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

Final Recommendation

Ontario Health, based on guidance from the Ontario Health Technology Advisory Committee, recommends against publicly funding homologous recombination deficiency (HRD) testing to inform patient decision-making about niraparib maintenance therapy for high-grade serous or endometrioid epithelial ovarian cancer.

Rationale for the Recommendation

The Ontario Health Technology Advisory Committee made the above recommendation after considering the clinical, economic, and patient preferences and values evidence reported in the health technology assessment,[1] and the recommendation of a subcommittee, the Ontario Genetics Advisory Committee.

The clinical evidence showed that in patients with newly diagnosed (advanced) or recurrent high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer (collectively referred to as *ovarian cancer*) who are in complete or partial response to platinum-based chemotherapy, niraparib maintenance therapy improves progression-free survival compared with no maintenance therapy for ovarian tumours classified as having HRD or homologous recombination proficiency (HRP). The evidence shows a median progression-free survival difference between niraparib maintenance therapy and no maintenance therapy of approximately 9 to 11 months for patients with HRD ovarian tumours and approximately 3 months for patients with HRP tumours. However, this evidence is uncertain because the variation in possible progression-free survival difference was not reported and the results between the HRD and HRP groups were not compared statistically. Therefore, the committee could not determine whether there was a true difference in niraparib maintenance therapy benefit between the HRD and HRP groups (i.e., clinical validity). Because of this, the committee concluded that the clinical validity of HRD testing with respect to the treatment benefit of niraparib maintenance therapy is uncertain, limiting its usefulness to guide patient decision-making. The committee was also concerned about the high rate of inconclusive results (15%) with HRD testing reported in the evidence, meaning that for every 100 patients tested, 15 may have test results that do not definitively classify the ovarian tumour as either HRD or HRP. As well, the short duration of patient

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follow-up in the evidence precluded conclusions about whether overall survival in patients treated with niraparib maintenance therapy differed from those who did not receive maintenance therapy. The evidence also showed that niraparib treatment is associated with an increased risk of serious adverse events compared with no maintenance therapy. The committee concluded that given the lack of clinical utility evidence for HRD testing, there is uncertainty about how testing affects treatment management, patient decisions about treatment, and clinical outcomes.

The primary economic evaluation showed that HRD testing may lead to cost savings to the health care system if some patients forgo niraparib maintenance therapy after considering the benefits and risks of treatment. It also showed that overall HRD testing may lead to some decrease in quality-adjusted life-years (QALYs, an outcome measure that combines both patients' survival time and quality of life) if patients with ovarian tumours classified as HRP choose to forgo niraparib maintenance therapy. The magnitude of cost savings and QALY losses depends on the proportion of patients with ovarian tumours classified as HRP who choose not to take niraparib maintenance therapy, which is unknown.

Ontario Health Technology Advisory Committee members took into account the lived experience of patients with ovarian cancer. Patients interviewed valued the information HRD testing gave them for decision-making about whether to receive niraparib maintenance therapy. A review of the quantitative evidence and findings from direct patient engagement noted that patients prioritized reducing treatment-related adverse events over improving progression-free survival, but other evidence supports the finding that patients prioritize treatment benefit over treatment-related adverse events.

HRD testing is not required or used to determine eligibility for niraparib maintenance therapy in patients with high-grade serous or endometrioid epithelial ovarian cancer, and its results are not intended to be used to withhold treatment, because the evidence does not support stratification according to HRD status; its use has been proposed to inform patient decision-making about accepting niraparib maintenance therapy. The committee acknowledged the potential for HRD testing to help patients facing difficult decisions about whether to receive niraparib maintenance therapy and risk experiencing the associated serious and severe adverse events if progression-free survival is potentially minimal. However, the committee based its recommendation on concerns about the lack of evidence regarding clinical validity of the test, uncertainty about how HRD test results would affect decision-making and patient management, and about how decisions made will affect the cost-effectiveness of HRD testing.

The committee is aware of planned and ongoing studies evaluating HRD testing to inform niraparib maintenance therapy for patients with ovarian cancer and will reconsider the funding recommendation when new evidence about clinical validity and clinical utility becomes available.

