DNA Mismatch Repair Deficiency Tumour Testing for Patients With Colorectal Cancer: Ethical Issues
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Cite as: DNA mismatch repair deficiency tumour testing for patients with colorectal cancer: ethical issues. Ottawa: CADTH; 2016 Aug. (CADTH optimal use report; vol.5, no.3c).

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ISSN: 1927-0127

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This document was not externally reviewed.

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David Kaunelis designed and executed the literature search strategies, wrote the literature search methods section, and managed the report referencing.

**Conflicts of Interest**
No conflicts of interest were reported.
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Background
Ethics is the inquiry into the goodness or rightness in life; it examines questions about what we owe to each other and what it means to be a good person. Applied ethics uses ethical or moral theory (ethics and morals are used interchangeably in this report) to find answers to these questions for particular topics and contexts. Topics or questions in which important values are clearly at stake for individuals or populations are called ethical issues. An ethical issue may also be an ethical dilemma if two competing values are at stake. For example, whether to restrain a patient is an ethical issue because it challenges two important values: the value of supporting freedom and independence, and the value of keeping the patient safe. It is also an ethical dilemma because it is not possible to live up to both values in their entirety at once. The goal of an applied ethics inquiry is to balance these values and arrive at a resolution for the question at hand.

Ethics analysis is also used to evaluate new technologies for ethical issues and dilemmas. Health technology assessment (HTA) is the evaluation of new technologies or new applications of existing technology to determine whether they should be implemented (and sometimes publicly funded) within a health care system. HTA is fundamentally value laden and proceeds with the following implicit values:

- The technology should achieve the goal it is set out to achieve.
- The technology should achieve that goal without creating more harm than good.
- The financial requirement to adopt and implement the technology should not be disproportionate to its benefit.
- Adopting the technology should not pose serious threats to human integrity and dignity.

In addition, there are two broad normative questions that are relevant to most HTAs:
1. Should the technology be endorsed or made widely available?
2. If yes, how should the technology be made available?

This HTA pertains to universal testing for deficient mismatch repair (dMMR) in colorectal cancer (CRC) patients. Tumour dMMR testing can serve two purposes: optimizing chemotherapy treatment in CRC patients and diagnosing Lynch syndrome (LS), a hereditary disorder that increases the risk of certain types of cancers. Universal testing is being considered because it is hypothesized that providing this testing on a broad scale will result in better chemotherapy outcomes for CRC patients and identification of potentially high-risk family members, which will amount to an overall reduction of cancer-related morbidity and mortality in the population. The intent is to initiate a process that could ultimately lead to fewer cancer-related harms in relatives of CRC patients who have LS. This inquiry analyzes and summarizes the ethical issues involved in the implementation of universal dMMR testing in CRC patients.

Summary of Relevant Ethical Issues
Whether universal dMMR testing should be implemented
Core values: maximizing benefit for the population; stewarding scarce resources; respecting core individual interests

dMMR tumour testing for the purposes of optimizing cancer treatment appears to live up to values of conferring benefit at a population level and stewarding scarce resources, as it has been shown to offer benefit to dMMR patients and to reduce overall costs. It is unlikely that
explicit informed consent should be required for this type of tumour testing, provided this is the only purpose of the test. As dMMR testing can be a precursor to germline genetic testing for the purpose of identifying LS, if genetic testing will also identify potential LS in first-degree relatives, informed consent should be required.

Provided we are confident that universal dMMR tumour testing for the eventual purpose of LS diagnosis does lead to a minimization of cancer-related harms for the population, that the costs of this testing are proportional to the benefits, and that testing does not pose threats to core individual interests or fairness, universal dMMR tumour testing can be ethically justified.

How dMMR testing should be provided for the purpose of LS diagnosis in CRC patients and relatives

Core values: respect for people; respect for individual autonomy; privacy; maximizing benefit and minimizing harm to others; supporting familial ties; distributing benefits and burdens fairly (access)

Tumour testing may live up to the values of maximizing benefit and minimizing harm to others provided the others do have LS and can respond to the diagnosis productively. However, this does not necessarily mean that CRC patients are required to submit to testing themselves to achieve this potential benefits for others. Tumour testing could result in the patient needing to initiate difficult family conversations and thus has the potential to affect familial relationships. That informed consent be sought for tumour testing because the results can affect the patient’s psychosocial well-being is an important consideration. While consideration and respect for the deceased is important, testing of deceased patients’ tumours can be justified on the grounds of its potential for minimizing harms to others.

Patients should also be supported with information and careful conversation to decide whether to proceed with germline testing. This includes having a discussion about the implications of a test result with the patient and his or her family members for their own health and life planning. When considering the harms and benefits that may be offered by germline testing both to the patient and family members, physiological and psychological harms and benefits are relevant. One might suppose that the benefit of knowing one’s predisposition to life-threatening cancer offsets any psychological or emotional harm; however, this is not true in all cases. Health care providers will need to be attentive to and respectful of the relational context within which decisions are being made.

As both the CRC patient (proband) and his or her health care providers consider how to inform family members, the value of respect (rather than respect for autonomy) is likely to be most helpful. In most scenarios, a supportive and collaborative approach in which the CRC patient and health care team develop a plan to inform family members together (whether it is the patient or particular health care provider who does the informing) is recommended. Consideration about the actual benefits available to the proband’s relative should take prominence. The value of maximizing benefit and minimizing harm may imply that elderly relatives and children should not undergo testing as the benefits of doing so are minimal. In situations where there is conflict or uncertainty, the health care provider should consider the material risks of harms to others, and could be justified in informing known relatives of the patient irrespective of the patient’s wishes. This should be done in a way that maximally preserves the patient’s privacy.

When considering how to offer universal dMMR tumour testing, attention should be paid to whether health care providers (including genetic counsellors, as well as others expected to have
such conversations with patients) have the training and skills to carry out these conversations well. Procedures and training for health care providers should be in place to enable patients to maintain (or at least not threaten) relationships with family as they proceed through dMMR testing. Clear procedures for how genetic information will be collected, stored, and protected should also be in place. Attention should also be paid to the extent to which access to appropriate expertise and services — including genetic counselling, surveillance, prevention, and treatment services — are available to those drawn into universalized dMMR tumour testing. Economic and geographical factors should not present undue barriers or burden to those of lesser means or who live in more rural or remote areas. If it is anticipated that universal dMMR tumour testing will increase demand for screening and interventions, efforts to increase resources should be considered.

**Inquiry**

There are two broad normative questions to consider regarding universal dMMR tumour testing:

1. Should we implement universal dMMR tumour testing in CRC patients?
2. If yes, how should universal dMMR testing or LS testing be provided in CRC patients and their relatives?

Both of these questions are matters of systems-level or population-level ethics, which examine questions that will affect a large number of people and in which outcomes and interests are considered in aggregate (organizational ethics, policy ethics, and public health ethics are all domains of systems-level ethics). For systems-level ethics, instead of asking “Does this technology benefit the patient?” and “Does this technology disadvantage vulnerable individuals?”, we ask, “Does this technology create overall benefit for the population?” and “Does this technology disadvantage marginalized groups?” Questions of individual autonomy are of lesser concern when using this approach; however, if a technology were to present broad challenges to individual choice within a relevant population, this would be reason to consider seriously whether it would be ethically justifiable to endorse or implement the technology universally.

