Part I: How to identify Familial Hypercholesterolemia and individuals most likely to benefit from referral to a lipid specialist

At least 1 in 500 Canadians is thought to have heterozygous familial hypercholesterolemia (HeFH, one mutation in one FH gene), however FH is significantly under-recognized in Canada. FH is more common in certain populations (e.g. 1/270 in French Canadians, ~1/100 in Lebanese and Afrikaners, and 1/67 in Ashkenazi Jews in South Africa) due to founder effects.

Table 1. Clinical features of familial hypercholesterolemia in heterozygotes (HeFH) and homozygotes (HoFH).

Clinical features	HeFH	HoFH
Genetics	Mutation in one copy of one FH gene	Mutation in both copies of an FH gene
LDL-C levels	≥ 5mmol/L with additional features shown in following boxes	>12 mmol/L *lower LDL-C levels, especially in children or in treated patients, do not exclude HoFH*
Cardiovascular disease onset	<55 years of age in men <65 years of age in women	<20 years of age (can be as early as the first year of life)
Physical findings	— Cholesterol deposits in the tendons (xanthomata) and/or around the eyes (xanthelasma) — Arcus cornealis (white, grey, or blue opaque ring in the corneal margin) onset <45years	
Family history	— Early onset CVD — Hyperlipidemia, often requiring treatment	

HOW TO RECOGNIZE INDIVIDUALS WITH FH:

- An individual (>30years) with hypercholesterolemia (LDL-C ≥5mmol/L)
  - Exclusion of secondary causes of elevated LDL-C, e.g. obstructive liver disease, hypothyroidism, nephrotic syndrome, anorexia nervosa

AND

- Personal or family history of clinical stigmata of FH

OR

- Personal or family history of premature CVD

OR

- Family history of significant hypercholesterolemia, often requiring treatment

Individuals with LDL-C ≥5mmol/L and at least one of the features above are considered to have a *possible* FH diagnosis. Those with LDL-C ≥ 5mmol/L and 2 additional features are considered to have a *probable* FH diagnosis. Individuals with possible or probable diagnosis should be referred to a lipid specialist for diagnosis and management.

While there are no Canadian-specific FH diagnostic criteria, the Canadian Cardiovascular Society (CCS) recommends using those published by the Dutch Lipid Clinic Network (below). Alternatively, criteria from the Simon Broome Registry, which include lower thresholds for children with suspected FH, can be used. Both sets of diagnostic criteria are internationally accepted and used for diagnosis of FH, although neither is designed to diagnose HoFH, for which other criteria have been suggested. See the FH GEC-KO Messenger for a comprehensive review, the Simon Broome Registry criteria, HoFH diagnostic criteria, and a complete reference list.

Table 2. Dutch Lipid Clinic Network - CCS recommended FH diagnostic criteria.

Criteria	Points
Family History	
First-degree relative with: ○ premature cardiovascular disease (<55 years in men, <60 years in women) **OR** ○ LDL-C >95th percentile for age and sex	1
First-degree relative: ○ With tendinous xanthomata and/or arcus cornealis **OR** ○ Child (<18 years) with LDL-C >95th percentile for age and sex	2
Clinical History	
Personal history of : ○ Premature peripheral or cerebrovascular disease ○ Coronary artery disease	1 2
Physical examination	
Tendinous xanthomata	6
Arcus cornealis <45 years of age	4
LDL-C	
Between 4.01 and 4.89mmol/L (155-189mg/dL)	1
Between 4.91 and 6.44mmol/L (190-249mg/dL)	3
Between 6.46 and 8.51mmol/L (250-329mg/dL)	5
Greater than 8.53mmol/L (>330mg/dL)	8
Genetics	
Pathogenic mutation in the *LDLR* gene or other gene known to cause FH e.g. *APOB, PCSK9*	8
Scoring	
Unlikely FH diagnosis	<3
Possible FH diagnosis	3 to 5
Probable FH diagnosis	6 to 7
Definite FH diagnosis	8 or more