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### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>CRC</td>
<td>colorectal cancer</td>
</tr>
<tr>
<td>dMMR</td>
<td>deficient mismatch repair</td>
</tr>
<tr>
<td>HTERP</td>
<td>Health Technology Expert Review Panel</td>
</tr>
<tr>
<td>IHC</td>
<td>immunohistochemistry</td>
</tr>
<tr>
<td>LS</td>
<td>Lynch syndrome</td>
</tr>
<tr>
<td>MSI</td>
<td>microsatellite instability</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>pMMR</td>
<td>proficient mismatch repair</td>
</tr>
<tr>
<td>QALY</td>
<td>quality-adjusted life-year</td>
</tr>
<tr>
<td>rBG</td>
<td>revised Bethesda Guidelines</td>
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Summary of Recommendations

Colorectal cancer (CRC) is the third most common cancer in men and the second in women worldwide. Approximately 3% to 5% of colorectal cancers are attributable to a hereditary cancer predisposition related to DNA mismatch repair (MMR) deficiency. Deficient MMR (dMMR) results in an inability to correct DNA replication errors and therefore results in an increased risk of cancer.

Individuals with LS have hereditary (germline) defects in one of their genes that encode for an MMR protein. This predisposes them to colorectal and other types of cancer. LS is the most common familial CRC syndrome.

The gold standard for detection of a germline mutation in MMR genes (MMR deficiency) is germline genetic testing by sequencing and deletion-duplication analysis. However, as mutations in one of four MMR genes can underlie LS, and because of the time-consuming nature and considerable economic burden associated with sequencing all four MMR genes, the decision to offer germline genetic testing to diagnose LS is commonly made in a stepwise manner. Patients may be pre-screened for potential hereditary CRC based on age or family history, followed by testing of tumour samples for signs of dMMR, and ultimately germline genetic testing.

To assist decision-makers considering the implementation of dMMR tumour testing, CADTH conducted a health technology assessment (HTA) on the clinical utility, diagnostic accuracy, cost-effectiveness, and related patient perspectives and experiences of dMMR testing strategies. The ability of dMMR tumour test results to inform CRC prognosis or chemotherapy response was also evaluated.

The Health Technology Expert Review Panel (HTERP) recommends universal dMMR tumour testing for patients with colorectal cancer, followed by reflex tumour testing for MLH1 promoter hypermethylation.

Technology

While germline genetic sequencing is considered the gold standard to find an MMR gene mutation, the presence of functional tumour MMR deficiency can be assessed by either tumour microsatellite instability (MSI) testing using polymerase chain reaction (PCR) to detect abnormalities in tumour DNA replication, or by testing tumours using immunohistochemistry (IHC) for loss of expression of proteins involved in MMR (i.e., MLH1, MSH2, MSH6, and PMS2) as a precursor to gene sequencing. Recent literature suggests that testing tumours for loss of protein expression is as accurate as microsatellite analysis, while being cheaper and simpler to perform, and having the advantage of identifying the defective MMR gene to guide further genetic testing. Depending on the protein lost, additional tumour tests can be used to exclude likely non-inherited MMR deficiencies prior to embarking on germline gene sequencing. In a subset of CRC patients for whom the tumour IHC analysis reveals a lack of MLH1 protein expression, a somatic (non-inherited) event is often responsible for the tumour MMR deficiency. These cases are due to somatically acquired hypermethylation of the MLH1 promoter, which is seen in the presence of somatic BRAF V600E mutations. Therefore, additional testing for the BRAF V600E (as an indicator of the likelihood of MLH1 promoter methylation) or direct MLH1
promotor methylation can be used as part of diagnostic tumour testing algorithms to exclude likely sporadic CRC cases. These tests can be conducted simultaneously with the initial IHC, or they can be ordered automatically upon an initial test result indicative of dMMR (reflex testing).

