91(5):649-51.

(96) Liao C, Mo QH, Li J, Li LY, Huang YN, Hua L, et al. Carrier screening for alpha- and beta-thalassemia in pregnancy: the results of an 11-year prospective program in Guangzhou Maternal and Neonatal Hospital. Prenat Diagn. 2005;25(2):163-71.
(97) Qamar ur N, Habibullah, Rizwan F, Memon F, Memon A. Frequency of thalassemia trait in pregnant women. Medical Channel. 2011;17(1):56-9.
(98) Ratanasiri T, Charoenthong C, Komwilaisak R, Changtrakul Y, Fucharoen S, Wongkham J, et al. Prenatal prevention for severe thalassemia disease at Srinagarind Hospital. J Med Assoc Thai. 2006;89 Suppl 4:S87-93.
(99) Tongsong T, Charoenkwan P, Sirivatanapa P, Wanapirak C, Piyamongkol W, Sirichotiyakul S, et al. Effectiveness of the model for prenatal control of severe thalassemia. Prenat Diagn. 2013;33(5):477-83.
(100) Wongprachum K, Sanchaisuriya K, Vidamaly V, Sorpasirth S, Dethvongphanh M, Norcharoen B, et al. Pilot screening program for thalassemia in a country with limited resources: a collaboration model between close neighboring countries. Southeast Asian J Trop Med Public Health. 2016;47(5):1040-7.
(101) Yang X, Zhang H, Tang X, Liu M, Zheng H, Zheng L, et al. Thalassemia gene detection and the prenatal diagnosis outcomes of pregnant women in Guiyang City. Int J Clin Exp Med. 2020;13(12):10025-30.
(102) Basel-Vanagaite L, Taub E, Drasinover V, Magal N, Brudner A, Zlotogora J, et al. Genetic carrier screening for spinal muscular atrophy and spinal muscular atrophy with respiratory distress 1 in an isolated population in Israel. Genet Test. 2008;12(1):53-6.
(103) Prior TW. Spinal muscular atrophy: newborn and carrier screening. Obstet Gynecol Clin North Am. 2010;37(1):23-36.
(104) Su YN, Hung CC, Lin SY, Chen FY, Chern JP, Tsai C, et al. Carrier screening for spinal muscular atrophy (SMA) in 107,611 pregnant women during the period 2005-2009: a prospective population-based cohort study. PLoS One. 2011;6(2):e17067.
(105) Zhang J, Wang Y, Ma D, Sun Y, Li Y, Yang P, et al. Carrier screening and prenatal diagnosis for spinal muscular atrophy in 13,069 Chinese pregnant women. J Mol Diagn. 2020;22(6):817-22.
(106) Holtkamp KCA, Henneman L, Gille JJP, Meijers-Heijboer H, Cornel MC, Lakeman P. Direct-to-consumer carrier screening for cystic fibrosis via a hospital website: a 6-year evaluation. J Community Genet. 2019;10(2):249-57.
(107) Picci L, Cameran M, Marangon O, Marzenta D, Ferrari S, Frigo AC, et al. A 10-year large-scale cystic fibrosis carrier screening in the Italian population. J Cyst Fibros. 2010;9(1):29-35.
(108) Morgenstern-Kaplan D, Raijman-Policar J, Majzner-Aronovich S, Aradhya S, Pineda-Alvarez DE, Aguinaga M, et al. Carrier screening in the Mexican Jewish community using a pan-ethnic expanded carrier screening NGS panel. Genet Med. 2022;24(4):821-30.
(109) Singh K, Bijarnia-Mahay S, Ramprasad VL, Puri RD, Nair S, Sharda S, et al. NGS-based expanded carrier screening for genetic disorders in north Indian population reveals unexpected results - a pilot study. BMC Med Genet. 2020;21(1):216.
(110) Capalbo A, Poli M, Riera-Escamilla A, Shukla V, Kudo Hoffding M, Krausz C, et al. Preconception genome medicine: current state and future perspectives to improve infertility diagnosis and reproductive and health outcomes based on individual genomic data. Hum Reprod Update. 2021;27(2):254-79.
(111) Punj S, Akkari Y, Huang J, Yang F, Creason A, Pak C, et al. Preconception carrier screening by genome sequencing: results from the clinical laboratory. Am J Hum Genet. 2018;102(6):1078-89.
(112) Martin J, Asan, Yi Y, Alberola T, Rodriguez-Iglesias B, Jimenez-Almazan J, et al. Comprehensive carrier genetic test using next-generation deoxyribonucleic acid sequencing in infertile couples wishing to conceive through assisted reproductive technology. Fertil Steril. 2015;104(5):1286-93.
(113) Hu P, Tan J, Yu F, Shao B, Zhang F, Zhang J, et al. A capillary electrophoresis-based multiplex PCR assay for expanded carrier screening in the eastern Han Chinese population. NPJ Genom Med. 2022;7(1):6.