The determination that a technology should not be implemented may be made for several reasons:

- The technology offers little to no evidence of benefit at the population level.
- The technology does offer benefit at the population level, but the degree of benefit is disproportionate to the cost.
- The technology presents significant issues for respect for populations affected by the technology, and these issues cannot be mitigated by careful implementation. Such issues include systematic affronts to dignity, autonomy, and personhood and the oppression of particular groups, especially those who are already vulnerable or who may become vulnerable as a result of the technology.

If the answer to the first question is “yes, the technology should be implemented,” or at least not “no,” the second question on how the technology should be implemented should be pursued.

The development of a response to this question requires the consideration of the nature of the technology from the individual perspective, invoking an individualist or bedside ethics approach (sometimes referred to as clinical ethics). Closer attention must be paid to considerations of respect, benefit, autonomy, dignity, and fairness from the individual perspective to uncover how
the technology could be implemented and delivered in a way that lives up to key values or principles. If the analysis determines that the technology cannot be implemented in a way that sufficiently lives up to core values, it may cause the first question to be reconsidered.

In this HTA, the use of universal dMMR tumour testing for two purposes — optimizing chemotherapy treatment in CRC patients and diagnosing LS — will be considered for both questions. Ethical issues are considered separately for these purposes to account for the possibility that testing for one purpose is implemented but not the other. For the question of dMMR tumour testing for the purpose of LS diagnosis, in this ethics analysis, the technology under consideration is understood to be represented by the pathway in Figure 1. This pathway may be considered extensive when compared with the pathway assumed by other dimensions of this HTA; however, we believe that consideration all the way to the final steps of this pathway — to the point where family members actually engage in increased surveillance — is important because these final steps are critical to achieving the anticipated benefits of universal application of this technology. This pathway is critical and underpins the array of ethical issues that were identified.

**Figure 1: dMMR Testing Pathway for Colorectal Cancer Patients and Their Relatives (CADTH)**

- **Phase 1**: Tumour screening for dMMR
  - Proband chooses to pursue further testing
  - Screening test Result +
  - Referral to Genetic Counselor
  - Decision to determine LS status through germ line testing
  - Proband chooses no further testing

- **Phase 2**: Proband undergoes testing
  - Pos result (LS)
  - Plan for informing family members
    - Patient lead?
    - HCP lead?

- **Phase 3**: Pos result
  - Offer/advise surveillance of family members
  - Family members follow through on recommended surveillance

- **Phase 4**: Neg result
  - No further action
  - Family member tested

- **Phase 5**: Neg result
  - No further action
  - Pos result

*dMMR = deficient mismatch repair; HCP = health care professional; LS = Lynch syndrome; neg = negative; pos = positive.*

The ethics analysis of universal dMMR tumour testing also involves a descriptive question:

- What are the key ethical concerns identified in the literature on dMMR tumour testing with CRC patients?
This question aims to uncover the arguments and values that others have proposed to be relevant to ethical deliberation about the provision of universal dMMR tumour testing and its subsequent pathway (Figure 1). Those arguments and values can then be used to inform the answers to the nominative questions posed by this HTA.

Methods
A systematic review of the normative bioethics literature was conducted to identify literature relevant to the identification and analysis of the potential ethical issues with dMMR testing (i.e., articles that explicitly and specifically raise ethical issues). Targeted literature searches were performed by a CADTH Information Specialist (DK) on Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily, and Ovid MEDLINE 1946 to Present. Key terms for ethics concepts and related terms were used and combined with search terms for CRC screening (Appendix 1); the latter were not necessarily limited to dMMR, to ensure any analogous screening technologies were captured. Because of the recent emergence of dMMR screening, the search was limited to English-language literature published from 2010 until June 10, 2015.

The selection of relevant literature occurred in two stages. In the first stage, the title and abstracts of citations were independently screened for relevance by two reviewers (KD, KB). Articles that met the following criteria were categorized as “potentially relevant” or “not relevant”:

- Explicitly identified an ethical issue related to dMMR testing (or relevant analogue) for CRC for either patients or family members or to guide adjuvant chemotherapy

In the second stage of screening, two reviewers (KD, KB) independently assessed the relevance of the full-text reports for all citations classified as “potentially relevant” in the first stage. Full-text reports that met the following three criteria were included in the analysis:

- Pertained to CRC
- Pertained to dMMR testing for the purpose of diagnosis and treatment (e.g., chemotherapy regime) or to assess the need to identify any first-degree relatives at increased risk and offer genetic testing for LS
- Explicitly mentioned ethical issues (either individual or societal).

At both stages, disagreements between reviewers were resolved by discussion to reach a consensus. The details of each report — including lead author, publication date, journal, potential ethical issues raised, and report conclusions — were summarized in a separate document.

During the screening process, we also identified ethical issues from articles captured by the literature search that did not meet the strict relevance criterion of explicitly mentioning ethical issues. This additional step reflects the more typical approach of ethics scholars of performing a comprehensive literature review to uncover relevant material, relying in part on reason and judgment. Although a formal systematic review is an excellent way to gather relevant articles within the scientific literature, ethics issues are often not named explicitly in articles, which can make identifying good search terms challenging. For example, an article may describe the inequities in access to genetic counselling without ever being explicit about the clearly ethical dimensions relating to fairness and justice. This can create issues if the inclusion/exclusion criteria require that the article’s subject matter be explicitly identified as about or relating to “ethics.” In addition, rigour in ethics scholarship comes from accurate contextualization and
strong argument, and unlike scientific findings, ethics conclusions do not become more significant as their frequency in the literature increases. Similarly, the lack of material about the ethics dimensions of a particular technology does not mean that there are no ethical issues raised by the technology. For these reasons, implicitly raised ethical issues identified by the reviewers were used to supplement the systematic review and achieve a robust ethics analysis by giving them equal weight.

Results
The literature search yielded 623 unique citations, of which 72 passed the first stage of screening and were reviewed in full. Based on the second-stage screening criteria, 43 articles were excluded for not pertaining to CRC or LS, six were excluded for not pertaining to the use of dMMR testing, and 15 for not explicitly mentioning ethical issues. The remaining eight articles1-8 passed the second stage of screening and were deemed relevant. See Appendix 2 for the full PRISMA flow diagram of the selection process, and Appendix 3 for the list of excluded articles with reasons for exclusion.

The eight included articles1-8 were published between 2010 and 2015 and, generally, considered ethical issues within the context of the authors’ country: Italy (n = 15), the Netherlands (n = 24,7), the United States (n = 41-3,8), and Wales (n = 11). Each article explicitly mentioned at least one issue related to patient autonomy, psychological harms and benefits to patients with CRC, psychosocial harms to CRC patients, screening, physiological harms and/or benefits to others, duty to warn and/or inform, equity, providing excellent health care, consistency, relational considerations, stewarding resources, or conferring benefit at a population level (see Appendix 4 for article summaries). Eight additional ethical issues were identified for use in the analysis from the examination of articles of interest in the systematic review. The issues identified are summarized in Table 1 and organized according to core values in ethics.

