Testing for Familial Hypercholesterolemia early may curb onset of cardiovascular disease

Introduction

Familial Hypercholesterolemia (FH) is a common, yet largely underdiagnosed genetically inherited disorder, leading to premature cardiovascular disease (CVD) characterized by very high low-density lipoprotein (LDL-C) levels that may cause abnormal lipid deposition in body tissues. The diagnosis of FH at an early age is critical for medical intervention, in that undiagnosed or misdiagnosed individuals will have significantly shortened life spans.[1] There are several genetic pathogenic alterations that are responsible for aberrant LDL-C metabolism.[2] FH typically shows autosomal dominant inheritance, and most of the cases are due to a single pathogenic variant in these genes, resulting in heterozygous FH (HeFH). However, a co-occurrence of two pathogenic variants gives rise to a markedly more severe form of the disease called homozygous FH (HoFH). HeFH is the most common form while HoFH is rare, affecting about 1:1,000,000. These patients typically have LDL-C levels that exceed 500 mg/dL.[1]

The prevalence of HeFH is estimated at 1:250 in the U.S. population, making it the most common morbid monogenic disorder. Despite this, it is estimated that fewer than 10% of those living with FH have been diagnosed.[3-4]

Labcorp's screening test for familial hypercholesterolemia, **Familial Hypercholesterolemia (FH) Lipid Profile With Interpretation [490500]** follows the Simon Broome criteria as outlined in Table 1. Patients are first segregated by age followed by interrogation LDL-C and total cholesterol (TC) levels. If either the LDL-C or TC cutoff values are exceeded, a diagnosis of FH is possible and genetic testing will be recommended. If the LDL-C or TC levels are not exceeded and there is clinical suspicion of FH, genetic testing may be considered.

Diagnosis

Using the Simon Broome criteria, a definite diagnosis of FH may be made by either biochemical findings in conjunction with a genetic mutation or clinical findings alone. In a small number of patients with clinical and biochemical evidence of FH, mutations are not manifested in those genes classically associated with FH, suggesting that other environmental factors or undiscovered genes may be involved.2 Numerous diagnostic strategies for FH have been advanced including Make Early Diagnosis to Prevent Early Death (MEDPED), Dutch Lipid Clinic, Simon Broome, National Lipid Association (NLA) and the American Heart Association (AHA). Tables 1-5 represent, but are not inclusive, of the diagnostic heterogeneity for each of these strategies.[5]

Key highlights

- Familial Hypercholesterolemia (FH) is a common, yet largely underdiagnosed genetically inherited disorder
- FH typically shows autosomal dominant inheritance, and most of the cases are due to a single pathogenic variant in these genes, resulting in heterozygous FH (HeFH)
- The prevalence of HeFH is estimated at 1:250 in the U.S. population, making it the most common morbid monogenic disorder
- Genetic testing for FH is now considered the gold standard for diagnosis

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Table 1. Simon Broome Criteria for the Diagnosis of FH (UK FH Registers Criteria)

Criteria	Possibility
In adults: TC >7.5 mmol/L (290.0 mg/dL) (or when available, LDL-C >4.9 mmol/L [189.5 mg.dL]) In pediatric patients: TC >6.7 mmol/L (259.1 mg/dL), or LDL-C >4 mmol/L (154.7 mg/dL), AND	Definite
Tendon xanthoma in the patient or first/second-degree relative, OR alternatively:	
Presence of LDL-R, ApoB, or PCSK9 mutation	
In adults: TC >7.5 mmol/L (290.0 mg/dL) (or when available, LDL-C >4.9 mmol/L [189.5 mg.dL]) In pediatric patients: TC >6.7 mmol/L (259.1 mg/dL), or LDL-C >4 mmol/L (154.7 mg/dL), AND	Possible
Family history of MI <50 y old in second-degree relative or <60 y old in first-degree relative OR alternatively	
Family history of TC >7.5 mmol/L (290.0 mg/dL) in a first- or second-degree relative.	

Table 2. US MEDPED Criteria for FH Diagnosis

Age, y	First-Degree Relative With FH	Second-Degree Relative With FH	Third-Degree Relative With FH	General Population
<20	220 mg/dL (5.7 mmol/L)	230 mg/dL (5.9 mmol/L)	240 mg/dL (6.2 mmol/L)	270 mg/dL (7.0 mmol/L)
20–29	240 mg/dL (6.2 mmol/L)	250 mg/dL (6.5 mmol/L)	260 mg/dL (6.7 mmol/L)	290 mg/dL (7.5 mmol/L)
30–39	270 mg/dL (7.0 mmol/L)	280 mg/dL (7.2 mmol/L)	290 mg/dL (7.5 mmol/L)	340 mg/dL (8.8 mmol/L)
≥40	290 mg/dL (7.5 mmol/L)	300 mg/dL (7.8 mmol/L)	310 mg/dL (8.0 mmol/L)	360 mg/dL (9.3 mmol/L)

