Medical Policy Manual Genetic Testing, Policy No. 11

Genetic Testing for Familial Hypercholesterolemia

Effective: February 1, 2023

Next Review: November 2023
Last Review: December 2022

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Homozygous familial hypercholesterolemia (FH) is a rare disorder that causes extremely high levels of low-density lipoprotein (LDL), leading to very early cardiovascular disease. Heterozygous FH is more common and can also cause elevated LDL levels and premature cardiovascular disease, though with reduced severity and more variable presentation than homozygous FH.

MEDICAL POLICY CRITERIA

I. Genetic testing of *LDLR, APOB, PCSK9,* and/or *LDLRAP1* genes to confirm a diagnosis of familial hypercholesterolemia (FH) may be considered **medically necessary** when there is documentation of an uncertain diagnosis of FH (see Policy Guidelines) and a definitive diagnosis is required for selection of specialty medications (e.g., PCSK9 inhibitors).

II. Genetic testing for known familial FH-causing gene variants may be considered **medically necessary** for children (younger than age 18) when there is an affected first or second-degree relative, to determine future risk of disease.

III. Genetic testing for FH is **investigational** for all other indications, including but not limited to, a diagnosis when Criterion I. or II. is not met, and genetic testing for other genes.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

UNCERTAIN DIAGNOSIS OF FH

There are no standardized definitions of uncertain diagnosis of FH, however there are tools that can be useful for this determination, including but not limited to the Simon Broom Registry Criteria and the Dutch Lipid Clinic Network Criteria (score of 3-8).

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

1. Name of the genetic test(s) or panel test
2. Name of the performing laboratory and/or genetic testing organization (more than one may be listed)
3. The exact gene(s) and/or variants being tested
4. Relevant billing codes
5. Brief description of how the genetic test results will guide clinical decisions that would not otherwise be made in the absence testing
6. Medical records related to this genetic test
    - History and physical exam
    - Conventional testing and outcomes
    - Conservative treatment provided, if any

CROSS REFERENCES

1. Genetic and Molecular Testing, Genetic Testing, Policy No. 20
2. PCSK9 Inhibitors (Leqvio, inclisiran; Praluent, alirocumab; Repatha, evolocumab), Medication Policy Manual, Policy No. dru697

BACKGROUND

Familial hypercholesterolemia (FH) is an inherited disorder characterized by markedly elevated low-density lipoprotein (LDL) levels, physical exam signs of cholesterol deposition, and premature cardiovascular disease. FH can be categorized as homozygous or heterozygous FH. Homozygous FH is an extremely rare disorder that arises from biallelic homozygous or compound heterozygous variants and has a prevalence of between 1:160,000 and 1:4,000,000. Individuals with homozygous (which includes compound heterozygous) FH have extreme elevations of LDL, and typically develop coronary artery disease (CAD) in the second or third decade of life[1].

Heterozygous FH is relatively common, with an estimated prevalence of 1 in 311 in the general population. Some populations such as Ashkenazi Jews and South Africans have higher prevalence of up to 1 in 100. The prevalence of FH in people with atherosclerotic cardiovascular disease (ASCVD) is 1 in 17. For affected individuals, the burden of illness is high. If untreated, the average age for presentation with CAD is in the fourth decade for males

and the fifth decade for females, and there is a 30% to 50% risk of a fatal or nonfatal cardiac event for men and women in the fifth and sixth decades, respectively[2-4].

The diagnosis of FH relies on elevated LDL levels in conjunction with a personal and/or family history of premature CAD and physical exam signs of cholesterol deposition. There is wide variability in cholesterol levels for patients with FH, and considerable overlap in levels between patients with FH and patients with non-FH. Physical exam findings can include tendinous xanthomas, xanthelasma, and corneal arcus. Physical signs of FH are uncommon in children. Xanthelasma and corneal arcus are common in the elderly population and therefore not specific. Tendinous xanthomas are relatively specific for FH but are not sensitive findings. They occur mostly in patients with higher LDL levels and treatment with statins likely delays or prevents the development of xanthomas.