Table 1: Values and Ethical Issues Raised by dMMR Testing for Lynch Syndrome and Analogous Screening Tests

<table>
<thead>
<tr>
<th>Respecting Patient Autonomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>This is a key value in Western society that recognizes individuals’ roles in determining their life course. In health care contexts, informed consent is a means of respecting patient autonomy by enabling patients to make an informed decision about their care.</td>
</tr>
<tr>
<td>Informed consent (implied vs. explicit)(^1)**</td>
</tr>
<tr>
<td>Consent for tumour test(^9)</td>
</tr>
<tr>
<td>Consent for germline testing(^3,6)</td>
</tr>
<tr>
<td>Respecting patient choice not to take the germline test(^2)</td>
</tr>
<tr>
<td>Maintaining patient confidentiality(^1,2)</td>
</tr>
<tr>
<td>Approaches to decision-making (using learning aids; nudging; the impact of physician perception)(^9-11)</td>
</tr>
</tbody>
</table>
Maximizing Benefits and Minimizing Harms to Patients
This value sits at the core of bioethics and describes duties at every level to fund, organize, and deliver health care services in a way that gives maximal chance of benefit and creates minimal harm. Benefits and harms can be physiological (relating to illness, comfort) and psychosocial (relating to emotional, relational, and psychological well-being).

<table>
<thead>
<tr>
<th>Physiological</th>
<th>Increasing chemotherapy effectiveness(^1,2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Minimizing risks of possible secondary cancer(^1,2)</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>Invasiveness or burden of testing(^1,3)</td>
</tr>
<tr>
<td></td>
<td>Anxiety with prospect of test(^1,3)</td>
</tr>
<tr>
<td></td>
<td>Managing inconclusive results(^1,3,12)</td>
</tr>
<tr>
<td></td>
<td>Fear of genetic discrimination(^1,3)</td>
</tr>
<tr>
<td></td>
<td>Impacts of LS on religious and existential well-being(^14)</td>
</tr>
</tbody>
</table>

Maximizing Benefits and Minimizing Harms to Others
This value describes duties to fund, organize, and deliver health care services in a way that takes into account impacts on those who are not the patient but who could be affected nonetheless. In most cases, the focus is on family and loved ones. At a systems level, this includes whether the technology creates harms for specific subpopulations that are not the intended target of the technology. Benefits and harms can be physiological (relating to illness, comfort) and psychosocial (relating to emotional, relational, and psychological well-being).

<table>
<thead>
<tr>
<th>Physiological</th>
<th>Harms of undiagnosed or late-diagnosed cancer(^1,2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dMMR tumour testing for deceased patients(^6)</td>
</tr>
<tr>
<td></td>
<td>Cancer screening in elderly populations(^15,16)</td>
</tr>
<tr>
<td></td>
<td>Prenatal testing for LS(^7)</td>
</tr>
<tr>
<td></td>
<td>Genetic testing for cancer-related mutations in minors(^18,19)</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>Invasiveness or burden of testing(^1,3)</td>
</tr>
<tr>
<td></td>
<td>Anxiety about prospect of test(^1,3)</td>
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<td></td>
<td>Impacts of LS on religious and existential well-being(^14)</td>
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</tbody>
</table>

Duty to Warn
Closely related to values of minimizing harm to others, this value (or duty, as it is phrased here) refers to a professional’s obligation to warn non-patients if the professional has good reason to believe that they may be subject to imminent and/or serious harm. There are challenges related to this value, as it often entails the professional disclosing some degree of patient information (violating patient confidentiality) in order to warn.

| By physician\(^4,7\) |
| By genetic counsellor\(^4,7\) |
| By CRC patient\(^4,7\) |

Distributing the Benefits and Burdens Fairly (Equity)
This value describes broad social duties to consider matters of justice and to avoid disproportionately benefiting or burdening particular individuals or populations without clear justification.

| Access to genetic counselling\(^2,3\) |
| Screening participation variation among socioeconomic, geographic (rural and/or urban), and race dimensions\(^20-24\) |
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Providing Excellent Health Care
This value refers to health care providers’ obligations to provide health care that meets agreed-upon standards of quality.

| Providing appropriate and comprehensive information⁶,²⁵ |
| Quality of genetic counselling³ |
| Medicalization and/or shifting focus away from family history³,²⁵ |

Consistency
The value of consistency describes the importance of treating like cases alike. Consistency is most valued when the consistent approach (whatever it may be) is well justified according to other values. The fact that one approach is consistent with another does not necessarily mean that the approach is ethically justified.

| Consent requirements for dMMR align with other tests⁸ |

Accounting for Relational Considerations
This value acknowledges the significance of social (often familial) relationships to the well-being of individuals and communities. It draws our attention to consider how health care interventions may affect these relationships.

| Communication of LS susceptibility within families²⁶,²⁷ |

CRC = colorectal cancer; dMMR = deficient mismatch repair; LS = Lynch syndrome; vs. = versus.

Articles obtained from the literature review predominantly examined the question of how dMMR testing should be provided and address specific points along the pathway, paying little regard to the broader question of whether it should be provided at all. As a result, systems-level values were not discussed in the literature and did not show up in our results (see Table 1). However, we believe that the systems-level questions are appropriate domains to begin our ethics analysis and so propose the addition of two broad values: maximizing benefit for populations and stewarding scarce resources (Table 2). These values are relevant to the discussion of the question of whether universal dMMR tumour testing should be provided for the purposes of CRC treatment optimization and identification of LS in CRC patients and their relatives.

Table 2: Relevant Systems-Level Ethics Considerations (Values) That Did Not Emerge in the Literature Review

Maximizing Benefit and Minimizing Burdens for Populations
Related to the value of maximizing benefits and minimizing burdens to patients and others, this value articulates the importance of actions that confer benefit to the community or population as a whole. In health care, benefits are typically taken to be minimized incidence and prevalence of disease, minimizing of suffering associated with illness, and a reduction in preventable deaths. In health technology assessment, we examine the extent to which a technology can be beneficial by looking at its clinical effectiveness.

Stewarding Scarce Resources
This value describes the duties to make wise use of scarce resources, especially if these resources are shared by many. Closely related to values of efficiency, this value places economic decisions within the realm of ethics, with the view that resources should be used to achieve agreed-upon aims, and further, that these aims are achieved within reasonable expenditures. In health care, the aim is typically to minimize suffering and improve health outcomes. To assess whether resources are being used appropriately, economists can support decision-makers by examining how much it costs for the technology to produce a quality-adjusted life-year (QALY). Although this is not without controversy, it is generally thought that a cost per QALY that is beyond a certain threshold is not an appropriate use of resources.
Analysis

Should we implement universal dMMR testing in CRC patients?

dMMR tumour testing for optimizing chemotherapy treatment in CRC patients

Maximizing benefit for populations and stewarding scarce resources

Evidence uncovered in the clinical effectiveness and economic evaluation dimensions of this HTA suggests that knowing a patient’s MMR status can be useful in making decisions regarding chemotherapy after tumour excision. Knowing tumour dMMR status enables clinicians to opt for treatment courses for dMMR patients that offer greater benefit and avoid the use of costly chemotherapy drugs. Universal dMMR tumour testing for the purposes of optimizing chemotherapy treatment effectiveness in CRC patients appears to live up to values of maximizing benefit for populations and stewarding scarce resources.