(114) Zhao S, Xiang J, Fan C, Asan, Shang X, Zhang X, et al. Pilot study of expanded carrier screening for 11 recessive diseases in China: results from 10,476 ethnically diverse couples. Eur J Hum Genet. 2019;27(2):254-62.
(115) Berkenstadt M, Ries-Levavi L, Cuckle H, Peleg L, Barkai G. Preconceptional and prenatal screening for fragile X syndrome: experience with 40,000 tests. Prenat Diagn. 2007;27(11):991-4.
(116) Cheng YK, Lin CS, Kwok YK, Chan YM, Lau TK, Leung TY, et al. Identification of fragile X pre-mutation carriers in the Chinese obstetric population using a robust FMR1 polymerase chain reaction assay: implications for screening and prenatal diagnosis. Hong Kong Med. 2017;23(2):110-6.
(117) Cizmeli C, Lobel M, Franasiak J, Pastore LM. Levels and associations among self-esteem, fertility distress, coping, and reaction to potentially being a genetic carrier in women with diminished ovarian reserve. Fertil Steril. 2013;99(7):2037-44.e3.
(118) Gao F, Huang W, You Y, Huang J, Zhao J, Xue J, et al. Development of Chinese genetic reference panel for fragile X syndrome and its application to the screen of 10,000 Chinese pregnant women and women planning pregnancy. Mol Genet Genomic Med. 2020;8(6):e1236.
(119) Hung CC, Lee CN, Wang YC, Chen CL, Lin TK, Su YN, et al. Fragile X syndrome carrier screening in pregnant women in Chinese Han population. Sci Rep. 2019;9(1):15456.
(120) Jang JH, Lee K, Cho EH, Lee EH, Kim JW, Ki CS. Frequency of FMR1 premutation carriers and rate of expansion to full mutation in a retrospective diagnostic FMR1 Korean sample. Clin Genet. 2014;85(5):441-5.
(121) Kim MJ, Kim DJ, Kim SY, Yang JH, Kim MH, Lee SW, et al. Fragile X carrier screening in Korean women of reproductive age. J Med Screen. 2013;20(1):15-20.
(122) Meraj N, Yasin M, Rehman ZU, Tahir H, Jadoon H, Khan N, et al. Fragile X premutation carrier screening in Pakistani preconception women in primary care consultation. BMC Womens Health. 2022;22(1):57.
(123) Xi H, Xie W, Chen J, Tang W, Deng X, Li H, et al. Implementation of fragile X syndrome carrier screening during prenatal diagnosis: a pilot study at a single center. Mol Genet Genomic Med. 2021;9(7):e1711.
(124) Ai S, Cliffe C, Kidson-Gerber G. Antenatal haemoglobinopathy screening--experiences of a large Australian centre. Obstet Med. 2021;14(2):89-94.
(125) Borbolla Foster A, Smith E, Ross B. Adherence to a selective antenatal haemoglobinopathy screening policy within a tertiary level obstetric unit in Australia. Aust N Z J Obstet Gynaecol. 2021;61(1):63-8.
(126) Shang X, Peng Z, Ye Y, Asan, Zhang X, Chen Y, et al. Rapid targeted next-generation sequencing platform for molecular screening and clinical genotyping in subjects with hemoglobinopathies. EBioMedicine. 2017;23:150-9.
(127) Yin A, Li B, Luo M, Xu L, Wu L, Zhang L, et al. The prevalence and molecular spectrum of α- and β-globin gene mutations in 14,332 families of Guangdong Province, China. PLoS One. 2014;9(2):e89855.
(128) Chang F, Pirzado MS, Qazi RA, Sahito RA. The prevalence and antenatal screening of beta thalassaemia trait in pregnancy by naked eye single tube red cell osmotic fragility test. Medical Forum Monthly. 2014;25(9):36-40.
(129) Hafezi-Nejad N, Khosravi M, Bayat N, Kariminejad A, Hadavi V, Oberkanins C, et al. Characterizing a cohort of alpha-thalassemia couples collected during screening for hemoglobinopathies: 14 years of an Iranian experience. Hemoglobin. 2014;38(3):153-7.
(130) Miri-Moghaddam E, Zadeh-Vakili A. Profile of beta-thalassemia and its prenatal diagnosis in Khorasan-e-Jonobi Province, Iran. Hemoglobin. 2012;36(5):456-63.
(131) Patel AP, Patel RB, Patel SA, Vaniawala SN, Patel DS, Shrivastava NS, et al. beta-Thalassemia mutations in western India: outcome of prenatal diagnosis in a hemoglobinopathies project. Hemoglobin. 2014;38(5):329-34.
(132) Suwannakhon N, Pongsawatkul K, Seeratanachot T, Mahingsa K, Pingyod A, Bumrungpakdee W, et al. The shortcut strategy for beta thalassemia prevention. Hematol Rep. 2018;10(2):7530.

(133) Wong P, Sritippayawan S, Suwannakhon N, Tapprom A, Deoisares R, Sanguansermsri T. Q Sepharose micro-column chromatography: a simple screening method for identifying beta thalassemia traits and hemoglobin E carriers. Clin Biochem. 2016;49(16-17):1288-91.
(134) Suwannakhon N, Pongsawatkul K, Seeratanachot T, Rasri W, Mahingsa K, Pingyod A, et al. Fast-track strategy for the prevention of Hb bart's hydrops fetalis syndrome. Thalassemia Reports. 2017;7(1):26-9.
(135) Li J, Li R, Li DZ. Identification of nondeletional alpha-thalassemia in a prenatal screening program by reverse dot-blot in southern China. Hemoglobin. 2015;39(1):42-5.
(136) Jiang F, Zuo L, Li D, Li J, Tang X, Chen G, et al. Molecular epidemiology and hematologic characterization of deltabeta-thalassemia and hereditary persistence of fetal hemoglobin in 125,661 families of greater Guangzhou area, the metropolis of southern China. BMC Med Genet. 2020;21(1):43.
(137) Weil LG, Charlton MR, Coppinger C, Daniel Y, Streetly A. Sickle cell disease and thalassaemia antenatal screening programme in England over 10 years: a review from 2007/2008 to 2016/2017. J Clin Pathol. 2020;73(4):183-90.
(138) Ruengdit C, Punyamung M, Khamphikham P, Pongpunyayuen P, Intasai N, Pornprasert S. Multiplex quantitative real-time polymerase chain reaction and high-resolution melting analysis for identification of a couple at-risk of having a newborn with severe thalassemia. Hemoglobin. 2021;45(5):309-13.
(139) Yamsri S, Sanchaisuriya K, Fucharoen G, Sae-Ung N, Ratanasiri T, Fucharoen S. Prevention of severe thalassemia in northeast Thailand: 16 years of experience at a single university center. Prenat Diagn. 2010;30(6):540-6.
(140) Jiang F, Chen GL, Li J, Xie XM, Zhou JY, Liao C, et al. Pre gestational thalassemia screening in mainland China: the first two years of a preventive program. Hemoglobin. 2017;41(4-6):248-53.
(141) Jiang F, Zuo L, Li J, Chen G, Tang X, Zhou J, et al. Evaluation of intervention strategy of thalassemia for couples of childbearing ages in Centre of Southern China. J Clin Lab Anal. 2021;35(10):e23990.
(142) Theodoridou S, Alemayehou M, Prappas N, Karakasidou O, Aletra V, Plata E, et al. Carrier screening and prenatal diagnosis of hemoglobinopathies. A study of indigenous and immigrant couples in northern Greece, over the last 5 years. Hemoglobin. 2008;32(5):434-9.
(143) Theodoridou S, Prapas N, Balassopoulou A, Boutou E, Vyzantiadis TA, Adamidou D, et al. Efficacy of the National Thalassaemia and Sickle Cell Disease Prevention Programme in Northern Greece: 15-year experience, practice and policy gaps for natives and migrants. Hemoglobin. 2018;42(4):257-63.
(144) Wong P, Thanormrat P, Srithipayawan S, Jermnim N, Niyomthom S, Nimnuch N, et al. Risk of a couple having a child with severe thalassemia syndrome, prevalence in lower northern Thailand. Southeast Asian J Trop Med Public Health. 2006;37(2):366-9.
(145) Khedri A, Asadi F, Rasouli Ghahfarokhi SM, Obeidi N, Talebi F, Moghbelinejad S. Spectrum of mutations of thalassemia among couples from Izeh City, Khuzestan province, Iran. IJBC. 2020;12(2):58-63.
(146) Zhao S, Wang W, Wang Y, Han R, Fan C, Ni P, et al. NGS-based spinal muscular atrophy carrier screening of 10,585 diverse couples in China: a pan-ethnic study. Eur J Hum Genet. 2021;29(1):194-204.
(147) Johansen Taber KA, Beauchamp KA, Lazarin GA, Muzzey D, Arjunan A, Goldberg JD. Clinical utility of expanded carrier screening: results-guided actionability and outcomes. Genet Med. 2019;21(5):1041-8.
(148) Johansen Taber K, Lim-Harashima J, Naemi H, Goldberg J. Fragile X syndrome carrier screening accompanied by genetic consultation has clinical utility in populations beyond those recommended by guidelines. Mol Genet Genomic Med. 2019;7(12):e1024.
(149) Kiani AA, Mohamadinejad M, Shokrgozar N, Abbasian S. Mutations in thalassemia carrier couples: the importance of prenatal diagnostic tests. Clin Lab. 2022;68(5).
(150) American College of Obstetricians and Gynecologists' Committee on Genetics. Committee opinion no. 691: carrier screening for genetic conditions. Obstet Gynecol. 2017;129(3):e41-e55.
(151) National Institute for Health and Care Excellence. Appendix I, quality appraisal checklist—economic evaluations. Sep 2012. In: Methods for the development of NICE public health