FH Is Diagnosed if Total Cholesterol Exceeds These Cut-Off Points in mg/dL (mmol/L)

Table 3. Dutch Lipid Network Criteria for Diagnosis of FH

Criteria	Score
Family history	Definite
Premature CVD (men <55 y old, women <60 y old) in first-degree relative, OR	1
LDL >95th percentile in first-degree relative AND/OR	1
Tendon xanthoma and/or arcus cornealis in first-degree relative, OR	2
LDL >95th percentile in children <18 y old	2
Personal history	
Premature CAD in patient (men <55 y old, women <60 y old)	2
Premature cerebral or peripheral vascular disease (men <55 y old, women <60 y old)	1
Clinical examination	
Tendon xanthomas, OR	6
Corneal arcus younger than 45 y old	4

Criteria	Score
LDL	
>330 mg/dL (8.5 mmol/L)	8
250–329 mg/dL (6.5–8.5 mmol/L)	5
190–249 mg/dL (4.9–6.4 mmol/L)	3
155–189 mg/dL (4.0–4.9 mmol/L)	1
Presence of functional LDL-R mutation (in the LDL-R, ApoB, or PCSK9 gene)	8
Diagnosis based on the overall score	
Definite	>8
Probable	6–8
Possible	3–5
Unlikely	<3

Table 4. Diagnostic considerations by the AHA

	Adults ≥20 y Old	Homozygous FH	Family History of FH
Clinical Criteria	LDL-C ≥160 mg/dL (4.1 mmol/L) for children LDL-C ≥190 mg/dL (4.9 mmol/L) for adults + one first-degree relative similarly affected or with premature CAD or positive genetic testing for an LDL-C-raising gene defect (LDL receptor, ApoB, or PCSK9)	LDL-C ≥400 mg/dL (10.3 mmol/L) + one or both parents has clinically diagnosed familial hypercholesterolemia, positive genetic testing for an LDL-C-raising gene defect, or autosomal recessive FH	Presence of first-degree relative with confirmed FH; LDL-C is not a criterion
		LDL-C >560 mg/dL (14.5 mmol/L) or LDL-C >400 mg/dL (10.3 mmol/L) with aortic valve disease or xanthomata at <20 years of age	
With Genetic Testing	Presence of one abnormal LDL-C-raising gene defect and LDL-C <160 mg/dL (4.1 mmol/L)	Occasionally, homozygotes will have LDL-C <400 mg/dL (10.3 mmol/L)	Genetic testing is not performed
	Occasionally, heterozygotes may have LDL-C >400 mg/dL (10.3 mmol/L) and should be treated similarly to homozygotes		
	Presence of both abnormal LDL-C-raising gene defect(s) and LDL-C-lowering gene variant(s) with LDL-C <160 mg/dL (4.1 mmol/L)		

Table 5. NLA Considerations for Screening and Diagnosis of FH

Children, Adolescents, Young Adults <20 y Old	Adults ≥20 y Old
LDL-C ≥160 mg/dL (4.1 mmol/L) Non-HDL-C ≥190 mg/dL (4.9 mmol/L)	LDL-C ≥190 md/dL (4.9 mmol/L) Non-HDL ≥220 mg/dL (5.7 mmol/L)
At the LDL-C levels listed below, the probability of FH is 80% in the setting of general population screening. These LDL-C levels should prompt the clinician to strongly consider a diagnosis of FH and obtain further family information:	
LDL-C ≥250 mg/dL (6.5 mmol/L) in a patient aged ≥30 y	
LDL-C >220 mg/dL (5.7 mmol/L) for patients aged 20 to 29 y	
LDL-C ≥190 mg/dL (4.9 mmol/L) in patients aged <20 y	

There is lack of consensus among the international medical community for FH lipid decision points, age brackets or other clinical attributes, which can lead to confusion for the non-lipid specialist. In addition, it poses an obstacle to cost-effective cascade testing as recommended by the NLA, World Health Organization and the Centers for Disease and Control and Prevention (CDC). In the United States, while clinical diagnosis alone has been responsible for most of the FH cases diagnosed, the Simon Broome Criteria provided a higher diagnostic yield than did the use of other diagnostic strategies.[6] Aside from the lipid abnormalities, patients with FH often demonstrate cutaneous xanthomas and/or arcus cornealis.

Genetic Testing

Genetic testing as a part of FH screening has been recommended by many key professional societies including American College of Cardiology/Heart Association and National Lipid Association. Identification of a pathogenic variant in genes associated with FH is included into formal FH diagnostic criteria, such as Simon Broome and Dutch Lipid Clinic Criteria. Most of FH cases are caused by pathogenic variants in the LDL Receptor (*LDLR*), apolipoprotein B (*APOB*), and the Protein Convertase Subtilisin Kinase type 9 (*PCSK9*) genes. *LDLR* is the most common genetic cause, comprising >80% of overall pathogenic variants, whereas *APOB* and *PCSK9* account for 5% to 10% and 3% to 5%, respectively. A single pathogenic

variant in these genes manifests as heterozygous FH, whereas biallelic pathogenic variants cause homozygous FH. Also, a rare autosomal recessive form of FH exists and is caused by biallelic pathogenic variants in the *LDLRAP1* gene.

