BlueCross BlueShield Federal Employee Program.

FEP Medical Policy Manual

FEP 2.04.139 Genetic Testing for Heterozygous Familial Hypercholesterolemia

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None

Genetic Testing for Heterozygous Familial Hypercholesterolemia

Description

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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. Familial hypercholesterolemia can be either homozygous or heterozygous. Heterozygous FH, which is more common and more difficult to diagnose, is the focus of this evidence review. Genetic testing for heterozygous FH can potentially improve the ability to make a diagnosis of FH and can identify asymptomatic relatives of affected individuals at risk for developing FH.

OBJECTIVE

The objective of this evidence review is to determine whether genetic testing to confirm a diagnosis or determine future risk of familial hypercholesterolemia improves the net health outcome.

POLICY STATEMENT

Genetic testing to confirm a diagnosis of familial hypercholesterolemia (FH) may be considered **medically necessary** when a definitive diagnosis is required as an eligibility criterion for specialty medications (see Policy Guidelines) and when the following criteria are met:

- Genetic testing is targeted to individuals who are in an uncertain category according to clinical criteria (personal and family history, physical exam, lipid levels) (see Policy Guidelines); AND
- Alternative treatment considerations are in place for individuals who have an uncertain diagnosis of FH and a negative genetic test.

Genetic testing to confirm a diagnosis of heterozygous FH is considered **investigational** in all other situations.

Genetic testing of adults who are close relatives of individuals with FH to determine future risk of disease is considered **investigational** (see Policy Guidelines).

Genetic testing of children of individuals with FH to determine future risk of disease may be considered **medically necessary** when the following criteria are met (see Policy Guidelines):

- A pathogenic variant is present in a parent; AND
- General lipid screening is not recommended based on age or other factors.

POLICY GUIDELINES

The definition of an "uncertain" diagnosis of familial hypercholesterolemia (FH) is not standardized. However, available diagnostic tools provide guidance on when a diagnosis is and is not definitive.[1,] When FH is suspected and evaluated against standardized diagnostic criteria, it can be interpreted that the individual is in an "uncertain" category when criteria for a definitive diagnosis are not met. Here are some examples of certain criteria not being met:

- Dutch Lipid Clinic Network Criteria. A score greater than 8 on the Dutch Lipid Clinic Network criteria is considered definitive FH. Scores between 3 and 8 are considered "possible" or "probable" FH. The latter 2 categories can be considered to represent "uncertain" FH.
- Simon-Broome Register Criteria. A definitive diagnosis of FH is made based on a total cholesterol level greater than 290 mg/dL in adults (or low-density lipoprotein [LDL] >190 mg/dL), together with either positive physical exam findings or a positive genetic test. Probable FH, which can be interpreted as "uncertain" FH, is diagnosed using the same cholesterol levels, plus family history of premature myocardial infarction or total cholesterol of at least 290 mg/dL in a first- or a second-degree relative.
- Make Early Diagnosis Prevent Early Death (MEDPED) Diagnostic Criteria. These criteria provide a yes/no answer for whether an individual has FH, based on family history, age, and cholesterol levels. An individual who meets criteria for FH can be considered to have definitive FH; however, there is no "possible" or "probable" category that allows assignment of an "uncertain" category.

When there is a clinical diagnosis of FH but no known pathogenic variant in the family, it is necessary to test an index case to determine variant status. Coverage of testing an index case to benefit family members depends on contract benefit language (see Benefit Application section).

It is unlikely that screening of adults who are close relatives of an index case of FH will improve outcomes because management decisions will be made according to lipid levels and will not differ based on a diagnosis of FH. However, there are conditions under which testing of relatives will lead to improved outcomes, particularly when testing is performed as part of a formal cascade screening program. Cascade testing refers to a coordinated program of population screening intended to identify additional patients with FH. Cascade screening may involve a combination of lipid levels and genetic testing; conversely, cascade screening may be performed with genetic testing alone. Beginning with an index case, close relatives are screened. For patients who screen positive, all close relatives are then identified and screened. This process is repeated until no further close relative eligible for screening can be identified. While such programs exist in Western Europe, there are barriers to implementation in the United States, such as a lack of an infrastructure to identify all individuals in the cascade; additionally there is a lack of coordination for patients with different types of medical insurance.