Because of the variable cholesterol levels, and the low sensitivity of physical exam findings, there are a considerable number of patients in whom the diagnosis is uncertain. For these individuals, there are a number of formal diagnostic tools for determining the likelihood of FH, including the Dutch Lipid Clinic Criteria, the Simon Broome Registry Criteria, and the Make Early Diagnosis Prevent Early Deaths Program Diagnostic Criteria.[5] Not all diagnostic tools for FH are appropriate for use in pediatric settings due to their reliance on physical signs of FH.

Treatment for FH in adults is similar to that for non-familial hypercholesterolemia and is based on LDL levels. Treatment for FH differs in that the approach is more aggressive (i.e., treatment may be initiated sooner, and a higher intensity medication regimen may be used). In children with FH, lipid screening and statin therapy are initiated at younger ages than in average risk children.

As with other forms of hypercholesterolemia, statins are the mainstay of treatment for FH. However, because of the degree of elevated LDL in many patients with FH, statins will often not be sufficient to achieve target lipid levels. Additional medications can be used in these patients. Ezetimibe inhibits absorption of cholesterol from the gastrointestinal tract and is effective for reducing LDL levels by up to 25% in patients already on statins. The IMPROVE-IT trial randomized patients with acute coronary syndrome to a combination of ezetimibe plus statins versus statins alone and reported that cardiovascular events were reduced for patients treated with combination therapy.[6]

The PCSK9 inhibitors are the most recently approved drugs for hyperlipidemia. These medications have potent LDL-lowering properties and have been tested in patients with FH. When added to statins, these drugs can result in additional LDL reduction of 30% to 70% and have been reported to reduce the incidence of nonfatal myocardial infarction.[4] Other antilipid medications (e.g., bile acid sequestrants, niacin) are effective at reducing LDL levels but have not demonstrated efficacy in reducing cardiovascular events when added to statins. For patients who continue to have elevated LDL levels despite maximum medical treatment, lipid apheresis is an option.

FH is most often inherited as an autosomal dominant condition. The primary physiologic defect in FH is impaired ability to clear LDL from the circulation, resulting in elevated serum levels. Four genes have been identified as harboring variants associated with FH. The LDL receptor gene (*LDLR*) is the most common gene in which a variant is identified, accounting for between 85-90% of genetically confirmed FH[2] Because the LDL receptor binds LDL and allows removal of LDL from the circulation, a defect in this receptor leads to reduced clearance of LDL. Over 1,500 different pathogenic variants have been identified in this gene.[5]

Other genes associated with FH include the *APOB* and *PCSK9* genes. Changes in the *APOB* gene account for approximately 5%-15% of FH cases. Apolipoprotein B is a cofactor in the binding of LDL to the LDL receptor, and variants in *APOB* lead to reduced clearance of LDL. Variants in the *PCSK9* gene that increase the levels of PCSK9, impairing the function of LDL receptors, account for approximately 1% of FH. *APOB* and *PCSK9* variants result in increased PCSK9 levels, which impair the function of the LDL receptors leading to reduced clearance of LDL.[2] Recessive FH is caused by homozygous *LDLRAP1* pathogenic (or likely pathogenic) variants.

Penetrance for heterozygous FH varies by gene and in some cases by specific variant but is at least 70%.Variable clinical expressivity may also be mediated by both environmental factors such as diet and exercise, and unknown genetic factors that modify gene expression.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[7] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

- The analytic validity of the test, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
- The clinical validity of the test, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
- The clinical utility of the test, which describes how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes.

This evidence review is focused on clinical validity and utility.

CLINICAL VALIDITY

The clinical sensitivity is defined as the proportion of patients with FH who have a pathogenic variant for FH, and the clinical specificity is defined as the proportion of patients without FH who do not have a pathogenic variant for FH.

