Ontario Health

ONTARIO HEALTH TECHNOLOGY ASSESSMENT SERIES

Homologous Recombination Deficiency Testing to Inform Patient Decisions About Niraparib Maintenance Therapy for High-Grade Serous or Endometrioid Epithelial Ovarian Cancer: A Health Technology Assessment

Key Messages

What Is This Health Technology Assessment About?

Epithelial ovarian cancer forms in the cells that line the ovaries and fallopian tubes. High-grade epithelial ovarian cancer grows more quickly than low-grade cancers, and treatment usually consists of surgery followed by chemotherapy. Patients who have responded to chemotherapy can undergo maintenance therapy, which is intended to postpone cancer progression or recurrence for as long as possible. One option for maintenance therapy is a drug called niraparib, but it can be associated with serious adverse events.

The homologous recombination repair pathway is a way of repairing damage to the DNA in our cells. A defect in the genes associated with this pathway leads to homologous recombination deficiency (HRD), which can lead to cancer. Certain treatments, including niraparib, are more likely to be effective in cancers associated with HRD. There are tests that can identify HRD, and HRD test results could be used to help people decide about whether to go ahead with niraparib maintenance therapy.

This health technology assessment looked at the clinical utility and cost-effectiveness of HRD testing to inform patient decisions about the use of niraparib maintenance therapy for patients with high-grade epithelial ovarian cancer. It also looked at the efficacy and safety of niraparib maintenance therapy in cancers with or without HRD. It explored the budget impact of publicly funding HRD testing, and the experiences, preferences, and values of people with ovarian cancer and their health care providers.

What Did This Health Technology Assessment Find?

Niraparib maintenance therapy improved progression-free survival compared with no maintenance therapy in cancers involving both HRD and homologous recombination proficiency (HRP), and treatment resulted in more adverse events.

HRD testing may save niraparib treatment–related costs but reduce quality-adjusted life years (QALYs), assuming that those with HRP would receive niraparib less often and thus have lower QALYs. We estimate that publicly funding HRD testing for people with newly diagnosed ovarian cancer in Ontario over the next 5 years would save $9 million to $12.67 million; for people with recurrent ovarian cancer, it would save $16.31 million to $21.67 million. The magnitude of cost savings and QALY losses would depend on the proportion of HRP patients who choose not to take niraparib maintenance therapy, which is unknown.

HRD testing for ovarian cancer was viewed favourably by those we interviewed. In studies of patient preferences, patients with recurrent ovarian cancer placed more importance on decreasing the risk of moderate to severe adverse events with treatment than on improving progression-free survival.

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A Note About Terminology

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

Abstract

Background

Ovarian cancer affects the cells of the ovaries, and epithelial cancer is the most common type of malignant ovarian cancer. The homologous recombination repair pathway enables error-free repair of DNA double-strand breaks. Damage of key genes associated with this pathway leads to homologous recombination deficiency (HRD), which results in unrepaired DNA and can lead to cancer. Tumours with HRD are believed to be sensitive to treatment with poly-adenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitors, such as niraparib. We conducted a health technology assessment to evaluate the clinical utility and cost-effectiveness of HRD testing to inform patient decisions about the use of niraparib maintenance therapy for patients with high-grade serous or endometrioid epithelial ovarian cancer. We also evaluated the efficacy and safety of niraparib maintenance therapy in patients with HRD or homologous recombination proficiency (HRP), the cost-effectiveness of HRD testing, the budget impact of publicly funding HRD testing, and patient preferences and values.

Methods

We performed a systematic literature search of the clinical evidence. We assessed the risk of bias of each included study using the Cochrane risk-of-bias tool for randomized trials version 2, and the quality of the body of evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. We performed a systematic economic literature search and conducted a cost–utility analysis with a 5-year time horizon from a public payer perspective. We also analyzed the budget impact of publicly funding HRD testing in people with ovarian cancer in Ontario. We performed a literature search for quantitative evidence of patient and provider preferences with respect to HRD testing and maintenance therapy with PARP inhibitors. To contextualize the potential value of HRD testing, we spoke with people with ovarian cancer.

Results

The clinical evidence review included two studies in high-grade epithelial ovarian cancer (one in patients with newly diagnosed advanced cases and one in patients with recurrent cancer). The studies evaluated niraparib maintenance therapy compared with no maintenance therapy and used HRD testing to group patients according to HRD status. Compared to placebo, niraparib maintenance therapy improved progression-free survival in patients with newly diagnosed and recurrent ovarian cancer, and in tumours with HRD or HRP (GRADE: High), but the studies did not compare the results between the HRD and HRP groups. The frequency of adverse events was higher in the niraparib group. We identified no studies that evaluated the clinical utility of HRD testing.

We conducted a primary economic evaluation to evaluate the cost-effectiveness of HRD testing for people with newly diagnosed ovarian cancer in an Ontario setting. Our analysis used a 5-year time horizon. HRD testing (for all eligible people or only for people with *BRCA* wild type) resulted in a lower proportion of patients receiving niraparib maintenance therapy, leading to lower costs and fewer quality-adjusted life-years (QALYs). The average total cost per patient was $131,375 for no HRD testing, $126,867 for HRD testing only in people with *BRCA* wild type, and $127,746 for HRD testing in all eligible people. The average total QALYs per patient were 2.087 for no HRD testing, 1.971 for HRD testing only in people with *BRCA* wild type, and 1.971 for HRD testing in all eligible people. Our budget impact analysis suggested that assuming a high uptake rate, publicly funding HRD testing for people with newly diagnosed ovarian cancer would lead to a total saving of $9.00 million (if HRD testing were funded for all) to $12.67 million (if HRD testing were funded for people with *BRCA* wild type) over the next 5 years.

Publicly funding HRD testing for people with recurrent cancer would lead to a total saving of $16.31 million (if HRD testing were funded for all) to $21.67 million (if HRD testing were funded for people with *BRCA* wild type) over the next 5 years.

We identified no studies that evaluated quantitative preferences for HRD testing. Based on two studies that evaluated patients and oncologists' preferences for maintenance therapy with a PARP inhibitor in the recurrent setting, a decrease in moderate to severe adverse events was more important for patients than an improvement in progression-free survival; however, improvement in progression-free survival was more important for oncologists. Both patients and oncologists accepted some trade-offs between efficacy and safety. The people with ovarian cancer we spoke with demonstrated a shared value for access to information, prevention of cancer recurrence, and overall survival with minimal adverse effects. This was consistent with findings from another survey in patients with ovarian cancer and at least one episode of recurrence, which suggest that patients prioritize treatment benefit over some treatment adverse events in the context of niraparib maintenance therapy. Interviewees also emphasized the importance of the patient–doctor partnership, access to local health care services, and patient education.

Conclusions

In patients with newly diagnosed (advanced) or recurrent high-grade serous or endometrioid ovarian cancer, niraparib maintenance therapy improved progression-free survival compared with no maintenance therapy in tumours with HRD or HRP (GRADE: High). Because we identified no studies on the clinical utility of HRD testing, we cannot comment on how it would affect patient decisions and clinical outcomes.

Over a 5-year time horizon, HRD testing for people with *BRCA* wild type could save $4,509 per person and lead to a loss of 0.116 QALY. The findings of our economic analyses are dependent on assumptions about the use of niraparib following HRD testing. We estimate that publicly funding HRD testing would lead to a total saving of $9 million to $12.67 million for newly diagnosed cancer, and a total saving of $16.31 million to $21.67 million for recurrent cancer over 5 years, assuming the use of niraparib maintenance therapy would be reduced following HRD testing.

Patients prioritized decreasing the risk of moderate to severe adverse events of maintenance therapy with PARP inhibitors over improving progression-free survival, and oncologists prioritized improving progression-free survival over decreasing the risk of moderate to severe adverse events. However, both patients and oncologists were open to accepting certain trade-offs between treatment efficacy and toxicity. The people we interviewed, who had lived experience with ovarian cancer and genetic testing, valued the potential clinical benefits of HRD testing for themselves and their family members. They emphasized patient education as an important consideration for public funding in Ontario.

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Objective

This health technology assessment evaluates the clinical utility and cost-effectiveness of homologous recombination deficiency (HRD) testing to inform patient decisions about the use of niraparib maintenance therapy for patients with high-grade serous or endometrioid epithelial ovarian cancer. It also evaluates the efficacy and safety of niraparib maintenance therapy in patients with HRD and those with homologous recombination proficiency (HRP) to inform patient decisions. Finally, it evaluates the budget impact of publicly funding HRD testing and the experiences, preferences, and values of people with ovarian cancer.

Background

Health Condition

Ovarian cancer is a type of cancer that affects the cells of the ovaries.[1] There are three main types of ovarian cancer, defined according to the cell of origin: epithelial, stromal, and germ cell.[1] Epithelial (affecting the cells that line the ovaries and fallopian tubes) is the most common type of malignant ovarian cancer, comprising approximately 90% of cases.[2] Serous carcinoma is the most common histological subtype of epithelial ovarian cancer (accounting for approximately 75% of epithelial ovarian cancers),[1,3] followed by endometrioid (approximately 10%), clear cell (approximately 10%), and mucinous (approximately 3%) ovarian cancers.[4]

Ovarian cancer is classified as stages I through IV by the International Federation of Gynecology and Obstetrics (FIGO) according to the extent of cancer spread.[5] The more the cancer has spread in the body, the higher the stage[6]:

- Stage I: the cancer is only in one ovary or both ovaries
- Stage II: the cancer involves one ovary or both ovaries and has grown into the surrounding pelvic organs
- Stage III: the cancer involves one or both ovaries, or it started in the peritoneum; the cancer has spread to areas outside the pelvis
- Stage IV: the cancer has spread to other parts of the body outside the abdomen and pelvis (distant metastasis)

Ovarian cancer is considered advanced if it spreads outside of the ovaries.[7] Serous ovarian cancer can also be classified as high or low grade.[6] High-grade cancer tends to grow more quickly and is more likely to spread than low-grade cancer.[6] Endometrioid epithelial ovarian cancer can be graded according to the FIGO[8] system used for endometrioid carcinomas of the endometrium (grade 1: ≤ 5% of nonsquamous, solid growth; grade 2: 6%–50% of nonsquamous, solid growth; grade 3: > 50% of nonsquamous, solid growth).

High-grade serous ovarian cancer (HGSOC) includes ovarian, fallopian tube, and primary peritoneal cancer; it is the most common histological subtype and the one with the highest mortality rate,[9] with an estimated 5-year survival rate of approximately 30% after standard treatment.[10] It is now understood that the majority of HGSOC arises from the distal fallopian tube.[4] HGSOC can also arise from the abdominal peritoneum.[11] Ovarian, fallopian tube, and primary peritoneal high-grade serous cancer all

have similar prognosis and treatment,[2] and we will consider them together when referring to HGSOC. Treatment for high-grade (grades 2 and 3) endometrioid epithelial ovarian cancer is similar to HGSOC[12,13] and will also be included in this health technology assessment. A biopsy or surgical specimen is generally collected before the start of treatment to aid in the diagnosis and staging of the disease.[11]

Risk factors for ovarian cancer include hereditary causes, such as germline mutations (pathogenic variants) in breast cancer susceptibility genes 1 or 2 (*BRCA1/2*), mutations in genes associated with Lynch syndrome, or other cancer susceptibility genes with lower penetrance (e.g., *BRIP1*, *RAD51C*, *RAD51D*).[2] Other risk factors include family history of cancer, endometriosis, nulliparity (never having given birth), infertility, and obesity.[2]

Clinical Need and Target Population

Globally, the estimated incidence of epithelial ovarian cancer is 6.6 cases per 100,000 women.[14] It was estimated that 1,277 people in Ontario[1] and 3,100 people in Canada[15] would be diagnosed with ovarian cancer in 2020. Among Canadian women, ovarian cancer is the eighth most common cancer and the fifth leading cause of cancer-related death.[1,15]

Data from the United States suggest that ovarian cancer occurs more frequently among non-Hispanic white women compared to Hispanic, Asian, or African American women.[11]

The incidence of ovarian cancer increases with age, and it is more commonly diagnosed during the sixth and seventh decades of life, but this may vary according to subtype,[11,12] and it is often diagnosed at an advanced stage of the disease.[16]

Homologous Recombination Deficiency

In human cells, genetic material is present in the form of double-strand DNA molecules, forming a double helix.[17] In normal cells, DNA damage happens continuously because of different factors, including errors during replication and exposure to genotoxic agents. If the damage is not repaired, it can lead to mutations in the cell's genomic material.[18] DNA damage can occur as a single-strand or a double-strand break (when one or both strands of DNA are damaged, respectively).[17]

A complex network of DNA repair pathways is required to maintain normal cell function and genomic stability.[19,20] Homologous recombination repair (HRR) is the key pathway that enables error-free repair of double-strand DNA breaks,[18-21] relying on different proteins (e.g., BRCA1, BRCA2, RAD51, PALB2, etc.) for the repair process.[18]

Damage or dysregulation of some key HRR pathway genes leads to HRD.[20] Cells harbouring HRD are unable to reliably repair DNA double-strand breaks, leading to error-prone repair[18] and genomic instability and mutations. This can eventually lead to cancer[20,22,23] by increasing the speed of mutation accumulation in the cell.[23] HRD is usually an early event in the evolution of the tumour and it is present in most, if not all, cells in the tumour.[23]

The best-described causes of HRD in patients with ovarian cancer are germline (hereditary) or somatic (acquired after conception) mutations in the *BRCA1/2* genes, but it can also arise through mutation or inactivation of other genes associated with HRR,[10] including *RAD51C*, *RAD51D*, *BRIP1*, and *PALB2*.[20]

HRD is present in approximately 50% of high-grade serous ovarian tumours,[18,24] including those carrying *BRCA1/2* germline (13%–21%) or somatic (6%) mutations.[18]

Tumours with HRD are believed to be sensitive to some treatments, including poly-adenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitors and platinum-based chemotherapy.[21] PARP inhibitors target the PARP enzyme family, which is involved in single-strand DNA repair.[25] Inhibiting the PARP enzyme results in accumulation of single-strand breaks, which then progress to double-strand breaks, requiring repair through the HRR pathway.[26,27] Normal cells can repair double-strand breaks, but cancer cells harbouring HRD cannot repair them, resulting in DNA damage and death to the cancer cells.[27] Patients with ovarian cancer and HRD may demonstrate a superior response to PARP inhibitors.[10] Platinum agents act by directly damaging cancer DNA and the impairment of DNA repair mechanisms caused by HRD leads to an increase in the accumulation of DNA damage in cancer cells, resulting in cancer cell death.[28]

Current Treatment Options

Primary treatment for advanced HGSOC and high-grade endometrioid epithelial ovarian cancer generally consists of cytoreductive surgery (also referred to as *primary debulking*) with the aim of removing all visible tumour, followed by systemic chemotherapy (cancer treatment that uses drugs to stop the growth of cancer cells, either by killing them or by stopping them from dividing), usually with platinum- and taxane-based regimens.[12,14,29] In cases where patients are not good candidates for primary debulking surgery because of advanced age, frailty, poor functional status, comorbidities, or a tumour that is not likely to be optimally resectable, chemotherapy (neoadjuvant chemotherapy) is given before surgery to reduce the tumour volume, followed by interval debulking surgery and chemotherapy.[2]

Primary treatment of advanced ovarian cancer (whether with primary surgery followed by first-line platinum-based chemotherapy or with neoadjuvant chemotherapy followed by surgery and platinum-based chemotherapy) results in complete clinical remission in up to 75% of cases.[29] However, 70% to 80% of patients with stage III or IV disease relapse (i.e., experience a recurrence) within 2 to 3 years of completing treatment.[27,30,31] These cases are generally considered incurable,[31] and patients eventually die of their disease,[32] with a 5-year survival rate of 47%.[27] After completion of chemotherapy, patients who experience disease recurrence receive second-line chemotherapy.[2] Repeat treatment with platinum-based chemotherapy can be used if the patient is considered to be platinum-sensitive (i.e., disease recurrence ≥ 6 months after treatment completion), but with diminishing effectiveness (i.e., shortened progression-free survival [time to disease progression or death]) and increasing toxicity with each subsequent treatment.[11,33]

Patients who have a complete or partial response after completion of platinum-based chemotherapy may choose between active surveillance (i.e., monitoring but no treatment) and maintenance therapy.[34,35] Maintenance therapy aims to kill cancer cells that persisted after the chemotherapy[36] and to prevent cancer recurrence[31] for as long as possible,[29] thus prolonging the time between chemotherapy treatments.[37] Options for maintenance therapy include bevacizumab, an intravenous multiclonal antibody that targets human vascular endothelial growth factor, and PARP inhibitors such as olaparib and niraparib.[27]

Maintenance Therapy With PARP Inhibitors

Two PARP inhibitors have been approved by Health Canada for use as maintenance therapy in patients with ovarian cancer: olaparib[38] and niraparib.[39] Two other PARP inhibitors, rucaparib and veliparib, have

been evaluated for maintenance therapy in clinical studies,[40,41] but have not yet been approved by Health Canada.

Olaparib was approved by Health Canada as monotherapy for maintenance treatment in adult patients with advanced, *BRCA*-mutated, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy, and in those with *BRCA*-mutated, platinum-sensitive, relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.[38] Health Canada has also given approval with conditions for the use of olaparib as monotherapy for maintenance treatment of adult patients with *BRCA* wild type, platinum-sensitive, relapsed, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.[38]

Niraparib was approved by Health Canada for use as monotherapy for maintenance treatment in adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy and for those with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.[39] Health Canada does not mention the need for *BRCA* mutation or HRD testing to determine eligibility for niraparib maintenance therapy.

The Canadian Agency for Drugs and Technologies in Health (CADTH) pan-Canadian Oncology Drug Review recommended niraparib maintenance therapy for patients with newly diagnosed, stage III or IV high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to first-line platinum-based chemotherapy (2021)[42] and for patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy and are platinum-sensitive (2020; Appendix 1).[43] These recommendations are consistent with the indications from Health Canada.[34,35]

For new diagnoses, oral maintenance therapy with olaparib can be provided for up to 2 years and niraparib for up to 3 years.[12,31] In recurrent disease, maintenance therapy with olaparib and niraparib is provided until disease progression or unacceptable treatment toxicity.[12,31]

According to a “dear health care provider” letter issued in the United States in December 2022, the US Food and Drug Administration restricted the niraparib maintenance therapy indication for recurrent ovarian cancer to patients with a germline *BRCA* mutation based on new, unpublished, overall survival data from a randomized controlled trial (RCT).[44] The indications in the newly diagnosed population did not change.[44]

Health Canada will review the RCT data for overall survival with niraparib maintenance therapy in recurrent ovarian cancer.[45] As of February 2023, there have been no changes to the approved indications in Canada.[45] However, health care professionals are advised to consider the information available before starting niraparib maintenance therapy in patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer without a germline *BRCA* mutation and to share that information with patients who may be affected.[45]

Toxicities associated with niraparib can be severe and most commonly include fatigue, hematologic toxicities (e.g., anemia, neutropenia, thrombocytopenia), and gastrointestinal toxicities such as nausea.[46,47] Myelodysplastic syndrome and acute myeloid leukemia are estimated to occur in 1% to 3%

of patients with ovarian cancer[47] and can be associated with treatment with PARP inhibitors, but they can also be caused by chemotherapy.[46]

Health Technology Under Review

HRD status may provide information about the magnitude of benefit of maintenance therapy with PARP inhibitors.[2] Given the risk of toxicity with niraparib (including serious hematologic adverse events)[2] and the fact that HRD status may be associated with clinical benefits from niraparib maintenance therapy,[15,48] it has been proposed that the results of HRD testing be used to help patients decide[49] whether or not to undergo maintenance therapy with niraparib.

Different types of tests have been developed to assess HRD, including tests that identify mutations in specific HRR pathway–related genes (*BRCA1/2* and other genes), genomic scar and mutational signature tests, and homologous recombination function tests.[10,49] Differences in HRD definition among the different tests (pathogenic mutations in single HRR pathway genes, genomic scars) may affect their utility in clinical practice.[49]

Tests That Identify Mutations in Specific HRR Pathway–Related Genes

These tests identify specific causes of HRD, including mutations in *BRCA1/2* and other genes associated with the HRR pathway.[10] The association between *BRCA1/2* pathogenic mutations and HRD is well established.[10] However, the association between other HRR pathway–related genes and HRD may be less consistent, requiring additional studies to understand their clinical implications.[49]

Genomic Scar and Mutational Signature Tests

Genomic scar and mutational signature tests measure the patterns of genomic changes that occur as a direct or indirect consequence of the DNA repair defect and that accumulate over the course of tumour evolution in HRD cancers, irrespective of the underlying genetic defect.[10,23] These tests provide historical information about HRD status and do not assess any potential homologous recombination gene reversion.[10] Some gene reversions may restore homologous recombination function, and in these cases, any genomic scar would still be detectable and lead to false-positive test results.[21,50]

GENOMIC SCAR TESTS

Genomic scars are specific genomic changes that occur as a consequence of an ongoing DNA repair defect.[23] These lead to imprecise repair and chromosomal alterations, including loss of chromosomal sequences (referred to as loss of heterozygosity, or LOH), and structural rearrangements (such as translocations). The degree of chromosomal alteration may be associated with HRD status.[23]

Commercial next-generation sequencing (NGS) genomic scar tests such as MyChoice CDx (Myriad Genetics) and FoundationOne CDx (Foundation Medicine) are available[10]; they interrogate DNA from a tumour sample.[2,6] These two tests differ in the specific genomic features they measure and in how they define HRD deficiency thresholds,[18] which can lead to discordant results between the two tests.[49]

MyChoice CDx

MyChoice CDx uses DNA isolated from a formalin-fixed, paraffin-embedded (FFPE) tumour tissue sample for the qualitative detection and classification of single nucleotide variants; insertions and deletions; and large rearrangement variants in protein coding regions and intron–exon boundaries of the *BRCA1* and *BRCA2* genes. MyChoice CDx is also used to determine the genomic instability score (GIS).[51] Because the

test is performed on DNA from tumour cells, it can identify both somatic and germline *BRCA* mutations, but it does not differentiate between the two.[51] The GIS is calculated using a combination of measures of chromosomal alterations that are associated with the HRD phenotype, equalling the unweighted sum of telomeric allelic imbalance (TAI), large scale transitions (LST; chromosome breaks: translocations, inversions, or deletions), and LOH.[10,23,49] HRD is defined as the presence of a pathogenic or likely pathogenic *BRCA1/2* mutation, or a GIS above a prespecified threshold.[51] The test is performed at Myriad Genetics Laboratories in Salt Lake City, Utah.[51]

The accuracy of the MyChoice CDx HRD status result was demonstrated using a validated NGS-based assay with a combination of nonclinical samples and FFPE clinical specimens from patients with cancer enrolled in clinical trials from whom sufficient DNA quantity and quality were available for testing with an NGS comparator assay (not specified).[51] Concordance analysis for HRD status results between MyChoice CDx and the comparator assay performed on DNA samples from FFPE tumour specimens from 206 patients with cancer resulted in a positive percent agreement of 98.5%, a negative percent agreement of 98.6%, and an overall percent agreement of 98.5%.[51] The result of an accuracy analysis showed 100% positive percent agreement for tumour *BRCA1/2* sequence variant calls and 100% overall percent agreement for large rearrangement analytical calls between MyChoice CDx and the comparator assay.[51] In a study that included 215 breast cancer tumours, the HRD score showed strong correlation with *BRCA1/2* deficiency.[52]

HRD scores (the unweighted sum of TAI, LST, and LOH) of a cohort of breast and ovarian chemotherapy-naive tumours with known *BRCA1/2* status were analyzed to define the threshold that would detect tumours with *BRCA1/2* mutations or *BRCA1* promoter methylation with 95% sensitivity. This was defined as the 5th percentile of HRD scores of tumours lacking a functional copy of *BRCA1/2*, which was determined to be a score of 42.[53] This threshold was based on the assumption that the loss of *BRCA1/2* function would lead to HRD, and that the distribution of HRD scores in the *BRCA1/2*-deficient samples would be representative of the score distribution in HRD samples because of any underlying mechanism.[53] The predefined HRD score (> 42) was then tested for its ability to identify tumours that responded to platinum-based neoadjuvant chemotherapy in a cohort of patients with triple-negative breast cancer. The sensitivity of the selected threshold of 42 was 85% for residual cancer burden and 93% for pathologic complete response.[53]

FoundationOne CDx

FoundationOne CDx uses DNA isolated from FFPE tumour tissue specimens to detect substitutions, insertion and deletions, and copy number alterations in 324 genes, including *BRCA1/2*. FoundationOne CDx can also assess genomic LOH. HRD status is defined by either a *BRCA*1/2 mutation or an LOH score above a predefined threshold.[49] The test is performed at Foundation Medicine sites located in the United States (Cambridge, Massachusetts and Morrisville, North Carolina).[54]

Other Genomic Scar HRD Tests

Other NGS-based genomic scar HRD assays may become available in the future, such as the Trusight Oncology (TSO) 500 HRD add-on kit to the Trusight Oncology 500 assay,[55,56] the SOPHiA DDM HRD Solution assay,[57,58] and the AmoyDx HRD Focus Panel.[59]

TSO 500 evaluates 523 genes, including *BRCA*1/2. The TSO 500 HRD add-on kit determines HRD status by calculating the GIS using a proprietary algorithm from Myriad Genetics using LOH, TAI, and LST.[55,56] The test can be performed at laboratories that use NGS technology.[55]

The SOPHiA DDM HRD Solution assay evaluates germline and somatic HRR mutations (including *BRCA1/2*) and uses an algorithm to measure genomic scarring by calculating the genomic integrity index.[57,58] The AmoyDx HRD Focus Panel evaluates *BRCA1/2* gene mutations and uses an algorithm to determine the genomic scar score.[59]

MUTATIONAL SIGNATURE TESTS

Whole-genome sequencing data can be used to detect changes in nucleotide sequences that have accumulated in the tumour DNA during tumour evolution.[23] Tumours with HRD rely on more error-prone pathways to repair double-strand breaks, and this leads to a characteristic mutational pattern (or mutational signature) that can be used to detect HRD, regardless of the underlying cause.[10,23,60] These HRD-related mutational signatures can be assessed using mutation-based computational algorithms, such as HRDetect[10,23] and CHORD.[23,60] The literature suggests that there is favourable preclinical evidence for these tests; however, studies are still needed to determine whether they can predict response to treatment with PARP inhibitors.[10]

Homologous Recombination Function Tests

Functional assays aim to directly assess current HRR status by assessing its functional parameters. One example is measurement of the accumulation of the RAD51 protein on double-strand breaks.[23] This approach allows for an analysis of homologous recombination function regardless of the causes of HRD upstream of RAD51.[61] Preclinical data suggest promising results for real-time estimates of HRD, but its ability to predict treatment outcomes with PARP inhibitors has not yet been studied.[10]

Guidelines for the Use of HRD Testing in Patients With Ovarian Cancer

The American Society of Clinical Oncology (ASCO),[62] the European Society for Medical Oncology (ESMO),[10] the US National Comprehensive Cancer Network (NCCN),[2] and the Pan-Canadian Consensus Statement[15] on first-line PARP inhibitor maintenance therapy have published guidelines or recommendations on the use of tumour HRD testing in patients with ovarian cancer.

ASCO[62] stated that no recommendations could be made to support routine tumour HRD testing in patients with epithelial ovarian cancer, because the assays available do not provide sufficient differentiation of response to PARP inhibitors in addition to what is provided by the identification of a pathogenic *BRCA* mutation.

NCCN[2] stated that HRD status may provide information about the magnitude of benefit of maintenance therapy with a PARP inhibitor in the absence of a *BRCA* mutation after first-line chemotherapy.

ESMO[10] stated that, in patients with newly diagnosed (after first-line chemotherapy) high-grade serous ovarian, fallopian tube, and peritoneal cancer without a *BRCA* mutation, it is reasonable to use a validated scar-based HRD test to predict the likely magnitude of benefit of maintenance therapy with PARP inhibitors and to identify the subgroup of patients who are least likely to benefit from this treatment. In patients with platinum-sensitive recurrent high-grade ovarian, fallopian tube, and peritoneal cancer, it is reasonable to use a *BRCA* mutation test and a validated scar-based HRD test to predict the likely magnitude of benefit of maintenance therapy with PARP inhibitors for consideration of treatment risks and benefits.

According to the Pan-Canadian Consensus Statement[15] on first-line PARP inhibitor maintenance therapy prepared by a panel of gynecologic and medical oncologists from across Canada, tumour HRD status is a predictive biomarker of treatment benefit from PARP inhibitors, and testing should be publicly funded.

The CADTH pan-Canadian Oncology Drug Review documents on niraparib maintenance therapy in patients with newly diagnosed or recurrent ovarian cancer did not include an evaluation of HRD testing, but the niraparib study results were examined in the overall population and by HRD status as reported in the studies.[34,35] Niraparib was recommended regardless of HRD status.[42,43] The authors stated that HRD testing is not routinely performed in Canadian practice and has not been clinically validated, and that "treatment decisions should not be guided based on the results of HRD testing alone."[42,43]

Additional information is provided in Appendix 1.

Regulatory Information

Both MyChoice CDx and FoundationOne CDx have been approved by the US Food and Drug Administration.[51,54]

MyChoice CDx is used to detect pathogenic or likely pathogenic variants in the *BRCA1/2* genes and to determine the GIS, which aids in evaluating the HRD status of patients with ovarian cancer who may be eligible for specific treatments. It is also stated that detection of a pathogenic or likely pathogenic *BRCA1/2* mutation or a positive GIS is associated with enhanced progression-free survival with niraparib maintenance therapy in patients with ovarian cancer.[51]

FoundationOne CDx was approved to identify gene mutations that may render patients eligible for specific treatments. It can also be used for the detection of genomic LOH from FFPE ovarian tumour tissue. HRD, defined as a tumour that is *BRCA*-positive and/or LOH high, is associated with improved progression-free survival from rucaparib maintenance therapy in patients with ovarian cancer.[54]

Neither test has been approved by Health Canada.

Ontario and Canadian Context

Ontario

In Ontario, two PARP inhibitors – olaparib and niraparib – are funded through the Exceptional Access Program.[63] Funding is consistent with the CADTH pan-Canadian Oncology Drug Review.

Funding for olaparib maintenance therapy as monotherapy is restricted to adult patients with *BRCA*-mutated (*BRCA1* or *BRCA2* genes, germline, or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, whether they have been newly diagnosed or have relapsed and meet specific criteria (please refer to the Exceptional Access Program[63] for further details).

Olaparib maintenance therapy funding is provided until disease progression, development of unacceptable toxicity, or up to a maximum of 2 years in patients with newly diagnosed ovarian cancer or until disease progression or unacceptable toxicity in patients with relapsed disease.[63] Retreatment with olaparib as maintenance therapy is not funded.[63]

Niraparib as monotherapy is funded for the maintenance treatment of newly diagnosed or recurrent high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer in adult patients,[63] regardless of *BRCA* mutation and HRD status, who meet specific criteria (please refer to the Exceptional Access Program[63] for further details).

Niraparib maintenance therapy funding is provided until there is disease progression or until the development of unacceptable toxicity in patients with newly diagnosed or recurrent cancer, or up to a maximum of 3 years if there is no evidence of disease recurrence in patients with newly diagnosed cancer.[63] The treatment is not funded in patients who had disease progression with niraparib or other PARP inhibitors.[63] However, treatment changes from other PARP inhibitors are funded in cases of intolerance or allergy and in the absence of disease progression.[63]

Additional details about eligibility for olaparib and niraparib maintenance therapy are provided on the Exceptional Access Program website.[63]

According to CADTH pan-Canadian Oncology Drug Review documents, niraparib was recommended regardless of HRD status because, although the magnitude of improvement in progression-free survival was greater in the HRD group, improvement was observed in all patients.[34,35]

Tumour *BRCA1/2* testing is publicly funded in Ontario in patients with high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer[64] to determine eligibility for olaparib treatment.[9,65]

Germline testing, including *BRCA1/2* mutations, is performed in patients with invasive (i.e., spread beyond the layer of tissue in which it developed) epithelial ovarian, fallopian tube, or peritoneal cancer.[66]

HRD testing is not used to determine eligibility for maintenance therapy in Ontario. MyChoice CDx is being used in Ontario after tumour *BRCA1/2* testing by some patients with *BRCA* wild type ovarian cancer. The test is not publicly funded, and unless patients are able to access it by participating in a clinical trial, patients must pay for it out of pocket. We are not aware if FoundationOne CDx is being used in Ontario to assess HRD status in patients with ovarian cancer.

Canada

We are not aware of public funding for HRD testing in patients with ovarian cancer in other Canadian provinces.

Terminology

- Best overall response: best response recorded from the start of the treatment until disease progression or recurrence
- *BRCA* wild type: a tumour that does not have either a pathogenic or likely pathogenic germline or somatic *BRCA* mutation
- Complete response: disappearance of all target lesions; any pathological lymph nodes must have reduction in short axis to less than 10 mm
- Large scale transitions: chromosomal breaks between adjacent regions of at least 10 Mb[59]

- Loss of heterozygosity: presence of a single allele from a cross-chromosomal event that results in the loss of entire genes and the surrounding chromosomal region[59]
- Neoadjuvant chemotherapy: cancer treatment that is given before interval debulking surgery to reduce the tumour burden, increasing the likelihood of optimal surgical cytoreduction
- Newly diagnosed ovarian cancer: patients are receiving maintenance therapy after completion of first-line chemotherapy
- Platinum-refractory: the disease progresses during platinum-based chemotherapy[2]
- Platinum-resistant: the disease recurs less than 6 months after completion of platinum-based chemotherapy
- Platinum-sensitive: the disease relapses 6 months or more after completion of platinum-based chemotherapy[2]
- Progressive disease: an increase of 20% or greater in the sum of the diameters of target lesions, taking as reference the smallest sum on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm
- Recurrent or relapsed ovarian cancer: patients have previously undergone two or more lines of chemotherapy
- Telomeric allelic imbalance: disparity in the 1:1 allele ratio in the chromosome's telomere due to reciprocal translocations[59]

Expert Consultation

We engaged with experts in the specialty areas of oncology, genetics, and laboratory medicine to help inform our understanding of aspects of the health technology and to contextualize the evidence.

PROSPERO Registration

This health technology assessment has been registered in PROSPERO, the international prospective register of systematic reviews (CRD42022341882), available at crd.york.ac.uk/PROSPERO.

Clinical Evidence

Research Questions

In patients with newly diagnosed or recurrent high-grade serous or endometrioid epithelial ovarian, fallopian tube, or peritoneal cancer (referred to as *ovarian cancer*) who are in complete or partial response to platinum-based chemotherapy:

1. What are the efficacy and safety of maintenance therapy with niraparib compared with no maintenance therapy in patients who have tumours with homologous recombination deficiency (HRD) and homologous recombination proficiency (HRP)? The HRD group was subgrouped according to *BRCA* mutation status (*BRCA* mutation and *BRCA* wild type)
2. What is the clinical utility of HRD testing compared with no HRD testing or tumour *BRCA* testing alone to inform patient decisions about the use of niraparib maintenance therapy?

Our review focused on the use of HRD testing to inform patient decisions about the use of niraparib maintenance therapy (as monotherapy). Because the eligibility for maintenance therapy with olaparib in the population of interest is based on *BRCA1/2* mutation status rather than on HRD testing, we excluded olaparib from our review. Other poly-adenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitors (rucaparib and veliparib) were out of scope because they have not been approved for use in Canada.

We did not assess the analytical validity of HRD testing because its accuracy has already been demonstrated for MyChoice CDx (Myriad Genetics) as noted in the Background.[51]

Methods

Clinical Literature Search

We performed a clinical literature search on May 25, 2022, to retrieve studies published from inception until the search date. We used the Ovid interface in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, the Health Technology Assessment database, and the National Health Service Economic Evaluation Database (NHS EED).

A medical librarian developed the search strategies using controlled vocabulary (e.g., Medical Subject Headings) and relevant keywords. The final search strategy was peer-reviewed using the PRESS Checklist.[67]

We created database auto-alerts in MEDLINE and Embase and monitored them until October 24, 2022. We also performed a targeted grey literature search of the International HTA Database, the websites of health technology assessment organizations and regulatory agencies, and clinical trial and systematic review registries, following a standard list of sites developed internally. See Appendix 2 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Inclusion Criteria

- English-language full-text publications
- Studies published since inception
- Randomized controlled trials (RCTs), comparative observational studies, health technology assessments, and systematic reviews

Exclusion Criteria

- Animal and in vitro studies
- Non-comparative observational studies, editorials, commentaries, case reports, conferences abstracts, letters

PARTICIPANTS

Inclusion Criterion

- Patients with newly diagnosed or recurrent high-grade serous or endometrioid epithelial ovarian, fallopian tube, or peritoneal cancer, who are in complete or partial response to platinum-based chemotherapy, and who are candidates for niraparib maintenance therapy

Exclusion Criterion

- Patients with ovarian or other cancers who are candidates for maintenance therapy with other PARP inhibitors or other drugs

INTERVENTIONS

Inclusion Criterion (Research Question 1)

- Maintenance therapy with niraparib as monotherapy based on studies in which HRD status and clinical outcomes were measured. Any type of HRD test was included (e.g., testing for homologous recombination repair [HRR] pathway–related gene mutations, genomic scar, mutational signature, or functional tests)

Exclusion Criteria (Research Question 1)

- Maintenance therapy with other PARP inhibitors or other drugs, or any chemotherapy
- Studies in which HRD testing was not performed, or in which *BRCA* testing alone was performed

Inclusion Criterion (Research Question 2)

- HRD testing used in studies that evaluated the clinical outcomes of maintenance therapy with niraparib as monotherapy. Any type of HRD test was included (e.g., testing for HRR pathway–related gene mutations, genomic scar, mutational signature, or functional tests)

Exclusion Criteria (Research Question 2)

- HRD testing used in studies that evaluated maintenance therapy with other PARP inhibitors or other drugs, or any chemotherapy
- Studies in which HRD testing was not performed, or in which *BRCA* testing alone was performed

COMPARATORS

Inclusion Criterion (Research Question 1)

- No maintenance therapy based on studies in which HRD status and clinical outcomes were measured. Any type of HRD test was included (e.g., testing for HRR pathway–related gene mutations, genomic scar, mutational signature, or functional tests)

Exclusion Criteria (Research Question 1)

- Any maintenance therapy or any chemotherapy
- Studies in which *BRCA* testing alone was performed

Inclusion Criterion (Research Question 2)

- No HRD testing performed or tumour *BRCA* testing alone was performed based on studies that evaluated the clinical outcomes of maintenance therapy with niraparib as monotherapy

Exclusion Criteria (Research Question 2)

- Studies in which HRD testing was performed
- Studies assessing maintenance therapy with other PARP inhibitors or other drugs, or any chemotherapy

OUTCOME MEASURES

- Progression-free survival
- Overall survival
- Chemotherapy-free interval and time to subsequent chemotherapy
- Quality of life
- Safety and adverse events related to treatment and testing
- Use of HRD testing to inform patient decisions about the use of niraparib maintenance therapy (research question 2 only)

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts and a second reviewer reviewed 20% of the titles and abstracts using Covidence.[68] A single reviewer obtained the full texts of studies that appeared eligible for review according to the inclusion criteria, and then examined the full-text articles and selected studies eligible for inclusion. A single reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

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

- Source (e.g., citation information, study type)
- Methods (e.g., study design, study duration and years, participant allocation, allocation sequence concealment, blinding, reporting of missing data, reporting of outcomes, whether the study compared two or more groups)
- Outcomes (e.g., outcomes measured, number of participants for each outcome, number of participants missing for each outcome, outcome definition and source of information, unit of measurement, upper and lower limits [for scales], time points at which the outcomes were assessed)

We contacted study authors to provide clarification as needed.

Statistical Analysis and Data Presentation

We did not perform a quantitative synthesis of the results of individual studies because the two studies identified were conducted in two distinct patient populations: patients with newly diagnosed ovarian cancer and recurrent ovarian cancer.

We reported the results as provided in the published studies (i.e., for time-to-event outcomes, such as progression-free and overall survival, chemotherapy-free interval, and time to subsequent chemotherapy), which were analyzed using the Kaplan–Meier methodology in the studies identified. We reported the median time to event and corresponding 95% confidence intervals (CIs) when they were provided in the studies. The studies estimated hazard ratios and 95% CIs using a stratified Cox proportional hazards model based on randomization stratification factors. Results for quality-of-life outcomes were reported as adjusted means and standard errors.

We reported the results in patients who had tumours with HRD or HRP, and in the overall population. We also reported subgroup analyses according to *BRCA1/2* mutation status, relevant prognostic factors, and any relevant PROGRESS-Plus factors[69] if this information was provided in the studies.

For consistency with the reporting of adverse events in the PRIMA study,[19] we included adverse events that occurred in at least 20% of patients based on the frequency of adverse events of any grade in the niraparib group.

Critical Appraisal of Evidence

We assessed risk of bias using the Cochrane risk-of-bias tool for randomized trials version 2 (Appendix 3).[70]

We evaluated the quality of the body of evidence for outcomes according to the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) *Handbook*.[71] The body of evidence was assessed based on the following considerations: risk of bias, inconsistency, indirectness, imprecision, and publication bias (Appendix 3). The overall rating reflects our certainty in the evidence.

We conducted GRADE assessments of only the outcomes that were reported according to HRD status, because this was the focus of our review; we did not conduct GRADE assessments of the results for the germline *BRCA* mutation cohort of the NOVA study,[33] because germline *BRCA* mutation status was not determined using an HRD test.

Results

Clinical Literature Search

The database search of the clinical literature yielded 1,930 citations published between inception and May 25, 2022, including grey literature searches and after duplicates were removed. We did not identify any additional eligible studies from other sources, including database alerts (monitored until October 24, 2022). In total, we identified seven publications that met the inclusion criteria for the first research question, consisting of two RCTs[19,33] and five secondary publications of those RCTs.[37,72-75] We did not identify any studies that compared HRD testing with no HRD testing or tumour *BRCA* testing alone to address the second research question.

We identified systematic reviews and meta-analyses on the use of niraparib maintenance therapy in patients with ovarian cancer, but we did not include these in our review because they did not report the results according to HRD status; they included a broader group of PARP inhibitors, different cancers, or both; or they addressed only part of our research questions, outcomes, or both.

See Appendix 4 for a list of selected studies excluded after full-text review. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the clinical literature search.

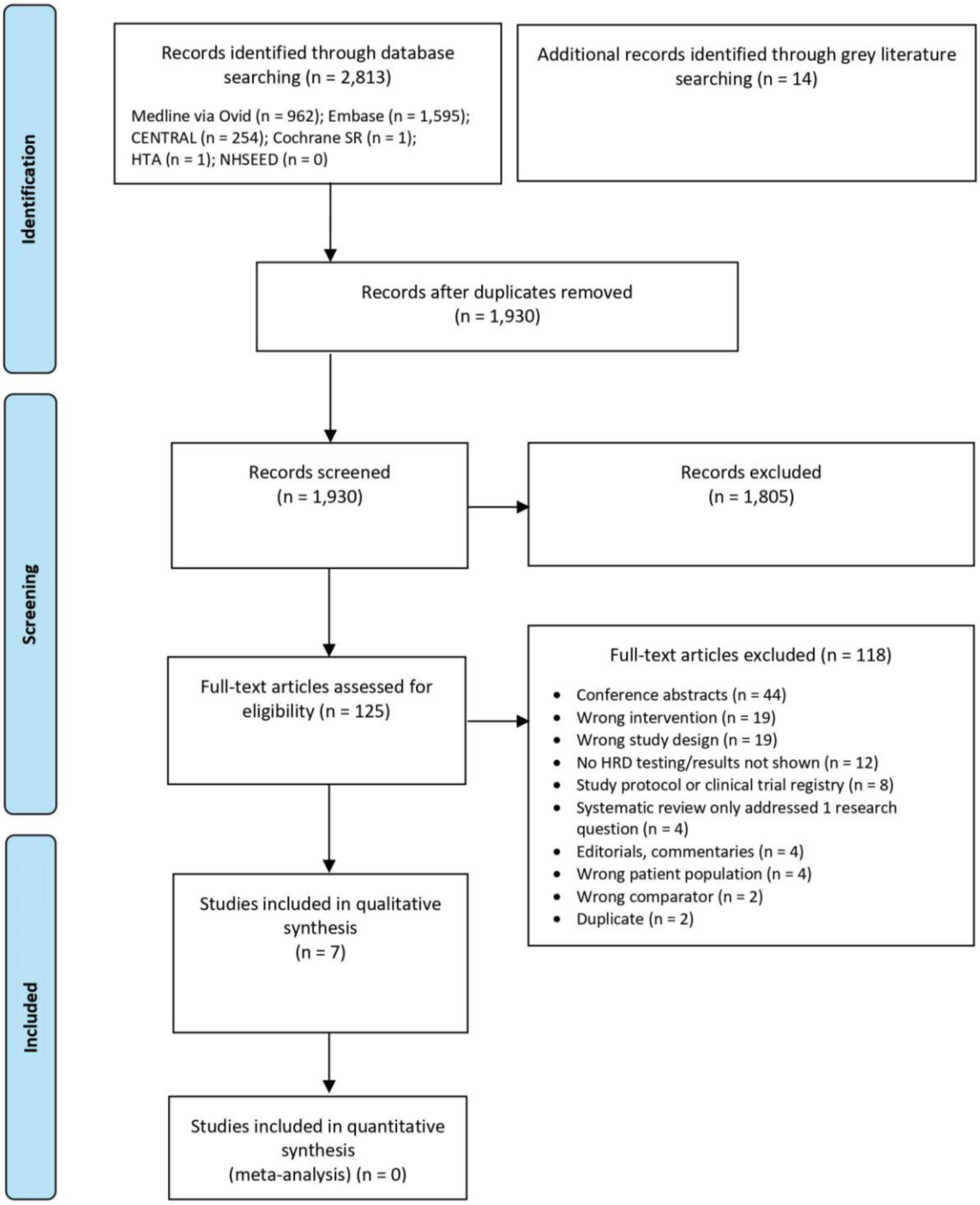


Figure 1: PRISMA Flow Diagram – Clinical Search Strategy

PRISMA flow diagram showing the clinical search strategy. The database search of the clinical literature yielded 2,813 citations published between database inception and May 25, 2022. We identified 14 additional eligible studies from other sources. After removing duplicates, we screened the abstracts of 1,930 studies and excluded 1,805. We assessed the full texts of 125 articles and excluded a further 118. In the end, we included seven articles in the qualitative synthesis.

Abbreviation: HRD, homologous recombination deficiency; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.

Source: Adapted from Page et al.[76]

Characteristics of Included Studies

PRIMA STUDY (NEWLY DIAGNOSED OVARIAN CANCER)

The PRIMA study was an RCT that evaluated the efficacy and safety of niraparib maintenance therapy compared with placebo in adult female patients with advanced, newly diagnosed high-grade serous or endometrioid ovarian, peritoneal, or fallopian tube cancer (hereafter referred to as high-grade serous or endometrioid ovarian cancer) at high risk for disease progression. Patients were eligible if they had stage III disease (International Federation of Gynecology and Obstetrics [FIGO] criteria) that was inoperable or with visible residual tumour after debulking surgery, or any stage IV disease (FIGO criteria). Prior use of neoadjuvant chemotherapy was permitted.[19] Patients had to have a complete or partial response after six to nine cycles of first-line platinum-based chemotherapy and have finished the last dose of chemotherapy within 12 weeks prior to enrolment.[19]

The study included 733 patients: 487 in the niraparib group and 246 in the placebo group.[19]

HRD testing was performed on tumour samples using MyChoice CDx.[19] Tumours with a genomic instability score (GIS) of 42 or greater, or with a pathogenic or likely pathogenic *BRCA1/2* mutation, were classified as having HRD; otherwise, tumours with a GIS of less than 42 and no *BRCA* mutation (*BRCA* wild type) were considered to have HRP.[19] The HRD group was further subgrouped according to *BRCA* mutation status in exploratory analyses.[19] If the HRD test was not conducted or if its results were inconclusive, tumours were considered "homologous recombination status not determined" and were included in the overall population.[19]

Randomization was stratified according to HRD status, clinical response after first-line platinum-based chemotherapy, and receipt of neoadjuvant chemotherapy.[19]

Initially, the starting dose for niraparib was 300 mg orally once per day, but a protocol amendment allowed a lower starting dose of 200 mg in patients with a baseline body weight of less than 77 kg or a platelet count of less than 150,000/mm^3.[19] Treatment interruption (for up to 28 days), dose reduction, or both were permitted for adverse events.[19] Treatment was administered for 36 months or until disease progression, provided that the patient was benefiting from the treatment and did not meet any prespecified criteria for discontinuation.[19]

The primary outcome was progression-free survival (PFS) in patients who had tumours with HRD and in the overall population.[19] Exploratory analyses of PFS were performed for factors such as HRP and HRD subgroups according to *BRCA* mutation status, among others.[19] Overall survival was a key secondary outcome; other secondary outcomes included time to first subsequent chemotherapy; time from randomization to progression on the next chemotherapy following study treatment or death for any cause (PFS 2); quality of life; and safety.[19]

Additional information about the study is provided in Appendix 5.

The study was powered to evaluate the primary outcome (PFS) in the overall and HRD populations, and to ensure enough data would be available to monitor patient safety and overall survival.[19]

The study is expected to be completed in March 2024.[77] The predetermined primary efficacy analysis (PFS) was to be conducted when at least 99 events had occurred in the HRD group.[19] Interim analyses of secondary endpoints were to be performed at the same time as the final primary efficacy analysis, and

the final overall survival analysis is expected to occur when the prespecified number of deaths has been reached in the intention-to-treat population.[19]

The publication includes the primary efficacy analysis (PFS) and interim analyses of secondary endpoints based on the database lock of May 2019.[19] At the time of the database lock, the median patient follow-up was 13.8 months (range < 1 to 28 months), 246 of 733 randomized patients were still receiving treatment, and 386 patients in the overall population had died or experienced disease progression (of whom 154 were in the HRD group).[19]

A secondary publication of the PRIMA study[75] reported on a post hoc analysis of the effect of surgical timing (primary debulking surgery or neoadjuvant chemotherapy followed by interval debulking surgery) and postoperative residual disease status (nonvisible or visible) on the efficacy of maintenance therapy with niraparib compared with placebo.