Decision Determinants for Homologous Recombination Deficiency Testing to Inform Patient Decisions About Niraparib Maintenance Therapy for High-Grade Serous or Endometrioid Epithelial Ovarian Cancer

Overall Clinical Benefit

Effectiveness

How effective is the health technology/intervention likely to be (taking into account any variability)?

In patients with high-grade serous or endometrioid ovarian cancer, niraparib maintenance therapy improved progression-free survival compared with no maintenance therapy in both HRD (somatic *BRCA* mutation/*BRCA* wild type) and HRP (hazard ratio for disease progression or death: HRD group 0.43 [95% CI 0.31–0.59] and HRP group 0.68 [0.49–0.94] in patients with newly diagnosed ovarian cancer; HRD group 0.38 [95% CI 0.24–0.59] and HRP group 0.58 [0.36–0.92] in patients with recurrent ovarian cancer; Grading of Recommendations, Assessment, Development and Evaluations [GRADE]: High). For niraparib maintenance therapy compared with no maintenance therapy, the median difference in progression-free survival for patients with newly diagnosed ovarian cancer was 11.5 months in the HRD group and 2.7 months in the HRP group; for patients with recurrent ovarian cancer, the median difference in progression-free survival was 9.1 months in the HRD group and 3.1 months in the HRP group. However, because the included studies showed that niraparib maintenance therapy improved progression-free survival in both the HRD and HRP groups but did not undertake direct statistical comparison between them, it was not yet possible to draw conclusions about whether there was a difference in treatment benefit for HRD versus HRP.

The studies did not provide evidence about the ability of HRD testing to distinguish between those who benefited from treatment and those who did not (i.e., clinical validity). As well, information about variation in the estimates for the median difference in progression-free survival between niraparib maintenance therapy and no maintenance therapy was not available. It was also not possible to draw conclusions about the effect of niraparib maintenance therapy on overall survival, given the limited duration of follow-up at the time of the analysis. No studies investigated the clinical utility of HRD testing, so it was not possible to comment on how it would affect treatment management, patient treatment choices, or clinical outcomes.

Safety

How safe is the health technology/intervention likely to be?

Compared with no maintenance therapy, niraparib maintenance therapy was associated with a higher risk of serious adverse events. The most common adverse events observed with niraparib treatment were anemia, nausea, fatigue, thrombocytopenia, and constipation. It is not clear whether HRD status affected the risk of adverse events.

Burden of Illness

What is the likely size of the burden of illness pertaining to this health technology/intervention?

In 2020, it was estimated that 1,277 people in Ontario would be diagnosed with ovarian cancer.

Need

How large is the need for this health technology/intervention?

HRD testing is not required to determine eligibility for niraparib maintenance therapy in patients with high-grade serous or endometrioid epithelial ovarian cancer. However, it has been suggested that the results of HRD testing may be used to inform decisions about niraparib maintenance therapy for these patients.

Patient Preferences and Privacy

Patient Preferences and Values

Do patients have specific preferences, values, or needs related to the health condition, health technology/intervention, or life impact that are relevant to this assessment?

Evidence from cross-sectional studies suggests that patients with recurrent ovarian cancer prioritize the potential for fewer moderate to severe adverse events over improved progression-free survival. The patients we spoke with valued treatments focused on cancer prevention and overall survival with minimal side effects. Other evidence supports the finding that patients prioritize treatment benefit over treatment-related adverse events.

The patients we spoke with perceived HRD testing to be noninvasive, and a potentially meaningful step toward informing their decision-making about cancer treatment and preventing cancer recurrence. They mentioned the importance of educating patients about HRD testing and the implications of the results for treatment options. Barriers included the out-of-pocket cost of the test and a lack of patient and provider awareness of HRD testing.

Autonomy, Privacy, Confidentiality, and/or Other Relevant Ethical Principles as Applicable

Are there concerns regarding accepted ethical or legal standards related to patient autonomy, privacy, confidentiality, or other ethical principles that are relevant to this assessment?

