Genetic Testing for Familial Hypercholesterolemia: Recommendation

Draft Recommendation

- Ontario Health, based on guidance from the Ontario Health Technology Advisory Committee, recommends publicly funding:
  - Genetic testing for familial hypercholesterolemia for people suspected to have familial hypercholesterolemia or people who have a diagnosis of familial hypercholesterolemia based on accepted diagnostic criteria (i.e., Canadian Cardiovascular Society, Simon Broome Register, or Dutch Lipid Clinics Network)
  - Genetic cascade screening for familial hypercholesterolemia for people who choose to undergo screening and who are biological relatives of people with a genetically confirmed diagnosis of familial hypercholesterolemia

Rationale for the Recommendation

The Ontario Health Technology Advisory Committee has reviewed the findings of the health technology assessment\(^1\) and the recommendation of a subcommittee, the Ontario Genetics Advisory Committee.

The Ontario Health Technology Advisory Committee made its recommendation after considering the clinical and economic evidence and patient preference and values. The clinical evidence supports that people with a genetically confirmed diagnosis of familial hypercholesterolemia (FH) may have increased use of cholesterol-lowering treatments and have lower total cholesterol and LDL-C blood levels, possibly due to treatment changes or improved treatment adherence. Additionally, genetic cascade screening for FH may help identify people at risk for cardiovascular disease.

The economic evidence supports that genetic testing for FH is cost-effective for people suspected of having, or clinically confirmed to have, FH. While genetic and lipid cascade screening are both cost-effective compared with no screening, the committee weighed in favour of genetic over lipid cascade screening because of its improved accuracy. Genetic testing for FH in people suspected of having or clinically confirmed to have FH would likely result in cost savings to the province. While the province would likely incur additional costs to publicly fund the genetic cascade screening tests for biological relatives, the committee recognized the potential for cost savings to the province if a reduction in cardiovascular disease was realized in those screened.
The evidence regarding patient preferences and values shows that people with high cholesterol levels perceive positive impacts of having a genetically confirmed diagnosis of FH on (1) their medical management, and (2) their ability to inform family members, who then have the option to discover their own FH status through genetic cascade screening. Similarly, genetic confirmation that a person does not have FH is also a perceived benefit of testing. However, individual desire for autonomy and privacy is an important consideration in the implementation of genetic cascade screening, and a person’s choice to undergo screening should guide practice.
# Decision Determinants for Genetic Testing for Familial Hypercholesterolemia