guidance [Internet]. London (UK): The Institute. 3rd. Available from: https://www.nice.org.uk/process/pmg4/chapter/appendix-i-quality-appraisal-checklist-economic-evaluations
(152) Dormandy E, Bryan S, Gulliford MC, Roberts TE, Ades AE, Calnan M, et al. Antenatal screening for haemoglobinopathies in primary care: a cohort study and cluster randomised trial to inform a simulation model. The Screening for Haemoglobinopathies in First Trimester (SHIFT) trial. Health Technol Assess. 2010;14(20):1-160.
(153) Bryan S, Dormandy E, Roberts T, Ades A, Barton P, Juarez-Garcia A, et al. Screening for sickle cell and thalassaemia in primary care: a cost-effectiveness study. Br J Gen Pract. 2011;61(591):e620-7.
(154) Wang T, Bahrampour M, Byrnes J, Scuffham P, Kirk E, Downes M. Economic evaluation of reproductive carrier screening for recessive genetic conditions: a systematic review. Expert Rev Pharmacoecon Outcomes Res. 2021:1-10.
(155) Radhakrishnan M, van Gool K, Hall J, Delatycki M, Massie J. Economic evaluation of cystic fibrosis screening: a review of the literature. Health Policy. 2008;85(2):133-47.
(156) Azimi M, Schmaus K, Greger V, Neitzel D, Rochelle R, Dinh T. Carrier screening by next-generation sequencing: health benefits and cost effectiveness. Mol Genet Genomic Med. 2016;4(3):292-302.
(157) Beauchamp KA, Johansen Taber KA, Muzzey D. Clinical impact and cost-effectiveness of a 176-condition expanded carrier screen. Genet Med. 2019;21(9):1948-57.
(158) Medical Services Advisory Committee. 1573 – Reproductive carrier testing for cystic fibrosis, spinal muscular atrophy and fragile X syndrome. 2020 [cited 2021 Oct 29]. Available from: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1573-public
(159) Zhang L, Bao Y, Riaz M, Tiller J, Liew D, Zhuang X, et al. Population genomic screening of all young adults in a health-care system: a cost-effectiveness analysis. Genet Med. 2019;21(9):1958-68.
(160) Avram CM, Dyer AL, Shaffer BL, Caughey AB. The cost-effectiveness of genotyping versus sequencing for prenatal cystic fibrosis carrier screening. Prenat Diagn. 2021;41(11):1449-59.
(161) Medical Services Advisory Committee. 1216.1 – Cystic fibrosis transmembrane regulator (CFTR) testing. 2016 [cited 2021 Oct 29]. Available from: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1216.1-public
(162) Hill M, Twiss P, Verhoef TI, Drury S, McKay F, Mason S, et al. Non-invasive prenatal diagnosis for cystic fibrosis: detection of paternal mutations, exploration of patient preferences and cost analysis. Prenat Diagn. 2015;35(10):950-8.
(163) Norman R, van Gool K, Hall J, Delatycki M, Massie J. Cost-effectiveness of carrier screening for cystic fibrosis in Australia. J Cyst Fibros. 2012;11(4):281-7.
(164) Maxwell S, Brameld K, Youngs L, Geelhoed E, O'Leary P. Informing policy for the Australian context--costs, outcomes and cost savings of prenatal carrier screening for cystic fibrosis. Aust N Z J Obstet Gynaecol. 2010;50(1):51-9.
(165) Weijers-Poppelaars FA, Wildhagen MF, Henneman L, Cornel MC, Kate LP. Preconception cystic fibrosis carrier screening: costs and consequences. Genet Test. 2005;9(2):158-66.
(166) Guo Q, Chang YY, Huang CH, Hsiao YS, Hsiao YC, Chiu IF, et al. Population-based carrier screening and prenatal diagnosis of fragile X syndrome in East Asian populations. J Genet Genomics. 2021;48(12):1104-10.
(167) Hollingsworth B, Harris A. Economic evaluation of prenatal population screening for fragile X syndrome. Community Genet. 2005;8(2):68-72.
(168) Musci TJ, Caughey AB. Cost-effectiveness analysis of prenatal population-based fragile X carrier screening. Am J Obstet Gynecol. 2005;192(6):1905-12; discussion 12-5.
(169) Medical Services Advisory Committee. 1531 – Alpha thalassaemia genetic testing. 2019 [cited 2021 Oct 29]. Available from: http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1531-Public
(170) Little SE, Janakiraman V, Kaimal A, Musci T, Ecker J, Caughey AB. The cost-effectiveness of prenatal screening for spinal muscular atrophy. Am J Obstet Gynecol. 2010;202(3):253 e1-7.