NOVA STUDY (RECURRENT OVARIAN CANCER)

The NOVA study was an RCT that evaluated the efficacy and safety of niraparib maintenance therapy compared with placebo in adult patients with recurrent, predominantly high-grade serous ovarian, primary peritoneal, or fallopian tube cancer (ovarian cancer).[33] Patients must have received at least two platinum-based chemotherapy regimens, and the last treatment had to be completed 8 weeks or less before enrolment.[33] Patients also had to have platinum-sensitive disease after the penultimate platinum-based chemotherapy and complete or partial response after the last platinum-based chemotherapy before study enrolment.[33]

The study included two independent cohorts based on the presence or absence of a germline *BRCA* (g*BRCA*) mutation, identified as the g*BRCA* and non-g*BRCA* cohorts, respectively.[33] For each cohort, randomization was stratified according to time to progression after completion of the penultimate platinum regimen, use of concomitant bevacizumab with the penultimate or last platinum regimen, and best response during the last platinum regimen.[33]

The g*BRCA* cohort included 203 patients: 138 in the niraparib group and 65 in the placebo group. The non-g*BRCA* cohort included 350 patients: 234 in the niraparib group and 116 in the placebo group.[33]

The initial niraparib dose was 300 mg orally once per day.[33] Treatment interruption (for up to 28 days), dose reduction, or both were permitted for adverse events.[33] Treatment continued until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up.[33]

HRD testing was performed using MyChoice CDx before the database lock (June 20, 2016) in the non-g*BRCA* cohort on archived tumour samples.[33] Tumours with a GIS of 42 or greater or with a pathogenic or likely pathogenic *BRCA1/2* mutation were classified as having HRD; otherwise, tumours were considered to have HRP.[33] Patients in the HRD group were further subgrouped based on the presence of a somatic *BRCA* mutation (HRD-positive/s*BRCA* mutation) or the lack of a *BRCA* mutation (HRD-positive/*BRCA* wild type).[33] If the test was not conducted or if its results were inconclusive, tumours were considered "homologous recombination status not determined" and the patients were included in the overall population of the non-g*BRCA* cohort.[33]

The primary endpoint was PFS in three primary efficacy populations: the g*BRCA* cohort, the HRD group of the non-g*BRCA* cohort, and the overall non-g*BRCA* cohort.[33] Exploratory PFS analyses were performed in the non-g*BRCA* cohort according to the different HRD status subgroups: HRD-positive/

s*BRCA* mutation, HRD-positive/*BRCA* wild type, and HRP.[33] Subgroup analyses were performed for baseline and demographic factors that might have affected the primary endpoint.[33]

Secondary endpoints included chemotherapy-free interval, time to first subsequent chemotherapy, time from randomization until progression during receipt of the first subsequent chemotherapy after the study treatment or death (PFS 2), time to second subsequent chemotherapy, overall survival, quality of life, and safety.[33]

The study was powered to evaluate the primary outcome (PFS) in the primary efficacy populations and to ensure enough data would be available to monitor patient safety and overall survival.[33]

The primary efficacy analyses for PFS were specified a priori to be performed once disease progression or death had occurred in at least 98 patients each in the g*BRCA* cohort and in the HRD group of the non-g*BRCA* cohort.[33]

The study was completed in December 2021,[78] but the analyses reported in the publication include prespecified primary efficacy (PFS) analyses and the secondary endpoint analyses data available at the time of database lock (June 20, 2016). At the time of the database lock, the overall median follow-up was 16.9 months; 51 of 203 patients in the g*BRCA* cohort and 58 of 350 patients in the non-g*BRCA* cohort were still receiving treatment. Disease progression or death had occurred in 103 patients in the g*BRCA* cohort, 101 patients in the HRD group of the non-g*BRCA* cohort, and 213 patients in the overall non-g*BRCA* cohort.[33]

Additional information is provided in Appendix 5.

We identified four secondary publications of the NOVA study, listed below:

- Long-term safety analysis performed when approximately 20% of patients included in the NOVA study had received niraparib for at least 2 years[73]
- Two post hoc analyses on the safety and efficacy of niraparib: one subgrouped according to age (< 70 years/≥ 70 years)[72] and the other according to response to the last platinum-based chemotherapy[37]
- An assessment of quality of life, including changes in EQ-5D-5L and Functional Assessment of Cancer Therapy Ovarian Cancer Symptom Index (FOSI) scores during treatment and the effect of hematological adverse events on quality of life[74]

Patient Characteristics

PRIMA STUDY (NEWLY DIAGNOSED OVARIAN CANCER)

The median patient age was 62 years (range: 32–88 years); 65% had stage III ovarian cancer at diagnosis, and the remainder had stage IV disease.[19] The majority (94.8%) presented with serous ovarian cancer, 2.7% had endometrioid ovarian cancer, and the rest had other histological types of ovarian cancer.[19] Patients were at high risk for progressive disease: 23.1% of the overall population had residual disease after primary debulking surgery, 35.0% had stage IV disease, and 66.7% had received neoadjuvant chemotherapy.[19] According to the authors, patient characteristics were balanced between the niraparib and placebo groups.[19] Additional information is provided in Appendix 6.

Overall, 373 (50.9%) patients had tumours with HRD; within this group, 223 (30.4%) had a *BRCA* mutation and 150 (20.5%) had *BRCA* wild type (Table 1).[19] HRD status could not be determined in approximately 15% of the patients; they were included in the overall population.[19]

Table 1: HRD Status,[a] PRIMA Study

Author, year N (niraparib/placebo)	HRD overall, n (%)	HRD (*BRCA* mutation), n (%)	HRD (*BRCA* wild type), n (%)	HRP, n (%)	HRD status not determined, n (%)
González-Martín et al, 2019[19]	Niraparib: 247 (50.7)	Niraparib: 152 (31.2)	Niraparib: 95 (19.5)	Niraparib: 169 (34.7)	Niraparib: 71 (14.6)
N = 733 (487/246)	Placebo: 126 (51.2)	Placebo: 71 (28.9)	Placebo: 55 (22.3)	Placebo: 80 (32.5)	Placebo: 40 (16.3)

Abbreviations: HRD, homologous recombination deficiency; HRP, homologous recombination proficiency.
[a] Among patients who received at least one dose of treatment.
Source: González-Martín et al.[19]

NOVA STUDY (RECURRENT OVARIAN CANCER)

The median age of the patients ranged from 57 to 63 years, depending on the cohort and study group, and approximately 90% of patients had stage III or IV disease.[33] Eighty-seven percent of the patients were white, and 13% were Black, Asian, other ethnicities, or unknown.[33]

About 50% of the patients in the g*BRCA* cohort and 30% in the non-g*BRCA* cohort had received three or more lines of chemotherapy prior to study enrolment.[33] Approximately half of the patients had had a complete response to the most recent platinum-based chemotherapy, the other half had exhibited a partial response.[33]

Forty-six percent of the patients in the non-g*BRCA* cohort had HRD-positive tumours (32.8% had *BRCA* wild type and 13.4% had a somatic *BRCA* mutation).[33] Additional information is provided in Table 2. HRD status could not be determined in 54 (15.4%) patients: 26 (7.4%) because of inconclusive results and 14 (4.0%) each because of an insufficient or missing specimen; these patients were included in the overall non-g*BRCA* cohort.[33]

Additional information about baseline characteristics in the NOVA study and its post hoc analysis is provided in Appendix 6.

Table 2: HRD Status,[a] NOVA Study (Non-g*BRCA* Cohort)

Author, year N (niraparib/placebo)	HRD overall, n (%)	HRD (s*BRCA*), n (%)	HRD (*BRCA* wild type), n (%)	HRP, n (%)	HRD status not determined, n (%)
Mirza et al, 2016[33]	Niraparib: 106 (45.3)	Niraparib: 35 (15.0)	Niraparib: 71 (30.3)	Niraparib: 92 (39.3)	Entire cohort: 54 (15.4)
N = 350 (234/116)	Placebo: 56 (48.3)	Placebo: 12 (10.3)	Placebo: 44 (37.9)	Placebo: 42 (36.2)	Inconclusive results: 26 (7.4)
					Insufficient sample: 14 (4.0)
					Missing specimen: 14 (4.0)

Abbreviations: HRD, homologous recombination deficiency; HRP, homologous recombination proficiency; *gBRCA*, germline *BRCA; sBRCA*, somatic *BRCA*.
[a] Among patients who received at least one dose of treatment.
Source: Mirza et al.[33]

Treatment Discontinuations

PRIMA STUDY (NEWLY DIAGNOSED OVARIAN CANCER)

In the overall population, a total of 307 (63.4%) of 484 patients who received niraparib discontinued treatment: 218 (45%) because of disease progression, 58 (12%) because of an adverse event, 12 (2.5%) because of a decision to withdraw from the study, and 19 (3.9%) for other reasons.[19]

In the placebo group, 175 (71.7%) of 244 patients discontinued treatment: 162 (66.4%) because of disease progression, 5 (2.0%) because of an adverse event, 1 (0.4%) because of a decision to withdraw from the study, and 7 (2.9%) for other reasons.[19]

Treatment discontinuations in the HRD group is shown in Table 3.

Table 3: Treatment Discontinuations in the HRD Group, PRIMA Study

Author, year N (niraparib/placebo)	Overall, n (%)	Disease progression, n (%)	Adverse events, n (%)	Decision to withdraw from treatment, n (%)	Other reasons, n (%)
González-Martín et al, 2019[19] N = 370 (245/125)[a]	Niraparib: 124 (50.6) Placebo: 83 (66.4)	Niraparib: 80 (32.6) Placebo: 76 (60.8)	Niraparib: 27 (11.0) Placebo: 2 (1.6)	Niraparib: 8 (3.3) Placebo: 0 (0.0)	Niraparib: 9 (3.7) Placebo: 5 (4.0)

Abbreviations: HRD, homologous recombination deficiency.

[a] Among patients who received at least one dose of treatment.

Source: González-Martín et al.[19]

NOVA STUDY

A total of 150 of 203 (73.9%) patients in the overall g*BRCA* cohort and 287 of 345 (83.2%) patients in the overall non-g*BRCA* cohort discontinued treatment because of disease progression, adverse events, decision to withdraw treatment, or other reasons. Table 4 provides additional information about the reasons for discontinuation in the niraparib and placebo groups. Information according to HRD status was not provided for the non-g*BRCA* cohort.

Table 4: Treatment Discontinuations, NOVA Study

Author, year N (niraparib/placebo)	Overall, n (%)	Disease progression, n (%)	Adverse events, n (%)	Decision to withdraw from treatment, n (%)	Other reasons, n (%)
Mirza et al, 2016[33] N = 201 (136/65)[a] g*BRCA* cohort	Niraparib: 89 (65.4) Placebo: 61 (93.8)	Niraparib: 63 (46.3) Placebo: 49 (75.4)	Niraparib: 17 (12.5) Placebo: 1 (1.5)	Niraparib: 8 (5.9) Placebo: 8 (12.3)	Niraparib: 1 (0.7) Placebo: 3 (4.6)
Mirza et al, 2016[33] N = 345 (231/114)[a] Non-g*BRCA* cohort	Niraparib: 185 (80.0) Placebo: 102 (89.5)	Niraparib: 129 (55.8) Placebo: 98 (86.0)	Niraparib: 33 (14.3) Placebo: 2 (1.8)	Niraparib: 11 (4.8) Placebo: 1 (0.9)	Niraparib: 12 (5.2) Placebo: 1 (0.9)

Abbreviations: g*BRCA*, germline *BRCA*.

[a] Among patients who received at least one dose of treatment.

Source: Mirza et al.[33]

Risk of Bias in the Included Studies

The risk of bias was considered low because the two studies used appropriate methods for randomization, allocation concealment, blinding of investigators and patients, and for dealing with missing data. As well, the intention-to-treat population was used for the efficacy analyses, and the analyses were conducted as specified a priori. For secondary outcomes, although the publications identified reported on interim analyses, these were performed at the same time as the primary efficacy analyses as specified a priori. Independent committees reviewed the efficacy and safety data. Detailed risk-of-bias assessments are provided in Appendix 3.

Progression-Free Survival

PRIMA STUDY (NEWLY DIAGNOSED OVARIAN CANCER)

PFS was defined as the time from randomization to the earlier date of assessment of objective disease progression (based on imaging), or death from any cause in the absence of progression.[19] Niraparib improved PFS compared with placebo in the overall population (Appendix 7) and in the different groups determined according to HRD status.[19]

The results for the HRD and HRP groups, including the HRD subgroups defined according to *BRCA* mutation status, are shown in Table 5. No statistical comparison was provided for the median difference in PFS between niraparib and placebo, and there was no direct comparison between the different HRD status groups.

Table 5: Progression-Free Survival by HRD Status,[a] PRIMA Study

HRD status N (niraparib/placebo)	Disease progression or death, n (%)	Disease progression or death, HR (95% CI)	Median PFS, mo (95% CI)	Median PFS difference, mo
HRD N = 373 (247/126)	Niraparib: 81 (32.8) Placebo: 73 (57.9)	0.43 (0.31–0.59) *P* < .001	Niraparib: 21.9 (NR) Placebo: 10.4 (NR)	11.5
HRD, *BRCA* mutation N = 223 (152/71)	Niraparib: 49 (32.2) Placebo: 40 (56.3)	0.40 (0.27–0.62) *P* < .001	Niraparib: 22.1 (19.3–NE) Placebo: 10.9 (8.0–19.4)	11.2
HRD, *BRCA* wild type N = 150 (95/55)	Niraparib: 32 (33.7) Placebo: 33 (60.0)	0.50 (0.31–0.83) *P* = .006	Niraparib: 19.6 (13.6–NE) Placebo: 8.2 (6.7–16.8)	11.4
HRP N = 249 (169/80)	Niraparib: 111 (65.7) Placebo: 56 (70.0)	0.68 (0.49–0.94) *P* = .02	Niraparib: 8.1 (5.7–9.4) Placebo: 5.4 (4.0–7.3)	2.7

Abbreviations: CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; HRP, homologous recombination proficiency; NE, not estimable; NR, not reported; PFS, progression-free survival.

[a] HRD and *BRCA* mutation were determined using MyChoice CDx.

Source: González-Martín et al.[19]

The GRADE quality of the evidence was considered high based on the hazard ratio of disease progression or death in the HRD and HRP groups, and for the *BRCA* mutation and *BRCA* wild type HRD subgroups (Appendix 3).

Improvement in PFS with niraparib compared with placebo was also observed in patients with a poor prognosis. For example, improvement was observed among patients who received neoadjuvant chemotherapy, or those with partial response to platinum-based chemotherapy based on prespecified

subgroup analyses,[19] regardless of the timing of debulking surgery and the presence or absence of residual disease based on post hoc analyses (Appendix 7).[75] These results were not analyzed according to HRD status.

NOVA STUDY (RECURRENT OVARIAN CANCER)

PFS was defined as the time from randomization to the earliest date of disease progression or death from any cause.[33] Niraparib improved PFS compared to placebo in the overall population of both cohorts (g*BRCA* and non-g*BRCA*), and in the different groups of the non-g*BRCA* cohort defined according to HRD status (Table 6).[33] No statistical comparison was reported for the median difference in PFS between niraparib and placebo, and there was no direct comparison between the HRD and HRP groups.

Table 6: Progression-Free Survival by HRD Status,[a] NOVA Study

HRD status N (niraparib/placebo)	Disease progression or death, HR (95% CI)[b]	Median PFS, mo[c]	Median PFS difference, mo
g*BRCA,* overall N = 203 (138/65)	0.27 (0.17–0.41) *P* < .001	Niraparib: 21.0 Placebo: 5.5	15.5
Non-g*BRCA*, overall N = 350 (234/116)	0.45 (0.34–0.61) *P* < .001	Niraparib: 9.3 Placebo: 3.9	5.4
Non-g*BRCA*, HRD, overall N = 162 (106/56)	0.38 (0.24–0.59) *P* < .001	Niraparib: 12.9 Placebo: 3.8	9.1
Non-g*BRCA*, HRD, s*BRCA* mutation N = 47 (35/12)	0.27 (0.08–0.90) *P* = .02	Niraparib: 20.9 Placebo: 11.0	9.9
Non-g*BRCA*, HRD, *BRCA* wild type N = 115 (71/44)	0.38 (0.23–0.63) *P* < .001	Niraparib: 9.3 Placebo: 3.7	5.6
Non-g*BRCA*, HRP N = 134 (92/42)	0.58 (0.36–0.92) *P* = .02	Niraparib: 6.9 Placebo: 3.8	3.1

Abbreviations: CI, confidence interval; g*BRCA*, germline *BRCA*; HR, hazard ratio; HRD, homologous recombination deficiency; HRP, homologous recombination proficiency; PFS, progression-free survival; s*BRCA*, somatic *BRCA*.

[a] HRD and *BRCA* mutation were determined using MyChoice CDx.

[b] Number of events not provided by the study authors.

[c] 95% CI not provided by the study authors.

Source: Mirza et al.[33]

The GRADE quality of the evidence was considered high based on the hazard ratio of disease progression or death in the HRD group (including the somatic *BRCA* and *BRCA* wild type subgroups) and the HRP group of the non-g*BRCA* cohort (Appendix 3).

The authors reported consistent results of niraparib improving PFS in the prespecified subgroup analyses, including the subgroup analysis according to ethnicity. The results suggest a similar direction of effect for niraparib compared with placebo in patients who were white and patients of other races or ethnicities; however, the confidence intervals were wider in the latter group, possibly because the sample size was smaller.[33]

Post hoc analyses of the NOVA study reported improvement in PFS with niraparib compared to placebo, regardless of the best response to the last platinum-based chemotherapy[37] and age group (< 70 years or ≥ 70 years; Appendix 8).[72] The results were not provided according to HRD status.

Overall Survival

PRIMA STUDY (NEWLY DIAGNOSED OVARIAN CANCER)

At the time of the interim analysis, 79 (10.8%) patients had died in the overall population (Appendix 8).[19] The results in the HRD and HRP groups are shown in Table 7. Median survival estimates were not reported in the publication because the event rate was low, and the follow-up time was insufficient.[19]

Table 7: Overall Survival by HRD Status,[a] PRIMA Study

HRD status N (niraparib/placebo)	Overall survival, 24-month Kaplan–Meier estimate	Death, HR (95% CI)
HRD	Niraparib: 91%	0.61 (0.27–1.39)
N = 373 (247/126)	Placebo: 85%	
HRP	Niraparib: 81%	0.51 (0.27–0.97)
N = 249 (169/80)	Placebo: 59%	

Abbreviations: CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; HRP, homologous recombination proficiency.

[a] HRD and *BRCA* mutation were determined using MyChoice CDx.

Source: González-Martín et al.[19]

According to the authors, the preliminary results of the interim analysis suggested that niraparib may improve overall survival compared with placebo, but it was too early to assess the outcome given the low number of events observed up to that point.[19]

The GRADE quality of the evidence was considered low for the HRD and HRP groups, given the low number of events and insufficient follow-up time (Appendix 3).

NOVA STUDY (RECURRENT OVARIAN CANCER)

At the time of the analysis, 60 (16.1%) patients in the niraparib group and 35 (19.3%) in the placebo group had died, but the authors stated that it was too early to evaluate the effect of niraparib on overall survival.[33] The publication did not report results separately for the g*BRCA* and non-g*BRCA* cohorts, or by HRD status.

Chemotherapy-Free Interval

PRIMA STUDY (NEWLY DIAGNOSED OVARIAN CANCER)

This outcome was not evaluated in the PRIMA study.

NOVA STUDY (RECURRENT OVARIAN CANCER)

Chemotherapy-free interval was defined as the time from the last platinum dose until initiation of the next chemotherapy.[33] Niraparib improved the chemotherapy-free interval compared with placebo in both the g*BRCA* and non-g*BRCA* cohorts (Appendix 8).[33] Results were not provided according to HRD status in the non-g*BRCA* cohort.

Time to Subsequent Chemotherapy

PRIMA STUDY (NEWLY DIAGNOSED OVARIAN CANCER)

Time to first subsequent chemotherapy was defined as the time from randomization to the start date of the first subsequent chemotherapy or death from any cause.[19] The results for the HRD and HRP groups are provided in Table 8, and the results in the overall population are provided in Appendix 7. The frequencies of patients requiring subsequent chemotherapy were not provided.

Table 8: Time to First Subsequent Chemotherapy by HRD Status,[a] PRIMA Study

HRD status N (niraparib/placebo)	Need for first subsequent chemotherapy, HR (95% CI)	Median time to first subsequent chemotherapy, mo (95% CI)
HRD	0.46 (0.33–0.64)	Niraparib: NE[c] (24.7–NE[b])
N = 373 (247/126)		Placebo: 13.7 (11.6–19.3)
HRP	0.64 (0.46–0.90)	Niraparib: 11.6 (9.7–14.2)
N = 249 (169/80)		Placebo: 7.9 (6.6–10.4)

Abbreviations: CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; HRP, homologous recombination proficiency; NE, not estimable.

[a] HRD and *BRCA* mutation were determined using MyChoice CDx.

[b] Could not be estimated because of an insufficient number of events.

Source: González-Martín et al.[19]

The GRADE quality of the evidence was considered low in the HRD and HRP groups, given the low number of events (Appendix 3).

NOVA STUDY (RECURRENT OVARIAN CANCER)

Time to first or second subsequent chemotherapy was defined as the time from randomization to the start date of the first or second subsequent chemotherapy, respectively.[33] Niraparib improved the time to the first subsequent chemotherapy compared with placebo in both the g*BRCA* and the non-g*BRCA* cohorts (Appendix 8).[33] Results were not provided according to HRD status in the non-g*BRCA* cohort. The authors stated that it was too early to analyze the results for time to second subsequent therapy.

PFS on the Next Chemotherapy Following Study Treatment (PFS 2)

PRIMA STUDY (NEWLY DIAGNOSED OVARIAN CANCER)

PFS 2 was defined as the time from randomization to the earlier date of assessment of progression at the next chemotherapy following study treatment or death from any cause.[19] Median PFS 2 could not be calculated because of the few events observed and the insufficient follow-up time.[19] The hazard ratio for progression to the next chemotherapy or death from any cause was 0.84 (95% CI 0.49–1.45) in the HRD group and 0.56 (95% CI 0.34–0.91) in the HRP group.[19]

The GRADE quality of the evidence was considered low for the HRD and HRP groups, given the low number of events and insufficient follow-up time (Appendix 3).

NOVA STUDY (RECURRENT OVARIAN CANCER)

PFS 2 was defined as the time from randomization to assessment of progression at the next chemotherapy following study treatment, or death by any cause. It encompassed the time to the second

subsequent chemotherapy if the date of the second progression was unknown.[33] According to the study authors, based on preliminary data, niraparib improved PFS 2 compared with placebo in both the g*BRCA* and non-g*BRCA* cohorts (Appendix 8).[33] Results were not provided according to HRD status in the non-g*BRCA* cohort.

Quality of Life

Quality of life was reported according to the FOSI and EQ-5D-5L instruments (descriptions are provided in Appendix 5).

PRIMA STUDY (NEWLY DIAGNOSED OVARIAN CANCER)

The authors of the PRIMA study reported that there were no differences in quality-of-life scores between the niraparib and placebo groups in the overall population as assessed using the FOSI instrument (actual scores not provided).[19] Results were not provided according to HRD status.

NOVA STUDY (RECURRENT OVARIAN CANCER)

The main publication of the NOVA study reported that quality of life was similar in the niraparib group compared with placebo in the overall g*BRCA* and non-g*BRCA* cohorts, assessed using the FOSI and EQ-5D-5L instruments (Appendix 8).[33] However, results were not provided according to HRD status in the non-g*BRCA* cohort.

A separate publication of the NOVA study reported that the baseline scores for these instruments were similar between the niraparib and placebo groups in both cohorts, and that changes from baseline during maintenance therapy were minimal and similar between the two groups, as were post-progression scores.[74] The authors also observed that hematologic toxicity did not have a significant negative effect on quality of life (FOSI), nor was it significantly associated with disutility in the EQ-5D-5L utility analysis or in the EQ visual analogue scale (EQ-VAS) score.[74]

In the HRD group of the non-g*BRCA* cohort, the adjusted mean FOSI and EQ-5D-5L scores were similar between the niraparib and placebo groups, and the standard error of the mean shown in a figure appeared to overlap between the two groups (Appendix 8).[74] For these reasons, the GRADE quality of the evidence was considered low for the HRD group (Appendix 3).

The results of a post hoc analysis of the NOVA study suggest that having a partial or complete response to the last platinum-based chemotherapy did not affect patients' quality of life.[37]

Safety

Adverse-event severity was classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4.03 [PRIMA trial], v4.02 [NOVA trial]).[79] Adverse events were graded from 1 (mild, asymptomatic, or mild symptoms) to 5 (death related to adverse event) and classified as serious or non-serious (definitions in Appendix 5). The studies reported the frequencies of overall adverse events, adverse events of grade 3 or higher, and serious adverse events.

A treatment-emergent adverse event was defined in the PRIMA study as any new adverse event that began, or any pre-existing condition that worsened in severity, after at least one dose of the study treatment had been administered.[19] In the NOVA study, treatment-emergent adverse events had to have occurred after the start of treatment and up to 30 days after the last dose of the study treatment.[73]

Safety results were reported for the overall population in the PRIMA and NOVA studies, but not according to HRD status.

PRIMA STUDY (NEWLY DIAGNOSED OVARIAN CANCER)

Almost all patients in the niraparib group experienced a treatment-related adverse event of any grade (n = 466, 96.3%); 168 (68.9%) patients in the placebo group experienced a treatment-related adverse event of any grade. Treatment-related adverse events of grade 3 or higher were reported in 316 (65.3%) patients in the niraparib group and 16 (6.6%) patients in the placebo group.[19] Serious treatment-related adverse events occurred in 118 (24.4%) patients in the niraparib group and 6 (2.5%) in the placebo group.[19]

The most common adverse events reported in the niraparib group included anemia, nausea, thrombocytopenia, and constipation, among others.[19] The most commonly reported adverse events of grade 3 or higher in the niraparib group were anemia (31.0% vs. 1.6% in the niraparib and placebo groups, respectively), thrombocytopenia (28.7% vs. 0.4%, respectively), platelet count decrease (13.0% vs. 0.0%, respectively), and neutropenia (12.8% vs. 1.2%, respectively).[19] There was one (0.3%) report of myelodysplastic syndrome in the niraparib group but none in the placebo group.[19]

The frequency of adverse events improved in the niraparib group after the incorporation of the lower starting dose amendment in patients with a baseline body weight of less than 77 kg or a platelet count of less than 150,000/mm^3.[19] For instance, 114 of 315 (36.2%) patients in the niraparib group experienced grade 3 or higher treatment-emergent thrombocytopenia before the amendment compared to 25 of 169 (14.8%) patients after the amendment.[19] Additional information is provided in Appendix 7.

According to the authors, hematologic toxicity was managed with treatment interruptions and dose reductions.[19]

Table 9 provides information about the frequencies of adverse events that led to treatment interruption, discontinuation, dose reduction, and death.

Table 9: Adverse Events Leading to Treatment Interruption, Dose Reduction, Discontinuation, or Death, PRIMA Study

Author, year N (niraparib/placebo)	Leading to treatment interruption, n patients (%)	Leading to dose reduction, n patients (%)	Leading to treatment discontinuation, n patients (%)	Leading to death,[b] n patients (%)
González-Martín et al, 2019[19] N = 733 (487/246)	Niraparib: 385 (79.5) Placebo: 44 (18.0)	Niraparib: 343 (70.9) Placebo: 20 (8.2)	Niraparib: 58[a] (12.0) Placebo: 6 (2.5)	Niraparib: 2 (0.4) Placebo: 1 (0.4)

[a] In the niraparib group, the most common adverse events that led to discontinuation were hematologic: thrombocytopenia (n = 21), neutropenia (n = 9), anemia (n = 9), and leukopenia (n = 10). None of these led to treatment discontinuation in the placebo group.[19]

[b] None during treatment.

NOVA STUDY (RECURRENT OVARIAN CANCER)

Similar to the PRIMA study, almost all patients in the niraparib group (358, 97.5%) and 127 (70.9%) patients in the placebo group experienced a treatment-emergent, related adverse event of any grade.[33] Grade 3 or higher treatment-emergent, related adverse events were reported in 237 (64.6%) patients in

the niraparib group and 8 (4.5%) in the placebo group.[33] Serious treatment-emergent, related adverse events occurred in 62 (16.9%) patients in the niraparib group and 2 (1.1%) in the placebo group.[33]

The most common adverse events reported in the niraparib group included nausea, thrombocytopenia, fatigue, anemia, and constipation, among others. The most commonly reported events of grade 3 or higher in the niraparib group included thrombocytopenia (33.8% vs. 0.6% in the niraparib and placebo groups, respectively), anemia (25.3% vs. 0.0%, respectively), and neutropenia (19.6% vs. 1.7%, respectively).[33] Additional information is provided in Appendix 8.

According to the authors, most hematologic laboratory abnormalities occurred within the first three treatment cycles. Thereafter, the occurrence of grade 3 or 4 thrombocytopenia, neutropenia, and fatigue was infrequent after dose adjustment.[33] The authors also stated that treatment-related hematologic toxicity resulted in dose modifications or delays but did not result in an increase in long-term mortality or morbidity.[33]

Myelodysplastic syndrome was reported in 5 (1.4%) patients in the niraparib group.[33] In the placebo group, there was 1 (0.6%) report of myelodysplastic syndrome and 1 (0.6%) report of acute myeloid leukemia.[33]

There were no deaths due to treatment-emergent adverse events during the NOVA study.[33] However, during the follow-up period, 1 (0.3%) patient in the niraparib group and 2 (1.1%) in the placebo group died from myelodysplastic syndrome or acute myeloid leukemia, of which, one from each group were considered treatment-related by the investigator.[33]

Post hoc analyses found that having a partial or complete response to the last platinum-based chemotherapy and age (< 70 and ≥ 70 years) generally did not affect the occurrence of adverse events of grade 3 or higher.[37,72]

Information about treatment interruptions, dose reductions, and treatment discontinuations are provided in Table 10.

Table 10: Treatment-Emergent Adverse Events Leading to Treatment Interruption, Dose Reduction, Discontinuation, or Death, NOVA Study

Author, year N (niraparib/placebo)	Leading to treatment interruption, n patients (%)	Leading to dose reduction, n patients (%)	Leading to treatment discontinuation, n patients (%)
Mirza et al, 2016[33]	Niraparib: 253 (68.9)	Niraparib: 244 (66.5)	Niraparib: 54 (14.7)
N = 546 (367/179)	Placebo: 9 (5.0)	Placebo: 26 (14.5)	Placebo: 4 (2.2)

Long-Term Safety Follow-Up (NOVA Study)

The results of a long-term safety follow-up of the NOVA study performed when approximately 20% of patients had received niraparib for at least 2 years found that treatment-emergent adverse events tended to occur early in the course of the study and were managed by dose modification (Appendix 8).[73]

Similarly, there was a trend toward dose reductions and interruptions to occur early in the study. In month 1, 34% of patients in the niraparib group required a dose reduction, 27% in month 2, and 20%

in month 3. A similar trend was reported for dose interruptions.[73] Treatment discontinuations due to treatment-emergent adverse events occurred in less than 5% of patients in the first month and remained low throughout the follow-up.[73]

Ongoing Studies

We are not aware of the any relevant ongoing studies.

Discussion

Our review evaluated the use of HRD testing to inform patient decisions about the use of niraparib maintenance therapy in patients with high-grade epithelial ovarian cancer. The goal of maintenance therapy is to prevent cancer recurrence for as long as possible after chemotherapy,[29] thus prolonging the time between chemotherapy treatments[37] and extending progression-free survival.

We identified two RCTs, PRIMA and NOVA, that compared the efficacy and safety of niraparib and placebo as maintenance therapy in patients with high-grade, epithelial, serous or endometrioid ovarian cancer (including fallopian tube and peritoneal cancer) who had responded to prior platinum-based chemotherapy.[19,33] The PRIMA study included patients with newly diagnosed ovarian cancer at high risk for relapse.[19] The NOVA study included patients with recurrent disease who were considered platinum-sensitive to the penultimate platinum-based chemotherapy before study enrolment.[33]

Both studies reported efficacy results according to HRD status, which was determined using MyChoice CDx,[19,33] but they did not compare results between the HRD and HRP groups. The results of both studies showed that niraparib maintenance therapy improved PFS not only in the overall population, but also in the HRD and HRP groups.[19,33] Therefore, the studies did not provide evidence for the ability of HRD testing to distinguish between those who responded to treatment and those who did not (i.e., clinical validity).

According to the authors of the PRIMA study, although preliminary secondary analyses results suggested an improvement in overall survival with niraparib compared with placebo, it was too early to assess this outcome because of the low number of events that had occurred at the time of analysis.[19] The NOVA study publication did not report the results of secondary outcomes according to HRD status.[33]

Treatment-related adverse events of grade 3 or higher occurred in approximately 65% of the patients in the niraparib group (vs. 4.6%–6.6% in the placebo group); the most common events in the niraparib group included hematologic events (anemia, thrombocytopenia, neutropenia), nausea, and fatigue.[19,33] The authors of both studies stated that treatment-related hematologic adverse events were often managed with dose interruptions and reductions. In the PRIMA study, the frequency of adverse events was lower in the niraparib group after the incorporation of a protocol amendment allowing patients weighing less than 77 kg or with a platelet count of less than 150,000/mm^3 to start treatment with a lower dose.[19] The frequencies of adverse events were not reported according to HRD status, and it is not clear whether HRD status affects the risk of adverse events; therefore, we could not make any conclusions about the safety of niraparib versus placebo by HRD status.

According to the authors of the NOVA study, "although *BRCA* mutation status and HRD status may provide important information regarding the magnitude of the potential treatment benefit in a given patient population, these biomarkers do not appear to be sufficiently precise to predict which individual

patients who meet our definition of platinum sensitivity will and will not derive benefit from niraparib treatment."[33]

ASCO did not recommend the use of currently available HRD tests because they do not provide sufficient differentiation in PARP inhibitor treatment response in ovarian cancer[62] and other organizations pointed out the current differences in HRD definitions and the lack of standardization in parameters and thresholds used across the different types of HRD tests.[49] The Canadian Agency for Drugs and Technologies in Health (CADTH) pan-Canadian Oncology Drug Review expressed concerns about the clinical validity of currently available HRD tests in patients with ovarian cancer and stated that the test alone should not be used to determine treatment decisions.[42,43]

Incorrect determination of HRD status may lead patients to make decisions about undergoing or forgoing maintenance therapy based on erroneous information.

According to the 2022 Pan-Canadian Consensus on first-line maintenance therapy in patients with high-grade ovarian cancer,[15] although HRD status should not be the only factor considered when deciding on the use of niraparib maintenance therapy, MyChoice CDx provides information about the estimated magnitude of benefit of niraparib maintenance therapy, which may help patients make informed treatment decisions.

Strengths and Limitations

The publications we identified included data obtained when the studies were still ongoing; complete study follow-up data were not available. As well, the confidence intervals for the median PFS estimates were not reported for some subgroups, and confidence intervals for the median PFS difference between niraparib and placebo were not available; these provide information about the possible range of the estimated benefit, which is also important for patient decision-making. It is also too early to assess the impact of niraparib on overall survival.

We identified no studies that assessed the clinical utility of HRD testing by comparing it with no HRD testing or with *BRCA* testing alone in this patient population. Therefore, we cannot comment on how HRD testing would directly affect changes in treatment management, patient decisions, or clinical outcomes.

Although our systematic review sought to include studies on any type of HRD test, the studies we identified included only one of these tests: MyChoice CDx. As a consequence, we cannot discuss the use of other HRD tests to inform patient decisions about the use of niraparib maintenance therapy in the population of interest. As well, the results reported may not be generalizable to other HRD tests, because the parameters used to determine HRD may differ across different tests.

Conclusions

Our systematic review did not identify any studies that assessed the clinical utility of HRD testing to inform patient decisions about the use of niraparib maintenance therapy in patients with high-grade epithelial ovarian cancer.

We identified two RCTs that evaluated the efficacy and safety of maintenance therapy with niraparib compared with placebo in patients with high-grade epithelial ovarian cancer: one in newly diagnosed

cases and one in recurrent disease.[19,33] These studies, which form the basis for our conclusions, reported efficacy results according to HRD status determined using MyChoice CDx.

- In adult patients with newly diagnosed, advanced high-grade serous or endometrioid epithelial ovarian, fallopian tube, or peritoneal cancer who are in complete or partial response to platinum-based chemotherapy (based on an RCT that specifically included patients at high risk of disease progression), maintenance therapy with niraparib improves PFS compared with no maintenance therapy in patients with HRD regardless of the presence of a *BRCA* mutation, and in those with HRP (GRADE: High)
    - The study authors considered that it was premature to draw conclusions about overall survival, time to subsequent chemotherapy, and PFS on the next chemotherapy based on the results of the interim analyses, given the low number of events observed
- In adult patients with platinum-sensitive, recurrent, high-grade serous ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy (based on an RCT that included predominantly stage III and IV disease), maintenance therapy with niraparib:
    - Improves PFS compared with no maintenance therapy in patients with HRD regardless of the presence of a somatic *BRCA* mutation, and in those with HRP (GRADE: High)
    - May result in no difference in quality of life (as measured using the FOSI and EQ-5D-5L instruments) compared with no maintenance therapy in patients with HRD (GRADE: Low due to imprecision)

The studies in both populations showed a higher frequency of adverse events with niraparib compared with no treatment, overall and grade 3 or higher. However, results according to HRD status were not provided. It is not clear if HRD status affects the risk of adverse events.

Only one type of HRD test, MyChoice CDx, was used to determine HRD status in the studies that were eligible for this review, and it is unclear whether their results can be generalized to other HRD tests, because different tests may use different parameters to determine HRD status.

As well, because we identified no studies on the clinical utility of HRD testing, we cannot comment on how HRD testing would directly affect changes in treatment management, patient decisions, or clinical outcomes.

Economic Evidence

Research Question

In patients with newly diagnosed or recurrent high-grade serous or endometrioid epithelial ovarian, fallopian tube, or peritoneal cancer (referred to as ovarian cancer) who are in complete or partial response to platinum-based chemotherapy, what is the cost-effectiveness of homologous recombination deficiency (HRD) testing to inform patient decisions about the use of niraparib maintenance therapy compared with usual care (i.e., no HRD testing)?

Methods

Economic Literature Search

We performed an economic literature search on May 25, 2022, to retrieve studies published from database inception until the search date. To retrieve relevant studies, we developed a search using the clinical search strategy with an economic and costing filter applied.

We created database auto-alerts in MEDLINE and Embase and monitored them until January 30, 2023. We also performed a targeted grey literature search following a standard list of websites developed internally, which includes the International HTA Database and the Tufts Cost-Effectiveness Analysis Registry. See Clinical Literature Search, above, for further details on methods used. See Appendix 2 for our literature search strategies, including all search terms.

Eligibility Criteria

STUDIES

Inclusion Criteria

- English-language full-text publications
- Cost–benefit analyses, cost-effectiveness analyses, cost-minimization analyses, or cost–utility analyses

Exclusion Criteria

- Animal and in vitro studies
- Noncomparative observational studies, editorials, commentaries, case reports, conferences, abstracts, letters

PARTICIPANTS

Inclusion Criterion

- People with newly diagnosed or recurrent high-grade serous or endometrioid epithelial ovarian, fallopian tube, or peritoneal cancer, who are sensitive to platinum-based chemotherapy, and who are candidates for niraparib maintenance therapy

Exclusion Criterion

- Patients with ovarian or other cancers who are candidates for maintenance therapy with other poly-adenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitors or other drugs

INTERVENTIONS

Inclusion Criterion

- Maintenance therapy with niraparib as monotherapy based on studies in which HRD status and clinical outcomes were measured. Any type of HRD test was included (e.g., testing for gene mutations related to the homologous recombination repair pathway, genomic scar tests, mutational signature tests, or functional tests)

Exclusion Criteria

- Maintenance therapy with other PARP inhibitors or other drugs, or any chemotherapy
- Studies in which HRD testing was not performed or in which *BRCA* testing alone was performed

COMPARATORS

Inclusion Criterion

- Usual care without HRD testing to inform niraparib maintenance therapy

Exclusion Criteria

- Any maintenance therapy or any chemotherapy
- Studies in which *BRCA* testing alone was performed

OUTCOME MEASURES

- Costs
- Health outcomes (e.g., quality-adjusted life-years [QALYs])
- Incremental costs
- Incremental effectiveness
- Incremental cost-effectiveness ratios (ICERs)

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[80] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion. The reviewer also examined reference lists and consulted content experts for any additional relevant studies not identified through the search.

Data Extraction

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

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

Study Applicability and Limitations

We determined the usefulness of each identified study for decision-making by applying a modified quality appraisal checklist for economic evaluations originally developed by the National Institute for Health and Care Excellence (NICE) in the United Kingdom to inform the development of NICE's clinical guidelines.[81] We modified the wording of the questions to remove references to guidelines and to make it specific to Ontario. Next, we separated the checklist into two sections. In the first section, we assessed the applicability of each study to the research question (directly, partially, or not applicable). In the second section, we assessed the limitations (minor, potentially serious, or very serious) of the studies.

Results

Economic Literature Search

The database search of the economic literature yielded 170 citations published from database inception to May 25, 2022, including grey literature searches and after duplicates were removed. We identified 12 additional eligible records from other sources, including database alerts (monitored until January 30, 2023). In total, we identified five studies (all cost-effectiveness analyses) that met our inclusion criteria. Figure 2 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the economic literature search.

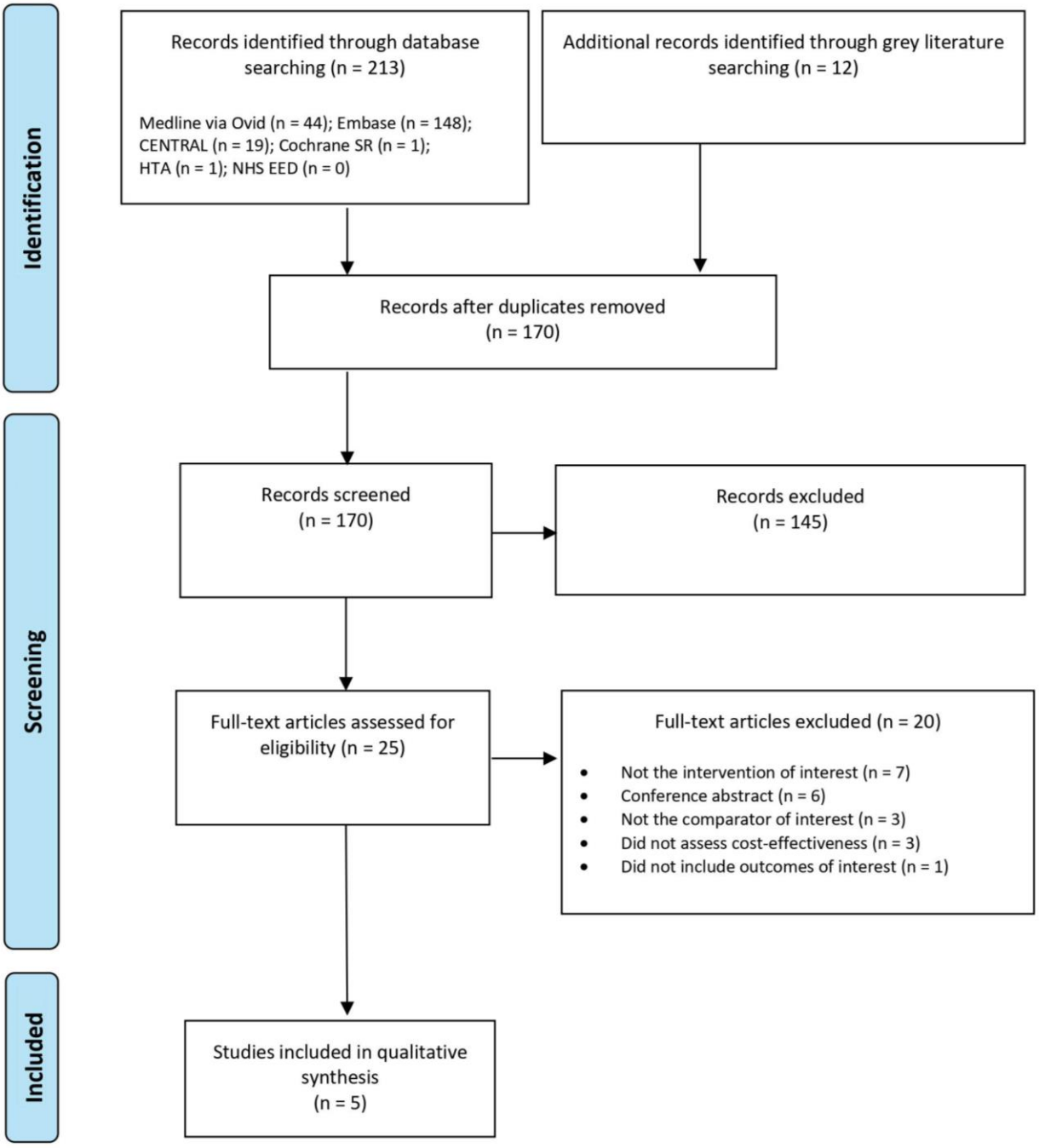


Figure 2: PRISMA Flow Diagram – Economic Search Strategy

PRISMA flow diagram showing the economic search strategy. The database search of the economic literature yielded 213 citations published between database inception and May 25, 2022. We identified 12 additional eligible reports from other sources. After removing duplicates, we screened the abstracts of 170 studies and excluded 145. We assessed the full texts of 25 articles and excluded a further 20. In the end, we included five articles in the qualitative synthesis.

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

Source: Adapted from Page et al.[76]

Overview of Included Economic Studies

We identified a total of five studies that met our inclusion criteria (Table 11). Of the five included studies, only one[82] directly evaluated the cost-effectiveness of HRD testing to inform niraparib maintenance therapy decisions compared to no HRD testing (i.e., PARP inhibitor treatment for all patients). Another study[83] evaluated the cost-effectiveness of germline *BRCA* (g*BRCA*) mutation testing plus HRD testing compared to three other strategies: g*BRCA* mutation testing alone, no testing (treat all patients), or no treatment (observation). Instead of evaluating the cost-effectiveness of HRD testing, the remaining three studies evaluated the cost-effectiveness of niraparib maintenance therapy in patients with different HRD statuses (i.e., the overall population, patients with HRD, or patients with homologous recombination proficiency [HRP]), which indirectly reflected the cost-effectiveness of HRD testing.[84-86]

The patient populations varied, including people with newly diagnosed ovarian cancer,[82,84,85] people with recurrent ovarian cancer,[83] or both.[86] Among the five studies, two considered only niraparib for maintenance therapy;[83,84] the other three also considered other maintenance therapies, such as bevacizumab,[85] olaparib,[82,85,86] and veliparib.[85] The authors of the studies obtained clinical data from the PRIMA trial (niraparib in patients with newly diagnosed ovarian cancer),[19] or the ENGOT-OV16/NOVA trial (niraparib in patients with recurrent ovarian cancer).[33] Both trials used MyChoice CDx (Myriad Genetics) to determine HRD status.[19,33]

All five of the included studies were model-based cost-effectiveness studies conducted in a United States setting and reported costs in US dollars. Details of model structure, time horizon, and study perspective were not reported for some studies.

Table 11: Results of Economic Literature Review – Summary

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
Barrington et al, 2020,[84] United States	Cost-effectiveness analysis Decision analysis model Third-party payer perspective Time horizon NR Discount rate NR	Five groups of patients with ovarian cancer: • Overall: all patients with newly diagnosed ovarian cancer • HRD: patients with HRD • *BRCA*: patients with *BRCA* mutations • *BRCA* wild type HRD: patients with HRD and no *BRCA* mutations • HRP: patients with HRP	*Intervention* Niraparib maintenance therapy after chemotherapy *Comparator* Observation	*QALYs* NR *Projected overall survival per patient, months* Overall Observation: 24.6 Niraparib: 41.4 HRD Observation: 31.2 Niraparib: 65.7 *BRCA* Observation: 32.7 Niraparib: 66.3 *BRCA* wild type HRD Observation: 24.6 Niraparib: 58.8 HRP Observation: 16.2 Niraparib: 24.3	2019 USD *Total costs per cohort (n ≈ 16,000)* Overall Observation: $5.8 billion Niraparib: $20.5 billion HRD Observation: $3.0 billion Niraparib: $14.8 billion *BRCA* Observation: $1.6 billion Niraparib: $8.2 billion *BRCA* wild type HRD Observation: $1.3 billion Niraparib: $6.1 billion HRP Observation: $2.8 billion Niraparib: $7.1 billion Costs included chemotherapy; niraparib; office visit; CA125 test; CBC; CT of chest, abdomen, and pelvis; HRD testing; germline panel testing; inpatient surgical care; blood product transfusion	*ICERs (per QALY saved)* Overall: $72,829 USD HRD group: $56,329 USD *BRCA*: $58,348 USD *BRCA* wild type HRD: $50,914 USD HRP: $88,741 USD *Sensitivity analysis* Probabilistic sensitivity analysis not conducted Multiple one-way sensitivity analyses conducted; ICER for niraparib maintenance was sensitive to drug cost

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
Dottino et al, 2019,[83] United States	Cost-effectiveness analysis Decision analysis model (did not specify whether it was a decision tree or Markov model) Societal perspective 21-month horizon 0% discount rate (i.e., not discounted)	Patients with platinum-sensitive recurrent ovarian cancer	*Interventions* • g*BRCA* mutation testing and selective treatment of carriers (g*BRCA* only) • g*BRCA* and tumour HRD testing and selective treatment of *BRCA* carriers or those with tumour HRD (g*BRCA* and HRD only) • Treat all with niraparib to progression (treat all) • Observation *Comparator* Sequential analysis, next less effective strategy	*PFS, months* Observation All patients: 4.22 g*BRCA* mutation: 5.5 g*BRCA* wild type: 3.9 HRD testing, positive: 3.8 HRD testing, negative: 3.8 Niraparib maintenance All patients: 11.64 g*BRCA* mutation: 21 g*BRCA* wild type: 9.3 HRD testing, positive: 12.9 HRD testing, negative: 6.9	2016/2017 USD *Cost per patient* Observation: $827 *gBRCA* testing/selective treatment: $46,157 *gBRCA* testing + HRD testing/selective treatment: $109,368 Treat all: $169,127 Assuming 5,507 patients with platinum-sensitive recurrent ovarian cancer per year Costs included niraparib, outpatient visits, estimated cost of adverse hematologic event, CT of abdomen, CBC, HRD testing, g*BRCA* testing	*ICERs (per PF-QALY) vs. the next less effective strategy* *gBRCA* testing/selective treatment vs. observation: $243,092 USD *gBRCA* testing + HRD testing/ selective treatment vs. g*BRCA* testing/selective treatment: $269,883 USD Treat all vs. *gBRCA* testing + HRD testing/selective treatment: $2.2 million USD Maintenance therapy guided by biomarker testing, based on *gBRCA* mutation or HRD status, had more favourable ICERs compared to treatment for all patients *Sensitivity analysis* Probabilistic sensitivity analysis not conducted Multiple one-way sensitivity analyses conducted; all PARP inhibitor maintenance strategies become more cost-effective compared to observation alone as the probability of *gBRCA* mutation increased Reducing the cost of HRD testing had no effect on cost-effectiveness rankings

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
Gonzalez et al, 2020,[82] United States	Cost-effectiveness analysis Markov decision models Third-party payer perspective Time horizons: 44 months, 28 months, 45 months (three models, different horizons) 3% discount rate	Women with newly diagnosed advanced-stage ovarian cancer who had completed primary treatment with surgery and chemotherapy	*Intervention* HRD testing (PARP inhibitor maintenance treatment for patients with g*BRCA* mutations or HRD) *Comparator* No HRD testing (PARP inhibitor maintenance treatment for all)	NR	2018 USD *Total cost per patient* No HRD testing (PARP inhibitor for all, niraparib): $166,269 HRD testing (PARP inhibitor for patients with g*BRCA* mutations or HRD, niraparib): $98,188 Costs included PARP inhibitor, HRD testing, costs associated with grade 3–4 hematologic toxicities	*ICERs (per PF-QALY gained)* PARP inhibitor for all vs. biomarker-directed maintenance: $593,250 USD PARP inhibitor for all was more costly and provided greater PFS benefit than a biomarker-directed strategy for each of the three models *Sensitivity analysis* Probabilistic sensitivity analysis conducted to assign confidence intervals surrounding model outcomes In one-way sensitivity analyses, the ICER was most sensitive to variation in the PFS hazard ratio of the biomarker-negative cohort and the cost of PARP inhibitor therapy In two-way sensitivity analysis, PARP inhibitors for all was more likely to be cost-effective if the PFS hazard ratio for the biomarker-negative cohort was < 0.5 and the cost of niraparib was < $4,295 USD/month

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
Penn et al, 2020,[85] United States	Cost-effectiveness analysis Decision tree US health care perspective 24-month time horizon 0% discount rate (i.e., not discounted)	Women with newly diagnosed advanced epithelial ovarian cancer: patients with *BRCA* mutations; patients with *BRCA* wild type HRD; patients with HRP	*Intervention* Niraparib *Comparator* No maintenance (observation)	*Incremental PF-LY saved (niraparib vs. no maintenance)* *BRCA*: 0.46 *BRCA* wild type HRD: 0.46 HRP: 0.05	USD, year unspecified *Total cost per patient* No maintenance: $3,051 *BRCA*: niraparib $492,226 *BRCA* wild type HRD: niraparib $492,226 HRP: niraparib $492,226 Costs included those associated with drug acquisition, administration, monitoring, and adverse events	*ICER of niraparib vs. no treatment (per PF-LY saved)* *BRCA*: $1,069,627 USD *BRCA* wild type HRD: $1,072,754 USD HRP: $10,870,576 USD *Sensitivity analysis* Probabilistic sensitivity analysis conducted For the *BRCA* group, olaparib remained the most cost-effective option For the *BRCA* wild type HRD group, olaparib–bevacizumab remained the most cost-effective option For the HRP group, bevacizumab remained the most cost-effective option Multiple one-way sensitivity analyses were conducted; in all cases, changes to the monthly price of niraparib most affected the ICER ICERs for all treatment plans for each reference case were least sensitive to fluctuations in cost associated with adverse events

Author, year, country	Analytic technique, study design, perspective, time horizon	Population	Intervention(s) and comparator(s)	Results		
				Health outcomes	Costs	Cost-effectiveness
Rose et al, 2021,[86] United States	Cost-effectiveness analysis Decision analysis model Perspective NR Time horizon NR Discount rate NR	Patients with platinum-sensitive recurrent epithelial ovarian cancer	*Intervention* Secondary maintenance PARP inhibitor therapy *Comparator* Primary maintenance PARP inhibitor therapy	*PFS (months)* Primary treatment *BRCA* mutation Niraparib: 22.1 Placebo: 10.9 HRD Niraparib: 19.6 Placebo: 8.2 HRP Niraparib: 8.1 Placebo: 5.4 Secondary treatment *RCA1/2* mutation Niraparib: 21.0 Placebo: 5.5 HRD Niraparib: 12.9 Placebo: 3.8 HRP Niraparib: 9.3 Placebo: 3.9	2017 USD *Total cost of primary or secondary PARP inhibitor maintenance per patient* *BRCA* mutation, olaparib Primary treatment: $512,857 Secondary treatment: $197,473 *BRCA* mutation, niraparib Primary treatment: $254,700 Secondary treatment: $242,590 HRD, niraparib Primary treatment: $225,780 Secondary treatment: $149,170 HRP, niraparib Primary treatment: $107,490 Secondary treatment: $93,540 Costs included those associated with drug acquisition, physician visits, additional lab work, and imaging	Up to 29% of patients with a *BRCA* mutation may be overtreated with primary PARP inhibitor maintenance, which is substantially more costly Cost-effectiveness not reported because of a current study suggesting that the incremental cost of earlier maintenance therapy did not result in improved survival *Sensitivity analysis* Not conducted

Abbreviations: CA125, cancer antigen 125; CBC, complete blood count; CT, computed tomography; g*BRCA*, germline *BRCA*; HRD, homologous recombination deficiency; HRP, homologous recombination proficiency; ICER, incremental cost-effectiveness ratio; NR, not reported; PARP, poly-adenosine diphosphate (ADP)-ribose polymerase; PF-LY, progression-free life-year; PF-QALY, progression-free quality-adjusted life-year; PFS, progression-free survival; QALY, quality-adjusted life-year.