**Methods**

CADTH conducted an HTA on the clinical and cost-effectiveness of dMMR tumour testing for patients with CRC, which included a review of published literature on patient preferences and experiences. A separate review of ethical considerations was also conducted. The Health Technology Expert Review Panel (HTERP) developed recommendations on the use of dMMR tumour testing based on the evidence presented in the HTA report and the Ethics Review report. HTERP members reviewed the evidence, discussed all elements of the HTERP deliberative framework, and developed a consensus-based recommendation. Additional information on the HTERP process is available on the HTERP page of the CADTH website: www.cadth.ca/collaboration-and-outreach/advisory-bodies/health-technology-expert-review-panel

**Detailed Recommendation**

The objective of this recommendation is to provide advice for Canadian health care decision-makers about the adoption of dMMR testing. This recommendation is relevant for all patients with colorectal cancer.

**HTERP recommends universal dMMR tumour testing for patients with colorectal cancer, followed by reflex tumour testing for MLH1 promoter hypermethylation.**

**Rationale**

- Both PCR-based and IHC-based tumour testing had high sensitivity and moderate-to-high specificity for detecting cases of LS. IHC-based testing provides more information about the nature of the mutation, which can guide subsequent tests, and is likely more widely available, cheaper, and more likely to be in current use. HTERP acknowledges that most health care providers will choose to use IHC-based tumour testing rather than PCR-based tumour testing.
- Knowledge of tumour dMMR status can be used to guide appropriate adjuvant chemotherapy decisions, which may be cost-effective compared with not using knowledge of tumour dMMR status to guide chemotherapy decisions.
- Universal tumour testing should improve equity by reaching those who do not actively seek a genetic assessment.
- Universal dMMR tumour testing followed by reflex tumour testing for MLH1 promoter hypermethylation, with dMMR status used to inform chemotherapy treatment, was shown to be a cost-effective strategy for the management of patients with colorectal cancer.
- Most people with a colorectal cancer diagnosis, and their family members, value the knowledge of their dMMR status so that family members can manage their future risk for colorectal or other cancers and implement preventive screening or other measures.

**Considerations**

The economic review identified six testing strategies that may be considered cost-effective depending on how much decision-makers are willing to pay for an additional quality-adjusted life-year (QALY) gain. In all of the potentially cost-effective strategies, the use of tumour dMMR
status to guide adjuvant chemotherapy decisions was considered cost-effective compared with not using tumour dMMR status to guide chemotherapy decisions. Universal dMMR testing of colorectal tumours, followed by reflex tumour testing for MLH1 promoter hypermethylation to identify patients for germline sequencing, with the tumour dMMR profile used to inform adjuvant chemotherapy decisions, was one of the cost-effective strategies and has the advantage of allowing more cases of LS to be identified. This result was robust to sensitivity analyses when varying the prevalence of LS, starting age of patients and relatives tested, the proportion of patients undergoing preventive treatment, or the number of relatives with subsequently diagnosed LS. At willingness to pay values between $28,902 and $387,330 per QALY, a universal screening strategy with reflex testing using hypermethylation would be cost-effective in the base-case analysis.

The majority of participants in the studies included in the patient experience literature were white and well educated, suggesting that this is the population that normally seeks testing or that is more inclined to participate in research studies. Universal testing should improve equity by reaching patients who would not normally seek testing.

Subsequent eligibility for germline genetic testing may create a tension between patient autonomy and privacy and duty to warn family members who may also be affected; for example, in the situation where a patient declines testing but family members are potentially at risk, or for those who are found to carry a germline mutation and do not inform their at-risk family members. Universal tumour screening will require a clear process that reflects that it is not, in itself, a germline genetic test, although it could lead to a germline test being offered, and also a process for patients to opt out of the tumour testing process. Routine seeking of consent or informing patients of the existence of tumour testing may not currently be in place prior to tumour testing in all settings. Education about the tumour test and its availability should therefore be considered when implementing a tumour testing program, to reach patients who may not otherwise seek germline genetic testing and to ensure informed consent is obtained. The information provided and the format of seeking consent for tumour testing needs to be considered for each setting.

