Hereditary Dyslipidemias

Genetic Testing Recommendations

PROVINCIAL GENETICS PROGRAM
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Ontario Health

Table of Contents

Introduction

Ontario Health is building a comprehensive and integrated system for clinical genetic services across the province. Through collaboration with health system partners, the Provincial Genetics Program (PGP) provides evidence-based guidance for genetic diagnostic testing and counselling services in key areas. PGP Expert Groups work with health care professionals, laboratory scientists, administrators, and patient and family advisors to establish standardized practices for collecting, using, and reporting clinical genetics data. These efforts ensure that people in Ontario can access high-quality genetic testing services when needed.

The PGP identified genetic testing for hereditary dyslipidemias as a domain for development in Ontario, resulting in the formation of the Hereditary Dyslipidemia Working Group (Working Group). The role of the Working Group was to develop evidence-based guidance for the provision of genetic testing and counselling services for individuals with/at risk for hereditary dyslipidemia syndromes in the province of Ontario.

Guidance Document Scope

The most common hereditary dyslipidemia is Familial Hypercholesterolemia (FH). For more details on genetic testing related to this condition, please refer to Ontario Health's Familial Hypercholesterolemia Genetic Testing Recommendations Report[i].

This document focuses on the recommended approach for genetic assessment and testing in individuals with confirmed or suspected non-FH hereditary dyslipidemia syndromes. Given the rarity of these conditions, it is not intended to provide guidance on population-level screening or dyslipidemia management. Instead, it offers direction for diagnostic genetic testing when a monogenic dyslipidemia is suspected, based on clinical features or biochemical findings.

The primary audience for this document includes medical geneticists, genetic counsellors, endocrinologists, lipidologists, and other health care professionals involved in the care of patients and families with known or suspected hereditary dyslipidemia syndromes.

[i] Note: panel genetic testing for FH in Ontario includes canonical genes associated with FH as well as genes for which hypercholesterolemia is on the differential diagnosis (e.g., sitosterolemia and lysosomal acid lipase deficiency).

Background

Dyslipidemias are a group of disorders characterized by disturbances in lipid and lipoprotein metabolism resulting in extreme blood levels of low-density lipoprotein cholesterol (LDL-C), triglycerides (very low-density lipoprotein cholesterol and chylomicrons), high-density lipoprotein cholesterol (HDL-C), and/or other lipids[1]. While lipid and lipoprotein levels are influenced by both genetic and environmental factors, known monogenic dyslipidemias follow classical Mendelian inheritance patterns[2]. These disorders can have variable prevalence rates, ranging from approximately 1 in 250 individuals for FH to as low as 1 in 1,000,000 for Tangier disease (see Table 1)[1,3].

Genetic testing is not yet a routine part of the diagnostic pathway in dyslipidemia, however, pursuing specific and targeted testing in patients with a high suspicion of a monogenic dyslipidemia can help yield a definitive diagnosis [4,5]. This in turn can reduce the patient diagnostic odyssey, allow for access to existing or emerging therapies, and facilitate family planning, cascade testing, and screening for undiagnosed family members [4,6].

At the time of this report, genetic testing in Ontario for genes associated with monogenic dyslipidemias is restricted to an 8 gene panel for FH. Comprehensive panel genetic testing for non-FH dyslipidemias is completed through the Ministry of Health's Out-of-Country (OOC) & Out-of-Province (OOP) Prior Approval (PA) Program for Laboratory Services, at commercial laboratories. This guidance document includes recommendations on:

- Who should be offered genetic testing for non-FH dyslipidemias
- What genetic testing strategy should be employed, and
- The composition of evidence-based genetic testing/gene panels for non-FH dyslipidemias

Table 1. Prevalence of Non-FH Monogenic Dyslipidemias.

Group of Lipid Disturbances	Reported Prevalence
Low LDL-C syndromes or disorders	1/300,000 – 1/1,000,000
Low HDL-C syndromes or disorders (e.g. Tangier disease)	<1/1,000,000
Hypertriglyceridemia syndromes or disorders	1/300,000 – 1/1,000,000
Cerebrotendinous xanthomatosis	3-5/100,000

Considerations for Dyslipidemia Genetic Testing

As many monogenic dyslipidemias (excluding FH) involve a significant lipid abnormality and/or a multi-systemic phenotype, patients typically follow specialized clinical pathways for assessment, diagnosis, and management. Physicians who are not content experts are encouraged to refer to relevant sub-specialists for consultation on challenging diagnostic cases, assistance with pre- and/or post-test genetic counselling, prenatal counselling, and support in interpreting genetic variants.

