ALBERTA PRECISION LABORATORIES
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Familial Hypercholesterolemia: Information for Ordering Providers

Familial hypercholesterolemia (FH) is a genetic condition that affects approximately 1 in 250 individuals and causes high cholesterol. Untreated, FH leads to early heart attacks and heart disease. Although lifestyle and diet are important factors in lowering cholesterol levels, most individuals with FH require treatment with statins to control their cholesterol levels.

Individuals who carry a pathogenic variant in a FH gene have an inherited form of heart disease and their at-risk family members should be screened for FH and have the option of genetic testing.

Testing for Familial Hypercholesterolemia

The *LDLR*, *APOB*, *PCSK9* and *LDLRAP1* genes will be analyzed for pathogenic variants. Pathogenic variants in these genes account for approximately 60-80% of FH. Since not all genes associated with familial hypercholesterolemia are known, a pathogenic variant will not be identified for every patient. The absence of a pathogenic variant does not exclude a clinical diagnosis. Management according to clinical guidelines is recommended when a pathogenic variant is not identified.

Pathogenic variants in the *LDLR*, *APOB* and *PCSK9* genes are inherited in a co-dominant manner. Individuals with pathogenic variants in both copies of the gene will generally have higher cholesterol levels than individuals with one variant. Variants in the *LDLRAP1* are inherited in a recessive manner.

Indications for Testing

FH testing can be ordered by any specialist. The likelihood of FH should be calculated using the Familial Hypercholesterolemia Calculator (Web CardioRisk (ubc.ca)) and individuals with probable or definite diagnosis of FH using the "Canadian Criteria for HeFH" should be considered for genetic testing. **Untreated LDL-C levels MUST be included on the requisition for testing to proceed.** The minimum requirement for testing is untreated cholesterol levels above the following cut-offs:

- LDL-C ≥5.0 mmol/L (40 years and up)
- LDL-C ≥4.5 mmol/L (18-39 years)
- LDL-C ≥4.0 mmol/L (less than 18 years)

How do I order familial hypercholesterolemia testing?

Please reference the Familial or inherited hypercholesterolemia (LAB4776) page in the APL Test Directory for a list of genes and ordering instructions.

If your patient has a family history of FH or a relative who has a molecular diagnosis of FH **AND your patient has an increased serum cholesterol level**, please provide the name of the relative and a copy of the molecular report. This will ensure that your patient has the appropriate testing. Cardiac gene panel, specific variant (LAB4148) should be ordered.

Predictive testing (for patients with a family history of FH and normal serum cholesterol level) is restricted to Clinical Genetics.

When can I expect results?

Results may take up to 4 months.

Requisition forms, contact information and other resources can be found at Genetics & Genomics

How are results reported?

Results are sent to the ordering provider and available in Netcare and Connect Care.

Result	Interpretation	Next Steps
Pathogenic Variant	A variant has been identified that is disease-causing.	• Manage based on patient's diagnosis, clinical presentation and practice guidelines. • Screen family members for FH with cholesterol testing. Confirm diagnosis for family members with elevated cholesterol levels with genetic testing for the familial variant(s). • Refer asymptomatic at-risk family members for genetic counselling to discuss the option of predictive testing.
Likely Pathogenic Variant	A variant has been identified and there is significant but not conclusive evidence that the variant is disease-causing.	
Variant of Uncertain Significance	A variant has been identified and there is not sufficient evidence to classify the variant as pathogenic/likely pathogenic or benign/likely benign.	• Variants of uncertain significance cannot be used to inform medical management decisions. Manage based on patient's clinical presentation and practice guidelines. • Refer for genetic counselling for possible segregation studies. • Screen family members with cholesterol testing.
No pathogenic variant (Uninformative)	No variants of clinical or uncertain significance were detected. This is an uninformative result and no explanation has been identified for the patient's phenotype. There may be other genes or variants not assessed by the current NGS panel associated with the patient's phenotype. A genetic condition or genetic component to the phenotype has not been excluded.	• Manage based on patient's clinical presentation and practice guidelines. • Screen family members with cholesterol testing.

Resources

Familial Hypercholesterolemia Canada

CardioRisk Calculator™ Familial Hypercholesterolemia

Contact Information

Healthcare providers may contact the Laboratory Genetic Counsellors, Genetics & Genomics North Sector at 780-407-1015.

References

Canadian Cardiovascular Society Position Statement on Familial Hypercholesterolemia: Update 2018
Canadian Journal of Cardiology 34 (2018) 1553-1563