Universal dMMR tumour testing will put additional pressure on genetic counselling capacity. Subsequent genetic counselling support is required by patients to properly understand and accept the role of germline testing and interpret both positive (germline mutation identified) and negative test results of germline testing, and is also useful to support patients through the process of disclosure of test results to family members, especially when a germline mutation is identified. The patient experience literature suggests that patients who receive negative tests may be less likely to pursue regular screening even when still indicated (e.g., routine population CRC screening by colonoscopy), which is an important risk to mitigate. While some genetic counselling costs were included in the cost-effectiveness analysis, an assessment of the actual local costs should be considered when implementing a testing program at a local level. As genetic counselling capacity may be limited, HTERP encourages an evaluation of the need for increased counselling resources or adaptations to genetic counselling practices in the local context to meet the demand. In rural hospitals and remote settings, telehealth may be used to improve access to genetic counselling services.

Universal dMMR tumour testing also has the potential to put pressure on hospital lab budgets. A sensitivity analysis using private lab costs was conducted, resulting in a higher cost per QALY gained, which indicates that it is more cost-effective to rely on public in-hospital lab services.
Background
Given the introduction and increasing diffusion of dMMR tumour testing in the work-up of patients presenting with colorectal cancer, together with the uncertainty regarding the optimal eligibility criteria for testing and the usefulness of the tumour test results in medical decision-making, a review of its diagnostic accuracy, clinical utility, economic effects, and related patient perspectives and experiences was needed and conducted to inform decisions about its use.

The clinical, economic, and patient perspective evidence used for developing this guidance was derived from the CADTH HTA report titled Mismatch Repair Deficiency Tumour Testing for Patients with Colorectal Cancer.

Research Questions
1. What is the clinical validity of IHC- or PCR-based dMMR testing, compared with germline sequencing, for detecting LS:
   a. When screening all colorectal cancer patients?
   b. When screening only patients at high risk of LS (e.g., selected based on Bethesda Guidelines [BG] or revised Bethesda Guidelines [rBG])?

2. What is the clinical utility of screening CRC patients for LS by IHC- or PCR-based dMMR testing for improving health outcomes of family members?

3. What is the clinical validity of molecular tests subsequent to dMMR testing for ruling out a germline mutation in MMR genes?
   a. What is the clinical validity of BRAF V600E testing by PCR for ruling out an MMR gene mutation in a CRC tumour with no MLH1 protein expression?
   b. What is the clinical validity of BRAF V600E testing by IHC for ruling out an MMR gene mutation in a CRC tumour with no MLH1 protein expression?
   c. What is the clinical validity of MLH1 promoter hypermethylation testing for ruling out an MMR gene mutation in a CRC tumour with no MLH1 expression?

4. What is the clinical utility of dMMR testing for improving health outcomes of CRC patients who do not receive adjuvant chemotherapy?

5. What is the clinical utility of dMMR testing for improving health outcomes of colon cancer patients who receive adjuvant chemotherapy?