Six of the larger, more recent published studies of clinical validity were identified and are shown in Table 1.[8-13] These cohorts included sample sizes ranging from 254 to 6,015 patients with definite or suspected FH. These studies were conducted in different countries in Western Europe; no similar studies of US individuals were identified. All studies reported clinical sensitivity and two studies reported on clinical specificity. In some cases, the analysis was stratified by the clinical likelihood of FH prior to genetic testing using the Dutch Lipid Clinic Network (DLCN) criteria.

The largest cohort, studied by Abul-Husn (2016), focused on genetic testing through exome sequencing of 46,321 adults from a single health system.[13] The test had low sensitivity (2%) and high specificity (99%), complicated by reliance on an incomplete electronic medical record for retrospective clinical diagnosis by the Dutch Lipid Clinic Network diagnostic criteria. This study further went on to note that within the 215 patients found to have genetic variants in the *LDR*, *PCSK9*, and *APOB* genes, only 25% met criteria for a clinical diagnosis of FH. Patients with relevant variants had higher LDL-H levels ($p<0.001$) with an increased risk of both general CAD (OR 2.6, $p<0.001$) and premature CAD (OR 3.7, $p<0.001$). Weaknesses of this study include reliance on a partially incomplete electronic medical record, as well as an ascertainment bias due to sampling within a single health care delivery system.

The clinical sensitivity of these studies ranged from 2% to 66.5%, with four studies clustering in the 34.5% to 41.2% range. The study that reported a substantially higher sensitivity of 66.5% included only patients with definite FH, unlike the other studies that included both definite and suspected FH cases. Two studies used the DLCN criteria to categorize individuals as definite, probable or possible FH.[9, 11] The proportion of individuals testing positive for FH varied by category. In the definite FH category, the sensitivity was 56.3% and 70.3%, respectively. This is in the same range as the study by Diakou (2011), which reported a sensitivity of 66.5% in patients with definite FH. In patients with probable or possible FH, the sensitivity was substantially lower (range, 10.8% to 29.5%).

Differences in the methodology of these studies may impact the reported sensitivities. The populations are from different countries and are comprised mostly of patients from tertiary referral centers. Different populations, especially those seen in primary care, may have different rates of variants. The type and number of variants tested for, and the methods of testing, also varied in these studies. For example, for *LDLR* gene variants, some studies used a defined set of known pathogenic variants while other studies searched for any variants and reported both known and unknown variants. There were also differences in the method for making a clinical diagnosis, and different diagnostic criteria may have resulted in different populations. Future studies may report on additional genes associated with FH (i.e., *STAP1*), and on copy number variation. Sensitivity and specificity have not yet been reported in large cohort studies for these tests.[14]

Table 1. Clinical Validity of Genetic Testing for FH

Study (Year)	Location	N	Genes Tested (Variants)	Clinical Sensitivity				Clinical Specificity
				Definite FH	Probable FH	Possible FH	Overall	
Diakou (2011)	Greece	254	*LDLR* (n=10) *APOB* (n=1) *PCSK9* (n=1) *ARH* (n=1)	66.5% (169/254)[a]	–	–	66.5% (169/254)[a]	100% (40/40)
Hooper (2012)	Australia	343	*LDLR* (n=18) *APOB* (n=2) *PCSK9* (n=1)	70.3% (90/128)	29.5% (26/88)	10.8% (12/111)	37.3% (128/343)	–
Palacios (2012)	Spain	5430	*LDLR* (any) *APOB* (n=1) *PCSK9* (n=4)	–	–	–	41.4%[b] (2246/5430)	–
Taylor (2010)	United Kingdom	635	*LDLR* (n=18) *APOB* (n=1) *PCSK9* (n=1)	56.3% (107/190)	–	28.4% (112/394)	34.5% (219/635)	–
Tichy (2012)	Czech Republic	2239	*LDLR* (any) *APOB* (n=1)	–	–	–	35.7%[c] (800/2239)	–

Study (Year)	Location	N	Genes Tested (Variants)	Clinical Sensitivity				Clinical Specificity
				Definite FH	Probable FH	Possible FH	Overall	
Abul-Husn (2016)	U.S.	50,726	*LDLR* (n=29) *APOB* (n=2) *PCSK9* (n=4)	30.2% (16/53)[a]	7.0% (35/497)	1.2% (68/5465)	2.0% (119/6015)[a]	99.8% (40,174/40,270)

FH: familial hypercholesterolemia.
a Individuals with a clinical diagnosis of FH based on Williams's clinical criteria.
b Individuals with possible, probable, definite FH but not separated by category.
c Individuals with a high clinical suspicion for FH based on personal history, family history, and low-density lipoprotein levels.

