Health Quality Ontario

Ontario Health Technology Assessment Series

Minimal Residual Disease Evaluation in Childhood Acute Lymphoblastic Leukemia: An Economic Analysis

KEY MESSAGES

Leukemia is the most common form of childhood cancer in Canada. The most common type of leukemia is called precursor B-cell acute lymphoblastic leukemia. At the beginning of chemotherapy, such tools as flow cytometry and polymerase chain reaction are used to see how many leukemia cells remain in bone marrow or peripheral blood. The results of this testing are used to assess patients and to change treatment according to the chances that leukemia will reappear.

In newly diagnosed patients, revealing remaining cancer cells by flow cytometry leads to better clinical outcomes than no testing: longer life, less chance that cancer will return, and reduced need for bone marrow transplant. In monetary terms, these tests give good value. In newly diagnosed patients, the 1-year cost of testing is estimated at $340,760. Our economic evaluation did not examine whether testing gives good value if cancer returns after treatment.

Our economic evaluation for Ontario shows that minimal residual disease testing by flow cytometry in newly diagnosed patients with precursor B-cell acute lymphoblastic leukemia is cost-effective and represents good value for money.

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HEALTH TECHNOLOGY ASSESSMENT AT HEALTH QUALITY ONTARIO

This report was developed by a multi-disciplinary team from Health Quality Ontario and the Toronto Health Economics and Technology Assessment Collaborative (THETA). The lead health economists were O. Gajic-Veljanoski, B. Pham, P. Pechlivanoglou, and M. Krahn, the medical librarians were Caroline Higgins and Joanna Bielecki, and the medical editor was Elizabeth Jean Betsch. Others involved in the development and production of this report were Irfan Dhalla, Nancy Sikich, Claude Soulodre, Natasha Sadasook, Anne Sleeman, and Jessica Verhey.

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ABSTRACT

Background

Minimal residual disease (MRD) testing by higher performance techniques such as flow cytometry and polymerase chain reaction (PCR) can be used to detect the proportion of remaining leukemic cells in bone marrow or peripheral blood during and after the first phases of chemotherapy in children with acute lymphoblastic leukemia (ALL). The results of MRD testing are used to reclassify these patients and guide changes in treatment according to their future risk of relapse.

We conducted a systematic review of the economic literature, cost-effectiveness analysis, and budget-impact analysis to ascertain the cost-effectiveness and economic impact of MRD testing by flow cytometry for management of childhood precursor B-cell ALL in Ontario.

Methods

A systematic literature search (1998–2014) identified studies that examined the incremental cost-effectiveness of MRD testing by either flow cytometry or PCR. We developed a lifetime state-transition (Markov) microsimulation model to quantify the cost-effectiveness of MRD testing followed by risk-directed therapy to no MRD testing and to estimate its marginal effect on health outcomes and on costs. Model input parameters were based on the literature, expert opinion, and data from the Pediatric Oncology Group of Ontario Networked Information System. Using predictions from our Markov model, we estimated the 1-year cost burden of MRD testing versus no testing and forecasted its economic impact over 3 and 5 years.

Results

In a base-case cost-effectiveness analysis, compared with no testing, MRD testing by flow cytometry at the end of induction and consolidation was associated with an increased discounted survival of 0.0958 quality-adjusted life-years (QALYs) and increased discounted costs of $4,180, yielding an incremental cost-effectiveness ratio (ICER) of $43,613/QALY gained. After accounting for parameter uncertainty, incremental cost-effectiveness of MRD testing was associated with an ICER of $50,249/QALY gained. In the budget-impact analysis, the 1-year cost expenditure for MRD testing by flow cytometry in newly diagnosed patients with precursor B-cell ALL was estimated at $340,760. We forecasted that the province would have to pay approximately $1.3 million over 3 years and $2.4 million over 5 years for MRD testing by flow cytometry in this population.

Conclusions

Compared with no testing, MRD testing by flow cytometry in newly diagnosed patients with precursor B-cell ALL represents good value for money at commonly used willingness-to-pay thresholds of $50,000/QALY and $100,000/QALY.

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BACKGROUND

The Toronto Health Economics and Technology Assessment (THETA) Collaborative was commissioned by Health Quality Ontario to evaluate the cost-effectiveness and predict the long-term costs and effects of tests for minimal residual disease after treatment for acute lymphoblastic leukemia. Published economic evaluations are reviewed, and the structure and inputs of the economic model used to estimate cost-effectiveness are summarized. The results of the economic analyses are presented for testing for minimal residual disease versus no testing, and the budget impact of implementing each intervention is estimated.

Health Quality Ontario conducts full evidence-based analyses, including economic analyses, of health technologies being considered for use in Ontario. These analyses are then presented to the Ontario Health Technology Advisory Committee, whose mandate is to examine proposed health technologies in the context of available evidence and existing clinical practice and to provide advice and recommendations to Ontario health care practitioners, the broader health care system, and the Ontario Ministry of Health and Long-Term Care.

DISCLAIMER: Health Quality Ontario uses a standardized costing method for its economic analyses. The main cost categories and associated methods of retrieval from the province's perspective are described below.

Hospital costs: Ontario Case Costing Initiative cost data are used for in-hospital stay, emergency department visit, and day procedure costs for the designated International Classification of Diseases diagnosis codes and Canadian Classification of Health Interventions procedure codes. Adjustments may be required to reflect accuracy in the estimated costs of the diagnoses and procedures under consideration. Due to difficulties in estimating indirect costs in hospitals associated with a particular diagnosis or procedure, Health Quality Ontario normally defaults to a consideration of direct treatment costs only.

Non-hospital costs: These include physician services costs obtained from the Ontario Benefits for Physician Services, laboratory fees from the Ontario Schedule of Laboratory Fees, drug costs from the Ontario Drug Benefit Formulary, and device costs from the perspective of local health care institutions whenever possible, or from the device manufacturer.

Discounting: For cost-effectiveness analyses, a discount rate of 5% is applied (to both costs and effects/quality-adjusted life-years), as recommended by economic guidelines.

Downstream costs: All reported downstream costs are based on assumptions of population trends (i.e., incidence, prevalence, and mortality rates), time horizon, resource utilization, patient compliance, health care patterns, market trends (i.e., rates of intervention uptake or trends in current programs in place in the province), and estimates of funding and prices. These may or may not be realized by the Ontario health care system or individual institutions and are often based on evidence from the medical literature, standard listing references, and educated hypotheses from expert panels. In cases where a deviation from this standard is used, an explanation is offered as to the reasons, the assumptions, and the revised approach.

The economic analysis represents ***an estimate only***, based on the assumptions and costing methods explicitly stated above. These estimates will change if different assumptions and costing methods are applied to the analysis.

NOTE: Numbers may be rounded to the nearest decimal point, as they may be reported from an Excel spreadsheet.

Objective of Analysis

This analysis aimed to ascertain the cost-effectiveness and economic impact of minimal residual disease (MRD) evaluation for management of childhood acute lymphoblastic leukemia (ALL) in Ontario.

Clinical Need and Target Population

Leukemia is the most common form of childhood cancer in Canada; ALL represents 75% of all types.[1] Every year in Ontario, approximately 109 new patients are diagnosed with ALL and

treated.[1] The precursor B-cell immunophenotype is the most common type of ALL, constituting 80% to 85% of all cases.[1]

Over time, the probability of long-term survival of patients with ALL has increased and is currently 80% to 90%.[2-6] The presence of MRD or of residual leukemic cells in the bone marrow after the first treatment phase (i.e., induction) is one of the key prognostic factors of a relapse of ALL.[7-10] Improvement over time in survival of patients with ALL has been largely explained through a more accurate detection of MRD by flow cytometry or by polymerase chain reaction (PCR) as compared with conventional morphologic examination by light microscopy.[8,11] Evaluation of MRD is used to reclassify patients' risks and identify those who are at a high risk or at a very low risk of relapse; it is also used to guide changes in the treatment of these populations.[8,10,12-16]

Ontario Context

Currently, MRD evaluation is the standard of care in North American and European protocols.[17] It is funded by the National Health Service in the United Kingdom. In Canada, MRD testing is done by flow cytometry and is funded in British Columbia, Nova Scotia, and Manitoba from the hospital or laboratory budgets. It is currently funded in Ontario through the Children's Oncology Group (COG) trial (ending June 2016).[17]

Intervention Under Evaluation

Minimal residual disease testing or evaluation by higher-performance techniques is used to detect the number of remaining leukemia cells in bone marrow or peripheral blood during and after the first phases of chemotherapy (i.e., induction and consolidation). The number of remaining leukemia cells can be detected through examining leukemia-associated immunophenotypes by flow cytometry or through assessing immunoglobulin and T-cell receptor gene rearrangements by PCR. Sensitivities and specificities of flow cytometry and PCR are comparable with concordance rates ranging between 78% and 97.1%; flow cytometry and PCR can detect 1 in 10,000 and 1 in 100,000 leukemia cells, respectively.[11] Thus, both techniques detect the number of leukemia cells at 0.01% level (1 in 10,000) versus morphologic examination by light microscopy that detects leukemia cells at 0.05% level (1 in 20).[8,11] A cut-off point for MRD testing by flow cytometry or PCR is defined at 0.01% level. Thus, the test is positive if MRD is greater than or equals 0.01%; otherwise it is negative.[11] Experts advise MRD testing be done at three points during the induction phase in all patients and one time at the end of consolidation in high-risk patients who have positive results on MRD Test 1 (Table 1).

Table 1: Frequency and Timing of Minimal Residual Disease Testing in Patients With De Novo Acute Lymphoblastic Leukemia

	MRD Test 1: Induction			MRD Test 2: Consolidation
Tissue	**Day 0**	**Day 8**	**Day 29**	**End**
Bone marrow	√		√	√ : MRD Test 1 positive
Peripheral blood		√		

Abbreviations: ALL, acute lymphoblastic leukemia; MRD, minimal residual disease testing by flow cytometry.

Results of MRD testing are used for clinical decision-making and for management of de novo ALL. For example, if patients were categorized into the standard-risk group before the first sets of MRD tests and were test positive for MRD at the end of induction (≥ 0.01%), they would be reclassified into the high-risk group and their therapy intensified.[14] Intensified chemotherapy is

associated with better clinical outcomes, but is more expensive and likely associated with greater treatment-related toxicity. Patients who have positive results for MRD at the end of consolidation are considered to be at very high risk of relapse and are offered a bone marrow transplant. In contrast, standard-risk patients who have negative results for MRD at the end of induction are considered to be at very low risk of relapse, and their therapy may be de-escalated.[15,16] De-escalation of treatment is not associated with better clinical outcomes, nor with important reductions of treatment-related toxicity, but is associated with lower costs.[15,16]

In cases of uncertainty, decision analysis can provide insights by quantifying trade-offs between costs and benefits and can help policymakers and clinicians make consistent, rational, and better decisions.[18,19] Decision analysis can use a mathematical model that represents the complexity of one disease; it is used to estimate trade-offs between costs and effects and to calculate the highest expected benefit.[20,21] For policymakers, the highest expected benefit refers to maximizing population health outcomes through an optimal and efficient allocation of scarce and fixed health care resources.[18]

In our economic evaluation, we examined the relationship between expected benefits and costs, aiming to answer whether MRD testing by flow cytometry followed by risk-directed treatment in certain patient groups represents good value for money.

ECONOMIC ANALYSIS

Research Question

In pediatric patients with de novo ALL, is MRD testing and subsequent MRD risk-directed therapy cost-effective compared with no testing?

Economic Literature Review

Methods

Literature Search

An economic literature search was performed on November 4, 2014, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations (1946–2014), Ovid Embase (1947–2014), Cochrane Library (1980–2014), Paediatric Economic Database Evaluation (1980–2014), EconLit, National Institute for Health Research Economic Evaluation Database (NHS EED) for studies published from January 1, 1998, to November 4, 2014. (Appendix 1 provides details of the search strategies.) Reference lists and health technology websites were also examined for any additional relevant studies not identified through the search.

Potentially relevant studies were identified through the title and abstract sifting. Full-text articles were retrieved and evaluated. A study was included if it met all of the inclusion criteria below.

Inclusion Criteria

- English-language full-text publications published between January 1, 1998, and November 4, 2014
- Full economic evaluations (cost-utility analyses, cost-effectiveness analyses, or cost-benefit analyses)
- Economic evaluations reporting incremental cost-effectiveness ratios (ICERs) (i.e., cost per quality-adjusted life-year [QALY] gained/life-years saved, or cost per event avoided)
- Studies in pediatric patients with leukemia
- Studies reporting MRD evaluation used to determine the number of remaining leukemic cells in blood or bone marrow (i.e., prognosis) and to guide the treatment of childhood leukemia
- Studies comparing MRD evaluation by flow cytometry or PCR to usual care (e.g., conventional morphologic examination by microscopy)

Exclusion Criteria

- Reviews, commentaries, letters, and editorials
- Noncomparative studies reporting the costs of MRD testing for childhood leukemia
- Economic evaluations of genetic tests used to determine the prognosis of childhood leukemia

- Studies with adult populations or populations with other types of cancer (e.g., multiple myeloma)

Methodologic Quality

A single reviewer assessed methodologic quality of the studies that met the entry criteria. It was decided a priori to use two different checklists to evaluate methodologic quality of the eligible economic studies: the Consensus on Health Economic Criteria for patient-level economic analyses, and the British Medical Journal Checklist for model-based economic analyses.[22,23] In addition, the applicability of the studies to the topic and Ontario's context was assessed using Section 1 of the National Institute for Health and Care Excellence (NICE) quality appraisal checklist.[24]

Results

Systematic Search

After removing duplicate publications, the search yielded 104 citations (86 from MEDLINE and Embase and 18 from Paediatric Economic Database Evaluation and National Health Service Economic Evaluation Database) (Figure 1). Two potentially relevant studies[25,26] were examined in full, and one study met the entry criteria.[25]

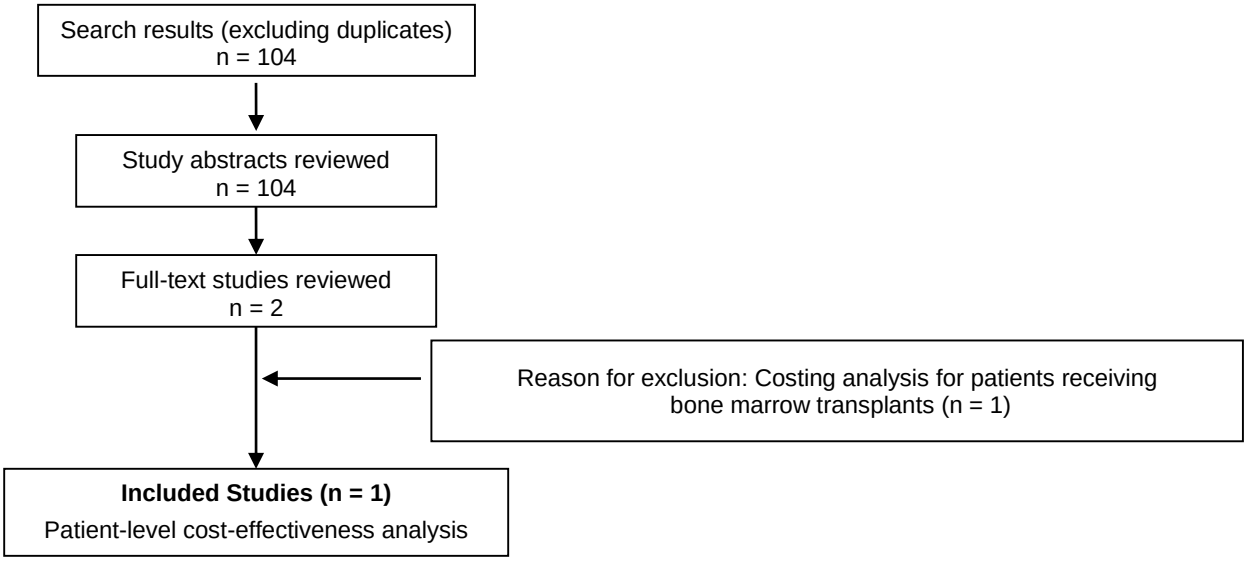

Figure 1: Search of Economic Literature

The included study is discussed below.[25] Table 2 summarizes its characteristics and results. Appendix 2 describes the methodologic quality and applicability of this study.

Table 2: Results of Economic Literature Review—Summary of Economic Evaluation

Study Design, Perspective, Time Horizon	Population	Comparators	Results		
			Life Expectancy, Years[a]	Total Direct Medical Costs (2008 US$)[a]	
			Mean	Mean (SD)	ICER ($/LYS)[a]
• Patient-level cost-effectiveness analysis • Study design: retrospective cohort • Perspective: Dutch hospital • Time horizon: lifetime	• 50 children diagnosed with ALL, treated between 2002 and 2006 with chemotherapy only • Age: up to 18 year, mean: 5.4–5.6 year • Male: 58%–71% • Two hospital-based cohorts, with different prognoses and severity of disease: 1) Cohort treated with ALL9: - Non–high risk: 69%, 5-year EFS = 84% - High risk: 31%, 5-year EFS = 72% 2) Cohort treated with ALL10: - Standard risk: 79%, 5-year EFS = 96% - Medium risk: 21%, 5-year EFS = 85%	• Intervention: new ALL10 protocol with MRD testing (104 wk) MRD testing was used to guide treatment decision: - Intensification of therapy in group with higher risk of relapse on basis of high MRD levels (n = 19) - Reduction of therapy in group with lower risk of relapse, on basis of low MRD levels (n = 5) • Control: old ALL9 protocol without MRD testing (109 wk) - Risk classification was based on clinical criteria and cytogenetics: non–high risk (n = 18) and high risk (n = 8)	1) ALL10: 66.0 2) ALL9: 60.2	1) ALL10: $163,350 (32,630) Discounted: $161,779 (32,033) Standard-risk group: $104,301 (20,677) Discounted: $103,667 (20,447) Medium-risk group: $189,548 (37,741) Discounted: $187,577 (37,062) 2) ALL9: $115,858 (37,781) Discounted: $114,777 (37,487) Non–high-risk group: $100,726 (31,682) Discounted: $99,818 (31,514) High-risk group: $149,885 (27,371) Discounted: $148,435 (27,142)	8,215 Discounted: 13,489

Abbreviations: ALL, acute lymphoblastic leukemia; EFS, event-free survival; ICER, incremental cost-effectiveness ratio; LYS, life-years saved; MRD, minimal residual disease evaluation; N, total sample size; SD, standard deviation.

[a]Not discounted.

Source: van Litsenburg.[25]

Design

Van Litsenburg et al conducted a patient-level cost-effectiveness analysis for a single-centre retrospective cohort of 50 Dutch patients (ages 0–18 years) with childhood ALL, treated with chemotherapy only. Two Dutch Childhood Oncology Group (COG) chemotherapy protocols were compared. Both protocols were used for about 2 years (i.e., ALL9 for 109 weeks and ALL10 for 104 weeks) and had a similar structure (prednisone phase, induction, methotrexate phase, intensification, and maintenance). The new ALL10 protocol included MRD evaluation and a more expensive/effective medication (i.e., *Escherichia coli* PEG-asparaginase). The old ALL9 protocol did not include MRD evaluation and was augmented with a less expensive and less effective medication (i.e., *Escherichia coli* L-asparaginase). The results of MRD evaluation were used to assess the risk of relapse and to guide changes in chemotherapy; therefore, treatment intensity was reduced for patients with a low risk of relapse (i.e., low MRD level) and was intensified for patients with a high risk of relapse (i.e., high MRD level).

Population

Cohorts of patients included in the analysis were stratified according to the risk of relapse. Very high-risk patients, eligible for stem-cell transplantation, were a priori excluded from the economic analysis. In addition, the criteria for risk stratification differed between the new ALL10 and old ALL9 protocols; as a result, the two cohorts were different in prognosis and in severity of disease. The cohort of patients undergoing ALL10 (n = 24) included standard-risk and medium-risk patients (mean age 5.5 and 5.4 years, respectively). Patients with a very high chance of relapse because of a poor response to prednisone, high MRD level of $\geq 10^{-3}$ during the methotrexate phase, or presence of unfavourable cytogenetics (e.g., presence of Philadelphia chromosome) were excluded. The cohort of patients undergoing ALL9 (n = 26) included non–high-risk and high-risk patients (mean age 5.8 and 5.2 years, respectively). As compared with the medium-risk group of ALL10, the high-risk group of ALL9 included patients at a higher risk of relapse given the presence of unfavourable cytogenetics, of mediastinal enlargement, or of central nervous system or testicular involvement.

Outcomes

The analysis included direct medical costs recorded in hospital electronic databases and medical records. Direct medical costs included in-hospital costs (room and board, nursing and physician fees); day-care treatment; medication; outpatient clinic visits, including emergency room visits and medical consultations; laboratory and microbiology visits; imaging studies; diagnostic tests (bone marrow aspirates, lumbar punctures, pathology examinations, and genetic examinations); blood transfusions; and surgical procedures. The costs were calculated in 2008 USD and were discounted by 4% (according to Dutch guidelines).

The effectiveness outcome used in the cost-effectiveness analysis was the number of life-years saved, discounted at 1.5% (according to Dutch guidelines). Life-years saved (LYS) were calculated from lifetime projections of 5-year event-free survival rates (i.e., time to relapse or death). The projected life expectancy until the age of 80 years was based on the normal mean life expectancy of Dutch children reported in national statistics resources. Five-year event-free survival rates for ALL9 were 72% for high-risk and 84% for non–high-risk patients.[27] Five-year event-free survival rates for ALL10 were 85% for medium-risk and 96% for standard-risk patients, and were extrapolated from a 4-year interim analysis of the ongoing trial.[25]

Perspective and Time Horizon

The analysis was done from a hospital perspective, for a patient's lifetime.

Results

Testing for MRD and subsequent MRD risk-directed change in therapy (ALL10) compared with no testing (ALL9) was associated with higher mean expected costs ($163,350 [discounted $161,779] vs. $115,858 [discounted $114,777]) and a greater mean expected survival (66.0 vs. 60.2 years), yielding an ICER of $8,215/LYS (discounted $13,489/LYS).

In terms of costs, high-risk groups incurred higher total costs than non–high-risk groups (Table 1). The medium-risk group undergoing the ALL10 protocol incurred the highest mean costs because of *E. coli* PEG-asparaginase use. In terms of differences in phase-specific costs, the highest costs were incurred in the maintenance phase for the medium-risk group using the ALL10 protocol and in the intensification phase using the ALL9 protocol.