6. What is the cost-effectiveness of dMMR testing in newly diagnosed CRC patients, considering the following two sub-questions?
   a. What is the comparative cost-effectiveness of the following four dMMR testing strategies, taking into account their impact on the choice of using adjuvant chemotherapy for the CRC patient or not and on cancer prevention of first-degree family members of the CRC patient:
      • dMMR testing in all CRC patients
      • dMMR testing all CRC patients younger than 70 years old
      • dMMR testing only patients at high risk of LS, based on the rBG
      • No dMMR testing in any CRC patients.
   b. What is the comparative cost-effectiveness of the following dMMR reflex testing algorithms for screening CRC patients for LS?
      • Initial four-panel IHC test (MLH1, MSH2, MSH6, PMS2), followed by germline testing if abnormalities are found in any gene
- Initial four-panel IHC test (MLH1, MSH2, MSH6, PMS2), followed by BRAF testing if the MLH1 protein is abnormal, or germline testing if abnormalities are found in MSH2, MSH6, PMS2, or MLH1 with normal BRAF
- Initial four-panel IHC test (MLH1, MSH2, MSH6, PMS2), followed by promoter hypermethylation if the MLH1 protein is abnormal, or germline testing if abnormalities are found in MSH2, MSH6, PMS2, or MLH1 without hypermethylation
- Single-step MMR + BRAF V600E IHC. Genetic testing if abnormal MSH2, MSH6, or PMS2, or abnormal MLH1 with normal BRAF
- Single-step MMR + BRAF V600E IHC. If MLH1 is abnormal and BRAF is normal, follow with MLH1 promoter hypermethylation. Genetic testing if abnormal MSH2, MSH6, or PSM2, or abnormal MLH1/normal BRAF without promoter hypermethylation.

7. What are the perspectives of CRC patients, their family members, and caregivers regarding the value and impact of dMMR testing on their health, health care, and lives?

Summary of Clinical Evidence

Based on the results of our review, both PCR-based and IHC-based tumour testing have similar sensitivity and specificity for detecting possible cases of LS, although IHC-based tumour testing has the added advantage of identifying which MMR protein is affected, which can guide follow-up testing to reduce the probability of a somatic mutation. Use of pre-screening criteria, such as the rBG criteria, can increase the prevalence of LS in the population being screened, but also increases the risk of missed cases (LS patients who do not meet pre-screening criteria screened out before testing, or patients not being pre-screened at all). No evidence was identified that examined the effect of dMMR tumour testing on the outcomes of family members. However, a supplementary review suggested a potential benefit of screening for LS for family members.

The results of the review show that MLH1 promoter hypermethylation testing has the highest sensitivity to detect sporadic CRC. Therefore, hypermethylation testing appears to have the best ability to rule out LS. PCR-based BRAF mutation testing has the highest specificity. Therefore, PCR-based BRAF mutation testing to rule out LS will result in the fewest number of patients with LS being misdiagnosed as having sporadic CRC. The results are inconclusive about the diagnostic accuracy of IHC-based BRAF mutation testing, due to a limited amount published data available.

Pooled results from a limited number of studies on the association between dMMR status and tumour relapse or survival rates of CRC patients who do not receive adjuvant chemotherapy show that patients with stage II dMMR tumours have statistically lower rates of relapse, and those with stage III dMMR tumours have a statistically better survival rate than patients with proficient MMR (pMMR) tumours. Limited evidence from individual studies also suggests that there are no differences between dMMR and pMMR tumours in terms of disease-free or overall survival rates in stage II, and relapse rates in stage III CRC, when no chemotherapy is administered.

The results of our meta-analyses suggest that among stage III colon cancer patients who receive 5-fluorouracil alone (with or without leucovorin or levamisole), dMMR was associated with a statistically improved disease-free survival, but similar overall survival rates. No survival difference was found between stage III dMMR and pMMR patients who received oxaliplatin-based or irinotecan-based chemotherapy regimens.
Overall, the limited number of studies included in this review does not permit a definitive conclusion about the value of knowing dMMR status in predicting prognosis of CRC patients, although the limited evidence included in our review may suggest beneficial effects of adjuvant chemotherapy in colon cancer patients who exhibit dMMR.

**Summary of Economic Evidence**

The economic model synthesized data from the clinical review, along with other data sources, to estimate the expected costs and outcomes (QALYs) of various options that combined different dMMR screening strategies, reflex testing strategies, and the use of tumour dMMR testing in guiding adjuvant chemotherapy decisions.