[a] Penn et al[85] reported results on the costs and cost-effectiveness of bevacizumab and olaparib–bevacizumab. We did not include these results in the table because they were of limited applicability to our research question.

STUDIES THAT EVALUATED TESTING STRATEGIES

The study by Gonzalez et al[82] assessed the cost-effectiveness of HRD testing to inform niraparib maintenance therapy versus no HRD testing (i.e., PARP inhibitor treatment for all) in people with newly diagnosed advanced-stage ovarian cancer who had completed primary treatment with surgery and chemotherapy in a United States setting. The study used a modified Markov model to simulate the populations of the three PARP inhibitor clinical trials (PRIMA for niraparib, VELIA for veliparib, and PAOLA-1 for bevacizumab). Because of a lack of overall survival data from the clinical trials, the study estimated health outcomes as progression-free QALYs (which do not take disease progression into consideration) instead of QALYs (which do consider disease progression). The study found that the mean cost per patient was $166,269 USD for treatment for all and $98,188 USD for HRD testing. Mean health outcomes per patient were not reported. The estimated ICER for treatment for all versus HRD testing was $593,250 USD per progression-free QALY. The authors concluded that treatment for all was not cost-effective compared to HRD testing.

Dottino et al[83] compared four different testing and niraparib treatment strategies in patients with recurrent ovarian cancer: observation (i.e., no testing and no treatment); g*BRCA* testing and selective treatment for carriers; g*BRCA* and HRD testing and selective treatment for carriers; and treatment for all (i.e., no HRD testing). Because of a lack of overall survival data from the NOVA trial, the study estimated health outcomes as progression-free QALYs instead of QALYs. The mean costs per patient were $827 USD for observation, $46,157 USD for g*BRCA* testing only, $109,368 USD for g*BRCA* and HRD testing, and $169,127 USD for treatment for all. The ICER for g*BRCA* testing only versus observation was $243,092 per progression-free QALY; the other strategies were not cost-effective. The authors concluded that selective treatment based on g*BRCA* mutation or HRD tumour status has a more favourable cost-effectiveness ratio than a treatment-for-all strategy.

STUDIES THAT EVALUATED MAINTENANCE THERAPIES IN DIFFERENT POPULATIONS

Barrington et al[84] assessed the cost-effectiveness of niraparib maintenance therapy versus no treatment (i.e., observation) in five different patient groups: the overall study population; patients with HRD; patients with *BRCA* mutations; patients with *BRCA* wild type HRD; and patients with HRP. The model used progression-free survival (PFS) data from the PRIMA trial. Because of a lack of overall survival data, the authors assumed that the ratio between overall survival and PFS was 3 to estimate QALYs. The study reported incremental cost per QALY saved. The ICER estimates for niraparib maintenance therapy versus observation were $72,829 USD per QALY for the overall population; $56,329 USD per QALY for the HRD group; $58,348 USD per QALY for the *BRCA* group; $50,914 USD per QALY for the HRD *BRCA* wild type group; and $88,741 USD per QALY for the HRP group.[84] Based on the ICERs, the authors concluded that niraparib maintenance therapy was more cost-effective in patients with HRD and *BRCA* mutations than in the overall population.

Penn et al[85] evaluated the cost-effectiveness of five different maintenance treatments (olaparib, olaparib plus bevacizumab, bevacizumab, niraparib, and no treatment) in three different groups with newly diagnosed ovarian cancer: patients with *BRCA* mutations; patients with *BRCA* wild type HRD; and patients with HRP. Because of a lack of overall survival data, the study estimated health outcomes as progression-free life-years. The study did not consider quality of life because of a lack of health-utility data. Across all three groups, the mean cost per patient for no treatment was $3,051 USD, and the mean cost per patient for niraparib was $492,226 USD. Compared to no treatment, niraparib maintenance therapy led to 0.46 incremental progression-free life-years for the *BRCA* group and the *BRCA* wild type

HRD group, and 0.05 incremental progression-free life-years for the HRP group. The resulting ICER estimates for niraparib maintenance treatment versus no treatment were $1,069,627 USD per progression-free life-year gained for the *BRCA* group, $1,072,754 USD for the HRD *BRCA* wild type group, and $10,870,576 for the HRP group.[85]

Rose et al[86] compared primary and secondary maintenance PARP inhibitor therapies in different groups (olaparib in patients with *BRCA* mutations, niraparib in patients with *BRCA* mutations, niraparib in patients with HRD, and niraparib in patients with HRP). The authors did not report incremental cost-effectiveness results, but they did report that in those with recurrent epithelial ovarian cancer and HRD-positive tumours, the cost of primary niraparib treatment was $225,780 USD per patient, compared to $149,170 USD for secondary treatment. For those with recurrent epithelial ovarian cancer and HRP, the cost of primary niraparib treatment was $107,490 USD, compared to $93,540 USD for secondary treatment. The increase between primary and secondary niraparib treatment costs was more substantial in the HRD group.[86]

Applicability and Limitations of the Included Studies

Appendix 9 provides the results of the quality appraisal checklist for economic evaluations applied to the included studies. One study that evaluated HRD testing to inform niraparib therapy versus no HRD testing (i.e., treatment for all) was deemed partially applicable to our research question.[82]

The applicability of the included studies was limited for several reasons. First, three studies assessed the cost-effectiveness of PARP inhibitor maintenance therapy in patients with different HRD statuses, rather than the cost-effectiveness of HRD testing.[83-86] Second, all studies were conducted in a United States setting; health care resource use and costs may be different from Ontario. In addition, the testing and treatment strategies evaluated by these studies might not reflect clinical practice in Ontario. In Ontario, *BRCA* testing is currently funded in people with ovarian cancer to aid in decisions about maintenance therapy with PARP inhibitors. For people with pathogenic or likely pathogenic *BRCA* mutations, olaparib is funded as a maintenance therapy through the Exceptional Access Program.[63] Niraparib is currently being used in people with *BRCA* wild type. The included studies did not consider the potential use of HRD testing as an add-on or replacement to the *BRCA* testing. In addition, when the disease progresses, patients in the United States may receive more lines of chemotherapy than patients in Canada, or they may receive treatment with a different PARP inhibitor.[87,88]

Discussion

The economic evidence for HRD testing is still very limited. Although we included five economic studies, only one was considered partially applicable.

Three studies included HRD testing costs in their models, and all used MyChoice CDx.[82-84] Gonzalez et al[82] reported directly on the cost-effectiveness of HRD testing-informed maintenance therapy with a PARP inhibitor and found that a biomarker-directed treatment strategy was less costly and less effective, providing a smaller PFS benefit compared to PARP inhibitor treatment for all patients with newly diagnosed advanced ovarian cancer and who had completed primary treatment with surgery and chemotherapy. Two studies indirectly[83,84] assessed the cost-effectiveness of HRD testing. Barrington et al[84] compared the cost-effectiveness of niraparib maintenance therapy in patients with varying HRD and *BRCA* statuses. The analysis was in a newly diagnosed population, and the authors found that compared to observation alone, the ICER was highest for the HRP group; the ICERs for the HRD, *BRCA,*

and *BRCA* wild type HRD groups were similar. This was consistent with the understanding that patients without HRD benefit less from PARP inhibitor treatment, and it indirectly showed the utility of HRD testing. The other analysis, by Dottino et al,[83] was conducted in patients with recurrent, platinum-sensitive ovarian cancer. The authors found that biomarker-informed maintenance therapy with PARP inhibitors (based on g*BRCA* mutation or HRD status) had more favourable ICERs than treatment for all patients. However, regardless of biomarker status, PARP inhibitor therapy was not cost-effective in patients with recurrent ovarian cancer.

Across studies that conducted sensitivity analyses, ICERs were consistently sensitive to variations in the price of PARP inhibitor maintenance therapy. Notably, Dottino et al[83] reported the results of a one-way sensitivity analysis of HRD testing costs; they found that the cost of HRD testing had no effect on the cost-effectiveness of treatment strategies, but that lowering the cost of PARP inhibitor therapies might make selective treatment based on biomarker status more cost-effective. This suggested that niraparib-related costs, rather than HRD testing costs, were the driving factor behind cost-effectiveness.

There was considerable heterogeneity in methodology across the studies included in our review. First, because of a lack of overall survival data from the clinical trials, most studies considered only PFS and reported their primary cost-effectiveness outcomes as some variation of progression-free QALYs rather than QALYs. This likely resulted in underestimates of costs because patients in the disease progression state usually have higher treatment costs. Penn et al[85] did not estimate QALYs, reporting progression-free life-years instead (i.e., not quality-adjusted), pointing to variability in how quality-of-life endpoints were assessed in the trials they used for clinical inputs as their rationale. This variation in reported clinical outcomes among our included studies creates difficulty in interpreting results and presenting them consistently. Because of limited availability of information about overall survival, Barrington et al[84] used an assumed ratio of overall survival to PFS based on observed ratios from phase III ovarian cancer trials. They also assumed a constant health state utility of 0.75, but this did not reflect disease progression, which would be more likely to be seen in clinical practice. Second, only one study assessed a population with recurrent ovarian cancer,[83] one assessed a population with both newly diagnosed and recurrent cancer,[86] and three assessed populations with newly diagnosed cancer.[82,84,85] Clinical data for some of the studies assessing the newly diagnosed population came from the PRIMA trial (which evaluated niraparib),[19] and some studies used other trials, such as VELIA[41] and PAOLA,[24] which evaluated other drugs such as veliparib and bevacizumab. Although all three of the trials in newly diagnosed populations assessed patients' HRD status,[19,24,41] they did not use the same cut-offs for HRD scores. Finally, not all studies explicitly reported information about the model structure and analysis perspective used. Time horizons were not explicitly reported or were not long enough to reflect the full effects of the outcomes and costs.

Strengths and Limitations

Our analysis had several strengths. We have provided a comprehensive review of the existing relevant available economic evidence about HRD testing to inform niraparib maintenance therapy. We conducted comprehensive literature searching and screening, and we critically appraised the applicability and limitations of the included studies.

Our reporting was affected by the limitations and quality of the included studies. Only one included study directly addressed our research question. The methods used in the economic studies also varied substantially (e.g., different treatment strategies and different reported health outcomes), preventing us from assessing the results consistently. Another possible limitation is that we excluded reports on the

use of *BRCA* testing only or HRD testing for other decisions about maintenance therapy, because these were out of our scope. Our narrow scope may be biased against the application of HRD testing.

Conclusions

We conducted a review of the cost-effectiveness of HRD testing to inform niraparib maintenance therapy. In general, the included studies suggested that niraparib maintenance therapy is more cost-effective in patients with HRD than in patients with HRP or the overall population. None of the included studies were conducted in a Canadian setting. Only one study was partially applicable to our research question and directly evaluated the cost-effectiveness of HRD testing to inform niraparib maintenance therapy decisions. The remaining studies focused on the cost-effectiveness of niraparib in people with different HRD statuses. The generalizability of these findings to the Ontario setting was limited.

Primary Economic Evaluation

In our economic literature review, we found five published studies that investigated either the cost-effectiveness of homologous recombination deficiency (HRD) testing versus no HRD testing in patients with ovarian cancer, or the cost-effectiveness of niraparib maintenance therapy versus no treatment in patients with ovarian cancer and different HRD statuses.[82-86] Only one study was partially applicable to our research question,[82] but it was conducted in a United States setting and it did not evaluate health outcomes using quality-adjusted life-years (QALYs) or consider the different potential roles of HRD testing in the clinical pathway (e.g., as an add-on or replacement for *BRCA* testing, which is currently publicly funded for people with ovarian cancer in Ontario).[82] Owing to these limitations, we conducted a primary economic evaluation for Ontario.

Research Question

In patients with newly diagnosed high-grade serous or endometrioid epithelial ovarian, fallopian tube, or peritoneal cancer (referred to as ovarian cancer) who are in complete or partial response to platinum-based chemotherapy, what is the cost-effectiveness of homologous recombination deficiency (HRD) testing to inform patient decisions about the use of niraparib maintenance therapy compared with usual care (i.e., no HRD testing)?

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[89] The content of this report is based on a previously developed economic project plan.

Type of Analysis

For the reference case, we conducted a probabilistic cost–utility analysis, as recommended by the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines for economic evaluation.[90] For the effectiveness outcome we used QALYs, which consider the person's survival and their quality of life (e.g., 1 QALY represents 1 year of perfect health). A generic outcome measure such as the QALY allows decision-makers to make comparisons across different conditions and interventions. We also conducted cost-effectiveness analyses with outcomes expressed in natural units, including life-years and years of progression-free survival (PFS).

Target Population

Our target population was patients with ovarian cancer who were in complete or partial response to platinum-based chemotherapy and who were about to receive maintenance therapy. We did not conduct a primary economic evaluation in patients with recurrent cancer due to a lack of clinical data (Appendix 10).[33] We based the characteristics of the target population on the PRIMA trial,[19] which recruited patients with newly diagnosed stage III or IV ovarian cancer, according to International Federation of Gynecology and Obstetrics criteria.[91] Patients had received six to nine cycles of first-line platinum-based chemotherapy, with complete or partial response, and their average age was 62 years.

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health.

Interventions and Comparators

Our analysis compared HRD testing with usual care (i.e., no HRD testing). With usual care, all patients with newly diagnosed ovarian cancer would receive *BRCA* testing. In Ontario, people with *BRCA* mutations would be eligible for olaparib maintenance therapy, and people with *BRCA* wild type would usually receive niraparib. With HRD testing, some commercially available HRD tests (e.g., MyChoice CDx; Myriad Genetics) could provide results on both *BRCA* gene mutations and HRD status for patients with ovarian cancer.[51] Thus, in addition to supporting maintenance therapy decisions related to niraparib, HRD testing could serve as a replacement for *BRCA* testing. We examined two HRD testing strategies:

- HRD testing for all patients with newly diagnosed ovarian cancer (i.e., HRD testing as a replacement for *BRCA* testing): the test result would inform treatment decisions for both olaparib and niraparib
- HRD testing for people with *BRCA* wild type (i.e., HRD testing as an add-on to *BRCA* testing): the test result would inform treatment decisions for niraparib only

Table 12 summarizes the interventions, comparator, and outcomes evaluated in the economic model. We assumed that decisions about olaparib treatment would not be affected by HRD testing, and as a result, health outcomes and costs related to olaparib treatment would cancel out for HRD testing versus no HRD testing. Therefore, we considered only incremental costs and outcomes associated with niraparib maintenance therapy.

Table 12: Interventions and Comparators Evaluated in the Primary Economic Analysis

Intervention	Comparator	Population	Outcome
HRD testing for all HRD testing for people with *BRCA* wild type (*BRCA* testing for all, followed by HRD testing for people with *BRCA* wild type)	No HRD testing (*BRCA* testing for all)	Adults with newly diagnosed ovarian cancer	Costs QALYs PFS years Life-years

Abbreviations: HRD, homologous recombination deficiency; PFS, progression-free survival; QALY, quality-adjusted life-year.

Several tests are commercially available for determining HRD status, including MyChoice CDx[51] and FoundationOne CDx (Foundation Medicine).[54] However, not all HRD tests are equivalent; some (e.g., MyChoice CDx) can detect *BRCA* and other homologous recombination pathway gene mutations, but others may not be able to detect *BRCA* mutations (e.g., functional HRD assays).[92] Because the Clinical Evidence Review identified clinical studies that used only MyChoice CDx,[19,33] we conducted the primary economic evaluation based on the clinical utility of MyChoice CDx. Our findings may not be generalizable to other HRD tests and should be interpreted with caution.

Decisions about poly-adenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitor maintenance therapy may depend on test results and HRD (including *BRCA* gene mutation) status. We assumed that patients with HRD, expecting more benefits in PFS, would be more likely to choose to receive niraparib than patients with homologous recombination proficiency (HRP).

Time Horizon and Discounting

We used a 5-year time horizon in our reference case analysis to capture the long-term effect of HRD testing on costs and outcomes. We chose this time horizon because only short-term data were available from the clinical trial: the median follow-up time for the PRIMA trial was 13.8 months.[19] For ovarian cancer, 5-year survival is 45.0%, and survival decreases steadily over the 5 years after diagnosis.[93] However, after 5 years, survival remains relatively stable, decreasing by only 6.7% from 5 to 10 years after diagnosis.[93] The prognosis for ovarian cancer also means that a 5-year time horizon is sufficient for capturing important differences in outcomes and costs. In accordance with the CADTH guidelines,[90] we applied an annual discount rate of 1.5% to both costs and QALYs incurred after the first year.

Main Assumptions

The model's main assumptions were as follows:

- Available clinical studies reporting the safety and effectiveness of niraparib maintenance therapy by HRD status were based on one type of HRD testing (MyChoice CDx); we assumed an HRD test equivalent to MyChoice CDx
- HRD testing is conducted before the initiation of niraparib maintenance therapy to inform treatment decision-making, and it would not cause a delay in treatment
- In the PRIMA trial, approximately 15.1% of patients had inconclusive test results.[19] We assumed that people with inconclusive results would have the same prognosis as people with HRD
- We assumed that HRD testing could provide information about patients' *BRCA* status, similar to the *BRCA* testing currently being used in Ontario. In other words, we assumed that for *BRCA* mutations, HRD testing would have the same sensitivity and specificity as *BRCA* testing
- HRD testing would affect only treatment decisions related to niraparib maintenance therapy; it would not impact the rest of the treatment pathway
- We assumed that the risk of niraparib-related toxicity would not differ according to HRD status, and that any impact on survival from such toxicities would be captured by the survival curves
- We assumed a constant rate of niraparib dose reduction, interruption, or discontinuation. We assumed that patients would not switch to a different PARP inhibitor because of niraparib-related toxicity

Model Structure

We developed a decision-analytic model combining a decision tree (Figure 3) and partitioned survival analysis (Figure 4) to estimate the cost-effectiveness of the different HRD testing strategies.

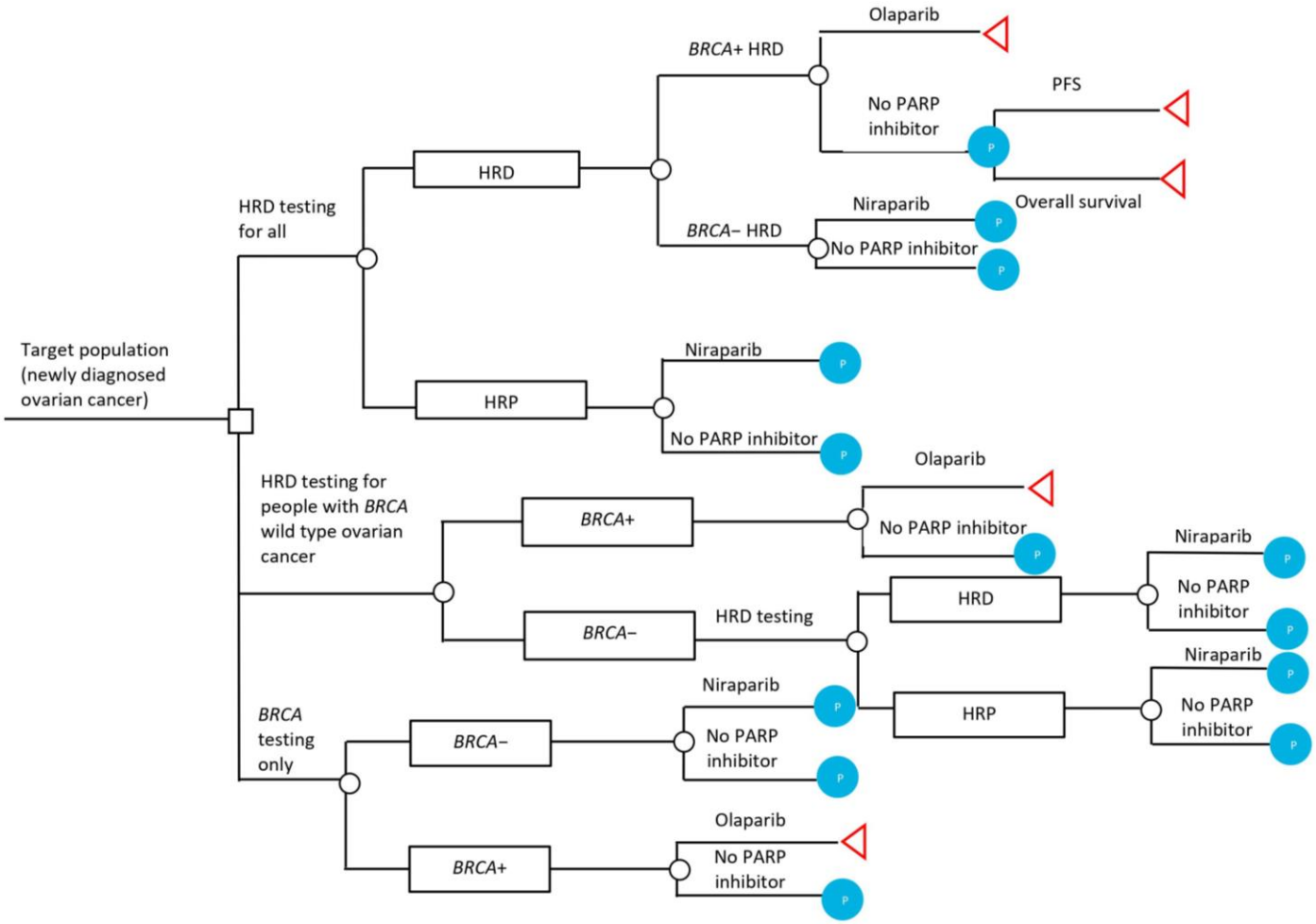


Figure 3: Model Structure – Decision Tree

Abbreviations: HRD, homologous recombination deficiency; HRP, homologous recombination proficiency; PARP, poly-adenosine diphosphate (ADP)-ribose polymerase; PFS, progression-free survival.
A flow chart displaying the decision tree used for this analysis. The target population (with newly diagnosed ovarian cancer) could undergo the following testing strategies: HRD testing for all, HRD testing for people with *BRCA* wild type, or *BRCA* testing only. Based on their test results, people would receive olaparib, niraparib, or no PARP inhibitor. *HRD for all* represents HRD testing as a replacement for *BRCA* testing. *HRD testing for people with BRCA* represents HRD testing as an add-on to *BRCA* testing, in which only patients with *BRCA* wild type would undergo HRD testing. After a treatment choice is made in the decision tree, *P* represents the partitioned survival analysis, which included two survival curves: progression-free survival and overall survival.

First, we used a decision tree to calculate the proportions of patients who would receive different treatments based on their test results (Figure 3). The decision tree consisted of three different strategies: HRD testing for all; HRD testing for people with *BRCA* wild type; and no HRD testing (i.e., *BRCA* testing only). The details of each strategy are as follows:

- HRD testing for all: In this strategy, all patients with ovarian cancer would receive HRD testing only. Based on the HRD testing results (test equivalent to MyChoice CDx), they might have *BRCA* mutations, *BRCA* wild type HRD, HRP, or inconclusive results. People with *BRCA* mutations would receive olaparib or no PARP inhibitor. People with *BRCA* wild type HRD would receive niraparib or no PARP inhibitor. People with HRP would receive niraparib or no PARP inhibitor, but they would be less likely to receive niraparib than people with HRD. For people with inconclusive results, treatment decisions and prognosis would be the same as for people with *BRCA* wild type HRD
- HRD testing for people with *BRCA* wild type: In this strategy, all patients would first receive *BRCA* testing and only those with *BRCA* wild type (i.e., no *BRCA* mutations) would receive HRD testing. Based on the HRD testing results, patients would be identified as *BRCA* wild type HRD, HRP, or inconclusive. Treatment decisions would be similar to those for HRD testing for all
- No HRD testing (*BRCA* testing only): In this strategy, patients with ovarian cancer would receive *BRCA* testing only. Based on their test results, they would have a *BRCA* mutation or *BRCA* wild type. Patients with a *BRCA* mutation would receive olaparib or no PARP inhibitor. Patients with *BRCA* wild type would receive niraparib or no PARP inhibitor

After receiving treatment based on their test results, patients would enter the partition survival model, which consists of three mutually exclusive health states: PFS, disease progression, and death (Figure 4). We also used the partition survival model to simulate the costs and QALYs associated with different treatments over a 5-year time horizon, with a cycle length of 1 month.

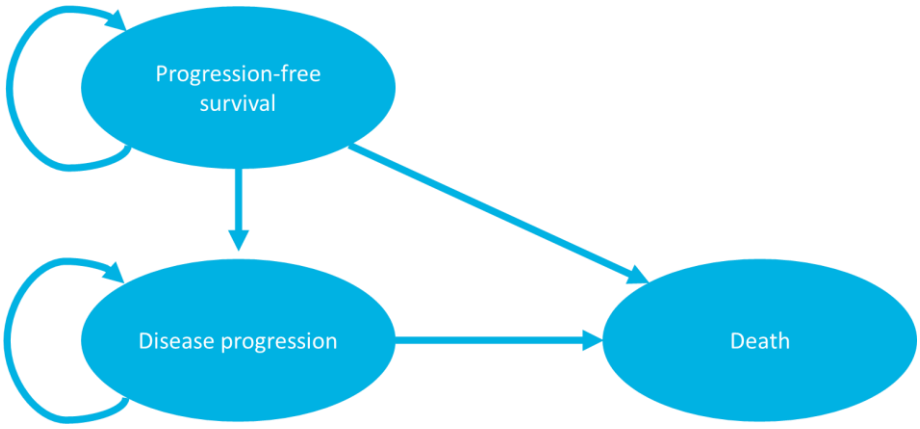


Figure 4: Model Structure – Health States of the Partition Survival Model

A flow chart showing the three health states of the partition survival model: progression-free survival, disease progression, and death. Patients in the progression-free survival state could remain there or move to disease progression or death. Patients in the disease progression state could remain there or move to death.

We estimated the proportion of patients in each health state from the PFS and overall survival curves commonly reported in cancer clinical trials (Figure 5).[94] We estimated the proportion of patients in the

death state in each branch of the decision tree (e.g., patients with HRD receiving niraparib, patients with HRP not receiving niraparib) as 1 minus the overall survival curve at each time point. We estimated the proportion of patients in the progression-free state directly from the PFS curve. The difference between the overall survival and PFS curves is the proportion of patients in the disease progression state.[94]

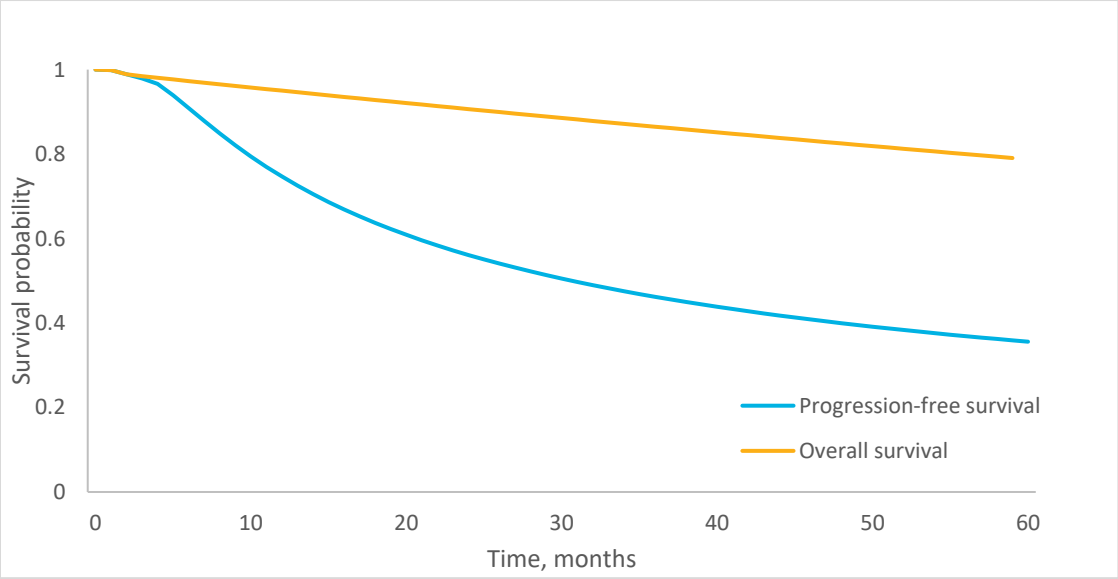


Figure 5: Sample Partitioned Survival Analysis

This figure shows a sample partitioned survival analysis for patients with HRD who received niraparib. The analysis has two curves: one for progression-free survival and one for overall survival, showing the average probabilities of 5,000 simulations.

The survival curves for each branch of the decision tree depend on HRD status (*BRCA* wild type HRD, HRP, or overall population) and the treatment received (niraparib or no PARP inhibitor); they were informed by the PRIMA clinical trial.[19] We did not model the survival of patients who received olaparib, for the reasons described above.

Clinical Outcomes and Utility Parameters

We used several types of clinical parameters to populate the model:

- Prevalence of HRD, HRP, and *BRCA* mutations
- Proportion of patients who received niraparib treatment following HRD or *BRCA* testing
- Overall survival and PFS of patients who received no treatment based on HRD status (i.e., HRD or HRP)
- Treatment effects of niraparib by HRD status
- Niraparib-related toxicities
- Health state utilities (i.e., health-related quality of life)

PREVALENCE OF HRD STATUS AND *BRCA* MUTATIONS

We obtained the prevalence of HRD (with or without *BRCA* mutations) and HRP in patients with newly diagnosed cancer from the PRIMA trial.[19] According to the PRIMA trial,[19] prevalence was as follows: *BRCA* mutations 30.4% (223 of 733 patients), *BRCA* wild type HRD 20.5% (150 of 733 patients), HRP 34.0% (249 of 733 patients), and inconclusive results 15.1% (111 of 733 patients). Table 13 summarizes the inputs for HRD status that we used in our model.

Table 13: HRD Status Inputs Used in the Economic Model

Model parameter	Mean prevalence (SE)	Distribution	Source
HRD (*BRCA* mutations)	0.304 (0.017)	Dirichlet	González-Martín et al, 2019[19]
HRD (*BRCA* wild type)	0.205 (0.015)	Dirichlet	González-Martín et al, 2019[19]
HRP	0.340 (0.017)	Dirichlet	González-Martín et al, 2019[19]
Inconclusive results	0.151 (0.013)	Dirichlet	González-Martín et al, 2019[19]

Abbreviations: HRD, homologous recombination deficiency; HRP, homologous recombination proficiency; SE, standard error.

IMPACT OF TESTING ON TREATMENT DECISIONS

No published study has assessed the impact of HRD testing on decisions about niraparib maintenance therapy. Following expert consultation (Sarah E. Ferguson, MD, email communication, August 26, 2022), we estimated that, without HRD testing, for those with *BRCA* wild type (HRD status was unknown), 70% would receive niraparib and 30% would receive no PARP inhibitor. For those with *BRCA* wild type HRD, 90% would receive niraparib and 10% would receive no PARP inhibitor. For those with HRP (expecting a smaller benefit in PFS), 20% would receive niraparib (Table 14) and 80% would receive no PARP inhibitor.

We also estimated that for people with *BRCA* mutations, about 95% would receive olaparib and 5% would receive no PARP inhibitor, regardless of the testing strategy (HRD testing or no HRD testing).

Table 14: PARP inhibitor Maintenance Therapy for Different Testing Strategies

			No niraparib, %	
Testing strategy	**Testing result**	**Niraparib, %**	**Olaparib**	**No PARP inhibitor**
No HRD testing (*BRCA* testing for all)	*BRCA* mutation	0	95	5
	BRCA wild type	70	0	30
HRD testing (for all, or for people with *BRCA* wild type)	HRD			
	BRCA mutation	0	95	5
	BRCA wild type	90	0	10
	HRP	20	0	80

Abbreviations: HRD, homologous recombination deficiency; HRP, homologous recombination proficiency; PARP, poly-adenosine diphosphate (ADP)-ribose polymerase.

To assess the robustness of our results, we varied the proportions of patients with and without HRD who received niraparib maintenance therapy in a sensitivity analysis.

SURVIVAL CURVES

The key clinical inputs were information related to PFS and overall survival by HRD status and niraparib treatment. We obtained PFS curves and overall survival information from the PRIMA trial (for newly diagnosed ovarian cancer)[19] identified in the Clinical Evidence Review.

Progression-Free Survival

In the PRIMA trial, González-Martín et al[19] reported Kaplan–Meier curves for PFS in all participants by HRD status. Among all participants, the median PFS was longer for people who received niraparib than for people who received placebo (13.8 vs. 8.2 months; hazard ratio 0.62, 95% confidence interval [CI] 0.50–0.76). The results were also available by HRD and HRP subgroups (HRD subgroup: 21.9 vs. 10.4 months, hazard ratio 0.43, 95% CI 0.31–0.59; HRP subgroup: 8.1 vs. 5.4 months, hazard ratio 0.68, 95% CI 0.49–0.94). The median follow-up was 13.8 months.

To estimate a patient's survival over the entire model time horizon, we extracted and extrapolated PFS from the PRIMA trial using survival analysis. To conduct the analysis using the Kaplan–Meier curves, we followed the approach recommended by Guyot et al.[95] First, we used an online tool to read in the coordinates of the Kaplan–Meier curves.[96] This step generated PFS probabilities at different time points over the follow-up period. Second, with numbers at risk and the total number of events from the Kaplan–Meier graph, we reconstructed the Kaplan–Meier data for each arm by finding numerical solutions to the inverted Kaplan–Meier equations.[95] We repeated these two steps to reconstruct individual patient data for different subgroups as determined by HRD status and treatment (niraparib vs. no niraparib).

The follow-up duration from the included trials was shorter than our 5-year time horizon, so our third step was to conduct parametric survival analysis to extrapolate Kaplan–Meier survival curves beyond the trial period. According to the National Institute for Health and Care Excellence Decision Support Unit guidelines,[97] we conducted survival analysis by fitting parametric regression models separately for two groups (niraparib and no niraparib), including exponential, Weibull, Gompertz, log-logistic, log-normal, generalized gamma, gamma, and generalized F models. We used the R package "flexsurv" to fit the survival models based on the reconstructed individual participant data from the previous step.[98] We then used goodness-of-fit (including the Akaike information criterion and the Bayesian information criterion) and visual inspection to select the best-fitting distribution.[97] The survival curves for the selected model are presented in the Results.

No separate report was available on prognosis for the different HRD subgroups with and without *BRCA* mutations. We assumed that people with HRD because of *BRCA* mutations and people with *BRCA* wild type HRD would have the same prognosis and niraparib treatment effect.

Overall Survival

For overall survival, the PRIMA trial reported only survival probabilities at 24 months and hazard ratios[19]; no published overall survival curves were available. In addition, the study authors considered it was premature to draw conclusions about overall survival due to insufficient study follow-up time. To model the potential impact of HRD testing on overall survival, we assumed that the monthly survival rates would be constant and estimated monthly survival probabilities using overall survival probabilities at

24 months. We then approximated the overall survival curves by HRD status (HRD or HRP) and treatment (niraparib or no treatment). This is a major limitation of our model.

TOXICITIES

Niraparib treatment may lead to toxicities that need treatment or dose adjustment. We assumed that adverse events would happen at the midpoint of each model cycle (1 month). The PRIMA trial reported that the most common adverse events of grade 3 or higher in the niraparib group included anemia (31.0%), thrombocytopenia (28.7%), and neutropenia (12.8%).[19] The risks of other common adverse events (grade 3 or higher) were low: 1.2% for nausea, 0.2% for constipation, 1.9% for fatigue, 0.4% for headache, 0.8% for insomnia, 0.8% for vomiting, and 1.4% for abdominal pain. We modelled the effect of hematological toxicities (including anemia, thrombocytopenia, and neutropenia) on costs and utilities, and we assumed that the effect lasted for 1 month (i.e., one model cycle). Because the frequencies of other adverse events were low, we assumed that they had no major effects on utilities or costs.

Toxicities may lead to dose modifications or treatment discontinuation if symptoms persist after dose modifications. For dose modifications, the PRIMA trial reported that the probability of dose reduction was 70.9%, of dose interruption was 79.5%, and of dose discontinuation was 12.0%, which meant that 63% of full doses were administered over the follow-up period.[19] We converted that 63% to monthly probabilities as a weight of 0.93 for each monthly cycle. We assumed that anemia, thrombocytopenia, and neutropenia of grade 3 or higher would need treatment. We also converted the probabilities of these adverse events to monthly probabilities, which we used as treatment probabilities for toxicities. We assumed that the effects of dose modifications on PFS and overall survival would be captured by the survival curves.

HEALTH STATE UTILITIES

A health state utility represents a person's preference for a certain health state or outcome, such as newly diagnosed, progression-free ovarian cancer or disease progression. Utilities are often measured on a scale ranging from 0 (death) to 1 (full health). Table 15 summarizes the health state utility values used in this analysis.

Table 15: Utilities Used in the Economic Model

Health state or treatment state	Utility or disutility (SE)	Distribution	Reference
Newly diagnosed, progression-free ovarian cancer	0.790 (0.020)[a]	Beta	Hess et al, 2013[99]
Under treatment	0.056 (0.017)[b]	Beta	Hettle et al, 2015[100]
Toxicity	−0.233 (0.047)[c,d]	Beta	Barretina-Ginesta et al, 2022[101]
Disease progression	−0.049 (0.023)[c,e]	Beta	Friedlander et al, 2018[102]; Oza et al, 2018[74]
Death	0	–	Assumption

Abbreviations: SD, standard deviation; SE, standard error.

[a] Hess et al[99] reported that the utility ranged from 0.33 to 1.00 but did not report the standard error. We assumed that the standard error was the same as for patients with recurrent cancer (Hettle et al[100]).

[b] Utility gain.

[c] Disutility.

[d] We estimated beta distribution by assuming that the standard error was 20% of the mean.

[e] Based on the pooled estimates of mean differences in utilities before and after disease progression: utility change from 0.845 (SD 0.231) to 0.809 (SD 0.342) in the niraparib group and 0.828 (SD 0.172) to 0.788 (SD 0.300) in the placebo group reported by Friedlander et al,[102] and from 0.79 (SD 0.15) to 0.69 (SD 0.28) in the pazopanib group and 0.81 (SD 0.16) to 0.77 (SD 0.21) in the placebo group reported by Oza et al.[74]

Hess et al[99] reported utility values for patients with ovarian cancer by mapping algorithms from the Functional Assessment of Cancer Therapy (FACT) quality-of-life instrument to EQ-5D utilities. The authors reported a utility of 0.790 for patients with suboptimal residual disease after primary cytoreductive surgery for advanced-stage ovarian cancer. We used this as the baseline utility value for patients with newly diagnosed cancer. We also used this baseline utility value for patients who were progression-free and not under treatment.

Ongoing treatment, toxicities, and disease progression can change utility values, but empirical evidence for disutility values associated with these factors is limited. Hettle et al[100] mapped utility results for patients with recurrent ovarian cancer, and based on their findings, we applied a utility gain of 0.056 for those receiving niraparib maintenance treatment. We applied the weight for dose modification (0.93) to adjust the utility gain for dose interruption and discontinuation. To capture utility loss as a result of treatment toxicity, we used information from a study by Barretina-Ginesta et al.[101] In this study, the authors collected quality-of-life data from the patients in the PRIMA trial. According to their analyses, the utility of people who experienced toxicity was 0.767 in the intention-to-treat population. We applied a utility loss of 0.233 for toxicity and multiplied this utility loss by the probability of toxicities in each cycle (1 month) to obtain the utility loss attributed to toxicity.

Two trials reported on utility loss after disease progression. One trial focused on the use of pazopanib on people with ovarian cancer,[103] and the other focused on the use of niraparib for people with recurrent ovarian cancer.[74] These two trials reported the mean differences between utility before and after progression or the utility loss attributed to disease progression, which ranged from 0.032 to 0.1. We pooled these estimates and their standard errors using meta-analysis and obtained a utility loss of 0.049 (95% CI 0.003 to 0.095) for disease progression.

Cost Parameters

We obtained cost inputs from standard Ontario sources, published literature, and clinical experts (Table 16). We obtained the fees for professional visits and procedures from the Ontario Schedule of Benefits for Physician Services and the Ontario Schedule of Benefits for Laboratory Services.[104,105] All costs are reported in 2023 CAD. When costs in 2023 CAD were not available, we adjusted costs using the health care component of the Statistics Canada Consumer Price Index.[106]

Table 16: Costs Used in the Economic Model

Variable	Unit cost, $[a]	Duration or quantity	Source
Testing			
HRD testing (MyChoice CDx)	$5,422.49[b]	1	Dottino et al, 2019[83]
BRCA testing	$750.00	1	Harriet Feilotter, PhD, email communication, August 26, 2022
Medication			
Niraparib	$131.79 per dose	3 doses per day	CADTH, 2020[107]
Relative dose of niraparib	0.630 (0.126)[c]	Median follow-up, 13.8 mo	González-Martín et al, 2019[19]
Monthly niraparib cost	$11,861.10 per mo	–	–
Monitoring			
Physician visit	$157.00	Monthly	*Schedule of Benefits for Physician Services* (A445)[104]
Laboratory			
Cancer antigen 125	$35.00	Every 3 mo	GBHS fee schedule for uninsured lab test[104]
CBC	$3.98	Baseline and weekly in the first month; monthly thereafter	*Schedule of Benefits for Laboratory Services* (L393)[105]
Comprehensive metabolic panel[d]	$21.57	Same as CBC	*Schedule of Benefits for Laboratory Services* (L393)[105]
Imaging			
Abdominal CT with and without contrast	$108.30	Every 3 mo in the first 2 y; every 6 mo thereafter	*Schedule of Benefits for Physician Services* (X126)[104]
Pelvic CT with and without contrast	$108.30	Same as for abdominal CT	*Schedule of Benefits for Physician Services* (X233)[104]
Thoracic CT with and without contrast	$86.60	Same as for abdominal CT	*Schedule Benefits for Physician Services* (X125)[104]
Chest x-ray	$40.55	Same as for abdominal CT	*Schedule of Benefits for Physician Services* (X092)[104]
Health outcomes			
Hematologic toxicity	$393.58[e,f]	Monthly	Lazzaro et al, 2019[108]
Progression	$1,619.58[e,g]	Monthly	Gilbert et al, 2020[87]
End-of-life care	$4,837.13[e,h]	4 mo before death	Yu et al, 2015[109]

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; CBC, complete blood count; CT, computed tomography; GBHS, Grey Bruce Health Services; HRD, homologous recombination deficiency.

[a] Costs in 2023 Canadian dollars.

[b] Converted from US dollars: 1 USD = 1.3422 CAD in January 2023.[110]

[c] We estimated beta distribution by assuming the standard error was 20% of the mean.

[d] Included glucose (quantitative, not by dipstick, L111), glucose (semiquantitative, dipstick if read with reflectance meter), calcium (L045), sodium (L226), potassium (L204), carbon dioxide (L061), chloride (L053), albumin-quantitative (L005), albumin-qualitative (L004), total protein (L208), ALP (L191), ALT (L223), AST (L222), bilirubin (total, L030), blood urea nitrogen (L251), creatinine (not with creatinine clearance, L067), creatinine clearance (L068).

[e] We estimated log-normal distribution by assuming the standard error was 20% of the mean.

[f] €2973.78 in 2018 euros; €1 in 2018 euros = €1.1549 in 2023 euros;[111] €1 in 2023 euros = $1.4468 in 2023 CAD;[110] we estimated that the total was an annual cost of $4,968.92 and an average monthly cost of $393.58.

[g] $1 in 2016 CAD = $1.1678 in 2023 CAD according to the health and personal care component of Consumer Price Index in Ontario.[106]

[h] $1 in 2012 CAD = $1.2111 in 2023 CAD according to the health and personal care component of Consumer Price Index in Ontario.[106]

HRD AND *BRCA* TESTING

According to the literature, the price was $4,040 USD for MyChoice CDx (1 USD = 1.3422 CAD based on the conversion rate in January 2023).[83,110] The price of *BRCA* testing is $750 (Harriet Feilotter, PhD, email communication, August 26, 2022). We conducted a one-way sensitivity analysis for the cost of genetic testing.

PARP INHIBITOR MAINTENANCE THERAPY

According to the CADTH recommendation report on niraparib, the cost of niraparib is $131.79 per 100 mg capsule.[107] Assuming a dose of 300 mg once daily, the monthly cost of niraparib maintenance therapy is $11,861 per person. We applied the monthly cost to our calculations and further accounted for the financial impacts of dose interruption, reduction, and discontinuation following adverse events. The PRIMA trial[19] reported that the median relative dose intensity (the proportion of administered doses relative to planned doses) was 63% for niraparib over a median follow-up period of 13.8 months. We converted this probability to a monthly probability of 93% to estimate the actual administered doses as a proportion of the full dose. We applied the monthly costs of $11,319 up to 36 months or until disease progression.

MONITORING

We assumed that people taking niraparib would receive a complete blood count and comprehensive metabolic panel at baseline, weekly in the first month of medication, and monthly after that.[104,105,112,113] According to the Ovarian Cancer Pathway Map,[113] the frequency of imaging follow-up and surveillance is every 3 months in year 1 and year 2, and every 6 months from year 3 to year 5. The costs for imaging follow-up, including abdominal, pelvic, and thoracic CT and chest x-ray were based on the Ontario Schedule of Benefits.[104]

OUTCOME-RELATED COSTS

We considered outcome-related costs for serious toxicity, disease progression, and end-of-life care.

To avoid double-counting for costs related to toxicities, we considered only treatment costs and excluded costs related to dose changes for niraparib treatment. According to Fan et al,[114] the incremental cost related to treatment of adverse events among breast and ovarian cancer patients receiving PARP inhibitors was driven by hematologic toxicity. We assumed that treatment costs related to other adverse events (e.g., nausea, vomiting) were negligible and would be the same regardless of whether or not someone received niraparib. From the perspective of the Italian National Health Service,[111] Lazzaro et al[108] reported that the annual cost of hematologic toxicity treatment per patient was €2973.78 (2018 euros; €1 in 2018 euros = €1.1549 in 2023 euros; €1 in 2023 euros = $1.4468 in 2023 CAD[110]) or $4,968.92; we applied a monthly treatment cost of $393.58 for toxicity.

Gilbert et al[87] reviewed the health care costs of 66 women with recurrent stage III or IV high-grade serous ovarian cancer in a Canadian university tertiary centre. This study estimated that the mean health care costs for patients receiving one line of chemotherapy for recurrent disease was $50,898 (2016 CAD; $1 in 2016 CAD = $1.1678 in 2023 CAD), over a median overall survival of 36.7 months. We estimated that the monthly cost for progression was $1,619.58 for newly diagnosed cancer.

Yu et al[109] reported an end-of-life care cost of $15,976.00 (2012 CAD) borne by public payers over a 4-month trajectory. We estimated the monthly cost as $4,837.13 (2023 CAD). We applied this monthly

cost according to the survival time in our model and calculated the total costs of end-of-life care before patients' death.

Internal Validation

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

Analysis

Our reference case and sensitivity analyses adhered to the CADTH guidelines[90] when appropriate. The reference case represents the analysis with the most likely set of input parameters and model assumptions.

We calculated the reference case of this analysis by running 5,000 simulations (probabilistic analysis) that simultaneously captured the uncertainty in all parameters that were expected to vary. We set distributions for variables within the model. Tables 13 to 16 list the model variables and corresponding distributions. We calculated mean costs and mean QALYs with credible intervals for each intervention assessed. We had planned to report incremental cost-effectiveness ratios (ICERs) according to CADTH guidelines.[90] However, when the new intervention is less effective and less costly than standard care, decision-making is more complex and there is no established willingness-to-pay (WTP) value (or in this case, willingness-to-accept [WTA]) for QALY loss. In this case, presenting results as ICERs is not recommended. Therefore, instead of calculating ICERs, we used net monetary benefit (NMB) to evaluate the cost-effectiveness of the three included treatments (see Glossary, *Incremental net benefit*). We calculated the NMB for each strategy (NMB for one strategy = total QALY × WTP or WTA value − total cost), and the incremental NMB (incremental NMB = incremental QALY × WTP or WTA value − incremental cost) to compare a strategy with the reference case. For each simulation, the strategy with the maximum NMB at the given WTP or WTA value was the most cost-effective of the three strategies. For pair-wise comparisons, a positive incremental NMB indicates that the strategy is cost-effective compared with the reference.