Sensitivity Analysis

Sensitivity analyses were performed on two parameters: life expectancy and discount rate. Reductions of life expectancy were associated with increases of the ICER, from $8,215/LYS for a life expectancy of 80 years to $16,428/LYS for a life expectancy of 42.5 years. Increases in the discount rate for health effects from 1.5% to 4% resulted in increases of the ICER from $13,489/LYS to $25,618/LYS, respectively.

Discussion

The authors of this patient-level cost-effectiveness analysis concluded that MRD testing (including the MRD risk-directed change in chemotherapy) compared with no testing resulted in an increase in survival and an acceptable ICER.[25] However, the study's internal validity and generalizability were compromised. There is a potential for selection and measurement bias owing to differences in patient selection and patients' risk of relapse between the two compared protocols. Also, the study findings cannot be generalized to all pediatric patients with ALL because patients at high risk of relapse, eligible for bone marrow transplant, were excluded from the analysis. There are also some limitations in terms of modelling. Patients who had a relapse were assumed to have died and their health-related quality of life was not measured, so QALYs were not calculated. Also, there is a large difference of 6 years in survival between the two cohorts that can result from a less accurate modelling approach of extrapolation of 4- or 5-year event-free survival over lifetime. Finally, large differences exist between the Netherlands and Ontario in terms of different classification systems used to categorize patients according to their risk of relapse and in terms of protocols used to treat them (e.g., as per the Dutch treatment protocols, response to prednisone is used to reclassify patients into three categories as opposed to the COG treatment protocol most frequently used in Ontario).

The findings by van Litsenburg et al[25] of a patient-level cost-effectiveness analysis are not fully applicable to all groups of patients with childhood ALL in Ontario who may be eligible for MRD testing. Therefore, the primary economic evaluation was conducted.

Primary Economic Evaluation

Our study considered patients with precursor B-cell immunophenotype who account for 80% to 85% of patients with childhood ALL.[1] Experts consider MRD testing of all patients followed by

treatment intensification in eligible subgroups of MRD-positive patients to be more clinically relevant[15,16] and more feasible than MRD testing followed by treatment de-escalation in a subset of MRD-negative patients at low risk of relapse.

Objectives

The primary objectives of our study were to ascertain whether:

1. MRD testing by flow cytometry **at the end of the induction and consolidation** phases of chemotherapy and subsequent MRD risk-directed intensification therapy is cost-effective compared with no MRD testing in pediatric patients with de novo ALL
2. MRD testing by flow cytometry **at the end of the induction** phase of chemotherapy and subsequent MRD risk-directed intensification therapy is cost-effective compared with no MRD testing in the same population

Methods

Type of Analysis

We developed a state-transition (Markov) probabilistic microsimulation model to quantify the cost-effectiveness of MRD testing followed by risk-directed therapy to no intervention. We conducted cost-effectiveness and cost-utility analyses to estimate the marginal effect of MRD testing on health outcomes: relapse rate, rate of bone marrow transplant, life expectancy, and QALYs, and on costs. We constructed a Markov microsimulation model to be able:

- To follow changes in patient's history over a lifetime to account for recurring events
- To track possible changes in the risk for relapse after the first and second MRD tests to simulate patients' prognosis and predict related treatment decisions in the consolidation and maintenance phases

Perspective

The analysis was conducted from the perspective of the Ontario Ministry of Health and Long-Term Care.

Discounting and Time Horizon

As suggested by the Canadian health technology assessment guidelines,[28] an annual discount rate of 5% was applied to both costs and QALYs (or life-years). A time horizon used in base-case analysis was the patient's lifetime.

Target Population

The hypothetical cohort evaluated by the model included children with newly diagnosed precursor B-cell ALL, mean age 6 years (age range 1 to < 10 years). This patient cohort was divided into two risk groups—standard-risk and high-risk, according to the National Cancer Institute clinical criteria (i.e., age and white blood cell count at diagnosis) and to the presence or absence of cytogenetics/genomic alterations. These criteria are part of the COG classification system.[5] Accordingly, standard-risk patients were aged between 1 and less than 10 years with white blood cell count less than 50,000/μL and with favourable cytogenetics; otherwise, patients

aged between 1 and less than 10 years with white blood cell count equal to or greater than 50,000/µL and unfavourable cytogenetics were classified as high risk.

We did not model the cost-effectiveness of MRD testing in infants or in patients classified at very high risk because these populations represent a smaller proportion of patients with ALL who are most likely treated with substantially different protocols.[29]

Comparators

We compared MRD testing by flow cytometry with no testing, as shown in Table 3. As described in Table 1, an MRD test is performed three times during the induction phase of chemotherapy (baseline, Day 8, and Day 29) and one time at the end of the consolidation phase of chemotherapy. According to our primary objectives, in one analysis we compared no testing with MRD evaluation in both chemotherapy phases (referred to as Test 1 and Test 2; Table 1), while in another analysis, we compared no testing with MRD evaluation in the induction phase only.

Table 3: Comparators Evaluated in Base-Case Analysis

Interventions	Comparators	Patient Population	Outcomes
MRD testing by flow cytometry	No testing	Precursor B-cell ALL pediatric patients at the beginning of induction	● Effectiveness outcomes: Life expectancy, quality-adjusted life years, relapse rate, rate of HSCT ● Cost outcomes: direct medical costs ● Incremental cost-effectiveness ratio

Abbreviations: ALL, acute lymphoblastic leukemia; HSCT, hematopoietic stem cell transplant; MRD, minimal residual disease.

Minimal residual disease test results at the end of induction (i.e., Test 1) and at the end of consolidation (i.e., Test 2) are used in clinical decision-making.[8,12-16] The results of the first test are used to reclassify initially standard-risk and high-risk patients into two groups: MRD positive (at a level of ≥ 0.01%) or MRD negative (< 0.01%). Three protocols are most often used to treat patients with de novo precursor B-cell ALL in Ontario: the Dana Faber Cancer Institute protocol, Berlin-Frankfurt-Münster (BFM) protocol, and COG protocol. According to experts, the COG protocol is used by four of five pediatric oncologists in Ontario, and its drugs and treatment phases are the most similar to those of the BFM protocol. Our modelling study assumed that the COG protocol was used to treat our hypothetical cohort of pediatric patients with de novo precursor B-cell ALL. According to the COG protocol, standard-risk MRD-positive patients undergo more intensive, longer, and more expensive treatment than their counterparts (i.e., standard-risk MRD-negative patients). Standard-risk MRD-positive patients follow the same treatment pathway as high-risk patients after the induction phase (Figure 2). The second MRD test is done only if patients test positive for MRD at the end of induction. Patients who remain MRD positive at the second MRD test are considered to be at a very high risk of relapse and are referred for hematopoietic stem cell transplant.

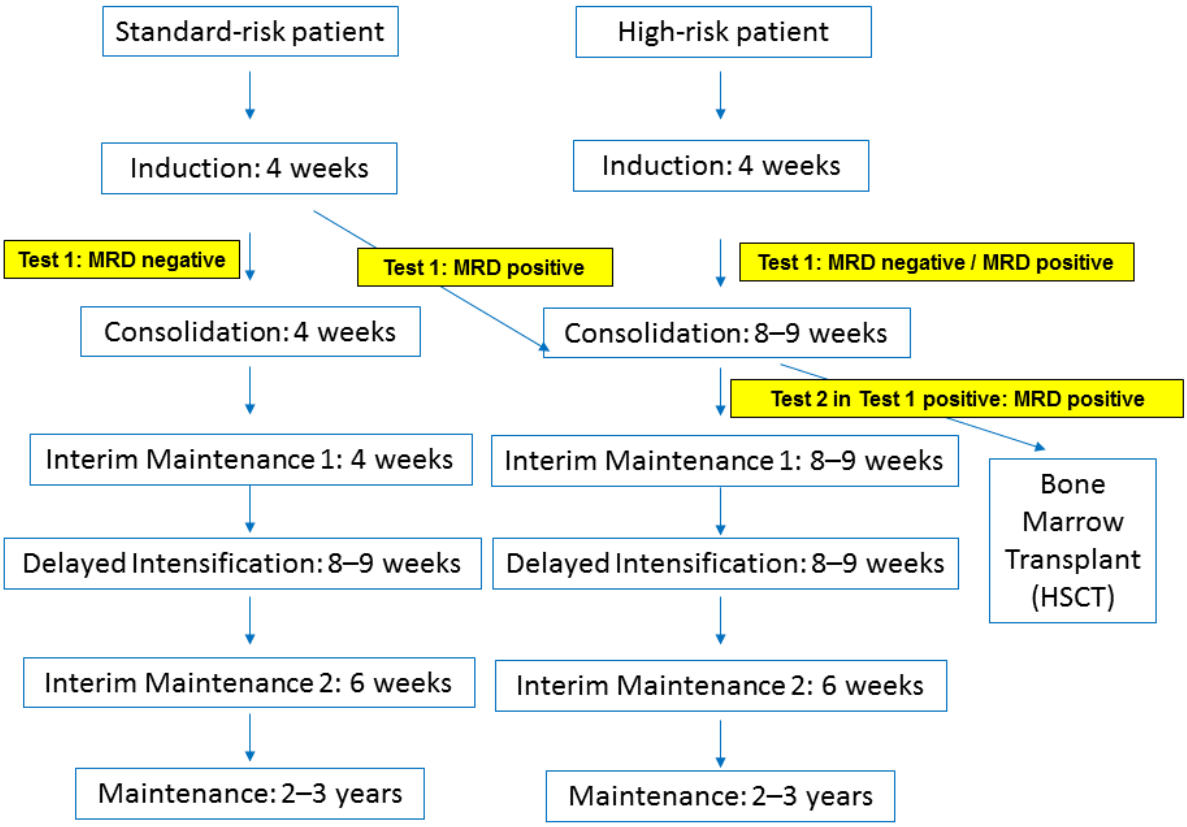

Figure 2: Children's Oncology Group Treatment Protocol and Minimal Residual Disease Testing

Abbreviations: HSCT, hematopoietic stem cell transplant; MRD, minimal residual disease.
Source: Treatment of precursor B-cell acute lymphoblastic leukemia according to the Children's Oncology Group protocol was developed for the purpose of this economic evaluation by pediatric oncology expert Dr. Paul Gibson.

Model Structure

The model structure was developed through consultations with pediatric oncology experts Drs. Sumit Gupta and Paul Gibson and was validated by the expert panel members of the Pediatric Oncology Group of Ontario (POGO). The model was developed and systematically checked by three health economists from the Toronto Health Economics and Technology Assessment Collaborative (THETA) and peer-reviewed by the director of THETA. The model was constructed using TreeAge Pro 2014 (TreeAge Software Inc., Williamstown, MA, 2014).

The model simulated the natural history of precursor B-cell ALL in each of the 10,000 hypothetical 6-year-old patients at the beginning of induction (Figure 3). We tracked survival, quality of life, number of relapses and bone marrow transplants, and costs over a patient's lifetime or until age 100. As previously mentioned, each patient was stratified into standard- or high-risk categories according to their risk of relapse (or the COG classification criteria).[5] They followed two distinct COG protocol pathways (Figures 2 and 3).

Each week, a patient had a chance of dying or of relapse from any of the following health states: induction, consolidation, interim maintenance 1, delayed intensification, interim maintenance 2,

maintenance, relapse, bone marrow transplant, and remission. We accounted for competing risks of dying from various causes by modelling death from all causes (background mortality), death from treatment toxicity,[30] and death from the disease itself.

The risk of relapse during the induction period depended on a patient's initial risk classification; afterward, it depended on the results of MRD Test 1 and Test 2, which occurred after the induction and consolidation phases.[12,31] Once the disease relapsed, we tracked the number of relapses a patient could have to distinguish different treatment pathways. All relapsed patients would undergo a 3-month course of chemotherapy to achieve remission. In case of a first relapse, after a 3-month course of chemotherapy, a patient had a 50:50 chance either to undergo bone marrow transplant or to continue with salvage chemotherapy for at most 152 weeks within the next relapse health state (referred to as rescue chemotherapy). Any patient who had a second (or any following) relapse after finishing a 3-month course of chemotherapy underwent a bone marrow transplant. The probability of dying from ALL was dependent on the number of relapses that the patient had, assuming a worse survival rate after the second relapse.

A patient could be assigned to receive a bone marrow transplant after consolidation or after a first relapse (Figures 2 and 3). Also, one could be assigned to receive a bone marrow transplant multiple times, but changes in health effects and costs were simulated short term (for 100 days) before transferring to either remission or relapse. The probability of dying after a transplant depended on the number of bone marrow transplants, with a much greater death rate after the second transplant.

A patient could enter remission after finishing the whole first course of chemotherapy ending with the maintenance phase, after finishing the whole second course of chemotherapy after a first relapse, or after successful treatment following bone marrow transplant.

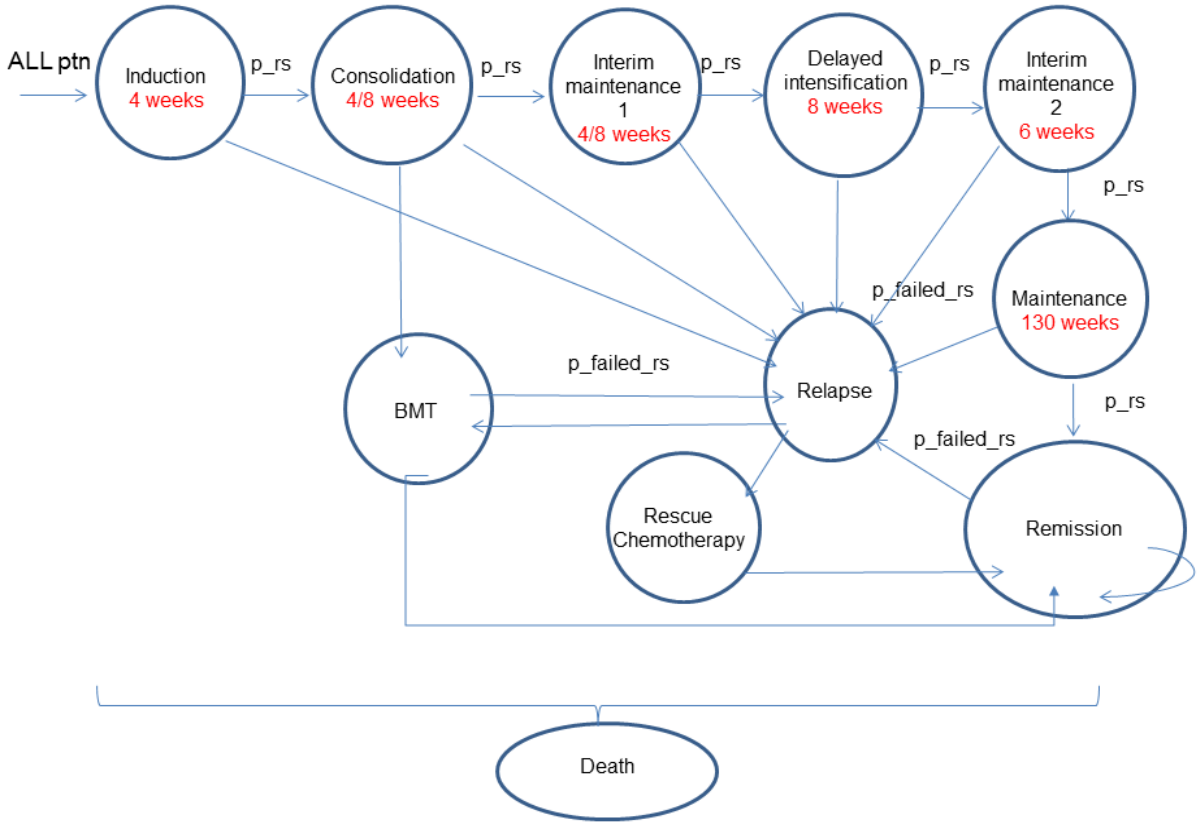

Figure 3: Simplified Schematic of Model Structure

Abbreviations: ALL, acute lymphoblastic leukemia; ALL ptn, patient with diagnosed precursor B-cell ALL at beginning of induction; BMT, bone marrow transplant (refers to hematopoietic stem cell transplant); HR, high risk; MRD, minimal residual disease; p_failed_rs, probability of failure or relapse for SR or HR patients by MRD status and based on annual probabilities of event-free survival; p_rs, risk stratification; SR, standard risk.

Source: Model structure was developed through consultations with pediatric oncology expert Dr. Sumit Gupta: 1 = SR–low MRD, 2 = SR–high MRD, 3 = HR–low MRD; 4 = HR–high MRD.[31]

Model Input Parameters: Probabilities, Risks, Utilities, and Costs

Several input parameters are related to the natural history of precursor B-cell ALL (Table 4).

Table 4: Input Parameters Used in the Economic Model: Probabilities and Risks

Model Parameter	Mean (95% CI/SE)[b]	Range[a]	Distribution[b]	Source
Probabilities				
Probability of initial stratification:				Borowitz et al, 2008[12]; Chen et al, 2012[31]
Standard risk	0.69	0.5–0.8		
High risk	0.31	0.2–0.5	NA	
Probability of re-stratification after MRD testing:				Borowitz et al, 2008[12]; Chen et al, 2012[31]
Standard risk, MRD negative	0.83	0.5–0.9		
Standard risk, MRD positive	0.17	0.1–0.5		
High risk, MRD negative	0.74	0.5–0.9		
High risk, MRD positive	0.26	0.1–0.5	NA	
Probability of non-relapse death in induction:				
Standard risk	0.59 (0.4–0.8)	0.1–0.8	Beta	Blanco et al, 2012[30]
High risk	0.43 (0.3–0.5)	0.1–0.8	Beta	Blanco et al, 2012[30]
Probability of positive results from MRD test after consolidation (Test 2+|Test 1+)	0.50	0.1–0.9	NA	Expert opinion
Probability of having BMT after detecting positive result from MRD Test 2	0.04 (0.01–0.27)	0.01–0.8	Beta	POGONIS Registry
Probability of BMT in a first relapse	0.50	0.1–0.8	Beta	POGONIS Registry
Probability of BMT in the next relapse	1.00	0.5–1.0	NA	Expert opinion
Probability of the first relapse in de novo ALL, based on 8-year relapse-free survival:				Chen et al, 2012[31]
Standard risk, MRD negative	0.90	NA	Log-normal Time-dependent	
Standard risk, MRD positive	0.61	NA	Log-normal Time-dependent	
High risk, MRD negative	0.77	NA	Log-normal Time-dependent	
High risk, MRD positive	0.39	NA	Log-normal Time-dependent	

Model Parameter	Mean (95% CI/SE)[b]	Range[a]	Distribution[b]	Source
Probabilities				
Probability of relapse in remission after 10 years, based on 20-year disease-free survival	0.63 (0.32)	0.0–0.7	Beta	Pui et al, 2003[32]
Probability of dying from ALL after a first relapse, based on 3-year disease-free survival of relapsed patients	0.50 (0.43–0.57)	0.1–0.6	Beta	Parker et al, 2010[33]
Probability of dying from ALL after a second or any successive relapse, based on 5-year disease-free survival of relapsed patients	0.15 (0.07)	0.1–0.4	Beta	Ko et al, 2010[34]
Probability of relapse after bone marrow transplant, based on 10-year event-free survival after:				Reismuller et al, 2013[35]
Second relapse[c]	0.09 (0.03)	0.01–0.7	Beta	
Third relapse[c]	0.06 (0.06)		Beta	
Probability of dying in first 6 months after bone marrow transplant:				
After a first relapse, based on 6-month overall survival	0.88 (0.68–0.96)	0.7–1.0	Beta	POGONIS Registry
After any next relapse, based on 6-month overall survival	0.30	0.1–0.5	NA	Shah, 2014[36]
Risks				
Risk of dying from subsequent malignancy, 10–14 years from diagnosis Relative risk	NA	1.9[a] (1.5–2.5)	NA	Armstrong et al, 2009[37]
Risk of relapse after MRD testing in induction and subsequent intensification of therapy Unadjusted odds ratio	0.61 (0.39–0.98)	0.5–1.0	Normal (log-odds ratio)	Vora et al, 2013[14]

Abbreviations: ALL, acute lymphoblastic leukemia; BMT, bone marrow transplant (refers to hematopoietic stem cell transplant); CI, confidence interval; MRD, minimal residual disease; NA, not applicable; POGONIS, Pediatric Oncology Group of Ontario Networked Information System; SE, standard error.

[a]Range used in one-way deterministic analysis.

[b]Distributions assigned in probabilistic sensitivity analysis.

[c]Used in sensitivity analysis only.

Survival, Relapse, and Mortality

For our hypothetical cohort of patients with de novo ALL, we estimated risk-specific probabilities of relapse over 8 years of follow-up from a study published by Chen et al.[31] The Chen study is a substudy of research by Borowitz et al[12] in 3,686 patients (of whom 3,303 patients had B-cell ALL), who were enrolled in three COG trials (P9904, P9905, and P9906), and were at standard or high risk of relapse according to the clinical National Cancer Institute and COG criteria. The Borowitz study is a seminal study that established the predictive value of MRD testing for the risk of relapse in B-cell ALL population. It predicted (1) event-free survival before MRD testing of initially stratified patients (by the COG criteria) and (2) event-free survival after MRD testing in the same population. The Borowitz study did not use MRD test results to guide changes in treatment, and it represented a good source for our control strategy (i.e., no MRD testing). Chen et al provided graphs of survival curves,[31] with more accurate estimates of relapse-free survival for all risk groups, so this study was deemed as a more appropriate source for our modelling study. The study by Chen et al[31] included 1,061 pediatric and adolescent patients enrolled in two COG trials (P9905 and P9906) at standard or high risk of relapse. Standard-risk and high-risk patients of P9905 were classified using the clinical National Cancer Institute criteria: white blood cell count (< 50,000/μL vs. ≥ 50,000/μL) and age (1–9.99 years vs. > 10 years). For four risk groups (MRD-positive and MRD-negative standard-risk and high-risk patients), we extracted relapse-free survival rates from the published Kaplan-Meier survival curves,[31] using the Universal Ruler software. From these data we estimated and modelled weekly rates of relapse over the first 10 years, and further, over a patient's lifetime using a log-normal distribution that fitted best compared with the other four survival distributions (Weibull, exponential, logistic, log-normal, log-logistic, Gaussian, as tested by the Akaike Information Criterion[38]).