Referral to Relevant Sub-specialists

- Monogenic dyslipidemias are a rare, heterogenous group of disorders with variable clinical presentations.
- The identification of individuals with suspicion of a monogenic etiology typically involves an initial referral to sub-specialists including endocrinologists and lipid specialists, medical geneticists, and other physicians who specialize in the diagnosis and/or management of lipid disorders.
- Patients may be referred to the above specialists for baseline assessment and monitoring based on the presence of biochemical disturbance in blood lipid levels with or without the presence of physical features[1].
- See Appendix C for a list of specialty lipid clinics in Ontario.
- A list of genetics and metabolic clinics in Ontario can be found here.

Clinical Assessment Considerations

- Only a small subset of patients with hypertriglyceridemia (HTG) are likely to have a monogenic dyslipidemia[4].
- Given the co-dominant or semi-dominant nature of many canonical dyslipidemia genes, characteristic features of different dyslipidemia syndromes may be variably present in heterozygotes [4,5].

Testing Recommendations

Indications for Genetic Testing

Individuals meeting one or more of the following indications suggestive of a hereditary dyslipidemia should be offered the respective diagnostic panel genetic testing:

1) Personal history of fasting triglyceride levels **≥ 10 mmol/L** on 3 occasions (not due to secondary causes) AND **under the age of 18 years**[ii]
2) Personal history of LDL-C levels **≤ 0.5 mmol/L OR extremely low/undetectable Apolipoprotein B levels at any age** (ApoB) AND/OR clinical features suggestive of a monogenic hypobetalipoproteinemia or abetalipoproteinemia
3) Personal history of HDL-C levels **≤ 0.5 mmol/L at any age** AND/OR clinical features suggestive of Tangier disease, LCAT deficiency, or Apolipoprotein A1 (ApoA1) deficiency
4) Personal history of elevated **plasma cholestanol at any age** AND/OR clinical features suggestive of Cerebrotendinous xanthomatosis (CTX)
5) In patients suspicious for a monogenic dyslipidemia, clinicians may use clinical judgment to order genetic testing in individuals who do not fit within criteria 1-4[iii]

A comprehensive list of clinical features for all groups of dyslipidemias discussed in this document can be found in Table 2.

- For individuals with a confirmed genetic diagnosis of any of the above dyslipidemia syndromes, family members should undergo initial biochemical screening for the relevant lipid.
- Cascade genetic testing is only recommended for first- or second-degree relatives who meet the above criteria and/or those who are family planning. Consultation or referral to a genetics service is strongly recommended.

The indications outlined above are intended as recommendations for when genetic testing is **most appropriate** in this patient population. They are not meant to restrict testing for individuals who may not meet the specified biochemical or age thresholds, but for whom a strong clinical suspicion remains.

[ii] As most severe hypertriglyceridemia (HTG) cases occur due to multifactorial chylomicronemia syndrome (MCS), a polygenic condition, genetic testing is only recommended in individuals whose age of onset is in childhood or adolescence, and without secondary factors such as obesity, insulin resistance, or diabetes. The intention of this recommendation is to avoid the testing of individuals who developed a triglyceride level ≥ 10 mmol/L in adulthood, given the extremely low likelihood that a monogenic etiology exists for these individuals.

[iii] A consultation with clinical/metabolic genetics or lipid specialists may be helpful for individuals that do not meet criteria, but for whom a strong clinical suspicion remains.

Table 2. Dyslipidemias and Associated Criteria, Clinical Characteristics, and Recommended Genes.