The results of the probabilistic analysis are presented on a cost-effectiveness acceptability curve. We present uncertainty quantitatively, as the probability that a treatment is cost-effective at WTP or WTA values of $0 to $100,000 per QALY.[115] The probability of each treatment being cost-effective was equal to the proportion of the 5,000 simulations for which the treatment had the highest NMB.

SENSITIVITY ANALYSES

In sensitivity analyses, we explored how the results would be affected by varying input parameters and model assumptions. We conducted 1-way sensitivity analyses on three key model inputs: the cost of HRD testing, utility loss because of toxicity and disease progression, and the proportion of patients receiving niraparib (for example, 100% for people with HRD, and 0% for people with HRP).

SCENARIO ANALYSES

We also examined the robustness of the cost-effectiveness results using the following scenario analyses.

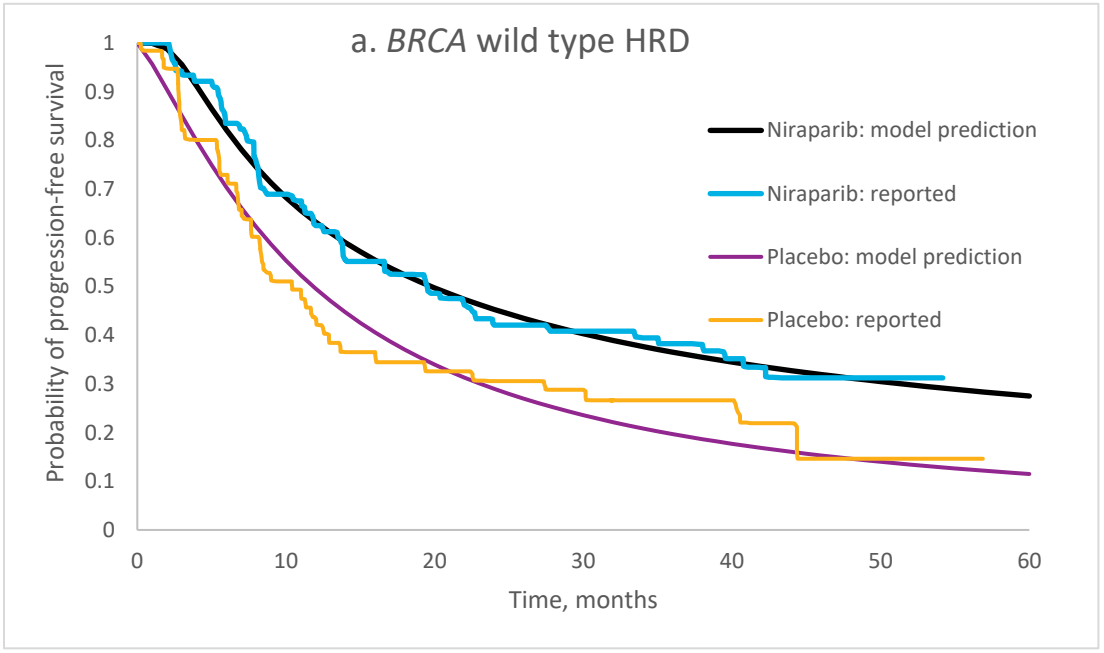
- Scenario 1, extended niraparib use: The reference case considered the use of niraparib until disease progression, death, or 36 months.[31] The scenario examined the cost-effectiveness of using niraparib over the 5 years of our analysis in people who are progression-free[13]

- Scenario 2, PFS only: The partitioned survival analysis in the reference case considered two survival curves, PFS and overall survival, but there was greater uncertainty around overall survival. The scenario analysis considered a partitioned survival analysis with only a PFS curve. We estimated quality-adjusted PFS and incremental cost per quality-adjusted PFS year gained as outcomes
- Scenario 3, 2-year time horizon: The reference case analysis used a 5-year time horizon, extrapolated based on unpublished long-term follow-up data from the PRIMA trial (available only as an abstract).[116] The scenario analysis used a time horizon of 2 years, based on information from the PRIMA trial[19]
- Scenario 4, inconclusive HRD status: The reference case assumed that people with inconclusive results from HRD testing had the same acceptance of niraparib as people with unknown HRD status, and that they had same prognosis as patients with HRD. This scenario assumed that patients with inconclusive results had the same prognosis as patients with HRP

Results

Survival Analysis Model Selection

To estimate a patient's survival over the entire model time horizon, we extracted long-term data on PFS from the PRIMA trial (available only as an abstract)[116] and conducted a survival analysis. We used an online tool to read in the coordinates of the Kaplan–Meier curves,[96] reconstructed the Kaplan–Meier data for each arm, and conducted parametric survival analysis to fit Kaplan–Meier survival curves over the 5-year time horizon.[95] We fit parametric regression model separately for two groups (niraparib and no niraparib group), including exponential, Weibull, Gompertz, log-logistic, log-normal, generalized gamma, gamma, generalized F models.[97] Appendix 10, Table A30 summarizes the Akaike information criterion and Bayesian information criterion statistics used to select a survival model for PFS in the different model groups. Based on the Bayesian information criterion statistic, generalized gamma distribution was the optimal model for patients with *BRCA* wild type HRD and niraparib maintenance treatment, and for patients with HRP, with or without niraparib maintenance treatment. Log-logistic distribution was the optimal model for patients with *BRCA* wild type HRD without niraparib maintenance treatment. Figure 6 presents the survival curves for the selected model, compared with the original reported curves.



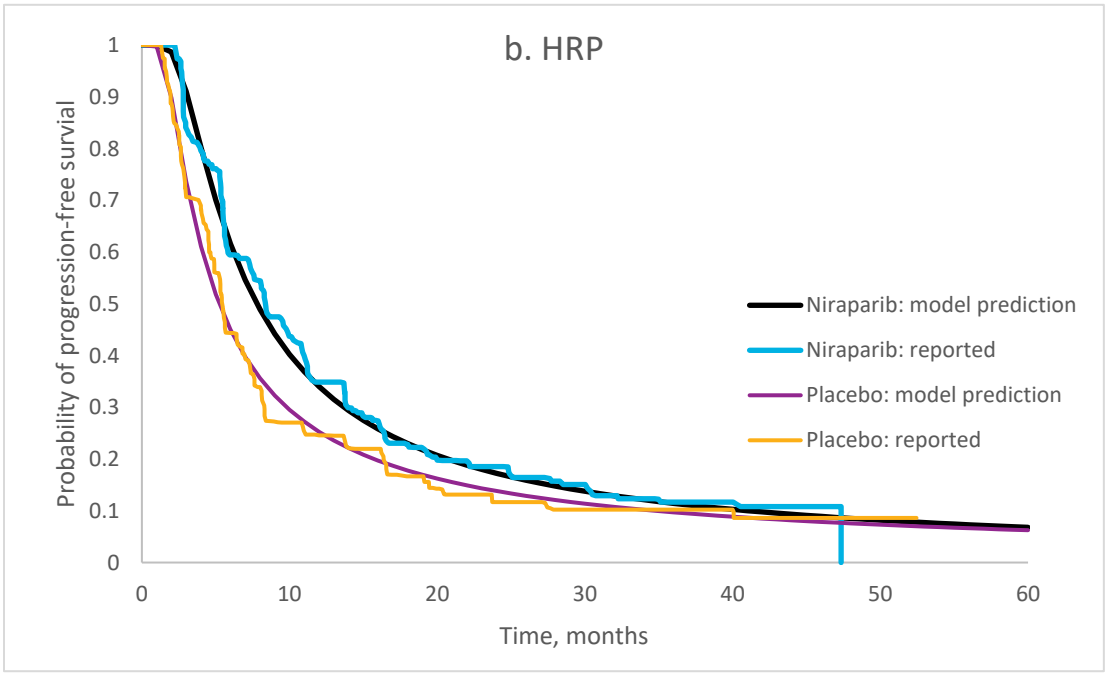


Figure 6: Progression-Free Survival for Subgroups With Different HRD Statuses

Abbreviations: HRD, homologous recombination deficiency; HRP, homologous recombination proficiency.
This figure shows the progression-free survival curves reported in the PRIMA trial (reported)[19,116] and reconstructed in this analysis (model prediction), by treatment decision (niraparib or placebo). Figure 6a shows that predictions with the selected model aligned well with the reported findings for patients with *BRCA* wild type HRD. Figure 6b shows that predictions with the selected model aligned well with the reported findings for patients with HRP.

Reference Case Analysis

Table 17 summarizes the results of our reference case analysis. The average total cost per patient was $131,375 for no HRD testing, $126,867 for HRD testing for people with *BRCA* wild type, and $127,746 for HRD testing for all. The average total QALYs per patient were 2.087 for no HRD testing, 1.971 for HRD testing for people with *BRCA* wild type, and 1.971 for HRD testing for all. With negative incremental costs and negative incremental QALYs, we did not calculate ICERs. The results should be interpreted with caution because there is no established WTP or WTA value for QALY loss.

Our analysis showed that both HRD testing strategies led to a lower proportion of patients receiving niraparib maintenance treatment (39.5% vs. 49.0% with no HRD testing), resulting in slightly lower costs and QALYs. The two HRD testing strategies had the same QALYs but different costs. This was because we assumed that HRD testing could provide results equivalent to *BRCA* testing alone (the current standard of care in Ontario); therefore, HRD testing would lead to equivalent decisions and outcomes after testing, and people with *BRCA* mutations would follow the same clinical pathway regardless of the testing strategy.

Table 17: Reference Case Analysis Results

Strategy	PARP inhibitor use[a]	Average total cost, $ (95% CrI)	Incremental cost, $[a,b,c]	Average total PFS, y (95% CrI)	Average total life-years (95% CrI)	Average total QALYs (95% CrI)	Incremental QALYs[a,d]	Incremental NMB, $[e]	
								WTA $10,000/ QALY	WTA $50,000/ QALY
Reference strategy: no HRD testing	Niraparib: 49.0% Olaparib: 28.5% No PARP inhibitor: 22.5%	131,375 (114,331 to 149,160)	–	1.149 (0.950 to 1.343)	2.767 (2.595 to 2.939)	2.087 (1.903 to 2.269)	–	–	–
HRD testing for people with *BRCA* wild type	Niraparib: 39.5% Olaparib: 28.5% No PARP inhibitor: 31.9%	126,867 (110,672 to 143,666)	−4,509 (−9,457 to −161)	1.167 (0.931 to 1.404)	2.605 (2.408 to 2.807)	1.971 (1.780 to 2.166)	−0.116 (−0.192 to −0.038)	3,351 (−709 to 7,969)	−1,283 (−5,618 to 3,320)
HRD testing for all[f]	Niraparib: 39.5% Olaparib: 28.5% No PARP inhibitor: 31.9%	127,746 (111,596 to 144,529)	−3,630 (−8,563 to 728)[f]	1.167 (0.931 to 1.404)	2.605 (2.408 to 2.807)	1.971 (1.780 to 2.166)	−0.116 (−0.192 to −0.038)[f]	2,472 (−1,573 to 7,076)	−2,162 (−6,492 to 2,467)

Abbreviations: CrI, credible interval; HRD, homologous recombination deficiency; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PARP, poly-adenosine diphosphate (ADP)-ribose polymerase; PFS, progression-free survival; QALY, quality-adjusted life-year; WTA, willingness to accept.

[a] Results may appear inexact due to rounding.

[b] Incremental cost = average cost (HRD testing for all or HRD testing for people with *BRCA* wild type) − average cost (no HRD testing).

[c] Negative costs indicate savings.

[d] Incremental QALY = average QALY (HRD testing for all or HRD testing for people with *BRCA* wild type) − average QALY (no HRD testing).

[e] Incremental net monetary benefit = incremental QALYs × WTA − incremental costs, which represents the value of an intervention in monetary terms when a WTA value for a unit of QALY is known. A positive incremental NMB indicates that the strategy is cost-effective compared to the alternative at the given WTA value.

[f] HRD testing for all was equivalent in outcomes but more costly than HRD testing for people with *BRCA* wild type.

COST-EFFECTIVENESS ACCEPTABILITY CURVE

We found that 94.8% of the 5,000 simulations showed cost savings with HRD testing for all, and 97.9% of the 5,000 simulations showed cost savings with HRD testing for people with *BRCA* wild type (Appendix 10, Figure A1). Only 0.18% of 5,000 simulations showed that strategies with HRD testing led to higher QALYs than no HRD testing (Appendix 10, Figure A1). We estimated the NMB for each strategy at various WTA values (NMB = total QALYs × WTA value − total costs) and the incremental NMB for the strategies with HRD testing compared to the reference strategy (i.e., no HRD testing; Table 18). When multiple strategies were compared, the strategy with the largest NMB was the most cost-effective. When two strategies were compared, the strategy with a positive incremental NMB compared to the reference strategy was cost-effective. At a WTA value of $0, HRD testing for people with *BRCA* wild type was the most cost-effective (probability of being cost-effective: 97.9%), because of a small loss in QALYs and costs saved. The probability of being cost-effective decreased to 94.5% at a WTA value of $10,000 per QALY gained and 27.2% at a WTA value of $50,000 per QALY gained. HRD testing for all was not cost-effective at any WTA value, because QALYs were equal and costs were higher compared to HRD testing for people with *BRCA* wild type. In contrast, the probability that no HRD testing would be cost-effective increased as WTA values increased. Figure 7 shows the probabilities of the different testing strategies being cost-effective at different WTA values.

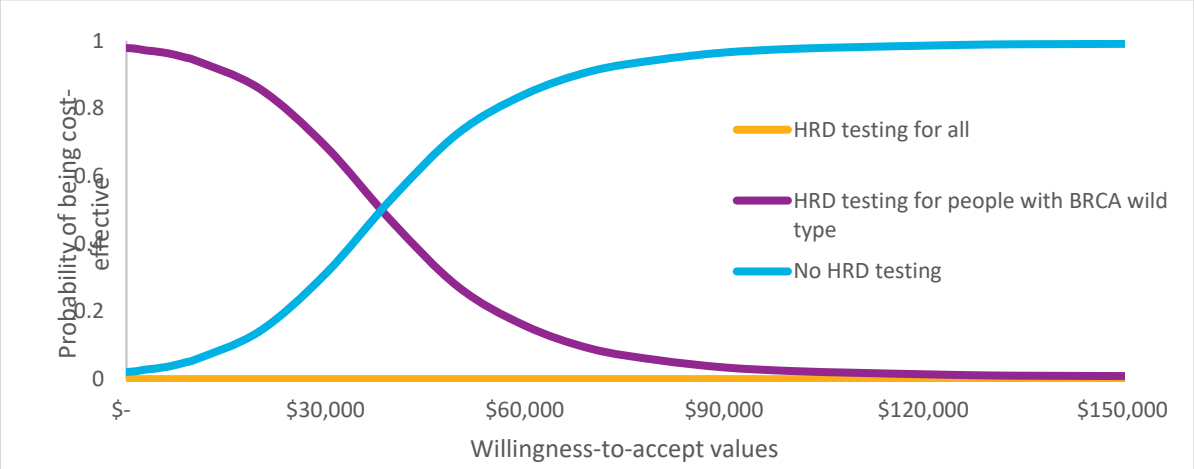


Figure 7: Reference Case, Cost-Effectiveness Acceptability Curve

Abbreviations: HRD, homologous recombination deficiency; NMB, net monetary benefit; QALY, quality-adjusted life-years; WTA, willingness to accept.

HRD testing for people with *BRCA* wild type was the most cost-effective strategy at a WTA value of 0. When the WTA value increased to $10,000 per QALY, the estimated incremental NMB was $3,351 compared to no HRD testing. No HRD testing became the most cost-effective strategy when the WTA value was greater than $40,000 per QALY.

Sensitivity Analysis

To examine the impact of parameter and structural model uncertainties, we conducted one-way sensitivity analyses by varying the values for the cost of HRD testing, the benefit of HRD testing, and the proportion of niraparib treatment in people with different HRD statuses. Because the two strategies with HRD testing led to the same outcomes, and HRD testing for all was more costly, we found no scenario in which HRD testing for all was more cost-effective than HRD testing for people with *BRCA* wild type.

COST OF HRD TESTING

Table 18 shows the results of one-way sensitivity analysis for changes in the cost of HRD testing. When the cost of testing decreased, HRD testing for people with *BRCA* wild type was more likely to be cost-effective. However, when the cost of testing cost was less than $2,000, HRD testing for all was less costly than HRD testing for people with *BRCA* wild type. Even when the cost of HRD testing increased to $9,000, the HRD testing strategies were still less costly than no HRD testing.

Table 18: Sensitivity Analysis Results, HRD Testing Costs

Strategy[a]	Average total costs, $[b]	Incremental NMB, $[c,d] When WTA = $10,000/QALY	Incremental NMB, $[c] When WTA = 50,000/QALY
No HRD testing	131,375 (114,331 to 149,160)	–	–
HRD testing cost $750			
HRD testing for people with *BRCA* wild type	123,598 (107,426 to 140,377)	6,619 (2,578 to 11,227)	1,986 (−2,346 to 6,611)
HRD testing for all	123,073 (106,923 to 139,856)	7,144[d] (3,099 to 11,748)	2,511 (−1,820 to 7,139)
HRD testing cost $1,000			
HRD testing for people with *BRCA* wild type	123,773 (107,594 to 140,555	6,444 (2,402 to 11,055)	1,811 (−2,523 to 6,435)
HRD testing for all	123,323 (107,173 to 140,106)	6,894[d] (2,849 to 11,498)	2,261 (−2,070 to 6,889)
HRD testing cost $2,000			
HRD testing for people with *BRCA* wild type	124,472 (108,287 to 141,265)	5,745 (1,705 to 10,378)	1,112 (−3,229 to 5,728)
HRD testing for all	124,323 (108,173 to 141,106)	5,894[d] (1,849 to 10,498)	1,261 (−3,070 to 5,889)
HRD testing cost $3,000			
HRD testing for people with *BRCA* wild type	125,172 (108,981 to 141,966)	5,045 (993 to 9,683)	412 (−3,927 to 5,021)
HRD testing for all	125,323 (109,173 to 142,106)	4,894 (849 to 9,498)	261 (−4,070 to 4,889)
HRD testing cost $4,000			
HRD testing for people with *BRCA* wild type	125,871 (109,679 to 142,668)	4,346 (291 to 8,974)	−288 (−4,625 to 4,314)[e]
HRD testing for all	126,323 (110,173 to 143,106)	3,894 (−151 to 8,498)	−739 (−5,070 to 3,889)[e]
HRD testing cost $5,000			
HRD testing for people with *BRCA* wild type	126,571 (110,377 to 143,370)	3,646 (−409 to 8,254)	−987 (−5,326 to 3,620)[e]
HRD testing for all	127,323 (111,173 to 144,106)	2,894 (−1,151 to 7,498)	−1,739 (−6,070 to 2,889)[e]
HRD testing cost $6,000			
HRD testing for people with *BRCA* wild type	127,271 (111,076 to 144,071)	2,947 (−1,105 to 7,558)	−1,687 (−6,029 to 2,908)[e]
HRD testing for all	128,323 (112,173 to 145,106)	1,894 (−2,151 to 6,498)	−2,739 (−7,070 to 1,889)[e]
HRD testing cost $7,000			
HRD testing for people with *BRCA* wild type	127,970 (111,773 to 144,773)	2,247 (−1,805 to 6,847)	−2,386 (−6,719 to 2,213)[e]
HRD testing for all	129,323 (113,173 to 146,106)	894 (−3,151 to 5,498)	−3,739 (−8,070 to 889)[e]

Strategy[a]	Average total costs, $[b]	Incremental NMB, $[c,d] When WTA = $10,000/QALY	Incremental NMB, $[c] When WTA = 50,000/QALY
HRD testing cost $8,000			
HRD testing for people with *BRCA* wild type	128,670 (112,484 to 145,475)	1,547 (−2,502 to 6,139)	−3,086 (−7,416 to 1,511)[e]
HRD testing for all	130,323 (114,173 to 147,106)	−106 (−4,151 to 4,498)	−4,739 (−9,070 to −111)[e]
HRD testing cost $9,000			
HRD testing for people with *BRCA* wild type	129,369 (113,186 to 146,207)	848 (−3,200 to 5,434)	−3,785 (−8,125 to 823)[e]
HRD testing for all	131,323 (115,173 to 148,106)	−1,106 (−5,151 to 3,498)	−5,739 (−10,070 to −1,111)[e]

Abbreviations: CrI, credible interval; HRD, homologous recombination deficiency; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; QALY, quality-adjusted life-year; WTA, willingness to accept.

[a] Strategies with HRD testing (for all eligible people or for people with *BRCA* wild type) had the same QALYs as the reference case.

[b] Incremental costs were omitted.

[c] Incremental net monetary benefit = incremental QALYs × WTA − incremental costs, which represents the value of an intervention in monetary terms when a WTA value for a unit of QALY is known. A positive incremental NMB indicates that the strategy is cost-effective compared to the alternative at the given WTA value.

[d] HRD testing for all was less costly than HRD testing for people with *BRCA* wild type when the testing cost was lower than $2,000.

[e] When the WTA was $50,000/QALY, no HRD testing was cost-effective.

UTILITY LOSS BECAUSE OF TOXICITIES OR PROGRESSION

Table 19 shows the results of sensitivity analyses in which we assumed that there was no utility loss because of toxicities or disease progression. The findings differed from the reference case in terms of estimated QALYs. Assuming no utility loss because of niraparib-related toxicities, we estimated the total QALYs to be 2.096 for no HRD testing and 1.980 for both HRD testing strategies (HRD testing for all and HRD testing for people with *BRCA* wild type). Assuming no utility loss because of disease progression, we estimated the total QALYs to be 2.163 for no HRD testing and 2.039 for both HRD testing strategies. However, the incremental NMB and the probability of HRD testing for people with *BRCA* wild type being cost-effective changed only slightly from the reference case.

Table 19: Sensitivity Analysis Results, Utility Loss Because of Toxicities or Disease Progression

Strategy[a]	PARP inhibitor use[b]	Average total QALYs (95% CrI)	Incremental QALYs[b,c]	Incremental NMB ($)[d]	
				WTA $10,000/QALY	WTA $50,000/QALY
Utility loss because of toxicities = 0					
Reference strategy: no HRD testing	Niraparib: 49.0% Olaparib: 28.5% No PARP inhibitor: 22.5%	2.096 (1.913 to 2.279)	–	–	–
HRD testing for people with *BRCA* wild type	Niraparib: 39.5% Olaparib: 28.5% No PARP inhibitor: 31.9%	1.980 (1.789 to 2.178)	−0.116 (−0.193 to −0.039)	3,348 (−708 to 7,962)	−1,297 (−5,617 to 3,295)
HRD testing for all[e]	Niraparib: 39.5% Olaparib: 28.5% No PARP inhibitor: 31.9%	1.980 (1.789 to 2.178)	−0.116 (−0.193 to −0.039)	2,469 (−1,573 to 7,067)	−2,176 (6,498 to 2,431)
Utility loss because of disease progression = 0					
Reference strategy: no HRD testing	Niraparib: 49.0% Olaparib: 28.5% No PARP inhibitor: 22.5%	2.163 (1.994 to 2.329)	–	–	–
HRD testing for people with *BRCA* wild type	Niraparib: 39.5% Olaparib: 28.5% No PARP inhibitor: 31.9%	2.039 (1.852 to 2.225)	−0.124 (−0.205 to −0.043)	3,266 (−761 to 7,844)	−1,705 (−6,083 to 2,928)
HRD testing for all[e]	Niraparib: 39.5% Olaparib: 28.5% No PARP inhibitor: 31.9%	2.039 (1.852 to 2.225)	−0.124 (−0.205 to −0.043)	2,387 (−1,656 to 6,981)	−2,584 (−6,941 to 2,059)

Abbreviations: CrI, credible interval; HRD, homologous recombination deficiency; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PARP, poly-adenosine diphosphate (ADP)-ribose polymerase; PFS, progression-free survival; QALY, quality-adjusted life-year; WTA, willingness to accept.

[a] The cost estimates were the same as the reference case.

[b] Results may appear inexact due to rounding.

[c] Incremental QALY = average QALY (HRD testing for all or HRD testing for people with *BRCA* wild type) − average QALY (no HRD testing).

[d] Incremental net monetary benefit = incremental QALYs × WTA − incremental costs, which represents the value of an intervention in monetary terms when a willingness-to-pay value for a unit of QALY is known. A positive incremental NMB indicates that the strategy is cost-effective compared to the alternative at the given willingness-to-pay value.

[e] HRD testing for all was equivalent in outcomes but more costly than HRD testing for people with *BRCA* wild type.

The two sensitivity analyses on utility provided information on the trade-off between benefits and harms of niraparib treatment for patients with different HRD status. Appendix 10, Table A31 shows the breakdown of QALY estimates for different testing strategies and different cohorts. In our analysis, the cohorts were characterized by HRD status (HRD vs. HRP) and treatment decisions (niraparib maintenance therapy vs. no niraparib maintenance therapy). We estimated that with or without HRD testing to inform niraparib treatment, the utility loss because of toxicities made no difference (0.009 QALY loss because of toxicities in both cases). However, HRD testing led to a small gain in PFS and a small loss in QALYs.

Through sensitivity analyses of utility, our model showed that with HRD testing, PFS increased (our model assumed that more patients with HRD and fewer patients with HRP would receive niraparib after HRD testing), but overall QALYs decreased (as a result of the decrease in overall survival, because fewer

HRP patients were taking niraparib). Appendix 10, Table A31 also shows the breakdown of benefits with respect to PFS and overall survival – and to toxicities – for people with different HRD statuses. For people known to have HRD, niraparib maintenance therapy led to 0.862 more years in PFS, and a gain of 0.379 QALY. These benefits were weighed against a loss of 0.027 QALY because of toxicities. For people known to have HRP, niraparib maintenance therapy led to 0.221 more years of PFS and a gain of 0.859 QALY, weighted against a loss of 0.011 QALY because of toxicities.

PROPORTION OF PATIENTS RECEIVING NIRAPARIB MAINTENANCE TREATMENT

We conducted one-way sensitivity analyses to examine the effect of the proportion of patients on niraparib maintenance treatment for different HRD statuses (Table 20). We found that the cost-effectiveness of HRD testing was sensitive to the proportion of patients receiving niraparib maintenance treatment. Assuming that the entire target population would receive niraparib if they were not tested for HRD, the costs would be $126,867 for HRD testing for people with *BRCA* wild type, $127,746 for HRD testing for all, and $171,377 for no HRD testing. The HRD testing strategies led to a QALY loss of 0.243 (1.971 QALYs for HRD testing strategies vs. 2.214 QALYs for no HRD testing). HRD testing for people with *BRCA* wild type remained the most cost-effective strategy in 100% of simulations when the WTA increased from $0 to $100,000 per QALY. The probability of this strategy being cost-effective decreased to 35.7% when the WTA value was $200,000 per QALY.

When we assumed a larger effect of HRD testing on treatment decisions, HRD testing for people with *BRCA* wild type remained the most cost-effective strategy. In our reference case, we assumed that 90% of people with *BRCA* wild type HRD and 20% of people with HRP would take niraparib. If the proportion of patients receiving niraparib increased to 100% for people with *BRCA* wild type HRD and decreased to 0% for people with HRP, HRD testing for people with *BRCA* wild type would be cost-effective in 100% of simulations when the WTA increased from $0 to $80,000 per QALY. The probability of this strategy being cost-effective decreased to 20.6% when the WTA value was $200,000 per QALY.

Table 20: Sensitivity Analysis Results, Proportion of Patients Receiving Niraparib Maintenance Treatment

Strategy	PARP inhibitor use[a]	Average total costs, $ (95% CrI)	Incremental cost, $[a,b,c]	Average total PFS, y (95% CrI)	Average total life-years (95% CrI)	Average total QALYs (95% CrI)	Incremental QALYs[a,d]	Incremental NMB, $[e]	
								WTA $10,000/ QALY	WTA $50,000/ QALY
Niraparib for all whose HRD status was unknown									
Reference strategy: no HRD testing	Niraparib: 70.0% Olaparib: 28.5% No PARP inhibitor: 1.5%	171,377 (150,004 to 193,248)	–	1.254 (1.022 to 1.483)	2.918 (2.724 to 3.108)	2.214 (2.019 to 2.413)	–	–	–
HRD testing for people with *BRCA* wild type	Niraparib: 39.5% Olaparib: 28.5% No PARP inhibitor: 31.9%	126,867 (110,672 to 143,666)	−44,510 (−52,995 to −36,814)	1.167 (0.931 to 1.404)	2.605 (2.408 to 2.807)	1.971 (1.780 to 2.166)	−0.243 (−0.361 to −0.124)	42,077 (34,732 to 50,105)	32,341 (24,476 to 40,436)
HRD testing for all[f]	Niraparib: 39.5% Olaparib: 28.5% No PARP inhibitor: 31.9%	127,746 (111,596 to 144,529)	−43,631 (−52,169 to −35,864)[f]	1.167 (0.931 to 1.404)	2.605 (2.408 to 2.807)	1.971 (1.780 to 2.166)	–0.243 (−0.361 to −0.124)	41,198 (33,827 to 49,232)	31,462 (23,550 to 39,609)
Niraparib for all whose HRD status was unknown or with *BRCA* wild type HRD; no niraparib for people with HRP									
Reference strategy: no HRD testing	Niraparib: 70.0% Olaparib: 28.5% No PARP inhibitor: 1.5%	171,377 (150,004 to 193,248)	–	1.254 (1.022 to 1.483)	2.918 (2.724 to 3.108)	2.214 (2.019 to 2.413)	–	–	–
HRD testing for people with *BRCA* wild type	Niraparib: 36.5% Olaparib: 28.5% No PARP inhibitor: 35.0%	125,213 (108,906 to 142,217)	−46,164 (−56,203 to −37,439)	1.180 (0.925 to 1.436)	2.543 (2.322 to 2.771)	1.927 (1.726 to 2.134)	–0.297 (−0.434 to −0.139)	43,294 (35,027 to 52,873)	31,816 (22,851 to 41,382)
HRD testing for all[f]	Niraparib: 36.5% Olaparib: 28.5% No PARP inhibitor: 35.0%	126,092 (109,882 to 142,983)	−45,285 (−55,347 to −36,508)[f]	1.180 (0.925 to 1.436)	2.543 (2.322 to 2.771)	1.927 (1.726 to 2.134)	−0.297 (−0.434 to −0.139)	42,415 (34,101 to 52,031)	30,937 (21,919 to 40,538)

Abbreviations: CrI, credible interval; HRD, homologous recombination deficiency; HRP, homologous recombination proficiency; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PARP, poly-adenosine diphosphate (ADP)-ribose polymerase; PFS, progression-free survival; QALY, quality-adjusted life-year; WTA, willingness to accept.

[a] Results may appear inexact due to rounding.

[b] Incremental cost = average cost (HRD testing for all or HRD testing for people with *BRCA* wild type) − average cost (no HRD testing).

[c] Negative costs indicate savings.

[d] Incremental QALY = average QALY (HRD testing for all or HRD testing for people with *BRCA* wild type) − average QALY (no HRD testing).

[e] Incremental net monetary benefit = incremental QALYs × WTA − incremental costs, which represents the value of an intervention in monetary terms when a WTA value for a unit of QALY is known. A positive incremental NMB indicates that the strategy is cost-effective compared with the alternative at the given WTA value.

[f] HRD testing for all was equivalent in outcomes but more costly than HRD testing for people with *BRCA* wild type.

Scenario Analysis

We conducted several scenario analyses to evaluate the effect of model uncertainties on the cost-effectiveness results.

In scenario 1, we assumed that people with ovarian cancer would continue use niraparib until disease progression or death (i.e., treatment duration could last longer than 36 months). This scenario assumed the same clinical benefits but different costs. Compared to the reference case, we found a smaller cost saving for HRD testing strategies ($157,670 for no HRD testing, $155,353 for HRD testing for people with *BRCA* wild type, and $156,232 for HRD testing for all; Table 21 and Appendix 10, Figure A2).

In scenario 2 (Table 17), we considered only PFS (excluding overall survival) and found that HRD testing strategies led to 1.167 years of PFS compared to 1.149 years of PFS without HRD testing. The incremental costs per quality-adjusted PFS year gained suggested that HRD testing strategies were dominant: that is, treatment informed by HRD testing led to more PFS years and were less costly. This divergence between PFS and QALYs occurred because although HRD testing led to less overall niraparib use, it also led to a higher proportion of people with HRD and a lower proportion of people with HRP receiving niraparib compared to no HRD testing. Our QALY estimates were driven by the benefits of niraparib for both PFS and overall survival, especially by the benefits for overall survival. Our model parameters were based on the published report from the PRIMA trial,[19] which suggested an overall survival benefit at 2-year follow-up (91% with niraparib vs. 85% without niraparib for people with HRD; 81% with niraparib vs. 59% without niraparib for people with HRP). This meant that when the overall proportion of niraparib maintenance therapy was higher, more QALYs were gained. In contrast, the PFS estimates depended solely on the benefits of niraparib for PFS, and people with HRD had larger gains in PFS from niraparib than people with HRP (see Clinical Evidence Review).

In scenario 3 (Table 21), we examined cost-effectiveness over a 2-year time horizon. Total costs were $87,315 for HRD testing for people with *BRCA* wild type, $88,194 for HRD testing for all, and $90,071 for no HRD testing. Total QALYs were 0.956 for both HRD testing strategies and 0.994 for no HRD testing. HRD testing for people with *BRCA* wild type was the most cost-effective when WTA values ranged from $0 to $80,000 per QALY.

In scenario 4 (Table 21), we assumed that people with inconclusive HRD status had the same prognosis as people with HRP. Total costs were $97,080 for HRD testing for people with *BRCA* wild type, $97,959 for HRD testing for all, and $121,181 for no HRD testing. Total QALYs were 1.782 for HRD testing in people with *BRCA* wild type, 1.782 for HRD testing for all, and 1.980 for no HRD testing. HRD testing only for people with *BRCA* wild type was cost-effective in 100% of simulations when the WTA value increased from $0 to $60,000/QALY. The probability of this strategy being cost-effective decreased to 80.1% when the WTA value was $100,000 per QALY and 6.3% when the WTA value was $200,000 per QALY.

Table 21: Scenario Analysis Results

Strategy	PARP inhibitor use[a]	Average total costs, $ (95% CrI)	Incremental cost, $[a,b,c]	Average total PFS, y (95% CrI)	Average total life-years (95% CrI)	Average total QALYs (95% CrI)	Incremental QALYs[a,d]	Incremental NMB, $[e]	
								WTA $10,000/ QALY	WTA $50,000/ QALY
Scenario 1: Niraparib use until disease progression or death									
Reference strategy: no HRD testing	Niraparib: 49.0% Olaparib: 28.5% No PARP inhibitor: 22.5%	157,670 (134,144 to 181,604)	–	1.149 (0.950 to 1.343)	2.767 (2.595 to 2.939)	2.087 (1.903 to 2.269)	–	–	–
HRD testing for people with *BRCA* wild type	Niraparib: 39.5% Olaparib: 28.5% No PARP inhibitor: 31.9%	155,353 (132,182 to 178,216)	−2,317 (−7,786 to 2,671)	1.167 (0.931 to 1.404)	2.605 (2.408 to 2.807)	1.971 (1.780 to 2.166)	−0.116 (−0.192 to −0.038)	1,159 (−3,575 to 6,375)	−3,475 (−8,309 to 1,723)
HRD testing for all[f]	Niraparib: 39.5% Olaparib: 28.5% No PARP inhibitor: 31.9%	156,232 (133,093 to 179,020)	−1,438 (−6,921 to 3,560)[f]	1.167 (0.931 to 1.404)	2.605 (2.408 to 2.807)	1.971 (1.780 to 2.166)	−0.116 (−0.192 to −0.038)[f]	280 (−4,448 to 5,494)	−4,354 (−9,194 to 870)
Scenario 3: 2-year time horizon									
Reference strategy: no HRD testing	Niraparib: 49.0% Olaparib: 28.5% No PARP inhibitor: 22.5%	90,071 (80,113 to 100,087)	–	0.730 (0.644 to 0.812)	1.263 (1.200 to 1.327)	0.994 (0.987 to 1.063)	–	–	–
HRD testing for people with *BRCA* wild type	Niraparib: 39.5% Olaparib: 28.5% No PARP inhibitor: 31.9%	87,315 (77,476 to 97,329)	−2,756 (−6,003 to 278)	0.719 (0.620 to 0.814)	1.225 (1.155 to 1.295)	0.956 (0.880 to 1.035)	−0.031 (−0.051 to −0.012)	2,449 (−528 to 5,670)	1,220 (−1,717 to 4,426)
HRD testing for all[f]	Niraparib: 39.5% Olaparib: 28.5% No PARP inhibitor: 31.9%	88,194 (78,367 to 98,135)	−1,877 (−5,145 to 1,185)[f]	0.719 (0.620 to 0.814)	1.225 (1.155 to 1.295)	0.956 (0.880 to 1.035)	−0.031 (−0.051 to −0.012)	1,570 (−1,447 to 4,823)	341 (−2,625 to 3,572)
Scenario 4: Inconclusive HRD status equivalent to HRP									
Reference strategy: no HRD testing	Niraparib: 49.0% Olaparib: 28.5% No PARP inhibitor: 22.5%	121,181 (104,959 to 138,169)	–	0.982 (0.802 to 1.164)	2.636 (2.448 to 2.823)	1.980 (1.796 to 2.164)	–	–	–
HRD testing for people with *BRCA* wild type	Niraparib: 28.1% Olaparib: 28.5% No PARP inhibitor: 43.3%	97,080 (83,544 to 111,779)	−24,101 (−30,522 to −18,218)	0.958 (0.744 to 1.178)	2.372 (2.141 to 2.612)	1.782 (1.580 to 1.993)	−0.198 (−0.307 to −0.088)	22,122 (16,533 to 28,285)	14,205 (7,754 to 20,785)

Strategy	PARP inhibitor use[a]	Average total costs, $ (95% CrI)	Incremental cost, $[a,b,c]	Average total PFS, y (95% CrI)	Average total life-years (95% CrI)	Average total QALYs (95% CrI)	Incremental QALYs[a,d]	Incremental NMB, $[e]	
								WTA $10,000/ QALY	WTA $50,000/ QALY
HRD testing for all[f]	Niraparib: 28.1% Olaparib: 28.5% No PARP inhibitor: 43.3%	97,959 (84,464 to 112,652)	−23,222 (−29,703 to −17,298)[f]	0.958 (0.744 to 1.178)	2.372 (2.141 to 2.612)	1.782 (1.580 to 1.993)	−0.198 (−0.307 to −0.088)	21,243 (15,620 to 27,452)	13,326 (6,911 to 19,958)

Abbreviations: CrI, credible interval; HRD, homologous recombination deficiency; HRP, homologous recombination proficiency; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; PARP, poly-adenosine diphosphate (ADP)-ribose polymerase; PFS, progression-free survival; QALY, quality-adjusted life-year; WTA, willingness to accept.

Note: see Table 17 for scenario 2.

[a] Results may appear inexact due to rounding.

[b] Incremental cost = average cost (HRD testing for all or HRD testing for people with *BRCA* wild type) − average cost (no HRD testing).

[c] Negative costs indicate savings.

[d] Incremental QALY = average QALY (HRD testing for all or HRD testing for people with *BRCA* wild type) − average QALY (no HRD testing).

[e] Incremental net monetary benefit = incremental QALYs × WTA − incremental costs, which represents the value of an intervention in monetary terms when a WTA value for a unit of QALY is known. A positive incremental NMB indicates that the strategy is cost-effective compared with the alternative at the given WTA value.

[f] HRD testing for all was equivalent in outcomes but more costly than HRD testing for people with *BRCA* wild type.

Discussion

We conducted a primary economic evaluation to determine the cost-effectiveness of HRD testing for people with ovarian cancer in the Ontario setting. Our analysis considered PFS and overall survival over a 5-year time horizon and found that HRD testing strategies, for all people or only for people with *BRCA* wild type, led to a lower proportion of patients receiving niraparib maintenance treatment, resulting in lower costs and lower QALYs. However, these cost-effectiveness results should be interpreted with caution. Because the QALY loss was small, HRD testing for people with *BRCA* wild type led to the largest NMB value in our analysis and would be considered cost-effective when the WTA value was lower than $40,000 per QALY.

Our results were driven by the benefits of niraparib for PFS and overall survival, and the proportion of patients receiving niraparib maintenance therapy. The clinical evidence suggested that niraparib improves PFS compared with no maintenance therapy for people with ovarian cancer (11.4 months for people with HRD and 2.7 months for people with HRP; the results of the two subgroups were not comparable; see Table 5). However, the evidence for a benefit in overall survival is limited. For the proportion of patients receiving niraparib maintenance therapy, we assumed that people would make informed decisions after HRD testing. Our reference case analysis assumed that 70% of people would receive niraparib if their HRD status were unknown, but 90% of people with HRD and 20% with HRP would receive niraparib if treatment were informed by HRD testing. With respect to the effect of HRD testing on decision-making, we conducted sensitivity analyses to evaluate the robustness of our results. Using various assumptions about the proportion of patients receiving niraparib maintenance therapy, HRD testing for people with *BRCA* wild type was still cost-effective. The higher the proportion of niraparib therapy among people with HRD, or the lower the proportion of niraparib therapy among people with HRP, the higher the likelihood that HRD testing for people with *BRCA* wild type would be cost-effective.

We incorporated the effect of toxicities on utilities and costs. Sensitivity analyses of these parameters suggested that our results were robust to parameter uncertainties. In Ontario, *BRCA* testing is currently funded for people with ovarian cancer. To further examine the role of HRD testing in the Ontario setting, we assumed that it could be used for all eligible people (as a replacement for the *BRCA* testing), or only for people with *BRCA* wild type (as an add-on to *BRCA* testing). In most scenarios, using HRD testing only for people with *BRCA* wild type was less costly. It is important to keep in mind that in our model, we assumed that the *BRCA* testing results from HRD testing was equivalent to the *BRCA* testing that is currently funded in Ontario; our results cannot be generalized to an HRD testing strategy that does not include *BRCA* testing or does not have validated *BRCA* testing results. As well, although HRD testing for all was slightly more costly in our reference case (an additional $879 per person compared to HRD testing for only people with *BRCA* wild type), it may be easier to implement in clinical practice. HRD testing for all could become less costly than HRD testing for people with *BRCA* wild type if the cost of HRD testing decreased. We used the list price of MyChoice CDx in our reference case, and we conducted a one-way sensitivity analysis to account for the effect of HRD testing costs. Notably, the list price covers direct and indirect costs, but the $750 cost for *BRCA* testing currently funded in Ontario may not represent the overall cost of *BRCA* testing in a comparable manner.

Our analyses assessed HRD testing from a cost-effectiveness perspective and should not be taken as a prescription for decision-making. For the capacity of HRD testing to predict response to niraparib, our analysis was based on results from the PRIMA trial,[19] which used MyChoice CDx.[51] To extrapolate our findings to other HRD tests, the equivalence of HRD test results should be examined. Furthermore, in

our reference case, the QALY loss after niraparib maintenance therapy informed by HRD testing was driven by a lower overall proportion of people receiving niraparib maintenance therapy (lower among people with HRP but higher among people with HRD). However, the Clinical Evidence Review found that for people with ovarian cancer and HRP, niraparib can still lead to benefit in PFS. This economic evaluation, based on findings from the Clinical Evidence Review, examined downstream costs and outcomes for people with different HRD statuses as a result of decisions informed by HRD testing results. In practice, clinical decisions about treatment may consider other factors.

Other important considerations for decision-making fall outside of the scope of this economic analysis. Nevertheless, these factors may be important for decision-making at various levels, including the health system or for individuals. For example, we did not consider implementation costs related to additional procedures, time, human error or delay of treatment because of additional procedures, education, and consultation on additional genetic information if HRD testing is conducted only after *BRCA* testing has found no mutations.

Strengths and Limitations

We examined the role of HRD testing in decision-making for niraparib maintenance therapy. We filled an evidence gap by considering therapy informed by HRD testing at different points in the clinical pathway. Our analysis was based on the best available evidence and applied Canadian data where possible. Compared with existing decision-analytic models on relevant topics,[82-86] our model has merits in terms of time horizon, strategies of interest, and outcomes. We used a time horizon of 5 years, which was long enough to capture the effects of outcomes and costs. We focused on the role of HRD testing in guiding niraparib therapy, and we considered the effect of HRD testing on overall survival, rather than on PFS only. We also conducted sensitivity and scenario analyses to examine the robustness of our results and explore critical uncertainties. Our analysis sheds light on the optimal use of HRD testing in Ontario.

However, our analysis also had some limitations. First, our model was limited by the low quality of the clinical evidence for overall survival outcomes. Only limited clinical trial data were available to inform the PFS analysis, and information about overall survival contained even greater uncertainties. We populated our model with probabilities of overall survival at 2-year follow-up. Further reports on overall survival curves, or survival probabilities at different time points, could provide more robust parameters for model-based analysis. In addition, treatment, utility losses, and costs associated with niraparib toxicities are uncertain. We conducted sensitivity analyses to address this issue, but further research may add certainty. For people with recurrent cancer, no sufficient data on PFS and overall survival were available to populate the model for cost-effectiveness analysis.

Our model also had important structural uncertainties. We used a partitioned survival analysis approach, which estimated the area or time in health states such as PFS, progression, and death. Our model did not consider dynamics in health states, such as the occurrence and relief of toxicity over the time horizon of 5 years.[117] Rather, we applied monthly utilities and costs weighted by the monthly probability of toxicities for people who were progression-free and using niraparib. We did the same for dose decreases, dose interruptions, and dose discontinuations. We assumed a monthly dosage proportion of 0.93 relative to the full dose (300 mg daily, 30 days per month) and estimated the unit cost accordingly. We did not consider the effect of test accuracy (e.g., sensitivity or specificity) or the performance of HRD testing; rather, we simulated the survival of people classified as HRD or HRP in the PRIMA trial.[19]

Finally, clinical pathways may be more complicated than what is simulated in our model. The use of HRD testing and decisions after HRD testing may differ from the assumptions we used. The HRD testing available in Ontario, costs, and management of toxicities may also differ. We conducted scenario and sensitivity analyses to address these uncertainties and overall, our results were robust, but caution is necessary if generalizing the results of this model-based analysis to other settings.

Conclusions

For people with newly diagnosed ovarian cancer, HRD testing may lead to lower costs and lower QALYs compared to no HRD testing. Over a 5-year time horizon, HRD testing led to cost savings ($4,509 per person for people with *BRCA* wild type, and $3,630 per person for all people); it also led to a 0.116 QALY loss. The lower costs and QALYs were driven by an assumption that fewer people with HRP would choose to take niraparib maintenance therapy and would therefore not receive the survival benefit associated with the drug. The impact of HRD testing on patient decisions is uncertain.

Budget Impact Analysis

Research Question

What is the potential 5-year budget impact for the Ontario Ministry of Health of publicly funding homologous recombination deficiency (HRD) testing to inform decisions about niraparib maintenance therapy in patients with high-grade serous or endometrioid epithelial ovarian cancer who are in complete or partial response to platinum-based chemotherapy?

Methods

Analytic Framework

We estimated the budget impact of publicly funding HRD testing to inform niraparib maintenance therapy decisions in patients with high-grade serous or endometrioid epithelial ovarian cancer who are in complete or partial response to platinum-based chemotherapy (hereinafter referred to as *ovarian cancer*) using the cost difference between two scenarios: (1) current clinical practice without public funding for HRD testing (the current scenario), and (2) anticipated clinical practice with public funding for HRD testing (the new scenario). Figure 8 presents the model schematic.

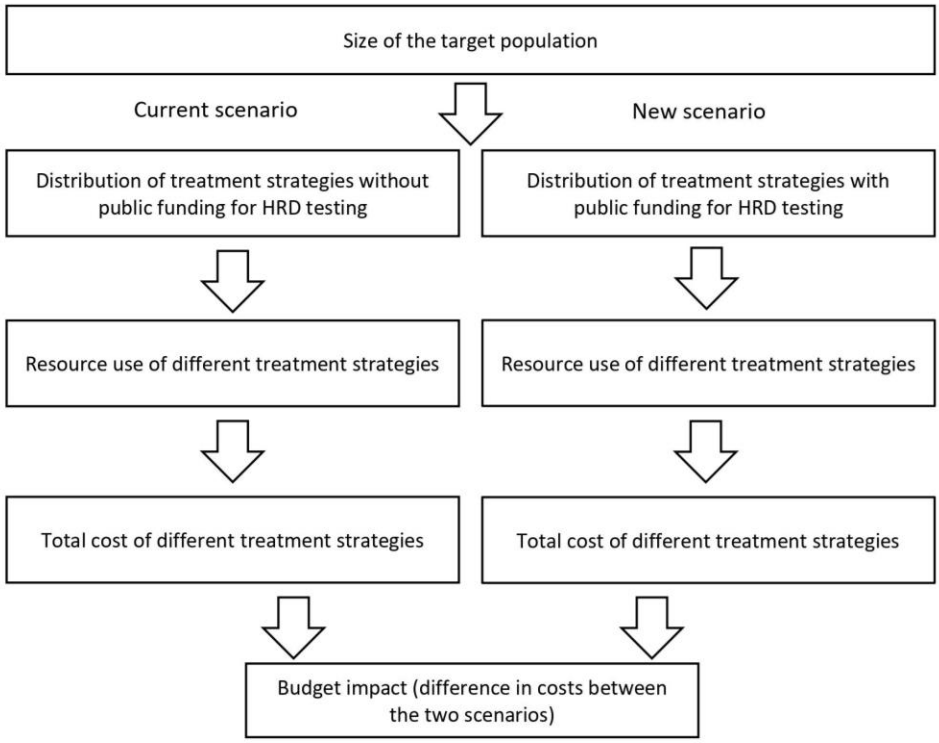


Figure 8: Schematic Model of Budget Impact

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

Key Assumptions

This budget impact analysis was based on our model-based analysis. We applied the assumptions in our cost-effectiveness analyses to the budget impact analyses. For the budget impact analysis, we also assumed the following:

- The risk of ovarian cancer would remain stable over the next 5 years
- HRD testing costs would stay constant over the next 5 years. The market price of HRD testing included start-up and implementation costs (e.g., training, lab renovation, and credentialling); these costs were not considered separately in the budget impact analysis
- The treatment strategies for and prognosis of patients taking or not taking niraparib would stay constant over the next 5 years
- The uptake of HRD testing for recurrent ovarian cancer would be independent of any previous history of HRD testing for newly diagnosed cancer

Target Population

Table 22 shows the estimates for the target population. In 2020, it was expected that 1,277 people in Ontario would be diagnosed with ovarian cancer.[1] We assumed that the risk of ovarian cancer diagnosis would remain stable over the next 5 years and used projections for the female population to estimate the number of ovarian cancer diagnoses from 2024 to 2028. Based on a study that reported the characteristics of ovarian cancer, we assumed that 75% of cases would have complete or partial response to platinum-based chemotherapy,[118] so that 1,012 to 1,069 patients would be eligible for HRD testing each year.