We modelled a probability of relapse after bone marrow transplant using the data of a population-based cohort study by Reismuller et al in 74 patients with a second relapse of ALL who underwent bone marrow transplant or salvage chemotherapy.[35] Seventeen of 74 patients had a third relapse. In this study, 10-year probabilities of event-free survival were 0.09 (standard error [SE] 0.03) and 0.06 (SE 0.06) after the second and third relapse, respectively. For patients who achieved remission for more than 10 years, we assumed a constant probability of relapse (disease-free survival 0.63, SE 0.32) on the basis of a study by Pui et al in 856 survivors of childhood ALL from 13 consecutive trials.[32]

Our model accounted for background mortality but also for mortality related to various disease-specific causes:

- First, age-specific background mortality was estimated from Ontario life tables
- Second, we modelled treatment-related mortality during induction according to the results of a meta-analytic study of 59 articles in 49,071 pediatric patients with ALL.[30] During induction, non-relapse (treatment-related) deaths were responsible for 59.27% of first events in standard-risk patients (17 studies in a meta-analysis), and for 42.25% of first events in high-risk patients (20 studies in a meta-analysis)
- Next, the probability of dying after first relapse was calculated from the estimate of 3-year disease-free survival (50.3%, 95% confidence interval [CI] 42.9–57.3) in 216 patients with ALL with a first relapse included in the ALLR3 open-label randomized trial by Parker et al.[33] The probability of dying after any next relapse was calculated from a 5-year disease-free survival of 15% (SE 7%) found in a retrospective cohort study of patients with relapsed and refractory ALL, done by Ko et al[34]
- Also, the probability of dying within the first 6 months after a bone marrow transplant was much smaller after a first than after any successive transplant. Cumulative data collected

in the Pediatric Oncology Group of Ontario Networked Information System (POGONIS) over 13 years showed that an overall survival of a patient with relapsed ALL with a first transplant was 88.1% within the first 6 months (95% CI 68.5–95.8). The probability of dying after multiple transplants was based on a 6-month overall survival of 30% from a retrospective cohort study of 93 relapsed patients who underwent a transplant for leukemia[36]

- Finally, in a sensitivity analysis, we accounted for an increased risk of dying of a second malignancy after 10 years of cancer diagnosis as shown for 5-year survivors of the Childhood Cancer Survivor Study (relative risk 1.9, 95% CI 1.5–2.5)[37]

Probabilities: MRD Testing

All newly diagnosed patients had MRD testing in induction. We assumed that 50% of patients with positive results from MRD Test 1 would have positive results at the second test. A patient whose MRD Test 1 results were positive and remained positive after consolidation had a chance of getting a bone marrow transplant. Data from POGONIS showed that approximately 8% of patients who had positive results from MRD Test 1 received a transplant after consolidation (Ms. Nicole Bradley, written communication, March 20, 2015). This assumption did not include information about patients who refused the transplant for various reasons. In our model, based on the literature data,[39-41] we assumed that approximately half of the identified MRD high-risk patients (i.e., 4%) would find a donor and accept the transplant during the consolidation phase.

Effectiveness of Treatment After MRD Testing

We modelled the effect of intensification of chemotherapy in standard-risk patients who had positive MRD results at the end of induction as a relative reduction in the rate of relapse. As shown in Table 4, we used the findings of a randomized controlled trial (UKALL 2003) by Vora et al that showed a 39% increase in 5-year event-free survival in MRD-positive patients who were initially classified by clinical and cytogenetics criteria into standard- and intermediate-risk groups and whose treatment was intensified after MRD testing at the end of induction.[14]

Quality of Life

We specified a quality-of-life weight (utility) for each health state to calculate QALYs. A QALY is a measure that jointly accounts for the changes in both quantity of life and quality of life (morbidity).[42,43] Utilities reflect the strength of preference for specified health states; they are measured on an interval scale, and by convention, are anchored on the best possible health and death (utility weight of 1 for perfect health and of 0 for death).[42,43] The value of QALY for a certain health state is calculated by multiplying time spent in that health state with the utility assigned for the health state. For example, 4 weeks spent in induction with a utility weight of 0.72 equals to 0.055 QALYs.

Utilities for different health states include those associated with treatment phases of chemotherapy in patients with de novo B-cell ALL (Table 5). Utilities associated with changes in health-related quality of life of patients with de novo B-cell ALL during treatment with two protocols, Dana Farber Cancer Institute and BFM, were estimated in an economic study by Rae et al.[44] The authors used the standard Health Utility Index (HUI) questionnaires to calculate patients' HUI Mark 3 (HUI3) utility scores of health-related quality of life[45] for each treatment phase. Parental HUI assessments were collected for patients aged 5 to 12 years, and patients' assessments were collected for those older than 12 years. The agreement between patient and parent pairs of health-related quality of life scores was moderate to very good (interclass

correlation coefficient 0.51–0.85). In this economic evaluation, health-related quality of life was assessed in 307 patients treated with the BFM protocol; no significant differences in the scores between patients on high-intensity and low-intensity treatments were found[44] (C. Rae, written communication, March 16, 2015).

In agreement with expert opinion, we assumed that the treatment phases and drugs of the BFM protocol used to treat de novo B-cell ALL are most similar to those of the COG protocol. As mentioned previously, the COG protocol includes the following chemotherapy phases (Figure 2): induction, consolidation, interim maintenance 1, delayed intensification, interim maintenance 2, and maintenance. Each phase was modelled as a separate health state (Figure 3). We used utilities from the study by Rae et al[44] for induction, consolidation, intensification, and maintenance phases (Table 5). We assumed the same utility weight of the BFM intensification phase for three intensification health states of the COG protocol (i.e., interim maintenance 1, delayed intensification, and interim maintenance 2). We assumed no differences in utility weights for patients in standard- and high-risk groups. Rae et al obtained an off-therapy utility related to the period after maintenance phase that lasted at least 2 years after the completion of treatment.[44] This utility was specified for the remission state.

For the bone marrow transplant state we used utilities reported by Sung et al for patients with leukemia who failed chemotherapy and underwent transplantation.[46] Using a visual analog scale, 12 physicians assessed health-related quality of life of their patients undergoing bone marrow transplantation at three tertiary centres in Toronto. Sung et al recalculated standard gamble utilities from visual analog scale scores using the formula:[47]

$$Utility = 1 - (1 - VAS\ score)^{2.29}$$

Our assumption regarding utilities for the relapse states was based on expert consultations and the constraint that quality of life during relapse should have the lowest utility weight compared with other health states (i.e., the utility weight of induction).

Table 5: Input Parameters Used in the Economic Model: Utilities and Lengths of Stay in Treatment Phases

Model Parameter	Value	Range[a]	Distribution[b]	Source
Utilities				
Induction	0.72 (0.27)[c]	0.40–0.85	Gamma	Rae et al, 2014[44]
Consolidation	0.90 (0.13)[c]	0.60–0.92	Gamma	Rae et al, 2014[44]
Intensification[d]	0.78 (0.29)[c]	0.40–0.85	Gamma	Rae et al, 2014[44]
Maintenance	0.85 (0.23)[c]	0.70–0.92	Gamma	Rae et al, 2014[44]
Relapse	0.72 (0.27)[c]	0.40–0.80	Gamma	Expert opinion
Bone marrow transplant	0.79 (0.45–0.97)[e]	0.40–0.99	Gamma	Sung et al, 2003[46]
Off-therapy (remission)	0.92 (0.14)[c]	0.90–0.99	Gamma	Rae et al, 2014[44]
Phase-specific length of stay (weeks)				
Induction Standard risk/High risk	4/8[f]	NA	NA	Expert opinion
Consolidation Standard risk/High risk	4/8[f]	NA	NA	Expert opinion
Interim maintenance 1 Standard risk/High risk	4/8[f]	NA	NA	Expert opinion
Delayed intensification Standard risk/High risk	8	NA	NA	Expert opinion
Interim maintenance 2 Standard risk/High risk	6	NA	NA	Expert opinion
Maintenance Standard risk/High risk	130	NA	NA	Expert opinion

Abbreviations: NA, not applicable.
[a]Range used in one-way deterministic analysis.
[b]Assigned in probabilistic sensitivity analysis, gamma distribution was set for the disutility values calculated as 1 − Mean (Utility).
[c]Interim maintenance 1, delayed intensification, interim maintenance 2.
[d]Mean (SD). [e]Mean (95% CI). [f]Weeks.

Costs

Direct medical costs associated with de novo ALL were derived from the literature (Table 6 and Appendix 3). Appendix 3 outlines detailed calculations of the in-patient and outpatient costs by treatment intensity (i.e., an additional analysis of cost data provided by Rae et al, written communication, November 11, 2014). All costs were inflated to 2014 Canadian dollars using the medical component of the Consumer Price Index.

The BFM protocol costs for Ontario were estimated by Rae et al.[44] In Table 6, we show the in-patient and outpatient costs incurred for standard-risk and high-risk patients: $91,106 and $124,298, respectively. To calculate the total costs associated with treatment of ALL, Rae et al linked data of administrative databases for a cohort of patients who started the treatment after March 2002 and completed it by December 31, 2006. The in-patient costs were calculated using the standardized and weighted costing procedures that accounted for service utilization. In-patient resource utilization, determined through resource intensity weights were derived from the Canadian Institute for Health Information Discharge Abstract Database. The in-patient costs

covered nursing and allied health professionals, operating room/surgical suites, drugs, diagnostic tests, traceable supplies, and general services. The cost of physician services was determined from the 2007 Ontario Health Insurance Plan Schedule of Benefits. The outpatient costs were obtained from the Ontario Case Costing Initiative (2007/08 fiscal year), based on the most reasonable diagnosis code for each visit recorded in the Canadian Institute for Health Information National Ambulatory Care Reporting System.

The costs of relapse were assumed to be equal to the treatment cost of the BFM protocol incurred by high-risk patients (i.e., 2007 CAD $124,298). In sensitivity analysis, we used data reported for the costs of relapse in the United Kingdom.[48]

The monthly cost incurred during remission (treatment, hospital visit, diagnostic tests) was obtained from a cost-effectiveness modelling study by Wang et al that examined long-term medical costs of adult patients with de novo acute myeloid leukemia in the United Kingdom.[49]

The costs of bone marrow transplant were based on a study of the hospital-based costs incurred by pediatric patients with acute leukemia who underwent primary stem cell transplant in Texas.[50] The initial costs of $208,987 (2008 USD) were applied to the first week (first cycle) in the bone transplant health state, and the remaining post-transplantation costs of $103,428 (2008 USD) were modelled over a period of 14 weeks.

Table 6: Input Parameters Used in the Economic Model: Costs of Acute Lymphoblastic Leukemia, Remission, Relapse[a], and Bone Marrow Transplant

Model Parameter	Mean (SD), $	Range, $	Distribution[b]	Source
Standard-risk patient				
In-patient costs	67,749 (18,410)	NA	NA	Rae et al, 2014[44]
Outpatient costs	23,360 (6,967)	NA	NA	Rae et al, 2014[44]
Total costs (BMF protocol) for ALL[c]	**91,106 (20,225)**	60,000–120,000	Gamma	**Rae et al, 2014[44]**
High-risk patient				
In-patient costs	67,749 (18,410)	NA	NA	Rae et al, 2014[44]
Outpatient costs	23,360 (6,967)	NA	NA	Rae et al, 2014[44]
Total costs (BFM protocol) for ALL[c]	**124,298 (52,097)**	60,000–180,000	Gamma	**Rae et al, 2014[44]**
Costs of remission, monthly[d]	121.7	0–200	Gamma	Wang et al, 2014[49]
Costs of relapse[a,d]	NA	89,500–179,000[a]	Gamma	UK data[48]
Costs of bone marrow transplant[e]				Lin et al, 2010[50]
Initial hospitalization	171,369	120,000–220,000	Gamma	
Costs of 100 days post-transplantation[e]	84,812	50,000–120,000	Gamma	

Abbreviations: ALL, acute lymphoblastic leukemia; BFM, Berlin-Frankfurt-Münster; NA, not applicable; SD, standard deviation; UK, the United Kingdom.

[a]Used in sensitivity analysis only.

[b]Distribution used in probabilistic sensitivity analysis.

[c]Original costs in 2007 Canadian dollars (CAD), not discounted.

[d]Original costs in 2007 UK Sterling, not discounted, exchange rate for 2007 CAD$ = 1.79.

[e]Original costs in 2008 US dollars (USD), not discounted, exchange rate for 2008 CAD$ = 0.82.

The reference laboratory from the Hospital for Sick Children in Toronto (SickKids) (POGO, written communication, March 25, 2015) estimated the costs associated with MRD testing (Table 7), which included the costs of testing three times during induction (baseline $500, Day 8 $300, and Day 29 $500), the cost of one-time testing at the end of consolidation ($500), and shipping costs ($75/test) incurred for 40% of the MRD samples.

Table 7: Input Parameters Used in the Economic Model: Cost of Minimal Residual Disease Testing

Strategy	Target Population	Frequency of Testing	Mean, $[a,b]	Range, $[a,c]	Distribution	Source
MRD testing: Induction and consolidation (2 tests)	Patients with de novo precursor B-cell ALL	Induction (3 times) and consolidation (1 time)	1,920	1,500–3,800	Fixed	POGO expert panel, SickKids Laboratory
MRD testing: Induction (1 test)	Patients with de novo precursor B-cell ALL	Induction (3 times)	1,390	NA	Fixed	POGO expert panel, SickKids Laboratory

Abbreviations: ALL, acute lymphoblastic leukemia; MRD testing, minimal residual disease testing by flow cytometry; NA, not applicable; POGO, Pediatric Oncology Group of Ontario.
[a]All costs in 2014 Canadian dollars.
[b]Total mean costs of MRD testing per patient include shipping costs, repeat test costs, and external quality assurance.
[c]Used in sensitivity analysis only.

For a scenario sensitivity analysis, we approximated how much the costs of ALL would change if the costs of COG treatment protocol were included. Estimates of the COG protocol phase-specific treatment costs were based on the protocols developed by experts. Thus, for the purpose of our modelling study, Dr. Paul Gibson, a pediatric oncologist, developed chemotherapy phase-specific protocols for average standard-risk and high-risk 6-year-old patients (weight 22 kg, height 110 cm, and body surface area 0.8 m^2, Appendix 4). For each chemotherapy phase, drug names, their doses, frequency of use, and administration (in-patient vs. outpatient) were reported. We calculated the 2014 CAD costs for each phase by obtaining drug prices from publicly available databases (Ontario Drug Benefit Formulary), drug companies, and personal communication with POGO personnel (e.g., for the per-vial cost of PEG-asparaginase, which is directly negotiated between the manufacturer and each hospital, written communication, December 3, 2014). Our total costs show upper and lower ranges, which relate to potential differences in the cost of PEG-asparaginase among Ontario's hospitals (Table 8). More details on costing of the COG treatment protocol are presented in Appendix 5.

Table 8: Costs of Children's Oncology Group Treatment Protocol for Standard-Risk and High-Risk Patients

Chemotherapy Phase	Mean Cost		Source
	Lower Range, $[a]	Upper Range, $[a]	
Standard-risk patient			
Induction	15,513	16,910	Appendix 5
Consolidation	114	114	Appendix 5
Interim maintenance 1	1,382	1,382	Appendix 5
Delayed intensification	19,534	20,932	Appendix 5
Interim maintenance 2	3,734	3,734	Appendix 5
Maintenance	4,134	4,134	Appendix 5
Total cost	44,411	47,207	NA
High-risk patient			
Induction	15,873	17,271	Appendix 5
Consolidation	32,217	35,013	Appendix 5
Interim maintenance 1	10,634	10,634	Appendix 5
Delayed intensification	35,531	38,326	Appendix 5
Interim maintenance 2	0	0	Appendix 5
Maintenance	5,052	5,052	Appendix 5
Total cost	**98,780**	**105,769**	**NA**

Abbreviation: NA, not applicable.
[a]All costs in 2014 Canadian dollars.

To generate the costs of de novo ALL for standard-risk and high-risk patients, we combined the following data from different sources (Appendices 5 and 6 offer details on the calculations):

- The length of in-patient stay provided by Rae et al,[44] which varied by intensity of treatment (low vs. high, Appendix 3)
- An estimate of the in-patient cost for an average oncology patient in an Ontario hospital, as provided by SickKids
- Children's Oncology Group treatment costs for standard-risk and for high-risk patients (Table 8)

The cost estimates of de novo ALL for standard-risk and high-risk patients, including the COG treatment protocol costs (Table 9 and Appendix 6), do not include costs of physician services, which are not paid out of hospital budgets.

Table 9: Total Costs of De Novo Acute Lymphoblastic Leukemia, Including Costs of Children's Oncology Group Treatment Protocol

Risk Group	Mean Cost, $[a]		Source
	Lower Range	Upper Range[a]	
Standard-risk patient	$106,426	$109,222	Appendix 6
High-risk patient	$174,263	$181,252	Appendix 6

[a]All costs in 2014 Canadian dollars.

Key Model Assumptions

We made several structural and parameter model assumptions.

First, we assumed that the accuracy of detecting remaining leukemic cells by MRD testing with either flow cytometry or PCR is similar. This assumption is supported by the literature.[11] In addition, regardless of which technique was used, clinical decisions following the MRD test result (i.e., change in treatment) would have been the same after detecting MRD positivity (at 0.01% level) with either of two techniques.

Second, in the base-case analysis, we modelled a probability of relapse-free survival for the first 20 years and a probability of ALL-related death according to the literature[31,32]; long-term survival and probability of death from other causes were modelled according to national statistics data for Ontario. In our sensitivity analysis, we addressed an increased risk of death from secondary malignant tumors in survivors of ALL.[37]

Next, we did not account for time-dependent changes in utility weights among patients with multiple events (e.g., relapses or transplants), but we tested this assumption in sensitivity analysis.

Also, we modelled the total costs of ALL based on the literature data, using the treatment costs of the BFM protocol.[44] In the sensitivity scenario analysis, we tested changes in the ICER when the total costs of ALL included the costs of COG treatment protocol.

Finally, we had no information regarding the cost of relapse in Ontario's patients with ALL. Therefore, in the base-case analysis, we assumed that the costs of chemotherapy for relapsed patients would be equal to the costs of BFM protocol chemotherapy for high-risk patients. We tested this assumption in sensitivity analysis using the estimate of relapse costs reported for the United Kingdom.[48]

Model Validation

We validated the model predictions by comparing our event-free survival curves over 10 years among patients who underwent MRD testing but did not subsequently change chemotherapy (i.e., control group) against the data published by Chen et al.[31] We also validated risk reduction of the rate of relapse at 5 years in standard-risk patients by comparing the number of first relapses between the MRD testing and no testing strategies as calculated by our model to the data published by Vora et al.[14]

Cost-Effectiveness Analyses

In base-case analysis, we calculated the ICER using a deterministic approach, which means that input model parameters were treated as constants or fixed values (i.e., we used the mean estimates).

The ICER is a statistic commonly used to present results of cost-effectiveness analyses. It is given by the difference in mean expected costs (i.e., incremental cost [ΔC]) between two compared strategies divided by the difference in mean expected outcomes (i.e., incremental effect [ΔE]) between these strategies (ICER = ΔC/ΔE).[51] Consequently, the ICER is expressed as a cost per additional unit of effect (e.g., life-year) in cost-effectiveness analysis, or as a cost per one QALY gained in cost-utility analysis.

The meaning of the ICER needs to be interpreted within the context of the cost-effectiveness plane: it depends on quadrant(s) of the cost-effectiveness plane in which the ICER resides.[51,52] A strategy is considered cost-effective if it is associated with greater expected effects and greater expected costs and if the ICER is below the maximum price that a decision-maker or a society is willing to pay for an extra unit of effect. Although the value of the willingness-to-pay threshold remains controversial,[53] we used a threshold of $50,000/QALY gained[54] and also examined a threshold of $100,000/QALY gained. A strategy is cost saving (thus, below a willingness-to-pay threshold) if it is associated with greater expected effects and lower expected costs. A strategy is dominated by another if it is associated with lower or equal expected effects for higher or equal expected costs.[55]

Sensitivity Analyses

Variability and uncertainty in the model were assessed through one-way sensitivity analysis and through probabilistic sensitivity analysis. In one-way deterministic sensitivity analysis, we varied the value of an input parameter within its plausible range (Tables 4–7).

Uncertainty: Probabilistic Sensitivity Analysis

Compared with the deterministic approach, probabilistic sensitivity analysis is a method used to address decision uncertainty and provide more valuable cost-effectiveness estimates to policymakers who are responsible for allocating resources at a societal level.[51,56]

Conducting probabilistic sensitivity analysis is important because poor-quality evidence may lead to the adoption of worse clinical strategies if the evidence is presented as fixed and not as unknown and uncertain.[57] Probabilistic sensitivity analysis is used to handle both parameter (second-order) uncertainty and non-linear relationships between model parameters (the latter are often present in Markov models). Consequently, it generates more accurate estimates of the mean expected effects and mean expected costs used to calculate the ICER.

To account for parameter uncertainty, we assigned distributions for input parameters and repeatedly sampled from those distributions (Tables 4–7).[56,58] For example, we specified the beta distribution for probabilities, the normal distribution for the effect measure of treatment efficacy (i.e., the log-odds ratio), and the gamma distribution for costs or disutilities (i.e., 1-utility). We simulated 1,000 trials, each of which included 500 patients, to obtain the mean expected costs and effects of two compared strategies. The cost of MRD testing by flow cytometry was modelled as fixed, and the probabilities of event-free survival or death were modelled as time- or age-dependent.

The method of cost-effectiveness acceptability curves is an alternative method to quantify and graphically present uncertainty in the ICER.[59,60] Cost-effectiveness acceptability curves show the probability of cost-effectiveness of one alternative over another across a range of willingness-to-pay thresholds ($0–$100,000/QALY gained).[56,60]

Scenarios

We examined three scenario analyses; all were conducted as deterministic. We examined incremental cost-effectiveness of MRD testing versus no testing:

- Scenario 1 used a hypothetical cohort of standard-risk patients (our base-case target population included all patients)
- Scenario 2 took into account the COG treatment protocol costs within the total costs for ALL (our base-case analysis used the total costs of ALL that included the costs of BFM protocol). Within this scenario, we conducted two analyses, making two different assumptions as to the cost of chemotherapy in the relapse states. In one analysis, we applied the COG cost of chemotherapy for a high-risk patient to the costs of chemotherapy in the relapse states. In another analysis, we applied the cost reported for relapse of ALL in the United Kingdom for the rescue relapse state (Table 6). For each of these analyses, we estimated the incremental cost-effectiveness of MRD testing over a patient's lifetime
- Scenario 3 accounted for shorter lengths of follow-up or 5-year and 10-year time horizons (the time horizon in our base-case analysis was lifetime)

Generalizability

The findings of this economic analysis cannot be generalized to an infant population or a very high-risk population aged 10 years or older, as our target population was restricted to pediatric patients (standard- and high-risk) aged between 1 and 10 years. However, the findings can be used to guide decision-making about these specific patient populations until a definite answer is obtained in future studies.