Section Summary: Clinical Validity

Evidence on clinical validity includes cohorts of patients with definite or suspected FH tested for genetic variants, and cohorts of unaffected patients tested for genetic variants. Five moderate-to-large cohorts were reviewed, from the U.S. and Europe. A wide range of clinical sensitivity was reported (range 2% to 66.5%). The sensitivity is higher in patients with definite FH (range 50% to 70%). In patients with probable or possible FH, the sensitivity is low (range 1.2% to 30%). Two studies reported clinical specificity (range 2% to 66.5%).

CLINICAL UTILITY

There is no direct evidence on the clinical utility of genetic testing for FH. However, FH is a disorder with a high burden of illness and potentially preventable morbidity and mortality. Accelerated atherosclerotic disease in the absence of treatment leads to premature CAD and increased morbidity and mortality for affected patients. There are cases in which the diagnosis cannot be made by standard clinical workup without genetic testing. There is an overlap in cholesterol levels between individuals with FH and those with other types of hypercholesterolemia, and family history of premature CAD may or may not be apparent for all individuals, leading to a substantial number of cases in which the diagnosis is uncertain based on family history and cholesterol levels.

For patients with an uncertain diagnosis of FH, genetic testing can confirm the diagnosis in a substantial proportion of patients. Identification of a known pathogenic variant has a high specificity for FH and therefore will confirm the disorder with a high degree of certainty. On the other hand, the sensitivity for identifying a pathogenic variant is suboptimal and therefore a negative genetic test will not rule out FH in the absence of a known pathogenic/likely pathogenic variant in a blood relative. For patients who are in an uncertain category by clinical criteria, a positive genetic test will confirm the diagnosis of FH. These patients will then be eligible for specialty medications (e.g., PCSK9 inhibitors) and these medications will be initiated in patients who have uncontrolled lipid levels despite treatment with statins and/or other agents. In patients who have uncontrolled lipid levels despite treatment with standard medications, these drugs have been demonstrated to improve outcomes.[15, 16]

There is evidence that children with FH benefit from genetic testing in order to confirm their diagnosis. A Cochrane meta-analysis found that statin therapy use in children with FH was safe and effectively lowered cholesterol levels. The meta-analysis included studies involving children treated with statins as young as age 6, which is younger than current population-based cholesterol screening guidelines of age 9. The Cochrane review emphasized the importance of molecular diagnosis of FH in order to identify children who are more likely to need specialty medications.[17]

A long-term follow-up study reported that former participants in a placebo-controlled RCT involving statin therapy in children for genetically confirmed FH had reduced risk for cardiovascular disease 20 years later. The follow-up study compared patients who received statins between age 8 and 18 to their parents who were not treated with statin therapy before adulthood.[18]

Section Summary: Clinical Utility

There is a lack of direct evidence for clinical utility, therefore indirect chains of evidence are used to determine whether testing has clinical utility. For diagnostic genetic testing, when a definitive diagnosis of FH is required to establish eligibility for specialty medications, the links in the chain of indirect evidence are intact and clinical utility is demonstrated. In other situations, there are gaps in the chain of indirect evidence that preclude conclusions on clinical utility. For this indication, genetic testing can confirm the presence of FH in some individuals who have an uncertain clinical diagnosis, but treatment decisions are made primarily on LDL levels and the establishment of definite FH will not change treatment recommendations. It is possible that some types of management changes are undertaken after a diagnosis of FH, such as intensification of medication treatment or referral to a lipid specialist, but these management changes have an uncertain impact on outcomes.