According to Ovarian Cancer Research Alliance, 70% of patients diagnosed with ovarian cancer will have a recurrence.[119] Assuming that the number of ovarian cancer diagnoses and the risk of recurrence stay stable, 945 to 998 recurrent ovarian cancer cases would be expected from 2024 to 2028 in Ontario (70% of newly diagnosed cases). This means 709 to 748 patients with recurrent cancer would have complete or partial response to platinum-based chemotherapy, and eligible for HRD testing.

Table 22: Target Population or Volume of Intervention

Population	Year 1	Year 2	Year 3	Year 4	Year 5
Newly diagnosed cancer	1,350	1,369	1,388	1,407	1,425
Complete or partial response to platinum-based	1,012	1,027	1,041	1,055	1,069
Recurrent cancer	945	958	972	985	998
Complete or partial response to platinum-based chemotherapy	709	719	729	739	748

Current Intervention Mix

At present, HRD testing is not publicly funded to inform niraparib maintenance therapy in Ontario. Therefore, we assumed that all patients in the current scenario would receive usual care (i.e., no HRD testing), which means that patients with *BRCA* wild type would be eligible for niraparib maintenance

therapy after *BRCA* testing). Based on estimates from clinical experts (Table 14), among those with *BRCA* mutations, 95% would receive olaparib and 5% would not receive a poly-adenosine diphosphate (ADP)-ribose polymerase (PARP) inhibitor; among those with *BRCA* wild type, 70% would receive niraparib and 30% would not receive a PARP inhibitor.

Uptake of the New Intervention and New Intervention Mix

We assumed that HRD testing would be adopted quickly if publicly funded, with uptake rates rising from 60% to 100% in 5 years. We estimated uptake separately for patients with newly diagnosed cancer (Table 23) and recurrent cancer (Table 24).

Assuming that 1,012 to 1,069 patients with newly diagnosed ovarian cancer from year 1 to year 5 would be eligible for testing, the uptake of HRD testing would increase from 607 patients in year 1 to 1,069 in year 5. Similarly, assuming that 709 to 748 patients with recurrent ovarian cancer from year 1 to year 5 would be eligible for testing, the uptake of HRD testing would increase from 425 patients in year 1 to 748 in year 5.

Table 23: Uptake of HRD Testing and Standard Care (*BRCA* Testing) in Ontario, Newly Diagnosed Cancer

Uptake[a]	Year 1	Year 2	Year 3	Year 4	Year 5
Patients with newly diagnosed cancer, with complete or partial response to platinum-based chemotherapy, n	1,012	1,027	1,041	1,055	1,069
Current scenario					
Uptake of HRD testing, %	0%	0%	0%	0%	0%
Patients with no HRD testing, n	1,012	1,027	1,041	1,055	1,069
Patients with HRD testing[b], n	0	0	0	0	0
New scenario[c]					
Uptake of HRD testing, %	60%	70%	80%	90%	100%
Patients with no HRD testing, n	405	308	208	106	0
Patients with HRD testing[b], n	607	719	833	950	1,069

Abbreviation: HRD, homologous recombination deficiency.

[a] Results may appear inexact due to rounding.

[b] For both strategies with HRD testing (HRD testing for all or people with *BRCA* wild type) the volume of target population was the same. However, the unit cost per person was different because the probability of receiving HRD testing differed between the two strategies.

[c] We calculated the volume of interventions by multiplying the total number of eligible patients by the uptake rate of the new scenario. For example, the total number of patients in year 1 is 1,012 and the uptake rate of HRD testing is 60%, so the volume of HRD testing in year 1 is 607 (1,012 × 60%).

Table 24: Uptake of HRD Testing and Standard Care (*BRCA* Testing) in Ontario, Recurrent Cancer

Uptake	Year 1[a]	Year 2[a]	Year 3[a]	Year 4[a]	Year 5[a]
Patients with recurrent cancer, with complete or partial response to platinum-based chemotherapy, n	709	719	729	739	748
Current scenario					
Uptake of HRD testing, %	0%	0%	0%	0%	0%
Patients with no HRD testing, n	709	719	729	739	748
Patients with HRD testing[b], n	0	0	0	0	0
New scenario[c]					
Uptake of HRD testing, %	60%	70%	80%	90%	100%
Patients with no HRD testing, n	283	216	146	74	0
Patients with HRD testing[b], n	425	503	583	665	748

Abbreviation: HRD, homologous recombination deficiency.

[a] Results may appear inexact due to rounding.

[b] For both strategies with HRD testing (HRD testing for all or people with *BRCA* wild type), the volume of target population was the same. However, the unit cost per person was different because the probability of receiving HRD testing differed between the two strategies.

[c] We calculated the volume of interventions by multiplying the total number of eligible patients by the uptake rate of the new scenario. For example, the total number of patients in year 1 is 709 and the uptake rate of HRD testing is 60%, so the volume of HRD testing in year 1 is 425 (709 × 60%).

Resources and Costs

Our primary economic evaluation considered only newly diagnosed ovarian cancer. It considered costs related to testing, niraparib treatment (and treatment of niraparib-related toxicities), and outcomes such as progression and end-of-life care.

For patients with newly diagnosed cancer, we used inputs on health care resource use and costs from our cost-effectiveness analyses, applying them over a 5-year period. We estimated annual costs per person from year 1 to year 5 and used these undiscounted costs in our budget impact analysis. We considered resource use associated with health technology and health states, including costs incurred with HRD testing, niraparib maintenance treatment (costs related to medication, treatment of toxicities, and monitoring), and health outcomes (e.g., disease progression and end-of-life care). Appendix 11, Table A32, shows the unit costs used for newly diagnosed cancer.

For patients with recurrent cancer, we considered costs incurred with HRD testing, niraparib treatment, and monitoring. We based the proportions of different HRD statuses on the ENGOT-OV16/NOVA trial (Table 25).[33] We also included a 1-year cost of niraparib maintenance treatment (costs related to medication, toxicity treatment, and monitoring). Without long-term information on clinical outcomes (e.g., overall survival), we were unable to estimate costs related to health outcomes and continued use of niraparib maintenance therapy. Appendix 11, Table A33, shows the unit costs used for recurrent cancer.

Table 25: HRD Status Inputs for Recurrent Cancer

Model parameter	Mean (SE)	Distribution	Reference
HRD (*BRCA* mutation)	0.476 (0.022)	Dirichlet	Mirza et al, 2016[33]
HRD (*BRCA* wild type)	0.219 (0.018)	Dirichlet	Mirza et al, 2016[33]
HRP	0.255 (0.019)	Dirichlet	Mirza et al, 2016[33]
Inconclusive	0.050 (0.009)	Dirichlet	Mirza et al, 2016[33]

Abbreviations: HRD, homologous recombination deficiency; HRP, homologous recombination proficiency; PFS, progression-free survival; SE, standard error.

Internal Validation

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

Analysis

We conducted a reference case analysis and sensitivity analyses. Our reference case analysis represents the analysis with the most likely set of input parameters and model assumptions. Our sensitivity analyses explored how the results are affected by varying input parameters and model assumptions.

We conducted sensitivity analyses for the cost and uptake of HRD testing. We also conducted a scenario analysis assuming that 100% of people with no HRD testing and unknown HRD status would take niraparib (in the reference case, 70% of people with HRD testing and unknown HRD status would take niraparib).

Results

Reference Case

Table 26 shows the results of the budget impact analysis for people with newly diagnosed ovarian cancer. Publicly funding HRD testing to inform niraparib maintenance therapy for people with *BRCA* wild type, at a high uptake of 60% in year 1 and 100% in year 5, would lead to a cost saving of $1.41 million in year 1 and $4.10 million in year 5. The estimated total saving would be $12.67 million over 5 years.

Overall cost savings were driven by reduced costs for niraparib treatment (savings of $3.96 million in year 1 and $6.30 million in year 5). If only testing costs were considered, public funding of HRD testing would increase the budget by $2.30 million in year 1 and $4.06 million in year 5, for a total of $15.85 million.

Table 26: Budget Impact Analysis Results, HRD Testing for People With Newly Diagnosed Ovarian Cancer, *BRCA* Wild Type

	Budget impact, $ million[a]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total[b,c,d]**
Current scenario						
Testing costs	0.76	0.77	0.78	0.72	0.79	3.90
Niraparib treatment costs[e]	51.17	78.72	98.93	100.50	102.02	431.34
Health state costs[f]	4.87	13.06	21.63	30.00	37.91	107.46
Total	56.80	92.55	121.34	131.28	140.73	542.70
New scenario						
Testing costs	3.06	3.50	3.94	4.39	4.86	19.75
Niraparib treatment costs[e]	47.22	73.98	93.98	94.88	95.72	405.78
Health state costs[f]	45.11	13.13	21.25	28.96	36.05	104.51
Total	55.39	90.61	119.17	128.24	136.63	530.03
Budget impact[b,c]						
Testing costs	2.30	2.73	3.16	3.60	4.06	15.85
Niraparib treatment costs[e]	−3.96	−4.74	−4.95	−5.62	−6.30	−25.56
Health state costs[f]	0.24	0.07	−0.38	−1.03	−1.86	−2.96
Total	−1.41	−1.94	−2.17	−3.05	−4.10	−12.67

Abbreviation: HRD, homologous recombination deficiency.

[a] In 2023 Canadian dollars.

[b] Negative costs indicate savings.

[c] Results may appear inexact due to rounding.

[d] All costs were calculated using the mean cost from the probabilistic results of the Primary Economic Analysis.

[e] Estimates included costs for medication, toxicity treatment, and monitoring.

[f] Estimates included costs for disease progression and palliative care.

Table 27 shows that with the same uptake rate, publicly funding HRD testing for all people with newly diagnosed ovarian cancer would lead to a smaller cost saving, from $0.88 million in year 1 to $3.16 million in year 5, for a total saving of $9.00 million. This finding was driven by increased testing costs, for which the estimated budget impact would be an additional $2.84 million in year 1 and $5.00 million in year 5.

Table 27: Budget Impact Analysis Results, HRD Testing for All People With Newly Diagnosed Ovarian Cancer

Scenario	Budget impact, $ million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b,c,d]
Current scenario						
Testing costs	0.76	0.77	0.78	0.72	0.79	3.90
Niraparib treatment costs[e]	51.17	78.72	98.93	100.50	102.02	431.34
Health state costs[f]	4.87	13.06	21.63	30.00	37.91	107.46
Total	56.80	92.55	121.34	131.28	140.73	542.70
New scenario						
Testing costs	3.60	4.13	4.67	5.23	5.80	23.42
Niraparib treatment costs[e]	47.22	73.98	93.98	94.88	95.72	405.78
Health state costs[f]	45.11	13.13	21.25	28.96	36.05	104.51
Total	55.92	91.24	119.90	129.07	137.56	533.71
Budget impact[b,c]						
Testing costs	2.84	3.36	3.89	4.44	5.00	19.52
Niraparib treatment costs[e]	−3.96	−4.74	−4.95	−5.62	−6.30	−25.56
Health state costs[f]	0.24	0.07	−0.38	−1.03	−1.86	−2.96
Total	−0.88	−1.31	−1.44	−2.21	−3.16	−9.00

Abbreviation: HRD, homologous recombination deficiency,

[a] In 2023 Canadian dollars.

[b] Negative costs indicate savings.

[c] Results may appear inexact due to rounding.

[d] All costs were calculated using the mean cost from the probabilistic results of the Primary Economic Analysis.

[e] Estimates included costs for medication, toxicity treatment, and monitoring.

[f] Estimates included costs for disease progression and palliative care.

Table 28 shows the results of the budget impact analysis for HRD testing in people with recurrent ovarian cancer. At a high uptake of 60% in year 1 to 100% in year 5, public funding of HRD testing for people with *BRCA* wild type would lead to a cost saving of $3.15 million in year 1 and $5.55 million in year 5, for a total saving of $21.67 million over 5 years. If only testing costs were considered, public funding of HRD testing would increase the budget by $1.21 million in year 1 and $2.12 million in year 5, for a total of $8.30 million over 5 years.

Table 28: Budget Impact Analysis Results, HRD Testing for People With Recurrent Ovarian Cancer, *BRCA* Wild Type

Scenario	Budget impact, $ million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b,c]
Current scenario						
Testing costs	0.53	0.54	0.55	0.55	0.56	2.73
Niraparib treatment costs[d]	36.87	37.39	37.91	38.43	38.94	189.53
Total	37.40	37.93	38.46	38.98	39.50	192.26
New scenario						
Testing costs	1.74	1.97	2.20	2.44	2.69	11.03
Niraparib treatment costs[d]	32.51	32.23	31.93	31.61	31.26	159.56
Total	34.25	34.20	34.14	34.06	33.95	170.59
Budget impact[b,c]						
Testing costs	1.21	1.43	1.65	1.89	2.12	8.30
Niraparib treatment costs[d]	−4.36	−5.16	−5.97	−6.81	−7.67	−29.97
Total	−3.15	−3.73	−4.32	−4.93	−5.55	−21.67

Abbreviation: HRD, homologous recombination deficiency.

[a] In 2023 Canadian dollars.

[b] Negative costs indicate savings.

[c] Results may appear inexact due to rounding.

[d] Estimates included costs for medication, toxicity treatment, and monitoring.

Table 29 shows that similar to newly diagnosed cancer, public funding of HRD testing for all people with ovarian cancer (rather than only those with *BRCA* wild type) would lead to smaller cost savings of $2.37 million in year 1 and $4.17 million in year 5. The budget impact attributed to testing costs alone would increase from $1.99 million in year 1 to $3.50 million in year 5.

Table 29: Budget Impact Analysis Results, HRD Testing for All People With Recurrent Ovarian Cancer

Scenario	Budget impact, $ million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b,c]
Current scenario						
Testing costs	0.53	0.54	0.55	0.55	0.56	2.73
Niraparib treatment costs[d]	36.87	37.39	37.91	38.43	38.94	189.53
Total	37.40	37.93	38.46	38.98	39.50	192.26
New scenario						
Testing costs	2.52	2.89	3.27	3.66	4.06	16.40
Niraparib treatment costs[d]	32.51	32.23	31.93	31.61	31.26	159.56
Total	35.03	35.12	35.20	35.27	35.32	175.95
Budget impact[b,c]						
Testing costs	1.99	2.35	2.72	3.16	3.50	13.66
Niraparib treatment costs[d]	−4.36	−5.16	−5.97	−6.81	−7.67	−29.97
Total	−2.37	−2.81	−3.25	−3.71	−4.17	−16.31

Abbreviation: HRD, homologous recombination deficiency.

[a] In 2023 Canadian dollars.

[b] Negative costs indicate savings.

[c] Results may appear inexact due to rounding.

[d] Estimates included costs for medication, toxicity treatment, and monitoring.

Sensitivity Analysis

NEWLY DIAGNOSED CANCER

Assuming that HRD testing was used for all eligible patients and the uptake was 100%, the budget impact for HRD testing in people with *BRCA* wild type would be cost savings of $2.35 million in year 1 and $4.83 million in year 5, for a total saving of $16.48 million over 5 years. The budget impact of HRD testing for all eligible people would be cost savings of $1.46 million in year 1 and $3.89 million in year 5, for a total saving of $11.90 million over 5 years (Table 30).

Table 30: Budget Impact Analysis Results, Sensitivity Analysis – 100% Uptake of HRD Testing in Newly Diagnosed Ovarian Cancer

Scenario	Budget impact, $ million[a]					
	Year 1	Year 2	Year 3	Year 4	Year 5	Total[b,c,d]
HRD testing for people with *BRCA* wild type						
Testing costs only	3.84	3.89	3.95	4.00	4.06	19.74
Total	−2.35	−2.83	−2.74	−3.73	−4.83	−16.48
HRD testing for all						
Testing costs only	4.73	4.80	4.86	4.93	5.00	24.32
Total	−1.46	−1.93	−1.82	−2.80	−3.89	−11.90

Abbreviation: HRD, homologous recombination deficiency.

[a] In 2023 Canadian dollars.

[b] Negative costs indicate savings.

[c] Results may appear inexact due to rounding.

[d] All costs were calculated using the mean cost from the probabilistic results of the Primary Economic Analysis.

Table 31 summarizes the sensitivity analysis for HRD testing costs. When costs were $2,000 or lower, HRD testing for all led to greater cost savings than HRD testing for people with *BRCA* wild type, because of testing costs saved. When HRD testing costs were $2,000 or lower, HRD testing for people with *BRCA* wild type was the strategy with the highest testing cost.

Table 31: Budget Impact Analysis Results, Sensitivity Analysis – HRD Testing Costs in Newly Diagnosed Ovarian Cancer

Scenario		Budget impact, $ million[a]					
		Year 1	Year 2	Year 3	Year 4	Year 5	Total[b,c,d]
HRD testing cost $1,000							
For people with *BRCA* wild type	Testing costs	0.42	0.50	0.58	0.66	0.75	2.92
	Total	−3.29	−4.16	−4.75	−5.99	−7.41	−25.60
For all	Testing costs	0.15	0.18	0.21	0.24	0.27	1.04
	Total	−3.56	−4.48	−5.12	−6.41	−7.89	−27.47
HRD testing cost $2,000							
For people with *BRCA* wild type	Testing costs	0.85	1.01	1.17	1.33	1.50	5.85
	Total	−2.87	−3.66	−4.16	−5.32	−6.66	−22.67
For all	Testing costs	0.76	0.90	1.04	1.19	1.34	5.22
	Total	−2.96	−3.77	−4.29	−5.46	−6.82	−23.30
HRD testing cost $3,000							
For people with *BRCA* wild type	Testing costs	1.27	1.51	1.75	1.99	2.24	8.70
	Total	−2.44	−3.16	−3,58	−4.66	−5.91	−19.75
For all	Testing costs	1.37	1.62	1.87	2.14	2.41	9,40
	Total	−2.35	−3.05	−3.46	−4.51	−5.75	−19.12
HRD testing cost $4,000							
For people with *BRCA* wild type	Testing costs	1.70	2.01	2.33	2.66	2.99	11.69
	Total	−2.02	−2.65	−3.00	−3.99	−5.16	−16.83
For all	Testing costs	1.97	2.34	2.71	3.09	3.47	13.58
	Total	−1.74	−2.33	−2.62	−3.57	−4.68	−14.94
HRD testing cost $5,000							
For people with *BRCA* wild type	Testing costs	2.12	2.51	2.91	3.32	3.74	14.61
	Total	−1.59	−2.15	−2.42	−3.33	−4.42	−13.91
For all	Testing costs	2.58	3.05	3.54	4.04	4.54	17.75
	Total	−1.14	−1.61	−1.79	−2.62	−3.61	−10.76

Abbreviation: HRD, homologous recombination deficiency.

[a] In 2023 Canadian dollars.

[b] Negative costs indicate savings.

[c] Results may appear inexact due to rounding.

[d] All costs were calculated using the mean cost from the probabilistic results of the Primary Economic Analysis.

RECURRENT CANCER

Assuming that HRD testing was used in reflex testing and the uptake was 100%, the budget impact for HRD testing in people with *BRCA* wild type would be cost savings of $5.25 million in year 1 and $5.55 million in year 5, for a total saving of $27.00 million over 5 years. The budget impact of HRD

testing for all eligible people would be cost savings of $3.95 million in year 1 and $4.17 million in year 5, for a total saving of $20.32 million over 5 years (Table 32).

Table 32: Budget Impact Analysis Results, Sensitivity Analysis – 100% Uptake of HRD Testing in Recurrent Ovarian Cancer

	Budget impact, $ million[a]					
Scenario	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Total[b,c]**
HRD testing for people with *BRCA* wild type						
Testing costs only	2.01	2.04	2.07	2.10	2.12	10.34
Total	−5.25	−5.33	−5.40	−5.47	−5.55	−27.00
HRD testing for all						
Testing costs only	3.31	3.36	3.40	3.45	3.50	17.02
Total	−3.95	−4.01	−4.06	−4.12	−4.17	−20.32

Abbreviation: HRD, homologous recombination deficiency.

[a] In 2023 Canadian dollars.

[b] Negative costs indicate savings.

[c] Results may appear inexact due to rounding.

Table 33 summarizes the sensitivity analysis for HRD testing costs. When costs were $2,000 or lower, HRD testing for all was less costly.

Table 33: Budget Impact Analysis Results, Sensitivity Analysis – HRD Testing Costs in Recurrent Ovarian Cancer

Scenario		Budget impact, $ million[a]					
		Year 1	Year 2	Year 3	Year 4	Year 5	Total[b,c]
HRD testing cost $1,000							
For people with *BRCA* wild type	Testing costs	0.22	0.26	0.31	0.35	0.39	1.53
	Total	−4.14	−4.89	−5.67	−6.47	−7.28	−28.44
For all	Testing costs	0.11	0.13	0.15	0.17	0.19	0.73
	Total	−4.25	−5.03	−5.83	−6.65	−7.48	−29.24
HRD testing cost $2,000							
For people with *BRCA* wild type	Testing costs	0.45	0.53	0.61	0.70	0.78	3.06
	Total	−3.91	−4.63	−5.36	−6.12	−6.89	−26.91
For all	Testing costs	0.53	0.63	0.73	0.83	0.94	3.66
	Total	−3.83	−4.53	−5.25	−5.98	−6.74	−26.32
HRD testing cost $3,000							
For people with *BRCA* wild type	Testing costs	0.67	0.79	0.92	1.04	1.18	4.59
	Total	−3.69	−4.37	−5.06	−5.77	−6.50	−25.38
For all	Testing costs	0.96	1.13	1.31	1.50	1.68	6.59
	Total	−3.40	−4.02	−4.66	−5.32	−5.99	−23.39
HRD testing cost $4,000							
For people with *BRCA* wild type	Testing costs	0.89	1.05	1.22	1.39	1.57	6.12
	Total	−3.47	−4.10	−4.75	−5.42	−6.10	−23.85
For all	Testing costs	1.38	1.63	1.89	2.16	2.43	9.50
	Total	−2.98	−3.52	−4.08	−4.65	−5.24	−20.47
HRD testing cost $5,000							
For people with *BRCA* wild type	Testing costs	1.11	1.32	1.53	1.74	1.96	7.65
	Total	−3.25	−3.84	−4.45	−5.07	−5.71	−22.32
For all	Testing costs	1.81	2.14	2.48	2.83	3.18	12.43
	Total	−2.55	−3.02	−3.50	−3.99	−4.49	−17.55

Abbreviations: HRD, homologous recombination deficiency.

[a] In 2023 Canadian dollars.

[b] Negative costs indicate savings.

[c] Results may appear inexact due to rounding.

In Appendix 11, Tables A34 and A35 summarize the results of budget impact analyses assuming that all eligible people received niraparib maintenance therapy. Publicly funding HRD testing to inform niraparib treatment decisions led to smaller budgets for newly diagnosed and recurrent cancer compared to niraparib maintenance therapy for all eligible people.

Discussion

We conducted a model-based budget impact analysis to examine the range of costs related to publicly funding HRD testing to inform decisions about niraparib maintenance treatment. For patients with newly diagnosed ovarian cancer, we based the cost and resource estimates on outputs from the model in our primary economic evaluation. Assuming a high uptake of 60% in year 1, increasing to 100% in year 5, publicly funding HRD testing for people with *BRCA* wild type would lead to cost savings of $1.41 million in year 1 and $4.10 million in year 5, for a total saving of $12.67 million over 5 years. This cost saving was driven by the fact that a lower proportion of patients would receive niraparib maintenance treatment in the new scenario. We did not conduct a primary economic evaluation for patients with recurrent cancer; we considered testing costs and 1 year of niraparib treatment for this population. We found that publicly funding HRD testing for patients with recurrent cancer would lead to cost savings of $3.15 million in year 1 and $5.55 million in year 5, for a total saving of $21.67 million over 5 years. Our budget impact analysis may be used to help estimate the resources needed to deliver HRD testing to people with ovarian cancer in Ontario.

We conducted sensitivity analyses to examine the robustness of our budget impact analysis. The findings of our primary economic evaluation suggested that HRD testing for people with *BRCA* wild type may be less costly than HRD testing for all. In our budget impact analysis, using the same assumptions about uptake for newly diagnosed cancer, we found that publicly funding HRD testing for all eligible people (not only for people with *BRCA* wild type) would lead to lower cost savings: 0.88 million in year 1 and $3.16 million in year 5, for a total saving of $9.00 million over 5 years. For recurrent cancer, the budget impact was a cost savings of $2.37 million in year 1 and $4.17 million in year 5, for a total saving of $16.31 million.

As noted above, our findings were driven by the fact that a lower proportion of patients would receive niraparib maintenance therapy in the new scenario with decision-making informed by HRD testing. In the current scenario of no HRD testing to inform niraparib treatment decision, if the proportion of patients who received niraparib were higher (for example, 100%), the cost saving of using HRD testing would be greater. We also expect that cost savings of using HRD testing would be greater if the cost parameters of niraparib or treatment for niraparib-related toxicities in our model were higher. However, to address potential uncertainties about niraparib treatment and long-term health outcomes, we estimated the budget impact considering only testing-related costs. Depending on the role of HRD testing (for all eligible people or for only people with *BRCA* wild type), the uptake of HRD testing, or the target population (newly diagnosed or recurrent cancer) the testing costs varied but never exceeded $6 million per year. This finding was driven by the size of the target population, which we estimated to be 607 to 1,069 for newly diagnosed cancer and 425 to 748 for recurrent cancer.

Strengths and Limitations

Our budget impact analysis had several strengths. First, it was a model-based analysis that considered testing costs, niraparib treatment costs, and health state costs. Second, we conducted sensitivity analyses to examine the budget impact of HRD testing costs and uptake levels. Our cost parameters were derived from Ontario or Canadian settings.

Our budget impact analysis was also limited by some uncertainties. First, it was based on the economic model used in our primary economic evaluation, so it contains the same structural uncertainties. Second, our analysis contained uncertainties related to clinical and cost parameters, particularly niraparib use, toxicity, and long-term outcomes such as overall survival. To overcome this limitation,

we used a breakdown of the undiscounted costs of testing, and we reported the budget impact considering only testing-related costs. Third, high-quality epidemiological information is lacking about the projected number of cases of ovarian cancer over the long term, the proportion of cases with complete or partial response to platinum-based chemotherapy, and the likelihood of recurrence, which led to uncertainties about the size of the target population.

Testing costs in our analysis were based on the list price of MyChoice CDx. The delivery model for HRD testing will determine actual costs. For example, costs in which samples are sent to a centralized laboratory in another country will differ from those using local laboratories. However, limited information is available about potential delivery models for HRD testing; implementation and price negotiations were outside the scope of this analysis. Furthermore, we used the list price of a test panel on the market and may not reflect the budget impact if a locally developed HRD test were to be used. We conducted sensitivity analyses on HRD testing costs to address this limitation.

Although our analysis considered different roles for HRD testing (i.e., for all eligible people vs. only for people with *BRCA* wild type) we were unable to consider the spillover effect of different testing strategies, such as costs incurred by treatment delay, extra procedures, and other effects.

Finally, because data were insufficient to support a model-based cost-effectiveness analysis for people with recurrent cancer, our analysis of the budget impact of publicly funding HRD testing for people with recurrent cancer considered only the costs of testing and 1 year of niraparib treatment (including treatment for toxicities). As a result, our analyses for newly diagnosed and recurrent cancer contained structural differences, and the findings for these populations cannot be compared. Nevertheless, the budget impact analyses for people with newly diagnosed and recurrent cancer cannot be simply added together; they should be considered separately.

Conclusions

Our budget impact analysis suggests that publicly funding HRD testing in Ontario for people with newly diagnosed ovarian cancer and *BRCA* wild type would save $1.41 million in year 1 (60% uptake) and $4.10 million in year 5 (100% uptake), for a total saving of $12.67 million over 5 years. Publicly funding HRD testing for all people with newly diagnosed ovarian cancer would save a total of $9.00 million over 5 years. Publicly funding HRD testing for people with recurrent ovarian cancer and *BRCA* wild type would save $3.15 million in year 1 (60% uptake) and $5.55 million in year 5 (100% uptake), for a total saving of $21.67 million over 5 years. Publicly funding HRD testing for all people with recurrent ovarian cancer would save a total of $16.31 million over 5 years. The estimated cost saving was due mainly to a lower proportion of niraparib use in the new scenario as a result of HRD testing.

Preferences and Values Evidence

Objective

The objective of this analysis was to explore the underlying values, needs, and priorities of those who have lived experience of ovarian cancer, as well as the preferences and perceptions of both patients and providers of homologous recombination deficiency (HRD) testing used to inform patient decisions about niraparib maintenance therapy.

Background

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

Information shared from lived experience can also identify gaps or limitations in published research (e.g., outcomes important to those with lived experience that are not reflected in the literature).[120-122] Additionally, lived experience can provide information and perspectives on the ethical and social values implications of health technologies or interventions.

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

For this analysis, we examined the preferences and values of people with newly diagnosed or recurrent ovarian, fallopian tube, or peritoneal cancer, and their health care providers in two ways:

- A review by Ontario Health of the quantitative evidence on patient and provider preferences and values
- Direct engagement by Ontario Health with people with ovarian, fallopian tube, or peritoneal cancer through interviews

Quantitative Evidence

Research Questions

1. What are the quantitative patient and health care provider preferences for HRD testing to inform patient decisions about the use of maintenance therapy with PARP inhibitors?
2. How does HRD testing affect patients' decision-making with respect to maintenance therapy with PARP inhibitors, as well as their psychological well-being?
3. What are the quantitative patient and health care provider preferences for maintenance therapy with PARP inhibitors?

Methods

LITERATURE SEARCH

We performed a literature search for quantitative preference evidence on June 20, 2022, to retrieve studies published from database inception until the search date. We used the Ovid interface of MEDLINE and the EBSCOhost interface to search the Cumulative Index to Nursing and Allied Health Literature (CINAHL).

The search was based on the population and intervention of the clinical search strategy with a methodological filter applied to limit retrieval to quantitative evidence of preferences and values (modified from Selva et al[68]).

We created database auto-alerts in MEDLINE and CINAHL and monitored them until October 24, 2022. See Appendix 2 for literature search strategies, including all search terms.

ELIGIBILITY CRITERIA

Studies

Inclusion Criteria

- English-language full-text publications
- Studies published since database inception
- Key study designs (e.g., surveys, discrete-choice experiments)
- Studies on patient and health care provider preferences for HRD testing that used quantitative measures:
    - Utility measures
        - Direct techniques such as standard gamble, time trade-off, rating scales, conjoint analysis (e.g., discrete-choice experiment, contingent valuation and willingness to pay, probability trade-off)
        - Indirect techniques such as prescored multi-attributable instruments (e.g., EQ-5D, 36-Item Short Form Health Survey, Health Utility Index)
    - Non-utility quantitative measures
        - Direct choice techniques such as decision aids, surveys, questionnaires

Exclusion Criteria

- Qualitative studies, editorials, commentaries, case reports, conferences abstracts, letters
- Animal and in vitro studies

Participants

Inclusion Criteria (Research Questions 1 to 3)

- Patients with newly diagnosed or recurrent ovarian, fallopian tube, or peritoneal cancer
- Health care providers for these patients

Exclusion Criterion (Research Questions 1–3)

- Patients with other cancers or other diseases

Interventions

Inclusion Criterion (Research Questions 1 and 2)

- HRD testing used in studies of maintenance therapy with PARP inhibitors. Any type of HRD test could be included (e.g., testing for homologous recombination repair pathway–related gene mutations, or genomic scar, mutational signature, or functional tests, if clinical outcomes were measured in the studies)

Exclusion Criteria (Research Questions 1 and 2)

- HRD testing in studies that evaluated maintenance therapy with other drugs or any chemotherapy
- Studies in which *BRCA* testing alone was performed

Inclusion Criterion (Research Question 3)

- Maintenance therapy with PARP inhibitors

Exclusion Criterion (Research Question 3)

- Maintenance therapy with other drugs or any chemotherapy

Comparators

Inclusion Criteria (Research Questions 1 to 3)

- No HRD testing
- Tumour *BRCA* testing
- No comparator

Exclusion Criterion (Research Questions 1 to 3)

- Studies in which HRD testing was performed

Outcome Measures

- Patient and health care provider preferences for HRD testing
- Patient and health care provider preferences for the use of HRD testing to inform patient decisions about the use of maintenance therapy with PARP inhibitors
- Decisional conflict of patients to undergo HRD testing and maintenance therapy with PARP inhibitors
- Psychological effects (e.g., anxiety, distress, worry) of HRD testing

Literature Screening

A single reviewer conducted an initial screening of titles and abstracts using Covidence[68] and then obtained the full texts of studies that appeared eligible for review according to the inclusion criteria. A single reviewer then examined the full-text articles and selected studies eligible for inclusion.

Data Extraction

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

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

STATISTICAL ANALYSIS

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

CRITICAL APPRAISAL OF EVIDENCE

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

Results

LITERATURE SEARCH

The literature search of the quantitative evidence of preferences and values yielded 146 citations published between database inception and June 20, 2022, including grey literature searches and after duplicates were removed. We did not identify any additional studies from other sources, including database alerts (monitored until October 24, 2022). In total, we identified two studies[123,124] (cross-sectional, quantitative surveys) that met our inclusion criteria for research question 3 (preferences for maintenance therapy with PARP inhibitors). No studies assessed patient or provider preferences for HRD testing (questions 1 and 2). Figure 9 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram for the literature search for quantitative evidence of preferences and values.

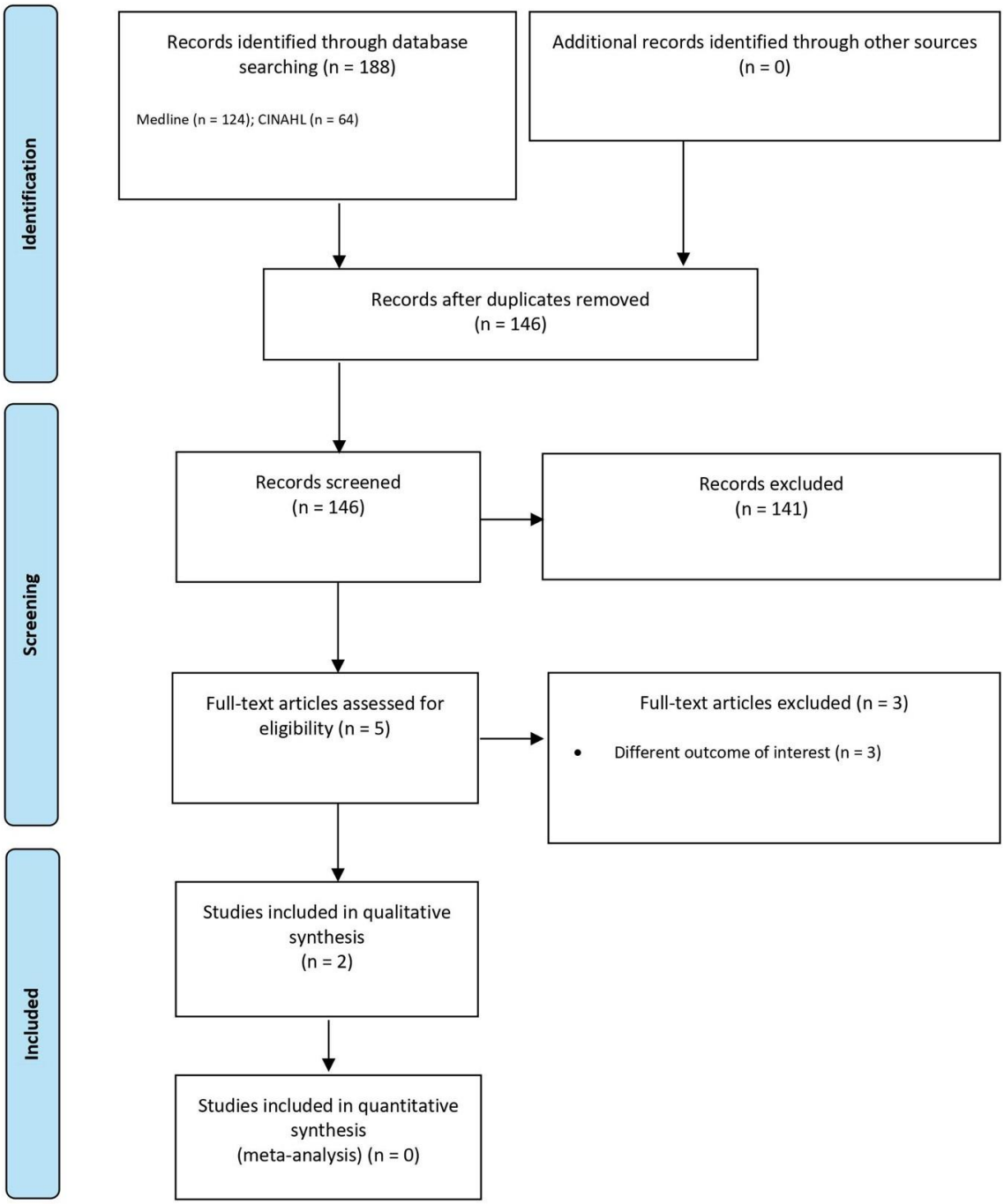


Figure 9: PRISMA Flow Diagram – Quantitative Evidence of Preferences and Values Search Strategy

PRISMA flow diagram showing the clinical search strategy. The database search of the clinical literature yielded 188 citations published between inception and June 20, 2022. We did not identify any additional eligible studies from other sources. After removing duplicates, we screened the abstracts of 146 studies and excluded 141. We assessed the full text of five articles and excluded a further three. In the end, we included two articles in the qualitative synthesis.

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

Source: Adapted from Page et al.[76]

CHARACTERISTICS OF INCLUDED STUDIES

The attributes evaluated in the two included studies are shown in Table 34.

Table 34: Attributes Evaluated in the Included Studies

Author, year	List of attributes	Levels
Stone et al, 2021[124]	Progression-free survival	17, 21, 30 months
	Grade 3 or 4 adverse events	37%, 54%, 74%
	Fatigue, all grades	59%, 69%
	Dosing form and frequency	3 capsules once a day, orally; 2 tablets twice a day, orally
	Diarrhea, all grades[a]	19%, 33%
	Thrombocytopenia, grade 3 or 4[b]	1%, 15%, 34%
	Anemia, grade 3 or 4[b]	19%, 25%
Havrilesky et al, 2020[123]	Overall survival	36, 38, 42 months
	Progression-free survival	15, 17, 21 months
	Nausea	None, mild, moderate
	Fatigue	None, mild, moderate
	Death from myelodysplastic syndrome/acute myeloid leukemia	0%, 1%, 5%, 10%
	Monthly out-of-pocket cost (US dollars)	$0, $50, $500, $1000

[a] Not included as an attribute in the oncologist survey.

[b] Not included as an attribute in the patient survey.

Stone et al[124]

This study was conducted in the United States and aimed to understand the preferences of patients and oncologists for attributes associated with second-line maintenance therapy with PARP inhibitors for epithelial ovarian cancer and the trade-offs that they were willing to make among those attributes.

The study consisted of a cross-sectional quantitative survey administered separately to patients and oncologists to assess treatment preferences using a discrete-choice experiment that described treatments according to a set of attributes (i.e., efficacy, toxicity, drug dosing form, and frequency). First, the authors performed a literature review and concept elicitation interviews to determine the key treatment attributes that influenced treatment choice. These attributes were then included in a draft quantitative survey. Then, the authors performed cognitive interviews with patients and oncologists to obtain feedback on the draft quantitative survey, which was then finalized. Patients received information about the definition of maintenance therapy to understand that treatment would continue until disease progression or unacceptable toxicity; patients also received descriptions of each treatment attribute included in the survey.

The attributes used in the survey included progression-free survival (PFS); grade 3 or 4 adverse events, overall or specific (anemia and thrombocytopenia); fatigue or diarrhea of any grade; drug dosing form; and frequency. Preference weights for the different treatment attributes were reported. Relative preferences for these attributes were also reported based on the respondents' willingness to accept

trade-offs between them. Additional information about the attributes and levels are provided in Table 34.

Patients were identified via relationships with advocacy groups for rare or low-incidence diseases in the United States, and oncologists were identified via a health care research panel that includes more than 400,000 health care professionals in the United States.

The study included patients 18 to 94 years old who had a self-reported diagnosis of ovarian cancer of epithelial or unknown histology and who had completed first-line chemotherapy. Oncologists were included if they had been in practice for 2 to 30 years; were board-certified or were eligible medical, hematological, or gynecological oncologists; had managed at least seven patients with epithelial ovarian cancer in the previous year who had completed first-line therapy; had prescribed maintenance therapy, bevacizumab, PARP inhibitors, or chemotherapy for ovarian cancer; and spent 65% or more of their time in direct patient care in a private or group practice, a cancer centre, a community hospital, or a university or teaching hospital. The study included 204 patients and 151 oncologists.

Havrilesky et al[123]

This study was conducted in the United States and aimed to assess preferences for PARP inhibitor maintenance therapy in the recurrent setting. Adult women diagnosed with ovarian, peritoneal, or fallopian tube cancer (referred to as ovarian cancer) were recruited from different sources, including gynecologic oncology outpatient clinics, an ovarian cancer registry, social media and internet interest groups, and an advocacy group.

The study consisted of a cross-sectional quantitative survey that used a discrete-choice experiment to assess patient preferences for six treatment attributes: overall survival, PFS, nausea, fatigue, death from myelodysplastic syndrome, and monthly cost. The levels chosen for the numeric attributes included clinically plausible values based on data available at the time the study was designed, in addition to more extreme upper and lower values (Table 34). Patients were educated about ovarian cancer treatment, maintenance therapy, and surveillance, as well as descriptions of each attribute. Additionally, strategies were used to address potential issues with low numeracy skills such as visual representations of probabilistic information.

Among 131 women with ovarian cancer who were eligible for participation, 95 (72.5%) completed the survey and were included in the study.

PARTICIPANT BASELINE CHARACTERISTICS

Stone et al[124]

Patients' mean age was 55 years (standard deviation [SD] 10), and 151 (74.0%) reported being in good, very good, or excellent health at the time of the survey. Approximately 60% of the patients reported being diagnosed with stage III or IV ovarian cancer, and half had a recurrence after completion of first-line chemotherapy (10% did not know whether they had a recurrence after first-line chemotherapy). Eighty-six patients (42.2%) were receiving second-line or later chemotherapy at the time of the survey. Of the total, 77 (37.7%) patients had a *BRCA* gene mutation; information was not available for 31 (15.2%) patients. In terms of race or ethnicity, 174 (85.3%) patients were white, 12 (5.9%) were African American or Black, 9 (4.4%) were Hispanic, 8 (3.9%) were Asian, and for one patient race or ethnicity was not specified.

The health care provider group included 80 (53.9%) medical oncologists, 55 (36.4%) hematological oncologists, and 16 (10.6%) gynecological oncologists. Oncologists had been in practice for a mean of 14.9 years (SD 7.2) and had treated a mean of 66.6 patients (SD 89) with ovarian cancer in the preceding 12 months.

Havrilesky et al[123]

Patients' mean age was 61.8 years (SD 9.1). Of the total, 65 patients (68%) had a college degree or higher education, 46 (48.4%) reported recurrent ovarian cancer, and 22 (23.2%) were receiving chemotherapy at the time of the survey. Twelve (12.6%) patients were being treated with a PARP inhibitor at the time of the survey, and 16 (16.8%) had been treated with a PARP inhibitor in the past. A total of 93 (97.9%) patients were white, 2 (2.1%) were Black, and 1 (1.1%) was Native American. According to the authors, age and clinical characteristics did not differ significantly between patients who completed the survey and those who did not.

ATTRIBUTE PREFERENCES

Stone et al[124]

The authors reported on patients' and oncologists' preference weights, which they interpreted by comparing the magnitude of change in one attribute with the change in another attribute.

Patients

Patients felt it was more important to decrease the risk of grade 3 or 4 adverse events from 54% to 37% (change in preference weight 5.70) than to improve PFS from 21 to 30 months (change in preference weight 4.06). Reducing the risk of grade 3 or 4 adverse events from 74% to 54% was more important than improving PFS from 17 to 30 months (changes in preference weights 7.98 and 6.37, respectively).

On the other hand, patients felt it was more important to improve PFS from 17 to 21 months (change in preference weight: 2.31) than to reduce diarrhea of any grade from 33% to 19% (change in preference weight 1.69), to reduce fatigue of any grade from 69% to 59% (change in preference weight 1.34), or to switch from taking three capsules once a day to two tablets twice a day (change in preference weight 0.06).

A mean 27.9-month increase in PFS would be needed for patients to accept an increase in risk of grade 3 or 4 adverse events from 37% to 74%. However, a mean PFS increase of only 3.4 months would be required for patients to accept an increase in risk of any grade of diarrhea from 19% to 33%, and a mean PFS increase of only 2.7 months to accept an increase in risk of any grade of fatigue from 59% to 69%.

Oncologists

Oncologists felt it was more important to improve PFS from 21 to 30 months than to reduce the risk of grade 3 or 4 adverse events from 54% to 37% (change in preference weights 5.42 and 1.75, respectively). They also felt it was also more important to increase PFS from 17 to 21 months (change in preference weight 3.20) than to reduce the risk of grade 3 or 4 adverse events from 54% to 37% (change in preference weight 1.75), reduce the risk of grade 3 or 4 thrombocytopenia from 15% to 1% (change in preference weight 1.26), reduce the risk of fatigue of any grade from 69% to 59% (change in preference weight 0.76), reduce the risk of anemia of any grade from 25% to 19% (change in preference weight 0.02), or switch from administering two tablets twice a day to three capsules once a day (change in preference weight: 0.27).

A mean 6.3-month increase in PFS would be needed for oncologists to accept an increase in risk of grade 3 or 4 adverse events from 37% to 74%. Oncologists would require a mean 3.1-month increase in PFS to accept an increase in grade 3 or 4 thrombocytopenia from 1% to 34% and a mean 1.1-month increase in PFS to accept an increase in fatigue of any grade from 59% to 69%.

Havrilesky et al[123]

The results showed that patients valued overall survival higher than PFS. In other words, the authors reported a statistically significant effect for a 2-month increase in overall survival (from 36 to 38 months; *P* = .001), but not for a 2-month increase in PFS (from 15 to 17 months; *P* = .62). On average, patients would tolerate a 6% risk of myelodysplastic syndrome or acute myeloid leukemia for an additional 6 months of PFS, but a higher (13%) risk of these events would be accepted for an additional 6 months of overall survival. Additional information is provided in Table 35.

Table 35: Benefits, Risks, and Cost Equivalents[a]

Treatment benefit	Treatment benefit gain (from–to)	MDS or AML risk considered acceptable (95% CI)	Monthly out-of-pocket cost considered acceptable, USD (95% CI)
PFS	2 months (15–17)	1% (−4% to 6%)	$6 (−$40 to $181)
	6 months (15–21)	6% (4% to 10%)	$424 ($50 to $702)
Overall survival	2 months (36–38)	4% (2% to 7%)	$159 ($24 to $516)
	6 months (36–42)	13% (10% to 23%)	$998 ($771 to $1455)

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; MDS, myelodysplastic syndrome; PFS, progression-free survival.
[a] Benefit equivalents represent the minimum improvement in treatment benefit (PFS or overall survival) that the respondent would require in exchange for a given level of treatment harm (MDS or AML). Risk equivalents represent the maximum increase in treatment-related risk that the respondent would to accept in exchange for a given level of treatment benefit (PFS or overall survival).[123] Cost equivalents represent the maximum increase in out-of-pocket costs that the respondent would accept for a given increase in PFS or overall survival.[123]
Source: Havrilesky et al.[123]

An average of 7.7 (95% CI 5.3–11.4) additional months of PFS or 3.8 (95% CI 2.5–5.0) additional months of overall survival would be required for patients to accept moderate treatment-related nausea compared to no nausea, and an average of 4.9 (95% CI 2.4–7.1) additional months of PFS or 2.3 (95% CI 0.9–3.4) additional months of overall survival would be required to accept moderate fatigue compared to no fatigue.

For an increase in risk of acute myeloid leukemia or myelodysplastic syndrome of 0% to 10%, patients would require a mean increase of 9 months (95% CI 6.0–13.3) in PFS or 4.5 months (95% CI 3.0–6.1) in overall survival.

When patients were presented with a choice between a treatment break (no anticancer medication) and a minimum-benefit maintenance therapy (2 months of additional PFS and no additional overall survival) with mild nausea, mild fatigue, and a cost of $50 per month, 78% of patients preferred the treatment break.

RELATIVE ATTRIBUTE IMPORTANCE

Stone et al[124]

Patients

The most important attribute for patients was a decrease in risk of grade 3 or 4 adverse events from 74% to 37%; this attribute was almost twice as important as an improvement in PFS of 17 to 30 months (second attribute in importance).

An increase in median PFS from 17 to 30 months was at least three times more important than a decrease in risk of diarrhea of any grade from 33% to 19%, a reduction in risk of fatigue of any grade from 69% to 59%, or a change in dosing form and frequency from two tablets twice a day to three capsules once a day. The least important attribute to patients was a change in dosing form or frequency.

Based on subgroup analyses, although a decrease in risk of grade 3 or 4 adverse events was more important to patients than other attributes regardless of disease status, patients with recurrent ovarian cancer gave less importance to a decrease in grade 3 or 4 adverse events from 74% to 37% than patients in remission or those unaware of their disease status (52.7%, 56.9%, and 60.2%, respectively, $P = .014$).

Oncologists

An increase in median PFS from 17 to 30 months was the most important attribute for oncologists and was almost twice as important as the second most important attribute (decreasing risk of grade 3 or 4 adverse events from 74% to 37%). The third most important attribute was a decrease in risk of grade 3 or 4 thrombocytopenia from 34% to 1%. Each of these three attributes was at least twice as important as a reduction in risk of fatigue of any grade from 69% to 59%, a change in dosing form or frequency, or a reduction in risk of grade 3 or 4 anemia from 25% to 19%. The authors did not observe any differences across oncologist subgroups.

Havrilesky et al[123]

The authors calculated the overall relative importance of each attribute as the maximum difference in preference weights estimated for an attribute. Overall survival (average importance weight 24.5) and monthly out-of-pocket costs (24.6) were the most highly valued attributes, followed by risk of death from myelodysplastic syndrome or acute myeloid leukemia (17.9), nausea (14.7), PFS (10.5) and fatigue (7.8).

The authors found that patient preferences did not vary according to use of PARP inhibitors, current chemotherapy, or cancer recurrence (values not provided), but that this may have been because of low statistical power to detect a difference.

Discussion

The two included studies[123,124] assessed patient preferences for maintenance therapy with PARP inhibitors in the context of ovarian cancer recurrence, and one study[124] also assessed oncologist preferences. The two studies differed somewhat with respect to the attributes they evaluated. For example, whereas both studies included PFS and some treatment adverse events as attributes,[123,124] Havrilesky et al[123] also included overall survival and monthly out-of-pocket costs. The two studies also differed with respect to the prespecified attribute levels used in the discrete-choice experiments.[123,124]

Stone et al[124] found that that for maintenance therapy with PARP inhibitors for recurrent cancer, patients prioritized a reduced risk of grade 3 or 4 adverse events (requiring medical intervention or

hospitalization) over extending PFS. This finding was in contrast to oncologists, who prioritized extending PFS. Havrilesky et al[123] also found that patients valued reducing the risk of certain adverse events more than increasing PFS. However, overall survival and out-of-pocket costs (attributes not evaluated by Stone et al[124]) were valued higher than reducing the risk of adverse events and PFS.