Results

In sections below, we present the results of our primary economic evaluation: model validation, base-case analysis, and sensitivity analyses.

Model Validation

As shown in Figures 4 and 5, in the arm with no MRD testing, event-free survival rates estimated by our model were the same as the data published by Chen et al.[31] The probability of a first relapse at 5 years in the standard-risk group was 9.0% in MRD-negative patients and 34.8% in MRD-positive patients. The probability of a first relapse at 5 years in the high-risk group was 21.9% in MRD-negative and 49.6% in MRD-positive patients. The corresponding probabilities of a first relapse at 10 years were 20.4% (MRD-negative) and 54.5% (MRD-positive) in the standard-risk group, and 35.9% (MRD-negative) and 69.6% (MRD-positive) in the high-risk group.

The model-estimated odds ratio associated with a reduction of relapse in the MRD testing strategy was 0.65 compared with an odds ratio of 0.61 provided by the UKALL2003 trial by Vora et al[14] (Table 4).

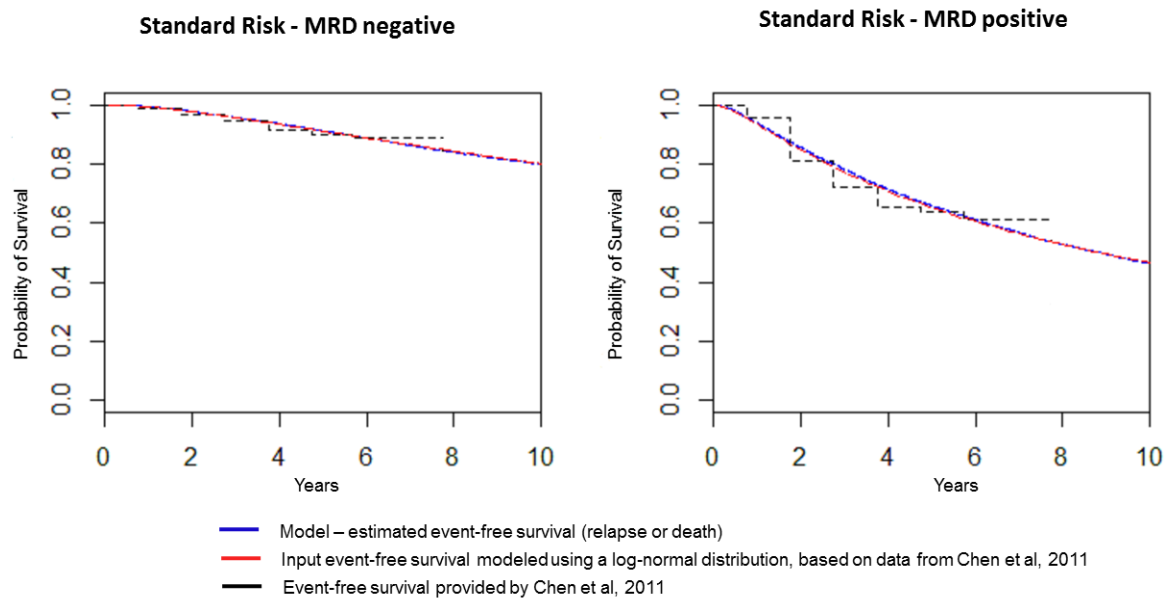

Figure 4: Model Validation: Event-Free Survival in Standard-Risk Group of Minimal Residual Disease Test–Negative and Minimal Residual Disease Test–Positive Patients

Abbreviation: MRD, minimal residual disease

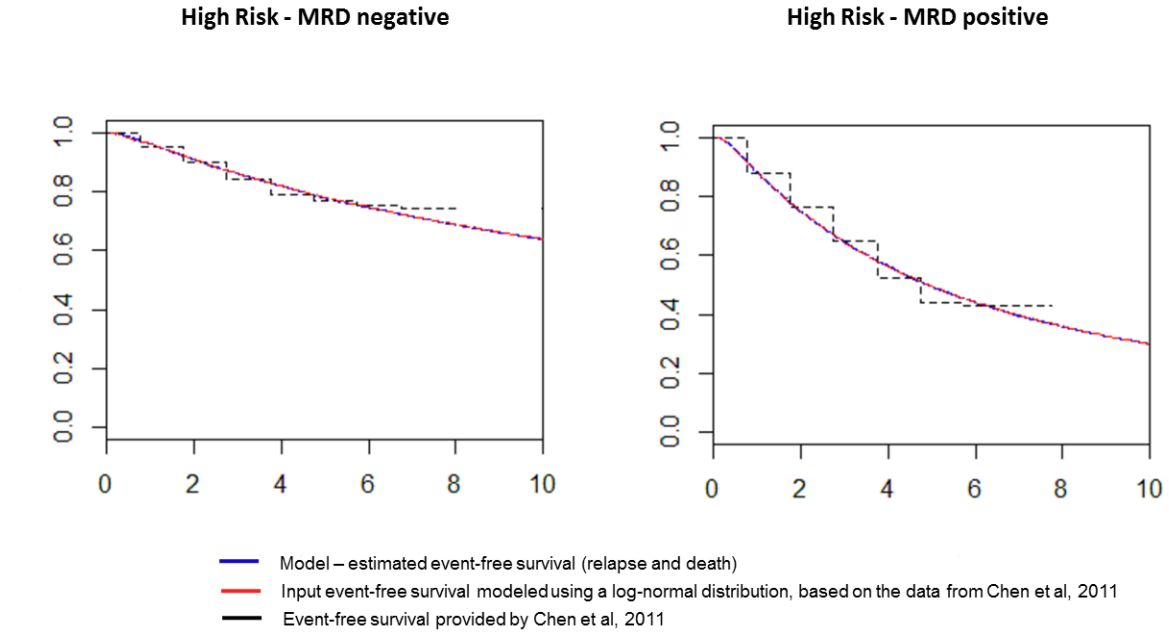

Figure 5: Model Validation: Event-Free Survival in High-Risk Group of Minimal Residual Disease Test–Negative and Minimal Residual Disease Test–Positive Patients

Abbreviation: MRD, minimal residual disease.

Base-Case Analysis

Our base-case analysis aimed to address two objectives that differed in the frequency of MRD testing in all patients (i.e., standard- and high-risk patients). In the first analysis, we examined incremental cost-effectiveness of MRD testing versus no testing after both induction and consolidation (Tables 10 and 11), while in the second analysis, we examined incremental cost-effectiveness of MRD testing versus no testing after induction only (Tables 12 and 13).

In terms of clinical outcomes, MRD testing after induction and consolidation versus no MRD testing resulted in lower rates of both relapse and transplants (first or multiple) and a better overall survival. Thus, over a lifetime, MRD testing resulted in a lower (1.29%) rate of a first relapse and a lower (0.38%) rate of any relapse (Table 10). MRD testing was associated with a lower number of first and multiple transplants (first: 20.97% vs. 21.07%; multiple: 27.22% vs. 27.97%).

Table 10: Overall Survival, Relapse, and Transplants: Minimal Residual Disease Testing at End of Induction and Consolidation Versus No Testing

		Outcomes			
Strategy	Life Expectancy[a] (Years)	Relapse: First (%)	Relapse: Multiple (%)	BMT: First (%)	BMT: Multiple (%)
No MRD testing	66.04	41.37	51.56	21.07	27.97
MRD testing	66.50	40.08	51.18	20.97	27.22

Abbreviations: BMT, bone marrow transplant; MRD testing, minimal residual disease testing by flow cytometry.
[a]Life expectancy for an average 6-year-old standard- or high-risk patient with precursor B-cell acute lymphoblastic leukemia.

Compared with no testing, MRD testing was associated with an increased survival of 0.46 years (66.04 vs. 66.50 years). After discounting, an overall survival gain was 0.104 life-years (Table 11). After discounting and adjustment for quality of life, MRD testing after induction and consolidation was associated with an increased survival of 0.0958 QALYs, and increased discounted costs of $4,180, yielding an ICER of $43,613/QALY gained (Table 11).

Table 11: Base-Case Analysis Results: Minimal Residual Disease Evaluation at End of Induction and Consolidation Phases

Strategy	Mean Costs, $[a]	Mean LYs	Mean QALYs	Incremental Costs, $[a]	Incremental LYs	Incremental QALYs	ICER: $/LY Gained[a]	ICER: $/QALY Gained[a]
No MRD testing	216,575	17.883	16.178					
MRD testing	220,755	17.987	16.274	4,179.6	0.104	0.09583	40,188.5	43,613.3

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life-years; MRD, minimal residual disease; QALYs, quality-adjusted life-years.
[a]All costs in 2014 Canadian dollars. All costs and effects were discounted at 5%.

Minimal residual disease testing after induction only versus no testing also resulted in lower rates of relapse and transplants (first or multiple) and a better overall survival (Table 12).

Table 12: Overall Survival, Relapse, and Transplants: Minimal Residual Disease Testing at End of Induction Versus No Testing

Strategy	Life Expectancy[a] (Years)	Outcomes			
		Relapse		BMT	
		First (%)	Multiple (%)	First (%)	Multiple (%)
No MRD testing	66.04	41.37	51.56	21.07	27.97
MRD testing: induction	66.44	40.29	49.61	20.28	26.64

Abbreviations: BMT, bone marrow transplant; MRD testing, minimal residual disease testing by flow cytometry.
[a]Life expectancy for an average 6-year-old standard- or high-risk patient with precursor B-cell acute lymphoblastic leukemia.

After discounting, MRD testing after induction compared with no testing was associated with an overall survival gain of 0.0981 life-years (Table 13). After discount and adjustment for quality of life, MRD testing after induction was associated with an increased survival of 0.092 QALYs and with increased discounted costs of $2,984, yielding an ICER of $32,585/QALY gained (Table 13).

Table 13: Base-Case Analysis Results: Minimal Residual Disease Evaluation at End of Induction Phase

Strategy	Mean Costs, $[a]	Mean LYs	Mean QALYs	Incremental Costs, $[a]	Incremental LYs	Incremental QALYs	ICER: $/LY Gained[a]	ICER: $/QALY Gained[a]
No MRD testing	216,575	17.883	16.178					
MRD testing: induction	219,560	17.981	16.270	2,984.1	0.0981	0.09158	30,417.9	32,584.8

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life-years; MRD, minimal residual disease; QALYs, quality-adjusted life-years.
[a]All costs in 2014 Canadian dollars. All costs and effects were discounted at 5%.

Sensitivity Analyses

We conducted one-way deterministic sensitivity analyses (Table 14). Over a patient's lifetime, MRD testing was not cost-effective at commonly used thresholds if there were changes in the following assumptions:

- If the initial clinical classification of patients and subsequent reclassification of patients after MRD testing resulted in a higher proportion of high-risk patients (i.e., 80%), then MRD testing versus no testing was not cost-effective at a willingness-to-pay threshold of $100,000/QALY
- If a higher proportion of high-risk MRD-positive patients received bone marrow transplant after consolidation (threshold probability = .3, base-case probability = .04), then MRD testing was not cost-effective at a threshold of $100,000/QALY

- If 50% of patients received bone marrow transplant after the first relapse instead of all 100% (i.e., base-case value), then MRD testing was not cost-effective at a threshold of $50,000/QALY
- If the probability of event-free survival after bone marrow transplant was high or if the probability of surviving after the second bone marrow transplant was high, then MRD testing was not cost-effective at a willingness-to-pay threshold of $50,000/QALY
- If the effectiveness of MRD testing on event-free survival was borderline (odds ratio [OR] = 0.98), then compared with no testing, MRD testing was not associated with better clinical outcomes but was associated with increased costs (i.e., dominated by no testing). An ICER of MRD testing was $53,515/QALY gained if the OR associated with an increased event-free survival after MRD risk-directed intensification was 0.68, and it was $115,934/QALY gained if the OR was 0.80
- The incremental cost-effectiveness of MRD testing was associated with an ICER over $50,000/QALY if we assumed a higher upper limit for (1) the costs of treatment in patients with de novo ALL ($120,000 for standard-risk patients and $180,000 for high-risk patients); (2) the initial costs of bone marrow transplant ($220,000); and (3) the cost of MRD test ($3,800)

Compared with no testing, MRD testing was cost-saving (i.e., associated with greater incremental benefits and lower incremental costs) if the costs of ALL were low (i.e., $60,000 vs. base case: $90,000–$125,000).

Table 14: One-Way Deterministic Sensitivity Analyses: Lifetime Cost-Effectiveness of Minimal Residual Disease Testing at End of Induction and Consolidation

Parameter	Base-Case Value	Sensitivity Analysis Value	ICER Compared With Thresholds: $50,000/QALY Gained $100,000/QALY Gained[a]
Base-case results			**43,613**
Probability of initial stratification	SR = 0.69/HR = 0.31	0.50/0.50	< 50,000
		0.80/0.20	< 50,000
		0.20/0.80	> 100,000
Probability of re-stratification after MRD testing	SR-MRD negative = 0.83 HR-MRD negative = 0.74	SR-MRD negative = 0.50 HR-MRD negative = 0.50	< 50,000
		SR-MRD negative = 0.10 HR-MRD negative = 0.10	< 50,000
		SR-MRD negative = 0.90 HR-MRD negative = 0.90	> 100,000
Probability of positive MRD test after consolidation	0.50	0.10	< 50,000
		0.90	> 50,000, < 100,000
Probability of BMT in consolidation	0.04	0.01	< 50,000
		0.80	> 100,000
Probability of BMT in a first relapse	0.50	0.10	< 50,000
		0.80	< 50,000
Probability of BMT in the next relapse	1.00	0.50	> 50,000; < 100,000
		1.00	Base case
Probability of relapse in remission	0.63	0.00	< 50,000
		0.70	< 50,000
Probability of dying from ALL after a first relapse	0.50	0.10	< 50,000
		0.60	< 50,000
Probability of dying from ALL after any next relapse	0.15	0.10	< 50,000
		0.40	< 50,000

Parameter	Base-Case Value	Sensitivity Analysis Value	ICER Compared With Thresholds: $50,000/QALY Gained $100,000/QALY Gained[a]
Probability of relapse after BMT, based on event-free survival	0.09/0.06	0.01	> 50,000
		0.70	< 50,000
Probability of dying after BMT, first relapse, based on survival	0.88	0.60	< 50,000
		0.95	< 50,000
Probability of dying after BMT next relapse, based on survival	0.30	0.10	< 50,000
		0.50	> 50,000
Risk of relapse after MRD testing and change in therapy	0.61	0.40	< 50,000
		0.98	Dominated[b]
Risk of dying from subsequent malignancy	NA	1.5	< 50,000
		1.9	< 50,000
		2.5	< 50,000
Utilities: Phase-specific treatment	Table 5	Low	< 50,000
		High	< 50,000
Utilities: Relapse	0.72	0.40	< 50,000
		0.80	< 50,000
Utilities: BMT	0.79	0.40	< 50,000
		0.99	< 50,000
Costs: Phase-specific treatment	$91,106/$124,298[a]	$60,000	Cost-saving[d]
		$120,000/$180,000[a]	> 50,000
Costs: Remission	$121.7[a]	$0[a]	< 50,000
		$200[a]	< 50,000
Costs: Relapse	$124,298[a]	$89,500[a]	< 50,000
		$179,000[a]	< 50,000
Costs: Initial hospitalization, BMT	$171,369[a]	$120,000[a]	< 50,000
		$220,000[a]	> 50,000
Costs: post-transplantation	$84,812[a]	$50,000[a]	< 50,000
		$120,000[a]	< 50,000
Cost: MRD testing (induction and consolidation)	$1,920[a]	$1,500[a]	< 50,000
		$3,800[a]	> 50,000
Discount rate[a]	0.05	0.01	< 50,000
		0.03	< 50,000
		0.06	> 50,000

Abbreviations: ALL, acute lymphoblastic leukemia; BMT, bone marrow transplant; HR, high risk; ICER, incremental cost-effectiveness ratio; MRD, minimal residual disease; NA, not applicable; QALY, quality-adjusted life-year; SR, standard risk.

[a]All costs in 2014 Canadian dollars.

[b]MRD testing was associated with less benefit and higher costs than no testing.

[c]Low and high limits of range were 0.40 (induction, intensification); 0.60 (consolidation); 0.70 (maintenance); 0.90 (off therapy).

[d]MRD testing was associated with more benefit and lower costs than no testing.

Probabilistic Sensitivity Analysis

In probabilistic sensitivity analysis, compared with no testing, MRD testing at the end of induction and consolidation was associated with an increased discounted survival of 0.077 QALYs (95% credible interval −0.29, 0.46), and increased discounted mean costs of $3,863.4 (95% credible interval −$8,498, $15,538), yielding an ICER of $50,249/QALY gained (Table 15).

As shown in Figure 6, incremental cost-effectiveness of the MRD testing at the end of induction and consolidation was associated with large uncertainty. In 676 of 1,000 simulations, MRD testing was associated with better clinical outcomes than no testing. Minimum residual disease testing was associated with greater health benefits and lower costs than no testing in 187

simulations (i.e., cost saving). It was associated with increased costs or worse health benefits, but at an ICER below $50,000/QALY in 305 simulations. It was associated with worse health benefits and higher costs (i.e., inferior) in 252 of 1,000 simulations.

The probability of cost-effectiveness of MRD testing in both induction and consolidation versus no testing was 49.2% at a $50,000/QALY threshold and 57.8% at a $100,000/QALY threshold (Figure 7).

Table 15: Probabilistic Sensitivity Analysis: Minimal Residual Disease Evaluation at End of Induction and Consolidation Phases

Strategy	Mean Costs (95% CrI), $[a]	Mean QALYs (95% CrI)	Incremental Costs (95% CrI), $[a]	Incremental QALYs (95% CrI)	ICER: $/QALY Gained[a]
No testing	216,606 (161,287; 279,863)	16.5015 (14.877; 17.691)			
MRD testing	220,469 (162,160; 285,499)	16.5784 (15.037; 17.716)	3,863.4 (−8,498; 15,530)	0.07688 (−0.29; 0.46)	50,249.2

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; MRD, minimal residual disease; QALY, quality-adjusted life-year.
[a]All costs in 2014 Canadian dollars. All costs and effects were discounted at 5%.

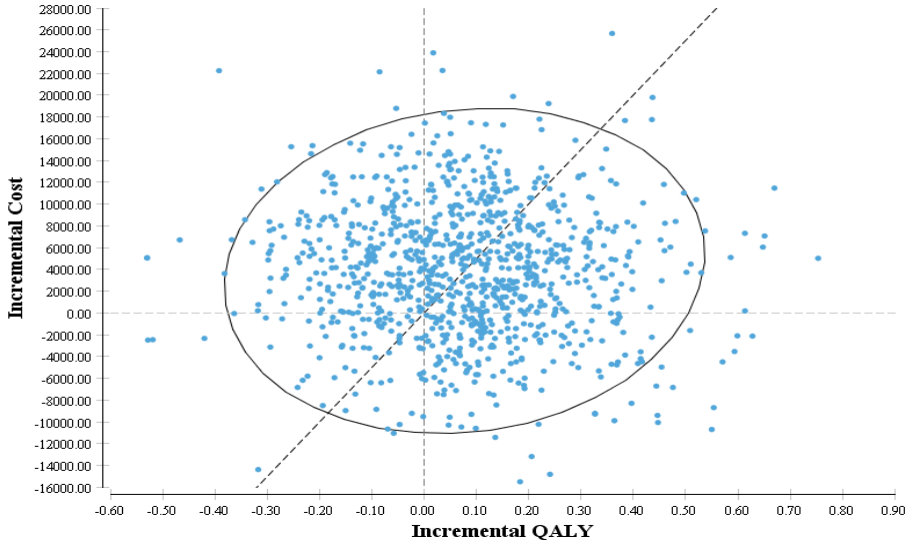

Figure 6: Scatter Plots of 1,000 Simulated Pairs of Incremental Costs and Effects in Cost-Effectiveness Plane: Minimal Residual Disease Testing at End of Induction and Consolidation

All costs are in 2014 Canadian dollars and discounted at 5%. Effectiveness is expressed in quality-adjusted life years (QALYs). Negative QALYs indicate that the minimal residual disease (MRD) testing strategy was associated with worse quality-adjusted survival, and negative costs indicate that the MRD testing strategy saved money relative to the no-testing strategy. The dashed line indicates a willingness-to-pay threshold of $50,000/QALY. The incremental cost-effectiveness ratio ($50,249/QALY gained) is the slope of a straight line from the origin that passes through (0.08 QALY, $3,863) coordinate. A 95% confidence ellipse covers 95% of the estimated joint density and was used to represent uncertainty around the incremental cost-effectiveness ratio estimated in probabilistic sensitivity analysis.

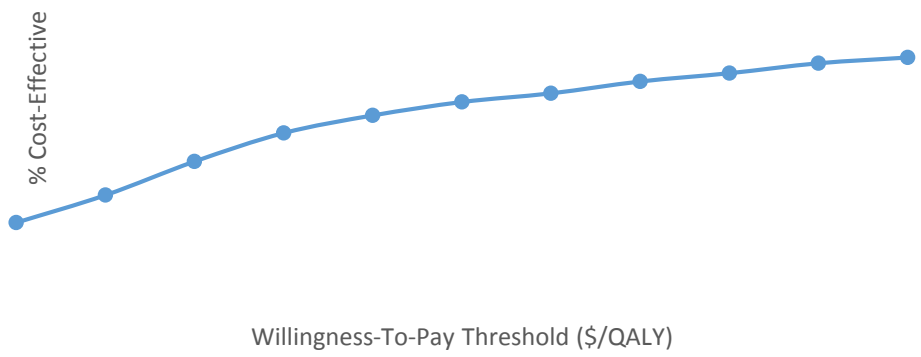

Figure 7: Cost-Effectiveness Acceptability Curve: Minimal Residual Disease Testing Versus No Testing at End of Induction and Consolidation

A cost-effectiveness acceptability curve is a graphic presentation of the probability of cost-effectiveness of the minimal residual disease (MRD) testing strategy at the end of induction and consolidation (vs. no testing) across various willingness-to-pay thresholds on the x-y coordinate system. The x-axis shows the probability of cost-effectiveness (range 0–1) and the y-axis represents willingness-to-pay thresholds (range $0–$100,000 per one quality-adjusted life-year [QALY] gained).