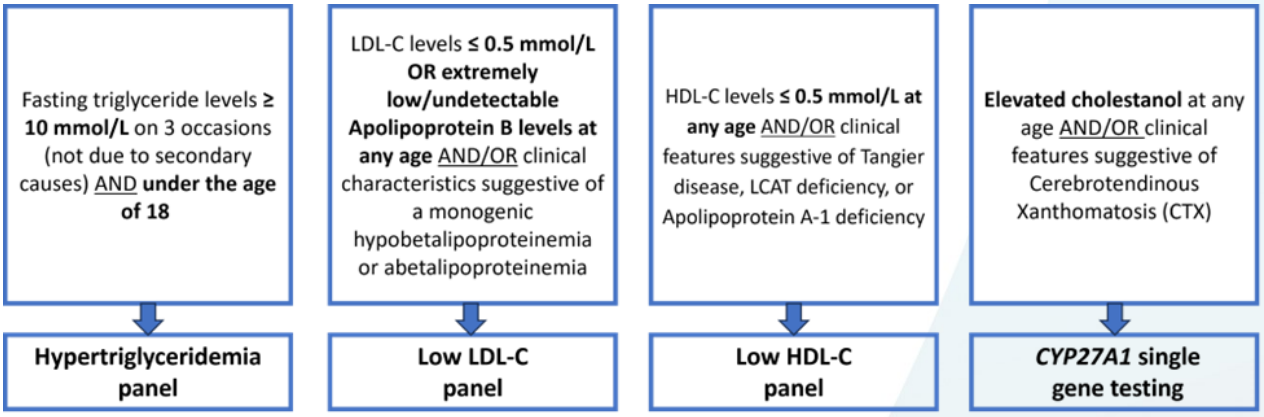
Lipid Disorder Category	Criteria	Clinical Characteristics[iv]	Recommended Genes[v]
Hypertriglyceridemia (HTG)	• Fasting triglyceride levels ≥ 10mmol/L on 3 separate occasions **AND** • Patient is under the age of 18 years	Abdominal pain, nausea/vomiting, recurrent pancreatitis, hepatosplenomegaly, eruptive xanthomas, lipaemia retinalis, proteinuria, jaundice	*AGPAT2, ALMS1, APOA5, APOC2, APOE, BSCL2, GPD1, GPIHBP1, LMF1, LMNA, LPL, PLIN1, PPARG*
Low Low-Density Lipoprotein-C (Low LDL-C)	• Personal history of LDL-C levels ≤ 0.5 mmol/L at any age **OR** extremely low or undetectable apo B levels **AND/OR** • Clinical characteristics suggestive of a monogenic hypobetalipoproteinemia or abetalipoproteinemia	Fat malabsorption/intolerance and associated features of fat-soluble vitamin deficiency including: retinopathy, ataxia, peripheral neuropathy, osteomalacia, osteopenia, areflexia, prolonged INR and easy bruising, steatosis, failure to thrive in infancy, acanthocytosis on blood film, elevated CK (up to 10x above reference range), absent chylomicrons, undetectable apo B	*ANGPTL3, APOB, MTTP, PCSK9, SAR1B*
Low High-Density Lipoprotein-C (Low HDL-C)	• Personal history of HDL-C levels ≤ 0.5 mmol/L at any age **AND/OR** • Clinical characteristics suggestive of Tangier disease, LCAT deficiency, or apo A1 deficiency	Corneal arcus, corneal opacities, web space xanthomas, variable atherosclerosis, proteinuria, renal disease, peripheral neuropathy, enlarged orange tonsils, cholesterol ester deposition in lymph nodes, bone marrow, liver, spleen, tonsils; low or absent apoA1	*ABCA1, APOA1, LCAT*
Cerebrotendinous xanthomatosis (CTX)	• Elevated plasma cholestanol **AND/OR** • Clinical characteristics suggestive of CTX[vi]	Infantile-onset diarrhea, jaundice, or cholestasis; childhood-onset cataract; adolescent to young adult-onset tendon xanthomas; adult-onset and progressive neurologic dysfunction[7]	*CYP27A1*

[iv] A list of secondary causes to consider for these groups of lipid disorders is listed in Appendix B.
[v] The genes recommended for the Hypertriglyceridemia panel also include those for syndromic causes of HTG such as some hereditary lipodystrophies and Alstrom syndrome. The genes included in this recommendation for panel genetic testing are not intended to provide comprehensive testing for the hereditary lipodystrophies.
[vi] The presence of tendon xanthomas can also be associated with FH and/or sitosterolemia.

Testing Approach

Due to the rarity of non-FH monogenic dyslipidemias, an overall limited number of causative genes, and the lack of overlap in clinical and biochemical phenotypes between different dyslipidemia syndromes, the Working Group recommends implementing the following approach to genetic testing for monogenic dyslipidemias, outlined in Figure 1.

Figure 1. Genetic testing strategy for monogenic dyslipidemias.