Stone et al[124] concluded that both patients and oncologists accepted trade-offs between efficacy and toxicity risks for second-line maintenance therapy with PARP inhibitors, but to different extents, suggesting a willingness to tolerate some risk of toxicity for an increase in PFS. Havrilesky et al[123] also showed that patients were willing to make trade-offs between efficacy and toxicity.

Stone et al[124] emphasized the importance of discussing the potential risks and benefits of treatment with patients, which may improve shared decision-making between patients and their oncologists.

Havrilesky et al[123] identified the need to better understand whether women who are likely to achieve only minimal improvement in PFS with PARP inhibitor maintenance therapy would believe that the benefit justified the treatment adverse events, risks, and cost.

STRENGTHS AND LIMITATIONS

We did not identify any studies that assessed preferences for HRD testing in patients with ovarian cancer, their health care providers, or both. We also did not identify any studies on quantitative preferences of patients with newly diagnosed ovarian cancer.

The two studies we did identify employed appropriate methodology by using a quantitative tool to elicit individual preferences and assess patient and oncologist preferences for the use of maintenance therapy with PARP inhibitors in the context of recurrent ovarian cancer,[123,124] one of the studies also evaluated oncologists' preferences.[124] However, both studies were performed in the United States, which may differ from the Canadian context, and the preferences elicited were limited to the specific attributes and attribute levels included in the studies.[123,124]

Conclusions

We identified no studies that evaluated preferences for HRD testing in patients with ovarian cancer or their health care providers.

The results of two studies that assessed patients' preferences for maintenance therapy with PARP inhibitors in recurrent ovarian cancer suggest that patients prioritized reducing the occurrence of moderate or severe adverse events over improvements in PFS, although this was specific to the attribute levels used in the studies. In contrast, one of the studies (which assessed oncologist preferences) showed that oncologists placed more importance on improving efficacy than on reducing adverse events.

The results of the one study that evaluated overall survival as a treatment attribute indicated that patients valued overall survival more than PFS.

The findings of these two studies suggest that both patients and oncologists are willing to make some trade-offs between efficacy and toxicity risks.

Direct Patient Engagement

Methods

PARTNERSHIP PLAN

The partnership plan for this health technology assessment focused on consultation to examine the experiences of people with ovarian cancer and their family members or caregivers. We engaged with participants via telephone interviews.

We used a qualitative interview, as this method of engagement allowed us to explore the meaning of central themes in the experiences of people with ovarian cancer.[125] The sensitive nature of exploring people's experiences of a health condition and their quality of life are other factors that support our choice of methodology.

PARTICIPANT OUTREACH

We used an approach called purposive sampling,[126-129] which involves actively reaching out to people with direct experience of the health condition and health technology or intervention being reviewed. We approached a variety of community organizations, clinical experts, and community-based health programs in Ontario that support people diagnosed with ovarian cancer to spread the word about this engagement activity and to contact people who wanted to share their lived experiences.

Inclusion Criteria

We sought to speak with adults with ovarian cancer and those with experience of genetic testing to inform their cancer treatment. Participants did not have to have direct experience of HRD testing.

Exclusion Criteria

We did not set exclusion criteria for participants who otherwise met the inclusion criteria.

Participants

For this project, we spoke with eight people living with cancer in Ontario: seven who had been diagnosed with ovarian cancer and one diagnosed with a non-ovarian cancer. None of the participants had experience with HRD testing, but six participants had experience with other forms of genetic testing, such as *BRCA2* testing. Four participants had experience with or knowledge of PARP inhibitors – specifically niraparib or olaparib.

Participants lived primarily in southern Ontario, with equal representation from rural and urban settings.

APPROACH

At the beginning of the interview, we explained the role of our organization, the purpose of the health technology assessment, the risks of participation, and how participants' personal health information would be protected. We gave this information to participants both verbally and in a letter of information (Appendix 12). We then obtained participants' verbal consent before starting the interview. With participants' consent, we audio-recorded and then transcribed the interviews.

Interviews lasted approximately 30 minutes. The interview was semistructured and consisted of a series of open-ended questions. Questions were based on a list developed by the Health Technology Assessment International Interest Group on Patient and Citizen Involvement in Health Technology Assessment.[130] Questions focused on participants' care journey, the physical and emotional impacts of ovarian cancer, their experiences with treatment options for maintenance therapy, and their

perceptions of the benefits or limitations of HRD testing to inform their cancer treatment. See Appendix 13 for the interview guide.

DATA EXTRACTION AND ANALYSIS

We used a modified version of a grounded-theory methodology to analyze interview transcripts. The grounded-theory approach allowed us to organize and compare experiences across participants. This method consists of a repetitive process of obtaining, documenting, and analyzing responses while simultaneously collecting, analyzing, and comparing information.[131,132] We used the qualitative data analysis software program NVivo[133] to identify and interpret patterns in the data. The patterns we identified allowed us to highlight the impact of ovarian cancer on those interviewed.

Results

CARE JOURNEY

Awareness and Access to Cancer Treatment

Pre-existing knowledge of HRD testing for ovarian cancer varied among those we interviewed. Most participants reported having limited knowledge of HRD testing or how it could inform their cancer treatment:

> *It wasn't an option that I knew of at the time. I was surprised I fell in that group of women that could go forward with this genetic testing – I didn't know there was anything else that I could do.*

> *I didn't know there was specific genetic testing for ovarian cancer; I guess I never really looked into that.*

This was in contrast to the experiences of two participants who had developed a general awareness of maintenance therapy or other forms of genetic testing based on the lived experience of family members or friends:

> *I've talked to a number of other people who had experience with loved ones with ovarian cancer that had died because maintenance therapy wasn't available to them. I also watched my mom have different types of maintenance treatments. She had really awful side effects and was really sick from a number of them.*

> *My mom also went through genetic testing when she was first diagnosed with ovarian cancer, and it revealed nothing, so I didn't bother going ahead with genetic testing at that point. But then when I was diagnosed, they offered it to me, so I did it.*

Once aware of genetic testing and their potential treatment options, those we spoke with relied primarily on their care team and online resources to learn more about the topic. Most participants felt that these initial conversations were limited, but their priority was to prevent cancer recurrence and achieve the best possible health outcomes given their diagnosis:

> *My understanding when [genetic testing] was explained to me was that it was more about my maintenance [therapy] referral. Maintenance was a big part, [but] I don't feel like it was a long conversation. I definitely think more conversations could have happened.*

> *Olaparib was available on prescription, and so I had a discussion with my gynecologist, and he said that he would be willing to prescribe olaparib for me if that's what I wanted. And so, at that*

> *point, I asked him, "Well, can I find out my HRD status?" He went away, came back, and said, "No, HRD testing is not available in Ontario."*
>
> *No one really talked to me about the other potential side effects [of treatment]. Any of the side effects mentioned seemed fairly mild versus having a recurrence.*
>
> *I'm a great Googler, so as soon as I got diagnosed with ovarian cancer, I Googled everything I could. I was completely open to [genetic testing] because the diagnosis was ovarian cancer, [and] the prognosis isn't good.*

Each participant had differential access to genetic testing and maintenance therapy, and several experienced barriers to accessing care. For instance, for several participants their ability to access further treatment appeared to be limited by their eligibility for publicly funded care options. The people we spoke with felt that having to pay for tests that could guide the course of their cancer care was not patient-centred and could put patients in a vulnerable position. Other participants were able to navigate this challenge by accessing treatment through clinical trials or paying out of pocket:

> *I remember the [gynecologic] oncologist mentioning [that] maintenance therapy [was] only approved by OHIP [Ontario Health Insurance Plan] for patients that were BRCA-positive. So, that just meant that I was going to have to consider alternative routes to be able to get that drug funded.*
>
> *I probably would have done it – pretty much whatever it costs. But the question becomes "Why should I have to pay for it?" If it's an effective means of finding out whether there's an effective treatment for me, then it should be covered by OHIP – the way everything else of that nature is covered by OHIP.*

In all cases, a core theme from participants' lived experiences was the role their care provider had in sharing information about genetic testing and facilitating their access to genetic testing and cancer treatment:

> *In that sense, there was a barrier because I'm not sure what [the doctor's] computer told him, but whatever it was … it sounds like there are variations in care depending on whom you go to – whether you actually get access to genetic testing or not. And it's just up to the oncologist or the surgeon or whatever medical provider you're going to.*
>
> *Suddenly, the opportunity to participate in a clinical trial appeared. I had done a lot of research on PARP inhibitors in clinical trials, and so … I was aware of the study [on] niraparib that suggested it was most helpful for people with a BRCA mutation; and secondly, quite helpful for people who [had] HRD.*

GENETIC TESTING AND MAINTENANCE THERAPY

Decision-Making

The decision to undergo genetic testing is highly individualized and context-specific. However, common themes emerged as participants described the key considerations that informed their decision-making during their cancer care journey. For instance, when it came to genetic testing, some participants considered their family history of cancer, the implications of the genetic test for their family members,

and the potential to reduce the risk of cancer recurrence. Participants also reported that their decision to pursue genetic testing was influenced by how it was presented to them by their care team:

> *I did [genetic testing] because I have nieces and nephews. … It was promoted that "You have the opportunity to save a life of one of your relatives or more of your relatives." And I have a lot of nieces and nephews. So, that's why I did it.*

> *I would say [genetic testing] was offered to me as a very good thing to do for my family, and it was simple in terms of getting the blood out at the lab.*

Participants shared how results of the genetic testing informed or would inform their decision to undergo chemotherapy:

> *I did have the oncotype test and the percentage of difference that it would have made for chemo was small; so rather than do chemo, I didn't. I've had two cancers, no chemo, and it's been 10 years. Obviously, that worked out fine.*

> *I knew I wasn't BRCA-mutated, but to make the decision about whether to go ahead and take the PARP inhibitor anyway would have really hinged on if I was HRD [positive or not].*

Notably, two participants described how the results of their genetic test made them question whether further treatment would be their best option. One participant felt that the results supported their decision not to have chemotherapy, while another ultimately pursued cancer treatment, but would have liked to have had access to more information – specifically their HRD status to inform their decision to have maintenance therapy.

In contrast, some participants felt that few options were available to them, and they did not perceive opportunities for shared decision-making when it came to genetic testing or their cancer treatment. In such cases, the people we spoke with relied on the guidance of their health care team:

> *I kind of understood at the time of diagnosis that there weren't very many options for the surgery. And then chemo was presented as "This is what your course of action is going to be" and I didn't question it. I'm not a medical person, so I wouldn't question it.*

> *There weren't very many options. Honestly, the options seemed to be "Chemo now, or die." But basically, recurrence is a death sentence – which is one of the reasons I was so keen on what I could do post-chemo.*

In fact, some participants highlighted the importance of the patient–doctor partnership and trust when considering different cancer treatment options:

> *But it's just that relationship; you build such a relationship with your [gynecologic] oncologist. … And then all of a sudden, I got switched to someone I'd never met before that I was only doing phone consults with because of COVID. So, just that piece I feel like would have helped a lot with that transition – do I feel like what I'm doing next is right? I didn't even feel confident that my medical oncologist would be able to really have that conversation with me.*

> *One of the things that did make the decision more on the apprehensive side is my care was transferred to a medical oncologist out of Thunder Bay who I've never met. We only have phone consultations. So again, trust isn't being built that way.*

The multitude of factors that can affect decision-making in this context highlights the complexity of each care journey. For those we interviewed, decision-making as it relates to genetic testing and chemotherapy was informed by the availability of genetic testing, implications for family members, potential medical benefits, and the patient–doctor partnership. Participants also valued instances in which health care providers made a point of providing contextualized information or reducing barriers through care coordination:

> *I suppose I'm in the mindset of "information is power." And I think that's something else; the genetic counsellor … even just saying "This doesn't mean that there is no genetic link. It just means that maybe we have found the genetic link yet." I found that was really helpful.*

> *I understood from discussions with others that I would be transferred to a different oncologist that was an hour and a half away instead, and I asked if I could stay with her, and she said yes. What that meant [if I had changed oncologists] is that I had to travel for my chemo an hour and a half each way during winter instead of having it in my hometown.*

The participants had differential access to genetic testing and treatment options, and this was reflected in the adverse effects reported. The majority of those we spoke with had chemotherapy or immunotherapy for newly diagnosed cancer. Overall, the participants felt that the adverse effects they experienced during their treatment aligned with their expectations. Such adverse effects included fatigue, hair loss, and muscle aches. Notably, participants had contrasting experiences regarding the severity of the adverse effects from treatment:

> *Chemo is never fun. I was on a 3-week cycle … but, I wouldn't say [there were] severe side effects in the sense that they never had to reduce the levels of my chemo. … I had the standard chemo side effects, and I basically spent most of the first week on the couch.*

> *The first chemotherapy [was] two drugs for six cycles and it was fine. A very good experience.*

> *I've had three [immunotherapy] sessions and it seemed to be working, because every time [I had] a CT scan and blood work of the tumour markers, it was slowly going down and getting smaller and smaller. But then after the third session, the treatment started to become toxic in my body. It was … attacking my liver, [and it was so] strong that it inflamed my gallbladder and I had to stop immediately because of that.*

> *I ended up deciding to do the clinical trial, which was supposed to be for 2 years, but I ended up being taken off the clinical trial after 3 months, because I had too many side effects.*

When it came to maintenance therapy, four participants reported having direct experience with PARP inhibitors – specifically niraparib and olaparib. Those we spoke with experienced severe fatigue, muscle pain, nausea, and vomiting while on maintenance therapy. For some, the severity of the adverse effects resulted in changes to their treatment plan via the introduction of new therapies (e.g., blood transfusion) or temporarily stopping the treatment:

> *Then by the time I got home, 2 days after they gave me the post-chemo [drugs], I was just like, "Oh my God, the pain." [It was the] leg pain, the nausea, vomiting, [couldn't] eat all day – I had the whole works. So, that would be really good if [HRD testing] could be done because it would help the patient.*
>
> *I did have to adjust my [maintenance] medication. [The medication] attacked my blood really badly, and I was really anemic and had to get a number of transfusions. But then I've also heard from professionals in that field that say that's fairly normal to have your medication adjusted and to have a break.*

Emotional Impacts

The emotional aspects of ovarian cancer and maintenance therapy can have a substantial impact on patients and their families. Participants described the emotional toll they experienced and the supports they sought at different stages of their cancer journey. At the time of diagnosis, several participants described feelings of shock as they processed the potential implications of their diagnosis and treatment for themselves and their family:

> *When she [oncologist] said "There's no cure, but we can treat it and extend your life," I mean, what else can I do? It was really hard for my kids too. I was not ready for this … Their father passed away 10 years ago, so it's almost 11 years [that] I'm supporting my kids on my own. So, in my mind, this can't happen. … So, when I spoke to my oncologist for my first interview, I asked if … after the chemotherapy I'm going to be cured and she told me there is no cure for this and so I cried again.*
>
> *And the new plan was that I would have surgery. So, basically from the first time somebody breathed the word cancer to my surgery, was less than 3 weeks – my head was spinning.*

Initial feelings of shock transitioned into other, equally complex emotions as participants navigated genetic testing and different therapeutic options. Each participant had differential access to genetic testing (e.g., *BRCA2* testing via physician referral or clinical trial), but many reported feelings of anxiety or stress:

> *I was certainly anxious waiting for the [genetic test] results. … I wanted to pursue every avenue there was to find out if there was a different treatment for my diagnosis.*
>
> *I was also offered to be part of a study [and] … it was very hard to comprehend everything that I was going through and what would be asked of me. [It] was very stressful.*

For the majority of participants, the psychological burden stemmed from concerns related to their prognosis, timely access to oncological care, heritability, and impact on their quality of life and that of their family members. Concerns about recurrence were more variable; some participants reported distress over the thought of their cancer growing or metastasizing, and others reported that it was a less prominent concern:

> *At the beginning, you don't believe that you're cancer-free and after you've had it, we have a saying amongst some of us in cancer forums: "It may get me one day, but not today." I have little kids, so that is on my mind. It's not on my mind a lot, like [it was] at the beginning. I didn't know what to plan for – [whether it was] 2 years or what. And you know, they're actually my*

> *grandchildren and so even without a cancer diagnosis, I'm always concerned that I wouldn't see them to adulthood. … But your life can change at any time, and now that I know that, I don't dwell on the cancer recurrence that is going to happen.*
>
> *Emotionally, … it's the fear of it coming back again. I know … the treatments worked, let's just say, but [the cancer] didn't disappear.*

The participants that had access to genetic testing and opted for further treatment spoke about material factors that affected their mental wellness as well. Out-of-pocket costs and work–life impacts were often raised as important factors, and they were mostly associated with negative emotionality, such as anxiety or stress:

> *I had hope for the chemotherapy, but then when she mentioned that it's not working, my hope shattered. Like, so, what now? And so that's why I said yes to this immunotherapy – even if I have to spend it from my own bucket. Like, I have the house, so that's how we got by, but it's not easy financially as well.*
>
> *I was anxious, and I didn't really know how it was going to happen. No one ever said I'm going to need to worry about the funding, but the [care team] just kind of kept saying "Someone's gonna call you about it." … I think at the time, you are worried about so many other things that you're just hopeful and trust that it will happen.*

However, there was also the potential benefit of working in a different environment and perceiving work to be a healthy distraction from the cancer diagnosis:

> *I managed to work full time. A lot of people have been [asking] me why [I] don't "use the disability benefit." But if I have this opportunity to work, I get my full salary and I need that. … First and foremost, I need my salary [to pay for the treatment]. Second, I need a distraction. I needed to work just to get my mind off of my cancer journey. If I'm not doing anything, my mind would just play around, and I know that's not good.*

When navigating the emotional effects of their cancer diagnoses, the people we spoke with sought out friends, family, and online communities for support. Participants also reported that their network of supports enhanced their experience as a patient and helped to reduce anxiety:

> *It's hard emotionally, [but] it's a good thing my kids are really supportive. They were great, and I have friends and family who expressed their support too.*
>
> *I'm thankful for the online programs that they have. I'm actively using almost all the programs that they've offered … and I've been talking to a lot of people who would understand me. That was a great help too.*
>
> *[The genetic counsellor] was excellent at explaining what I should be worried about … and what we just don't know yet. [For example], she was very good about explaining how young genetics is. We certainly have some hard and fast facts. … But there's a lot of areas where we see some abnormalities, [and] we really don't know what it means yet – and it could mean absolutely nothing. So that was good from [the] anxiety point of view.*

In some instances, participants felt it was challenging to seek support from their family members because the results of the genetic test would have substantial implications for others. For example, one participant valued genetic testing for its potential impact in terms of continued monitoring. However, at the time, they felt overwhelmed and questioned whether or not they would want to know the results given the implications it may have for their family:

> *I shared [the genetic testing results] with my family and some of my nieces are … having their first child and they're at pretty high risk. So they have decisions to make because of that, and that is an overwhelming responsibility – especially when I was already overwhelmed by cancer in my household. So I'm not sure it's the best thing that I know, but I'm glad my oncologist has all the information she can have in order to treat me as best possible.*

HRD TESTING

All participants were presented with a general overview of HRD testing to inform maintenance therapy for ovarian cancer. Then, they were asked to share their experiences with cancer treatment and what impact publicly funding HRD testing might have for themselves, their caregivers, or people diagnosed with ovarian cancer in Ontario.

Perceived Benefits

Overall, participants supported the potential public funding of HRD testing in patients with ovarian cancer in Ontario. Key factors that informed their view included the technology's perceived clinical effectiveness and potential benefits of targeted therapy as it relates to the patient experience. For example, many described undergoing multiple different therapies and having to manage the physical and emotional impacts of less effective treatments:

> *I would agree that if the science backs [it] up, we would need the testing to know how your genes are working in order to provide the best treatment. I agree with that wholeheartedly.*

> *This technology would really be beneficial. Instead of going from one treatment to another and subjecting our bodies to chemotoxicity, immunotherapy, and whatnot. At least if we're going to do [HRD testing], we know what we're targeting immediately, once and for all.*

> *I think more specific testing for ovarian cancer would be very valuable and necessary. … I think anything that you can offer a woman going through this is helpful. Again, because [treatment] hasn't [changed] that much. Yeah, there's probably more women that are surviving, but it still isn't a great prognosis, generally.*

Participants' perception of publicly funding HRD testing was also influenced by their value for access to personal health information. Participants felt that knowing their HRD status was critical because of its ability to inform maintenance therapy and potentially lead to better health outcomes. For instance, one participant shared that when faced with limited treatment options, maintenance therapy became a pivotal component of their cancer journey. Therefore, knowing their HRD status would have been very impactful for them and their care team as they planned the next steps of the care plan:

> *Knowing whether or not I was HRD deficient would have been enormously helpful because I was trying to decide whether a PARP inhibitor would be helpful to me. Taking a PARP inhibitor is not*

> *nothing, you know? It's a very small percentage, but some of the side effects can be life-threatening and can certainly affect your quality of life.*
>
> *In general, it all depends on the type of cancer we're talking about and what's known about the genetic testing. … In my particular case, that would have been really key for questions about maintenance [therapy]. And maintenance always sounds, like a mild word like, "It's only maintenance – who cares?" But for me, maintenance meant possibly life or death. … So yeah, I think [HRD testing is] vitally important in treatment.*

Overall, when reflecting on their experiences with other genetic testing, the majority of participants valued the information HRD testing would provide about maintenance therapy and its future use for themselves and their family members. All participants supported the possibility of public funding for HRD testing for ovarian cancer and spoke about its perceived value:

> *[HRD testing] should be readily accessible, and we shouldn't have to pay or do anything. It should be available and part of the regular [diagnostic] process.*
>
> *I'm on the directive of more information is better. … [HRD testing can offer] really helpful information because then maybe it's not worth it to be on this medication.*

Additional Considerations

When considering the potential effect of publicly funding HRD testing, several participants commented on the essential need for more patient education. They expressed concerns related to the complexity of genetic testing and challenges navigating the administrative process. For example, a participant shared that administrative complexity influenced a peer's decision to undergo genetic testing for breast cancer. Ultimately, after reflecting on their own lived experiences, participants felt that additional patient education supports should be provided if HRD testing were publicly funded in Ontario:

> *The hard part is going to be explaining [HRD testing] to people. I mean, most people know someone who's had cancer, but you don't really know the ins and outs. … When my father had cancer, I knew almost nothing about what was going on – why he was getting with treatment or what it meant. So, I think most people don't really pay attention or have any reason to pay attention, because it's all big words. If you can create material that is easy for people to understand, you've won most of the battle.*
>
> *I think at the time, your brain can only take in so much information that it's also hard to ask questions and even know what to ask.*
>
> *I have a close friend who has lost her mom and aunt to breast cancer, and she has been putting off doing genetic testing … because by the time you get to the paperwork, you're already apprehensive about whether or not you even want to know – and then doing that paperwork was too overwhelming.*

Patients also expressed concerns about people's eligibility for maintenance therapy based on their HRD status. In fact, one participant referenced their own experience dealing with a similar ambiguity after halting their ovarian cancer treatment because of immunotherapy toxicity and later developing breast

cancer. The participant's experience reflected a broader preference for equitable access to treatment when HRD testing shows a borderline result:

> *It would be nice if it's funded, and it's readily available for us – even if they say we're "on the borderline." My initial surgeon said, "You're on the borderline and you don't need treatment," or "The treatment that you would need is to remove everything." … But then 8 months later, the cancer came back. I've heard that word "borderline" before – it was the same thing with my breast [cancer]: "Your ductal carcinoma in situ is noninvasive. It's localized [and] we removed it," but then 4 months later, we had to remove the entire breast. I mean, should we have known? Should I have had my breast removed in the beginning and saved my body from going through that healing and stuff like that. And so even if something's "borderline," we should be able to have access to it, you know?*

Discussion

Our direct engagement included eight people who had been diagnosed with cancer and had experience with different types of genetic testing. They provided diverse perspectives on the potential for HRD testing for ovarian cancer to be publicly funded in Ontario. We conducted direct engagement through telephone interviews, allowing for a thorough examination of the effects of ovarian cancer on health, emotional well-being, and decision-making from a patient perspective.

Participants' detailed accounts of the emotional and physical effects of ovarian cancer demonstrated a shared value for access to information, prevention of cancer recurrence, and overall survival with minimal adverse effects. Participants' lived experiences highlighted how the decision to undergo genetic testing and maintenance therapy is personal and context-specific. This finding is also reflected in the results of a survey conducted by Ovarian Cancer Canada, in which respondents with ovarian cancer and at least one episode of recurrence stated that they prioritized treatment benefits over some adverse events of treatment and their willingness to endure side effects if it meant they might prolong their life.[34,35] However, it was in contrast to the findings from studies we identified that assessed patients' quantitative preferences for maintenance therapy with PARP inhibitors in recurrent ovarian cancer: those findings suggested that patients prioritized reducing the occurrence of moderate or severe adverse events over improvements in progression-free survival.[123,124]

Participants also shared their experiences navigating the health care system and the barriers they faced in accessing care. They emphasized the importance of the patient–doctor partnership, access to local health care services, and patient education. A barrier that underpinned these core elements of the patient experience was the cost of genetic testing and treatment. Although some participants were able to overcome financial barriers by restructuring their personal finances, participating in clinical trials, or receiving external coverage, they confirmed that this did not align with their values around patient-centred and equitable care. Moreover, the variability in funding solutions suggests greater systemic barriers for patients trying to navigate funding in this specific context. Overall, the people we spoke with felt that publicly funding HRD was aligned with their preferences and values.

Potential limitations of our engagement included the limited number of participants interviewed and the absence of the caregiver perspective. This may have been a result of the availability of HRD testing and differential access to genetic testing, because none of the participants had experience with this specific genetic test. As such, the findings of our direct engagement may not be representative of a larger sampling of people with ovarian cancer who are considering genetic testing to inform their maintenance therapy.

Nevertheless, all of the participants were able to comment on the potential impact of broad access to HRD testing using their lived experience with other genetic testing as a reference. In this way, direct engagement through interviews generated a relevant thematic analysis of diverse perspectives and values among people diagnosed with ovarian cancer who are considering genetic testing to inform their cancer treatment.

Conclusions

Publicly funding HRD testing for ovarian cancer was viewed favourably by those we interviewed. The health technology was perceived to be critical for informing maintenance therapy and aligned with participants' values and preferences, such as cancer prevention and patient-centred care (e.g., treatment with minimal adverse effects). Participants also highlighted existing barriers for patients who are considering genetic testing for ovarian cancer. Many of the barriers were related to access to information and out-of-pocket costs. Overall, those with lived experience of ovarian cancer and genetic testing valued the potential clinical benefits of HRD testing for themselves and their family members, and they emphasized patient education as an important consideration for public funding in Ontario.

Conclusions of the Health Technology Assessment

In patients with newly diagnosed or recurrent high-grade serous or endometrioid ovarian cancer, niraparib maintenance therapy improved progression-free survival compared with no maintenance therapy in both the HRD and HRP groups. The frequency of adverse events (both overall and grade 3 or higher) was higher in the niraparib group. We identified no studies that evaluated the clinical utility of HRD testing to inform patient decisions about the use of niraparib maintenance therapy.

Our systematic review of the economic evidence found only one study that was partially applicable to our research question and that directly evaluated the cost-effectiveness of HRD testing to inform decisions about niraparib maintenance therapy. The generalizability of these findings to the Ontario setting was limited.

For people with ovarian cancer considering niraparib maintenance therapy, our primary economic evaluation found that treatment informed by HRD testing led to lower costs and lower QALYs compared to no HRD testing. Over a 5-year time horizon, HRD testing led to cost savings ($4,509 per person for people with *BRCA* wild type and $3,639 per person for all people); it also led to a 0.116 QALY loss. Our findings were dependent on our assumption about the use of niraparib after HRD testing, which is uncertain.

Over 5 years, publicly funding HRD testing in Ontario for people with newly diagnosed ovarian cancer would lead to a total saving of $9.00 million (if HRD testing were funded for all) to $12.67 million (if HRD testing were funded for people with *BRCA* wild type). Publicly funding HRD testing for people with recurrent ovarian cancer would lead to a total saving of $16.31 million (if HRD testing were funded for all) to $21.67 million (if HRD testing were funded for people with *BRCA* wild type). The estimated cost saving would be due mainly to a lower proportion of HRP patients using niraparib as a result of HRD testing.

Two studies of quantitative preferences found that it was more important for patients to decrease the risk of moderate to severe adverse events than to improve progression-free survival, but oncologists prioritized improvements in progression-free-survival over a reduction in moderate to severe adverse events.

Publicly funding HRD testing for ovarian cancer was viewed favourably by those interviewed, but participants highlighted existing barriers for patients who are considering genetic testing for ovarian cancer. Many of the barriers related to access to information and out-of-pocket costs. Overall, those with lived experience of ovarian cancer and genetic testing valued the potential clinical benefits of HRD testing for themselves and their family members, and they emphasized patient education as an important consideration for public funding in Ontario.

Abbreviations

ADP: adenosine diphosphate
ASCO: American Society of Clinical Oncology
CADTH: Canadian Agency for Drugs and Technologies in Health
CI: confidence interval
CrI: credible interval
ESMO: European Society for Medical Oncology
FACT: Functional Assessment of Cancer Therapy
FFPE: formalin-fixed, paraffin-embedded
FIGO: International Federation of Obstetrics and Gynecology
FOSI: Functional Assessment of Cancer Therapy Ovarian Cancer Symptom Index
g*BRCA*: germline *BRCA*
GIS: genomic instability score
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
HGSOC: high-grade serous ovarian cancer
HR: hazard ratio
HRD: homologous recombination deficiency
HRP: homologous recombination proficiency
HRR: homologous recombination repair
ICER: incremental cost-effectiveness ratio
LOH: loss of heterozygosity
LST: large scale transitions
NCCN: National Comprehensive Cancer Network
NCI CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events
NHS EED: National Health Service Economic Evaluation Database
NICE: National Institute for Health and Care Excellence
NMB: net monetary benefit
PARP: poly-adenosine diphosphate (ADP)-ribose polymerase
PFS: progression-free survival
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY: quality-adjusted life-year
RCT: randomized controlled trial
SD: standard deviation
SE: standard error
TAI: telomeric allelic imbalance
VAS: visual analogue scale
WTA: willingness to accept
WTP: willingness to pay

Glossary

Adverse event: An adverse event is an unexpected medical problem that happens during treatment for a health condition. Adverse events may be caused by something other than the treatment.

Budget impact analysis: A budget impact analysis estimates the financial impact of adopting a new health care intervention on the current budget (i.e., the affordability of the new intervention). It is based on predictions of how changes in the intervention mix will impact the level of health care spending for a specific population. Budget impact analyses are typically conducted for a short-term period (e.g., 5 years). The budget impact, sometimes referred to as the net budget impact, is the estimated cost difference between the current scenario (i.e., the anticipated amount of spending for a specific population without using the new intervention) and the new scenario (i.e., the anticipated amount of spending for a specific population following the introduction of the new intervention).

Cost-effective: A health care intervention is considered cost-effective when it provides additional benefits, compared with relevant alternatives, at an additional cost that is acceptable to a decision-maker based on the maximum willingness-to-pay value.

Cost-effectiveness acceptability curve: In economic evaluations, a cost-effectiveness acceptability curve is a graphical representation of the results of a probabilistic analysis. It illustrates the probability of health care interventions being cost-effective over a range of willingness-to-pay values. Willingness-to-pay values are plotted on the horizontal axis of the graph, and the probability of the intervention of interest and its comparator(s) being cost-effective at corresponding willingness-to-pay values is plotted on the vertical axis.

Cost-effectiveness analysis: Used broadly, "cost-effectiveness analysis" may refer to an economic evaluation used to compare the benefits of two or more health care interventions with their costs. It may encompass several types of analysis (e.g., cost-effectiveness analysis, cost–utility analysis). Used more specifically, "cost-effectiveness analysis" may refer to a type of economic evaluation in which the main outcome measure is the incremental cost per natural unit of health (e.g., life-year, symptom-free day) gained.

Cost–utility analysis: A cost–utility analysis is a type of economic evaluation used to compare the benefits of two or more health care interventions with their costs. The benefits are measured using quality-adjusted life-years, which capture both the quality and quantity of life. In a cost–utility analysis, the main outcome measure is the incremental cost per quality-adjusted life-year gained.

Decision tree: A decision tree is a type of economic model used to assess the costs and benefits of two or more alternative health care interventions. Each intervention may be associated with different outcomes, which are represented by distinct branches in the tree. Each outcome may have a different probability of occurring and may lead to different costs and benefits.

Discounting: Discounting is a method used in economic evaluations to adjust for the differential timing of the costs incurred and the benefits generated by a health care intervention over time. Discounting reflects the concept of positive time preference, whereby future costs and benefits are reduced to reflect their present value. The health technology assessments conducted by Ontario Health use an annual discount rate of 1.5% for both future costs and future benefits.

Disutility: A disutility is a decrease in utility (i.e., a decrease in preference for a particular health outcome) typically resulting from a particular health condition (e.g., experiencing a symptom or complication).

Dominant: A health care intervention is considered dominant when it is more effective and less costly than its comparator(s).

EQ-5D: The EQ-5D is a generic health-related quality-of-life classification system widely used in clinical studies. In economic evaluations, it is used as an indirect method of obtaining health state preferences (i.e., utility values). The EQ-5D questionnaire consists of five questions relating to different domains of quality of life: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For each domain, there are three response options: no problems, some problems, or severe problems. A newer instrument, the EQ-5D-5L, includes five response options for each domain. A scoring table is used to convert EQ-5D scores to utility values.

Health-related quality of life: Health-related quality of life is a measure of the impact of a health care intervention on a person's health. It includes the dimensions of physiology, function, social life, cognition, emotions, sleep and rest, energy and vitality, health perception, and general life satisfaction.

Health state: A health state is a particular status of health (e.g., sick, well, dead). A health state is associated with some amount of benefit and may be associated with specific costs. Benefit is captured through individual or societal preferences for the time spent in each health state and is expressed in quality-adjusted weights called utility values. In a Markov model, a finite number of mutually exclusive health states are used to represent discrete states of health.

Incremental cost: The incremental cost is the additional cost, typically per person, of a health care intervention versus a comparator.

Incremental cost-effectiveness ratio (ICER): The incremental cost-effectiveness ratio (ICER) is a summary measure that indicates, for a given health care intervention, how much more a health care consumer must pay to get an additional unit of benefit relative to an alternative intervention. It is obtained by dividing the incremental cost by the incremental effectiveness. Incremental cost-effectiveness ratios are typically presented as the cost per life-year gained or the cost per quality-adjusted life-year gained.

Incremental net benefit: Incremental net benefit is a summary measure of cost-effectiveness. It incorporates the differences in cost and effect between two health care interventions and the willingness-to-pay value. Net health benefit is calculated as the difference in effect minus the difference in cost divided by the willingness-to-pay value. Net monetary benefit is calculated as the willingness-to-pay value multiplied by the difference in effect minus the difference in cost. An intervention can be considered cost-effective if either the net health or net monetary benefit is greater than zero.

Markov model: A Markov model is a type of decision-analytic model used in economic evaluations to estimate the costs and health outcomes (e.g., quality-adjusted life-years gained) associated with using a particular health care intervention. Markov models are useful for clinical problems that involve events of interest that may recur over time (e.g., stroke). A Markov model consists of mutually exclusive, exhaustive health states. Patients remain in a given health state for a certain period of time before

moving to another health state based on transition probabilities. The health states and events modelled may be associated with specific costs and health outcomes.

Ministry of Health perspective: The perspective adopted in economic evaluations determines the types of costs and health benefits to include. Ontario Health develops health technology assessment reports from the perspective of the Ontario Ministry of Health. This perspective includes all costs and health benefits attributable to the Ministry of Health, such as treatment costs (e.g., drugs, administration, monitoring, hospital stays) and costs associated with managing adverse events caused by treatments. This perspective does not include out-of-pocket costs incurred by patients related to obtaining care (e.g., transportation) or loss of productivity (e.g., absenteeism).

Net monetary benefit: Net monetary benefit is a summary statistic that represents the value of an intervention in monetary terms when a willingness-to-pay value for a unit of benefit (e.g., a quality-adjusted life-year) is known. It allows comparisons to be made without the use of ratios (such as incremental cost-effectiveness ratios).[134]

One-way sensitivity analysis: A one-way sensitivity analysis is used to explore uncertainty in the results of an economic evaluation. It is done by varying one model input (i.e., a parameter) at a time between its minimum and maximum values to observe the potential impact on the cost-effectiveness of the health care intervention of interest.

Probabilistic analysis: A probabilistic analysis (also known as a probabilistic sensitivity analysis) is used in economic models to explore uncertainty in several parameters simultaneously and is done using Monte Carlo simulation. Model inputs are defined as a distribution of possible values. In each iteration, model inputs are obtained by randomly sampling from each distribution, and a single estimate of cost and effectiveness is generated. This process is repeated many times (e.g., 10,000 times) to estimate the number of times (i.e., the probability) that the health care intervention of interest is cost-effective.

Quality-adjusted life-year (QALY): The quality-adjusted life-year (QALY) is a generic health outcome measure commonly used in cost–utility analyses to reflect the quantity and quality of life-years lived. The life-years lived are adjusted for quality of life using individual or societal preferences (i.e., utility values) for being in a particular health state. One year of perfect health is represented by one quality-adjusted life-year.

Reference case: The reference case is a preferred set of methods and principles that provide the guidelines for economic evaluations. Its purpose is to standardize the approach of conducting and reporting economic evaluations, so that results can be compared across studies.

Scenario analysis: A scenario analysis is used to explore uncertainty in the results of an economic evaluation. It is done by observing the potential impact of different scenarios on the cost-effectiveness of a health care intervention. Scenario analyses include varying structural assumptions from the reference case.

Sensitivity analysis: Every economic evaluation contains some degree of uncertainty, and results can vary depending on the values taken by key parameters and the assumptions made. Sensitivity analysis allows these factors to be varied and shows the impact of these variations on the results of the evaluation. There are various types of sensitivity analysis, including deterministic, probabilistic, and scenario.

Time horizon: In economic evaluations, the time horizon is the time frame over which costs and benefits are examined and calculated. The relevant time horizon is chosen based on the nature of the disease and health care intervention being assessed, as well as the purpose of the analysis. For instance, a lifetime horizon would be chosen to capture the long-term health and cost consequences over a patient's lifetime.

Uptake rate: In instances where two technologies are being compared, the uptake rate is the rate at which a new technology is adopted. When a new technology is adopted, it may be used in addition to an existing technology, or it may replace an existing technology.

Utility: A utility is a value that represents a person's preference for various health states. Typically, utility values are anchored at 0 (death) and 1 (perfect health). In some scoring systems, a negative utility value indicates a state of health valued as being worse than death. Utility values can be aggregated over time to derive quality-adjusted life-years, a common outcome measure in economic evaluations.

Visual analogue scale (VAS): The visual analogue scale (VAS) is a direct method of measuring people's preferences for various health states. Respondents are first asked to rank a series of health states from least to most preferable. Then, they are asked to place the health states on a scale with intervals reflecting the differences in preference among the given health states. The scale ranges from 0 (worst imaginable health) to 100 (best imaginable health). The value of a respondent's preference for each health state is given by their placement of each health state on the scale.

Willingness-to-pay value: A willingness-to-pay value is the monetary value a health care consumer is willing to pay for added health benefits. When conducting a cost–utility analysis, the willingness-to-pay value represents the cost a consumer is willing to pay for an additional quality-adjusted life-year. If the incremental cost-effectiveness ratio is less than the willingness-to-pay value, the health care intervention of interest is considered cost-effective. If the incremental cost-effectiveness ratio is more than the willingness-to-pay value, the intervention is considered not to be cost-effective.

Appendices

Appendix 1: Guidelines on HRD Testing and Niraparib Maintenance Therapy in Ovarian Cancer

Table A1: Guidelines for HRD Testing in Ovarian Cancer

Organization, year Cancer type	Conclusions or recommendations
National Comprehensive Cancer Network, 2023 (version 1.2023)[2] Ovarian, fallopian tube, or peritoneal cancer	After first-line chemotherapy, in the absence of a *BRCA1/2* mutation, HRD status may provide information on the magnitude of benefit of PARP inhibitor maintenance therapy
Pan-Canadian consensus statement on first-line PARP inhibitor maintenance, 2022[15] Advanced, high-grade serous and endometrioid tubal, ovarian, and primary peritoneal cancer	*Genetic testing to inform PARP inhibitor maintenance strategies* • All patients with high-grade EOC should have *BRCA1/2* mutation testing to inform hereditary cancer predisposition and the need for cascade testing of family members, and to guide first-line PARP inhibitor maintenance therapy in advanced-stage cases • Tumour HRD status is a predictive biomarker of treatment benefit from PARP inhibitors, and testing should be publicly funded • Assessment of mutations in HRR genes other than *BRCA1/2* should not be used as a substitute for HRD testing
American Society of Clinical Oncology, 2020[62] Epithelial ovarian cancer	• All women diagnosed with EOC should be offered germline genetic testing. Somatic tumour testing for *BRCA1* and *BRCA2* pathogenic or likely pathogenic variants should be performed in women who do not carry a germline pathogenic or likely pathogenic *BRCA1/2* variant • Women with EOC who have not had germline testing at the time of diagnosis should be offered germline genetic testing as soon as feasibly possible. In women who do not carry a germline pathogenic or likely pathogenic *BRCA1/2* variant, somatic tumour testing for *BRCA1* and *BRCA2* pathogenic or likely pathogenic variants should be offered. Somatic tumour testing for *BRCA1* and *BRCA2* pathogenic or likely pathogenic variants may be reserved for time of recurrence for women who have completed upfront therapy and are currently in observation, as presence of these mutations qualifies the patient for FDA-approved treatments • No recommendations can be made to support routine tumour testing using currently available HRD assays. Current assays evaluating HRD have been applied to stratify women with ovarian cancer for treatment

Organization, year Cancer type	Conclusions or recommendations
European Society for Medical Oncology, 2020[10] Ovarian cancer	*Clinical validity* • *BRCA* mutation tests (germline, tumour and somatic) exhibit good clinical validity by consistently identifying the subgroup of ovarian cancer patients who derive the greatest magnitude of benefit from PARP inhibitor therapy • There is insufficient evidence for other HRR gene tests • HRD tests that incorporate scores of allelic imbalance (GIS or LOH) identify a subgroup of *BRCA* wild type platinum-sensitive cancers that derive a greater magnitude of benefit from PARP inhibitor therapy in some settings *Clinical utility* First-line maintenance • Germline and somatic *BRCA* mutation testing are routinely recommended to identify HGSC patients who should receive a PARP inhibitor • It is reasonable to use a validated scar-based HRD test to establish the magnitude of PARP inhibitor benefit in *BRCA* wild type in HGSC • It is reasonable to use a validated scar-based HRD test to identify the subgroup of *BRCA* wild type least likely to benefit from PARP inhibitor therapy Platinum-sensitive relapse maintenance setting • It is reasonable to use *BRCA* mutation testing and validated scar-based HRD tests to predict the likely magnitude of PARP inhibitor benefit for consideration of risks and benefits of maintenance therapy

Abbreviations: EOC, epithelial ovarian cancer; FDA, Food and Drug Administration; GIS, genomic instability score; HGSC, high-grade serous cancer; HRD, homologous recombination deficiency; HRR, homologous recombination repair; GIS genome instability score; LOH, loss of heterozygosity; PARP, poly-adenosine diphosphate (ADP)-ribose polymerase.

Table A2: CADTH Pan-Canadian Oncology Drug Review Recommendations on Niraparib Maintenance Therapy in Patients With Ovarian Cancer

Organization, year	Recommendations and conclusions
CADTH pan-Canadian Oncology Drug Review, 2021[42,43]	*Newly diagnosed* • Niraparib recommended as maintenance treatment of adult patients with newly diagnosed, high-grade, stage III or IV, serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy • Patients should have completed 6–9 cycles of first-line platinum-based chemotherapy and be in complete or partial response • Maintenance therapy with niraparib should start within 12 weeks of the last dose of platinum-based chemotherapy and continue until unacceptable toxicity, disease progression, or completion of 3 years of therapy • Patients should have good performance status *Recurrent* • Niraparib as monotherapy recommended for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy • Patients should have platinum-sensitive disease[a] and have completed at least two prior lines of platinum-based chemotherapy and be in complete or partial response to their most recent platinum-based chemotherapy regimen • Patients must have received at least four cycles of their most recent platinum-based chemotherapy before starting treatment with niraparib • Maintenance therapy with niraparib should start within 8 weeks of the last dose of platinum-based chemotherapy and continue until unacceptable toxicity or disease progression • Patients should have good performance status and no active or uncontrolled metastases in the central nervous system *Both populations* • HRD testing has not been clinically validated and therefore not commonly used in Canadian practice • Treatment decisions should not be guided based on the results of HRD testing alone

Abbreviations: CADTH, Canadian Agency for Drugs and Technologies in Health; HRD, homologous recombination deficiency.

[a] Disease progression occurring at least 6 months after completion of platinum-based chemotherapy.