In probabilistic sensitivity analysis, compared with no testing, the MRD testing at the end of induction was associated with an increased discounted survival of 0.09 QALYs (95% credible interval −0.10, 0.33), and increased discounted mean costs of $2,683 (95% credible interval −$6,391, $13,220), yielding an incremental cost-effectiveness ratio of $29,535/QALY gained (Table 16). However, it was also associated with uncertainty (Figure 7).

In 819 of 1,000 simulations, MRD testing was associated with better clinical outcomes than no testing (Figure 8). MRD testing was associated with greater health benefits and lower costs than no testing in 255 simulations (i.e., dominant or cost-saving) and was associated with increased costs or worse health benefits but at an ICER below $50,000/QALY in 358 simulations. It was associated with worse health benefits and higher costs (i.e., was inferior) in 125 of 1000 simulations.

The probability of cost-effectiveness of MRD testing at the end of induction versus no testing was 61.3% at a $50,000/QALY threshold and 71.4% at a $100,000/QALY threshold (Figure 9).

Table 16: Probabilistic Sensitivity Analysis: Minimal Residual Disease Evaluation at End of Induction

Strategy	Mean Costs (95% CrI), $[a]	Mean QALYs (95% CrI)	Incremental Costs (95% CrI), $[a]	Incremental QALYs (95% CrI)	ICER: $/QALY Gained[a]
No testing	216,689 (162,144, 280,185)	16.482 (14.91, 17.70)			
MRD testing	219,372 (164,889, 286,628)	16.573 (15.04, 17.49)	2,683.1 (−6,361; 13,220)	0.09084 (−0.098; 0.328)	29,534.7

Abbreviations: CrI, credible interval; ICER, incremental cost-effectiveness ratio; MRD, minimal residual disease; QALY, quality-adjusted life-year.
[a]All costs in 2014 Canadian dollars. All costs and effects were discounted at 5%.

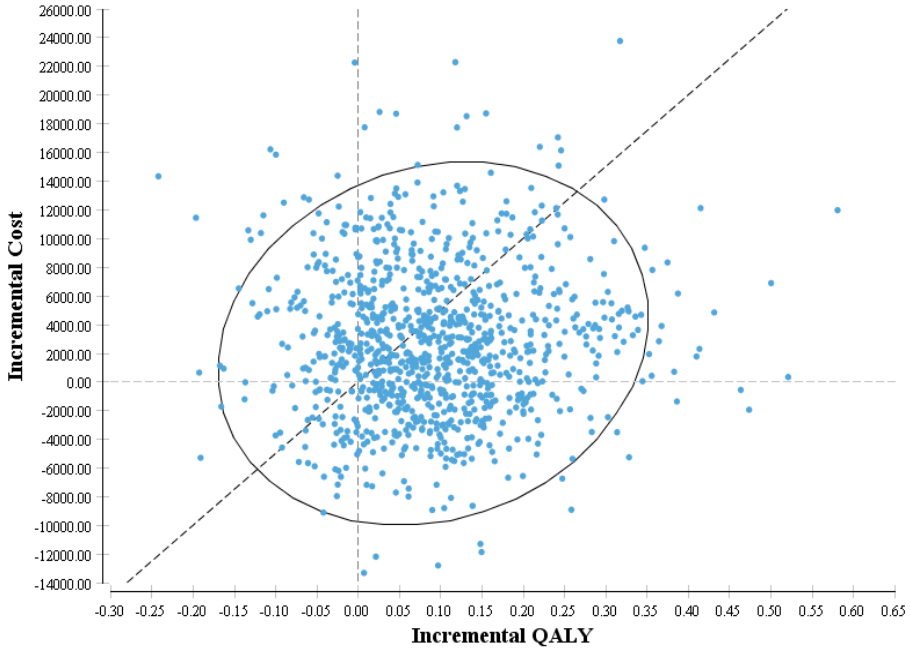

Figure 8: Scatter Plots of 1,000 Simulated Pairs of Incremental Costs and Effects in Cost-Effectiveness Plane: Minimal Residual Disease Testing at End of Induction

All costs are in 2014 Canadian dollars and discounted at 5%. Effectiveness is expressed in quality-adjusted life-years (QALYs). Negative QALYs indicate that the minimal residual disease (MRD) testing strategy was associated with worse quality-adjusted survival, and negative costs indicate that the MRD testing strategy saved money relative to the no-testing strategy. The dashed line indicates a willingness-to-pay threshold of $50,000/QALY. The incremental cost-effectiveness ratio ($29,535/QALY gained) is the slope of a straight line from the origin that passes through (0.09 QALY, $2,683) coordinate. A 95% confidence ellipse covers 95% of the estimated joint density and was used to represent uncertainty around the incremental cost-effectiveness ratio estimated in probabilistic sensitivity analysis.

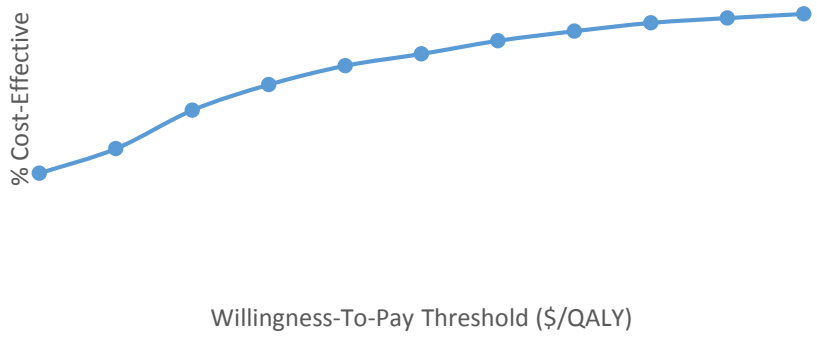

Figure 9: Cost-Effectiveness Acceptability Curve: Minimal Residual Disease Testing at End of Induction

A cost-effectiveness acceptability curve is a graphic presentation of the probability of cost-effectiveness of the minimal residual disease testing strategy at the end of induction (vs. no testing) across various willingness-to-pay thresholds on the x-y coordinates. The x-axis shows the probability of cost-effectiveness (range 0–1), and the y-axis represents willingness-to-pay thresholds (range $0–$100,000 per one quality-adjusted life-year gained).

Scenarios

We performed three scenario analyses for specifically defined target population or model parameters: in standard-risk patients, with COG protocols, and by time horizon.

Scenario 1: Standard-Risk Patients

The first scenario analysis was conducted for a subpopulation of standard-risk patients. In this patient group, regardless of the frequency of testing, MRD evaluation was associated with better clinical outcomes over lifetime and acceptable cost-effectiveness ratios below a willingness-to-pay threshold of $50,000/QALY (Tables 17–19).

More specifically, MRD testing after induction and consolidation versus no MRD testing was associated with a 1.72% and 0.86% reduction of a first relapse and a first transplant, respectively, and a 3.08% and a 1.77% reduction of multiple relapses and multiple transplants (Table 17).

Table 17: Scenario 1—Overall Survival, Relapse, and Transplants for Standard-Risk Patients

		Outcomes			
Strategy	Life Expectancy[a] (Years)	Relapse: First (%)	Relapse: Multiple (%)	BMT: First (%)	BMT: Multiple (%)
No MRD testing	68.392	35.52	42.74	18.07	23.06
MRD testing[b]	69.098	33.80	39.66	17.21	21.29

Abbreviations: BMT, bone marrow transplant (refers to hematopoietic stem cell transplant); MRD testing, minimal residual disease testing by flow cytometry.
[a]Life expectancy for an average 6-year old standard-/high-risk patient with precursor B-cell ALL.
[b]MRD testing done at end of induction and consolidation.

Compared with no MRD testing, MRD testing was associated with an increase in life expectancy of 0.71 years. After discounting and adjustment for quality of life, MRD testing after induction and consolidation was associated with an increased survival of 0.16 QALYs and was associated with increased discounted costs of $4,373, yielding an ICER of $29,815/QALY gained over lifetime (Table 18). In the evaluation of MRD testing after induction only versus no testing, ICER was $23,568/QALY gained (Table 19).

Table 18: Scenario 1—Minimal Residual Disease Evaluation at End of Induction and Consolidation Phases in Standard-Risk Patients

Strategy	Mean Costs, $[a]	Mean LYs	Mean QALYs	Incremental Costs, $[a]	Incremental LYs	Incremental QALYs	ICER: $/LY Gained[a]	ICER: $/QALY Gained[a]
No testing	188,078	18.404	16.669					
MRD testing	192,451	18.561	16.816	4,373.2	0.1572	0.14667	27,819.3	29,815.3

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life-year; MRD, minimal residual disease; QALY, quality-adjusted life-year.
[a]All costs in 2014 Canadian dollars. All costs and effects were discounted at 5%.

Table 19: Scenario 1—Minimal Residual Disease Evaluation at End of Induction in Standard-Risk Patients

Strategy	Mean Costs, $[a]	Mean LYs	Mean QALYs	Incremental Costs, $[a]	Incremental LYs	Incremental QALYs	ICER: $/LY Gained[a]	ICER: $/QALY Gained[a]
No testing	188,078	18.404	16.669					
MRD testing[b]	191,632	18.565	16.820	3,554.4	0.1616	0.1508	21,995.0	23,567.8

Abbreviations: ICER, incremental cost-effectiveness ratio; LY, life-year; MRD, minimal residual disease; QALY, quality-adjusted life-year.
[a]All costs in 2014 Canadian dollars. All costs and effects were discounted at 5%.
[b]MRD testing done at the end of induction and consolidation.

Scenario 2: Children's Oncology Group Protocol Costs

In the next scenario, we used costing data that included the treatment cost of the COG protocol (upper range estimates, Table 8). Within this scenario, we conducted two analyses: one using the COG treatment protocol data for all health states (i.e., assuming that the COG cost of chemotherapy for a high-risk patient is applicable to the costs of relapse states), and another assuming that the cost of chemotherapy in the rescue relapse state is the same as the cost of relapse in the United Kingdom.

In a scenario including the COG treatment costs for all chemotherapy health states (Table 20), MRD testing at the end of induction and consolidation was associated with an incremental cost-effectiveness ratio of $82,390/QALY gained. If MRD testing was performed at the end of induction only, the ICER was $72,100/QALY gained (data not shown).

Table 20: Scenario 2—Cost-Effectiveness Analysis Using Children's Oncology Group Treatment Protocol Costs for All Chemotherapy States

Strategy	Mean Costs, $[a]	Mean LYs	Mean QALYs	Incremental Costs, $[a]	Incremental LYs	Incremental QALYs	ICER: $/LY Gained[a]	ICER: $/QALY Gained[a]
No testing	247,669	17.883	16.178					
MRD testing	255,564	17.987	16.274	7,895.7	0.1040	0.09583	75,920.2	82,389.9

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.
[a]All costs in 2014 Canadian dollars. All costs and effects were discounted at 5%.
[b]MRD testing done at end of induction and consolidation.

In a scenario estimating the costs of ALL from different sources (Table 21), MRD testing at the end of induction and consolidation was associated with an ICER of $87,650/QALY gained. If MRD testing was performed at the end of induction only, the ICER was $73,740/QALY gained (data not shown).

Table 21: Scenario 2—Cost-Effectiveness Analysis Using Relapse Costs From United Kingdom in Addition to Children's Oncology Group Treatment Protocol Costs for Initial Chemotherapy States

Strategy	Mean Costs, $[a]	Mean LYs	Mean QALYs	Incremental Costs, $[a]	Incremental LYs	Incremental QALYs	ICER: $/LY Gained[a]	ICER: $/QALY Gained[a]
No testing	260,026	17.883	16.178					
MRD testing	268,152	17.987	16.274	8,126.6	0.1040	0.0958	78,140.4	87,650.3

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life-years; MRD, minimal residual disease; QALYs, quality-adjusted life-years.
[a]All costs in 2014 Canadian dollars. All costs and effects were discounted at 5%. MRD testing done at the end of induction and consolidation

Scenario 3: Time Horizon

As shown in previous methodologic studies,[61,62] short-term time horizons (i.e., the duration of follow-up visits assumed for a hypothetical cohort) greatly influenced the cost-effectiveness results. In our analysis, although MRD testing versus no testing was associated with gains in discounted survival and quality-adjusted survival, it was not cost-effective even at a higher willingness-to-pay benchmark of $100,000/QALY after 5 or 10 years of follow-up (Tables 22 and 23).

Table 22: Scenario 3—Effect of Time Horizon on Cost-Effectiveness Results for Minimal Residual Disease Testing at End of Induction and Consolidation

Strategy	Mean Costs, $[a]	Mean LYs	Mean QALYs	Incremental Costs, $[a]	Incremental LYs	Incremental QALYs	ICER: $/LY Gained[a]	ICER: $/QALY Gained[a]
Time horizon: 5 years								
No testing	161,570	4.356	3.772					
MRD testing	166,180	4.365	3.763	4,606.7	0.009157	0.00876	503,080	525,624
Time horizon: 10 years								
No testing	191,966	7.548	6.677					
MRD testing	196,030	7.580	6.706	4,064.3	0.03226	0.02958	125,983	137,390

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life-years; MRD, minimal residual disease; QALYs, quality-adjusted life-years.
[a]All costs in 2014 Canadian dollars. All costs and effects were discounted at 5%.

Table 23: Scenario 3—Effect of Time Horizon on Cost-Effectiveness Results for Minimal Residual Disease Testing at End of Induction

Strategy	Mean Costs, $[a]	Mean LYs	Mean QALYs	Incremental Costs, $[a]	Incremental LYs	Incremental QALYs	ICER: $/LY Gained[a]	ICER: $/QALY Gained[a]
Time horizon: 5 years								
No testing	161,570	4.3559	3.763					
MRD testing	165,797	4.3598	3.767	4,226.9	0.003829	0.003773	1,103,917	1,120,368
Time horizon: 10 years								
No testing	191,966	7.548	6.677					
MRD testing	194,827	7.580	6.697	2,860.8	0.02032	0.019921	140,787	143,606

Abbreviations: ICER, incremental cost-effectiveness ratio; LYs, life-years; MRD, minimal residual disease; QALYs, quality-adjusted life-years.
[a]All costs in 2014 Canadian dollars. All costs and effects were discounted at 5%.

Budget-Impact Analysis

We estimated the 1-year cost burden of MRD testing by flow cytometry at the end of induction and consolidation phases of chemotherapy in patients with de novo precursor B-cell ALL. We also forecasted the cost burden over 3 and 5 years. The budget-impact analysis was conducted from the perspective of the Ontario Ministry of Health and Long-Term Care. All costs are reported in 2014 Canadian dollars.

Methods

Target Population

The target population included all newly diagnosed patients with precursor B-cell ALL, eligible for MRD testing at the end of induction and consolidation. Based on Ontario data (the POGONIS registry), an annual number of new incident cases of precursor B-cell ALL varied between 88 (in 2007) and 127 (in 2010) (Appendix 7; Ms. N. Bradley, written communication, March 11, 2015). In the base-case analysis, we used the mean estimate of 94 newly diagnosed cases per year for the period 2007 to 2013. Over a 3-year period, some patients with de novo ALL would fail treatment (relapsed ALL). The numbers of relapses for two compared strategies were predicted from our model (Table 24).

Table 24: Target Population

Strategy	Target Population	Incidence Years 1–5, n	Prevalence[a]			
			Year 2, n	Year 3, n	Year 4, n	Year 5, n
MRD testing at end of induction and consolidation	De novo patients with precursor B-cell ALL	94	181	259	325	379
No testing	De novo patients with precursor B-cell ALL	94	181	258	323	375

Abbreviations: ALL, acute lymphoblastic leukemia; MRD, minimal residual disease; n, sample size.
[a]Prevalence accounts for newly diagnosed patients and patients who relapsed in that year, as estimated by our cost-effectiveness model.

Resources

Based on consultation with experts, it was assumed that all newly diagnosed patients will undergo MRD testing (i.e., uptake of 100%). Currently, there is no Ontario Health Insurance Plan (OHIP) fee code assigned for MRD testing in children with acute leukemia. The in-patient and outpatient resource use of a patient with precursor B-cell ALL were calculated from published data, mainly on the Ontario costing study by Rae et al[44] (refer to the section Model Input Parameters in Primary Economic Evaluation).

Canadian Costs

Thus far, costs of MRD testing have been covered within the budget of the COG trial (ends in June 2016), in which testing was performed by the reference laboratory in Seattle, Washington.[17] For our analysis, the costs of MRD testing were provided by the reference laboratory of SickKids, which was at the time of analysis the only laboratory ready to take on MRD testing for precursor B-cell ALL in Ontario (refer to the section Model Input Parameters in Primary Economic Evaluation). Other costs included in the budget-impact model were related to treatment of ALL and were based on estimates from the literature. In the base-case analysis, the costs of ALL reflected phase-specific treatment costs of the BFM protocol. As previously mentioned, this protocol is the most similar to the Children's Oncology Group (COG) protocol, most frequently used to treat de novo B-cell ALL in Ontario.

Analysis

The budget-impact analysis was based on the predictions of our Markov model, developed for the primary economic evaluation. It accounted for both the costs of MRD testing and downstream costs of the disease. As per current economic guidelines, estimates of costs were derived from the deterministic model and were not discounted.[63]

In the sensitivity analysis we examined changes in the net budget impact of MRD testing after making changes in the following parameters:

- Frequency of MRD testing: for example, done one time at the end of induction
- Estimate of incident cases: for example, done in all patients with ALL
- Probability of getting bone marrow transplant at the end of consolidation
- Patient population: that is, done in the high-risk group

- Costs of de novo ALL: costs from a scenario analysis that was related to the costs of the COG treatment protocol

Results

Using our budget-impact model, we estimated that the total current 1-year costs associated with MRD testing by flow cytometry at the end of induction and consolidation are $340,760 (Table 25). This 1-year budgetary impact included the costs of the test itself in 94 patients with precursor B-cell ALL, accounting for approximately $180,500. We forecasted that the total economic impact of MRD testing over 3 years is approximately $1.28 million and over 5 years is approximately $2.36 million.

Table 25: Budget-Impact Analysis: Base-Case Results

						Budget Impact		
Strategy	**Year 1, $[a]**	**Year 2, $[a]**	**Year 3, $[a]**	**Year 4, $[a]**	**Year 5, $[a]**	**1 Year, $[a]**	**3 Years, $[a,b]**	**5 Years, $[a,b]**
No testing	4,689,194	9,287,912	13,205,775	13,988,841	14,539,821			
MRD testing	5,029,951	9,685,516	13,745,084	14,541,876	14,274,940	340,757	1,277,670	2,362,616

Abbreviation: MRD, minimal residual disease.

[a]All costs in 2014 Canadian dollars.

[b]Calculated as sum of incremental costs for the period of 3 or 5 years: e.g., Budget impact for 3 years = MRD testing ($Year1 + $Year2 + $Year3) − No testing ($Year1 + $Year2 + $Year3) = $28,460,551 − $27,182,882 = $1,277,670.

Tables 26 to 28 present changes in the 1-year, 3-year, and 5-year budgetary impacts generated by one-way sensitivity analysis. The total budgetary impact was sensitive to the frequency of MRD testing, incidence rate, probability of getting bone marrow transplant after consolidation, definition of the target population, and costs of the protocol used for treatment of ALL.

As expected, the budgetary impact for the first year would be smaller (1) if MRD testing were done after induction only; (2) if the number of incident cases per year were smaller (i.e., 84); and (3) if the probability of bone marrow transplant after consolidation were very small (i.e., .01). Also, the 1-year budgetary impact was smaller if MRD testing was done only in high-risk patients because of higher rates of relapse and death in this group.

Additional expenditures were expected (1) if we assumed that all newly diagnosed cases with ALL would be tested (i.e., 140 incident cases per year; Appendix 7); (2) if most patients with positive results from MRD Test 2 underwent transplant after consolidation (i.e., probability of .80); (3) if only standard-risk patients were tested (as they have better survival and incur more costs); and (4) if the costs of ALL treatment were higher (Table 26). Compared with the estimated 1-year budgetary impact in base-case analysis, the 1-year budgetary impact in sensitivity analysis increased from 1.18 times (i.e., for parameter: probability of MRD testing in high-risk group = 0) to 5.82 times (i.e., for parameter: probability of transplant after consolidation = .80).

Table 26: Sensitivity Analysis: 1-Year Budget Impact

Parameter	Base-Case Value	Sensitivity Analysis Value	Expenditure With No Testing, $[a]	Expenditure With MRD Testing, $[a]	Budget Impact 1 Year, $[a]
Base-case results	**2 MRD tests**		**4,689,194**	**5,029,951**	**340,757**
One MRD test (induction only)	$1,920[a]				
		$1,390[a]	4,689,194	4,952,671	263,477
Incidence of precursor B-cell ALL	94				
		84	4,190,344	4,494,850	304,506
		140	6,983,906	7,491,416	507,510
Probability of transplant after consolidation	0.04				
		0.01	4,689,194	4,971,109	281,916
		0.80	4,689,194	6,672,324	1,983,130
Probability of MRD testing (2 tests) in high-risk patients	0.31				
		0.00[b]	4,028,231	4,430,771	402,540
		1.00	5,797,152	5,951,364	154,212
Costs of ALL including the costs of COG treatment protocol	NA[c]				
	Costs: lower limit	$106,426/ $174,263[a,d]	5,394,743	5,842,644	447,901
	Costs: upper limit	$109,222/ $181,252[a,d]	5,567,632	6,029,717	462,084

Abbreviations: ALL, acute lymphoblastic leukemia; COG, Childhood Oncology Group; MRD, minimal residual disease; NA, not applicable.
[a]All costs in 2014 Canadian dollars.
[b]Probability of 0 implies that tests are done in standard-risk group only.
[c]Used in sensitivity analysis only.
[d]Costs for standard-risk/high-risk group.

The cost burden changed with the same trend over 3 or 5 years (Table 27 and 28). As compared with the estimate in base-case analysis, the 3-year expenditures increased from 1.19 times (i.e., for parameter: incidence = 140) to 4.10 times (i.e., for parameter: probability of transplant after consolidation = .80) in sensitivity analysis.

