



**Ontario
Health**

Genetic Testing for Familial Hypercholesterolemia: Implementation Recommendations

The Ontario Approach

October 19, 2022

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Acknowledgement

Ontario Health would like to acknowledge the contribution of the Familial Hypercholesterolemia Working Group (Working Group) members in the development of this recommendation report. Special thanks to the Working Group chair, Dr. Elaine Goh, for her leadership and direction in the creation of this document.

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The Working Group would like to thank the individuals and organizations that participated in the external review process. Their review and feedback were invaluable in the development of this document.

Familial Hypercholesterolemia

Familial hypercholesterolemia (FH) is an inherited disorder of lipid metabolism that results in elevated levels of low-density lipoprotein (LDL) cholesterol. As a result, people with FH have a higher risk of heart disease and heart attack at an early age. FH is one of the most common monogenic disorders, affecting approximately 1 in 250-300 Canadians (with higher prevalence in certain populations due to founder effects¹), yet is underdiagnosed in Canada and worldwide.¹ FH is diagnosed using well-established clinical criteria (i.e., Canadian Cardiovascular Society,² Dutch Lipid Clinics Network,³ or the Simon Broome Register⁴), and/or through genetic testing.

Background

In February 2022, Ontario Health (OH) posted draft recommendations regarding a Health Technology Assessment (HTA) on genetic testing for FH.⁵ The HTA examined the effectiveness of genetic testing, evaluated through projected health outcomes, patient experience and preferences, cost, and the budget impact of publicly funding genetic testing in Ontario. The HTA found that, compared to clinical evaluation without genetic testing, genetic testing would be cost-effective to confirm FH in individuals with a clinical diagnosis of FH. They also found that genetic and lipid cascade screening are both cost-effective compared to no cascade screening. The final recommendation report was published August 23, 2022 to the following link hqontario.ca/Evidence-to-Improve-Care/Health-Technology-Assessment/Reviews-And-Recommendations/Genetic-Testing-for-Familial-Hypercholesterolemia. Based on the HTA guidance, Ontario Health recommends publicly funding:

- Genetic testing for FH for people suspected to have or who have a clinical diagnosis of FH based on accepted diagnostic criteria (i.e., Canadian Cardiovascular Society, Dutch Lipid Clinics Network, or the Simon Broome Register), *and*
- Genetic cascade screening for FH for people who choose to undergo screening and who are blood relatives of people with a genetically confirmed diagnosis of FH.

OH has been mandated to “ensure the successful implementation of genetic testing and establishment of a comprehensive provincial program for all genetics with robust provincial oversight to deliver these services to drive better outcomes for Ontarians and improved value.” Given this mandate, and in anticipation of the final HTA guidance, OH formed the FH Working Group to develop recommendations for the provincial implementation of FH genetic testing. The Working Group focused on developing guidance on the key elements required for implementation, specifically **who** should be offered testing, **what** genes should be tested, and **how** patients should access testing in Ontario.

The following three recommendations are proposed to guide successful implementation of FH testing in Ontario, and are further described in the recommendation section of this report:

1. Establish standardized eligibility criteria for genetic testing for FH in Ontario
2. Implement a comprehensive standardized FH genetic testing panel in Ontario
3. Increase access to FH genetic testing through patient and provider education, and improved patient care pathways

Utilizing the guidance from the HTA and the implementation recommendations within this document, OH will submit a funding request to the Ministry of Health for FH genetic testing in Ontario.

ⁱ In certain areas of Quebec, the prevalence is 1 in 90. For Lebanese and Afrikaners, the prevalence is approximately 1 in 100. For South African Ashkenazi Jews, it is approximately 1 in 67.

Recommendations

1. Establish standardized eligibility criteria for genetic testing for FH in Ontario

The diagnosis of FH using clinically validated diagnostic criteria can occur at any age and the associated genetic testing should also be made available at the earliest opportunity to support diagnosis, treatment and care decisions, and to identify families that would benefit from cascade testing.

Establishing standardized eligibility criteria for the province will help to facilitate equitable access for patients regardless of where they reside in Ontario. The FH Working Group developed a set of standardized FH genetic testing eligibility criteria that is recommended for implementation in Ontario. The criteria are based on existing criteria⁶ and clinical guidelines,^{2,3,4} literature review, and expert consensus (see Appendix A).