Implementation Considerations

To achieve thorough, standardized, and equitable access to dyslipidemia testing in Ontario, the following points should be considered:

1) **Technological considerations:**
    a. **Copy number variant (CNV) analysis:** Gene panels should be designed to capture regions and flanking intron/exon boundaries and should include testing for known pathogenic and likely pathogenic variants in non-coding regions. Given the emerging evidence implicating CNVs in dyslipidemias beyond FH, panels should be developed to ensure they are able to identify relevant CNVs of all included genes[8–10]. If the above methods are unable to assess for CNVs, alternative methods should be considered such as multiplex ligation probe analysis (MLPA) or chromosomal microarrays (CMA) for larger structural variants.
2) **Genetic counselling:**
    a. **Pre- and post-test counselling:** Genetic counselling support can be critical in ensuring patients are informed about the risks, benefits, and limitations of genetic testing before testing is offered. Upon disclosure of genetic test results, all patients should be offered genetic counselling. If there is uncertainty in interpreting a result when genetic testing yields a variant of uncertain significance (VUS), clinicians should seek expert consultation either through eConsult or through a referral to a medical genetics or lipid clinic.
    b. **Cascade testing:** Cascade testing is currently only recommended for confirmatory diagnostic testing in first- or second-degree relatives with a clinical and/or biochemical phenotype, and/or for individuals who are family planning.
3) **Ordering providers:** To support timely, equitable access to genetic testing, physicians across multiple specialties with relevant expertise in the diagnosis of dyslipidemias (e.g., medical geneticists, lipid specialists, endocrinologists, and/or multidisciplinary groups) should be supported to order genetic testing for individuals with a suspicion of a monogenic dyslipidemia. Physicians without subspecialist training are encouraged to utilize educational and training materials related to genetic testing, and to work in collaboration with local medical genetics clinics to adopt innovative models of care delivery (e.g., mainstreaming) to increase timely access to genetic testing.
4) **Reporting:** The association with *APOE* genotypes and the risk for Alzheimer's disease will not be revealed as common polymorphisms for *APOE* will not be reported.
5) **Polygenic risk scores (PRS):** Given the current lack of standardization in scoring, as well as limited evidence of its clinical utility, the Working Group currently does not recommend the reporting of PRS for individuals with suspicion of a hereditary dyslipidemia[5].

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Appendices

Appendix A: Common Secondary Causes

Dyslipidemia Group	Common Secondary Causes to Consider
Hypertriglyceridemia	Obesity, high fat diet, high glycemic index diet, metabolic syndrome, insulin resistance, diabetes, chronic renal failure, Cushing syndrome, Human immunodeficiency virus (HIV) infection, systemic lupus erythematosus, alcohol, certain medications[vii]
Low LDL-C	Lipid-lowering medications, malnutrition, vegan diet, malabsorption, chronic liver disease, chronic pancreatitis, cystic fibrosis, end-stage renal disease, cachexia, hyperthyroidism
Low HDL-C	Obesity, high fat diet, high glycemic index diet, metabolic syndrome, insulin resistance, diabetes, chronic renal failure, Cushing syndrome, HIV infection, medications
Cerebrotendinous xanthomatosis	FH, sitosterolemia, cholestasis and other liver disease Plasma cholestanol levels may be decreased through use of bile acids (chenodeoxycholic acid), statins, and steroids[11]

[vii] Including oral estrogens, retinoic acid derivatives, selective estrogen receptor modulators (e.g., tamoxifen), glucocorticoids, bile acid sequestrants, thiazide diuretics, non-cardioselective beta blockers, L-asparaginase, second generation antipsychotics, older protease inhibitors, mTOR inhibitors.

Appendix B: Evidence Review

Guideline Synthesis

- All guidelines recommended in this report were synthesized following the review of pertinent scientific literature, existing criteria, and published clinical guidelines. Input from clinical and laboratory specialists with expertise in the diagnosis and management of hereditary dyslipidemias was used to ensure the recommendations in this report were in concordance with the best available evidence and current clinical practices.
- Prevalence, detection rate of molecular testing, penetrance, and age of diagnosis referenced in this report represent the best data available in the literature, which, due to the rarity of many of the associated conditions, is limited.

Gene Inclusion Framework

- The Working Group followed an evidence-based framework (Table B1) to achieve consensus on which genes should be recommended for inclusion in a hereditary dyslipidemia panel. ClinGen, Genomic England PanelApp, and PanelApp Australia curations, alongside Working Group consensus, were used to identify evidence levels for each gene on the panel[12,13].
- A review of the technical specifications for genes listed in the panel should be completed prior to the implementation of the panel in Ontario. The panels should be designed to capture the coding regions and flanking intron/exon boundaries, identify relevant copy number variants (CNVs) of all included genes, and identify known likely pathogenic/pathogenic non-coding variants.