(171) Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Value Health. 2013;16(2):e1-5.
(172) Rowley PT, Loader S, Kaplan RM. Prenatal screening for cystic fibrosis carriers: an economic evaluation. Am J Hum Genet. 1998;63(4):1160-74.
(173) Musci TJ, Moyer K. Prenatal carrier testing for fragile X: counseling issues and challenges. Obstet Gynecol Clin North Am. 2010;37(1):61-70.
(174) Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. 2013;16(2):231-50.
(175) Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation of health technologies: Canada. 4th ed. Ottawa (ON): The Agency; 2017. p. 76.
(176) Health Quality Ontario. Noninvasive Prenatal testing for trisomies 21, 18, and 13, sex chromosome aneuploidies, and microdeletions: a health technology assessment. Ont Health Technol Assess Ser. 2019;19(4):1-166.
(177) Xie X, Gajic-Veljanoski O, Falk L, Schaink AK, Lambrinos A, Wang M, et al. Challenges in health technology assessments of genetic tests. [Internet]: J Hosp Manag Health Policy; 2020 [cited 2021 Nov 11]. Available from: https://jhmhp.amegroups.com/article/view/6254/pdf
(178) Grosse SD. What is the value for money of prenatal carrier screening for spinal muscular atrophy? Too soon to say. Am J Obstet Gynecol. 2010;202(3):209-11.
(179) Shackley P, Cairns J. Evaluating the benefits of antenatal screening: an alternative approach. Health Policy. 1996;36(2):103-15.
(180) Gregg AR, Aarabi M, Klugman S, Leach NT, Bashford MT, Goldwaser T, et al. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021;23(10):1793-806.
(181) Haque IS, Lazarin GA, Kang HP, Evans EA, Goldberg JD, Wapner RJ. Modeled fetal risk of genetic diseases identified by expanded carrier screening. JAMA. 2016;316(7):734-42.
(182) Hogan GJ, Vysotskaia VS, Beauchamp KA, Seisenberger S, Grauman PV, Haas KR, et al. Validation of an expanded carrier screen that optimizes sensitivity via full-exon sequencing and panel-wide copy number variant identification. Clin Chem. 2018;64(7):1063-73.
(183) Lazarin GA, Haque IS, Nazareth S, Iori K, Patterson AS, Jacobson JL, et al. An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. Genet Med. 2013;15(3):178-86.
(184) Molecular testing for fragile X syndrome [Internet]. Toronto (ON): The Hospital for Sick Children; 2021 [cited 2021 Nov 11]. Available from: https://www.sickkids.ca/en/care-services/for-health-care-providers/lab-tests/249-Fragile-X-Syndrome
(185) CHEO. Molecular testing for fragile X syndrome [Internet]. 2021 [cited 2021 Nov 11]. Available from: https://www.cheo.on.ca/en/clinics-services-programs/genetic-tests-available.aspx#Test-details
(186) Berry-Kravis E, Zhou L, Jackson J, Tassone F. Diagnostic profile of the AmplideX Fragile X Dx and Carrier Screen Kit for diagnosis and screening of fragile X syndrome and other FMR1-related disorders. Expert Rev Mol Diagn. 2021;21(3):255-67.
(187) Langlois S, Ford JC, Chitayat D, CCMG Prenatal Diagnosis Committee, SOGC Genetics Committee. Carrier screening for thalassemia and hemoglobinopathies in Canada. J Obstet Gynaecol Can. 2008;30(10):950-9.
(188) Waye JS, Eng B, Cai SP, Patterson M, Smith J, Tang W, et al. Carrier detection and prenatal diagnosis of hemoglobinopathies in Ontario. Clin Invest Med. 1993;16(5):358-71.
(189) Molecular testing for spinal muscular atrophy [Internet]. Toronto (ON): The Hospital for Sick Children; 2021 [cited 2021 Nov 11]. Available from: https://www.sickkids.ca/en/care-services/for-health-care-providers/lab-tests/257-Spinal-Muscular-Atrophy/
(190) Verheij JB, Hilderink HB, Verzijl JG, Wildhagen MF, Habbema JD, ten Kate LP. Preconception screening of parents and carrier state of cystic fibrosis in the Netherlands: expenses and savings. Ned Tijdschr Geneeskd. 1998;142(13):706-10.