Appendix 2: Literature Search Strategies
Clinical Evidence Search

Search date: May 25, 2022
Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, CRD Health Technology Assessment Database, NHS Economic Evaluation Database

Database: EBM Reviews – Cochrane Central Register of Controlled Trials <April 2022>, EBM Reviews – Cochrane Database of Systematic Reviews <2005 to May 18, 2022>, EBM Reviews – Health Technology Assessment <4th Quarter 2016>, EBM Reviews – NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2022 Week 20>, Ovid MEDLINE(R) ALL <1946 to May 24, 2022>
Search Strategy:

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1 exp Ovarian Neoplasms/ (251251)
2 (((ovar* or oviduct* or fallopian* or peritone*) adj3 (cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or dysplas* or malignan* or adenocarcinoma* or sarcoma* or metastas#s or oncolog*)) or HGSOC).ti,ab,kf. (283969)
3 ((high-grade adj2 serous carcinoma*) or HGSC).ti,ab,kf. (3951)
4 or/1-3 (348681)
5 (niraparib* or zejula*).ti,ab,kf,nm. (1480)
6 4 and 5 (1036)
7 "Poly(ADP-ribose) Polymerase Inhibitors"/ (13210)
8 ((inhibit* adj5 (parp* or "poly(adp-ribose) polymerase*")) or PARPi or PARP-i or (nicotinamide adj3 ribosyltransferas* inhibitor*)).ti,ab,kf,nm. (26160)
9 or/7-8 (28615)
10 4 and 9 (6999)
11 Recombinational DNA Repair/ (4134)
12 Homologous Recombination/ (22461)
13 (((homolog* or repair* or double-strand*) adj3 recombina*) or HRD* or HRR*).ti,ab,kf. (72306)
14 "Loss of Heterozygosity"/ (24478)
15 ((heterozygosit* adj3 loss*) or LOH or gLOH).ti,ab,kf. (30262)
16 Allelic Imbalance/ (2296)
17 (((allelic* or biallelic*) adj2 (loss* or imbalance* or alteration*)) or TAI).ti,ab,kf. (24523)
18 ((genom* adj3 (scar* or instabilit*)) or scar* based or GIS).ti,ab,kf. (55143)
19 (large-scale* transition* or LST).ti,ab,kf. (5413)
20 (mutation* adj3 signature*).ti,ab,kf. (6492)
21 (functional* adj3 (test* or assay*)).ti,ab,kf. (93976)
22 Biomarkers, Tumor/ (266884)
23 (biomarker* adj2 (direct* or guid* or tumo?r or cancer*)).ti,ab,kf. (41817)
24 Whole Genome Sequencing/ (40625)
25 (((whole* or complete* or full or entire) adj3 genom*) or WGS).ti,ab,kf. (206299)
26 exp High-Throughput Nucleotide Sequencing/ (137234)
27 ((sequenc* adj2 (deep or high-throughput* or high-through-put* or nucleotide* or RNA or illumina* or ion proton* or ion torrent* or massive* parallel* or next-gen* or nextgeneration*)) or NGS or MPS or comprehensive* genom* profiling* or CGP).ti,ab,kf. (504738)
28 (myriad* or mychoice* or foundation medicine* or foundation one* or foundationone* or F1CDx* or sophia* genetic* or sophia* DDM* or CDx or companion diagnostic* or HRDetect*).ti,ab,kf. (50504)

29 or/11-28 (1339835)
30 10 and 29 (3180)
31 6 or 30 (3812)
32 exp Animals/ not Humans/ (16609174)
33 31 not 32 (2957)
34 Case Reports/ or Congress.pt. (2337406)
35 33 not 34 (2921)
36 limit 35 to english language [Limit not valid in CDSR; records were retained] (2845)
37 36 use medall,coch,cctr,clhta,cleed (1218)
38 exp ovary tumor/ (157186)
39 (((ovar* or oviduct* or fallopian* or peritone*) adj3 (cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or dysplas* or malignan* or adenocarcinoma* or sarcoma* or metastas#s or oncolog*)) or HGSOC).tw,kw,kf. (286382)
40 ((high-grade adj2 serous carcinoma*) or HGSC).tw,kw,kf. (3955)
41 or/38-40 (329100)
42 niraparib/ (1872)
43 (niraparib* or zejula*).tw,kw,kf,dq,tn. (1501)
44 or/42-43 (2488)
45 41 and 44 (1589)
46 nicotinamide adenine dinucleotide adenosine diphosphate ribosyltransferase inhibitor/ (8260)
47 ((inhibit* adj5 (parp* or "poly(adp-ribose) polymerase*")) or PARPi or PARP-i or (nicotinamide adj3 ribosyltransferas* inhibitor*)).tw,kw,kf,dq,tn. (25128)
48 or/46-47 (27551)
49 41 and 48 (6814)
50 recombination repair/ (4133)
51 homologous recombination/ (22461)
52 (((homolog* or repair* or double-strand*) adj3 recombina*) or HRD* or HRR*).tw,kw,kf,dv. (72694)
53 heterozygosity loss/ (24478)
54 ((heterozygosit* adj3 loss*) or LOH or gLOH).tw,kw,kf,dv. (30332)
55 allelic imbalance/ (2296)
56 (((allelic* or biallelic*) adj2 (loss* or imbalance* or alteration*)) or TAI).tw,kw,kf,dv. (24835)
57 genomic instability/ (32652)
58 ((genom* adj3 (scar* or instabilit*)) or scar* based or GIS).tw,kw,kf,dv. (55221)
59 (large-scale* transition* or LST).tw,kw,kf,dv. (5430)
60 (functional* adj3 (test* or assay*)).tw,kw,kf,dv. (94700)
61 *tumor marker/ (125073)
62 (biomarker* adj2 (direct* or guid* or tumo?r or cancer*)).tw,kw,kf,dv. (47339)
63 exp whole genome sequencing/ (48139)
64 (((whole* or complete* or full or entire) adj3 genom*) or WGS).tw,kw,kf,dv. (206673)
65 exp high throughput sequencing/ (137234)
66 ((sequenc* adj2 (deep or high-throughput* or high-through-put* or nucleotide* or RNA or illumina* or ion proton* or ion torrent* or massive* parallel* or next-gen* or nextgeneration*)) or NGS or MPS or comprehensive* genom* profiling* or CGP).tw,kw,kf,dv. (509646)
67 (myriad* or mychoice* or foundation medicine* or foundation one* or foundationone* or F1CDx* or sophia* genetic* or sophia* DDM* or CDx or companion diagnostic* or HRDetect*).tw,kw,kf,dv. (51131)
68 or/50-67 (1237382)

69 49 and 68 (3088)
70 45 or 69 (4059)
71 (exp animal/ or nonhuman/) not exp human/ (11439717)
72 70 not 71 (3940)
73 Case Report/ or conference abstract.pt. or conference review.pt. (9066409)
74 72 not 73 (2801)
75 limit 74 to english language [Limit not valid in CDSR; records were retained] (2710)
76 75 use emez (1595)
77 37 or 76 (2813)
78 77 use medall (962)
79 77 use emez (1595)
80 77 use coch (1)
81 77 use cctr (254)
82 77 use clhta (1)
83 77 use cleed (0)
84 remove duplicates from 77 (1972)

Economic Evidence Search

Search date: May 25, 2022
Databases searched: Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, CRD Health Technology Assessment Database, NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <April 2022>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 18, 2022>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2022 Week 20>, Ovid MEDLINE(R) ALL <1946 to May 24, 2022>
Search strategy:

---

1 exp Ovarian Neoplasms/ (251251)
2 (((ovar* or oviduct* or fallopian* or peritone*) adj3 (cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or dysplas* or malignan* or adenocarcinoma* or sarcoma* or metastas#s or oncolog*)) or HGSOC).ti,ab,kf. (283969)
3 ((high-grade adj2 serous carcinoma*) or HGSC).ti,ab,kf. (3951)
4 or/1-3 (348681)
5 (niraparib* or zejula*).ti,ab,kf,nm. (1480)
6 4 and 5 (1036)
7 "Poly(ADP-ribose) Polymerase Inhibitors"/ (13210)
8 ((inhibit* adj5 (parp* or "poly(adp-ribose) polymerase*")) or PARPi or PARP-i or (nicotinamide adj3 ribosyltransferas* inhibitor*)).ti,ab,kf,nm. (26160)
9 or/7-8 (28615)
10 4 and 9 (6999)
11 Recombinational DNA Repair/ (4134)
12 Homologous Recombination/ (22461)
13 (((homolog* or repair* or double-strand*) adj3 recombina*) or HRD* or HRR*).ti,ab,kf. (72306)
14 "Loss of Heterozygosity"/ (24478)
15 ((heterozygosit* adj3 loss*) or LOH or gLOH).ti,ab,kf. (30262)
16 Allelic Imbalance/ (2296)
17 (((allelic* or biallelic*) adj2 (loss* or imbalance* or alteration*)) or TAI).ti,ab,kf. (24523)

18 ((genom* adj3 (scar* or instabilit*)) or scar* based or GIS).ti,ab,kf. (55143)
19 (large-scale* transition* or LST).ti,ab,kf. (5413)
20 (mutation* adj3 signature*).ti,ab,kf. (6492)
21 (functional* adj3 (test* or assay*)).ti,ab,kf. (93976)
22 Biomarkers, Tumor/ (266884)
23 (biomarker* adj2 (direct* or guid* or tumo?r or cancer*)).ti,ab,kf. (41817)
24 Whole Genome Sequencing/ (40625)
25 (((whole* or complete* or full or entire) adj3 genom*) or WGS).ti,ab,kf. (206299)
26 exp High-Throughput Nucleotide Sequencing/ (137234)
27 ((sequenc* adj2 (deep or high-throughput* or high-through-put* or nucleotide* or RNA or illumina* or ion proton* or ion torrent* or massive* parallel* or next-gen* or nextgeneration*)) or NGS or MPS or comprehensive* genom* profiling* or CGP).ti,ab,kf. (504738)
28 (myriad* or mychoice* or foundation medicine* or foundation one* or foundationone* or F1CDx* or sophia* genetic* or sophia* DDM* or CDx or companion diagnostic* or HRDetect*).ti,ab,kf. (50504)
29 or/11-28 (1339835)
30 10 and 29 (3180)
31 6 or 30 (3812)
32 31 use coch,clhta,cleed (2)
33 economics/ (263751)
34 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (982999)
35 economics.fs. (467344)
36 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (1154841)
37 exp "costs and cost analysis"/ (656570)
38 (cost or costs or costing or costly).ti. (312940)
39 cost effective*.ti,ab,kf. (414269)
40 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kf. (270696)
41 models, economic/ (15324)
42 markov chains/ or monte carlo method/ (100058)
43 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (58796)
44 (markov or markow or monte carlo).ti,ab,kf. (164710)
45 quality-adjusted life years/ (50915)
46 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (100376)
47 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (169569)
48 or/33-47 (3123703)
49 31 and 48 (267)
50 49 use medall,cctr (68)
51 32 or 50 (70)
52 Case Reports/ (2270436)
53 51 not 52 (69)
54 limit 53 to english language [Limit not valid in CDSR; records were retained] (65)
55 exp ovary tumor/ (157186)
56 (((ovar* or oviduct* or fallopian* or peritone*) adj3 (cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or dysplas* or malignan* or adenocarcinoma* or sarcoma* or metastas#s or oncolog*)) or HGSOC).tw,kw,kf. (286382)
57 ((high-grade adj2 serous carcinoma*) or HGSC).tw,kw,kf. (3955)

58 or/55-57 (329100)
59 niraparib/ (1872)
60 (niraparib* or zejula*).tw,kw,kf,dq,tn. (1501)
61 or/59-60 (2488)
62 58 and 61 (1589)
63 nicotinamide adenine dinucleotide adenosine diphosphate ribosyltransferase inhibitor/ (8260)
64 ((inhibit* adj5 (parp* or "poly(adp-ribose) polymerase*")) or PARPi or PARP-i or (nicotinamide adj3 ribosyltransferas* inhibitor*)).tw,kw,kf,dq,tn. (25128)
65 or/63-64 (27551)
66 58 and 65 (6814)
67 recombination repair/ (4133)
68 homologous recombination/ (22461)
69 (((homolog* or repair* or double-strand*) adj3 recombina*) or HRD* or HRR*).tw,kw,kf,dv. (72694)
70 heterozygosity loss/ (24478)
71 ((heterozygosit* adj3 loss*) or LOH or gLOH).tw,kw,kf,dv. (30332)
72 allelic imbalance/ (2296)
73 (((allelic* or biallelic*) adj2 (loss* or imbalance* or alteration*)) or TAI).tw,kw,kf,dv. (24835)
74 genomic instability/ (32652)
75 ((genom* adj3 (scar* or instabilit*)) or scar* based or GIS).tw,kw,kf,dv. (55221)
76 (large-scale* transition* or LST).tw,kw,kf,dv. (5430)
77 (functional* adj3 (test* or assay*)).tw,kw,kf,dv. (94700)
78 *tumor marker/ (125073)
79 (biomarker* adj2 (direct* or guid* or tumo?r or cancer*)).tw,kw,kf,dv. (47339)
80 exp whole genome sequencing/ (48139)
81 (((whole* or complete* or full or entire) adj3 genom*) or WGS).tw,kw,kf,dv. (206673)
82 exp high throughput sequencing/ (137234)
83 ((sequenc* adj2 (deep or high-throughput* or high-through-put* or nucleotide* or RNA or illumina* or ion proton* or ion torrent* or massive* parallel* or next-gen* or nextgeneration*)) or NGS or MPS or comprehensive* genom* profiling* or CGP).tw,kw,kf,dv. (509646)
84 (myriad* or mychoice* or foundation medicine* or foundation one* or foundationone* or F1CDx* or sophia* genetic* or sophia* DDM* or CDx or companion diagnostic* or HRDetect*).tw,kw,kf,dv. (51131)
85 or/67-84 (1237382)
86 66 and 85 (3088)
87 62 or 86 (4059)
88 Economics/ (263751)
89 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (142232)
90 Economic Aspect/ or exp Economic Evaluation/ (523326)
91 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw,kf. (1175739)
92 exp "Cost"/ (656570)
93 (cost or costs or costing or costly).ti. (312940)
94 cost effective*.tw,kw,kf. (424175)
95 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kw,kf. (281501)
96 Monte Carlo Method/ (77960)
97 (decision adj1 (tree* or analy* or model*)).tw,kw,kf. (62219)

98 (markov or markow or monte carlo).tw,kw,kf. (168193)
99 Quality-Adjusted Life Years/ (50915)
100 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw,kf. (103864)
101 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw,kf. (190605)
102 or/88-101 (2676071)
103 87 and 102 (220)
104 103 use emez (151)
105 Case Report/ (4913251)
106 104 not 105 (150)
107 limit 106 to english language [Limit not valid in CDSR; records were retained] (148)
108 54 or 107 (213)
109 108 use medall (44)
110 108 use emez (148)
111 108 use coch (1)
112 108 use cctr (19)
113 108 use clhta (1)
114 108 use cleed (0)
115 remove duplicates from 108 (166)

Quantitative Evidence of Preferences and Values Search

Search date: June 20, 2022
Databases searched: Ovid MEDLINE, Cumulative Index to Nursing & Allied Health Literature (CINAHL)
Search filter used: Quantitative preference evidence filter, modified from Selva et al.

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <April 2022>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 18, 2022>, EBM Reviews - Health Technology Assessment <4th Quarter 2016>, EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>, Embase <1980 to 2022 Week 20>, Ovid MEDLINE(R) ALL <1946 to May 24, 2022>
Search strategy:

---

1 exp Ovarian Neoplasms/ (251251)
2 (((ovar* or oviduct* or fallopian* or peritone*) adj3 (cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or dysplas* or malignan* or adenocarcinoma* or sarcoma* or metastas#s or oncolog*)) or HGSOC).ti,ab,kf. (283969)
3 ((high-grade adj2 serous carcinoma*) or HGSC).ti,ab,kf. (3951)
4 or/1-3 (348681)
5 (niraparib* or zejula*).ti,ab,kf,nm. (1480)
6 4 and 5 (1036)
7 "Poly(ADP-ribose) Polymerase Inhibitors"/ (13210)
8 ((inhibit* adj5 (parp* or "poly(adp-ribose) polymerase*")) or PARPi or PARP-i or (nicotinamide adj3 ribosyltransferas* inhibitor*)).ti,ab,kf,nm. (26160)
9 or/7-8 (28615)
10 4 and 9 (6999)
11 Recombinational DNA Repair/ (4134)
12 Homologous Recombination/ (22461)
13 (((homolog* or repair* or double-strand*) adj3 recombina*) or HRD* or HRR*).ti,ab,kf. (72306)
14 "Loss of Heterozygosity"/ (24478)
15 ((heterozygosit* adj3 loss*) or LOH or gLOH).ti,ab,kf. (30262)

16 Allelic Imbalance/ (2296)
17 (((allelic* or biallelic*) adj2 (loss* or imbalance* or alteration*)) or TAI).ti,ab,kf. (24523)
18 ((genom* adj3 (scar* or instabilit*)) or scar* based or GIS).ti,ab,kf. (55143)
19 (large-scale* transition* or LST).ti,ab,kf. (5413)
20 (mutation* adj3 signature*).ti,ab,kf. (6492)
21 (functional* adj3 (test* or assay*)).ti,ab,kf. (93976)
22 Biomarkers, Tumor/ (266884)
23 (biomarker* adj2 (direct* or guid* or tumo?r or cancer*)).ti,ab,kf. (41817)
24 Whole Genome Sequencing/ (40625)
25 (((whole* or complete* or full or entire) adj3 genom*) or WGS).ti,ab,kf. (206299)
26 exp High-Throughput Nucleotide Sequencing/ (137234)
27 ((sequenc* adj2 (deep or high-throughput* or high-through-put* or nucleotide* or RNA or illumina* or ion proton* or ion torrent* or massive* parallel* or next-gen* or nextgeneration*)) or NGS or MPS or comprehensive* genom* profiling* or CGP).ti,ab,kf. (504738)
28 (myriad* or mychoice* or foundation medicine* or foundation one* or foundationone* or F1CDx* or sophia* genetic* or sophia* DDM* or CDx or companion diagnostic* or HRDetect*).ti,ab,kf. (50504)
29 or/11-28 (1339835)
30 10 and 29 (3180)
31 6 or 30 (3812)
32 31 use coch,clhta,cleed (2)
33 economics/ (263751)
34 economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (982999)
35 economics.fs. (467344)
36 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).ti,ab,kf. (1154841)
37 exp "costs and cost analysis"/ (656570)
38 (cost or costs or costing or costly).ti. (312940)
39 cost effective*.ti,ab,kf. (414269)
40 (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kf. (270696)
41 models, economic/ (15324)
42 markov chains/ or monte carlo method/ (100058)
43 (decision adj1 (tree* or analy* or model*)).ti,ab,kf. (58796)
44 (markov or markow or monte carlo).ti,ab,kf. (164710)
45 quality-adjusted life years/ (50915)
46 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).ti,ab,kf. (100376)
47 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).ti,ab,kf. (169569)
48 or/33-47 (3123703)
49 31 and 48 (267)
50 49 use medall,cctr (68)
51 32 or 50 (70)
52 Case Reports/ (2270436)
53 51 not 52 (69)
54 limit 53 to english language [Limit not valid in CDSR; records were retained] (65)
55 exp ovary tumor/ (157186)

56 (((ovar* or oviduct* or fallopian* or peritone*) adj3 (cancer* or neoplas* or tumo?r* or lesion* or carcinoma* or adenoma* or dysplas* or malignan* or adenocarcinoma* or sarcoma* or metastas#s or oncolog*)) or HGSOC).tw,kw,kf. (286382)
57 ((high-grade adj2 serous carcinoma*) or HGSC).tw,kw,kf. (3955)
58 or/55-57 (329100)
59 niraparib/ (1872)
60 (niraparib* or zejula*).tw,kw,kf,dq,tn. (1501)
61 or/59-60 (2488)
62 58 and 61 (1589)
63 nicotinamide adenine dinucleotide adenosine diphosphate ribosyltransferase inhibitor/ (8260)
64 ((inhibit* adj5 (parp* or "poly(adp-ribose) polymerase*")) or PARPi or PARP-i or (nicotinamide adj3 ribosyltransferas* inhibitor*)).tw,kw,kf,dq,tn. (25128)
65 or/63-64 (27551)
66 58 and 65 (6814)
67 recombination repair/ (4133)
68 homologous recombination/ (22461)
69 (((homolog* or repair* or double-strand*) adj3 recombina*) or HRD* or HRR*).tw,kw,kf,dv. (72694)
70 heterozygosity loss/ (24478)
71 ((heterozygosit* adj3 loss*) or LOH or gLOH).tw,kw,kf,dv. (30332)
72 allelic imbalance/ (2296)
73 (((allelic* or biallelic*) adj2 (loss* or imbalance* or alteration*)) or TAI).tw,kw,kf,dv. (24835)
74 genomic instability/ (32652)
75 ((genom* adj3 (scar* or instabilit*)) or scar* based or GIS).tw,kw,kf,dv. (55221)
76 (large-scale* transition* or LST).tw,kw,kf,dv. (5430)
77 (functional* adj3 (test* or assay*)).tw,kw,kf,dv. (94700)
78 *tumor marker/ (125073)
79 (biomarker* adj2 (direct* or guid* or tumo?r or cancer*)).tw,kw,kf,dv. (47339)
80 exp whole genome sequencing/ (48139)
81 (((whole* or complete* or full or entire) adj3 genom*) or WGS).tw,kw,kf,dv. (206673)
82 exp high throughput sequencing/ (137234)
83 ((sequenc* adj2 (deep or high-throughput* or high-through-put* or nucleotide* or RNA or illumina* or ion proton* or ion torrent* or massive* parallel* or next-gen* or nextgeneration*)) or NGS or MPS or comprehensive* genom* profiling* or CGP).tw,kw,kf,dv. (509646)
84 (myriad* or mychoice* or foundation medicine* or foundation one* or foundationone* or F1CDx* or sophia* genetic* or sophia* DDM* or CDx or companion diagnostic* or HRDetect*).tw,kw,kf,dv. (51131)
85 or/67-84 (1237382)
86 66 and 85 (3088)
87 62 or 86 (4059)
88 Economics/ (263751)
89 Health Economics/ or Pharmacoeconomics/ or Drug Cost/ or Drug Formulary/ (142232)
90 Economic Aspect/ or exp Economic Evaluation/ (523326)
91 (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw,kw,kf. (1175739)
92 exp "Cost"/ (656570)
93 (cost or costs or costing or costly).ti. (312940)
94 cost effective*.tw,kw,kf. (424175)

95 (cost* adj2 (util* or efficac* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab,kw,kf. (281501)
96 Monte Carlo Method/ (77960)
97 (decision adj1 (tree* or analy* or model*)).tw,kw,kf. (62219)
98 (markov or markow or monte carlo).tw,kw,kf. (168193)
99 Quality-Adjusted Life Years/ (50915)
100 (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw,kw,kf. (103864)
101 ((adjusted adj1 (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw,kw,kf. (190605)
102 or/88-101 (2676071)
103 87 and 102 (220)
104 103 use emez (151)
105 Case Report/ (4913251)
106 104 not 105 (150)
107 limit 106 to english language [Limit not valid in CDSR; records were retained] (148)
108 54 or 107 (213)
109 108 use medall (44)
110 108 use emez (148)
111 108 use coch (1)
112 108 use cctr (19)
113 108 use clhta (1)
114 108 use cleed (0)
115 remove duplicates from 108 (166)

CINAHL

#	Query	Results
S1	(MH "Ovarian Neoplasms+")	15,068
S2	(((ovar* or oviduct* or fallopian* or peritone*) N3 (cancer* or neoplas* or tumor* or tumour* or lesion* or carcinoma* or adenoma* or dysplas* or malignan* or adenocarcinoma* or sarcoma* or metastas#s or oncolog*)) or HGSOC)	22,843
S3	((high-grade N2 serous carcinoma*) or HGSC)	314
S4	S1 OR S2 OR S3	22,914
S5	(niraparib* or zejula* or olaparib* or lynparza* or rucaparib* or rubraca* or veliparib*)	784
S6	((inhibit* N5 (parp* or polymerase*)) or PARPi or PARP-i or (nicotinamide N3 ribosyltransferas* inhibitor*))	1,835
S7	(((homolog* or repair* or double-strand*) N3 recombina*) or HRD* or HRR*)	1,998
S8	((genom* N3 (scar* or instabilit*)) or scar* based or GIS)	2,646
S9	(large-scale* transition* or LST)	420
S10	(myriad* or mychoice* or foundation medicine* or foundation one* or foundationone* or F1CDx* or sophia* genetic* or sophia* DDM* or CDx or companion diagnostic* or HRDetect*)	4,738
S11	S5 OR S6 OR S7 OR S8 OR S9 OR S10	11,518
S12	S4 AND S11	791
S13	(MH "Attitude to Health")	48,013
S14	(MH "Health Knowledge")	34,425
S15	(MH "Consumer Participation")	22,898
S16	(MH "Patient Preference")	1,799
S17	(MH "Attitude of Health Personnel")	50,607
S18	(MM "Professional-Patient Relations")	14,304
S19	(MM "Physician-Patient Relations")	17,211

S20 (MM "Nurse-Patient Relations") 14,790
S21 TI (choice or choices or value* or valuation* or knowledg*) 110,108
S22 (preference* or expectation* or attitude* or acceptab* or point of view) 523,871
S23 ((patient or patients or user or users or men or women or personal or provider* or professional or professionals or (health* N2 worker*) or clinician* or physician* or doctor* or nurse* or practitioner* or oncologist* or geneticist* or genetic counselor*) N2 (participation or perspective* or perception* or misperception* or perceiv* or view* or understand* or misunderstand* or value or values or knowledg*)) 938,832
S24 health perception* 5,028
S25 (MH "Decision Making, Shared") 2,706
S26 (MH "Decision Making, Patient") 15,666
S27 (MH "Decision Making, Family") 4,186
S28 (MM "Decision Making") 25,047
S29 TI (patient or patients or user or users or men or women or personal or provider* or professional or professionals or (health* N2 worker*) or clinician* or physician* or doctor* or nurse* or practitioner* or oncologist* or geneticist* or genetic counselor*) 1,331,216
S30 S28 AND S29 5,342
S31 TI (decision* and mak*) 20,346
S32 (decision mak* or decisions mak*) 172,850
S33 S31 OR S32 173,075
S34 (patient or patients or user or users or men or women or personal or provider* or professional or professionals or (health* N2 worker*) or clinician* or physician* or doctor* or nurse* or practitioner* or oncologist* or geneticist* or genetic counselor*) 3,721,623
S35 S33 AND S34 123,045
S36 (discrete choice* or decision board* or decision analy* or decision support or decision tool* or decision aid* or latent class* or decision* conflict* or decision* regret*) 34,011
S37 (MH "Decision Support Techniques") 7,561
S38 TI (health and utilit*) 1,080
S39 (gamble* or prospect theory or health utilit* or utility value* or utility score* or utility estimate* or health state or feeling thermometer* or best worst scaling or time trade off or TTO or probability trade off) 20,207
S40 (preference based or preference score* or preference elicitation or multiattribute or multi attribute) 1,735
S41 S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S30 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 1,427,861
S42 S12 AND S41 65
S43 S42 Narrow by Language: - english 64

Grey Literature Search

Performed on: May 28 – June 02, 2020
Websites searched: Alberta Health Evidence Reviews, Alberta Health Services, BC Health Technology Assessments, Canadian Agency for Drugs and Technologies in Health (CADTH), Institut national d'excellence en santé et en services sociaux (INESSS), Institute of Health Economics (IHE), McGill University Health Centre Health Technology Assessment Unit, Centre Hospitalier de l'Université de Quebec-Université Laval, Health Technology Assessment Database, Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Centers, Centers for Medicare & Medicaid Services Technology Assessments, Veterans Affairs Health Services Research and Development, Institute for Clinical and

Economic Review, Oregon Health Authority Health Evidence Review Commission, Washington State Health Care Authority Health Technology Reviews, National Institute for Health and Care Excellence (NICE), Healthcare Improvement Scotland, Health Technology Wales, Ireland Health Information and Quality Authority Health Technology Assessments, Australian Government Medical Services Advisory Committee, Australian Safety and Efficacy Register of New Interventional Procedures -Surgical (ASERNIP-S), Italian National Agency for Regional Health Services (AGENAS), Belgian Health Care Knowledge Centre, Ludwig Boltzmann Institute for Health Technology Assessment, Swedish Agency for Health Technology Assessment and Assessment of Social Services, Ministry of Health Malaysia Health Technology Assessment Section, Tuft's Cost-Effectiveness Analysis Registry, PROSPERO, EUnetHTA, clinicaltrials.gov

Keywords used: niraparib, parp inhibitors, parp-i, inhibitors, homologous recombination, hrd, hrr, heterozygosity, allelic imbalance, genomic instability, genomic scar, scar based, large scale transition*, functional test/assay, ovarian/high grade carcinoma/cancer, fallopian, peritone*, mychoice*, foundationone*, cdx, companion diagnostic*

Clinical results (included in PRISMA): 14
Economic results (included in PRISMA): 12
Ongoing HTAs (PROSPERO/EUnetHTA/): 2
Ongoing RCTs (clinicaltrials.gov): 72

Appendix 3: Critical Appraisal of Clinical Evidence

Table A3: Risk of Bias[a] Among Randomized Controlled Trials (Cochrane Risk-of-Bias Tool)

Author, year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data	Outcome measurement	Selective reporting	Other bias
González-Martín et al, 2019[19]	Low	Low	Low	Low	Low	Low	–
Mirza et al, 2016[33]	Low	Low	Low	Low	Low	Low	–

[a] Possible risk-of-bias levels: low, high, and unclear.

Source: Sterne et al.[70]

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Table A4: GRADE Evidence Profile for the Comparison of Niraparib and Placebo According to HRD Status (Newly Diagnosed Ovarian Cancer)

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Progression-free survival (HRD, includes HRD overall, HRD *BRCA* mutation, and *BRCA* wild type)[a]							
1 RCT[19]	No serious limitations	Could not be evaluated	No serious limitations	No serious limitations	Undetected	NA	⨁⨁⨁⨁ High
Progression-free survival (HRP)[a]							
1 RCT[19]	No serious limitations	Could not be evaluated	No serious limitations	No serious limitations	Undetected	NA	⨁⨁⨁⨁ High
Overall survival (HRD)							
1 RCT[19]	No serious limitations	Could not be evaluated	No serious limitations	Very serious limitations (−2)[b]	Undetected	NA	⨁⨁ Low
Overall survival (HRP)							
1 RCT[19]	No serious limitations	Could not be evaluated	No serious limitations	Very serious limitations (−2)[c]	Undetected	NA	⨁⨁ Low
Time to subsequent chemotherapy (HRD)							
1 RCT[19]	No serious limitations	Could not be evaluated	No serious limitations	Very serious limitations (−2)[d]	Undetected	NA	⨁⨁ Low

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Time to subsequent chemotherapy (HRP)							
1 RCT[19]	No serious limitations	Could not be evaluated	No serious limitations	Very serious limitations (−2)[d]	Undetected	NA	⨁⨁ Low
Progression-free survival 2 (HRD)							
1 RCT[19]	No serious limitations	Could not be evaluated	No serious limitations	Very serious limitations (−2)[e]	Undetected	NA	⨁⨁ Low
Progression-free survival 2 (HRP)							
1 RCT[19]	No serious limitations	Could not be evaluated	No serious limitations	Very serious limitations (−2)[f]	Undetected	NA	⨁⨁ Low

Abbreviations: GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HRD, homologous recombination deficiency; HRP, homologous recombination proficiency; NA, not applicable; RCT, randomized controlled trial.

[a] Based on the hazard ratio for disease progression or death results in each group.

[b] The confidence interval includes the null, the result is based on an interim analysis, and the study authors stated that the number of events was too low for conclusions to be drawn for this outcome.

[c] The confidence interval did not include the null but was wide; the results were based on an interim analysis, and the study authors stated that the number of events was too low for conclusions to be drawn for this outcome.

[d] The confidence interval did not include the null, but the result was based on an interim analysis and the number of events was low.

[e] The confidence interval included the null, the result was based on an interim analysis, the number of events was low, and follow-up time was short.

[f] The confidence interval did not include the null, but the result was based on an interim analysis, the number of events was low, and follow-up time was short.

Table A5: GRADE Evidence Profile for the Comparison of Niraparib and Placebo According to HRD Status (Recurrent Ovarian Cancer, Non-g*BRCA* Cohort)

Number of studies (design)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Upgrade considerations	Quality
Progression-free survival (HRD includes HRD overall, HRD *BRCA* mutation and *BRCA* wild type)[a]							
1 RCT[33]	No serious limitations	Could not be evaluated	No serious limitations	No serious limitations	Undetected	NA	⨁⨁⨁⨁ High
Progression-free survival (*BRCA* cohort, HRP)[a]							
1 RCT[33]	No serious limitations	Could not be evaluated	No serious limitations	No serious limitations	Undetected	NA	⨁⨁⨁⨁ High
FOSI (HRD overall)							
1 RCT[33]	No serious limitations	Could not be evaluated	No serious limitations	Very serious limitations (−2)[b]	Undetected	NA	⨁⨁ Low
EQ-5D-5L (HRD overall)							
1 RCT[33]	No serious limitations	Could not be evaluated	No serious limitations	Very serious limitations (−2)[b]	Undetected	NA	⨁⨁ Low

Abbreviations: FOSI, Functional Assessment of Cancer Therapy Ovarian Cancer Symptom Index; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; g*BRCA*, germline *BRCA*; HRD, homologous recombination deficiency; HRP, homologous recombination proficiency; RCT, randomized controlled trial.

[a] Based on the hazard ratio for disease progression or death results in each group. The quality of the evidence was not assessed based on the median difference in progression-free survival between niraparib and placebo.

[b] Statistical test result was not provided by the investigators, but because the scores in the niraparib and placebo groups were very similar and the standard error of the means were overlapping between the two groups, we assumed that the difference between the groups was not significant. As well, the study was not powered to evaluate this secondary outcome.

Appendix 4: Selected Excluded Studies – Clinical Evidence

For transparency, we provide a list of studies that readers might have expected to see but that did not meet the inclusion criteria, along with the primary reason for exclusion.

Citation	Primary reason for exclusion
Barretina-Ginesta MP, Monk BJ, Han S, Pothuri B, Auranen A, Chase DM, et al. Quality-adjusted time without symptoms of disease or toxicity and quality-adjusted progression-free survival with niraparib maintenance in first-line ovarian cancer in the PRIMA trial. Ther Adv Med Oncol. 2022;14:17588359221126149.	Included simulation analyses
Berek JS, Matulonis UA, Peen U, Ghatage P, Mahner S, Redondo A, et al. Safety and dose modification for patients receiving niraparib. Ann Oncol. 2018;29(8):1784-92.	Not compared to no maintenance therapy
Cheng H, Yang J, Liu H, Xiang Y. Poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors as maintenance therapy in women with newly diagnosed ovarian cancer: a systematic review and meta-analysis. Arch Gynecol Obstet. 2021;304(2):285-96.	Not specific to niraparib
Hirte H, Yao X, Ferguson SE, May T, Elit L. Consolidation or maintenance systemic therapy for newly diagnosed stage II, III, or IV epithelial ovary, fallopian tube, or primary peritoneal carcinoma: a systematic review. Crit Rev Oncol Hematol. 2021;162:103336.	Addressed only one of the research questions
Ibrahim EM, Refae AA, Bayer AM, Sagr ER. Poly(ADP-ribose) polymerase inhibitors as maintenance treatment in patients with newly diagnosed advanced ovarian cancer: a meta-analysis. Future Oncol. 2020;16(10):585-96.	Not specific to niraparib
Kaneko M. Effect of PARP inhibitors as maintenance treatment on restricted mean survival time in platinum-sensitive recurrent ovarian cancer: a systematic review and meta-analysis. Ann Pharmacother. 2022;56(1):27-34.	Not specific to niraparib
Matulonis UA, Walder L, Nøttrup TJ, Bessette P, Mahner S, Gil-Martin M, et al. Niraparib maintenance treatment improves time without symptoms or toxicity (TWiST) versus routine surveillance in recurrent ovarian cancer: a TWiST analysis of the ENGOT-OV16/NOVA Trial. J Clin Oncol. 2019;37(34):3183-91.	Included simulation analyses
Morice PM, Ray-Coquard I, Moore KN, Diéras V, Alexandre J. PARP inhibitors and newly second primary malignancies in cancer patients: a systematic review and safety meta-analysis of placebo randomized controlled trials. Ann Oncol. 2021;32(8):1048-50.	Not specific to niraparib, no HRD testing
Pagkali A, Mamais I, Michalinos A, Agouridis AP. Safety profile of niraparib as maintenance therapy for ovarian cancer: a systematic review and meta-analysis. Curr Oncol. 2022;29(1):321-36.	No HRD testing
Skelin M, Šarčević D, Lešin Gaćina D, Mucalo I, Dilber I, Javor E. The effect of PARP inhibitors in homologous recombination proficient ovarian cancer: meta-analysis. J Chemother. 2022;13:1-8.	Not specific to niraparib
Tattersall A, Ryan N, Wiggans AJ, Rogozińska E, Morrison J. Poly(ADP-ribose) polymerase (PARP) inhibitors for the treatment of ovarian cancer. Cochrane Database Syst Rev. 2022;2(2):CD007929.	Addressed only one of the research questions
Wu XH, Zhu JQ, Yin RT, Yang JX, Liu JH, Wang J, et al. Niraparib maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer using an individualized starting dose (NORA): a randomized, double-blind, placebo-controlled phase III trial. Ann Oncol. 2021;32(4):512-21.	No HRD testing

Abbreviation: HRD, homologous recombination deficiency.

Appendix 5: Characteristics of Included Studies

Table A6: Characteristics of Included Studies

Author, year Name N (niraparib/placebo) Median follow-up at analysis Support	Study design and methods	Participants	HRD testing	Intervention and control	Outcomes
González-Martín et al, 2019[19] PRIMA Study N = 733 (487/246) 13.8 mo GlaxoSmithKline	Multinational Double-blind Centralized randomization Stratified according to clinical response to first-line platinum-based chemotherapy, receipt of neoadjuvant chemotherapy, and HRD status Crossover from the placebo to the niraparib group was not permitted Independent committees reviewed efficacy and safety data (blinded committee for efficacy) Efficacy analyses: ITT population Safety analyses: as-treated population (patients who received at least 1 dose of the study treatment)	Female ≥ 18 y Newly diagnosed high-grade serous or endometrioid ovarian (includes fallopian tube, peritoneum, and ovarian) cancer Stage III disease with visible residual tumour after primary debulking surgery, inoperable stage III disease, or any stage IV disease, and patients who had received neoadjuvant chemotherapy. Received 6–9 cycles of first-line platinum-based chemotherapy Complete to partial response to first-line platinum-based chemotherapy Within 12 wk of completing first-line platinum-based chemotherapy HRD or HRP (after amendment, initially only HRD enrolled, n = 44) Excluded: stage III disease with nonvisible residual disease after debulking surgery; > 2 debulking surgeries	*BRCA1/2* and GIS using tumour samples (MyChoice CDx, Myriad Genetics) Centralized testing HRD definition: tumour *BRCA1/2* mutation or GIS ≥ 42	Intervention: Maintenance therapy: niraparib 200–300 mg/d depending on weight and platelet count Control: Placebo Duration: 28 d cycles continued for 36 mo or until disease progression A dose reduction to 200 mg/d and a second reduction to 100 mg/d were allowed for toxicity Dose interruption of up to 28 d and dose reductions were permitted for any grade of treatment toxicity considered intolerable by the patient, but were mandatory in case of hematologic toxicities	PFS (HRD and overall population as primary endpoint); exploratory analyses for PFS were performed for the subgroups based on age, race, geographic region, HRD status, neoadjuvant chemotherapy, best response to first platinum regimen, and *BRCA* mutation Overall survival Time to first subsequent therapy Adverse events (NCI CTCAE version 4.03 grading)[a] – causality determined by the study investigator[b] Quality of life, generic (EQ-5D-5L, EORTC-QLQ-C30) and disease-specific (FOSI, EORTC-QLQ-OV28)[c]
Mirza et al, 2016[33] NOVA Study g*BRCA* mutation cohort: N = 203 (138/65)	Multinational Double-blind g*BRCA* and non-g*BRCA* cohorts; centralized randomization within each cohort	Adults Recurrent ovarian cancer Predominantly high-grade serous ovarian cancer ≥ 2 previous platinum-based chemotherapy treatments, ≥ 4 cycles for latest treatment	All patients: g*BRCA* (*BRCA* analysis, Myriad Genetics) Patients without g*BRCA* mutation: HRD testing	Maintenance therapy: niraparib 300 mg/d, 28 d cycles Placebo	PFS (g*BRCA* cohort, HRD group of non-g*BRCA* cohort, and overall non-g*BRCA* cohort as primary); exploratory analysis (non-g*BRCA* cohort for the subgroups HRD + s*BRCA* mutation, HRD + *BRCA* wild type, and HRP)

Author, year Name N (niraparib/placebo) Median follow-up at analysis Support	Study design and methods	Participants	HRD testing	Intervention and control	Outcomes
Non-g*BRCA*) mutation cohort: N = 350 (234/116) 16.9 mo Support: Tesaro	Stratified according to time to progression after completion of the penultimate platinum regimen, use of bevacizumab in conjunction with the penultimate or last platinum regimen, and best response during the last platinum regimen Crossover from the placebo to niraparib group was not permitted after disease progression Independent committees reviewed efficacy and safety data Efficacy analyses: ITT population Safety analyses: as-treated population (patients who received at least 1 dose of the study treatment)	Complete or partial response to latest platinum-based chemotherapy[d] Platinum-sensitive disease to penultimate platinum-based chemotherapy[e] Observable residual disease < 2 cm Within 8 wk of completing latest platinum-based chemotherapy ECOG performance status 0–1 CA-125 within normal range or > 90% decrease that was stable for ≥ 7 d Availability of FFPE archival tumour sample from the primary or recurrent cancer No prior use of a PARP inhibitor Adequate hematologic, renal, and liver function	(MyChoice CDx; Myriad Genetics) after amendment Centralized testing using archived sample HRD definition: tumour *BRCA1/2* mutation or GIS ≥ 42 (MyChoice CDx; Myriad Genetics)	Duration: Until disease progression, unacceptable toxicity, death, withdrawal of consent, or loss to follow-up, whichever came first A dose reduction to 200 mg/d and a second reduction to 100 mg/d were allowed for toxicity Dose reductions were mandatory in case of thrombocytopenia (recurrence of grade 1 or occurrence of grade ≥ 2)	Subgroup PFS analyses were performed for the primary efficacy populations for age, race, geographic region, time to progression after the penultimate platinum therapy before study enrolment, use of bevacizumab in conjunction with the penultimate or last platinum regimen, best response during the last platinum regimen, number of prior platinum regimens, and number of prior chemotherapy regimens *Secondary* PFS 2 Overall survival Chemotherapy-free interval Time to first subsequent treatment Quality of life, generic (EQ-5D-5L) and disease-specific (FOSI)[c] Adverse events (NCI CTCAE v4.03 grading)[a] – causality determined by the study investigator

Abbreviations: CA-125, cancer antigen 125; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organization for the Research and Treatment of Cancer; QLQ-C30, Quality of Life Questionnaire C30; QLQ-OV28, Quality of Life Questionnaire Ovarian Cancer Model; FFPE, formalin-fixed, paraffin-embedded; FOSI, Functional Assessment of Cancer Therapy Ovarian Cancer Symptom Index; g*BRCA*, germline *BRCA* mutation; GIS, genomic instability score; HRD homologous recombination deficiency; HRP, homologous recombination proficiency; ITT, intention to treat; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PARP, poly-adenosine diphosphate (ADP)-ribose polymerase; PFS, progression-free survival; s*BRCA*, somatic *BRCA*.

[a] Definitions in Table A7, below.

[b] Some adverse events that were considered of special interest were reported regardless of causality; these included myelodysplastic syndrome, acute myeloid leukemia, and secondary cancers.[135]

[c] Description of quality-of-life instruments is provided in Table A8, below.

[d] Complete or partial response: observable residual disease of < 2 cm and CA-125 values either within the normal range, or a decrease of more than 90% that was stable for at least 7 days.

[e] Complete or partial response and disease progression more than 6 months after completion of the last round of platinum therapy.

Table A7: Definition of Adverse Events

Adverse event criterion	Definition
National Cancer Institute Common terminology criteria for adverse events (NCI CTCAE, version 4.03[79]	• Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated • Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). (Instrumental ADL refer to [e.g.] preparing meals, shopping for groceries or clothes, using the telephone, managing money) • Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. (Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden) • Grade 4: Life-threatening consequences; urgent intervention indicated • Grade 5: Death related to adverse event
Serious adverse event[136]	• Any untoward medical occurrence that, at any dose: ○ Results in death ○ Is life-threatening ○ Requires inpatient hospitalization or prolongation of existing hospitalization ○ Results in persistent or significant disability or incapacity ○ Is a congenital anomaly or birth defect ○ Is an important medical event(s)
Treatment-emergent adverse event	• Any new adverse event that begins, or any pre-existing condition that worsens in severity, after at least 1 dose of study treatment has been administered (PRIMA study[136]) • Adverse event must have occurred after the start of study treatment and within 30 days following the final dose of study treatment (NOVA study[73])

Abbreviations: ADL, activities of daily living.

Table A8: Description of Quality-of-Life Instruments

Instrument	Description
Functional Assessment of Cancer Therapy Ovarian Cancer Symptom Index (FOSI)[19]	• Validated questionnaire including eight items measuring symptom response to ovarian cancer treatment • Questionnaire based on a subset of questions from the Functional Assessment of Cancer Therapy – Ovarian Cancer questionnaire • For each question, patients are asked about their symptoms over the previous 7 days using a five-point Likert scale of "not at all" (0) to "very much" (4) • Score ranges from 0 (severely symptomatic) to 32 (asymptomatic)
EQ-5D-5L Questionnaire[137]	• Measures the patient's perceived health state. It consists of two parts: ○ Descriptive system: includes five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with five levels of responses (no problems, slight problems, moderate problems, severe problems, extreme problems/unable to) and provides information to describe the patient's health state profile, from which health state index scores that generally range from less than 0 (0 being equivalent to dead and negative values worse than dead) to 1 (the value of full health) ○ EQ visual analogue scale: elicits the patient's self-rated overall current health on a vertical visual analogue scale ranging from 0 (worst health you can imagine) to 100 (best health you can imagine)
EORTC Quality of Life Questionnaire (QLQ-C30)[19]	• Validated 30-item, health-related quality-of-life instrument that includes three domains: ○ First domain: asks patients to rate their need for assistance with or difficulty completing certain activities (such as walking or lifting) and daily self-care tasks on a Likert-type scale ranging from 0 (not at all, i.e., no difficulty or assistance needed) to 4 (very much, i.e., very much difficulty or assistance required) ○ Second domain: uses the same Likert scale and asks the patient to rate their limitations on work or hobbies, family life, social activities, and finances; shortness of breath; need for rest, or tiredness; pain and its interference with activity; ability to sleep; weakness; appetite; symptoms of nausea, vomiting, constipation, and diarrhea; ability to concentrate or remember; and emotions (irritability and depression) during the previous week ○ Third domain: asks patients to rate their overall health and overall quality of life on a Likert scale ranging from 1 (very poor) to 7 (excellent) • Can be used with other disease-specific instruments including the ovarian-specific EORTC-QLQ-OV28
EORTC Quality of Life Questionnaire Ovarian Cancer Model (QLQ-OV28)[19]	• Evaluates ovarian cancer patients' abdominal and gastrointestinal symptoms, other chemotherapy side effects, hormonal and menopausal symptoms, body image, attitude to disease and treatment, and sexual functioning • Score ranges from 0 to 100; a high score for a functional scale represents a higher level of functioning, whereas a higher score for a symptom scale represents a higher level of symptoms or problems

Abbreviations: EORTC, European Organization for the Research and Treatment of Cancer; VAS, visual analogue scale.

Appendix 6: Patient Characteristics in the Included Studies

Table A9: Patient Characteristics, PRIMA Study

Author, year N (niraparib/ placebo)	Median age (range), y	ECOG performance status, n (%)	FIGO stage, n (%)	Primary tumour location, n (%)	Histologic type, n (%)	Receipt of neoadjuvant chemotherapy, n (%)	Clinical response after platinum-based chemotherapy, n (%)
González-Martín et al, 2019[19] Overall Population N = 733 (487/246)	Niraparib: 62 (32–85) Placebo: 62 (33–88)	*0* Niraparib: 337 (69.2) Placebo: 174 (70.4) *1* Niraparib: 150 (30.8) Placebo: 72 (29.3)	*III* Niraparib: 318 (65.3) Placebo: 158 (64.2) *IV* Niraparib: 169 (34.7) Placebo: 88 (35.8)	*Ovary* Niraparib: 388 (79.7) Placebo: 201 (81.7) *Fallopian tube* Niraparib: 65 (13.3) Placebo: 32 (13.0) *Peritoneum* Niraparib: 34 (7.0) Placebo: 13 (5.3)	*Serous* Niraparib: 465 (95.5) Placebo: 230 (93.5) *Endometrioid* Niraparib: 11 (2.3) Placebo: 9 (3.7) *Other* Niraparib: 11 (2.3) Placebo: 6 (2.4)	Niraparib: 322 (66.1) Placebo: 167 (67.9)	*Complete* Niraparib: 337 (69.2) Placebo: 172 (70.0) *Partial response* Niraparib: 150 (30.8) Placebo: 74 (30.0)
González-Martín et al, 2019[19] HRD population N = 373 (247/126)	Niraparib: 58 (32–83) Placebo: 58 (33–82)	*0* Niraparib: 182 (73.7) Placebo: 97 (77.0) *1* Niraparib: 65 (26.3) Placebo: 29 (23.0)	*III* Niraparib: 161 (65.2) Placebo: 78 (61.9) *IV* Niraparib: 86 (34.8) Placebo: 48 (38.1)	*Ovary* Niraparib: 201 (81.4) Placebo: 105 (83.3) *Fallopian tube* Niraparib: 32 (13.0) Placebo: 13 (10.3) *Peritoneum* Niraparib: 14 (5.7) Placebo: 8 (6.3)	*Serous* Niraparib: 234 (94.7) Placebo: 116 (92.1) *Endometrioid* Niraparib: 5 (2.0) Placebo: 6 (4.8) *Other* Niraparib: 8 (3.2) Placebo: 4 (3.2)	Niraparib: 156 (63.2) Placebo: 80 (63.5)	*Complete* Niraparib: 185 (74.9) Placebo: 93 (73.8) *Partial* Niraparib: 62 (25.1) Placebo: 33 (26.2)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; HRD, homologous recombination deficiency.

Table A10: Patient Characteristics, NOVA Study

Author, year N (niraparib/ placebo)	Median age (range), y	ECOG performance status, n (%)	FIGO stage, n (%)	Time to progression after penultimate platinum therapy, n (%)	Best response to most recent platinum therapy, n (%)	Previous lines of chemotherapy, n (%)
Mirza et al, 2016[33] g*BRCA* mutation cohort N = 203 (138/65)	Niraparib: 57 (36–83) Placebo: 58 (38–73)	*0* Niraparib: 91 (65.9) Placebo: 48 (73.8) *1* Niraparib: 47 (34.1) Placebo: 17 (26.2)	*I/II* Niraparib: 23 (16.7) Placebo: 10 (15.4) *III* Niraparib: 95 (68.8) Placebo: 46 (70.8) *IV* Niraparib: 20 (14.5) Placebo: 9 (13.8)	*6 to < 12 mo* Niraparib: 54 (39.1) Placebo: 26 (40.0) *≥ 12 mo* Niraparib: 84 (60.9) Placebo: 39 (60.0)	*Complete* Niraparib: 71 (51.4) Placebo: 33 (50.8) *Partial* Niraparib: 67 (48.6) Placebo: 32 (49.2)	*1* Niraparib: 1 (0.7) Placebo: 0 *2* Niraparib: 70 (50.7) Placebo: 30 (46.2) *≥ 3* Niraparib: 67 (48.6) Placebo: 35 (53.8)
Mirza et al, 2016[33] Non-g*BRCA* mutation cohort N = 350 (234/116)	Niraparib: 63 (33–84) Placebo: 61 (34–82)	*0* Niraparib: 160 (68.4) Placebo: 78 (67.2)*1* Niraparib: 74 (31.6) Placebo: 38 (32.8)	*I/II* Niraparib: 22 (9.4) Placebo: 5 (4.3) *III* Niraparib: 173 (73.9) Placebo: 86 (74.1)*IV* Niraparib: 38 (16.2) Placebo: 24 (20.7)	*6 to < 12 mo* Niraparib: 90 (38.5) Placebo: 44 (37.9) *≥ 12 mo* Niraparib: 144 (61.5) Placebo: 72 (62.1)	*Complete* Niraparib: 117 (50.0) Placebo: 60 (51.7) *Partial* Niraparib: 117 (50.0) Placebo: 56 (48.3)	*1* Niraparib: 0 Placebo: 0 *2* Niraparib: 155 (66.2) Placebo: 77 (66.4) *≥ 3* Niraparib: 79 (33.8) Placebo: 38 (32.8)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; g*BRCA*, germline *BRCA*.

Table A11: Patient Characteristics According to Best Response to the Last Platinum-Based Chemotherapy, NOVA Study

Author, year N (niraparib/ placebo)	Median age (range), y	ECOG performance status, n (%)	Mean (SD) duration of last platinum-based chemotherapy, mo	Prior use of bevacizumab, n (%)	Best response to penultimate platinum-based chemotherapy, n (%)	Time to progressive disease after penultimate platinum-based dose, mo	Lines of previous chemotherapy, n (%)
Del Campo et al, 2019[37] g*BRCA* cohort N = 203 (138/65) 99 PR, 104 CR	PR: 60 (39–83) CR: 52 (36–76)	*0* PR: 62 (62.6) CR: 77 (74.0) *1* PR: 37 (37.4) CR: 27 (26.0)	PR: 4.7 (1.95) CR: 4.8 (2.01)	PR: 15 (15.2) CR: 35 (33.7)	*Partial* PR: 40 (40.4) CR: 17 (16.3) *Complete* PR: 58 (58.6) CR: 87 (83.7)	*6 to < 12* PR: 44 (44.4) CR: 36 (34.6) *≥ 12* PR: 55 (55.6) CR: 68 (65.4)	*Overall* 2 PR: 46 (46.5) CR: 54 (51.9) ≥ 3 PR: 52 (52.5) CR: 50 (48.1) *Platinum-based* 2 PR: 53 (53.5) CR: 63 (60.6) ≥ 3 PR: 45 (45.5) CR: 41 (39.4)
Del Campo et al, 2019[37] Non-g*BRCA* cohort N = 350 (234/116) 173 PR, 177 CR	PR: 63 (33–83) CR: 63 (40–84)	*0* PR: 106 (61.3) CR: 132 (74.6) *1* PR: 67 (38.7) CR: 45 (25.4)	PR: 4.7 (1.76) CR: 4.7 (2.09)	PR: 44 (25.4) CR: 48 (27.1)	*Partial* PR: 73 (42.2) CR: 23 (13.0) *Complete* PR: 99 (57.2) CR: 152 (85.9)	*6 to < 12* PR: 78 (45.1) CR: 56 (31.6) *≥ 12* PR: 95 (54.9) CR: 121 (68.4)	*Overall* 2 PR: 100 (57.8) CR: 132 (74.6) ≥ 3 PR: 73 (42.2) CR: 44 (24.9) *Platinum-based* 2 PR: 114 (65.9) CR: 147 (83.1) ≥ 3 PR: 59 (34.1) CR: 29 (16.4)

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; g*BRCA*, germline *BRCA*; PR, partial response; SD, standard deviation.

Table A12: Patient Characteristics According to Age, NOVA Study

Author, year N (niraparib/placebo)	Median age (range), y	ECOG performance status, n (%)	FIGO stage, n (%)	Time to progression after penultimate platinum therapy, n (%)	Best response to most recent platinum therapy, n (%)	Number of lines of previous chemotherapy, n (%)
Fabbro et al, 2019[72] Overall study cohort (g*BRCA* and non-g*BRCA* cohorts) N = 553 (372/181) < 70 y, N = 458 (311/147) ≥ 70 y, N = 95 (61/34)	*< 70 y* Niraparib: 58 (33–69) Placebo: 58 (34–69) *≥ 70 y* Niraparib: 74 (70–84) Placebo: 72 (70–82)	*< 70 y* 0 Niraparib: 211 (67.8) Placebo: 104 (70.7) 1 Niraparib: 100 (32.2) Placebo: 43 (29.3) *≥ 70 y* 0 Niraparib: 40 (65.6) Placebo: 22 (64.7) 1 Niraparib: 21 (34.4) Placebo: 12 (35.3)	*< 70 y* I/II Niraparib: 42 (13.5) Placebo: 10 (6.8) III Niraparib: 221 (71.1) Placebo: 110 (74.8) IV Niraparib: 48 (15.4) Placebo: 26 (17.7) *≥ 70 y* I/II Niraparib: 3 (4.9) Placebo: 5 (14.7) III Niraparib: 47 (77.0) Placebo: 22 (64.7) IV Niraparib: 10 (16.4) Placebo: 7 (20.6)	*< 70 y* 6 to < 12 mo Niraparib: 117 (37.6) Placebo: 55 (37.4) ≥ 12 mo Niraparib: 194 (62.4) Placebo: 92 (62.6) *≥ 70 y* 6 to < 12 mo Niraparib: 27 (44.3) Placebo: 15 (44.1) ≥ 12 mo Niraparib: 34 (55.7) Placebo: 19 (55.9)	*< 70 y* Complete Niraparib: 162 (52.1) Placebo: 79 (53.7) Partial Niraparib: 149 (47.9) Placebo: 68 (46.3) *≥ 70 y* Complete Niraparib: 26 (42.6) Placebo: 14 (41.2) Partial Niraparib: 35 (57.4) Placebo: 20 (58.8)	*< 70 y* 1 Niraparib: 1 (0.3) Placebo: 0 (0.0) 2 Niraparib: 185 (59.5) Placebo: 85 (57.8) ≥ 3 Niraparib: 125 (40.2) Placebo: 61 (41.5) *≥ 70 y* 1 Niraparib: 1 (0.7) Placebo: 0 (0.0) 2 Niraparib: 40 (65.6) Placebo: 22 (64.7) ≥ 3 Niraparib: 21 (34.4) Placebo: 12 (35.3)
Fabbro et al, 2019[72] No g*BRCA* cohort N = 350 (234/116)	Niraparib: 63 (33–84) Placebo: 61 (34–82)	0 Niraparib: 160 (68.4) Placebo: 78 (67.2) 1 Niraparib: 74 (31.6) Placebo: 38 (32.8)	*I/II* Niraparib: 22 (9.4) Placebo: 5 (4.3) *III* Niraparib: 173 (73.9) Placebo: 86 (74.1) *IV* Niraparib: 38 (16.2) Placebo: 24 (20.7)	*6 to < 12 mo* Niraparib: 90 (38.5) Placebo: 44 (37.9) *≥ 12 mo* Niraparib: 144 (61.5) Placebo: 72 (62.1)	*Complete* Niraparib: 117 (50.0) Placebo: 60 (51.7) *Partial* Niraparib: 117 (50.0) Placebo: 56 (48.3)	*1* Niraparib: 0 Placebo: 0 *2* Niraparib: 155 (66.2) Placebo: 77 (66.4) *≥ 3* Niraparib: 79 (33.8) Placebo: 38 (32.8)

Abbreviations: CR, complete response; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; g*BRCA*, germline *BRCA*; PR, partial response; SD, standard deviation.