Table 1 summarizes the results of the base-case analysis. The strategy of screening CRC patients younger than 70 years old using MLH1 promoter hypermethylation as the reflex testing strategy would be considered the most cost-effective option if maximum willingness to pay for a QALY was between $20,757 and $28,902. Universal screening with MLH1 promoter hypermethylation as part of the reflex testing strategy would be considered the most cost-effective option if maximum willingness to pay for a QALY was between $28,902 and $387,330. The incremental cost per QALY of universal screening with PCR-based BRAF tumour testing as the reflex testing strategy compared with MLH1 promoter hypermethylation was more than $350,000 per QALY. This high incremental cost-effectiveness ratio was due to the small difference in specificity to detect likely sporadic CRC between the two supplemental tests. Although the higher specificity in PCR-based BRAF testing would lead to fewer false-negative LS diagnoses compared to testing by MLH1 promoter hypermethylation, the number of additional LS cases detected was small. Using tumour dMMR status to help guide adjuvant chemotherapy decisions was found to always lead to lower costs and higher QALYs compared with not using dMMR status, regardless of the combination of screening and reflex testing strategy used. The model results were found to be fairly robust in sensitivity analyses to changes in the prevalence of LS, the starting age of patients and relatives tested, the proportion of patients undergoing preventive treatment, or the number of relatives with subsequently diagnosed LS.
### Table 1: Base-Case Incremental Cost-Effectiveness Results for Comparators on the Efficiency Frontier (Probabilistic Results)

<table>
<thead>
<tr>
<th>Screening</th>
<th>Reflex Tumour Testing</th>
<th>Use dMMR for Chemo?</th>
<th>Costs</th>
<th>Life-Years</th>
<th>QALYs</th>
<th>$/Life-Year</th>
<th>$/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Screen</td>
<td>Not applicable</td>
<td>yes</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
<td>ref</td>
</tr>
<tr>
<td>rBG</td>
<td>BRAF-IHC + MLH1 promoter hypermethylation</td>
<td>yes</td>
<td>$79</td>
<td>0.0173</td>
<td>0.0162</td>
<td>$4,561</td>
<td>$4,866</td>
</tr>
<tr>
<td>rBG</td>
<td>MLH1 promoter hypermethylation</td>
<td>yes</td>
<td>$4</td>
<td>0.0006</td>
<td>0.0005</td>
<td>$6,368</td>
<td>$6,794</td>
</tr>
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<td>Younger Than 70</td>
<td>MLH1 promoter hypermethylation</td>
<td>yes</td>
<td>$111</td>
<td>0.0061</td>
<td>0.0057</td>
<td>$19,455</td>
<td>$20,757</td>
</tr>
<tr>
<td>Universal</td>
<td>MLH1 promoter hypermethylation</td>
<td>yes</td>
<td>$211</td>
<td>0.0098</td>
<td>0.0092</td>
<td>$27,089</td>
<td>$28,902</td>
</tr>
<tr>
<td>Universal</td>
<td>BRAF-PCR</td>
<td>yes</td>
<td>$275</td>
<td>0.0100</td>
<td>0.0093</td>
<td>$363,043</td>
<td>$387,330</td>
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<tr>
<td>Universal</td>
<td>All receive germline testing</td>
<td>yes</td>
<td>$382</td>
<td>0.0101</td>
<td>0.0095</td>
<td>$610,447</td>
<td>$651,283</td>
</tr>
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</table>

dMMR = deficient mismatch repair; IHC = immunohistochemistry; PCR = polymerase chain reaction; QALY = quality-adjusted life-year; rBG = Revised Bethesda Guidelines; ref = reference.

Note: Other strategies are not shown because they were dominated (strictly or extendedly) by other strategies.

The model was found to be sensitive in the following situations: higher risks of patients with LS developing CRC, costs from a private Canadian laboratory, and assuming the same diagnostic accuracy between IHC-based BRAF tumour testing and PCR-based BRAF tumour testing (Table 2).