Respecting patient autonomy

Informed consent processes offer a means of respecting patient autonomy by ensuring that patients understand particular medical procedures and can elect to consent them. However, informed consent is not sought for all medical interventions. For example, consent is implied for low-risk, minimally invasive, or regular procedures (e.g., blood draws, administration of regular medications). Regular pathology tests for which the patient is completely physically uninvolved because the tissue sample is already excised are also done without actively seeking consent from patients, likely on the grounds that the test is part of a larger activity (e.g., cancer treatment) to which the patient has already consented. If we accept that levels of risk, invasiveness, and the context of the test are relevant criteria for assessing whether informed consent is required, it is reasonable to conclude that tumour testing for the purposes of determining treatment pathways for the patient can be conducted without explicit consent from the patient.

dMMR tumour testing for diagnosing Lynch syndrome

Maximizing benefit for populations

The hypothesis that universal dMMR tumour testing on a broad scale will lead to a reduction in cancer-related morbidity and mortality rests on a very specific clinical picture. It assumes that a subset of CRC patients who find out that their cancer may be caused by a hereditary deficiency in the genes for mismatch repair proteins will undergo further confirmatory germline genetic testing, and if positive (LS), they will inform some of their blood relations. It further posits that some of these first-degree relatives will also choose to undergo a confirmatory genetic test and, if positive, a subset of them will choose to and be able to seek out increased cancer surveillance. This surveillance must then catch developing cancers before they might have been caught if the person was not aware of their increased risk of cancer due to LS. We presume that catching the cancer earlier will result in earlier treatment and, therefore, better treatment outcomes.

There is currently no clinical evidence to demonstrate that universal dMMR tumour testing leads to improved cancer outcomes for family members of CRC patients with LS. Presumably, the lack of evidence is in large part due to the difficulty in setting up a study to directly examine the outcomes of this complex pathway. Nevertheless, an economic model was created using various parameters to estimate what might be the costs and benefits of the pathway. There was a significant degree of uncertainty in the model assumptions, but the model did yield estimates for incremental costs per quality-adjusted life-year (QALY) using several screening strategies. Seven screening strategies were identified as potentially cost-effective (see the economic analysis).
**Stewarding scarce resources**

From an ethics perspective, the value of stewarding scarce resources describes duties of decision-makers in our health system to use scarce public resources in such a way that provides as much benefit (broadly interpreted) as possible. The evaluation of how a resource can most appropriately be spent requires knowledge not only about QALYs for a particular technology, but also about opportunity costs and relative QALYs for competing technologies and services within the same budget. Because this contextual knowledge cannot be known here, it is difficult to conclude whether universal dMMR tumour testing for LS diagnosis delivers on our values of maximizing benefit for populations and stewarding scarce resources.

**Distributing the benefits and burdens fairly (equity)**

Another consideration for the implementation of universal dMMR tumour testing for both treatment optimization and LS diagnosis is whether access to the necessary expertise and services is fairly distributed among the affected population regardless of income level, education, or cultural background. If it is found that the current system favours access only for those of a particular group (especially a privileged group) and that this injustice cannot be rectified, decision-makers would need to think carefully about implementing such a program.

**General implications**

Provided that universal testing does minimize cancer-related harms for the population, that the costs of this testing are proportional to the benefits, and that it does not pose threats to core individual interests or fairness, universal dMMR tumour testing can be ethically justified. However, if subsequent testing will also be used to identify LS in first-degree relatives, informed consent should be required.

**How should universal dMMR testing or LS testing be provided in CRC patients and their relatives?**

For the purposes of this analysis, we will assume that universal dMMR testing does create benefit for populations in the form of decreased cancer-related morbidity and mortality at a reasonable cost in a way that does not inherently pose a threat to human dignity or integrity. From here, we consider the ethics dimensions of how we might organize and implement universal technology. We will examine this question with reference to the five phases of the dMMR pathway indicated in Figure 1.

**Phase 1: Testing of excised cancer tumour**

In this phase, the dMMR pathway is initiated with the testing of the CRC patient’s excised tumour to determine whether the patient potentially has LS. Three key values are relevant to this phase of the pathway: respecting individual autonomy, maximizing benefits and minimizing harms to others, and respecting human dignity.

**Respecting individual autonomy**

Informed consent processes offer a means of respecting patient autonomy by ensuring that patients understand particular medical procedures and can elect to consent to them. It provides patients with the ability to determine what happens to their body and, more broadly, their life course. An informed consent process would require that the patient is given full information about the testing and its implications and given an option to accept or decline this test. The decision needs to be informed, voluntary, and given by a capable patient. There are mixed perspectives about whether a patient should be asked to give informed consent for tumour testing. Some have argued that the dMMR test is on a tissue that is no longer within the patient’s body, so it poses no physiological risk and is non-invasive; therefore, informed consent
is not required. However, a positive test would trigger the patient to be informed that there is a chance they have LS and, if LS is confirmed, that biological family members may also be affected. Because patients are likely to be involved in the difficult conversation of informing their family members of their potential to have LS, there could be conflict within family relationships. Patients may also find themselves having to support family members to understand risks and to make a decision regarding testing. On the grounds that patients may experience psychological and relational impacts due to the tumour testing, it is reasonable that patients should at least be made aware of the fact that their tumour will be tested for dMMR and that there may be consequences to this test for themselves and their family.

Empirical data obtained from the literature on patient experience regarding dMMR testing does not indicate which testing experiences (i.e., the initial tumour test or a subsequent germline genetic test) are being discussed. However, the reports suggest that patients often do not remember the process that led up to the testing and seem to minimize the importance of whatever that process was, instead placing emphasis on the value of knowing the results, as these are most relevant to patient and family well-being. There is no indication as to why patients do not tend to recall the testing process; it could be related to whether and how the testing process was discussed by their health care providers or because the test took place amid other tests and conversations relating to cancer treatment. However, the fact that patients do not recall or place much emphasis on this testing process does not necessarily mean that the process is unimportant or insignificant, or that informed consent is not necessary.

Respecting autonomy is a duty-in-principle and is not pursued based on whether a subset of a particular group says they want it or not. People can decline to participate in decisions in certain ways, however, but they must at least be asked about how they want to be included. The research participants in the patient experience data on dMMR tumour testing were primarily white, married, educated, and middle-class and therefore may be more likely to have high levels of trust in the health system. For these reasons, their responses cannot be assumed to be representative of all CRC patients to whom dMMR tumour testing may be offered. The medical literature shows that other socioeconomic groups are less participatory in health care and may not share such an unquestioning view. For this reason, as well as the fact that test results can have impacts on the patient’s psychosocial well-being, informed consent procedures for dMMR tumour testing are advisable.