TESTING INDIVIDUALS WITH A CLOSE RELATIVE WITH A DIAGNOSIS OF FH FOR FUTURE RISK OF DISEASE

Genetic testing for children at risk for FH has clinical utility. Targeted testing for a known pathogenic variant has positive and negative predictive values, both approaching 100%. Genetic testing in children is superior to standard risk stratification in determining future disease risk. Genetic testing is used to determine the age to start cholesterol testing in order to enable prompt statin therapy, and to rule out FH in children who have a blood relative with a known FH-causing gene variant. Evidence is sufficient that the technology leads to improvement in net health outcome.

There is no direct evidence on the clinical utility of genetic testing for FH in adults based on known familial variants. Cascade testing for FH in adults is unlikely to lead to changes in clinical management or improved outcomes for adults with FH since cholesterol levels are routinely assessed during adulthood. FH treatment is based on LDL levels and response to therapy.

There is some evidence regarding the outcomes of familial testing from studies of cascade screening in countries where this method has been used.

A systematic review (2019) of cascade screening included six studies of genetic cascade testing and four studies of biochemical testing.[19] Due to the constraints associated with cascade screening noted below, none of the included studies were conducted in the United States. The review found similar diagnostic yield with genetic (44.3%) and biochemical (45.2%) testing, but the new cases identified per index case by genetic testing was nearly six times larger than cases identified by biochemical testing (2.42 versus 0.42 cases). Results favoring new case identification with genetic testing were consistent when excluding one outlier study (1.37 versus 0.42 cases).

Cascade screening for FH was evaluated by Leren (2004) in a national screening program from the Netherlands in a large study not included in the systematic review.[20] This program

was initiated at a time when cholesterol screening was recommended for the general population. The addition of cascade screening for FH led to more than 9000 additional individuals diagnosed with FH. The rate of statin use increased in this population from an estimate of 39% prior to initiation of the program to 85% after full implementation. s While cascade screening is likely to improve outcomes, it requires an infrastructure that allows access to the entire population, and that is not likely to be feasible when only a limited population is available for screening. As a result of these barriers, cascade screening has not been used in the U.S., and the applicability of these studies to a U.S. population is unclear.

SUMMARY OF EVIDENCE

For individuals who have signs and/or symptoms of familial hypercholesterolemia (FH) and who receive genetic testing to confirm the diagnosis of FH, the evidence includes case series and cross-sectional studies. Relevant outcomes are test accuracy and validity, other test performance measures, symptoms, change in disease status, and morbid events. No published empiric evidence on analytic validity was identified; however, there are claims in the literature that the analytic validity approaches 100%.For clinical validity, there are large samples of individuals with FH who have been systematically tested for FH variants. In these cohorts of patients, the clinical sensitivity ranges from 30% to 70% for those with definite FH. For suspected FH, the sensitivity is lower, ranging from 1% to 30%. Clinical specificity ranges from 99% to 100%. False positives are expected to be low for known pathogenic variants, but the false-positive rate is unknown for novel variants or for variants of unknown significance.

Direct evidence of clinical utility is lacking. However, for patients who are in an uncertain diagnostic category, a positive genetic test can confirm the diagnosis of FH and establish eligibility for specialty medications. Specialty medications (e.g., PCSK9 inhibitors) have known efficacy in patients with FH and uncontrolled lipid levels despite treatment with statins and/or other medications.

There is evidence that children with blood relatives who have known FH-causing gene variants benefit from targeted testing to determine future disease risk. Long-term follow-up data demonstrate reduced disease risk after childhood statin therapy for FH. Because FH causes, on average, earlier onset of symptoms, and there is a long pre-symptomatic phase; identification through genetic testing in order to enable preventative strategies and prompt treatment is warranted. The evidence is sufficient to determine qualitatively that the technology results in a meaningful improvement in the net health outcome.