Rationale:

- Limited family history was included for situations where there is lack of information (e.g., adoption).
- Clinical judgement was included for situations where criteria are not met but suspicion remains.
- For the purposes of cascade testing, 1st and 2nd degree relatives can be offered genetic testing for the familial known variant whereas more distant blood relatives need to meet additional criteria.
- If baseline/untreated LDL-cholesterol is unknown, an imputed level can be derived using the CardioRiskCalculator™ Imputed LDL-C Calculator found here www.circl.ubc.ca/english/web_ldl2.html.⁷ Bloodwork does not need to be fasting.

Age related considerations:

- The Canadian Cardiovascular Society/Canadian Pediatric Cardiology Association Clinical Practice Update recommends universal lipid screening to be performed in the first decade of life (after 2 years old), coupled with genetic testing for identified cases of probable/definite FH.⁸
- Universal screening of cholesterol for all children between the ages of 9 and 11 years and targeted screening at other ages has been recommended by the National Heart, Lung and Blood Institute⁹
- The pediatric cut-off was lowered to ≥ 3.5 mmol/L from ≥ 4.0 mmol/L used in the Canadian definition for the clinical diagnosis of FH based on literature^{8,10} and consensus of the Working Group. The Working Group recommended a modified approach to that implemented in Quebec to simplify criteria and shorten time to diagnosis in the pediatric population.
 - Pediatric individuals from Quebec are currently accepted for initial evaluation and counselling about lifestyle factors in the Pediatric Lipid Clinic with a cut-off LDL-cholesterol level of ≥ 3.5 mmol/L. Genetic testing is offered to patients with LDL-cholesterol level of >4.0 mmol/L at least twice, and a family history of FH (Dr. Anne-Marie Laberge, email communication June 24, 2022).
- Genetic testing of children can increase the efficiency of detecting affected adults with undiagnosed FH (reverse cascade screening).^{11,12}
- Statins can potentially reverse or slow progression of carotid intima-media thickening (CIMT), which supports treatment at an earlier age.¹³ For pediatric patients with FH, early treatment may increase event-free survival.¹⁴

- Limited use medications can still be covered for individuals over the age of 65 years if the criteria are fulfilled through the Ontario Drug Benefit.

2. Implement a comprehensive standardized FH genetic testing panel in Ontario

The working group recommends a broad 8-gene panel that includes **LDLR**, **APOB**, **PCSK9** and **LDLRAP1**, as well as **ABCG8**, **ABCG5**, **APOE**, and **LIPA**. See Appendix B for a sample FH genetic testing requisition.

Rationale:

- While the genes in **bold** are the main ones associated with FH, there is evidence that variants in the other four genes also cause FH, as curated through 2021 ClinGen Curation¹⁵ and 2021 Genomics England PanelApp curation¹⁶ (see Table 1).
- While sitosterolemia due to **ABCG5** and **ABCG8** presents similarly to isolated FH, variants in these genes can also cause an inherited platelet disorder and therefore would have additional management recommendations.¹⁷
- The 8 genes were used as part of the OH - Health Technology Assessment (HTA)¹⁸
 - **STAP1** was part of the HTA but has been delisted based on lack of evidence for association with FH.
- Expected turnaround times, ordering and technical criteria should be determined prior to implementation
 - Technical criteria are important since 15% of pathogenic variants could be due to copy number variation (R. Hegele, personal communication, July 11, 2022).
- Clear reporting is needed given the presentation of the 4 additional genes, which may have additional features other than hypercholesterolemia.
- The association with **APOE** and the risk for Alzheimer’s disease will not be revealed as common polymorphisms for **APOE** will not be reported. Reporting will be limited to pathogenic/likely pathogenic variants for FH.