Eligibility for specialty medicines (eg, proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors) may require a definitive diagnosis of FH. The labeled indications for these agents state they are for individuals with FH, although criteria for diagnosis are not given. In the key trials that led to U.S. Food and Drug Administration approval of these inhibitors, having a diagnosis of FH served as an eligibility criterion. The diagnosis in these trials was based on clinical factors with or without genetic testing.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society"s nomenclature is recommended by the Human Variome Project, the HUman Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology<97>"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"<97>to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at individuals who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

Recommendations indicate that, when possible, genetic testing for familial hypercholesterolemia be performed in an affected family member so that testing in unaffected, at-risk family members can focus on the variant found in the affected family member. However, coverage for testing of the affected index case (proband) depends on contract benefit language.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

RATIONALE

Summary of Evidence

For individuals who have signs and/or symptoms of familial hypercholesterolemia (FH) when a definitive diagnosis is required to establish eligibility for specialty medications or who have signs and/or symptoms of FH undergoing lipid-lowering therapy who receive genetic testing to confirm the diagnosis of FH, the evidence includes case series and cross-sectional studies. Relevant outcomes are test validity, other test performance measures, symptoms, change in disease status, and morbid events. 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 uncertain significance. Direct evidence for clinical utility is lacking. The clinical utility of genetic testing was evaluated using a chain of evidence in the following situations:

- *When a definitive diagnosis of FH is required to establish eligibility for specialty medications.* A chain of evidence demonstrates that clinical utility is present. 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 (eg, PCSK9 inhibitors) have known efficacy in patients with FH and uncontrolled lipid levels despite treatment with statins and/or other medications. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

- *All other situations.* Clinical utility of testing for diagnosis cannot be demonstrated through a chain of evidence. No changes in management occur as a result of establishing a definitive diagnosis with genetic testing compared with standard clinical evaluation. For adolescents and adults, measurement of lipid levels is indicated, and management decisions will be made primarily on lipid levels and will not differ in the presence of FH. Therefore, an improvement in health outcomes cannot be demonstrated. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are adults or children and have a close relative with a diagnosis of FH who receive genetic testing to determine future risk of FH, the evidence includes a randomized controlled trial (RCT), case series, and cross-sectional studies. Relevant outcomes include test validity, other test performance measures, symptoms, change in disease status, and morbid events. For clinical validity, there are large samples of individuals with FH who have been systematically tested for FH variants. In these cohorts, 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 uncertain significance. Direct evidence for clinical utility is lacking. Clinical utility was evaluated using a chain of evidence in the following situations:

- *Adults*. Clinical utility cannot be demonstrated through a chain of evidence. While targeted genetic testing is superior to standard risk stratification for determining future risk of disease, it is unlikely that management changes will occur as a result of genetic testing. Adults who are close relatives of individuals with FH will have their lipid levels tested, and management decisions for adults are made primarily by low-density lipoprotein (LDL) levels and will not differ for patients with a diagnosis of FH. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

- *Children*. Clinical utility can be demonstrated through a chain of evidence. Targeted genetic testing is superior to standard risk stratification for determining future risk of disease. It is recommended that the children of individuals who have a pathogenic variant initiate screening at an early age; further, the affected children should begin treatment with statins as early as possible. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Migliara et al (2017) conducted a systematic review of guidelines on genetic testing and patient management of individuals with familial hypercholesterolemia (FH).[26,] The literature search, conducted through April 2017, identified 10 guidelines for inclusion. Three of the guidelines were developed within the U.S.: those by the National Lipid Association,[27,] International FH Foundation,[28,] and American Association of Clinical Endocrinologists and American College of Endocrinology.[29,] Guidance from NICE was also included in the review.[30,] The quality of the guidelines was assessed using the Appraisal of Guidelines for Research and Evaluation II instrument, with guideline quality ranging from average to good. Most guidelines agreed that genetic testing follows cholesterol testing, physical findings distinctive of FH, and highly suggestive family history of FH. Universal screening for FH was not recommended. This review highlighted the importance of genetic testing for FH in children, because aggressive treatment at an earlier age may prevent premature coronary heart disease.