With higher incidence rates of CRC, it is more cost-effective to screen: the incremental cost-effectiveness ratio of a universal screening strategy with MLH1 promoter hypermethylation as part of the reflex testing strategy reduced to $14,265 from $28,902, while the incremental cost per QALY of a universal screening strategy with PCR-based BRAF tumour testing reduced to $245,480 from $387,330 (Table 2). The costs of diagnostic tests were obtained from a British Columbia public hospital lab for the base case, with sensitivity analysis conducted based on higher diagnostic test costs from a private laboratory in Alberta. Results were sensitive to the cost of diagnostic tests. Based on the costs obtained from Alberta, screening using Bethesda Guidelines criteria with MLH1 promoter hypermethylation in reflex testing would be cost-effective if willingness to pay for a QALY was between $24,240 and $103,000. Lastly, as the economic model was based on limited data on the diagnostic accuracy of IHC-based BRAF tumour testing, a sensitivity analysis was conducted assuming that the diagnostic accuracy for IHC-based BRAF tumour testing was the same as that of PCR-based BRAF tumour testing. In this sensitivity analysis, universal screening with BRAF-IHC tumour testing and MLH1 promoter hypermethylation as part of the reflex testing strategy would be considered cost-effective if willingness to pay for a QALY is between $25,534 and $212,542. Universal screening with MLH1 promoter hypermethylation as part of the reflex testing strategy would be considered cost-effective if willingness to pay for a QALY is between $212,542 and $232,676.
Table 2: Results of Sensitivity Analyses

<table>
<thead>
<tr>
<th>Screening</th>
<th>Reflex Tumour Testing</th>
<th>dMMR Used in Chemo?</th>
<th>Base Case</th>
<th>Higher CRC Incidence Rate</th>
<th>Private Lab Costs</th>
<th>IHC BRAF Diagnostic Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Screening</td>
<td>Not applicable</td>
<td>yes</td>
<td>ref</td>
<td>X</td>
<td>X</td>
<td>ref</td>
</tr>
<tr>
<td>No screening</td>
<td>Not applicable</td>
<td>no</td>
<td>X</td>
<td>X</td>
<td>ref</td>
<td>X</td>
</tr>
<tr>
<td>rBG</td>
<td>BRAF-IHC + MLH1 promoter hypermethylation</td>
<td>yes</td>
<td>$4,866</td>
<td>X</td>
<td>X</td>
<td>$4,451</td>
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<td>Younger than 70</td>
<td>MLH1 promoter hypermethylation BRAF-IHC + MLH1 promoter hypermethylation</td>
<td>yes</td>
<td>$6,794</td>
<td>Ref</td>
<td>$24,240</td>
<td>X</td>
</tr>
<tr>
<td>Younger than 70</td>
<td>MLH1 promoter hypermethylation</td>
<td>yes</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>$18,375</td>
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<td>$20,757</td>
<td>$9,011</td>
<td>$103,000</td>
<td>X</td>
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<tr>
<td>Universal</td>
<td>BRAF-PCR</td>
<td>yes</td>
<td>$387,330</td>
<td>$245,480</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Universal</td>
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<td>yes</td>
<td>X</td>
<td>$651,283</td>
<td>X</td>
<td>$232,676</td>
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<tr>
<td>Universal</td>
<td>All receive germline testing</td>
<td>yes</td>
<td>$415,752</td>
<td>X</td>
<td>X</td>
<td>$805,937</td>
</tr>
</tbody>
</table>

CRC = colorectal cancer; IHC = immunohistochemistry; PCR = polymerase chain reaction; rBG = Revised Bethesda; ref = reference.

Note: Other strategies are not shown because they were dominated (strictly or extendedly).

Universal screening with hypermethylation as part of the reflex testing strategy would be considered the most cost-effective strategy under most circumstances. Although there is no consensus on a willingness to pay value for a QALY, it is likely within the range that this strategy would be considered cost-effective.