Table 1: Familial Hypercholesterolemia Panel Evidence

Gene	2021 ClinGen Curation	2021 GE PanelApp Curation
<i>ABCG5</i>	Definitive for Sitosterolemia	Green for FH, Green for inherited bleeding disorders and sitosterolemia
<i>ABCG8</i>	Definitive for Sitosterolemia	Green for FH, Green for inherited bleeding disorders and sitosterolemia
<i>APOB</i>	Definitive for FH	Green for FH
<i>APOE</i>	No Gene-Disease validity curated	Green for FH
<i>LDLR</i>	Definitive for FH	Green for FH
<i>LDLRAP1</i>	No Curations published	Green for FH
<i>LIPA</i>	No Gene-Disease validity curated	Green for FH
<i>PCSK9</i>	Definitive for FH	Green for FH

3. Increase access to FH genetic testing through patient and provider education, and improved patient care pathways

To meet the objective of optimizing access to genetic testing for all Ontarians who are eligible for genetic testing for FH, the working group agreed that primary care is where case finding would be maximized. However, a phased approach to implementation is needed to allow for patient and provider education, and to build capacity for the laboratory and specialized clinical services needed to meet the expected demand. Phase 1 should focus on education to non-genetics providers and increasing awareness of the availability of genetic testing for FH through referral to existing specialists or on advice from a geneticist (e.g., lipid specialists, cardiologists, endocrinologists, and applicable genetics clinics). This would allow for the eligibility criteria to be implemented provincially and for laboratories to ensure optimal reporting. Phase 2 should consist of expansion to additional ordering providers, including primary care. Cascade genetic testing should continue to be offered after genetic counselling to an individual with a blood relative with a known FH disease-causing pathogenic/likely pathogenic variant.

It is important to emphasize that criteria and implementation pathways were selected using best available evidence and expert consensus. Clinical relevance and appropriateness to guide patient care were prioritized over existing resource limitations. Sustainability of an expanded hereditary genetic testing program in Ontario requires a robust workforce in laboratory and clinical genetics, however, there is a current shortage of health human resources available to provide this expert clinical care. Additional health human resources will be required to expand access to testing, and the implementation plan will need to include where and how the required resources should be implemented. For example, facilitating access to FH genetic testing through non-genetics ordering providers requires collaboration with genetics for test interpretation and consultation support. With limited existing capacity for general genetics clinics to take on this additional work, a dedicated provincial resource (e.g., clinical or laboratory based genetic counsellor(s)) may be required.

Implementation objectives:

- Diagnose, educate, and inform treatment for individuals with FH
- Expand knowledge of FH to physicians, other health care professionals, and the public

Phase 1: Improve access to genetic testing through existing care pathways

- Implement in-province testing
- Target existing ordering providers: specialists and genetics clinics
- Expand knowledge of FH to health care providers and the public
- Implement standardized provincial eligibility criteria and reporting
- Estimate the demand for future expansion
- Explore opportunities for program evaluation

Phase 2: Mainstream ordering of genetic testing by non-genetics providers (e.g., primary care, endocrinologists, cardiologists)

- Develop a strong education program that is broad reaching to non-genetics providers, including primary care
- Optimize the use of resources
 - Maximize case finding through multiple settings
 - Genetic counsellors should support ordering providers and help with interpretation of genetic test results. Given the current capacity constraints in the system, additional health human resources will be required to facilitate access to genetic counselling services for index and cascade FH genetic testing.
 - Management of affected individuals would be best served in a specialist setting and/or on advice of a specialist provider. Referral for ongoing management should be coordinated by primary care.

Rationale

- With a prevalence of 1 in 250-300, the volume would overwhelm Ontario's existing genetics clinics lipid clinics. There are currently 7 lipid clinics in Ontario (see Appendix C for details).
- Due to capacity limitations, there would be inequity in access if the ordering provider is restricted to specialists, especially in Northern Ontario. While health human resource pressures are seen across Ontario, there are unique challenges in northern Ontario that would need to be addressed to support equitable implementation.

Appendix A: FH Genetic Testing Eligibility Criteria

Individuals meeting **one or more** of the following criteriaⁱⁱ should be offered FH genetic testing:

1. Confirmed FH disease-causing pathogenic/likely pathogenic variant (mutation) in a close blood relativeⁱⁱⁱ

Note: In a family with confirmed FH, cascade genetic testing should be offered to at risk first- and second-degree blood relatives for the known familial pathogenic/likely pathogenic variant(s) regardless of the individual's lipid levels or clinical presentation. Panel testing can be considered if there is clinical suspicion on the other side of the family, and/or increase risk related to founder variants.