Labcorp's **GeneSeq®: Cardio – Familial Hypercholesterolemia Panel [482261]** provides testing for all four genes associated with FH—*LDLR*, *APOB*, *PCSK9* and *LDLRAP1*—thereby facilitating establishing or confirming the diagnosis of FH.[7] Early identification of individuals with pathogenic variants allows timely initiation of treatment that may alleviate early-onset CVD and allow for subsequent testing of at-risk family members. Genetic testing in pediatric patients has a diagnostic yield of ~95%.[8] Knowing the exact genetic defect permits a more accurate differentiation between heterozygous and homozygous FH, provides a more precise recurrence risk assessment and could assist with treatment strategy. Testing for FH alleles is also recommended for pedigree testing in families where FH has been identified, beginning with first degree relatives, then extending to second- and third-degree relatives.[1,4,8] In such cases, consultation with a genetic counselor may be of benefit prior to testing.[5] Genetic testing may also be of benefit in patients with acute coronary syndrome (ACS) where as many as 9% of ACS patients may have genetically confirmed FH where clinical algorithms do not correctly identify FH.[9]

Genetic testing for FH is now considered the gold standard for diagnosis.[8] The American Academy of Pediatrics (AAP) now recommends that in a clinical setting of FH suspicion or family history, children should be offered genetic testing for diagnosis. Genetic testing for FH has a 95% diagnostic yield in children. The AAP also recommends universal lipid screening for all children 9 to 11 years of age for early detection of FH.[4]

Summary

FH is an inherited disease and is the most common of the monogenic dyslipidemias. Approximately 90% of individuals with FH are undiagnosed or misdiagnosed. Early childhood diagnosis is imperative due to the eventual onset of premature CVD shortening the lifespan of the affected individual. FH is characterized by very high LDL-C and TC levels with 80% of patients expressing genetic mutations. Xanthomas or arcus cornealis may occur in patients due to abnormal lipid deposition in body tissues. Aggressive pharmacologic treatment is usually undertaken beginning as early as 8 to 10 years of age upon diagnosis.[4,7] Genetic testing has been shown to be of benefit in diagnosis, prognosis, family pedigree testing and in therapeutic choices.

Labcorp offers

Test Name	Test No.
Familial Hypercholesterolemia (FH) Lipid Profile With Interpretation	**409500**
GeneSeq®: Cardio–Familial Hypercholesterolemia Panel	**482261**

References

1. Gidding SS, Champagne MA, de Ferranti SD, et al. The agenda for familial hypercholesterolemia: a scientific statement from the American Heart Association. *Circulation*. 2015 Dec 1;132(22):2167-2192.
2. Raal FJ, Hovingh GK, Catapano AL. Familial hypercholesterolemia treatments: guidelines and new therapies. *Atherosclerosis*. 2018 Oct;277:483-492.
3. Banda JM, Sarraju A, Abbasi F, et al. Finding missed cases of familial hypercholesterolemia in health systems using machine learning. *NPJ Digit Med*. 2019 Apr 11;2:23.
4. Landstrom AP, Kim JJ, Gelb BD, et al. Genetic testing for heritable cardiovascular diseases in pediatric patients: a scientific statement from the American Heart Association. *Circ Genom Precis Med*. 2021 Oct;14(5):e000086.
5. McGowan MP, Dehkordi SHH, Moriarty PM, Duell PB. Diagnosis and treatment of heterozygous familial hypercholesterolemia. *J Am Heart Assoc*. 2019 Dec 17;8(24):e013225.
6. Ahmad ZS, Andersen RL, Andersen LH, et al. US physician practices for diagnosing familial hypercholesterolemia: data from the CASCADE-FH registry. *J Clin Lipidol*. 2016 Sep-Oct;10(5)1223-1229.
7. Goldberg AC, Hopkins PN, Toth PP, et al. Familial Hypercholesterolemia: screening, diagnosis and management of pediatric and adult patients: clinical guidance from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *J Clin Lipidol*. 2011 May-Jun;5(3)133-140.
8. Sturm AC, Knowles JW, Gidding SS, et al. Clinical genetic testing for familial hypercholesterolemia: JACC Scientific Expert Panel. *J Am Coll Cardiol*. 2018 Aug 7;72(6):662-680.
9. Amor-Salamanca A, Castillo S, Gonzalez-Vioque E, et al. Genetically confirmed familial hypercholesterolemia in patients with acute coronary syndrome. *J Am Coll Cardiol*. 2017 Oct 3;70(14):1732-1740.

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