Table 27: Sensitivity Analysis: 3-Year Budget Impact

Parameter	Base-Case Value	Sensitivity Analysis Value	Expenditure With No Testing, $[a]	Expenditure With MRD Testing, $[a]	Budget Impact 3 Years, $[a]
Base-case results	**2 MRD tests**		**27,182,882**	**28,460,551**	**1,277,670**
One MRD test (induction only)	$1,920[a]				
		$1,390[a]	27,182,882	28,252,857	1,069,976
Incidence of precursor B-cell ALL	94				
		84	24,276,939	25,475,662	1,198,722
		140	40,389,769	42,424,739	1,527,460
Probability of transplant after consolidation	0.04				
		0.01	27,182,882	28,312,113	1,129,232
		0.80	27,182,882	32,421,333	5,238,451
Probability of MRD testing (2 tests) in high-risk patients	0.31				
		0.00[b]	23,934,254	25,668,668	1,734,414
		1.00	32,055,211	32,501,029	445,819
Costs of ALL including the costs of COG treatment protocol	NA[c]				
	Costs: lower limit	$106,426/ $174,263[a,d]	31,134,004	33,022,623	1,888,619
	Costs: upper limit	$109,222/ $181,252[a,d]	32,101,272	34,072,049	1,970,777

Abbreviations: ALL, acute lymphoblastic leukemia; COG, Childhood Oncology Group; MRD, minimal residual disease; NA, not applicable.
[a]All costs in 2014 Canadian dollars.
[b]Probability of 0 implies that tests are done in standard-risk group only.
[c]Used in sensitivity analysis only.
[d]Costs for standard-risk/high-risk group.

Compared with the estimate in base-case analysis, the 5-year budgetary impact increased from 1.38 times (i.e., for parameter: probability of MRD testing in high-risk patients = 0) to 3.51 times (i.e., for parameter: probability of transplant after consolidation = .80) in sensitivity analysis.

Table 28: Sensitivity Analysis: 5-Year Budget Impact

Parameter	Base-Case Value	Sensitivity Analysis Value	Expenditure With no Testing, $[a]	Expenditure with MRD Testing, $[a]	Budget Impact 5 years, $[a]
Base-case results	**2 MRD tests**		**55,711,544**	**58,074,159**	**2,362,616**
One MRD test (induction only)	$1,920[a]				
		$1,390[a]	55,711,544	57,755,938	2,044,394
Incidence of precursor B-cell ALL	94				
		84	49,718,938	52,005,038	2,286,099
		140	82,735,630	86,580,527	3,844,897
Probability of transplant after consolidation	0.04				
		0.01	55,711,544	57,840,947	2,129,403
		0.80	55,711,544	64,008,169	8,296,625
Probability of MRD testing (2 tests) in high-risk patients	0.31				
		0.00[b]	49,271,404	52,529,765	3,258,361
		1.00	64,915,959	64,714,254	798,295
Costs of ALL including the costs of COG treatment protocol	NA[c]				
	Costs: lower limit	$106,426/ $174,263[a,d]	63,695,149	67,287,128	3,591,979
	Costs: upper limit	$109,222/ $181,252[a,d]	65,635,722	69,395,413	3,759,691

Abbreviations: ALL, acute lymphoblastic leukemia; COG, Children's Oncology Group; MRD, minimal residual disease.
[a]All costs in 2014 Canadian dollars.
[b]Probability of 0 implies that tests are done in standard risk group only.
[c]Used in sensitivity analysis only.
[d]Costs for standard-risk/high-risk group.

Limitations

Our primary economic evaluation and budget-impact analysis are associated with some limitations that stem from simplifying assumptions made for our modelling study.

The effectiveness of MRD testing on reduction of relapse-free survival was based on the published data of one trial.[14] According to expert opinion, it is not likely that there will be many trials in the future that will examine the effectiveness of MRD testing in all patients given that it has been accepted as the standard of care.[17] To our knowledge, there is only one ongoing North American study in patients newly diagnosed with ALL that examines the effectiveness of MRD intervention on clinical outcomes using the COG treatment protocol (ClinicalTrials.gov identifier NCT01142427). The results of this study are expected to be revealed in 2016.

Our cost-effectiveness estimates depended on the probability of getting a bone marrow transplant in consolidation. Data of the POGONIS registry (relevant to the Ontario setting) were used to inform this parameter. According to POGONIS, a small proportion of patients (i.e., 8%) received transplants during consolidation. If the probability of transplantation during consolidation were much larger (e.g., 30%), MRD testing followed by changes in treatment

would not be cost-effective over lifetime at a willingness-to-pay threshold of $100,000/QALY gained.

Cost-effectiveness of MRD testing also depended on the proportion of patients classified as high risk after MRD testing (base-case values were 17%–26%). It is not clinically plausible to expect that this population is large (i.e., 80%); but if MRD testing were done in high-risk populations only, it would not represent good value for money over lifetime.

Our study was based on several assumptions related to the costs of de novo and relapsed ALL. In the base-case analysis, we used data from currently available literature, and in scenario analyses we estimated the costs of ALL accounting for the COG protocol costs. Between these analyses, differences in the estimate of total ALL costs in de novo patients were around $20,000 for the standard-risk group and around $65,000 for the high-risk group. If the costs of ALL treatment were high, as shown in our COG costs scenario analysis, MRD testing would not be cost-effective at a threshold of $50,000/QALY. Our results need to be corroborated in future studies that more precisely determine the phase-specific treatment costs for patients with de novo ALL and those with relapsed ALL.[64]

Our study is limited to standard- and high-risk patients aged between 1 and 10 years, and its generalizability is restricted. However, we conducted a sensitivity analysis assuming that all high-risk patients would undergo testing. Although not examined in this study, patients with T-cell ALL, infants with ALL, and older patients with B-cell ALL have a very high risk of relapse. Data from our sensitivity analysis may be used to guide policymaking in other populations who are not specifically examined in our base-case analysis until more information is available.

Currently, no professional fee code is specified for MRD testing in Ontario. The costs of MRD testing were justified by experts from the POGO MRD Working Group. Thus far, MRD testing has been funded from trials or hospital budgets. The experts estimate the cost of MRD testing used for our analysis to be half the cost of testing funded by trials (and done by the reference laboratory in Seattle, Washington). According to our sensitivity analysis, if the costs of MRD testing at the end of induction and consolidation doubled (from $1,900 to $3,800), the incremental cost-effectiveness of MRD testing would not represent good value for money at a threshold of $50,000/QALY.

Discussion

This economic evaluation examined the incremental cost-effectiveness and the cost burden of MRD testing by flow cytometry after induction and consolidation phases of chemotherapy followed by subsequent intensification of treatment in children diagnosed with de novo precursor B-cell ALL. We estimated trade-offs between the costs and benefits of two alternatives (MRD testing vs. no testing) using a probabilistic microsimulation state-transition model that represented the natural history and progression of precursor B-cell ALL in a hypothetical cohort of patients aged between 1 and 10 years (mean age 6 years). The model's face validity was verified by experts from POGO. The model's output estimates were validated against the literature.[31]

We found that MRD testing versus no testing (either after both induction and consolidation or after induction only) improves clinical outcomes over a patient's lifetime. Minimal residual disease testing at the end of induction and consolidation was associated with a 1.3% reduction in the rate of a first relapse and with a 0.8% reduction in the rate of a first transplant. According to our modelling study, the life expectancy of a 6-year-old child with precursor B-cell ALL who

underwent MRD evaluation was 66.5 years and was 0.5 years larger than the life expectancy of a child who did not have the intervention. Our estimate of the life expectancy of 66.5 years is comparable to the life expectancy of 66 years for Dutch 6-year-olds with ALL who underwent MRD testing and treatment with the ALL10 protocol in a patient-level economic evaluation by van Litsenburg et al.[25]

We also found that MRD testing versus no testing represents good value for money. Compared with no testing, MRD testing at the end of induction and consolidation was associated with an increased discounted survival of 0.0958 QALYs and increased discounted costs of $4,180, yielding an ICER of $43,613/QALY gained. After accounting for parameter uncertainty in the probabilistic sensitivity analysis, MRD testing was borderline cost-effective at a threshold of $50,000/QALY (ICER = $50,249/QALY gained). An estimate of the ICER was much lower in an economic evaluation by van Litsenburg et al.[25] This disparity could be explained by important differences in the design between our analysis and the economic study done in the Netherlands.

However, by doing a probabilistic sensitivity analysis, we detected substantial uncertainty around the estimate of ICER. For example, about 50% of simulated ICERs were below a threshold of $50,000/QALY and about 58% were below a threshold of $100,000/QALY. Minimal residual disease testing compared with no testing was associated with smaller effects and larger costs (i.e., was inferior) in as many as 25% of simulated ICERs. These results indicate that the values for many model parameters could not be viewed as fixed because they are either unknown or uncertain—and using them as fixed in an economic evaluation could lead to an incorrect decision.[57]

Our one-way deterministic analysis indicated some important drivers of the cost-effectiveness analysis. First, if MRD testing followed by treatment intensification in the high-risk group improved event-free survival by 32% (OR = 0.68) instead of 39% (base-case OR = 0.61), then MRD testing versus no testing did not represent good value for money at a threshold of $50,000/QALY (ICER = $53,515/QALY). If MRD intervention increased the survival by 20% (OR = 0.80), then MRD testing would not represent good value for money at a threshold of 100,000/QALY (ICER = $115,934/QALY). If MRD intervention was borderline effective (OR = 0.98), then MRD testing was dominated by no testing.

Second, the incremental cost-effectiveness of MRD testing depended on the percentage of high-risk patients who were referred to transplantation at the end of consolidation. These data were derived from the POGONIS registry and were based on a small sample of patients eligible for transplant at the time of consolidation. It is plausible to expect the proportion of patients at very high risk of relapse who require bone marrow transplant at the end of consolidation to be small. Minimal residual disease testing versus no testing would not represent good value for money at a threshold of $100,000/QALY if this proportion were seven times larger than base case (30% vs. 4%), as this group would require more intensive and more costly treatments.

Also, our cost-effectiveness results were sensitive to a probability of survival after multiple bone marrow transplants (assumed to be 30% in base-case analysis[36]). Our modelling study sought to answer whether MRD testing is cost-effective at commonly used thresholds in all patients with de novo ALL (standard- and high-risk groups). Research has suggested that MRD testing before getting a bone marrow transplant in high-risk and relapsed patients can be used to differentiate the group with better clinical outcomes.[65-67] Therefore, future studies should examine the cost-effectiveness of MRD testing in very high-risk groups of patients with multiple relapses and multiple transplants.

Next, our results were sensitive to the estimates of total costs incurred during ALL treatment. We showed that MRD testing was not cost-effective if we used the costs of the COG treatment protocol, which include very expensive drugs (ICER > $70,000/QALY). Further studies should use established methods[64,68] and publicly available administrative data to determine more precisely resource utilization and phase-specific costs associated with progression and treatment of de novo and relapsed ALL cases for Ontario.

Our scenario analysis assuming short-term time horizons suggested that compared with no testing, MRD testing was associated with gains in discounted survival and quality-adjusted survival, but it was not cost-effective at commonly used willingness-to-pay benchmarks. It is possible that a 5-year time horizon represents quite a short follow-up to account for the complexity of a chronic disease such as childhood ALL. Our findings agree with methodologic studies suggesting that the assessment of outcomes over the long term can make an important difference in the results of a cost-effectiveness analysis.[61,62] Moreover, current guidelines for good modelling practice suggest using a lifelong time horizon for cost-effectiveness modelling.[69-71]

Next, our study was done from the perspective of Ministry of Health and Long-Term Care to guide the Ontario Health Technology Advisory Committee's decision on whether MRD testing should be made available in Ontario. It was not done from a societal perspective. It did not include indirect costs of ALL borne by families. Productivity loss and costs associated with it as well as decreases in quality of life of caregivers could be substantial.[72] Therefore, in our study, the overall costs of ALL and benefits associated with MRD testing are likely underestimated.

Finally, our primary economic evaluation and budget-impact analysis evaluated the benefits and costs of MRD testing for management of de novo precursor B-cell ALL; therefore, the results from this study should be used with caution if justifying the funding of MRD testing in relapsed populations.

Our budget-impact analysis includes downstream costs of the disease and is based on predictions of the current model, assuming an annual target population of 94 newly diagnosed patients with precursor B-cell ALL. It suggests that the 1-year cost expenditure for MRD testing at the end of induction and consolidation is $340,760. In sensitivity analysis, this budgetary impact increased up to $500,000 when we assumed that all patients with ALL were to be tested (annual incidence of 140). We forecasted that the total economic impact of MRD testing in patients with precursor B-cell ALL over 3 years was approximately $1.3 million and over 5 years was around $2.4 million.

We do not expect any difficulties regarding the implementation of MRD testing. It will be supervised by the POGO MRD Working Group that is developing a plan for the implementation of MRD testing in Ontario. Minimal residual disease testing will be done by the SickKids reference laboratory that is in the process of preparing resources for conducting MRD testing for precursor B-cell ALL across all Ontario's pediatric oncology centres (the expected start date is June 2016). If there is a need for a new reference laboratory, an economic study should be conducted before any additional funding is approved.

Conclusions

Minimal residual disease testing by flow cytometry versus no testing improves clinical outcomes in all newly diagnosed patients with precursor B-cell ALL over their lifetime, and it represents good value for money.

In our base-case analysis, compared with no testing, MRD testing by flow cytometry at the end of induction and consolidation was associated with an increased discounted survival of 0.0958 QALYs and increased discounted costs of $4,180, yielding an ICER of $43,613/QALY gained. After accounting for parameter uncertainty in probabilistic sensitivity analysis, incremental cost-effectiveness of MRD testing was associated with an ICER of $50,249/QALY gained. However, there was uncertainty around this estimate: approximately 58% of simulated ICERs were below the threshold of $100,000/QALY gained.

In the budget-impact analysis, the 1-year cost expenditure for MRD testing by flow cytometry at the end of induction and consolidation in patients newly diagnosed with precursor B-cell ALL was estimated at $340,760. In sensitivity analysis, this budgetary impact could increase up to $500,000 if all Ontario patients with ALL underwent MRD testing. We forecasted that the economic burden of MRD testing in patients with precursor B-cell ALL over 3 years was approximately $1.3 million and over 5 years was approximately $2.4 million.

Our primary economic evaluation and budget-impact analysis evaluated the benefits and costs of MRD testing for the management of de novo precursor B-cell ALL; therefore, the results from this study should be used with caution when considering testing in relapsed populations.

On the basis of evidence from our economic evaluation relevant to the Ontario setting, we conclude that MRD testing by flow cytometry in newly diagnosed patients with precursor B-cell ALL is cost-effective compared with no testing at commonly used willingness-to-pay thresholds.

LIST OF ABBREVIATIONS

ALL	Acute lymphoblastic leukemia
BFM	Berlin-Frankfurt-Münster
CI	Confidence interval
COG	Children's Oncology Group
ICER	Incremental cost-effectiveness ratio
LYS	Life-years saved
MRD	Minimal residual disease
OR	Odds ratio
PCR	Polymerase chain reaction
POGO	Pediatric Oncology Group of Ontario
POGONIS	Pediatric Oncology Group of Ontario Networked Information System
QALY	Quality-adjusted life-year
SE	Standard error
SickKids	Hospital for Sick Children (Toronto, Ontario)
THETA	Toronto Health Economics and Technology Assessment Collaborative

APPENDICES

Appendix 1: Literature Search Strategies

MEDLINE SEARCH

Databases searched: Database(s): Ovid MEDLINE(R) 1946 to October Week 4 2014, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations November 04, 2014
Limits: English language, Humans, 1998 -Current
Filters: Economic Evaluation Filter: NHS EED MEDLINE, best sensitivity validated filter from Glanville2009

Search Strategy:

#	Searches	Results
1	exp Precursor Cell Lymphoblastic Leukemia-Lymphoma/ or exp Leukemia, Myeloid, Acute/ or Leukemia, Myelomonocytic, Acute/ or Leukemia, Myelomonocytic, Juvenile/ or Hematopoietic Stem Cell Transplantation/ or ((hematopoietic adj5 stem cell transplant*) or HSCT).ti,ab.	96705
2	(Leukemia, B-Cell/ or Leukemia, T-Cell/ or Leukemia, Lymphoid/ or Leukemia, Myeloid/ or Hematologic Neoplasms/) and Acute Disease/	7678
3	((((leuk?emi* or leuc?emi*) adj3 (lympho* or lymphat* or myelo* or granulocyt* or nonlympho* or promyelo* or megakaryoblast* or monocyt* or erythroblast* or B-cell or T-cell or B-ALL or T-ALL)) or ((childhood or precursor-B-cell) adj3 ALL) or ANLL or AML or (lymphoma adj lymphoblast*)) and (acute or precursor or primary or relapse or recurren*)).ti,ab.	79713
4	1 or 2 or 3	135152
5	Neoplasm, Residual/ or (MRD or (residual adj3 (minimal or disease* or leuk?emi* or leuc?emi* or test*))).ti,ab.	18789
6	4 and 5	3889
7	case reports/ or comment/ or editorial/ or letter/ or comment.pt. or editorial.pt. or letter.pt. or congresses.pt. or conference abstract.pt.	3007951
8	6 not 7	3484
9	economics/ or exp "costs and cost analysis"/ or economics, dental/ or exp "economics, hospital"/ or economics, medical/ or economics, nursing/ or economics, pharmaceutical/ or (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or (expenditure$ not energy) or (value adj1 money) or budget$).ti,ab.	625462
10	(((energy or oxygen) adj cost) or (metabolic adj cost) or ((energy or oxygen) adj expenditure)).ti,ab.	21693
11	(letter or editorial or historical article).pt.	1547907
12	Animals/ not (Animals/ and Humans/)	3987901
13	9 not (10 or 11 or 12)	556268
14	8 and 13	53
15	limit 14 to (english language and yr="1998 -Current")	47
16	remove duplicates from 15	44

EMBASE SEARCH

Databases searched: Embase Classic+Embase 1947 to 2014 Week 44; November 04, 2014
Limits: Humans,
Filters: Economic Evaluation Filter: NHS EED EMBASE, best sensitivity validated filter from Glanville2009

#	Searches	Results
1	exp acute leukemia/ or exp childhood leukemia/ or Hematopoietic Stem Cell Transplantation/ or ((hematopoietic adj5 stem cell transplant*) or HSCT).ti,ab.	135641
2	(B cell leukemia/ or T cell leukemia/ or lymphatic leukemia/ or myeloid leukemia/) and Acute Disease/	1333
3	((((leuk?emi* or leuc?emi*) adj3 (lympho* or lymphat* or myelo* or granulocyt* or nonlympho* or promyelo* or megakaryoblast* or monocyt* or erythroblast* or B-cell or T-cell or B-ALL or T-ALL)) or ((childhood or precursor-B-cell) adj3 ALL) or ANLL or AML or (lymphoma adj lymphoblast*)) and (acute or precursor or primary or relapse or recurren*)).ti,ab.	105083
4	1 or 2 or 3	172023
5	minimal residual disease/ or (MRD or (residual adj3 (minimal or disease* or leuk?emi* or leuc?emi* or test*))).ti,ab.	25218
6	4 and 5	5909
7	case report/ or editorial/ or letter/ or comment.pt. or editorial.pt. or letter.pt. or congresses.pt. or conference abstract.pt.	4737154
8	6 not 7	3737
9	health-economics/ or exp economic-evaluation/ or exp health-care-cost/ or exp pharmacoeconomics/	489561
10	(econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$ or (expenditure$ not energy) or (value adj2 money) or budget$).ti,ab.	673141
11	9 or 10	948775
12	((metabolic adj cost) or ((energy or oxygen) adj cost) or ((energy or oxygen) adj expenditure)).ti,ab.	24880
13	11 not 12	943281
14	8 and 13	85
15	limit 14 to (english language and yr="1998 -Current")	80

Cochrane Library Issue 11 of 12, November 2014

Search Name: HQO_LeukemiaChild_Cochrane_Econ Eval_FINAL
Date Run: 06/11/14 17:59:33.342
Limits: English language, Humans, 1998 -Current
Filters: Economic Evaluation Filter: NHS EED MEDLINE, best sensitivity validated filter from Glanville2009 (translated into Cochrane)

ID	Search	Hits
#1	MeSH descriptor: [Precursor Cell Lymphoblastic Leukemia-Lymphoma] explode all trees	754
#2	MeSH descriptor: [Leukemia, Myeloid, Acute] explode all trees	853
#3	MeSH descriptor: [Leukemia, Myelomonocytic, Acute] this term only	22
#4	MeSH descriptor: [Leukemia, Myelomonocytic, Juvenile] this term only	0
#5	MeSH descriptor: [Hematopoietic Stem Cell Transplantation] this term only	980
#6	((hematopoietic adj5 stem cell transplant*) or HSCT):ti,ab,kw (Word variations have been searched)	243
#7	#1 or #2 or #3 or #4 or #5 or #6	2557
#8	MeSH descriptor: [Leukemia, B-Cell] this term only	9
#9	MeSH descriptor: [Leukemia, T-Cell] this term only	5
#10	MeSH descriptor: [Leukemia, Lymphoid] this term only	255
#11	MeSH descriptor: [Leukemia, Myeloid] this term only	349
#12	MeSH descriptor: [Leukemia, Myeloid] this term only	349
#13	#8 or #9 or #10 or #11 or #12	598
#14	MeSH descriptor: [Acute Disease] this term only	8954
#15	#13 and #14	278
#16	(((leuk?emi* or leuc?emi*) adj3 (lympho* or lymphat* or myelo* or granulocyt* or nonlympho* or promyelo* or megakaryoblast* or monocyt* or erythroblast* or B-cell or T-cell or B-ALL or T-ALL)) or ((childhood or precursor-B-cell) adj3 ALL) or ANLL or AML or (lymphoma adj lymphoblast*)):ti,ab,kw (Word variations have been searched)	1561
#17	(acute or precursor or primary or relapse or recurren*):ti,ab,kw (Word variations have been searched)	170479
#18	#16 and #17	1216
#19	#7 or #13 or #18	3659
#20	MeSH descriptor: [Neoplasm, Residual] this term only	214
#21	(MRD or (residual adj3 (minimal or disease* or leuk?emi* or leuc?emi* or test*))):ti,ab,kw (Word variations have been searched)	100
#22	#20 or #21	287
#23	#19 and #22	55
#24	MeSH descriptor: [Case Reports] this term only	1
#25	MeSH descriptor: [Comment] this term only	0
#26	MeSH descriptor: [Editorial] this term only	0
#27	MeSH descriptor: [Letter] this term only	1
#28	comment or editorial or letter or congresses or conference abstract:pt (Word variations have been searched)	16299
#29	#24 or #25 or #26 or #27 or #28	16301
#30	#23 not #29	53
#31	MeSH descriptor: [Economics] this term only	58
#32	MeSH descriptor: [Costs and Cost Analysis] explode all trees	22933
#33	MeSH descriptor: [Economics, Dental] this term only	3
#34	MeSH descriptor: [Economics, Hospital] explode all trees	1646
#35	MeSH descriptor: [Economics, Medical] this term only	38
#36	MeSH descriptor: [Economics, Nursing] this term only	16
#37	MeSH descriptor: [Economics, Pharmaceutical] this term only	236
#38	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic*) or (expenditure* not energy) or (value near/1 money) or budget*:ti,ab,kw (Word variations have been searched)	46113
#39	#31 or #32 or #33 or #34 or #35 or #36 or #37 or #38	46197