(191) Asch DA, Hershey JC, Dekay ML, Pauly MV, Patton JP, Jedrziewski MK, et al. Carrier screening for cystic fibrosis: costs and clinical outcomes. Med Decis Making. 1998;18(2):202-12.
(192) Wildhagen MF, Hilderink HB, Verzijl JG, Verheij JB, Kooij L, Tijmstra T, et al. Costs, effects, and savings of screening for cystic fibrosis gene carriers. J Epidemiol Community Health. 1998;52(7):459-67.
(193) ten Kate LP, Verheij JB, Wildhagen MF, Hilderink HB, Kooij L, Verzijl JG, et al. Comparison of single-entry and double-entry two-step couple screening for cystic fibrosis carriers. Hum Hered. 1996;46(1):20-5.
(194) Asch DA, Hershey JC, Pauly MV, Patton JP, Jedrziewski MK, Mennuti MT. Genetic screening for reproductive planning: methodological and conceptual issues in policy analysis. Am J Public Health. 1996;86(5):684-90.
(195) Arjunan A, Torres R, Gardiner A, Kaseniit KE, Wootton J, Ben-Shachar R, et al. Evaluating the efficacy of three carrier screening workflows designed to identify at-risk carrier couples. Prenat Diagn. 2021;41(7):896-904.
(196) Massie J, Ioannou L, Delatycki M. Prenatal and preconception population carrier screening for cystic fibrosis in Australia: where are we up to? Aust N Z J Obstet Gynaecol. 2014;54(6):503-9.
(197) Kuppermann M, Nease RF, Learman LA, Gates E, Blumberg B, Washington AE. Procedure-related miscarriages and Down syndrome-affected births: implications for prenatal testing based on women's preferences. Obstet Gynecol. 2000;96(4):511-6.
(198) CADTH. CADTH drug reimbursement review: pharmacoeconomic report - onasemnogene abeparvovec (Zolgensma)2021 [cited 2021 Nov 11]. Available from: https://cadth.ca/sites/default/files/DRR/2021/sg0649-zolgensma-pharmacoeconomic-review-report.pdf
(199) CADTH. Risdiplam (Evrysdi)2021 [cited 2021 Nov 11]. Available from: https://www.cadth.ca/sites/default/files/DRR/2021/SR0661-combined-report-final.pdf
(200) CADTH. CADTH reimbursement review: elexacaftor-tezacaftor-ivacaftor and ivacaftor (Trikafta) [Internet]. Ottawa (ON): CADTH; 2021 [cited 2022 July 07, 2022]. Available from: https://www.cadth.ca/elexacaftortezacaftorivacaftor-and-ivacaftor
(201) Basran RK, Patterson M, Walker L, Nakamura LM, Eng B, Chui DH, et al. Prenatal diagnosis of hemoglobinopathies in Ontario, Canada. Ann N Y Acad Sci. 2005;1054:507-10.
(202) Nolin SL, Glicksman A, Ding X, Ersalesi N, Brown WT, Sherman SL, et al. Fragile X analysis of 1112 prenatal samples from 1991 to 2010. Prenat Diagn. 2011;31(10):925-31.
(203) Zhang HJ, Amid A, Janzen LA, Segbefia CI, Chen S, Athale U, et al. Outcomes of haemoglobin Bart's hydrops fetalis following intrauterine transfusion in Ontario, Canada. Arch Dis Child Fetal Neonatal Ed. 2021;106(1):51-6.
(204) Akolekar R, Beta J, Picciarelli G, Ogilvie C, D'Antonio F. Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. Ultrasound Obstet Gynecol. 2015;45(1):16-26.
(205) Ontario Health. Genome-wide sequencing for unexplained developmental disabilities or multiple congenital anomalies: a health technology assessment. Ont Health Technol Assess Ser. 2020;20(11):1-178.
(206) National Organization for Rare Disorders. Rare disease database: fragile X syndrome [Internet]. Danbury (CT): National Organization for Rare Disorders; 2021 [cited 2021 Nov 11]. Available from: https://rarediseases.org/rare-diseases/fragile-x-syndrome
(207) Kohne E. Hemoglobinopathies: clinical manifestations, diagnosis, and treatment. Dtsch Arztebl Int. 2011;108(31-32):532-40.
(208) Hayeems RZ, Campitelli M, Ma X, Huang T, Walker M, Guttmann A. Rates of prenatal screening across health care regions in Ontario, Canada: a retrospective cohort study. CMAJ Open. 2015;3(2):E236-43.
(209) Kessels SJM, Carter D, Ellery B, Newton S, Merlin TL. Prenatal genetic testing for cystic fibrosis: a systematic review of clinical effectiveness and an ethics review. Genet Med. 2020;22(2):258-67.
(210) Committee on Genetics. Committee opinion No. 691: carrier screening for genetic conditions. Obstet Gynecol. 2017;129(3):e41-e55.