**Maximizing benefit and minimizing harm to others**

Testing for LS in CRC patients, in addition to benefitting the patient, is also sought for the benefit of relatives who may also have LS but have not yet had an onset of cancer. In other words, testing the CRC patient’s tumour is justified by the value of protecting others from harm (maximizing benefit for others), not just the patient. However, does the CRC patient (proband) have a duty to get tested? While it may be morally praiseworthy for individuals to act in a way that benefits others, with the exception of those who are in clear fiduciary relationships (e.g., physicians with their patients; parents and their children), it is not clear if people always have a moral duty to do so. In this case, the results of the LS test may not be uniformly beneficial for others, and the benefit would depend on the degree to which a positive test for the CRC patient would result in increased anxiety and distress for others. It would also depend on the likelihood that relatives are positive for LS and whether the relatives’ knowledge of their dMMR status would ultimately reduce the eventual harms caused by cancer. See further discussion of the duty to protect others in Phase 2 and Phase 3. Tumour testing may live up to the values of maximizing benefit and minimizing harm to others, provided the others do have LS and can
respond to this diagnosis productively. However, this does not necessarily mean that probands are required to submit to testing themselves to achieve this potential benefits for others.

**Respecting dignity and privacy of the deceased**

There is some question about the ethical dimensions of tumour testing on deceased patients. Some argue that testing tumours from deceased patients is not permissible, because to do so would constitute an invasion of privacy that the deceased cannot consent to, provided the testing leads to more extensive uncovering of the deceased's genetic information. The living have an interest to treat decedents and their memories with respect and dignity, but those who have died are no longer moral agents and so cannot have meaningful moral claims on the living. If there is some potential for benefit (the well-being of living relatives of the decedent), it can be ethically justified to test a deceased CRC patient’s tumours for dMMR on the grounds of the potential for minimizing harms to others.

**Phase 2: Referral to genetic counsellor and germline testing**

This phase of the pathway describes the period during which the proband receives a positive result from the initial tumour test and is referred to a genetic counsellor. In discussion with the genetic counsellor, the proband decides whether to proceed with germline testing to confirm LS. This phase also includes the germline genetic test if the proband chooses testing. This phase involves four key values: distributing the benefits and burdens fairly (equity), respecting patient autonomy (and privacy), maximizing benefit and minimizing harm to patients, and maximizing benefits and minimizing harms to others.

**Distributing the benefits and burdens fairly (equity)**

If crucial components of the pathway cannot be made reasonably accessible to most patients — not simply those who have the social, geographic, or financial means — universal screening may be more difficult to justify. Specifically, if access to a qualified genetic counsellor is a key element to achieving the potential benefit of universal dMMR tumour testing, careful consideration needs to be given to the ease of accessibility to counsellors. This includes whether universal dMMR tumour testing would result in a significant increase in demand for genetic counselling, whether there is enough existing capacity to meet this demand, and how to minimize barriers for patients who may be at a disadvantage (e.g., by living in a rural area).

**Respecting patient autonomy (and privacy)**

The health care system and the providers therein have a duty to respect a patient’s autonomy. This means informed consent at every phase of the pathway is crucial. There is general agreement within the ethics literature on dMMR testing that patients should provide explicit informed consent for the germline genetic test to confirm their LS status. Meaningful informed consent requires that patients receive accurate information that is presented at their level of understanding. Decision aids can help patients make informed decisions in this pathway, particularly for those with a low level of medical literacy. Another view is that it is ethically justifiable for health care providers to “nudge” their patients to make decisions that the provider believes are in the patient’s or others’ best interests. Regardless of the means, patients should be supported with information and careful conversation to decide whether to proceed with germline testing. This includes having a discussion about the implications of a positive test, both for the patient and his or her family members.

The value of protecting patient privacy is argued to be a matter of individual autonomy because it is about an individual’s ability to decide who, how, and when others have access to his or her personal information. Genetic screening poses particular challenges to autonomy and privacy.
because the choice of one person to undergo screening uncovers information about related individuals who likely have not had an opportunity to consent to the test.

**Maximizing benefit and minimizing harm to colorectal cancer patients**

Although dMMR testing of the CRC patient does not generally confer direct physiological benefit to the patient, our review of the patient experience literature indicates that they could potentially face emotional and psychological burdens related to the testing. Harms could include increased anxiety and uncertainty and threats to religious and existential well-being; there are also concerns that finding out information about one’s genetic lineage could lead to genetic discrimination, affecting a patient’s ability to secure life insurance or a mortgage. Although the literature shows that patients tend to choose to undergo germline genetic testing in spite of these concerns, some individuals are compelled enough by the potential for these harms that they elect not to undergo germline testing. In addition, these burdens may emerge whether or not the patient chooses further testing. Whatever the decision, it should be respected by the patient’s health care team to respect patient autonomy.

**Maximizing benefit and minimizing harm to others**

As indicated in the patient experience data, in Phase 2, the general concern of minimizing the harms related to cancer risk in others rightly underlies the decisions made by the CRC patient. The patient may be considering the harms of potential cancers on family members as well as the psychological and emotional harms that the knowledge of mutation status could impose. The knowledge that one may actually have LS could create anxiety, uncertainty, and existential discomfort in family members and, for a small proportion of individuals, worries about genetic discrimination may also be a factor. The benefits of knowing one’s predisposition to life-threatening cancer might be presumed to offset any psycho-emotional harms; however, this is not true in all cases. Health care providers will need to be attentive to and respectful of the relational context within which decisions are being made. Although this value does not morally require the CRC patient to proceed with testing, it should be considered in the decision.

From a health care provider’s perspective, this value should not take precedence over considerations of autonomy. In other words, it would not generally be permissible to override a patient’s decision not to proceed with testing in order to live up to the value of maximizing benefit and minimizing harms for the patient’s relatives. Ultimately, the relative relevance of this value will be modulated by the presence and demographics of the patient’s blood relatives. A patient who has no identifiable relatives (including children) or whose relations are elderly may not see this value as determinative. This is not because they do not care for their relatives if they exist, but because the actual harms and benefits posed by the test are minimal.

**Phase 3: Decision on whether, and how, to inform others**

Phase 3 of the pathway is when the proband has received a confirmatory germline genetic test and has a positive LS diagnosis. This positive diagnosis suggests that first-degree relatives have a chance of having LS as well and are therefore subject to increased risk of developing various cancers. There are three key values involved in this phase: respecting individual autonomy (and privacy), maximizing benefits and minimizing harms to others, and supporting familial ties.

**Respecting individual autonomy (and privacy)**

The duty to respect the proband’s decisions related to dMMR testing and, therefore, his or her autonomy remains important in this phase. However, with the confirmation of the CRC patient’s LS status and the concomitant confirmation of risk to relatives, considerations for others begin...
to take more prominence. There are several perspectives on this matter.\textsuperscript{4,7} It could be argued that respecting the patient’s autonomy extends to his or her decision about whether to inform relatives about their potential risk. An alternative argument is that the patient’s judgment about when and how to inform relatives should be respected, but the decision of whether to inform relatives should not be decided by the proband alone. Still others have argued that the appropriate health care provider has a duty to inform a patient’s relatives irrespective of the patient’s wishes. The question of whether to inform a patient’s relatives without his or her consent becomes more complex if the relatives are unaware of the patient’s cancer diagnosis. Informing the patient’s relatives in a way that is clear and that would motivate them to follow through with germline genetic testing would likely require sharing some of the patient’s medical information, thus breaking patient confidentiality.