#40	((energy or oxygen) near cost) or (metabolic near cost) or ((energy or oxygen) near expenditure):ti,ab,kw (Word variations have been searched)	2337
#41	#39 not #40	45688
#42	letter or editorial or historical article:pt (Word variations have been searched)	6557
#43	#41 not #42	45591
#44	MeSH descriptor: [Animals] explode all trees	6716
#45	MeSH descriptor: [Humans] explode all trees	1037
#46	#44 not (#44 and #45)	5679
#47	#43 not #46	45416
#48	#23 and #47	1

The Paediatric Economic Database Evaluation (PEDE)

Date Run: 30 September, 2014
Keywords: (TITLE_ABSTRACT_KEYWORDS "leukemia")
Age groups: Perinates Neonates Infants Children Adolescents
Years: 1980 – 2012

PEDE Search Results - 10 records

1 Close P, Burkey E, Kazak A, Danz P, Lange B. A prospective, controlled evaluation of home chemotherapy for children with cancer. Pediatrics 1995;95(6):896-900.
2 Donnan JR, Ungar WJ, Mathews M, Hancock-Howard RL, Rahman P. A cost effectiveness analysis of thiopurine methyltransferase testing for guiding 6-mercaptopurine dosing in children with acute lymphoblastic leukemia. Pediatric blood & cancer 2011;57(2):231-9.
3 Donnan JR, Ungar WJ, Mathews M, Hancock-Howard RL. Health technology assessment of thiopurine methyltransferase testing for guiding 6-mercaptopurine doses in pediatric patients with acute lymphoblastic leukemia. Toronto: Technology Assessment Unit of the Hospital for Sick Children (TASK); 2010.
4 Jaing TH, Tsay PK, Hung IJ, Yang CP, Hu WY. Single-dose oral granisetron versus multidose intravenous ondansetron for moderately emetogenic cyclophosphamide-based chemotherapy in pediatric outpatients with acute lymphoblastic lukemia. Pediatric Hematology & Oncology 2004;21(3):227-235.
5 Lin Y-F, Lairson DR, Chan W, Du XL, Leung KS, Kennedy-Nasser AA, et al. The costs and cost-effectiveness of allogeneic peripheral blood stem cell transplantation versus bone marrow transplantation in pediatric patients with acute leukemia. Biology of Blood & Marrow Transplantation 2010;16(9):1272-81.
6 Luo X-Q, Ke Z-Y, Guan X-Q, Zhang Y-C, Huang L-B, Zhu J. The comparison of outcome and cost of three protocols for childhood non-high risk acute lymphoblastic leukemia in China. Pediatric Blood & Cancer 2008;51(2):204-9.
7 Pui CH, Boyett JM, Hughes WT, Rivera GK, Hancock ML, Sandlund JT, et al. Human granulocyte colony-stimulating factor after induction chemotherapy in children with acute lymphoblastic leukemia. New England Journal of Medicine 1997;336(25):1781-1787.
8 Schaison GS. Cost effectiveness of teicoplanin and ceftriaxone: a once-daily antibiotic regimen. Hospital Formulary 1993;1:20-2.
9 Vicent MG, Madero L, Chamorro L, Madero R, Diaz MA. Comparative cost analysis of autologous peripheral blood progenitor cell and bone marrow transplantation in pediatric patients with malignancies. Haematologica 2001;86(10):1087-94.
10 van Litsenburg RRL, Uyl-de Groot CA, Raat H, Kaspers GJL, Gemke RJBJ. Cost-effectiveness of treatment of childhood acute lymphoblastic leukemia with chemotherapy only: the influence of new medication and diagnostic technology. Pediatric blood & cancer 2011;57(6):1005-10.

National Institute for Health Research Economic Evaluation Database (NHSEED)

Date Run: 22 October, 2014
Keywords: (children) AND (leukemia), HTA

Results for: (children) AND (leukemia) IN NHSEED, HTA (8 hits)

Year	Database	Source	Title
1997	NHS EED	Chemotherapy	Cost-effectiveness of ceftriaxone and amikacin as single daily dose for the empirical management of febrile granulocytopenic children with cancer [Preview]
1997	NHS EED	New England Journal of Medicine	Human granulocyte colony-stimulating factor after induction chemotherapy in children with acute lymphoblastic leukemia [Preview]
1997	NHS EED	Pediatric Infectious Disease Journal	Once daily ceftriaxone plus amikacin vs. three times daily ceftazidime plus amikacin for treatment of febrile neutropenic children with cancer [Preview]
1996	NHS EED	Pediatrics	An evaluation of measles revaccination among school-entry-aged children [Preview]
1996	HTA	Alberta Heritage Foundation for Medical Research (AHFMR)	Cord blood transplantation [Preview]
1995	NHS EED	Pediatrics	A prospective, controlled evaluation of home chemotherapy for children with cancer [Preview]
1995	NHS EED	PharmacoEconomics	Pharmacoeconomic analysis of empirical therapy with ceftazidime alone or combination antibiotics for febrile neutropenia in cancer patients [Preview]
1991	HTA	The Swedish Council on Health Technology Assessment (SBU)	Bone marrow transplantation [Preview]

Appendix 2: Methodologic Quality Assessment

Table A1: Assessment of Methodologic Quality by Consensus Health Economic Criteria List

Checklist Criteria	Yes/Partly/No/Unclear/ Not Applicable	Comment
Is the study population clearly described?	Yes	
Are competing alternatives clearly described?	Yes	
Is a well-defined research question posed in answerable form?	Partly	
Is the economic study design appropriate for the stated objective?	No	Retrospective cohort design
Is the chosen time horizon appropriate in order to include relevant costs and consequences?	Partly	Lifetime horizon, but projections and simplifying assumptions made
Is the actual perspective chosen appropriate?	Partly	Hospital
Are all important and relevant costs for each alternative identified?	Partly	Direct medical costs for chemotherapy only, for 2 different treatment protocols-older ALL 9 (without MRD testing) vs ALL 10 (with MRD testing and change in therapy); societal costs were not addressed
Are all costs measured appropriately in physical units?	Yes	
Are costs valued appropriately?	Yes	
Are all important and relevant outcomes for each alternative identified?	No	QALYs, relapse rates
Are all outcomes measured appropriately?	No	Extrapolations were made for ALL10, based on personal communication
Are outcomes valued appropriately?	Partly	Simplifying assumptions made; relapse not modelled; adverse effects or disutility due to chemotherapy not accounted for; costs address the costs of chemotherapy
Is an incremental analysis of costs and outcomes of alternatives performed?	Yes, for measured outcome	
Are all future costs and outcomes discounted appropriately?	Yes	According to Dutch guidelines
Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Partly	
Do the conclusions follow from the data reported?		
Does the study discuss the generalizability of results to other settings and patient/client groups?	No	
Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	No	
Are ethical and distributional issues discussed appropriately?	No	

Abbreviations: ALL, acute lymphoblastic leukemia; MRD, minimal residual disease; QALY, quality-adjusted life-year.

Table A2: NICE Quality Appraisal Checklist

Section 1: Applicability (relevance to specific topic review question)	**Yes/Partly/No/Unclear/ Not Applicable**	**Comment**
1.1 Is the study population appropriate for the topic being evaluated?	Partly	Pediatric patients with ALL; patients eligible for bone marrow transplant excluded
1.2 Are the interventions appropriate for the topic being evaluated?	Yes	Two protocols used in the Netherlands; one incorporated MRD evaluation
1.3 Is the system in which the study was conducted sufficiently similar to the current Ontario context?	No	The Netherlands—irrelevant when it comes to cost analysis (non-transferable) and treatment protocols (Ontario: DFCI and COG protocols)
1.4 Was/were the perspective(s) clearly stated and what were they?	Yes, hospital	
1.5 Are all direct health effects on individuals included, and are all other effects included where they are material?	No	Not assessed QALYs, relapse rates
1.6 Are all future costs and outcomes discounted appropriately?	Yes	According to Dutch guidelines
1.7 Is the value of health effects expressed in terms of QALYs?	No	
1.8 Are costs and outcomes from other sectors fully and appropriately measured and valued?	Partially	Measured: direct medical costs for chemotherapy only Not measured: indirect medical costs, productivity loss
Overall judgment: Directly applicable/partially applicable/not applicable	Not applicable	Our question sought to answer whether MRD evaluation is cost-effective for management of ALL in all patients It is done from the Ontario Ministry of Health's perspective It is model-based cost-utility analysis with a lifetime time horizon

Abbreviations: ALL, acute lymphoblastic leukemia; COG, Children's Oncology Group; DFCI, Dana Faber Cancer Institute; MRD, minimal residual disease; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life-year.

Appendix 3: Costs of Acute Lymphoblastic Leukemia

Table A3: Costs of Acute Lymphoblastic Leukemia According to Berlin-Frankfurt-Münster Protocol by Treatment Intensity

	Low Treatment Intensity			High Treatment Intensity		
BFM Protocol	**Mean**	**SD**	**Sample (n)**	**Mean**	**SD**	**Sample (n)**
Total in-patient cost[a]	$67,749.94	$18,410.95	41	$82,920.87	$52,046.28	25
Total outpatient cost[a]	$23,360.12	$6,967.15	41	$41,377.59	$11,300.66	25
Total length of stay, days	39.83	12.17	41	48.48	29.75	25
Total number of admissions	9	2	41	8	4	25
Total number of outpatients visits	88.8	27.46	41	146.64	39.65	25
Total cost	$91,110.06	$20,225.11	41	$124,298.46	$52,097.38	25

Abbreviations: BFM, Berlin-Frankfurt-Münster; SD, standard deviation.

[a]All costs in 2007 Canadian dollars.

Source: Data provided by Ms. Charlene Rae et al; they were based on additional (unpublished) analyses of original data provided in article (written communication on 2014 November 11).

Appendix 4: Children's Oncology Group Treatment Protocol Used for Modelling Study

Table A4.1: Treatment for Average Standard-Risk 6-Year-Old Patient, Weight 22 kg, Height 110 cm, BSA 0.8 m^2

Treatment Stage	Drug Names	Daily Dose and Administration	Frequency (Days Given)	IP/OP/Home
INDUCTION: 4 wk				
	Cytarabine	70 mg IT	Once	IP
	Methotrexate	12 mg IT	Twice	IP
	Dexamethasone	4.8 mg	28 d	IP/Home
	Vincristine	1.2 mg IV	Weekly x 4	IP/OP
	Pegaspargase	2,000 IU IV	Once	IP
CONSOLIDATION: 4 wk				
	6-Mercaptopurine	40 mg	28 d	Home
	Methotrexate	12 mg IT	Weekly x 4	OP
INTERIM MAINTENANCE 1: 4 wk				
	Vincristine	1.2 mg	Q10 d x 5	OP
	Methotrexate	Variable; average is about 160 mg IV	Q10 d x 5	OP
	Methotrexate	12 mg IT	Twice	OP
DELAYED INTENSIFICATION: 8–9 wk				
	Dexamethasone	8 mg	14 days total	Home
	Vincristine	1.2 mg	Weekly x 3	OP
	Doxorubicin	20 mg	Weekly x 3	OP
	Pegaspargase	2,000 IU IV	Once	OP
	Cyclophosphamide	800 mg	Once	OP
	Mesna	600 mg	Once	OP
	6-Thioguanine	50 mg	Daily x 14 d	Home
	Cytarabine	60 mg SC	8 total doses	OP
	Methotrexate	12 mg IT	2 doses	OP
INTERIM MAINTENANCE 2: 6 wk				
	Vincristine	1.2 mg	Q10 d x 5	OP
	Methotrexate	Variable; average is about 240 mg IV	Q10 d x 5	OP
MAINTENANCE: 2–3 y				
	Dexamethasone	4.8 mg	5 d for 4 wk	Home
	6-Mercaptopurine	60 mg	Daily	Home
	Methotrexate	17.5 mg PO	Weekly	Home
	Vincristine	1.2 mg	Every 4 wk	OP
	Methotrexate	12 mg IT	Every 12 wk	OP

Abbreviations: BSA, body surface area; COG, Children's Oncology Group; IP, in-patient; IT, intrathecal; IU, international units; IV, intravenous; OP, outpatient; PO, by mouth; Q10 d, every 10 days; SC, subcutaneous.

Source: Protocols for average standard-risk and high-risk patients were developed in collaboration with Dr. Paul Gibson, pediatric oncologist.

Table A4.2: Treatment for Average High-Risk 6-Year-Old Patient, Weight 22 kg, Height 110 cm, BSA 0.8 m^2

Treatment Stage	Drug Names	Daily Dose and Administration	Frequency (Days Given)	IP/OP/Home
INDUCTION: 4 wk				
	Cytarabine	70 mg IT	Once	IP
	Methotrexate	12 mg IT	Twice	IP
	Dexamethasone	8 mg	14 d	IP/Home
	Vincristine	1.2 mg IV	Weekly x 4	IP/OP
	Pegaspargase	2,000 IUIV	Once	IP
	Daunorubicin	20 mg	Weekly x 4	IP
CONSOLIDATION: 8–9 wk				
	Pegaspargase	2,000 IU	Twice	OP
	Cyclophosphamide	800 mg	Twice	OP
	Mesna	600 mg	Twice	OP
	6-Mercaptopurine	50 mg	Daily x 28 d	Home
	Cytarabine	60 mg SC	16 total doses	OP
	Methotrexate	12 mg IT	4 doses	OP
	Vincristine	1.2 mg	4 doses	OP
INTERIM MAINTENANCE 1: 8–9 wk				
	6-Mercaptopurine	50 mg	Daily x 56 d	IP/Home
	Vincristine	1.2 mg	4 doses	IP
	HD Methotrexate	4,000 mg	4 doses x 4d	IP
	Leucovorin	12 mg IV	~16–20 doses	IP
	Methotrexate	12 mg IT	Twice	IP
DELAYED INTENSIFICATION: 8–9 wk				
	Dexamethasone	8 mg	14 days total	Home
	Vincristine	1.2 mg	Weekly x 5	OP
	Doxorubicin	20 mg	Weekly x 3	OP
	Pegaspargase	2,000 IU	Twice	OP
	Cyclophosphamide	800 mg	Once	OP
	Mesna	600 mg	Once	OP
	6-Thioguanine	50 mg	Daily x 14 d	Home
	Cytarabine	60 mg SC	8 total doses	OP
	Methotrexate	12 mg IT	3 doses	OP
INTERIM MAINTENANCE 2: 6 wk				
		Not typically done in HR ALL		
MAINTENANCE: 2–3 years				
	Prednisone	35 mg	5 d/wk for 4 wk	Home
	6-Mercaptopurine	60 mg	Daily	Home
	Methotrexate	17.5 mg PO	Weekly	Home
	Vincristine	1.2 mg	Every 4 wk	OP
	Methotrexate	12 mg IT	Twice every 12 wk (first year) Once every 12 wk (subsequent years)	OP

Abbreviations: ALL, acute lymphoblastic leukemia; avg, average; BSA, body surface area; COG, Children's Oncology Group; HD, high dose; HR, high risk; IP, in-patient; IT, intrathecal; IU, international units; IV, intravenous; OP, outpatient; PO, by mouth; SC, subcutaneous.

Source: Protocols for average standard-risk and high-risk patients were developed in collaboration with Dr. Paul Gibson, pediatric oncologist.

Appendix 5: Phase-Specific Costing of Children's Oncology Group Treatment Protocol

Table A5.1: Costs of Induction According to COG Treatment Protocol for a Standard-Risk Patient

Drug, Daily Dose, Frequency, IP/OP/Home	Drug Name/Dose in ODB Formulary or Another Source	Source; Date Accessed	Unit Cost, $[a]	Cost Estimate for Dose Used, $[a]	Total Cost (Adjusted for Frequency), $[a]
Induction (4 wk)					
IT cytarabine 70 mg, Once, IP	Cytosar: 100-mg Inj Pd-Vial Pack (price per vial) 1 vial used	ODB formulary, 2003; Dec 3, 2014	9.48	9.48	9.48
IT methotrexate 12 mg, Twice, IP	Methotrexate sodium, 20 mg/2 mL Inj Sol 2-mL Pk; 1 vial	https://www.healthinfo.moh.gov.on.ca/formulary; Dec 3, 2014	12.50	12.50	25.00
Dexamethasone 4.8 mg, 28 d, IP	Ratio-dexamethasone, 4-mg Tab	https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet; Dec 3, 2014	0.30	0.37	10.23
Vincristine 1.2 mg IV, weekly x 4, IP	Vincristine sulfate, 1 mg/mL Inj Sol (vials can be kept open and stored for 14 hr; dose of 1.2 mg/mL)	https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet; Dec 3, 2014	30.60	36.72	146.88
Pegasparaginase, 2,000 IU, IV, Once, IP	Oncaspar vial of 750 IU/mL (1 vial used)	Estimated price used in COG trial: **upper range**	5,106.98	15,320.94	15,320.94[b]
Pegasparaginase, 2,000 IU, IV, Once, IP	Oncaspar vial of 750 IU/mL (1 vial used)	Estimated price used in COG trial: **lower range**	5,572.95	16,718.85	16,718.85[b]
Total Cost: lower range[b]					**15,512.54**
Total Cost: upper range[b]					**16,910.45**

Abbreviations: COG, Children's Oncology Group; Inj, injection; IP, in-patient; IT, intrathecal; IV, intravenous; ODB, Ontario Drug Benefit; OP, outpatient; Pd, powder; Pk, package; Tab, tablet.

[a]All costs in 2014 Canadian dollars.

[b]Lower range or upper range costs are due to realistic variations in cost estimate of PEG-asparaginase between different hospitals in Ontario (personal communication with Ms. Nicole Bradley, Pediatric Oncology Group of Ontario), for dose of 2,000 IU (Once); 3 vials are assumed to be used.

Table A5.2: Costs of Induction According to COG Treatment Protocol for High-Risk Patient

Drug, Daily Dose, Frequency, IP/OP/Home	Drug Name/Dose in ODB Formulary or Other Source	Source; Date Accessed	Unit Cost, $[a]	Cost Estimate for Dose Used, $[a]	Total Cost (Adjusted for Frequency), $[a]
Induction (4 wk)					
IT cytarabine, 70 mg, Once, IP	Cytosar: 100-mg Inj Pd-Vial Pk (price per vial) 1 vial used	ODB formulary, 2003; Dec 3, 2014	9.48	9.48	9.48
IT methotrexate, 12 mg, Twice, IP	Methotrexate sodium, 20 mg/2 mL Inj Sol; 2-mL Pk: 1 vial	https://www.healthinfo.moh.gov.on.ca/formulary; Dec 3, 2014	12.50	12.50	25.00
Dexamethasone, 4.8 mg, 28 d, IP	Ratio-dexamethasone, 4-mg Tab	https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet; Dec 3, 2014	0.30	0.37	10.23
Vincristine, 1.2 mg IV, weekly x 4, IP	Vincristine sulfate, 1 mg/mL Inj Sol (vials can be kept open and stored for 14 h, dose of 1.2 mg/mL)	https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet; Dec 3, 2014	30.60	36.72	146.88
Pegasparaginase, 2,000 IU, IV, Once, IP	Oncaspar vial of 750 IU/mL (one vial used)	Estimated price used in the COG trial: **upper range**	5,106.98	15,320.94	15,320.94[b]
Pegasparaginase, 2,000 IU, IV, Once, IP	Oncaspar vial of 750 IU/mL (one vial used)	Estimated price used in the COG trial: **lower range**	5,572.95	16,718.85	16,718.85[b]
Daunorubicin, 20 mg, Weekly x 4, IP	Cerubidine 20 mg Inj Pk, 1 vial, box of 1	https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet; Dec 8, 2014	90.20	90.20	360.80
Total Cost: lower range[b]					**15,873.34**
Total Cost: upper range[b]					**17,271.25**

Abbreviations: COG, Children's Oncology Group; Inj, injection; IP, in-patient, IT, intrathecal; IU, International units; IV, intravenous; ODB, Ontario Drug Benefit; OP, outpatient; Pd, powder; Pk, package; Sol, solution; Tab, tablet.

[a]All costs in 2014 Canadian dollars.

[b]Lower range or upper range costs are due to realistic variations in the cost estimate of PEG-asparaginase between different hospitals in Ontario (personal communication with Ms. Nicole Bradley, Pediatric Oncology Group of Ontario), for the dose of 2,000 IU (Once), 3 vials are assumed to be used.

Table A5.3: Costs of Consolidation According to COG Treatment Protocol for Standard-Risk Patient

Drug, Daily Dose, Frequency, IP/OP/Home	Drug Name/Dose in ODB Formulary or Other Source	Source; Date Accessed	Unit Cost, $[a]	Cost Estimate for Dose Used, $[a]	Total Cost (Adjusted for Frequency), $[a]
Consolidation (4 wk)					
6-Mercaptopurine, 40 mg, 28 d, Home	6-MP, tbl 50 mg	https://www.healthinfo.moh.gov.on.ca/formulary; Dec 8, 2014	2.86	2.29	64.09
IT methotrexate, 12 mg, weekly x 4, OP	Methotrexate sodium, 20 mg/2 mL Inj Sol 2-mL Pk, 1 vial	https://www.healthinfo.moh.gov.on.ca/formulary; Dec 8, 2014	12.50	12.50	50.00
Total Cost: Consolidation (4 wk)[a]					**114.09**

Abbreviations: COG, Children's Oncology Group; Inj, injection; IP, in-patient; IT, intrathecal; ODB, Ontario Drug Benefit; OP, outpatient; Pk, package; Sol, solution.
[a]All costs in 2014 Canadian dollars.