2. Personal history of high LDL-cholesterol level of ≥ 8.5 mmol/L at any age

3. Personal history of untreated elevated LDL-cholesterol level (not due to secondary causes)^{iv,v}

- Untreated LDL-cholesterol level ≥ 5.0 mmol/L for age 40 years and over
- Untreated LDL-cholesterol level ≥ 4.5 mmol/L for age between 18 years and 39 years
- Untreated LDL-cholesterol level ≥ 3.5 mmol/L for age under 18 years

AND at least one of the following:

- Tendon xanthomas and/or corneal arcus in proband^{vi}
- First-degree relative with high LDL-cholesterol level (not due to secondary causes)^{vii}
- Proband or first-degree relative with early onset atherosclerotic cardiovascular disease (men under 55 years; women under 65 years)^{vii}
- Limited family history information (e.g., adopted)

4. In families that are suspicious for FH, a clinician may use clinical judgement to order genetic testing in individuals who do not fit the above criteria, following consultation with genetics and/or lipid disorder expert(s).

ⁱⁱ Modified from www.fhcanada.net/uploads/05_Testing-eligibility-criteria_FH_EN_FH-panel.pdf

ⁱⁱⁱ Close relative typically refers to first- or second-degree blood relative but may include a more distant relative in combination with additional family history or clinical suspicion.

^{iv} Secondary causes of high LDL-cholesterol should be ruled out (severe or untreated hypothyroidism, nephrotic syndrome, hepatic disease [primary biliary cirrhosis], or medication especially antiretroviral agents).

^v If baseline/untreated LDL-cholesterol is unknown, an imputed level can be derived using the CardioRiskCalculator (www.circl.ubc.ca/cardiorisk-calculator.html). Bloodwork does not need to be fasting.

^{vi} Major criteria –definite FH when at least 1 major criterion is present along with elevated LDL-cholesterol

^{vii} Minor criteria –at least probable FH when at least 1 minor criterion is present along with elevated LDL-cholesterol

Appendix B: Sample FH Genetic Testing Requisition

PATIENT INFORMATION

Name:
Address:
Date of Birth:
Health Card No.:
Sex:
Ethnicity:

REFERRING PROVIDER

Name:	
Email:	
Clinic/Hospital:	
Address:	
Telephone:	Fax:
Signature:	

CC Report To:
Name:
Email:
Telephone:
Fax:

TEST SELECTION:

- FH panel (8 genes: **LDLR APOB, PCSK9, LDLRAP1, ABCG8, ABCG5, APOE, LIPA**)
- Known familial variant, please include:
 - Relationship to proband (*parent, sibling, etc.*): _____
 - Copy of report (or report ID if testing completed here) OR gene, variant, reference genome NM#: _____

SAMPLE COLLECTION: EDTA blood (lavender top) (min 2ml at room temp) *Note: to be confirmed by testing lab*
Date drawn (YYYY/MM/DD): _____

FAMILIAL HYPERCHOLESTEROLEMIA PANEL – ELIGIBILITY CRITERIA FOR TESTING:

Individual must meet **one or more** of the following:

- 1. **Confirmed FH disease-causing pathogenic/likely pathogenic variant in a close blood relative**^{viii}
- 2. **High LDL-cholesterol level of ≥ 8.5 mmol/L at any age**
- 3. **Untreated elevated LDL-cholesterol level (not due to secondary causes)**^{ix}
Specify: _____ mmol/L
 - Untreated LDL-cholesterol level ≥ 5.0 mmol/L for age 40 years and over
 - Untreated LDL-cholesterol level ≥ 4.5 mmol/L for age 18 to 39 years
 - Untreated LDL-cholesterol level ≥ 3.5 mmol/L for age under 18 years**AND at least one of the following:**
 - Tendon xanthomas and/or corneal arcus in proband
 - First-degree relative (FDR) with high LDL-cholesterol level (not due to secondary causes)
 - Proband or FDR with early onset ASCVD (men under 55 years; women under 65 years)
 - Limited family history information (e.g., adopted)
- 4. **Clinical judgement:** Criteria above not met, but suspicion remains. Describe: _____

^{viii} Close relative typically refers to first- or second-degree blood relative but may include a more distant relative in combination with additional family history or clinical suspicion.

^{ix} If baseline/untreated LDL-cholesterol is unknown, an imputed level can be derived using the CardioRiskCalculator™ Imputed LDL-C Calculator www.circl.ubc.ca/english/web_ldl2.html. Bloodwork does not need to be fasting.