\textit{Maximizing benefit and minimizing harm to others}

By Phase 3, the value of maximizing benefit and minimizing harms to others becomes more important because the actual risk to relatives has become more certain in light of the CRC patient’s LS diagnosis. As discussed above, both physiological and psycho-emotional harms and benefits should be considered. Few would disagree that the overall benefits of early cancer detection offset the burdens of learning about the risk of LS, and it is this assessment of the value that motivates those who argue that health care providers should ensure that the patient’s relatives are informed of their LS status, no matter who shares the information.

As with other phases of the pathway, consideration about the \textit{actual} benefits available to a patient’s relative should take prominence. Timelines and availability of screening are key factors in assessing the weight of this value. For elderly relatives, there may be no practical benefit to LS testing because they are unlikely to live long enough to see the development of the cancer to which they may be susceptible.\textsuperscript{15,16} For children, there are multiple factors that should be considered with care. Appropriate screening may not be available for children, so test results may not lead to active prevention; anticipated cancers may be unlikely to form until adulthood, so potential harms would go unrealized for years; and the psychological and emotional harms may be of greater concern for children, who lack the capacity to understand the meaning of the test or its outcomes.\textsuperscript{19,28} Together, this suggests that there is little benefit to testing children, and the best way to maximize benefit and minimize harm to children may be to inform them of their risks and their options for testing when they reach adulthood.

\textit{Supporting familial ties}

Generally, it is in the patient’s interest to maintain and strengthen social ties, including those with family members, and to be supported to do so. It is therefore important to be attentive to the extent to which a technology could alter or threaten such ties. In the case of dMMR testing, the potential for overall benefit depends heavily on the nature and function of the patient’s family relationships, as it is up to the CRC patient to choose to proceed with testing (likely with consideration of family) and to maintain relationships with family (such as they are). In addition, the patient is either the person who directly informs family about their potential risk or, at a minimum, is the reason for family members being informed about their risk by another (genetic counsellor or physician). The patient experience literature shows that some patients, especially in the role of informing family about their potential risk, can feel rejected and isolated by family, at least initially. Concerns for familial relationships also appeared to motivate whom the patient informed of the potential for risk. For example, some patients chose not to inform nieces and nephews because they believed that this would be a more appropriate task for their parents (the patient’s siblings).
As both the patient and his or her health care providers consider how to move through Phase 3, the values of trust and collaboration (rather than respect for autonomy) are more likely to be helpful. In most scenarios, a supportive and collaborative approach where the patient and team work out a plan to inform family members together (whether it is the patient or health care provider who does the informing) is recommended. In situations where there is conflict or uncertainty, the health care provider should consider the material risks of harms to others and could be justified in informing known relatives of the patient irrespective of the patient’s wishes.

Phase 4: Genetic counselling and familial germline genetic testing
In this phase, family members who have been informed of their potential of having LS are referred to genetic counselling and decide whether to confirm their LS status through germline testing. Key values include distributing benefits and burdens fairly, respecting individual autonomy, and maximizing benefit and minimizing harm.

Distributing benefits and burdens fairly
As in Phase 2, consideration should be given to fair access to needed expertise, such as a genetic counsellor or professional support for when individuals are deciding whether to proceed with testing and when they are making sense of the results. If universal dMMR tumour testing is implemented, fairness requires that those affected have reasonable access (both in terms of financial burden and geography) to the services needed.

Respecting individual autonomy
As in all previous phases, the value of individual autonomy remains relevant. In this case, this value applies to the CRC patient’s family member who is deciding whether to proceed with germline genetic testing. Here, unlike with the CRC patient’s decision (where proband testing benefits someone other than the proband), the decision for the CRC patient’s relative to undergo testing benefits that relative (as well as potentially that relative’s family members). The patient experience data show that there can be confusion about the meaning of a positive test for LS, where some have interpreted this to mean that they have a positive cancer diagnosis. Patients should be supported with careful conversation to decide whether to proceed with germline genetic testing. Clear and accurate information appropriate to the relative’s level of understanding would be crucial. This includes having a discussion about the implications of a positive test for their own health and for life planning. Ultimately, the decision should be respected without judgment regardless of what it may be; options should also remain open, in case patients change their minds.

Maximizing benefit and minimizing harm
Once again, harms and benefits should be considered for both physiological and psycho-emotional domains. Minimizing the physiological risks of cancer as well as the psycho-emotional burdens relating to testing and uncovering genetic information will likely be relevant to an individual considering whether to pursue confirmatory germline genetic testing.

In this case, the person choosing to undergo testing may be considering the implications for life plans. The patient experience literature shows that individuals may use their LS diagnosis for decisions regarding marriage and child-bearing, including engaging in prenatal testing to assess the LS status of an embryo or fetus.17

Phase 5: Surveillance and treatment
In this phase, proband relatives (now patients) who have received results from a germline genetic test indicating that they have LS are encouraged to engage in increased cancer
surveillance, of which a subset actually do. The key value in this phase is distributing benefits and burdens fairly (access).

**Maximizing benefit and minimizing harm**

In this phase, the value of maximizing benefits and minimizing harms is best realized through proactive engagement with screening for LS positive patients. The patient experience literature has shown that, even though they are encouraged to screen as often as the “general population,” pMMR patients (i.e., dMMR-negative patients) sometimes elect to screen less often as a result of their diagnosis, thus potentially increasing their risk for cancer-related harms.

**Distributing benefits and burdens fairly (access)**

Generating overall benefit from universal dMMR tumour testing relies on those with LS having access to and actually using cancer screening services. The patient experience literature shows that some patients do not disclose their positive status to their regular physicians because they do not think their physician will understand. This highlights the need for patients to be supported in their LS status and to have access to informed guidance for how to move ahead in responding to their status, should they choose.

Further, the ethics literature on cancer screening shows that there is variation in the use of screening services according to race and socioeconomic class. Data on whether this is true for cancer screening in LS patients are not available; however, evidence for other forms of screening is strong enough to be worth considering within the dMMR context. The value of distributing benefits and burdens fairly requires health care decision-makers to uncover cultural or socioeconomic factors that may indicate the presence of barriers to screening services. Such barriers should be minimized or eliminated where possible. These considerations are equally relevant for those seeking treatment once a cancer has been identified.

Once again, attention should be paid to the extent to which access to appropriate expertise and services, including cancer screening and treatments, are available to those in need. If it is anticipated that universal dMMR tumour testing will increase demand for screening and interventions, efforts to increase resources should be considered. Economic and geographical factors should not present undue barrier or burden to those of fewer means or who live in more rural or remote areas.

**Policy implications of ethics considerations for universal dMMR tumour testing**

**Testing to optimize cancer treatment**

Universal tumour testing for the purposes of optimizing treatment effectiveness can be ethically justified because it appears to live up to values of creating benefit and stewarding public resources, as screening can improve outcomes for dMMR patients while avoiding the costs of unnecessary (and even harmful) chemotherapy drugs. It is unlikely that explicit informed consent should be required for this type of tumour testing, provided this is the only purpose of the test.

**Testing to identify LS in relatives**

Provided that universal testing does minimize cancer-related harms for the population, that the costs of this testing are proportional to the benefits, and that it does not pose threats to core individual interests or fairness, universal dMMR tumour testing can be ethically justified
How should universal dMMR tumour testing be provided?