Table B1. Evidence Framework for Gene Inclusion

Resource	Evidence Threshold
Clinical Genome Resource (ClinGen)	Genes curated as Moderate, Strong, or Definitive for gene-disease validity in ClinGen
Genomics England PanelApp	Genes identified as Green using the Genomics England PanelApp and nominated by the Working Group member(s)
Panel App Australia	Genes identified as Green using the PanelApp Australia and nominated by the Working Group member(s)
Expert Consensus	Genes for which there is supportive evidence in the literature and vetted by the Working Group member(s).

Appendix C: Existing Lipid Clinics in Ontario

Clinic Name	Location and Contact Information	Adult or Paediatric
Toronto General Hospital – Type 2 diabetes and lipid disorders Dr. Gary Lewis	200 Elizabeth St, EN 12-243 Toronto, ON M5G 2C4 T: 416-340-4270 F: 416-340-3314 or 4730 uhn.ca/Medicine/Clinics/Endocrinology	Adult
The Hospital for Sick Children – Lipid Clinic Dr. Brian McCrindle	555 University Ave, 4A, Atrium, 4th Floor Toronto, ON M5G 1X8 T: 416-813-5848 F: 416-813-5582 sickkids.ca/en/care-services/clinics/cardiology-clinic/	Paediatric
St. Michael's Hospital – Lipid Clinic Dr. Cynthia T. Luk	61 Queen St E, 7th Floor Toronto ON M5C 2T2 T: 416-867-7424 F: 416--867-3654 unityhealth.to/clinics-services/lipids-clinic/	Adult
Hamilton General Hospital – Lipid Clinic Dr. Guillaume Pare	237 Barton St E Hamilton, ON L8L 2X2 T: 905- 527-4322 ext. 44537 F: 905-528-3148 hamiltonhealthsciences.ca/areas-of-care/cardiac-vascular-care/cardiac-ambulatory-clinics/lipid-clinic/	Adult
McMaster Children's Hospital – Pediatric Lipid Clinic Dr. Katherine Morrison	Level 2, Section G (Red) 1200 Main St W Hamilton, ON L8N 3Z5 T: 905-521-2100 ext. 76990 F: 905-385-5033 hamiltonhealthsciences.ca/mcmaster-childrens-hospital/areas-of-care/medicine/lipid-clinic/	Paediatric
Endocrinology & Metabolism Department, LHSC University Hospital – Lipid Genetics Clinic Dr. Robert Hegele	4th Floor Out-Patient Department 339 Windermere Rd London, ON N6A 5A5 T: 519-931-5774 F: 519-931-5218 lipidgeneticsclinic.ca/index.html	Adult
St. Joseph's Hospital Dr. Amanda Berberich	St. Joseph's Health Care London 268 Grosvenor St London, ON N6A 4V2 T: 519-646-6245 F: 519-646-6067	Adult

Clinic Name	Location and Contact Information	Adult or Paediatric
University of Ottawa Heart Institute – Lipid Clinic Dr. Ruth McPherson	40 Ruskin St Ottawa, ON K1Y 4W7 T: 613 696 7341 F: 613 696 7130 ottawaheart.ca/clinic/lipid-clinic	Adult
Children's Hospital of Eastern Ontario (CHEO) – Endocrinology Clinic Dr. Stasia Hadjiyannakis	Clinic C-10 401 Smyth Rd Ottawa, ON K1H 8L1 T: 613-737-7600 F: 613-738-4236 cheo.on.ca/en/clinics-services-programs/endocrinology-clinic.aspx	Paediatric

Appendix D: Acronyms

ApoA1	Apolipoprotein A1
ApoB	Apolipoprotein B
APOE	Apolipoprotein E
CK	Creatine kinase
CMA	Chromosomal microarray
CNV	Copy number variant
CTX	Cerebrotendinous xanthomatosis
FH	Familial hypercholesterolemia
HDL-C	High density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HTG	Hypertriglyceridemia
INR	International normalized ratio
LCAT	Lecithin-cholesterol acyl transferase
LDL-C	Low density lipoprotein cholesterol
MCS	Multifactorial chylomicronemia syndrome
MLPA	Multiplex ligation-dependent probe amplification
PGP	Provincial Genetics Program
PRS	Polygenic risk score
VUS	Variant of uncertain significance