FAMILIAL HYPERCHOLESTEROLEMIA

Updated April 2024

DIAGNOSIS

Familial hypercholesterolemia (FH) is a common (~1/250) autosomal dominant condition that results in a 6- to 22-fold increase in premature cardiovascular disease (CVD) and death. Early diagnosis and treatment can normalize life expectancy.

The Canadian Cardiovascular Society (CCS) recommends the use of the Canadian diagnostic criteria for FH proposed by the Familial Hypercholesterolemia Canada (FH Canada) network (Figure 1).

While clinical criteria can be used for diagnosis, there are limitations to using the classical presentation since few affected persons will exhibit physical findings (e.g. xanthomas, xanthelasmas) at the time of testing. Screening for FH based on family history alone has been shown to miss 30-60% of cases. Genetic testing is not essential for diagnosis and is not yet routinely clinically available in most of Canada.

WHO TO CONSIDER OFFERING GENETIC TESTING

- A close blood relative had a positive genetic test result (include family member's test report if available, and relation to patient)
- High LDL-cholesterol level of >8.5 mmol/L at any age
- Untreated* LDL-cholesterol level of:
  - >5.0 mmol/L+ for age 40 years and over
  - >4.5 mmol/L+ for age 18 to 39 years
  - >3.5 mmol/L+ for age under 18 years

  AND at least one of the following:
  - Tendon xanthomas and/or corneal arcus
  - First-degree relative (FDR) with high LDL- cholesterol level (not due to secondary causes)
  - Patient or FDR with early onset atherosclerotic cardiovascular disease (men under 55 years; women under 65 years)
  - Limited family history information (e.g., adopted)

+Secondary causes of high LDL-C to be ruled out.