<table>
<thead>
<tr>
<th>Decision criteria</th>
<th>Subcriteria</th>
<th>Decision determinants considerations</th>
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<tbody>
<tr>
<td><strong>Overall clinical benefit</strong></td>
<td><strong>Effectiveness</strong></td>
<td>Genetic testing is likely to improve four outcomes measuring treatment change (increased statin dose, initiating statin treatment, adding ezetimibe to existing LDL-C lowering therapy, and remaining untreated with cholesterol lowering drugs), and is likely lead to a reduction in LDL-C blood level and total cholesterol levels (GRADE: Moderate). Additionally, it may lead to a change in treatment regimen and increased use in cholesterol-lowering drug regimens; it may also allow for LDL-C targets to be reached after using cholesterol-lowering drugs (GRADE: Low).</td>
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<tr>
<td>How likely is the health technology/intervention to result in high, moderate, or low overall benefit?</td>
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<tr>
<td><strong>Safety</strong></td>
<td></td>
<td>Genetic testing for FH requires a blood test. Blood testing is associated with minimal to no harm. Genetic testing for FH provides information to a person about their risk of cardiovascular disease. This information may be helpful to some people. It may also cause anxiety in some people. About 1 in 250 Canadians have the heterozygous form of FH. FH can increase a person’s risk for cardiovascular disease (i.e., heart attack or stroke, or even premature death).</td>
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<tr>
<td>How safe is the health technology/intervention likely to be?</td>
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<tr>
<td><strong>Burden of illness</strong></td>
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<td>FH is underdiagnosed and undertreated in Canada. A genetic confirmation of FH can support treatment with publicly funded PCSK9 inhibitors.</td>
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<td>What is the likely size of the burden of illness pertaining to this health technology/intervention?</td>
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<tr>
<td><strong>Need</strong></td>
<td></td>
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<td>How large is the need for this health technology/intervention?</td>
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<td><strong>Patient preferences and values</strong></td>
<td><strong>Patient preferences and values</strong></td>
<td>Participants valued having a genetically confirmed diagnosis of FH due to their perceived ability to access new and effective treatments and inform family members of the risk of the condition.</td>
</tr>
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<td>How likely is adoption of the health technology/intervention to be congruent with patient preferences and values and with ethical or legal standards?</td>
<td>Do patients have specific preferences, values, or needs related to the health condition, health technology/intervention, or life impact that are relevant to this assessment? (Note: The preferences and values of family members and informal caregivers are to be considered as appropriate.)</td>
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<td>Autonomy, privacy, confidentiality, and/or other relevant ethical principles as applicable</td>
<td>Are there concerns regarding accepted ethical or legal standards related to patient autonomy, privacy, confidentiality, or other ethical principles that are relevant to this assessment? (Note: The preferences and values of the public are to be considered as appropriate.)</td>
<td>FH genetic testing aligns with current practice of diagnosis through non-genetic tests. Individual preference for autonomy and privacy has implications for cascade testing, as participants may have concerns about confidentiality and may not want to receive genetic information or have it shared with family members.</td>
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**Equity and patient care**

How could the health technology/ intervention affect equity of access and coordination of patient care?

**Equity of access or outcomes**

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

Currently, there is only one laboratory in Ontario that provides genetic testing for FH. As a result, there may be inequity in access to the service. Additionally, one laboratory may not be able to meet the additional demand for testing that may result from expanding access to genetic screening. Coordinating care between clinical areas involved in the care and management of people with high cholesterol will be required to enable the successful implementation of both genetic testing and genetic cascade screening of FH.

**Patient care**

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

### Cost-effectiveness

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

### Economic evaluation

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

### Decision determinants considerations

At commonly used willingness-to-pay values of $50,000 or $100,000 per QALY gained, genetic testing for individuals with a clinical diagnosis of FH would be dominant (less costly and more effective than usual care). Our economic evaluation suggested that, compared to a clinical diagnosis based on lipid testing only, genetic testing for individuals with a clinical diagnosis of FH would reduce the number of FH diagnoses, lead to fewer cases of cardiovascular disease, and improve QALYs, while lowering costs.

When comparing genetic cascade screening strategies to no cascade screening for biological relatives of genetically confirmed FH index cases, our model suggested that the most likely estimate of the ICER is between $50,220 and $58,390 per QALY gained.

### Feasibility of adoption into health system

How feasible is it to adopt the health technology/intervention into the Ontario health care system?

### Economic feasibility

- **Subcriteria**
  - How economically feasible is the health technology/intervention?

### Organizational feasibility

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

### Economic feasibility

The cost of genetic testing for FH is $490 per person. We estimated that publicly funding genetic testing for individuals with a clinical diagnosis of FH in Ontario would lead to a total cost saving of $141 million over the next 5 y. For relatives of genetically confirmed FH index cases, we estimated that publicly funding genetic cascade screening would lead to a total additional cost of $73 million over the next 5 y.

Genetic testing for FH is already publicly funded in Ontario as an out-of-country service. For FH diagnosis, we expect most of the processes to remain the same if the service is to be repatriated to Ontario. There may be costing and ethical challenges in implementing cascade screening.

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**Abbreviations:** ICER, incremental cost effectiveness ratio; FH, familial hypercholesterolemia; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; LDL, low-density lipoprotein; QALY, quality adjusted life year.
Reference
(1) TBD

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