Table A5.4: Costs of Consolidation According to COG Treatment Protocol for High-Risk Patient

Drug, Daily Dose, Frequency, IP/OP/Home	Drug Name/Dose in ODB Formulary or Other Source	Source; Date Accessed	Unit Cost, $[a]	Cost Estimate for Dose Used, $[a]	Total Cost (Adjusted for Frequency), $[a]
Consolidation (8 wk)					
Pegasparaginase, 2,000 IU, IV, Twice, IP	Oncaspar vial of 750 unit/mL (one vial used)	Estimated price used in COG trial: **upper range**	5,106.98	33,437.71	33,437.71[b]
Pegasparaginase, 2,000 IU, IV, Twice, IP	Oncaspar vial of 750 unit/mL (one vial used)	Estimated price used in COG trial: **lower range**	5,572.95	30,641.89	30,641.89[b]
Cyclophosphamide, 800 mg, Twice, OP	Procytox, 50 mg, Tab	https://www.healthinfo.moh.gov.on.ca/formulary; Dec 8, 2014	0.47	7.58	15.17
Mesna, 600 mg, Twice, OP	Mesna for injection is available as 100 mg/mL in 10-mL multiple-dose vials: C730310 10-mL vials in packages of 10 vials	Pharmaceutical Partners of Canada; Dec 10, 2014	943.10	565.86	1,131.72
6-Mercaptopurine, 50 mg, Daily x 28 d, Home	6-MP, tbl 50 mg	https://www.healthinfo.moh.gov.on.ca/formulary; Dec 8, 2014	2.86	2.86	80.11
SC cytarabine,60 mg,16 total doses, OP	Cytosar: 100 mg Inj Pd-Vial Pk (price per vial) 1 vial used	ODB formulary 2003; Dec 3, 2014	9.48	9.48	151.65
IT methotrexate, 12 mg, 4 doses, OP	Methotrexate sodium, 20 mg/2 mL Inj Sol 2-mL Pk, 1 vial	https://www.healthinfo.moh.gov.on.ca/formulary; Dec 8, 2014	12.50	12.50	50.00
Vincristine,1.2 mg,4 doses, OP	Vincristine sulfate, 1 mg/mL Inj Sol	https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet; Dec 3, 2014	30.60	36.72	146.88
Total: Consolidation (lower range)[b]					**32,217.41**
Total: Consolidation (upper range)[b]					**35,013.23**

Abbreviations: COG, Children's Oncology Group; Inj, injection; IP, in-patient; IT, intrathecal; IU, international units; IV, intravenous; ODB, Ontario Drug Benefit; OP, outpatient; Pd, powder; Pk, package; PO, by mouth; SC, subcutaneous; Tab, tablet.

[a]All costs in 2014 Canadian dollars.

[b]Lower range or upper range costs are due to realistic variations in cost estimate of PEG-asparaginase between different hospitals in Ontario (personal communication with Ms. Nicole Bradley, Pediatric Oncology Group of Ontario), for dose of 2,000 IU (Twice); 6 vials are assumed to be used.

Table A5.5: Costs of Interim Maintenance 1 According to COG Treatment Protocol for Standard-Risk Patient

Drug, Daily Dose, Frequency, IP/OP/Home	Drug Name/Dose in ODB Formulary or Other Source	Source; Date Accessed	Unit Cost, $[a]	Cost Estimate for Dose Used, $[a]	Total Cost (Adjusted for Frequency), $[a]
Interim Maintenance 1 (4 Wk)					
Vincristine, 1.2 mg, Q10 d x 5, OP	Vincristine sulfate, 1 mg/mL Inj Sol	https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet; Dec 3, 2014	30.60	36.72	367.20
IV methotrexate, 160 mg, Q10 d x 5, OP	Methotrexate sodium, 20 mg/2 mL Inj Sol 2-mL Pk, 1 vial	https://www.healthinfo.moh.gov.on.ca/formulary; Dec 8, 2014	12.50	200.00	1,000.00[b]
IT methotrexate, 12 mg, Twice, IP	Methotrexate sodium, 20 mg/2 mL Inj Sol 2-mL Pk, 1 vial	https://www.healthinfo.moh.gov.on.ca/formulary; Dec 8, 2014	12.50	7.50	15.00[b]
Total Cost: Interim Maintenance 1[a]					**1,382.20**

Abbreviations: COG, Children's Oncology Group; Inj, injection; IP, in-patient; IT, intrathecal; IV, intravenous; ODB, Ontario Drug Benefit; OP, outpatient; Pk, package; Q10 d, every 10 days; Sol, solution.

[a]All costs in 2014 Canadian dollars.

[b]Costs of methotrexate were adjusted for dose used.

Table A5.6: Costs of Interim Maintenance 1 According to COG Treatment Protocol for a High-Risk Patient

Drug, Daily Dose, Frequency, IP/OP/Home	Drug Name/Dose in ODB Formulary or Another Source	Source; Date Accessed	Unit Cost, $[a]	Cost Estimate for Dose Used, $[a]	Total Cost (Adjusted for Frequency), $[a]
Interim Maintenance 1 (8 wk)					
6-Mercaptopurine, 50 mg, Daily x 56 d, IP	6-MP, tbl 50 mg	https://www.healthinfo.mohca/formulary; Dec 8, 2014	2.86	2.86	160.22
Vincristine, 1.2 mg,4 doses, IP	Vincristine sulfate, 1 mg/mL Inj Sol	https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet; Dec 3, 2014	30.60	36.72	146.88
HD methotrexate, 4,000 mg, 4 doses, IP	Methotrexate sodium, 20 mg/2 mL Inj Sol 2-mL Pk, 1 vial	https://www.healthinfo.moh.gov.on.ca/formulary; Dec 8, 2014	12.50	2,500.00	10,000.00
Leucovorin, 12 mg IV, ~16–20 doses, IP	Leucovorin calcium, 5-mg Tab	https://www.healthinfo.moh.gov.on.ca/formulary; Dec 10, 2014	6.29	15.09	301.86
IT methotrexate, 12 mg, twice, IP	Methotrexate sodium, 20 mg/2 mL Inj Sol	https://www.healthinfo.moh.gov.on.ca/formulary; Dec 8, 2014	12.50	12.50	25.00
Total Cost: Interim Maintenance 1[a]					**10,633.95**

Abbreviations: COG, Children's Oncology Group; Inj, injection; IP, in-patient; IT, intrathecal; IV, intravenous; ODB, Ontario Drug Benefit; OP, outpatient; Pk, package; Tab, tablet.

[a]All costs in 2014 Canadian dollars.

[b]Costs of methotrexate were adjusted for dose used.

Table A5.7: Costs of Delayed Intensification According to COG Treatment Protocol for a Standard-Risk Patient

Drug, Daily Dose, Frequency, IP/OP/Home	Drug Name/Dose in ODB Formulary or Another Source	Source; Date Accessed	Unit Cost, $[a]	Cost Estimate for Dose Used, $[a]	Total Cost (Adjusted for Frequency), $[a]
DELAYED INTENSIFICATION (8 wk)					
Dexamethasone, 8 Mg, 14 D total, home	Ratio-dexamethasone, 4-mg Tab	https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet; Dec 3, 2014	0.31	0.61	8.53
Vincristine, 1.2 mg, weekly x 3, OP	Vincristine sulfate, 1 mg/mL Inj Sol	https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet; Dec 3, 2014	30.60	36.72	991.44
Doxorubicin, 20 mg, weekly x 3, OP	Doxorubicin, 10 mg/5 mL for one vial	Pfizer Canada, oral communication on Dec 11, 2014	35.00	70.00	1,890.00
Pegasparaginase, 2,000 IU, Once, OP	Oncaspar vial of 750 IU/mL (one vial used)	Provided by experts, POGO data for COG trial: upper range	5,572.95	16,718.85	16,718.85[b]
Pegasparaginase, 2,000 IU, Once, OP	Oncaspar vial of 750 unit/mL (one vial used)	Provided by experts, POGO data for COG trial: lower range	5,106.98	15,320.94	15,320.94b
Cyclophosphamide, 800 mg, Once, OP	Cyclophosphamide, Procytox, 50-mg Tab	https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet; Dec 10, 2014	0.47	7.58	7.58
Mesna, 600 mg, Once, OP	Mesna for injection, 100 mg/mL in 10 mL: C730310 10-mL vials in packages of 10 vials	Pharmaceutical Partners of Canada; communication on Dec 10, 2014	943.10	565.86	1,131.72
6-Thioguanine, 50 mg, Daily x 14 d, Home	6-Thioguanine, Lanvis, 40-mg Tab	https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet; Dec 10, 2014	4.44	5.54	77.63
SC cytarabine, 60 mg, 8 total doses, OP	Cytosar: 100 mg Inj Pd-Vial Pk (price per vial) 1 vial used	ODB formulary 2003; Dec 3, 2014	9.48	9.48	75.82
IT methotrexate, 12 mg, 2 doses, OP	Methotrexate sodium, 20 mg/2 mL Inj Sol 2-mL Pk, 1 vial	https://www.healthinfo.moh.gov.on.ca/formulary; Dec 8, 2014	12.50	15.00	30.00
Total Cost: Delayed Intensification (lower range)[b]					**19,533.67**
Total Cost: Delayed Intensification (upper range)[b]					**20,931.58**

Abbreviations: COG, Children's Oncology Group; IP, in-patient; IT, intrathecal; IV, intravenous; ODB, Ontario Drug Benefit; OP, outpatient; POGO, Pediatric Oncology Group of Ontario; Inj, injection; Pk, package; Tab, tablet;

[a]All costs in 2014 Canadian dollars.

[b]Lower range or upper range costs are due to realistic variations in cost estimate of PEG-asparaginase between different hospitals in Ontario (personal communication with Ms. Nicole Bradley, Pediatric Oncology Group of Ontario), for dose of 2,000 IU (Twice), 6 vials are assumed to be used.

[c]Costs of methotrexate were adjusted for dose used.

Table A5.8: Costs of Delayed Intensification According to COG Treatment Protocol for a High-Risk Patient

Drug, Daily Dose, Frequency, IP/OP/Home	Drug Name/Dose in ODB Formulary or Another Source	Source; Date Accessed	Unit Cost, $[a]	Cost Estimate for Dose Used, $[a]	Total Cost (Adjusted for Frequency), $[a]
Delayed Intensification (8 wk)					
Dexamethasone, 8 mg, 14 d total, home	Ratio-dexamethasone, 4-mg Tab	https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet; Dec 3, 2014	0.31	0.61	8.53
Vincristine, 1.2 mg, weekly x 3, OP	Vincristine sulfate, 1 mg/mL Inj Sol	https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet; Dec 3, 2014	30.60	36.72	991.44
Doxorubicin, 20 mg, weekly x 3, OP	Doxorubicin, 10 mg/5 mL in one vial	Pfizer Canada, communication on Dec 11, 2014	35.00	70.00	1,890.00
Pegasparaginase, 2,000 IU, twice, OP	Oncaspar vial of 750 IU/mL (one vial used)	Provided by experts—POGO data for COG trial: upper range	5,572.95	16,718.85	33,437.71[b]
Pegasparaginase, 2,000 IU, twice, OP	Oncaspar vial of 750 unit/mL (one vial used)	Provided by experts—POGO data for COG trial: lower range	5,106.98	15,320.94	30,641.89[b]
Cyclophosphamide, 800 mg, once, OP	Cyclophosphamide, Procytox, 50-mg Tab	https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet; Dec 10, 2014	0.47	7.58	7.58
Mesna, 600 mg, once, OP	Mesna for injection, 100 mg/mL in 10 mL: C730310 10-mL vials in packages of 10 vials	Pharmaceutical Partners of Canada, communication on Dec 10, 2014	943.10	565.86	1,131.72
6-Thioguanine, 50 mg, daily x 14 d, home	6-Thioguanine, Lanvis, 40-mg Tab	https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet; Dec 10, 2014	4.44	5.55	77.63
SC cytarabine, 60 mg, 8 total doses, OP	Cytosar: 100 mg Inj Pd-Vial Pk (price per vial) 1 vial used	ODB formulary 2003; Dec 3, 2014	9.48	9.48	75.82
IT methotrexate, 12 mg, 3 doses, OP	Methotrexate sodium, 20 mg/2 mL Inj Sol 2-mL Pk, 1 vial	https://www.healthinfo.moh.gov.on.ca/formulary; Dec 8, 2014	12.50	15.00	45.00[c]
Total: Delayed Intensification (lower range)[b]					**35,530.58**
Total: Delayed Intensification (upper range)[b]					**38,326.39**

Abbreviations: COG, Children's Oncology Group; Inj, injection; IP, in-patient; IT, intrathecal; IV, intravenous; ODB, Ontario Drug Benefit; OP, outpatient; Pk, package; Tab, tablet.
[a]All costs in 2014 Canadian dollars.
[b]Lower range or upper range costs are due to realistic variations in the cost estimate of PEG-asparaginase between different hospitals in Ontario (personal communication with Ms. Nicole Bradley, Pediatric Oncology Group of Ontario), for the dose of 2,000 IU (Twice), 6 vials are assumed to be used.
[c]Costs of methotrexate were adjusted for the dose used.

Table A5.9: Costs of Interim Maintenance 2 According to COG Treatment Protocol for a Standard-Risk Patient

Drug, Daily Dose, Frequency, IP/OP/Home	Drug Name/Dose in ODB Formulary or Another Source	Source; Date Accessed	Unit Cost, $[a]	Cost Estimate for Dose Used, $[a]	Total Cost (Adjusted for Frequency), $[a]
Interim Maintenance 2 (6 wk)					
Vincristine, 1.2 mg, Q10 d x 5, OP	Vincristine sulfate, 1 mg/mL Inj Sol	https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet; Dec 3, 2014	30.60	36.72	734.40
IV methotrexate, 240 mg, Q10 d x 5, OP	Methotrexate sodium, 20 mg/2 mL Inj Sol 2-mL Pk, 1 vial	https://www.healthinfo.moh.gov.on.ca/formulary; Dec 8, 2014	12.50	600.00	3,000.00[b]
Total Cost: Interim Maintenance 2					**3,734.40**

Abbreviations: COG, Children's Oncology Group; Inj, injection; IP, in-patient; IT, intrathecal; IV, intravenous; ODB, Ontario Drug Benefit; OP, outpatient; Q10 d, every 10 days.
[a]All costs in 2014 Canadian dollars.
[b]Costs of Methotrexate were adjusted for the dose used.

Table A5.10: Costs of Maintenance According to COG Treatment Protocol for a Standard-Risk Patient

Drug, Daily Dose, Frequency, IP/OP/Home	Drug Name/Dose in ODB Formulary or Another Source	Source; Date Accessed	Unit Cost, $[a]	Cost Estimate for Dose Used, $[a]	Total Cost (Adjusted for Frequency), $[a]
Maintenance[b]					
Dexamethasone, 4.8 mg, 5 d/4 wk, home	Ratio-dexamethasone, 4-mg Tab	https://www.healthinfo.moh.gov.on.ca/ formulary/SearchServlet; Dec 3, 2014	0.31	7.31	102.35
6-Mercaptopurine, 60 mg, daily, Home	6-MP, tbl 50 mg	https://www.healthinfo.moh.gov.on.ca/ formulary; Dec 8, 2014	2.86	2.38	2,175.55
PO methotrexate, 17.5 mg, weekly, home	Apo-methotrexate, 2.5-mg Tab	https://www.healthinfo.moh.gov.on.ca/ formulary; Dec 8, 2014	0.63	4.43	577.35
Vincristine, 1.2 mg, every 4 wk, OP	Vincristine sulfate, 1 mg/mL Inj Sol	https://www.healthinfo.moh.gov.on.ca/ formulary/SearchServlet; Dec 3, 2014	30.60	36.72	1,197.07
IT methotrexate, 12 mg, every 12 wk, OP	Methotrexate sodium, 20 mg/2 mL Inj Sol 2-mL Pk, 1 vial	https://www.healthinfo.moh.gov.on.ca/ formulary; Dec 08, 2014	12.50	7.50	81.75
Total Cost: Maintenance					**4,134.07**

Abbreviations: COG, Children's Oncology Group; Inj, injection; IP, in-patient; IT, intrathecal; ODB, Ontario Drug Benefit; OP, outpatient; Tab, tablet.

[a]All costs in 2014 Canadian dollars.

[b]Length of maintenance is assumed to be 2.5 y (130 wk).

Table A5.11: Costs of Maintenance According to COG Treatment Protocol for a High-Risk Patient

Drug, Daily Dose, Frequency, IP/OP/Home	Drug Name, Dose in ODB Formulary or Another Source	Source; Date Accessed	Unit Cost, $[a]	Cost Estimate for Dose Used, $[a]	Total Cost (Adjusted for Frequency), $[a]
Maintenance[b]					
Prednisone, 35 mg, 5 d/4 wk, home	Apo-Prednisone, 50-mg tab	https://www.healthinfo.moh.gov.on.ca/formulary; Dec 8, 2014	0.17	0.12	2.43
6-Mercaptopurine, 60 mg, daily, home	6-MP, 50-mg tab	https://www.healthinfo.moh.gov.on.ca/formulary; Dec 8, 2014	2.86	3.43	3,132.79
PO methotrexate, 35 mg, weekly, home	Apo-Methotrexate, 2.5-mg tab	https://www.healthinfo.moh.gov.on.ca/formulary; Dec 8, 2014	0.63	4.43	577.35
Vincristine, 2 mg, every 4 wk, OP	Vincristine sulfate, 1 mg/mL Inj Sol	https://www.healthinfo.moh.gov.on.ca/formulary/SearchServlet; Dec 3, 2014	30.60	36.72	1,197.07
IT methotrexate, 15 mg, twice every 12 wk (year 1), once every 12 wk (subsequent years), OP	Methotrexate sodium, 20 mg/2 mL Inj Sol 2-mL Pk, 1 vial	https://www.healthinfo.moh.gov.on.ca/formulary; Dec 8, 2014	12.50	9.38	142.19
Total Cost: Maintenance					**5,051.83**

Abbreviations: COG, Children's Oncology Group; Inj Sol, injected solution; IP, in-patient; IT, intrathecal; OP, outpatient; Pk, package; Tab, tablet.

[a]All costs in 2014 Canadian dollars.

[b]Length of maintenance is assumed to be 2.5 y (130 wk).

Appendix 6: Incorporation of Children's Oncology Group Treatment Protocol Costs Into Costs of Acute Lymphoblastic Leukemia

For the Children's Oncology Group (COG) scenario, we combined the COG treatment protocol costs with those reported in the literature (Table 6 and Appendix 3) and an estimate of in-patient costs to approximate costs of acute lymphoblastic leukemia (ALL) for standard-risk and high-risk patients.

The average cost of in-patient stay for an oncology patient was approximately $1,557 per day. This estimate excluded the cost of drugs. According to the study by Rae et al and to costs of ALL in patients treated with the Berlin-Frankfurt-Münster (BFM) protocol, we assumed the length of stay for standard-risk patients was 39.83 days and for high-risk patients was 48.48 days (Table A3.1). Given these data, we estimated the in-patient costs for standard-risk and high-risk patients to be $62,015 and $75,483, respectively.

We approximated the total costs of treating a precursor B-cell ALL patient by adding the in-patient cost to the COG treatment protocol cost, as presented below.

Table A6: Costs of De Novo Acute Lymphoblastic Leukemia Including Children's Oncology Group Treatment Protocol

Cost Components	Mean Cost, $[a]		Source
	Lower Range[b]	Upper Range[b]	
Standard-Risk Patient			
In-patient costs	62,015	75,483	Appendices 3, 5
COG treatment protocol	44,411	47,207	Appendices 3, 5
Total cost of all phases[b]	106,426	109,222	NA
High-Risk Patient			
In-patient costs	62,015	75,483	Appendices 3, 5
COG treatment protocol	98,780	105,769	Appendices 3, 5
Total cost of all phases[b]	174,263	181,252	NA

Abbreviations: COG, Children's Oncology Group; NA, not applicable.

[a]All costs in 2014 Canadian dollars.

[b]Weekly estimates of costs for standard-risk and high-risk patients were obtained by dividing total cost by 124.8 weeks of treatment as suggested by Rae et al.

Appendix 7: Number of Incident Acute Lymphoblastic Leukemia Cases in Ontario, 2007–2013

Table A7: Number of Newly Diagnosed Pediatric Leukemia Cases in POGONIS (2007–2013)

Type of Pediatric Leukemia	Year of Diagnosis							Mean ± SD	Median	Range
	2007	2008	2009	2010	2011	2012	2013			
Total ALL	103	97	103	140	95	109	112	108.4 ± 15	103	95–140
Precursor B-cell ALL	88	84	90	127	85	94	93	94.4 ± 15	90	84–127

Abbreviations: ALL, acute lymphoblastic leukemia; POGONIS, Pediatric Oncology Group of Ontario Networked Information System; SD, standard deviation.

Source: Analysis provided by Ms. Nicole Bradley, Senior Health Care Analyst & Project Manager of POGONIS for budget-impact analysis (written communication 2015 March 11), derived from POGONIS; Number of Newly Diagnosed Pediatric Leukemia Cases, 0–19 years of age, diagnosed and treated in a POGO-affiliated tertiary centre in Ontario, 2007–2013, by type of pediatric leukemia

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About Health Quality Ontario

Health Quality Ontario is the provincial advisor on the quality of health care. We are motivated by a single-minded purpose: **Better health for all Ontarians.**

Who We Are.

We are a scientifically rigorous group with diverse areas of expertise. We strive for complete objectivity, and look at things from a vantage point that allows us to see the forest and the trees. We work in partnership with health care providers and organizations across the system, and engage with patients themselves, to help initiate substantial and sustainable change to the province's complex health system.

What We Do.

We define the meaning of quality as it pertains to health care, and provide strategic advice so all the parts of the system can improve. We also analyze virtually all aspects of Ontario's health care. This includes looking at the overall health of Ontarians, how well different areas of the system are working together, and most importantly, patient experience. We then produce comprehensive, objective reports based on data, facts and the voice of patients, caregivers and those who work each day in the health system. As well, we make recommendations on how to improve care using the best evidence. Finally, we support large scale quality improvements by working with our partners to facilitate ways for health care providers to learn from each other and share innovative approaches.

Why It Matters.

We recognize that, as a system, we have much to be proud of, but also that it often falls short of being the best it can be. Plus certain vulnerable segments of the population are not receiving acceptable levels of attention. Our intent at Health Quality Ontario is to continuously improve the quality of health care in this province regardless of who you are or where you live. We are driven by the desire to make the system better, and by the inarguable fact that better has no limit.

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