*To calculate untreated LDL-C levels in treated patients see the CardioRisk App

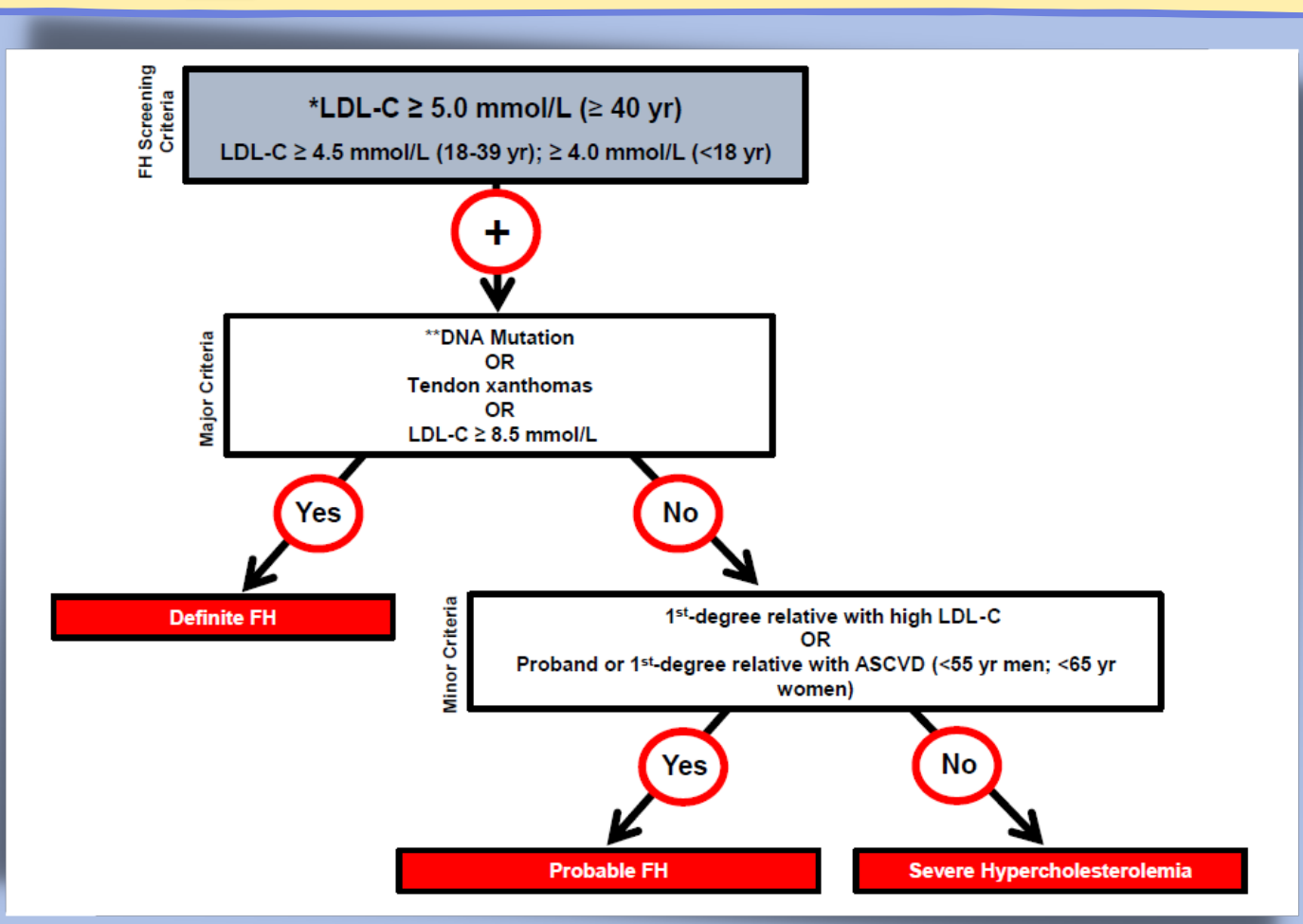

Figure 1. Canadian criteria for the clinical diagnosis of familial hypercholesterolemia (FH).

ASCVD: atherosclerotic cardiovascular disease; LDL-C: low-density lipoprotein cholesterol. * Secondary causes of high LDL-C should be ruled out (severe or untreated hypothyroidism, nephrotic syndrome, hepatic disease [biliary cirrhosis], medication, especially antiretroviral agents) ** DNA mutation refers to the presence of a known FH-causing variant in a FH gene in the individual or a first-degree relative

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The LDL-C levels cited are untreated levels. For a patient who is on lipid lowering medications, the CardioRisk Calculator app has a validated algorithm to assign a baseline value.

FAMILIAL HYPERCHOLESTEROLEMIA (FH)

GECKO Genetics Education Canada: Knowledge Organization
Centre d'éducation en génétique canadien: Connaissances organisées
POINT OF CARE TOOL

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GENETIC TESTING FOR FH

See the links (accessed March 2024) below to where testing is clinically available and the testing criteria. Other provinces are exploring how to implement genetic testing and screening.

Genetic testing in Ontario can be ordered by any physician and does not require a referral for genetic assessment. Requisitions, including testing criteria, can be found on the Ontario Provincial Genetics Program site. Blood can be drawn at any community lab.

Québec		Ontario		
The Core Molecular Diagnostic Laboratory at the McGill University Health Centre	CHU Sainte Justine Molecular Laboratory	London Health Sciences Centre molecular laboratory	Trillium Health Partners – Credit Valley Site	Hamilton Regional Laboratory Medicine Program

WHAT DO I DO WITH MY PATIENT'S GENETIC TEST RESULTS?

Positive results

One or more pathogenic/likely pathogenic (P/LP) variants in an FH gene have been identified and are known to be associated with FH.

This confirms a diagnosis of FH.

These results can be used to guide management and refine risk stratification.

For those with two copies of a P/LP variant in FH genes, homozygous FH, consider referral to specialized lipid clinic.

Cascade Screening

This patient now becomes the index case and their first-and second-degree relatives can be offered genetic testing for the familial gene variant(s).

Facilitate family communication and testing.

Cascade screening is the most cost-effective approach for identification of new FH cases.

Cascade screening reduces the average age at which an individual is diagnosed and results in an increased number of individuals who are treated with statins and have subsequent lowered lipid levels.

Genetic counselling

Genetics clinics vary in their referral criteria and may or may not accept referrals for familial testing of FH. Check your local genetics centre for more.

Negative results (uninformative)

No pathogenic/likely pathogenic (P/LP) variants in the FH genes tested, were identified.

This **does not rule out a diagnosis of** FH

Utility of the results depend upon the extent of analysis (e.g. ancestry based targeted testing vs. full gene sequencing) as well as the genes included on the panel.