American Heart Association

According to a scientific statement from the American Heart Association (2020), genetic testing for cardiovascular diseases, including FH, "typically should be reserved for patients with a confirmed or suspected diagnosis of an inherited cardiovascular disease or for individuals at high a priori risk resulting from a previously identified pathogenic variant in their family" and should include taking an extensive family history.[31,]

In another scientific statement focused on genetic testing for heritable cardiovascular diseases in children, the AHA (2021) notes the following:[32,] "It is imperative to identify individuals with FH in childhood so that lipid-lowering therapies and lifestyle interventions can be established. Left untreated, children with FH are at high risk for atherosclerotic cardiovascular disease in early to middle adulthood attributable to the cumulative burden of elevated LDL-C levels."

American Lipid Association

Subsequent to the publication of the Migliara systematic review (2017)[26,], the American Lipid Association (ALA) issued updated guidance on genetic testing for dyslipidemias, including FH.[33,] Recommendations are summarized in Table 1.

Table 1. ALA Recommendations on Genetic Testing for FH

Recommendation	SOE	GOE
"Genetic testing is reasonable when heterozygous familial hypercholesterolemia is suspected but not definitively diagnosed based on clinical criteria alone."	Moderate evidence of benefit	Moderate, based on nonrandomized studies
"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."	Strong evidence of benefit	Consensus expert opinion

ALA: American Lipid Association; FH: familial hypercholesterolemia; GOE: grade of evidence; SOE: strength of evidence.

Familial Hypercholesterolemia Foundation/Journal of the American College of Cardiology Expert Panel

In 2018, the Familial Hypercholesterolemia Foundation (FHF) commissioned an expert panel through the Journal of the American College of Cardiology (JACC) to issue detailed guidelines on the use of genetic testing for FH (Table 2).[34,]

Table 2. FHF/JACC Recommendations on Genetic Testing for FH

Recommendation	SOE	GOE
"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."	Moderate evidence of benefit	Moderate, based on nonrandomized studies
"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 an 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."	Weak evidence of benefit	Consensus expert opinion
"Cascade genetic testing for the specific variant(s) identified in the FH proband (known familial variant testing) should be offered to all first-degree relatives. If first-degree relatives are unavailable, or do not wish to undergo testing, known familial variant testing should be offered to second-degree relatives. Cascade genetic testing should commence throughout the entire extended family until all at-risk individuals have been tested and all known relatives with FH have been identified."	Strong evidence of benefit	Moderate, based on randomized studies

CAD: coronary artery disease; FH: familial hypercholesterolemia; FHF: Familial Hypercholesterolemia Foundation; GOE: grade of evidence; JACC: Journal of the American College of Cardiology; LDL-C: low-density lipoprotein cholesterol; SOE: strength of evidence.

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.[35,] The report contained the following recommendations (see Table 3).

Table 3. Recommendations on Cardiovascular Health and Risk Reduction in Children and Adolescents

Recommendation	GOE
"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.”	B
"TC and LDL-C levels fall as much as 10-20% or more during puberty.”	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. For most children, this age range will precede onset of puberty.”	D

CVD: cardiovascular disease; FH: familial hypercholesterolemia; GOE: grade of evidence; LDL-C: low-density lipoprotein cholesterol; TC: triglycerides.

U.S. Preventive Services Task Force Recommendations

The **U.S. Preventive Services Task Force** (2016) published recommendations on statin use for the primary prevention of cardiovascular disease in adults.[36,]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 40 years of age 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.[37] 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."

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2023	New Policy	Policy updated with literature review through August 22, 2022; references added. Policy statements unchanged. 2024 FEP Benefit changes.FEP new policy.