(211) Srinivasan BS, Evans EA, Flannick J, Patterson AS, Chang CC, Pham T, et al. A universal carrier test for the long tail of Mendelian disease. Reprod Biomed Online. 2010;21(4):537-51.
(212) Arber M, Garcia S, Veale T, Edwards M, Shaw A, Glanville J. Sensitivity of a search filter designed to identify studies reporting health state utility values [abstract]. Paper presented at: Mosaic, 116th Annual Meeting, Medical Library Association; 2016 May 15-20; Toronto, ON. 2016. In: Mosaic '16 Paper Abstracts [Internet]. Forest Hill (MD): CadmiumCD. Available from: https://www.eventscribe.com/2016/mla/assets/Paper_Abstracts_Updated.pdf
(213) Guertin JR, Feeny D, Tarride JE. Age- and sex-specific Canadian utility norms, based on the 2013-2014 Canadian Community Health Survey. CMAJ. 2018;190(6):E155-E61.
(214) Chevreul K, Berg Brigham K, Brunn M, des Portes V, Network B-RR. Fragile X syndrome: economic burden and health-related quality of life of patients and caregivers in France. J Intellect Disabil Res. 2015;59(12):1108-20.
(215) Bach JR, Vega J, Majors J, Friedman A. Spinal muscular atrophy type 1 quality of life. Am J Phys Med Rehabil. 2003;82(2):137-42.
(216) Lopez-Bastida J, Pena-Longobardo LM, Aranda-Reneo I, Tizzano E, Sefton M, Oliva-Moreno J. Social/economic costs and health-related quality of life in patients with spinal muscular atrophy (SMA) in Spain. Orphanet J Rare Dis. 2017;12(1):141.
(217) Spackman E, Sculpher M, Howard J, Malfroy M, Llewelyn C, Choo L, et al. Cost-effectiveness analysis of preoperative transfusion in patients with sickle cell disease using evidence from the TAPS trial. Eur J Haematol. 2014;92(3):249-55.
(218) John MJ, Jyani G, Jindal A, Mashon RS, Mathew A, Kakkar S, et al. Cost effectiveness of hematopoietic stem cell transplantation compared with transfusion chelation for treatment of thalassemia major. Biol Blood Marrow Transplant. 2018;24(10):2119-26.
(219) Genetic testing: get answers before your next ob-gyn visit [Internet]. San Francisco, CA: Invitae Corporation; 2021 [cited 2021 Nov 11]. Available from: https://www.invitae.com/en/individuals/reproductive-genetic-testing/carrier-screening-cpc-2/?gclid=EAIaIQobChMI1_X814GP9AIVWI1oCR00CgjCEAAYAiAAEgKxqvD_BwE
(220) LifeLabs Genetics. Plan for your family with a simple genetic screen [Internet]. 2021 [cited 2021 11 Nov]. Available from: https://www.lifelabsgenetics.com/product/expanded-carrier-screening/?gclid=EAIaIQobChMIurqK8PGO9AIVWI9oCR1MagnOEAMYAyAAEgIM2fD_BwE
(221) Canadian Institute for Health Information. Cost Estimator [Internet]. Ottawa (ON): CIHI. 2021. Available from: https://www.cihi.ca/en/patient-cost-estimator
(222) Lunsky Y, De Oliveira C, Wilton A, Wodchis W. High health care costs among adults with intellectual and developmental disabilities: a population-based study. J Intellect Disabil Res. 2019;63(2):124-37.
(223) Tsiplova K, Zur RM, Ungar WJ. A microcosting and cost-consequence analysis of genomic testing strategies in autism spectrum disorder. [Internet]. Toronto, Ontario: TASK: Technology Assessment at SickKids; 2016 [cited 2022 Nov 04]. Available from: https://lab.research.sickkids.ca/task/wp-content/uploads/sites/66/2018/06/2016-02.2-Microcosting-FULL-REPORT.pdf
(224) Ministry of Health, editor. Schedule of benefits: physician services under the Health Insurance Act. Toronto (ON): Queen's Printer for Ontario; 2021.
(225) Health Data Branch. Health data branch web portal: Ontario case costing [Internet]. Toronto (ON): King's Printer for Ontario. 2022. Available from: https://hsim.health.gov.on.ca/HDBPortal
(226) Ministry of Health. Get fertility treatments [Internet]. Toronto (ON): Queen's Printer for Ontario; 2021 [cited 2022 07 Jul 2022]. Available from: https://www.ontario.ca/page/get-fertility-treatments
(227) Lipton JH, Zargar M, Warner E, Greenblatt EE, Lee E, Chan KKW, et al. Cost effectiveness of in vitro fertilisation and preimplantation genetic testing to prevent transmission of BRCA1/2 mutations. Hum Reprod. 2020;35(2):434-45.
(228) Widger K, Seow H, Rapoport A, Chalifoux M, Tanuseputro P. Children's end-of-life health care use and cost. Pediatrics. 2017;139(4).
(229) Krahn M, Miller F, Bayoumi A, Brooker AS, Wagner F, Winsor S, et al. Development of the Ontario decision framework: a values based framework for health technology assessment. Int J Technol Assess Health Care. 2018;34(3):290-9.

(230) TreeAge Pro decision analysis software. TreeAge Software, Inc. Williamstown (MA). Available at: http://www.treeage.com.
(231) Statistics Canada. Consumer price index: table 326-0020 [Internet]. Ottawa (ON): King's Printer for Canada. 2018. Available from: http://www5.statcan.gc.ca/cansim/a26?lang=eng&id=3260020
(232) Kassim AA, Leonard A. Debating the future of sickle cell disease curative therapy: haploidentical hematopoietic stem cell transplantation vs. gene therapy. J Clin Med. 2022;11(16).
(233) Kauf TL, Coates TD, Huazhi L, Mody-Patel N, Hartzema AG. The cost of health care for children and adults with sickle cell disease. Am J Hematol. 2009;84(6):323-7.
(234) Statistics Canada. Table 13-10-0414-01 live births, by place of residence of mother [Internet]. Ottawa (ON): King's Printer for Canada. 2021. Available from: https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310041401
(235) Toronto Public Health. Before pregnancy [Internet]. Toronto (ON): City of Toronto; 2021 [cited 2021 Nov 11]. Available from: https://www.toronto.ca/community-people/children-parenting/pregnancy-and-parenting/pregnancy/before-pregnancy
(236) Excel spreadsheet software. Microsoft Corporation. Redmond (WA). Available at: http://www.products.office.com/Microsoft/Excel.
(237) Barham L. Public and patient involvement at the UK National Institute for Health and Clinical Excellence. Patient. 2011;4(1):1-10.
(238) Messina J, Grainger DL. A pilot study to identify areas for further improvements in patient and public involvement in health technology assessments for medicines. Patient. 2012;5(3):199-211.
(239) OHTAC Public Engagement Subcommittee. Public engagement for health technology assessment at Health Quality Ontario—final report from the Ontario Health Technology Advisory Committee Public Engagement Subcommittee [Internet]. Toronto (ON): Queen's Printer for Ontario; 2015 [cited 2018 Apr 30]. Available from: http://www.hqontario.ca/Portals/0/documents/evidence/special-reports/report-subcommittee-20150407-en.pdf
(240) Selva A, Solà I, Zhang Y, Pardo-Hernandez H, Haynes RB, Martínez García L, et al. Development and use of a content search strategy for retrieving studies on patients' views and preferences. Health Qual Life Outcomes. 2017;15(1):126.
(241) Best S, Long J, Theodorou T, Hatem S, Lake R, Archibald A, et al. Health practitioners' perceptions of the barriers and enablers to the implementation of reproductive genetic carrier screening: a systematic review. Prenat Diagn. 2021;02:02.
(242) Janssens S, De Paepe A, Borry P. Attitudes of health care professionals toward carrier screening for cystic fibrosis: a review of the literature. J Community Genet. 2014;5(1):13-29.
(243) Moultrie RR, Kish-Doto J, Peay H, Lewis MA. A review on spinal muscular atrophy: awareness, knowledge, and attitudes. J Genet Couns. 2016;25(5):892-900.
(244) Yu J. A systematic review of issues around antenatal screening and prenatal diagnostic testing for genetic disorders: women of Asian origin in western countries. Health Soc Care Community. 2012;20(4):329-46.
(245) Hanprasertpong T, Raungrongmorakot K, Geater A, Puapornpong P, Laosooksathit W, Hemachandra A, et al. Survey on knowledge, attitude, acceptance and related factors among pregnant women in Thailand regarding antenatal thalassaemia screening. J Obstet Gynaecol. 2018;38(7):950-5.
(246) Janssens S, Chokoshvilli D, Binst C, Mahieu I, Henneman L, De Paepe A, et al. Attitudes of cystic fibrosis patients and parents toward carrier screening and related reproductive issues. Eur J Hum Genet. 2016;24(4):506-12.
(247) Ames AG, Jaques A, Ukoumunne OC, Archibald AD, Duncan RE, Emery J, et al. Development of a fragile X syndrome (FXS) knowledge scale: towards a modified multidimensional measure of informed choice for FXS population carrier screening. Health Expect. 2015;18(1):69-80.
(248) Bailey DB, Jr., Bishop E, Raspa M, Skinner D. Caregiver opinions about fragile X population screening. Genet Med. 2012;14(1):115-21.