Phase 1: Testing of excised cancer tumour
Seeking informed consent for tumour testing is important because the results of the test can have impacts on the patient’s psychosocial well-being. Further, the testing may require that the patient initiate difficult family conversations and can therefore affect familial relationships and, correspondingly, have further impact on the patient’s psychological well-being.

Tumour testing may live up to the values of maximizing benefit and minimizing harm to others provided the others do have LS and can respond to this diagnosis productively. This does not necessarily mean that probands are required to submit to testing themselves to achieve this potential benefit for others. While consideration and respect for the deceased is important, testing of deceased patients’ tumours can be justified on the grounds of their potential for minimizing harms to others.

Phase 2: Referral to genetic counsellor and germline genetic testing
Patients should be supported with careful conversation to decide whether to proceed with germline genetic testing. This includes having a discussion about the implications of a positive and negative test, both for the patient and his or her family members. When considering how to implement universal dMMR tumour testing, attention should be paid to whether there are sufficient numbers of health care providers and whether health care providers (including genetic counsellors, as well as others expected to have such conversations with patients) have the training and skills to carry out these conversations well. Clear procedures for how genetic information will be collected, stored, and protected should also be in place.

When considering the harms and benefits that may be offered by dMMR testing both to the proband and family members, both physiological and psychological harms and benefits are relevant. One might suppose that the benefit of knowing one’s predisposition to life-threatening cancer offsets any psychological or emotional harm; however, this is not true in all cases. Health care providers will need to be attentive to and respectful of the relational context within which decisions are being made.

Phase 3: Decision on whether, and how, to inform others
As with all phases of the pathway, consideration about the actual benefits available to the proband’s relative should take prominence. The value of maximizing benefit and minimizing harm may imply that elderly relatives and children ought not to undergo testing because the benefits of doing so are minimal.

As the proband and his or her health care providers consider how to move through Phase 3, the value of respect (rather than respect for autonomy) is likely to be most helpful. In most scenarios, a supportive and collaborative approach where the proband and health care team work out a plan to inform family members together (whether it is the proband or particular health care provider who does the informing) is an important consideration. In situations where there is conflict or uncertainty, the health care provider should consider the material risks of harms to others, and could be justified in informing known proband relatives irrespective of the proband’s wishes.

Procedures and training for health care providers should be in place to enable patients to maintain (or at least not threaten) relationships with family as they proceed through dMMR testing.
Phase IV: Genetic counselling and familial germline testing
Once again, attention should be paid to the extent to which access to appropriate expertise, including genetic counselling, is available to those exposed to universalized dMMR tumour testing. Economic and geographical factors ought not to present undue barrier or burden to those of fewer means or who live in more rural or remote areas. Patients should be supported with information and careful conversation to decide whether to proceed with germline genetic testing. This includes having a discussion about the implications of a positive test, for their own health and for life planning.

When considering how to offer universal dMMR tumour testing, attention should be paid to whether health care providers (including genetic counsellors, as well as others expected to have such conversations with patients) have the training and skills to carry out these conversations well. Clear procedures for how genetic information will be collected, stored, and protected should also be in place.

Phase V: Surveillance and treatment
Attention should be paid to the extent to which access to appropriate expertise and services, including cancer screening and treatments, are available to those in need. If it is anticipated that universal dMMR tumour testing will increase demand for screening and interventions, efforts to increase resources should be considered. Economic and geographical factors ought not to present undue barrier or burden to those of fewer means or who live in more rural or remote areas.

Contextualizing Questions
The ethical implications of a health technology are often determined by the nature of the local context. The implications of values of fair access and consistency of service within the population, in particular, are determined by facts about how health care services are arranged and provided. To understand localized impact, decision-makers could consider the following questions:

1. How accessible is qualified genetic counselling in your area? If genetic counsellors are limited to a particular area, how difficult might it be for those outside that area to access these counsellors?
2. How accessible is ongoing CRC surveillance in your area? If surveillance services are limited to a particular area, how difficult might it be for those outside those areas to access these counsellors?
3. What kind of training and oversight is available to health care providers (including physicians and genetic counsellors) who are likely to be involved somewhere along the LS screening pathway? Training on family dynamics and support and the health care provider’s role in informing are all necessary.
4. What are the localized practices and beliefs regarding dMMR-related activities among health care providers involved in the dMMR screening pathway? Do different sites offer differing services?
5. What potential is there to change any of the factors identified in questions 1 to 4?
References


Appendix 1: Ethics Literature Search (Combined With Search Strings Used for Condition and Technology for Clinical Search)

### Database Search

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### SYNTAX GUIDE

- `/` At the end of a phrase, searches the phrase as a subject heading
- `exp` Explode a subject heading
- `*` Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
- `adj` Requires words are adjacent to each other (in any order)
- `.ti` Title
- `.ab` Abstract
- `.tw` Text word
- `.freq` Frequency of word
- `.fs` Floating subheading
- `yr` Year published

### OVID MEDLINE SEARCH

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<td>limit 37 to yr=&quot;2010 -Current&quot;</td>
</tr>
<tr>
<td>39</td>
<td>limit 38 to english language</td>
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<tr>
<td>40</td>
<td>remove duplicates from 39</td>
</tr>
</tbody>
</table>
Appendix 2: PRISMA Flow Diagram of Literature Search and Selection Process

Records identified through database searching (n = 665)

Records after duplicates removed (n = 624)

Records screened (n = 623)

Full-text articles assessed for eligibility (n = 72)

Reports explicitly identifying ethical issues (n = 8)

Additional records identified through other sources (n = 0)

Records excluded (n = 551)

Full-text reports excluded, with reasons (n = 64)
- Not colorectal cancer or Lynch syndrome (n = 43)
- Not deficient mismatch repair (n = 6)
- No explicit mention of ethical issues (n = 15)
Appendix 3: Excluded Reports

The literature search for reports explicitly mentioning ethical issues concerning deficient mismatch repair (dMMR) testing for patients with colorectal cancer (CRC) identified 73 potentially relevant articles. Of the potentially relevant reports, the following reports did not meet the inclusion criteria for the following reasons: 44 reports were excluded for not pertaining to CRC or Lynch syndrome (LS), six were excluded for not pertaining to the use of dMMR testing, and 15 for not explicitly mentioning ethical issues. Reports are listed below by reason for exclusion.

Study Population Not Colorectal Cancer or Lynch Syndrome (n = 43)

Blumenthal-Barby JS, Cantor SB, Russell HV, Naik AD, Volk RJ. Decision aids: when ‘nudging’ patients to make a particular choice is more ethical than balanced, nondirective content. Health Aff (Millwood). 2013 Feb;32(2):303-10.