Appendix C: List of clinics treating familial hypercholesterolemia in Ontario

Clinic Name	Location and Contact Information	Referral Requirements
Toronto General Hospital - Type 2 diabetes and lipid disorders Dr. Gary Lewis	Toronto 200 Elizabeth St., EN 12-243 Toronto, ON M5G 2C4 T: 416 340 4270 F: 416 340 3314 or 4730 www.uhn.ca/Medicine/Clinics/Endocrinology/team	<ul style="list-style-type: none"> Adults Any referral form Reason for the referral, including medical history and medications, recent lab work within 3 months and family history of early CAD or hyperlipidemia Copy of death investigation reports, in particular the genetic testing report
The Hospital for Sick Children – Lipid Clinic Dr. Brian McCrindle	Toronto 555 University Avenue, 4A, Atrium, 4th Floor T: 416 813 5848 F: 416 813 5582 www.sickkids.ca/en/care-services/clinics/cardiology-clinic/	<ul style="list-style-type: none"> Children Electronic referral system: www.sickkids.ca/HealthcareProfessionalsandStudents/Referring-a-Patient/index.html Reason for the referral, including medical history and medications, recent lab work within 3 months and family history of early CAD or hyperlipidemia Copy of death investigation reports, in particular the genetic testing report
Hamilton General Hospital – Lipid Clinic Dr. Guillaume Pare	Hamilton 237 Barton St E, Hamilton, ON L8L 2X2 T: 905 527 4322 ext. 44537 F: 905 528 3148 www.hamiltonhealthsciences.ca/areas-of-care/cardiac-vascular-care/cardiac-ambulatory-clinics/lipid-clinic/	<ul style="list-style-type: none"> Adults Lipid Clinic referral form Reason for the referral, including past medical history and medications (esp. lipid medications), recent lab work within past 3 months and family history of early CAD or hyperlipidemia Copy of death investigation reports, in particular the genetic testing report
McMaster Children’s Hospital - Pediatric Lipid Clinic Dr. Katherine Morrison	Hamilton 1200 Main Street West, Hamilton, ON, L8N 3Z5 Level 2, Section G (Red) T: 905 521 2100 ext. 76990 F: 905 385 5033 www.hamiltonhealthsciences.ca/mcmaster-childrens-hospital/areas-of-care/medicine/lipid-clinic/	<ul style="list-style-type: none"> Children Pediatric Lipid Clinic referral form Reason for the referral, including past medical history and medications (esp. lipid medications), recent lab work within past 3 months and family history of early CAD or hyperlipidemia Copy of death investigation reports, in particular the genetic testing report

<p>Lipid Genetics Clinic Dr. Robert Hegele</p>	<p>London Endocrinology & Metabolism Department LHSC - University Hospital 4th Floor Out-Patient Department 339 Windermere Road, London, ON, Canada N6A 5A5 T: 519 931 5774 F: 519 931 5218 www.lipidgeneticsclinic.ca/index.html</p>	<ul style="list-style-type: none"> • Adults • Email or call the clinic to ask the about their referral requirements: esimon@robarts.ca
<p>Lipid Clinic Dr. Ruth McPherson</p>	<p>Ottawa 40 Ruskin Street, Ottawa, ON K1Y 4W7 T: 613 696 7341 F: 613 696 7130 www.ottawaheart.ca/clinic/lipid-clinic</p>	<ul style="list-style-type: none"> • Adults • Any referral form • Reason for the referral, including medical history and medications, recent lab investigations; family history of ASCVD or hyperlipidemia
<p>Endocrinology Clinic, CHEO Children’s Hospital of Eastern Ontario Dr. Stasia Hadjiyannakis</p>	<p>Ottawa Clinic C-10, 401 Smyth Road, Ottawa, ON K1H 8L1 T: 613 737 7600 F: 613 738 4236 eConsultation is available through LHINWorks. eConsultations are available for general pediatric endocrinology and pediatric diabetes, hyperlipidemia and obesity. www.cheo.on.ca/en/clinics-services-programs/endocrinology-clinic.aspx</p>	<ul style="list-style-type: none"> • Children • CHEO referral form • Reason for the referral, including medical history and medications, recent lab work within past 3 months and family history of early CAD or hyperlipidemia • Copy of death investigation reports, in particular the genetic testing report

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