(249) Boardman FK, Young PJ, Griffiths FE. Population screening for spinal muscular atrophy: a mixed methods study of the views of affected families. Am J Med Genet A. 2017;173(2):421-34.
(250) Boardman FK, Young PJ, Griffiths FE. Impairment experiences, identity and attitudes towards genetic screening: the views of people with spinal muscular atrophy. J Genet Couns. 2018;27(1):69-84.
(251) Boardman FK, Clark C, Jungkurth E, Young PJ. Social and cultural influences on genetic screening programme acceptability: a mixed-methods study of the views of adults, carriers, and family members living with thalassemia in the UK. J Genet Couns. 2020;29(6):1026-40.
(252) Brown K, Dormandy E, Reid E, Gulliford M, Marteau T. Impact on informed choice of offering antenatal sickle cell and thalassaemia screening in primary care: a randomized trial. J Med Screen. 2011;18(2):65-75.
(253) Ioannou L, Massie J, Collins V, McClaren B, Delatycki MB. Population-based genetic screening for cystic fibrosis: attitudes and outcomes. Public Health Genomics. 2010;13(7-8):449-56.
(254) Ioannou L, Massie J, Lewis S, McClaren B, Collins V, Delatycki MB. 'No thanks'-reasons why pregnant women declined an offer of cystic fibrosis carrier screening. J Community Genet. 2014;5(2):109-17.
(255) Maxwell SJ, Kyne G, Molster C, Barker NM, Ormsby J, O'Leary P. Perceptions of population cystic fibrosis prenatal and preconception carrier screening among individuals with cystic fibrosis and their family members. Genet Test Mol Biomarkers. 2011;15(3):159-64.
(256) Mayo-Gamble TL, Middlestadt SE, Lin HC, Cunningham-Erves J, Barnes P, Jackson PB. Identifying factors underlying the decision for sickle cell carrier screening among African Americans within middle reproductive age. J Genet Couns. 2018;27(5):1302-11.
(257) Prior TW, Snyder PJ, Rink BD, Pearl DK, Pyatt RE, Mihal DC, et al. Newborn and carrier screening for spinal muscular atrophy. Am J Med Genet A. 2010;152A(7):1608-16.
(258) van Elderen T, Mutlu D, Karstanje J, Passchier J, Tibben A, Duivenvoorden HJ. Turkish female immigrants' intentions to participate in preconception carrier screening for hemoglobinopathies in the Netherlands: an empirical study. Public Health Genomics. 2010;13(7-8):415-23.
(259) Vuthiwong C, Panichkul P, Punpuckdeekoon P. Causes and attitude of husbands toward thalassemic carrier screening test when their partners have abnormal screening tests. J Med Assoc Thai. 2012;95 Suppl 5:S162-7.
(260) Widayanti CG, Ediati A, Tamam M, Faradz SM, Sistermans EA, Plass AM. Feasibility of preconception screening for thalassaemia in Indonesia: exploring the opinion of Javanese mothers. Ethn Health. 2011;16(4-5):483-99.
(261) Zafari M, Kosaryan M, Mirzayi MR. Reproductive behavior in carrier couples for transfusion-dependent thalassemia major: evaluation of knowledge, attitude and practice. J Nurs Midwifery Sci. 2016;3(1):66-73.
(262) Cunningham F, Lewis S, Curnow L, Glazner J, Massie J. Respiratory physicians and clinic coordinators' attitudes to population-based cystic fibrosis carrier screening. J Cyst Fibros. 2014;13(1):99-105.
(263) Stark Z, Massie J, McClaren B, Ioannou L, Cousens N, Lewis S, et al. Current practice and attitudes of Australian obstetricians toward population-based carrier screening for inherited conditions. Twin Res Hum Genet. 2013;16(2):601-7.
(264) Darcy D, Tian L, Taylor J, Schrijver I. Cystic fibrosis carrier screening in obstetric clinical practice: knowledge, practices, and barriers, a decade after publication of screening guidelines. Gen Test Mol Biomarkers. 2011;15(7-8):517-23.
(265) Jans SM, de Jonge A, Henneman L, Cornel MC, Lagro-Janssen AL. Attitudes of general practitioners and midwives towards ethnicity-based haemoglobinopathy-carrier screening. Eur J Hum Genet. 2012;20(11):1112-7.
(266) Lieberman S, Zuckerman S, Levy-Lahad E, Altarescu G. Conflicts regarding genetic counseling for fragile X syndrome screening: a survey of clinical geneticists and genetic counselors in Israel. Am J Med Genet A. 2011;155A(9):2154-60.
(267) Valente GM, Amor DJ, Ioannou LJ, Archibald AD. Factors influencing medical practitioner participation in population carrier screening for cystic fibrosis. Aust N Z J Obstet Gynaecol. 2020;02:02.