Not Deficient Mismatch Repair (dMMR) (n = 6)


No Explicit Mention of Ethical Issues (n = 15)


## Appendix 4: Characteristics of Included Studies Examining Ethical Issues With Universal dMMR Testing

<table>
<thead>
<tr>
<th>Lead Author &amp; Year</th>
<th>Study Objective</th>
<th>Issues Considered</th>
<th>Argumentation or Approach to Analysis</th>
<th>Conclusions</th>
</tr>
</thead>
</table>
| Chubak 2011<sup>1</sup>  
United States  
Not described  
(literature review) | To assess necessity of obtaining explicit informed consent for MSI and IHC testing of colorectal tumours for assessing increased risk of LS | Physical invasiveness or burden of test  
Potential psychosocial harm accompanying screening (anxiety, stigmatization, discrimination, etc.)  
Need for consent based on status as genetic test  
Significance of implications for patient management  
Potential to create moral obligations to share results with family members | Examination of similarities and differences of results of MSI and IHC testing to other genetic tests in terms of psychosocial risks | No ethical requirement to obtain explicit informed consent for MSI testing of colorectal tumour samples for LS  
Support for obtaining explicit consent for IHC testing, given similarities with other genetic analysis, but unclear in terms of whether IHC reaches same threshold as other tests because it is non-diagnostic and is conducted in other contexts without consent |
| Cragun 2015<sup>2</sup>  
United States  
Not described  
(literature review) | To assess ethical implications of UTS by comparison with universal newborn screening using criteria to assess appropriateness of screening program | Respect for autonomy (informed consent, confidentiality)  
Satisfaction of public health screening criteria (Wilson and Jungner)  
Overall benefits and harms  
Equity  
Minimizing risk | Comparison and/or contrast with universal newborn screening using Wilson and Jungner criteria and criteria developed by Andermann for genetic screening | There are a few criteria that are not met by UTS.  
Comparison highlights the importance of assessing potential benefits and potential harms when new genomic tests are implemented. DNA sequencing enables detection of multiple inherited predisposition to multiple diseases and lower cost |
<table>
<thead>
<tr>
<th>Lead Author &amp; Year</th>
<th>Country</th>
<th>Method of Data Collection</th>
<th>Study Objective</th>
<th>Issues Considered</th>
<th>Argumentation or Approach to Analysis</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hall 2010&lt;sup&gt;3&lt;/sup&gt;</td>
<td>United States</td>
<td>Not described (literature review)</td>
<td>To examine whether Population IHC screening could harm unsuspecting patients by creating unanticipated burdens that are unwanted and unjustified by survival or quality-of-life benefits</td>
<td>Need for consent based on Status as genetic test Inconclusive results Access to and quality of genetic counselling Potential of shifting physician practice away from family history Access to DNA testing Responsibility for informing risk</td>
<td>Balancing of 3 main values via ethics analysis: 1. Respect for patient autonomy and potential harms 2. Professional duty to provide quality health care 3. Societal benefit (both population health and resource use)</td>
<td>Universal LS screening using IHC testing not ethically well justified in current US health care environment</td>
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<tr>
<td>Menko 2013&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Netherlands</td>
<td>Literature review and survey</td>
<td>To summarize the development of a revised guideline for clinical geneticists that aims to improve procedures to inform family members who have predisposition for LS and other hereditary and familial cancer syndromes</td>
<td>Barriers of nondisclosure despite the fact that the patient is willing to inform family members and has started to do so Ethical and legal obligations of physician and/or genetic counsellor to inform family members (duty to warn) Patient responsibility to inform Information needs for adequate communication with family members (for hereditary vs. familial syndromes)</td>
<td>Literature search of existing issues and survey of clinical geneticists and patients Brief description of support for individual recommendations</td>
<td>Identification of MMR mutation may be relevant for close and distant relatives In the complex situation in which the patient does not wish to inform family members and will not permit a breach of confidentiality, confidentiality could be overruled if all efforts have been taken to receive the patient’s permission without success</td>
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<tr>
<td>Sciallero 2010&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Italy</td>
<td>Letter to editor</td>
<td>To challenge assumption that “decision to pursue MSI testing is not difficult or distressing”</td>
<td>Large minority of people (42%) refused testing in study on informed consent&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Moral distinction between testing for adjuvant chemo response (predictive testing) and testing to identify family members at high-risk for LS</td>
<td>Unclear, but implies that universal screening without consent may not be ethically justified because of large minority of people who may refuse testing</td>
</tr>
<tr>
<td>Lead Author &amp; Year</td>
<td>Country</td>
<td>Method of Data Collection</td>
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<td>Shipman 2013&lt;sup&gt;6&lt;/sup&gt;</td>
<td>Wales (UK)</td>
<td>Semi-structured interviews</td>
<td>To describe the significance of MSI testing in terms of &quot;genetic responsibility&quot; for individuals who have consented to the test without genetic counselling.</td>
<td>The understanding, beliefs, and significance of consenting to MSI testing Understanding of MSI testing and its implications for family members</td>
<td>Contrasting expressions of “genetic responsibility” of individuals who have consented to MSI testing with those who have been given germline testing</td>
<td>The information provided by MSI testing does not appear to create new feelings of ethical obligation and genetic identification. Individuals consenting to MSI testing tend to justify decisions to consent to screening by either generalizing or diminishing responsibility.</td>
</tr>
<tr>
<td>Stol 2010&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Netherlands</td>
<td>Semi-structured interviews</td>
<td>To describe attitudes of clinical geneticists concerning the interests of relatives to be informed of a positive test and whether they have a corresponding “duty to warn” relatives themselves (when patients do not).</td>
<td>Mores of clinical genetics practice are against informing relatives “Wish not to be informed” and “right not to know” suggest that clinical geneticists may not be justified in informing relatives Degree to which accepted criteria for establishing a duty to warn are satisfied Potential legal barriers to informing relatives Resource limitations</td>
<td>Semi-structured interviews and content analysis of results</td>
<td>In general, clinical geneticists believed they have a moral duty to warn. If informing relatives is considered to be in the best interests of relatives, clinical geneticists should consider informing relatives themselves.</td>
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<tr>
<td>Williams 2011&lt;sup&gt;8&lt;/sup&gt;</td>
<td>United States</td>
<td>Letter to editor Note: Response to Chubak et al.&lt;sup&gt;4&lt;/sup&gt;</td>
<td>To assess necessity of obtaining explicit informed consent for MSI and IHC testing of colorectal tumours for assessing increased risk of LS</td>
<td>Other pathological examinations identifying lesions that may indicate unanticipated genetic disease are conducted without informed consent (medullary thyroid cancer, trichilemmoma, etc.) Implied prediction threshold beyond which consent required</td>
<td>Balancing of benefits and harms including: Need for consent based on other tests and/or institutions Benefit of IHC and MSI results to family and to patient Insurance discrimination Psychological harm</td>
<td>Balance of harms and benefits supports universal LS screening using MSI or IHC. Informed consent not required for either IHC or MSI testing because results are not clinically actionable by patient or family without confirmatory DNA test Other groups considering this issue may come to</td>
</tr>
<tr>
<td>Lead Author &amp; Year</td>
<td>Study Objective</td>
<td>Issues Considered</td>
<td>Argumentation or Approach to Analysis</td>
<td>Conclusions</td>
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<td></td>
<td></td>
<td>Informed consent not required for family history screening (analogy)</td>
<td></td>
<td>different conclusions</td>
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<td></td>
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<td>No concerns about positive screen result raised by patients in screening program</td>
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IHC = immunohistochemistry; LS = Lynch syndrome; MMR = mismatch repair; MSI = microsatellite instability; UTS = universal tumour screening; vs. = versus.