CADTH Optimal Use Report

Mismatch Repair Deficiency Tumour Testing for Patients with Colorectal Cancer: Recommendations

Draft Recommendations Report

April 2016
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# ABBREVIATIONS

<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>CRC</td>
<td>Colorectal cancer</td>
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<tr>
<td>dMMR</td>
<td>Deficient DNA mismatch repair</td>
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<tr>
<td>HTERP</td>
<td>Health Technology Expert Review Panel</td>
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<tr>
<td>IHC</td>
<td>Immunohistochemistry</td>
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<tr>
<td>MSI</td>
<td>Microsatellite instability</td>
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<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
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<tr>
<td>QALY</td>
<td>Quality-adjusted Life-year</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.\(^1\) Approximately 3% to 5% of colorectal cancers are attributable to a hereditary cancer predisposition related to DNA mismatch repair (MMR) deficiency.\(^2\) Deficient MMR (dMMR) results in an inability to correct DNA replication errors and are therefore results in an increased risk of cancer.

Individuals with Lynch syndrome 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. Lynch syndrome is the most common familial CRC syndrome.\(^3\)

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 Lynch syndrome, 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 Lynch syndrome is commonly made in a stepwise manner.\(^4\) Patients may be pre-screened based on age or family history\(^5,6\) followed by testing of tumor samples for signs of dMMR, and ultimately 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.

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

Technology

While germline genetic testing is considered the gold standard to find an MMR gene mutation, the presence of functional tumour mismatch repair deficiency can be assessed by either tumour microsatellite instability (MSI) testing to detect abnormalities in tumour DNA replication or by testing tumours 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, simpler to perform, and having the advantage of identifying the defective MMR protein to guide further genetic testing.7-10 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.11

METHODS

CADTH conducted an HTA on the clinical and cost-effectiveness of dMMR tumour testing for patients with colorectal cancer, which included a review of published literature on patient preferences and experiences. A 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. HTERP members reviewed the evidence, discussed all elements of the HTERP deliberative framework, and developed a consensus based recommendation through discussion and deliberation. Additional information on the HTERP process are found on the HTERP page of the CADTH website: https://www.cadth.ca/collaboration-and-outreach/advisory-bodies/health-technology-expert-review-panel

DETAILED RECOMMENDATIONS

The objective of these recommendations is to provide advice for Canadian health care decision makers about the adoption of dMMR testing. These recommendations are relevant for all patients with colorectal cancer.

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

Rationale

• Knowledge of tumour dMMR status can be used to guide appropriate adjuvant chemotherapy decisions, which may be cost-effective compared to not using knowledge of tumour dMMR status to guide chemotherapy decisions.
• Universal tumour testing may improve equity by reaching those who do not actively seek a genetic assessment.
• Universal dMMR tumour testing by immunohistochemistry of MLH1, MSH2, MSH6 and PMS2 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 cancer and implement preventive screening
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 QALY. In all of the potentially cost-effective strategies, the use of tumour dMMR status to guide adjuvant chemotherapy decisions was considered cost-effective compared to not using tumour dMMR status to guide chemotherapy decisions. Universal dMMR testing of colorectal tumours followed by tumour MLH1 promoter hypermethylation reflex testing 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 identifying more cases of Lynch Syndrome and decreasing the potential for missed diagnoses of Lynch Syndrome due to pre-screening criteria. This result was robust to sensitivity analyses when varying the prevalence of Lynch Syndrome, starting age of patients and relatives tested, the proportion of patients undergoing preventative treatment, or the number of relatives with subsequently diagnosed with Lynch Syndrome. At willingness to pay values between $28,902 and $387,330 per QALY, a universal screening strategy with reflex testing using hypermethylation had the highest probability of being 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 who normally seeks testing or who are more inclined to participate in research studies. Universal testing may improve equity by reaching patients who would not normally seek testing.