While P/LP variants in the L*DLR, APOB* and *PCSK9* genes account for the majority (~80%) of FH, many other genes are known to affect hereditary risk of hypercholesterolemia.

Genetic testing cannot be offered to unaffected relatives. Lipid screening can be used for at-risk relatives.

Genetic testing may improve and re-referral may be considered.

True Negative results

The familial P/LP variant in the FH gene tested is not present.

This person is not at risk for FH.

This testing *only* looked for the presence or absence of the familial variant.

Variant of Uncertain Significance (VUS)

A variant in FH-related gene is detected, but there is insufficient evidence to determine if it is truly associated with disease.

This **does not rule out a diagnosis of** FH

Cascade screening of relatives is rarely offered in the context of a VUS.

Genetic counselling may be available. Check your local genetics centre for referral criteria.

Lipid screening can be used for at-risk relatives.

Over time a VUS may be reclassified, re-referral to genetics can be considered.

Patient resources

https://www.fhcanada.net/patients

HF Canada Hypercholestérolémie Familiale
FH Canada Familial Hypercholesterolemia

More FH resources

GECKO Genetics Education Canada: Knowledge Organization

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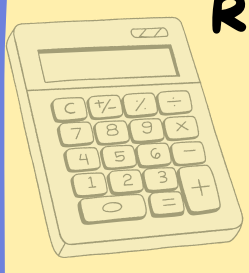
FH - familial hypercholesterolemia; CCS - Canadian Cardiovascular Society; CVD- cardiovascular disease; ASCVD - atherosclerosis cardiovascular disease

RISK ASSESSMENT



The use of conventional cardiovascular risk calculators in individuals with FH is not recommended as these greatly underestimate lifetime CVD risk. FH-specific cardiovascular risk calculators (e.g. the FH Risk Score, SAFEHEART) should be considered to assess the risk of ASCVD.

Routine assessment and stratification of the risk of ASCVD in all patients with FH should be used to guide personalized treatment and management.

Those with homozygous status (HoFH, two pathogenic/likely pathogenic (P/LP) variants in an FH gene) should be referred to a specialized lipid centre.

PHARMACEUTICALS (ADULTS)

- Statins are the drug class of choice for individuals with one P/LP variant in a FH gene (heterozygous FH (HeFH)).
- LDL-C should be lowered as fast and as far as possible.
- **The CCS recommends a >50% reduction of LDL-C from baseline beginning at age 18 as primary prevention and that an ideal goal of LDL-C <1.8 mmol/L is recommended for secondary prevention.**
- Observational studies have shown a dramatic decrease in cardiac events in statin-treated individuals with FH.
- Non-fasting lipid profiles should be used to monitor treatment in those whose treatment is stable.

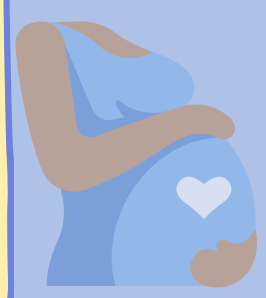
LIFESTYLE

All families with FH (including children and adolescents) should be counselled about the importance of lifestyle modification and heart healthy behaviour such as:

- smoking cessation and avoidance of passive smoking
- diet (e.g. high fibre, low in trans and saturated fatty acids)
- exercise
- stress reduction
- maintenance of ideal body weight

PREGNANCY

- For most persons assigned female at birth who are of reproductive age, an effective birth control method is recommended with discontinuation of statin therapy ideally 3 months prior to planned pregnancy or at the time of a positive pregnancy test.
- A pregnant person with FH and additional risk factors, e.g. established ASCVD, should be referred to a specialty lipid clinic for further treatment advice.



CHILDREN/ADOLESCENTS

- Selective lipid screening (fasting or non-fasting, non-HDL-C or LDL-C) can be considered at any age when there is a positive family history of premature CVD or dyslipidemia, or other cardiovascular risk factors.
- Based on current randomized control trials, the ideal age to begin treatment for FH is between ages 8-12 years.
  - Pharmacological treatment can be considered, incorporating clinical judgement, family and patient preferences.
- Lifestyle modifications as above remain the cornerstone of CVD prevention in both children and adolescents with FH.
- The CCS recommends that children with HoFH are referred to a lipid specialist centre for cholesterol-lowering therapies when >15kg in weight.