HRD testing using next-generation sequencing techniques in a tumour sample identifies germline and somatic gene variants, but it does not distinguish between the two. Therefore, the test may not reveal genetic susceptibility in offspring and family members, although it may lead to incidental findings and further genetic testing that may identify such information.

The patients we spoke with felt that having access to information is an integral part of patient autonomy; they perceived HRD testing to be an important tool that could help them make an informed decision about maintenance therapy, particularly when fewer treatment options are available.

Equity and Patient Care

Equity of Access or Outcomes

Are there disadvantaged populations or populations in need whose access to care or health outcomes might be improved or worsened that are relevant to this assessment?

The MyChoice CDx (Myriad Genetic Laboratories) HRD test is used in some hospitals in Ontario to inform decisions about niraparib maintenance therapy for patients with high-grade serous or endometrioid epithelial ovarian cancer. To help patients and their physicians have informed individual risk–benefit discussions, an industry-funded patient support program funds the cost of HRD testing for eligible patients with ovarian cancer for 2023 only; eligibility is defined within the support program.

Some participants highlighted the burden of out-of-pocket costs and how paying for a critical element of their care may negatively affect the accessibility of cancer treatment.

Patient Care

Are there challenges in the coordination of care for patients or other system-level aspects of patient care (e.g., timeliness of care, care setting) that might be improved or worsened that are relevant to this assessment?

Patients and providers may need additional procedures, education, and consultation, as well as time to process additional genetic information, if HRD testing is conducted. Currently in Ontario, tumour *BRCA* testing is performed at the time of diagnosis in patients with high-grade serous or endometrioid epithelial ovarian cancer. It is proposed that HRD testing (if performed) also be done at the time of diagnosis – as a replacement for tumour *BRCA* testing (if the HRD test interrogates *BRCA* mutations), or as an add-on if no *BRCA* mutation is identified. HRD testing as an add-on would require sequential testing (i.e., *BRCA* testing first, and then HRD testing if no *BRCA* mutation is identified), which might extend the time to obtain the HRD test result compared with HRD testing for all patients with high-grade serous or endometrioid epithelial ovarian cancer at the time of diagnosis.

Cost-Effectiveness

Economic Evaluation

How efficient is the health technology/intervention likely to be?

For people with newly diagnosed ovarian cancer and considering niraparib maintenance therapy, HRD testing led to lower costs ($4,509 saved for HRD testing for people with *BRCA* wild type, and $3,630 saved for HRD testing for all) and lower QALYs (0.116 QALY loss over 5 years) compared with no HRD testing. The lower costs and QALYs were based on an assumption that fewer people with HRP would choose to take niraparib maintenance therapy and would not receive the survival benefit associated with treatment. The effect of HRD testing on patient decision-making is unknown.

Feasibility of Adoption Into Health System

Economic Feasibility

How economically feasible is the health technology/intervention?

Publicly funding HRD testing may lead to cost savings because fewer patients would receive niraparib maintenance therapy. Funding HRD testing for people with *BRCA* wild type would save $12.67 million for newly diagnosed ovarian cancer and $21.67 million for recurrent cancer over the next 5 years. Funding HRD testing for all people with high-grade serous or endometrioid epithelial ovarian cancer would lead to smaller savings ($9.00 million for newly diagnosed cancer and $16.31 million for recurrent cancer).

Organizational Feasibility

How organizationally feasible is it to implement the health technology/intervention?

One type of HRD test (MyChoice CDx) is used in some hospitals in Ontario, and the samples are sent to a laboratory in the United States. However, HRD testing may be performed at Ontario laboratories in the future. HRD testing for all people with high-grade serous or endometrioid epithelial ovarian cancer may be easier to implement than HRD testing for those with *BRCA* wild type because of reduced requirements for testing referral and coordination.

Reference

(1) Ontario Health. 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. Ont Health Technol Assess Ser [Internet]. 2023 Aug;23(5):1–188. Available from: www.hqontario.ca/evidence-to-improve-care/health-technology-assessment/reviews-and-recommendations/homologous-recombination-deficiency-testing-to-inform-patient-decisions-about-niraparib-maintenance-therapy-for-high-grade-serous-or-endometrioid-epithelial-ovarian-cancer

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