Appendix 7: PRIMA Study Results

Table A13: Secondary Efficacy Outcome Results in the Overall Population, PRIMA Study

Author, year N	PFS	Overall survival	Time to first subsequent chemotherapy	PFS on the next chemotherapy
González-Martín et al, 2019[19] N = 733 (487/246)	*Disease progression or death, n (%)* Niraparib: 232 (47.6) Placebo: 155 (63.0) HR (95% CI): 0.62 (0.50–0.76); *P* < .001 *Median PFS, mo* Niraparib: 13.8 Placebo: 8.2 *Patients who received neoadjuvant chemotherapy* Disease progression or death HR (95% CI): 0.59 (0.46–0.76) Median PFS, mo Niraparib: 13.9 Placebo: 8.2 *Partial response to platinum-based chemotherapy* Disease progression or death HR (95% CI): 0.60 (0.43–0.85) Median PFS, mo Niraparib: 8.3 Placebo: 5.6	24-mo Kaplan-Meier estimate Niraparib: 84% Placebo: 77% HR (95% CI): 0.70 (0.44–1.11)	*Median (95% CI), mo* Niraparib: 18.6 (15.8–24.7) Placebo: 12.0 (10.3–13.9) *Need for subsequent chemotherapy* HR (95% CI): 0.65 (0.52–0.80)	HR (95% CI): 0.81 (0.58–1.14)

Abbreviations: CI, confidence interval; HR; hazard ratio; PFS, progression-free survival.

Table A14: PFS According to Timing of Surgery and Postoperative Residual Disease, PRIMA Study

Author, year N	Primary debulking surgery	Neoadjuvant chemotherapy and debulking surgery	Nonvisible postoperative residual disease[a]	Visible postoperative residual disease	Primary debulking surgery and visible postoperative residual disease	Neoadjuvant chemotherapy and debulking surgery and postoperative residual disease status
O'Cearbhaill et al, 2022[75] N = 733 (487/246)	*Disease progression or death, n (%)* Niraparib: 77/158 (48.7) Placebo: 48/78 (61.5) HR (95% CI): 0.67 (0.47–0.96) *Median PFS, mo* Niraparib: 13.7 Placebo: 8.2	*Disease progression or death, n (%)* Niraparib: 145/316 (45.9) Placebo: 105/165 (63.6) HR (95% CI): 0.57 (0.44–0.73) *Median PFS, mo* Niraparib: 14.2 Placebo: 8.2	*Disease progression or death, n (%)* Niraparib: 92/224 (41.1) Placebo: 62/117 (53.0) HR (95% CI): 0.70 (0.50–0.96) *Median PFS, mo* Niraparib: 18.2 Placebo: 11.0	*Disease progression or death, n (%)* Niraparib: 115/220 (52.3) Placebo: 83/112 (74.1) HR (95% CI): 0.50 (0.38–0.67) *Median PFS, mo* Niraparib: 11.2 Placebo: 5.7	*Disease progression or death, n (%)* Niraparib: 62/124 (50.0) Placebo: 41/59 (69.5) HR (95% CI): 0.58 (0.39–0.86) *Median PFS, mo* Niraparib: 11.8 Placebo: 7.8	*Nonvisible residual disease* Disease progression or death, n (%) Niraparib: 82/202 (40.6) Placebo: 57/102 (55.9) HR (95% CI): 0.65 (0.46–0.91) Median PFS, mo Niraparib: 18.2 Placebo: 10.9 *Visible residual disease* Disease progression or death, n (%) Niraparib: 53/96 (55.2) Placebo: 42/53 (79.2) HR (95% CI): 0.41 (0.27–0.62) Median PFS, mo Niraparib: 11.1 Placebo: 5.6

Abbreviations: CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

[a] All stage IV disease as per study eligibility criteria.

Table A15: Most Common Treatment-Emergent Adverse Events, PRIMA Study, Part 1

Author, year N (niraparib/placebo)	Anemia, n (%)	Nausea, n (%)	Thrombocytopenia, n (%)	Constipation, n (%)	Fatigue, n (%)	Decreased platelet count, n (%)
González-Martín et al, 2019[19] N = 728 (484/244)	*Any grade* Niraparib: 307 (63.4) Placebo: 43 (17.6) *Grade ≥ 3* Niraparib: 150 (31.0) Placebo: 4 (1.6)	*Any grade* Niraparib: 278 (57.4) Placebo: 67 (27.5) *Grade ≥ 3* Niraparib: 6 (1.2) Placebo: 2 (0.8)	*Any grade* Niraparib: 222 (45.9) Placebo: 9 (3.7) *Grade ≥ 3* Niraparib: 139 (28.7) Placebo: 1 (0.4)	*Any grade* Niraparib: 189 (39.0) Placebo: 46 (18.9) *Grade ≥ 3* Niraparib: 1 (0.2) Placebo: 0 (0.0)	*Any grade* Niraparib: 168 (34.7) Placebo: 72 (29.5) *Grade ≥ 3* Niraparib: 9 (1.9) Placebo: 1 (0.4)	*Any grade* Niraparib: 133 (27.5) Placebo: 3 (1.2) *Grade ≥ 3* Niraparib: 63 (13.0) Placebo: 0 (0.00)

Table A16: Most Common Treatment-Emergent Adverse Events, PRIMA Study, Part 2

Author, year N (niraparib/placebo)	Neutropenia, n (%)	Headache, n (%)	Insomnia, n (%)	Vomiting, n (%)	Abdominal pain, n (%)
González-Martín et al, 2019[19] N = 728 (484/244)	*Any grade* Niraparib: 128 (26.4) Placebo: 16 (6.6) *Grade ≥ 3* Niraparib: 62 (12.8) Placebo: 3 (1.2)	*Any grade* Niraparib: 126 (26.0) Placebo: 36 (14.8) *Grade ≥ 3* Niraparib: 2 (0.4) Placebo: 0 (0.0)	*Any grade* Niraparib: 119 (24.6) Placebo: 35 (14.3) *Grade ≥ 3* Niraparib: 4 (0.8) Placebo: 1 (0.4)	*Any grade* Niraparib: 108 (22.3) Placebo: 29 (11.9) *Grade ≥ 3* Niraparib: 4 (0.8) Placebo: 2 (0.8)	*Any grade* Niraparib: 106 (21.9) Placebo: 75 (30.7) *Grade ≥ 3* Niraparib: 7 (1.4) Placebo: 1 (0.4)

Table A17: Grade ≥ 3 Treatment-Emergent Adverse Events in Patients Who Received a Fixed or Individualized Dose of the Treatment Drug, PRIMA Study, Part 1

Author, year N (niraparib/placebo)	Thrombocytopenia, n (%)	Anemia, n (%)	Platelet count decreased, n (%)	Neutropenia, n (%)	Neutrophil count decreased, n (%)
González-Martín et al, 2019[19] N = 728 (484/244) Fixed dose N = 473 (315/158) Individualized dose N = 255 (169/86)	*Niraparib* Fixed: 114 (36.2) Individualized: 25 (14.8) *Placebo* Fixed: 0 (0.0) Individualized: 1 (1.2)	*Niraparib* Fixed: 112 (35.6) Individualized: 38 (22.5) *Placebo* Fixed: 3 (1.9) Individualized: 1 (1.2)	*Niraparib* Fixed: 51 (16.2) Individualized: 12 (7.1) *Placebo* Fixed: 0 (0.0) Individualized: 0 (0.0)	*Niraparib* Fixed: 46 (14.6) Individualized: 16 (9.5) *Placebo* Fixed: 2 (1.3) Individualized: 1 (1.2)	*Niraparib* Fixed: 28 (8.9) Individualized: 9 (5.3) *Placebo* Fixed: 0 (0.0) Individualized: 0 (0.0)

Table A18: Grade ≥ 3 Treatment-Emergent Adverse Events in Patients Who Received a Fixed or Individualized Dose of the Treatment Drug, PRIMA Study, Part 2

Author, year N (niraparib/placebo)	Febrile neutropenia, n (%)	Myelodysplastic syndrome, n (%)	Pancytopenia, n (%)	Neutropenic sepsis, n (%)
González-Martín et al, 2019[19] N = 728 (484/244) Fixed dose N = 473 (315/158) Individualized dose N = 255 (169/86)	*Niraparib* Fixed: 3 (1.0) Individualized: 1 (0.6) *Placebo* Fixed: 0 (0.0) Individualized: 0 (0.0)	*Niraparib* Fixed: 1 (0.3) Individualized: 0 (0.0) *Placebo* Fixed: 0 (0.0) Individualized: 0 (0.0)	*Niraparib* Fixed: 1 (0.3) Individualized: 0 (0.0) *Placebo* Fixed: 0 (0.0) Individualized: 0 (0.0)	*Niraparib* Fixed: 0 (0.0) Individualized: 1 (0.6) *Placebo* Fixed: 0 (0.0) Individualized: 0 (0.0)

Appendix 8: NOVA Study Results

Table A19: Post Hoc Analyses of PFS, NOVA Study

Author, year N (niraparib/placebo)	Disease progression or death, HR (95% CI)	Median PFS, mo
Del Campo et al, 2019[37] g*BRCA* cohort CR: N = 104 (71/33); PR: N = 99 (67/32)	CR: 0.30 (0.16–0.55) PR: 0.24 (0.13–0.44)	NR
Del Campo et al, 2019[37] Non-g*BRCA* cohort CR: N = 177 (117/60); PR: N = 173 (117/56)	CR: 0.58 (0.38–0.87) PR: 0.35 (0.23–0.53)	NR
Fabbro et al, 2019[72] g*BRCA* cohort < 70 y: N = 182 (124/58); ≥ 70 y: N = 21 (14/7)	< 70 y: 0.30 (0.19–0.47) ≥ 70 y: 0.09 (0.01–0.73)	< 70 y: niraparib 15.5; placebo: 5.8 ≥ 70 y: niraparib not reached at the time of the analysis; placebo 3.7
Fabbro et al, 2019[72] Non-g*BRCA* cohort < 70 y: N = 182 (124/58); ≥ 70 y: N = 21 (14/7)	< 70 y: 0.47 (0.34–0.66) ≥ 70 y: 0.35 (0.18–0.71)	< 70 y: niraparib 7.5; placebo: 3.9 ≥ 70 y: niraparib: 11.3; placebo: 3.8

Abbreviations: CI, confidence interval; CR, complete response; g*BRCA*, germline *BRCA*; HR, hazard ratio; PFS, progression-free survival; PR, partial response.

Table A20: Efficacy Results in the Overall g*BRCA* and Overall Non-g*BRCA* Populations, NOVA Study

Author, year N (niraparib/placebo)	Median chemotherapy-free interval (95% CI), mo HR (95% CI)	Median time to first subsequent chemotherapy (95% CI), mo HR (95% CI)	Median PFS 2 (95% CI), mo HR (95% CI)
g*BRCA*[33] N = 203 (138/65)	Niraparib: 22.8 (17.9–NR[a]) Placebo: 9.4 (7.9–10.6) HR 0.26 (0.17–0.41) *P* < .001	Niraparib: 21 (17.5–NR[a]) Placebo: 8.4 (6.6–10.6) HR: 0.31 (0.21–0.48) *P* < .001	Niraparib: 25.8 (20.3–NR[a]) Placebo: 19.5 (13.3–NR[a]) HR: 0.48 (0.28–0.82) *P* = .006
Non-g*BRCA*[33] N = 350 (234/116)	Niraparib: 12.7 (11.0–14.7) Placebo: 8.6 (6.9–10.0) HR: 0.50 (0.37–0.67) *P* < .001	Niraparib: 11.8 (9.7–13.1) Placebo: 7.2 (5.7–8.5) HR: 0.55 (0.41–0.72) *P* < .001	Niraparib: 18.6 (16.2–21.7) Placebo: 15.6 (13.2–20.9) HR: 0.69 (0.49–0.96) *P* = .003

Abbreviations: CI confidence interval; g*BRCA*, germline *BRCA*; HR, hazard ratio; NR, not reached; PFS 2, progression-free survival on the next chemotherapy.

[a] Upper limit of the 95% CI was not reached at the time of the analysis.

Table A21: Most Common[a] Adverse Events, NOVA Study, Part 1

Author, year N (niraparib/placebo)	Nausea, n (%)	Thrombocytopenia[b], n (%)	Fatigue, n (%)	Anemia[c], n (%)	Constipation, n (%)
Mirza et al, 2016[33] N = (367/179)	*Any grade* Niraparib: 270 (73.6) Placebo: 63 (35.2) *Grade ≥ 3* Niraparib: 11 (3.0) Placebo: 2 (1.1)	*Any grade* Niraparib: 225 (61.3) Placebo: 10 (5.6) *Grade ≥ 3* Niraparib: 124 (33.8) Placebo: 1 (0.6)	*Any grade* Niraparib: 218 (59.4) Placebo: 74 (41.3) *Grade ≥ 3* Niraparib: 30 (8.2) Placebo: 1 (0.6)	*Any grade* Niraparib: 184 (50.1) Placebo: 12 (6.7) *Grade ≥ 3* Niraparib: 93 (25.3) Placebo: 0 (0.0)	*Any grade* Niraparib: 146 (39.8) Placebo: 36 (20.1) *Grade ≥ 3* Niraparib: 2 (0.5) Placebo: 1 (0.6)

[a] For consistency with how adverse events were reported in the PRIMA study, we included adverse events with a frequency (any grade) ≥ 20% in the niraparib group. The frequencies reported in this table are as provided in the publication, without mention of whether they were related to treatment or whether they were treatment-emergent. Additional information on other adverse events is provided in the publication.

[b] Includes thrombocytopenia and decreased platelet count.

[c] Includes anemia and decreased hemoglobin count.

Table A22: Most Common[a] Adverse Events, NOVA Study, Part 2

Author, year N (niraparib/placebo)	Vomiting, n (%)	Neutropenia[b], n (%)	Headache, n (%)	Decreased appetite, n (%)	Insomnia, n (%)	Abdominal pain, n (%)
Mirza et al, 2016[33] N = (367/179)	*Any grade* Niraparib: 126 (34.3) Placebo: 29 (16.2) *Grade ≥ 3* Niraparib: 7 (1.9) Placebo: 1 (0.6)	*Any grade* Niraparib: 111 (30.2) Placebo: 11 (6.1) *Grade ≥ 3* Niraparib: 72 (19.6) Placebo: 3 (1.7)	*Any grade* Niraparib: 95 (25.9) Placebo: 17 (9.5) *Grade ≥ 3* Niraparib 1 (0.3) Placebo: 0 (0.0)	*Any grade* Niraparib: 93 (25.3) Placebo: 26 (14.5) *Grade ≥ 3* Niraparib: 1 (0.3) Placebo: 1 (0.6)	*Any grade* Niraparib: 89 (24.3) Placebo: 13 (7.3) *Grade ≥ 3* Niraparib: 1 (0.3) Placebo: 0 (0.0)	*Any grade* Niraparib: 83 (22.6) Placebo: 53 (29.6) *Grade ≥ 3* Niraparib: 4 (1.1) Placebo: 3 (1.7)

[a] For consistency with how adverse events were reported in the PRIMA study, we included adverse events with a frequency (any grade) ≥ 20% in the niraparib group. The frequencies reported in this table are as provided in the publication, without mention of whether they were related to treatment or whether they were treatment-emergent. Additional information on other adverse events is provided in the publication.

[b] Includes neutropenia decreased neutrophil count and febrile neutropenia.

Table A23: Long-Term Safety Results: Treatment-Emergent Adverse Events[a], NOVA Study, Part 1

Author, year N (niraparib/placebo)	Nausea, n (%)	Thrombocytopenia,[b] n (%)	Fatigue, n (%)	Anemia,[c] n (%)	Diarrhea, n (%)	Vomiting, n (%)
Mirza et al, 2020[73] N = (367/179) Adverse events were reported for the months/periods provided in the publication	*Any grade* Niraparib Month 1: 62% Month 2: 13% Continued to be detected in patients treated > 1 y Placebo Month 1: 20% Month 2: 4% *Grade ≥ 3* Symptomatic TEAEs were rare (< 5%) across all time intervals	*Any grade* Niraparib Month 1: 49% Month 2: 34% Month 4: 8% Month 6: 2% Placebo < 5% for period reported[c] *Grade ≥ 3* Month 1: 28% Month 2: 9% Month 4: < 1% Thereafter: < 1% until discontinuation Placebo NR	*Any grade* Niraparib Month 1: 32% Month 2: 15% Month 3: 15% Month 5: 7% Continued to be detected in patients treated > 1 y Duration Mean: 533 d Median: 330 d Placebo Month 1: 20% Month 2: < 6% Duration Mean: 600 d Median: 767 d	*Any grade* Niraparib Month 1: 17% Month 3: 25% Month 5: 13% Month 6: 6% Placebo < 5% for period reported[d] Grade ≥ 3 Niraparib Month 1: 2% Month 3: 10% Month 5: 5% Placebo NR	*Any grade* Niraparib Month 1: 10% Month 2: 3% Continued to be detected in patients treated > 1 y Placebo Month 1: 10% Month 2: 4%	*Any grade* Niraparib Month 1: 20% Month 2: 6% Placebo < 5% per month Continued to be detected in patients treated > 1 y *Grade ≥ 3* Symptomatic TEAEs were rare (< 5%) across all time intervals

Abbreviation: NR, not reported; TEAE, treatment-emergent adverse event.

[a] Monthly incidence of TEAEs for the first year and the pooled incidence over 6-month intervals thereafter until month 48. The percentages reported were calculated based on the number of patients followed for TEAEs during each period evaluated.

[b] Includes thrombocytopenia and decreased platelet count.

[c] Includes anemia and decreased hemoglobin count.

[d] Placebo group: hematologic toxicities of any grade were < 5% of patients for all months and intervals reported.

Table A24: Long-Term Safety Results: Treatment-Emergent Adverse Events[a], NOVA Study, Part 2

Author, year N (niraparib/placebo)	Neutropenia,[b] n (%)	Hypertension, n (%)	Insomnia, n (%)	Hepatic toxicity, n (%)	Renal toxicity, n (%)	Acute myeloid leukemia and myelodysplastic syndrome
Mirza et al, 2020[73] N = (367/179) Adverse events were reported for the months/periods provided in the publication	*Any grade* Niraparib Month 1: 17% Month 2: 19% Month 3: 8% Month 6: 2% (remained low until discontinuation) Placebo < 5% for period reported[c] *Grade ≥ 3* Niraparib Month 1: 9% Month 2:12% Month 3: 3% Month 6: 0% Placebo NR	*Any grade* Niraparib Month 1: 10% Month 2: 2% Thereafter remained < 5% per month Continued to be detected in patients treated > 1 y	*Any grade* Niraparib Month 1: 16% Month 2: 4% Thereafter remained < 5% per month Placebo NR	*Any grade liver transaminase elevations (> 3x ULN)* Niraparib: 15 (4) Placebo: 6 (3) *Grade ≥ 3 liver transaminase elevations (> 5x ULN)* Niraparib: 6 (2%) Placebo: 3 (2%) *Concurrent elevations in transaminase and bilirubin levels (grade unclear)* Niraparib: 2 (1%) Placebo: NR	*Any grade creatinine level increase (> 1.5x ULN)* Niraparib: 21 (6) Placebo: 3 (2) *Grade ≥ 3 creatinine level increase (> 3x ULN)* Niraparib: 2 (1) Placebo: 2 (1)	*Acute myeloid leukemia* Niraparib: 2 (0.5/100 patient-years) Placebo: 1 (0.8/100 patient-years) *Myelodysplastic syndrome*[d] Niraparib: 6[e] (1.6/100 patient-years) Placebo: 1 (0.8/100 patient-years)

Abbreviations: NR, not reported; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

[a] Monthly incidence of TEAEs for the first year and the pooled incidence over 6-month intervals thereafter until month 48. The percentages reported were calculated based on the number of patients followed for TEAEs during each period evaluated.

[b] Includes neutropenia decreased neutrophil count and febrile neutropenia.

[c] Placebo group: hematologic toxicities of any grade were < 5% of patients for all months and intervals reported.

[d] Myelodysplastic syndrome occurred after treatment discontinuation in all cases (i.e., within 1 week to 15 months after discontinuation in the niraparib group and 8 months in the placebo group). Among 5 of the 10 patients who developed myelodysplastic syndrome or acute myeloid leukemia (4 in the niraparib group and 1 in the placebo group), the event occurred within 2 months of last exposure to the study drug.

[e] One patient first developed myelodysplastic syndrome and then developed acute myeloid leukemia after 1 year.

Table A25: FOSI Scores[a] – Overall Population, NOVA Study

Author, year N (niraparib/ placebo)	FOSI score, adjusted mean								
	Screening	Cycle 2	Cycle 4	Cycle 6	Cycle 8	Cycle 10	Cycle 12	Cycle 14	Post-progression
Mirza et al, 2016[33]	Niraparib: 24.8	Niraparib: 24.0	Niraparib: 24.6	Niraparib: 25.3	Niraparib: 25.3	Niraparib: 25.1	Niraparib: 25.3	Niraparib: 25.2	Niraparib: 23.8
g*BRCA* mutation	Placebo: 24.9	Placebo: 24.6	Placebo: 24.6	Placebo: 24.5	Placebo: 24.6	Placebo: 24.4	Placebo: 24.5	Placebo: 24.1	Placebo: 23.7
N = 203 (138/65)									
Mirza et al, 2016[33]	Niraparib: 25.0	Niraparib: 24.0	Niraparib: 24.3	Niraparib: 24.7	Niraparib: 25.1	Niraparib: 25.1	Niraparib: 24.9	Niraparib: 25.3	Niraparib: 22.5
Non-g*BRCA* mutation	Placebo: 24.9	Placebo: 24.6	Placebo: 24.0	Placebo: 23.7	Placebo: 24.8	Placebo: 24.4	Placebo: 24.8	Placebo: 23.7	Placebo: 22.9
N = 350 (234/116)									

Abbreviation: FOSI, Functional Assessment of Cancer Therapy Ovarian Cancer Symptom Index; g*BRCA*, germline *BRCA*.

[a] Scores range from 0 to 32; a higher score reflects better function.

Table A26: EQ-5D-5L Utility[a] – Overall Population, NOVA Study

Author, year N (niraparib/ placebo)	EQ-5D-5L score, adjusted mean								
	Screening	Cycle 2	Cycle 4	Cycle 6	Cycle 8	Cycle 10	Cycle 12	Cycle 14	Post-progression
Mirza et al, 2016[33]	Niraparib: 0.851	Niraparib: 0.843	Niraparib: 0.839	Niraparib: 0.849	Niraparib: 0.849	Niraparib: 0.838	Niraparib: 0.841	Niraparib: 0.840	Niraparib: 0.816
g*BRCA* mutation	Placebo: 0.849	Placebo: 0.841	Placebo: 0.822	Placebo: 0.844	Placebo: 0.825	Placebo: 0.836	Placebo: 0.827	Placebo: 0.834	Placebo: 0.832
N = 203 (138/65)									
Mirza et al. 2016[33]	Niraparib: 0.839	Niraparib: 0.834	Niraparib: 0.839	Niraparib: 0.848	Niraparib: 0.844	Niraparib: 0.838	Niraparib: 0.837	Niraparib: 0.837	Niraparib: 0.800
Non-g*BRCA* mutation	Placebo: 0.836	Placebo: 0.824	Placebo: 0.819	Placebo: 0.821	Placebo: 0.819	Placebo: 0.835	Placebo: 0.804	Placebo: 0.827	Placebo: 0.780
N = 350 (234/116)									

Abbreviation: g*BRCA*, germline *BRCA*.

[a] Scores range from 0 to 1; a higher score reflects a better quality of life.

Table A27: Adjusted FOSI Score and EQ-5D-5L Utility in the HRD Population of the Non-g*BRCA* Cohort, NOVA Study

Author, year N (niraparib/ placebo)	Adjusted mean[a]								
	Screening	Cycle 2	Cycle 4	Cycle 6	Cycle 8	Cycle 10	Cycle 12	Cycle 14	Post-progression
Oza et al, 2018[74] N = 162 (106/56) FOSI score	Niraparib: 25.8 Placebo: 25.7	Niraparib: 24.4 Placebo: 25.2	Niraparib: 25.1 Placebo: 24.2	Niraparib: 25.2 Placebo: 24.4	Niraparib: 25.7 Placebo: 25.8	Niraparib: 25.6 Placebo: 24.0	Niraparib: 25.5 Placebo: 24.8	Niraparib: 25.9 Placebo: 23.6	Niraparib: 22.4 Placebo: 23.1
Oza et al, 2018[74] N = 162 (106/56) EQ-5D-5L utility	Niraparib: 0.845 Placebo: 0.837	Niraparib: 0.839 Placebo: 0.825	Niraparib: 0.845 Placebo: 0.815	Niraparib: 0.850 Placebo: 0.830	Niraparib: 0.857 Placebo: 0.818	Niraparib: 0.845 Placebo: 0.822	Niraparib: 0.843 Placebo: 0.814	Niraparib: 0.848 Placebo: 0.833	Niraparib: 0.804 Placebo: 0.786

Abbreviations: FOSI, Functional Assessment of Cancer Therapy Ovarian Cancer Symptom Index; g*BRCA*, germline *BRCA*.

[a] Adjusted for histology, region, previous treatment, age (continuous), planned treatment, and baseline FOSI score or EQ-5D-5L utility.

Appendix 9: Results of Applicability and Limitation Checklists for Studies Included in the Economic Literature Review

Table A28: Assessment of the Applicability of Studies Evaluating the Cost-Effectiveness of HRD Testing to Inform Niraparib Maintenance Therapy Decisions

Author, year, country	Is the study population similar to the question?	Are the interventions similar to the question?	Is the health care system studied sufficiently similar to Ontario?	Were the perspectives clearly stated? If yes, what were they?	Are all direct effects included? Are all other effects included where they are material?	Are all future costs and outcomes discounted? If yes, at what rate?	Is the value of health effects expressed in terms of quality-adjusted life-years?	Are costs and outcomes from other sectors fully and appropriately measured and valued?	Overall judgment[a]
Barrington et al, 2019,[84] United States	Yes	No	Partially	Yes, third-party payer	Yes	Unclear	Yes	Yes	Not applicable
Dottino et al, 2019,[83] United States	Yes	No	Partially	Yes, societal	No, overall survival not considered	No	No	Yes	Not applicable
Gonzalez et al, 2020,[82] United States	Yes	Yes	Partially	Yes, third-party payer	No, overall survival not considered	Yes, 3%	No	Yes	Partially applicable
Penn et al, 2020,[85] United States	Yes	No	Partially	Yes, United States health care	No, overall survival not considered	No	No	Yes	Not applicable
Rose et al, 2020,[86] United States	Yes	No	Partially	No	Yes	Unclear	No	Yes	Not applicable

Abbreviations: HRD, homologous recombination deficiency.

Note: Response options for all items were “yes,” “partially,” “no,” “unclear,” and “NA” (not applicable).

[a] Overall judgment may be “directly applicable,” “partially applicable,” or “not applicable.”

Table A29: Assessment of the Limitations of Studies Evaluating the Cost-Effectiveness of HRD Testing to Inform Niraparib Maintenance Therapy Decisions

Author, year, country	Does the model structure adequately reflect the nature of the health condition under evaluation?	Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Are all important and relevant health outcomes included?	Are the clinical inputs[a] obtained from the best available sources?	Do the clinical inputs[a] match the estimates contained in the clinical sources?	Are all important and relevant (direct) costs included in the analysis?	Are the estimates of resource use obtained from the best available sources?	Are the unit costs of resources obtained from the best available sources?	Is an appropriate incremental analysis presented, or can it be calculated from the reported data?	Are all important and uncertain parameters subjected to appropriate sensitivity analysis?	Is there a potential conflict of interest?	Overall judgment[b]
Barrington et al, 2019,[84] United States	Partially, unclear model structure	Unclear	Yes	Partially (assuming an empirical overall/PFS ratio of 3)	Partially	No, HRD testing costs not considered	Yes	Yes	Yes	Partially	No	Potentially serious limitations
Dottino et al, 2019,[83] United States	Partially, unclear model structure	No (less than 24 months)	No, overall survival not considered	Partially	Yes	No, HRD testing costs not considered	Yes	Yes	Yes	Partially	Partially, private funding received	Potentially serious limitations
Gonzalez et al, 2020,[82] United States	Yes	No	No, overall survival not considered	Partially	Yes	Yes	Yes	Yes	Yes	Partially	Partially, private funding received	Potentially serious limitations
Penn et al, 2020,[85] United States	Partially, unclear model structure	No	No, overall survival not considered	Partially	Yes	No, HRD testing costs not considered	Yes	Yes	Yes	Partially	Partially, private funding received	Potentially serious limitations
Rose et al, 2020,[86] United States	Partially, unclear model structure	Unclear	Yes	Partially	Yes	No, HRD testing costs not considered	Yes	Yes	Yes	Partially	No	Potentially serious limitations

Abbreviations: HRD, homologous recombination deficiency; PFS, progression-free survival.

Note: Response options for all items were "yes," "partially," "no," "unclear," and "NA" (not applicable).

[a] Clinical inputs include relative treatment effects, natural history, and utilities.

[b] Overall judgment may be "minor limitations," "potentially serious limitations," or "very serious limitations."

Appendix 10: Primary Economic Evaluation

Rationale for Not Conducting a Primary Economic Evaluation for Recurrent Cancer

The Clinical Evidence Review identified a clinical trial of niraparib versus placebo for patients with recurrent cancer (the ENGOT-OV16/NOVA trial).[33] The authors reported Kaplan–Meier curves for progression-free survival (PFS) for people with germline *BRCA* (g*BRCA*) mutations, people with somatic *BRCA* mutations, people with homologous recombination deficiency (HRD) but without *BRCA* mutations, and people with homologous recombination proficiency (HRP). The median PFS was longer for people who received niraparib than for people who received placebo (21.0 months vs. 5.5 months for people with g*BRCA* mutations). Furthermore, the estimated hazard ratios for PFS in the niraparib group versus the placebo group were 0.27 (95% confidence interval [CI] 0.17–0.41) for people with g*BRCA* mutations, 0.27 (95% CI 0.08–0.90) for people with somatic *BRCA* mutations, 0.38 (95% CI 0.23–0.63) for people with HRD but without *BRCA* mutations, and 0.58 (95% CI 0.36–0.92) for people with HRP. However, limited information was available about overall survival.[33] The authors stated that 60 (16.1%) patients in the niraparib group and 35 (19.3%) in the placebo group had died, but that it was too early to evaluate the effect of niraparib on overall survival.[33] Without overall survival results for the *gBRCA* and *BRCA* wild type cohorts, or by HRD status in the *BRCA* wild type cohort, we could not conduct a model-based analysis of the cost-effectiveness of therapy informed by HRD testing in patients with recurrent cancer.

Table A30: Model Statistics for Progression-Free Survival

Study population	Model	Intervention	Control
Non-*BRCA* HRD	Exponential	rate: 0.02786 Log-likelihood = −247.3517, df = 1 AIC: 496.7035 BIC: 499.2573	rate: 0.04565 Log-likelihood = −175.7341, df = 1 AIC = 353.4682 AIC: 353.4682 BIC: 355.4756
	Weibull	shape: 0.967 scale: 36.127 Log-likelihood = −247.3062, df = 2 AIC: 498.6123 BIC: 503.7201	shape: 0.868 scale: 21.570 Log-likelihood = −175.0482, df = 2 AIC: 354.0965 BIC: 358.1111
	Gompertz	shape: −0.022947 rate: 0.040027 Log-likelihood = −245.0596, df = 2 AIC: 494.1192 BIC: 499.2269	shape: −0.03339 rate: 0.07089 Log-likelihood = −172.7078, df = 2 AIC: 349.4157 BIC: 353.4303
	Log-normal	meanlog: 3.096 sdlog: 1.263 Log-likelihood = −241.4643, df = 2 AIC: 486.9285 BIC: 492.0363	meanlog: 2.515 sdlog: 1.346 Log-likelihood = −171.6955, df = 2 AIC: 347.391 BIC: 351.4056
	Log-logistic	shape: 1.309 scale: 21.325 Log-likelihood = −243.1866, df = 2 AIC: 490.3733 BIC: 495.481	shape: 1.284 scale: 11.826 Log-likelihood = −171.5818, df = 2 AIC: 347.1635 BIC: 351.1782[a]
	Generalized γ	μ: 2.310 σ: 1.176 Q: −1.447 Log-likelihood = −238.0123, df = 3 AIC: 482.0247 BIC: 489.6863[a]	μ: 2.410 σ: 1.370 Q: −0.180 Log-likelihood = −171.6006, df = 3 AIC: 349.2013 BIC: 355.2233
	γ	shape: 1.03813 rate: 0.02929 Log-likelihood = −247.3247, df = 2 AIC: 498.6495 BIC: 503.7572	shape: 0.8815 rate: 0.0392 Log-likelihood = −175.496, df = 2 AIC: 354.992 BIC: 359.0067
	Generalized F distribution	μ: 2.309427 σ: 1.174274 Q: −1.447857 P: 0.009736 Log-likelihood = −238.0148, df = 4 AIC: 484.0297 BIC: 494.2452	μ: 1.931639 σ: 0.125675 Q: −5.949885 P: 146.397083 Log-likelihood = −169.1815, df = 4 AIC: 346.363 BIC: 354.3923

Study population	Model	Intervention	Control
HRP	Exponential	rate: 0.06748 Log-likelihood = −546.9965, df = 1 AIC: 1095.993 BIC: 1099.1229	rate: 0.0877 Log-likelihood = −240.3441, df = 1 AIC: 482.6882 BIC: 485.0703
	Weibull	shape: 1.0777 scale: 15.1584 Log-likelihood = −546.2869, df = 2 AIC: 1096.5738 BIC: 1102.8336	shape: 0.9279 scale: 11.1050 Log-likelihood = −239.9743, df = 2 AIC: 483.9487 BIC: 488.7127
	Gompertz	shape: −0.01050 rate: 0.07682 Log-likelihood = −545.9204, df = 2 AIC: 1095.8408 BIC: 1102.1005	shape: −0.0448 rate: 0.1330 Log-likelihood = −234.1566, df = 2 AIC: 472.3132 BIC: 477.0772
	Log-normal	meanlog: 2.2510 sdlog: 0.9359 Log-likelihood = −527.0624, df = 2 AIC: 1058.1248 BIC: 1064.3846	meanlog: 1.8885 sdlog: 1.0305] Log-likelihood = −227.5347, df = 2 AIC: 459.0694 BIC: 463.8334
	Log-logistic	shape: 1.814 scale: 8.972 Log-likelihood = −529.593, df = 2 AIC: 1063.1859 BIC: 1069.4457	shape: 1.689 scale: 6.041 Log-likelihood = −227.2598, df = 2 AIC: 458.5196 BIC: 463.2836
	Generalized γ	μ: 1.6777 σ: 0.7212 Q: −1.3529 Log-likelihood = −517.9241, df = 3 AIC: 1041.8482 BIC: 1051.2379[a]	μ: 1.199 σ: 0.724 Q: -1.585 Log-likelihood = −219.3909, df = 3 AIC: 444.7817 BIC: 451.9278[a]
	γ	shape: 1.2904 rate: 0.0885 Log-likelihood = −544.15, df = 2 AIC: 1092.3 BIC: 1098.5598	shape: 1.0379 rate: 0.0914 Log-likelihood = -240.313, df = 2 AIC: 484.6259 BIC: 489.39
	Generalized F distribution	μ: 1.677613 σ: 0.721104 Q: −1.353027 P: 0.000433 Log-likelihood = −517.9254, df = 4 AIC: 1043.8509 BIC: 1056.3705	μ: 1.200645 σ: 0.724384 Q: -1.579006 P: 0.003254 Log-likelihood = −219.3936, df = 4 AIC: 446.7873 BIC: 456.3154

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; df, degree of freedom; HRD, homologous recombination deficiency; HRP, homologous recombination proficiency.

[a] Chosen model.

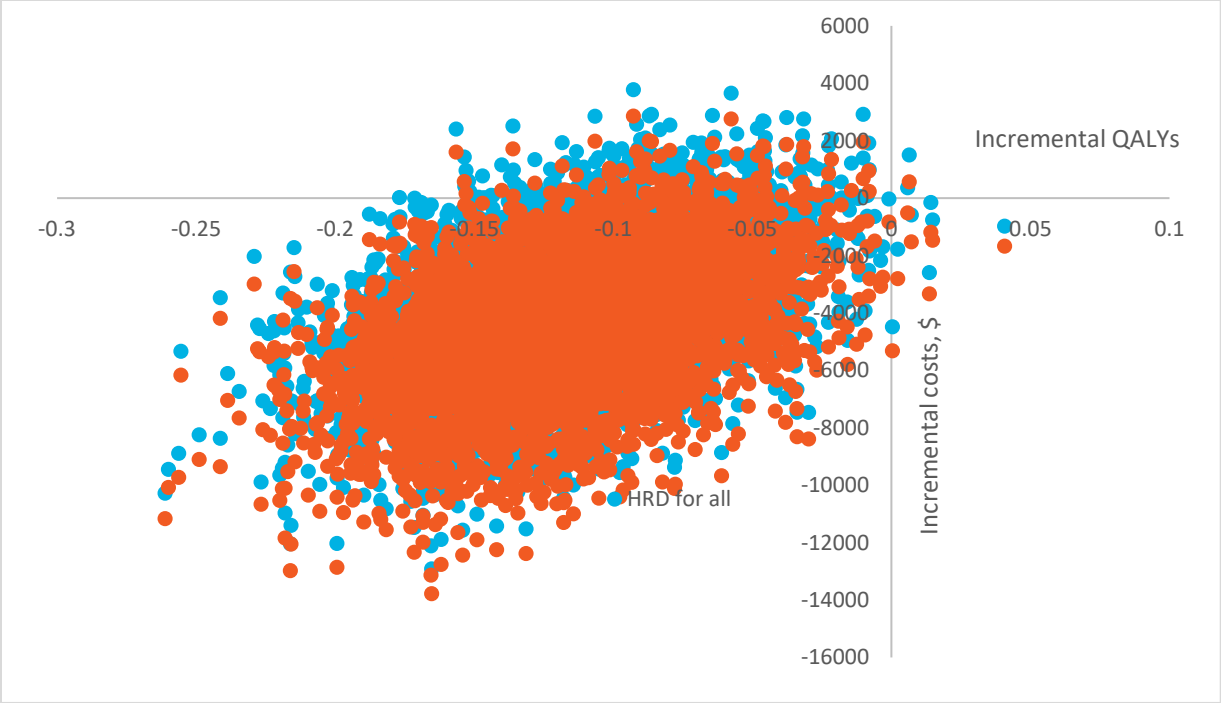

Figure A1: Scatter Plot, Incremental Costs, and Incremental QALYs for the Reference Case Analysis

Abbreviation: HRD, homologous recombination deficiency; QALY, quality-adjusted life-years.

Note: The scatter plot shows the incremental costs and QALYs of the two HRD testing strategies versus no HRD testing. Compared with no HRD testing, 94.8% of the 5,000 simulations were cost-saving with HRD testing for all, and 97.9% of the 5,000 simulations were cost-saving with HRD testing for people with *BRCA* wild type. Only 0.18% of the 5,000 simulations showed that strategies with HRD testing led to higher QALYs than no HRD testing.

Table A31: Trade-Off Between PFS and QALY Gains and Toxicities

Strategy[a]	PFS, y	QALYs in reference case	QALYs assuming no utility loss because of toxicities[b]	QALYs because of toxicities[b]	Trade-off	
					PFS in relation to toxicities	QALYs in relation to toxicities
Therapy informed by HRD testing						
No HRD testing	1.149	2.087	2.096	0.009	HRD testing led to PFS gain and similar toxicities	No HRD testing led to QALY gain and similar toxicities
HRD testing[c]	1.167	1.971	1.980	0.009		
People with HRD[d]						
Niraparib	2.361	3.410	3.437	0.027	Niraparib led to 0.802 y PFS with a 0.027 QALY loss because of toxicities	Niraparib led to a 0.379 QALY gain with a 0.027 QALY loss because of toxicities
No niraparib	1.599	3.031	3.031	–		
People with HRP[d]						
Niraparib	1.175	2.900	2.911	0.011	Niraparib led to 0.221 y PFS with a 0.011 QALY loss because of toxicities	Niraparib led to a 0.870 QALY gain with a 0.011 QALY loss because of toxicities
No niraparib	0.954	2.041	2.041	–		

Abbreviations: HRD, homologous recombination deficiency; HRP, homologous recombination proficiency; PFS, progression-free survival; QALY, quality-adjusted life-year.

[a] We presented QALY and PFS estimates for different testing strategies (no HRD testing and strategies with HRD testing), and cohorts including people with HRD treated with niraparib, people with HRD people without niraparib, people with HRP treated with niraparib, and people with HRP without niraparib.

[b] We used the scenario analysis that assumed no utility loss because of toxicities, to estimate the QALY loss because of toxicities for each strategy (QALY estimate for no utility loss because of toxicities − QALY estimate in the reference case).

[c] Two strategies with HRD testing (for all eligible people or only for people with *BRCA* wild type) had the same PFS or QALY estimates.

[d] The trade-off between benefits and toxicities was based on model-based prediction of PFS, overall survival, and utility values, given patients' HRD status and treatment. The trade-off was not dependent on the use of HRD testing, the accuracy of HRD testing, or any change in the proportion of niraparib maintenance therapy among the different HRD status groups.

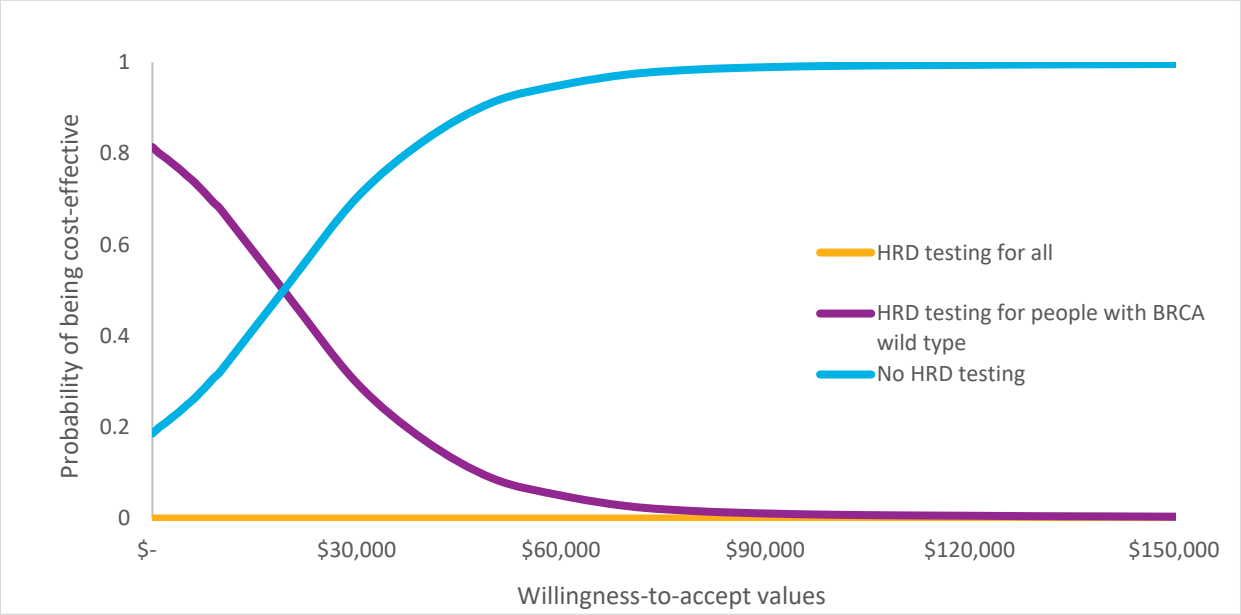

Figure A2: Cost-Effectiveness Acceptability Curve for Extended Niraparib Use

Abbreviation: HRD, homologous recombination deficiency; WTA, willingness to accept.

Note: HRD testing for people with *BRCA* wild type was the most cost-effective strategy at a WTA value of 0. When the WTA value increased to $10,000 per QALY, the estimated incremental NMB was $1,159 compared to no HRD testing. No HRD testing became the most cost-effective strategy when the WTA value was greater than $20,000 per QALY.

Appendix 11: Budget Impact Analysis

Table A32: Unit Costs Used in the Budget Impact Analysis for Newly Diagnosed Ovarian Cancer[a]

Strategies	Costs, $				
	Year 1	Year 2	Year 3	Year 4	Year 5
No HRD testing					
Testing costs	750	0	0	0	0
Treatment costs (including medication, toxicity treatment, and monitoring)	50,549	26,496	18,879	196[b]	164[b]
Health state costs	4,810	8,024	8,284	7,966	7,407
Total	56,109	34,521	27,163	8,162	7,571
HRD testing for people with *BRCA* wild type					
Testing costs	4,543	0	0	0	0
Treatment costs (including medication, toxicity treatment, and monitoring)	44,035	26,406	19,761	211[b]	180[b]
Health state costs	5,205	7,676	7,536	7,010	6,348
Total	53,783	34,082	27,297	7,221	6,528
HRD testing for all					
Testing costs	5,422	0	0	0	0
Treatment costs (including medication, toxicity treatment, and monitoring)	44,035	26,406	19,761	211[b]	180[b]
Health state costs	5,205	7,676	7,536	7,010	6,348
Total	54,662	34,082	27,297	7,221	6,528

[a] In 2023 Canadian dollars.

[b] Monitoring costs only.

Table A33: Unit Costs Used in the Budget Impact Analysis for Recurrent Ovarian Cancer[a,b]

Strategy	Testing cost, $	Niraparib treatment cost, $	Health state cost, $	Total, $[c]
No HRD testing	750	52,028	0	52,778
HRD testing for people with *BRCA* wild type	3,589	41,778	0	45,366
HRD testing for all	5,422	41,778	0	47,200

[a] In 2023 Canadian dollars.

[b] Only costs in year 1 were considered.

[c] Results may appear inexact due to rounding.

Table A34: Budget Impact Analysis Results, Scenario Analysis – Niraparib for People With Newly Diagnosed Ovarian Cancer

Scenario		Budget impact, $ million[a]					
		Year 1	Year 2	Year 3	Year 4	Year 5	Total[b,c,d]
For people with *BRCA* wild type	Testing costs	2.30	2.73	3.16	3.60	4.06	15.85
	Total	−13,90	−23.39	−32.11	−37.75	−43.79	−150.94
For all	Testing costs	2.84	3.36	3.89	4.44	5.00	19.52
	Total	−13.37	−22.75	−31.38	−36.92	−42.85	−147.27

[a] In 2023 Canadian dollars.

[b] Negative costs indicate savings.

[c] Results may appear inexact due to rounding.

[d] All costs were calculated using the mean costs from the probabilistic results of the Primary Economic Evaluation.

Table A35: Budget Impact Analysis Results, Scenario Analysis – Niraparib for People With Recurrent Ovarian Cancer

Scenario		Budget impact, $ million[a]					
		Year 1	Year 2	Year 3	Year 4	Year 5	Total[b,c]
For people with *BRCA* wild type	Testing costs	1.21	1.43	1.65	1.89	2.12	8.30
	Total	−12.39	−14.66	−16.99	−19.38	−21.81	−85.24
For all	Testing costs	1.99	2.35	2.72	3.11	3.50	13.66
	Total	−11.61	−13.74	−15.92	−18.16	−20.44	−79.87

[a] In 2023 Canadian dollars.

[b] Negative costs indicate savings.

[c] Results may appear inexact due to rounding.

Appendix 12: Letter of Information

Ontario Health is conducting a review of **homologous recombination deficiency (HRD) testing.** This is a genetic test to help determine the potential impact and benefit of chemotherapy for those with ovarian cancer. The purpose is to understand whether this technology should be publicly funded in Ontario.

An important part of this review involves learning more about the experiences of patients, families, and caregivers to better understand the context and impact of HRD testing.

What Do You Need From Me

- Willingness to share your story
- 20-40 minutes of your time for a phone
- Permission to audio- (not video-) record the interview

What Your Participation Involves

If you agree to share your experiences, you will be asked to have an interview with Ontario Health staff. The interview will last about 20-40 minutes. It will be held over the telephone and with your permission, the interview will be audio-taped. The interviewer will ask you questions about your or your loved one's condition and your perspectives about care options in Ontario.

Participation is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before or at any point during your interview. Withdrawal will in no way affect the care you receive.

Confidentiality

All information you share will be kept confidential and your privacy will be protected except as required by law. The results of this review will be published, however, no identifying information will be released or published. Any records containing information from your interview will be stored securely until project completion. After the project's completion, the records will be destroyed.

Risks to Participation

There are no known physical risks to participating. Some participants may experience discomfort or anxiety after speaking about their experiences.

If you are interested, please contact us before December 16, 2022.

Appendix 13: Interview Guide

Interview for HRD Testing for Ovarian Cancer HTA
What are the values, decision-making preferences and factors of patients with ovarian cancer around the use of niraparib as maintenance therapy? What is their understanding of risk, decision-making, and potential impact of using an HRD test?

Intro
Explain OH(Q) purpose, HTA process, and purpose of interview

Journey to Ovarian Cancer (or other cancer if a more general interview)
Describe ovarian/other cancer journey
- Impact, quality of life
- Other?

Decision-Making
Information around ovarian/other cancer treatment
- Information helpful? Source?

Decision-making surrounding treatment
Access to additional screening/treatments; any barriers that existed?

HRD Testing
Information around HRD testing
What would be valuable?
Perceptions of strengths/limitations/pros/cons/etc
- (ex. Wait time for test?)
- Barriers to testing?

Any final thoughts/questions about something I may not have asked?

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About Us

We are an agency created by the Government of Ontario to connect, coordinate and modernize our province's health care system. We work with partners, providers and patients to make the health system more efficient so everyone in Ontario has an opportunity for better health and wellbeing. We work to enhance patient experience, improve population health, enhance provider experiences, improve value and advance health equity.

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