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. Universal tumour screening will require a clear consent 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 tumor testing in all settings. Education about the tumour test and its availability should therefore be considered when implementing a tumour testing program to both 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 may 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 may also be 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 (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 and remote areas, 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 indicating that it is more cost-effective to rely on 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 on 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 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: Mismatch Repair Deficiency 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 Lynch syndrome (LS):
   a. when screening all colorectal cancer patients?
   b. when screening only patients at high risk of LS (e.g., selected based on BG/rBG)?

2. What is the clinical utility of screening colorectal cancer patients for Lynch syndrome 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 \textit{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 \textit{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 colorectal
cancer 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 Lynch syndrome based on the revised Bethesda Guidelines
      • 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 Lynch syndrome?
      • 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 gene is abnormal, 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 gene is abnormal, 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 PSM2; 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 colorectal cancer 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 Lynch Syndrome, though 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 prescreening criteria, such as the revised Bethesda criteria, can increase the prevalence of Lynch Syndrome 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). No evidence was identified examining the effect of dMMR testing on the outcomes of family members. However, a supplementary review suggested a potential benefit of screening for Lynch Syndrome 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 Lynch syndrome. PCR-based BRAF mutation testing has the highest specificity. Therefore PCR-based BRAF mutation testing to rule out Lynch syndrome will result in the fewest number of patients with Lynch Syndrome 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 tumor relapse or survival rates of CRC patients, who do not receive adjuvant chemotherapy, show that patients with stage II dMMR tumors have statistically lower rates of relapse and those with stage III dMMR tumors have a statistically better survival rate than patients with pMMR tumors. Limited evidence from individual studies also suggests that there are no differences between dMMR and pMMR tumors 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 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 which combined different dMMR screening strategies, reflex testing strategies and the use of tumour dMMR testing in adjuvant chemotherapy decisions.

In the base-case, the strategy of screening CRC patients under 70 years old using MLH1 promoter hypermethylation as the reflex testing strategy would be considered the 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 cost-effective option if maximum willingness to pay for a QALY was between $28,902 and $387,330. Using tumour dMMR status to help guide adjuvant chemotherapy decisions was found to always lead to lower costs and higher QALYs compared to 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. The exceptions being when patients with LS had a higher risks of developing CRC, when using costs based on those from a private Canadian laboratory and when the diagnostic accuracy of IHC based BRAF tumour testing was assumed to be the same as the diagnostic accuracy of PCR based BRAF tumour testing.

The current model found the incremental cost per QALY of using tumour BRAF PCR-based testing in the reflex testing strategy compared to using MLH1 promoter hypermethylation to be over $350,000. This relatively high incremental cost 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 for MLH1 promoter hypermethylation, the number of LS cases detected was small.

In the base case analysis, the costs of diagnostic tests were from a BC public hospital lab. Sensitivity analysis was conducted when the costs of diagnostic test were based on costs from a private laboratory in Alberta where testing costs were higher. Cost-effectiveness results were different when the alternative costs were used in the model. If the alternative costs were used, then screening using Bethesda 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.

Based on the current analysis, universal screening with hypermethylation as part of the reflex testing strategy would be considered the cost-effective strategy under most circumstances. Though 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 to be cost-effective.

Summary of Patient Perspective and Experience Evidence

Participants represented in the included studies, including people with a diagnosis of colorectal cancer 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 colorectal cancer 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 colorectal cancer. Family members, however, expressed value for themselves and their family members, also in relation to an ability to clarify risk and participate in enhanced colorectal cancer surveillance. Perceived value was articulated when participants described their reasons for learning their mutation status, their perceptions of genetic testing, how they made the decision to pursue testing and through their expressed confidence in the 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 testing process. Some barriers and disadvantages to testing were also articulated, and some people decline the offer for 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 levels of knowledge about 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 does the nature of family relationships and an individual’s coping style and their baseline levels of depression, anxiety and distress.

Learning of 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 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

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, four expert members were appointed; their expertise included internal medicine, clinical chemistry, pathology, and family medicine. 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 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 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.