PRACTICE GUIDELINE SUMMARY

NATIONAL LIPID ASSOCIATION EXPERT PANEL

Recommendations on the diagnosis and screening for FH were developed by the National Lipid Association Expert Panel on Familial Hypercholesterolemia and published in 2011[21] and built upon by a scientific statement published in 2020.[22] This statement includes the following recommendations:

- Genetic testing is reasonable when heterozygous familial hypercholesterolemia is suspected but not definitively diagnosed based on clinical criteria alone. (Strength of recommendation: IIa, Level of evidence: B-NR [Nonrandomized])
- Cascade screening for FH either by lipid profile or genetic testing is recommended in all first-degree relatives (children and siblings) of an individual who has tested genetically

positive for FH. (Strength of recommendation: I; Level of evidence: C-EO [Consensus of expert opinion])

AMERICAN COLLEGE OF CARDIOLOGY

The Journal of the American College of Cardiology (JACC) Scientific Expert Panel published consensus guidelines regarding clinical genetic testing for FH in 2018.[23] These included the following recommendations:

- Genetic testing for FH should be offered to individuals of any age in whom a strong clinical index of suspicion for FH exists based on examination of the patient's clinical and/or family histories. This index of suspicion includes the following:
    - Children with persistent LDL-C levels ≥160 mg/dl or adults with persistent LDL-C levels ≥190 mg/dl without an apparent secondary cause of hypercholesterolemia and with at least 1 first-degree relative similarly affected or with premature CAD or where family history is not available (e.g., adoption)
    - Children with persistent LDL-C levels ≥190 mg/dl or adults with persistent LDL-C levels ≥250 mg/dl without an apparent secondary cause of hypercholesterolemia, even in the absence of a positive family history
- Genetic testing for FH may be considered in the following clinical scenarios:
    - Children with persistent LDL-C levels ≥160 mg/dl (without an apparent secondary cause of hypercholesterolemia) with and LDL-C level ≥190 mg/dl in at least 1 parent or a family history of hypercholesterolemia and premature CAD
    - Adults with no pre-treatment LDL-C levels available but with a personal history of premature CAD and family history of both hypercholesterolemia and premature CAD
    - Adults with persistent LDL-C levels ≥160 mg/dl (without an apparent secondary cause of hypercholesterolemia) in the setting of a family history of hypercholesterolemia and either a personal history or a family history of premature CAD.

In 2017, the American College of Cardiology (ACC) published a focused update to the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk.[24] This guide included definitions of heterozygous and homozygous FH, based on clinical criteria alone or with genetic testing performed. However, no specific recommendations regarding such testing.

AMERICAN HEART ASSOCIATION

According to a scientific statement from the American Heart Association (2021), "Children with a strong clinical suspicion for FH should be offered genetic testing for diagnosis. Furthermore, if a pathogenic/likely pathogenic variant is found in an individual with FH, risk-predictive genetic testing should be performed in the family, including children."[25]

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE

Recommendations from an expert panel on cardiovascular health and risk reduction in children and adolescents were published in 2011.[26] The report contained the following recommendations:

- "The evidence review supports the concept that early identification and control of dyslipidemia throughout youth and into adulthood will substantially reduce clinical CVD risk beginning in young adult life. Preliminary evidence in children with heterozygous FH with markedly elevated LDL-C indicates that earlier treatment is associated with reduced subclinical evidence of atherosclerosis. (Grade B)
- TC and LDL-C levels fall as much as10-20% or more during puberty. (Grade B) Based on this normal pattern of change in lipid and lipoprotein levels with growth and maturation, age 10 years (range age 9-11 years) is a stable time for lipid assessment in children. (Grade D) For most children, this age range will precede onset of puberty."

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

The U.S. Preventive Services Task Force (2016) published recommendations on lipid disorders in adults.[27] This publication did not make specific recommendations for genetic testing for FH, and recommends neither for nor against general screening for dyslipidemia in adults under age 40 due to lack of evidence. However, the Task Force acknowledged the rationale for screening for dyslipidemia in adults under age 40 years to identify those at risk for the development of early atherosclerosis, including those with familial hypercholesterolemia.