(268) Ioannou L, Massie J, Lewis S, Collins V, McClaren B, Delatycki MB. Attitudes and opinions of pregnant women who are not offered cystic fibrosis carrier screening. Eur J Hum Genet. 2014;22(7):859-65.
(269) Ghoreyshyzadeh F, Pour Feizi AAH, Ghaffari R, Nourdadgar A. Educational needs assessment of family health providers in Tabriz health care centers in 2015. Res Dev Med Educ. 2017;6(1):12-8.
(270) Ishaq F, Abid H, Kokab F, Akhtar A, Mahmood S. Awareness among parents of beta-thalassemia major patients, regarding prenatal diagnosis and premarital screening. J Coll Physicians Surg Pak. 2012;22(4):218-21.
(271) Clarke EV, Schneider JL, Lynch F, Kauffman TL, Leo MC, Rosales AG, et al. Assessment of willingness to pay for expanded carrier screening among women and couples undergoing preconception carrier screening. PLoS One. 2018;13(7):e0200139.
(272) Kvale S. Interviews: an introduction to qualitative research interviewing. Thousand Oaks (CA): Sage; 1996.
(273) Kuzel AJ. Sampling in qualitative inquiry. In: Miller WL, Crabtree BF, editors. Doing qualitative research. Thousand Oaks (CA): Sage; 1999. p. 33–45.
(274) Morse J. Emerging from the data: cognitive processes of analysis in qualitative research. In: Morse J, editor. Critical issues in qualitative research methods. Thousand Oaks (CA): Sage; 1994. p. 23-41.
(275) Patton MQ. Qualitative research and evaluation methods. 3rd ed. Thousand Oaks (CA): Sage; 2002.
(276) Strauss AL, Corbin JM. Basics of qualitative research: techniques and procedures of developing a grounded theory. 2nd ed. Thousand Oaks (CA): Sage; 1998.
(277) Health Technology Assessment International. Introduction to health technology assessment [Internet]. Edmonton (AB): Health Technology Assessment International; 2015 [cited 2018 Apr 30]. Available from: http://www.htai.org/fileadmin/HTAi_Files/ISG/PatientInvolvement/v2_files/Resource/PCISG-Resource-Intro_to_HTA__KFacey__Jun13.pdf
(278) Strauss AL, Corbin JM. Grounded theory research: procedures, canons, and evaluative criteria. Qual Sociol. 1990;13(1):3-21.
(279) Strauss AL, Corbin JM. Grounded theory methodology: an overview. In: Denzin NK, Lincoln YS, editors. Handbook of qualitative research. Thousand Oaks (CA): Sage; 1994. p. 273-85.
(280) Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 1994;330(23):1639-44.
(281) US Centers for Disease Control and Prevention. Sickle cell disease (SCD) [Internet]. Washington DC: U.S. Department of Health & Human Services; 2021 [cited 2021 Jan 11]. Available from: https://www.cdc.gov/ncbddd/sicklecell/index.html
(282) Cystic Fibrosis Foundation. Treatments and therapies [Internet]. Bethesda (MD): Cystic Fibrosis Foundation; 2021 [cited 2021 Jan 11]. Available from: https://www.cff.org/Life-With-CF/Treatments-and-Therapies
(283) Genetic and Rare Diseases Information Center. Spinal muscular atrophy [Internet]. Gaithersburg (MD): National Institutes of Health; 2021 [cited 2021 Jan 11]. Available from: https://rarediseases.info.nih.gov/diseases/7674/spinal-muscular-atrophy
(284) Ma Y, Wei X, Pan H, Wang S, Wang X, Liu X, et al. The prevalence of CGG repeat expansion mutation in FMR1 gene in the northern Chinese women of reproductive age. BMC Med Genet. 2019;20(1):81.
(285) Eissa NRH, H.A.; Senousy, S.M.; Soliman, H.N.; Essawi, M.L. SMA carrier testing using real-time PCR as a potential preconception screening tool. Egypt J Med Hum Genet. 2021;23(24).
(286) Ghiossi CE, Goldberg JD, Haque IS, Lazarin GA, Wong KK. Clinical utility of expanded carrier screening: reproductive behaviors of at-risk couples. J Genet Couns. 2018;27(3):616-25.
(287) Koren A, Zalman L, Palmor H, Zamir RB, Levin C, Openheim A, et al. Sickle cell anemia in northern Israel: screening and prevention. Isr Med Assoc J. 2009;11(4):229-34.

(288) Shi M, Liauw AL, Tong S, Zheng Y, Leung TY, Chong SC, et al. Clinical implementation of expanded carrier screening in pregnant women at early gestational weeks: a Chinese cohort study. Genes (Basel). 2021;12(4):29.
(289) Singer A, Sagi-Dain L. Impact of a national genetic carrier-screening program for reproductive purposes. Acta Obstet Gynecol Scand. 2020;99(6):802-8.
(290) Aboagye S, Torto M, Asah-Opoku K, Nuamah MA, Oppong SA, Samba A. Sickle cell education: a survey of antenatal healthcare givers. Am J Trop Med Hyg. 2019;101(3):684-8.
(291) Boardman FK, Young PJ, Warren O, Griffiths FE. The role of experiential knowledge within attitudes towards genetic carrier screening: a comparison of people with and without experience of spinal muscular atrophy. Health Expect. 2018;21(1):201-11.

About Us

We are an agency created by the Government of Ontario to connect, coordinate and modernize our province's health care system. We work with partners, providers and patients to make the health system more efficient so everyone in Ontario has an opportunity for better health and wellbeing. We work to enhance patient experience, improve population health, enhance provider experiences, improve value and advance health equity.

For more information about Ontario Health, visit OntarioHealth.ca.

Equity, Inclusion, Diversity and Anti-Racism

Ontario Health is committed to advancing equity, inclusion and diversity and addressing racism in the health care system. As part of this work, Ontario Health has developed an Equity, Inclusion, Diversity and Anti-Racism Framework, which builds on existing legislated commitments and relationships and recognizes the need for an intersectional approach.

Unlike the notion of equality, equity is not about sameness of treatment. It denotes fairness and justice in process and in results. Equitable outcomes often require differential treatment and resource redistribution to achieve a level playing field among all individuals and communities. This requires recognizing and addressing barriers to opportunities for all to thrive in our society.

ontariohealth.ca/equity-inclusion-diversity-and-anti-racism

About the Ontario Health Technology Advisory Committee

How to Obtain Reports From the Ontario Health Technology Assessment Series

Disclaimer

Ontario Health
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Toll Free: 1-877-280-8538
TTY: 1-800-855-0511
Email: OH-HQO_HTA@OntarioHealth.ca
hqontario.ca

ISSN 1915-7398 (online)
ISBN 978-1-4868-7272-5 (PDF)