Summary of Patient Perspective and Experience Evidence

Data on patient preferences and experience are based on germline genetic testing as there are limited data regarding tumour dMMR testing. Participants represented in the included studies, including people with a diagnosis of CRC and their family members, see value in knowing whether hereditary cancer runs in their family. Participants described value in relation to either how they anticipated they would react to the information, or how they did react to the information about their mutation status. Generally, people with a diagnosis of CRC expressed perceived value in terms of the benefits to their family members, including clarifying their risk and offering the opportunity for prevention or early detection of CRC. Family members, however, expressed value for themselves and their family members, also in relation to an ability to clarify risk and participate in enhanced...
CRC surveillance. Perceived value was articulated when participants described their reasons for learning their mutation status, their perceptions of germline genetic testing, how they made the decision to pursue testing, and through their expressed confidence in the germline testing process and satisfaction with their decision to learn their mutation status. While perceived value was articulated in many ways, people do hold some reservations or hesitations about the germline testing process. Some barriers and disadvantages to germline testing were also articulated, and some people decline the offer for germline genetic testing or express regret in their decision to learn their mutation status.

The experience of deciding to learn about one’s mutation status is influenced by several factors relevant to the individual and family, which interact to make the experience unique for each individual. First, deciding to learn about one’s mutation status takes place in the context of relatively low community levels of knowledge about germline genetic testing in general, and genetic testing for hereditary colorectal cancer specifically. Further, people’s prior expectations of their mutation status will likewise influence their experience, as do the nature of family relationships and an individual’s coping style and their baseline levels of depression, anxiety, and distress.

Learning about one’s mutation status has implications for individuals and their families that encompass behavioural changes, psychological impacts, changes in family relationships, and subsequent decisions regarding disclosure of mutation status. Through our review, it became apparent that living with knowledge of one’s mutation status requires an individual to face a series of subsequent decisions, including whether to modify their behaviour; for example, to participate in recommended medical surveillance or engage in other preventive behaviours, such as diet and lifestyle modifications, and whether to disclose their mutation status and to whom, when, and how. Further, these decisions take place in the context of psychological change, including a range of positive and negative emotions, as people learn to cope with knowledge of their mutation status. Living with knowledge of one’s mutation status is a process that can include an initial period of shock, anger, and worry, and subsequently progress to acceptance and coping, at which time decisions about disclosure and behaviour changes can be made. The process is individualized, and varies based on many factors, including personal mutation status (i.e., whether an individual is mutation positive or mutation negative), the mutation status of family members, personal and family history of cancer, the family dynamic, and individual coping style.
References


APPENDIX 1: Health Technology Expert Review Panel

The Health Technology Expert Review Panel (HTERP) is an advisory body to CADTH and is convened to develop guidance or recommendations on non-drug health technologies to inform a range of stakeholders within the Canadian health care system. Further information regarding HTERP is available at www.cadth.ca/en/advisory-bodies/health-technology-expert-review-panel.

HTERP consists of up to seven core members appointed to serve for all topics under consideration during their term of office, and up to five expert members appointed to provide their expertise for a specific topic. For this project, three expert members were appointed; their expertise included clinical chemistry, pathology, and medical oncology. The core members include health care practitioners and other individuals with expertise and experience in evidence-based medicine, critical appraisal, health technology assessment, bioethics, and health economics. One public member is also appointed to the core panel to represent the broad public interest.

HTERP Core Members

Dr. Stirling Bryan (Chair)
Dr. Leslie Anne Campbell
Dr. Charlotte Moore
Dr. Lisa Schwartz
Dr. Jenny Basran
Dr. Hilary Jaeger
Dr. Jeremy Petch

Expert Members

Dr. Ronald A. Booth
Dr. Gillian Mitchell
Dr. Terence Moyana

Conflict of Interest

No members declared any conflicts of interest. Conflict of Interest Guidelines are posted on the CADTH website.