A Task Force evidence report, conducted by Lozano et al (2016), evaluated lipid screening in children and adolescents to detect familial hypercholesterolemia.[28] This report stated that genetic screening for FH was beyond the scope of the report. Further, the report stated that "because implementing this approach [cascade screening] in the U.S. would require new infrastructure, cascade screening is outside of the purview of U.S. primary care and beyond the scope of this review."

SUMMARY

There is enough research to show that genetic testing to confirm a diagnosis of familial hypercholesterolemia (FH) can help identify patients that may benefit from certain cholesterol-lowering medications. Treatment with these medications can lower the risk of cardiovascular disease and improve health outcomes in patients with FH. Clinical guidelines based on research state that genetic testing may be useful when patients have an uncertain diagnosis of FH. Therefore, genetic testing of the genes *LDLR, APOB, PCSK9,* and *LDLRAP1* to confirm a diagnosis of FH may be considered medically necessary when policy criteria are met.

There is enough research to show that testing in children for known familial FH-causing gene variants in order to determine future disease risk can improve health outcomes. Standard approaches without genetic testing are insufficient to identify and prevent complications from FH in children. Therefore, this testing may be considered medically necessary when policy criteria are met.

There is not enough research to show that genetic testing in other situations can improve health outcomes for patients. This includes testing patients that already have a diagnosis of FH, , and testing genes other than genes *LDLR, APOB, PCSK9,* and *LDLRAP1.* Therefore, testing that does not meet the policy criteria is considered investigational.

REFERENCES

1. Ison HE, Clarke SL, Knowles JW. Familial Hypercholesterolemia. In: MP Adam, DB Everman, GM Mirzaa, et al., eds. GeneReviews(®). Seattle (WA): University of Washington, Seattle, Copyright © 1993-2022, University of Washington, Seattle. GeneReviews is a registered trademark of the University of Washington, Seattle. All rights reserved., 1993.
2. McGowan MP, Hosseini Dehkordi SH, Moriarty PM, et al. Diagnosis and Treatment of Heterozygous Familial Hypercholesterolemia. *J Am Heart Assoc.* 2019;8(24):e013225. PMID: 31838973
3. Hu P, Dharmayat KI, Stevens CAT, et al. Prevalence of Familial Hypercholesterolemia Among the General Population and Patients With Atherosclerotic Cardiovascular Disease: A Systematic Review and Meta-Analysis. *Circulation.* 2020;141(22):1742-59. PMID: 32468833
4. Patel RS, Scopelliti EM, Savelloni J. Therapeutic management of familial hypercholesterolemia: current and emerging drug therapies. *Pharmacotherapy.* 2015;35(12):1189-203. PMID: 26684558
5. Bilen O, Pokharel Y, Ballantyne CM. Genetic testing in hyperlipidemia. *Endocrinology and metabolism clinics of North America.* 2016;45(1):129-40. PMID: 26893002
6. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *The New England journal of medicine.* 2015;372(25):2387-97. PMID: 26039521
7. den Dunnen JT, Dalgleish R, Maglott DR, et al. HGVS Recommendations for the Description of Sequence Variants: 2016 Update. *Human mutation.* 2016;37(6):564-9. PMID: 26931183
8. Diakou M, Miltiadous G, Xenophontos SL, et al. Spectrum of LDLR gene mutations, including a novel mutation causing familial hypercholesterolaemia, in North-western Greece. *European journal of internal medicine.* 2011;22(5):e55-9. PMID: 21925044
9. Hooper AJ, Nguyen LT, Burnett JR, et al. Genetic analysis of familial hypercholesterolaemia in Western Australia. *Atherosclerosis.* 2012;224(2):430-4. PMID: 22883975
10. Palacios L, Grandoso L, Cuevas N, et al. Molecular characterization of familial hypercholesterolemia in Spain. *Atherosclerosis.* 2012;221(1):137-42. PMID: 22244043
11. Taylor A, Wang D, Patel K, et al. Mutation detection rate and spectrum in familial hypercholesterolaemia patients in the UK pilot cascade project. *Clinical genetics.* 2010;77(6):572-80. PMID: 20236128
12. Tichy L, Freiberger T, Zapletalova P, et al. The molecular basis of familial hypercholesterolemia in the Czech Republic: spectrum of LDLR mutations and genotype-phenotype correlations. *Atherosclerosis.* 2012;223(2):401-8. PMID: 22698793
13. Abul-Husn NS, Manickam K, Jones LK, et al. Genetic identification of familial hypercholesterolemia within a single U.S. health care system. *Science (New York, NY).* 2016;354(6319). PMID: 28008010
14. Wang J, Dron JS, Ban MR, et al. Polygenic Versus Monogenic Causes of Hypercholesterolemia Ascertained Clinically. *Arteriosclerosis, thrombosis, and vascular biology.* 2016;36(12):2439-45. PMID: 27765764
15. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. *The New England journal of medicine.* 2015;372(16):1500-9. PMID: 25773607

16. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. *The New England journal of medicine.* 2015;372(16):1489-99. PMID: 25773378
17. Vuorio A, Kuoppala J, Kovanen PT, et al. Statins for children with familial hypercholesterolemia. *Cochrane Database of Systematic Reviews.* 2019(11). PMID: CD006401
18. Luirink IK, Wiegman A, Kusters DM, et al. 20-Year Follow-up of Statins in Children with Familial Hypercholesterolemia. *The New England journal of medicine.* 2019;381(16):1547-56. PMID: 31618540
19. Lee C, Rivera-Valerio M, Bangash H, et al. New Case Detection by Cascade Testing in Familial Hypercholesterolemia: A Systematic Review of the Literature. *Circ Genom Precis Med.* 2019;12(11):e002723. PMID: 31638829
20. Leren TP. Cascade genetic screening for familial hypercholesterolemia. *Clinical genetics.* 2004;66(6):483-7. PMID: 15521974
21. Hopkins PN, Toth PP, Ballantyne CM, et al. Familial hypercholesterolemias: prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. *Journal of clinical lipidology.* 2011;5(3 Suppl):S9-17. PMID: 21600530
22. Brown EE, Sturm AC, Cuchel M, et al. Genetic testing in dyslipidemia: A scientific statement from the National Lipid Association. *Journal of clinical lipidology.* 2020;14(4):398-413. PMID: 32507592
23. Sturm AC, Knowles JW, Gidding SS, et al. Clinical Genetic Testing for Familial Hypercholesterolemia: JACC Scientific Expert Panel. *Journal of the American College of Cardiology.* 2018;72(6):662-80. PMID: 30071997
24. Lloyd-Jones DM, Morris PB, Ballantyne CM, et al. 2017 Focused Update of the 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk: A Report of the American College of Cardiology Task Force on Expert Consensus Decision Pathways. *Journal of the American College of Cardiology.* 2017;70(14):1785-822. PMID: 28886926
25. 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;14(5):e000086. PMID: 34412507
26. National Heart L, and Blood Institute,. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. [cited 12/13/2022]. 'Available from:' http://www.nhlbi.nih.gov/health-pro/guidelines/current/cardiovascular-health-pediatric-guidelines/summary#chap9.
27. US Preventive Services Task Force (USPSTF). Statin Use for the Primary Prevention of Cardiovascular Disease in Adults: Preventive Medication. [cited 12/13/2022]. 'Available from:' https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/statin-use-in-adults-preventive-medication#bootstrap-panel--7.
28. Lozano P, Henrikson NB, Dunn J, et al. Lipid Screening in Childhood and Adolescence for Detection of Familial Hypercholesterolemia: Evidence Report and Systematic Review for the US Preventive Services Task Force. *Jama.* 2016;316(6):645-55. PMID: 27532919

CODES

Codes	Number	Description
CPT	81401	Molecular pathology procedure, Level 2
	81405	Molecular pathology procedure, Level 6
	81406	Molecular pathology procedure, Level 7
	81407	Molecular pathology procedure, Level 8
HCPCS	None	

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