2.04.139	Genetic Testing for Heterozygous Familial Hypercholesterolemia		
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Section:	2.0 Medicine	**Page:**	Page 1 of 21

Policy Statement

I. 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 **both** of the following criteria are met:
   A. 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)
   B. Alternative treatment considerations are in place for individuals who have an uncertain diagnosis of FH and a negative genetic test

II. Genetic testing to confirm a diagnosis of FH is considered **investigational** in all other situations (see Policy Guidelines).

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

IV. Genetic testing of children of individuals with FH to determine future risk of disease may be considered **medically necessary** when **both** of the following criteria are met (see Policy Guidelines):
   A. A pathogenic variant is present in a parent
   B. General lipid screening is not recommended based on age or other factors

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

This policy does not apply to genes transmitted in autosomal recessive fashion.

This policy applies only to testing of individuals with uncertain diagnosis of familial hypercholesterolemia (FH) and thereby are unlikely to have homozygous variants in genes transmitted in autosomal dominant fashion. Testing individuals with severe presentation at high risk of homozygous variants may be necessary for guiding testing and management of unaffected relatives. That is, 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).

The definition of an "uncertain" diagnosis of 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.

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 (e.g., 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—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—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.

Coding

See the Codes table for details.

Description

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 due to an inherited variant transmitted in autosomal dominant fashion, 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.

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 (e.g., proprotein convertase subtilisin/kexin type 9 [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.

Additional Information
Not applicable.

Related Policies

- N/A

Benefit Application

Benefit determinations should be based in all cases on the applicable member health services contract language. To the extent there are conflicts between this Medical Policy and the member health services contract language, the contract language will control. Please refer to the member's

contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

Regulatory Status

Cal. Health & Safety Code §1367.667, Insurance Code Section 10123.209, and Welfare and Institutions Code 14132.09

California laws that requires insurers to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed.

Clinical Laboratory Improvement Amendments (CLIA) and FDA Regulatory Overview

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

Background

Familial Hypercholesterolemia

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 categorized as homozygous or heterozygous FH. Homozygous FH is an extremely rare disorder that arises from biallelic variants in a single gene, and the disorder has a prevalence of between 1:160,000 and 1:1,000,000.[2,] Individuals with homozygous FH have extreme elevations of LDL, develop coronary artery disease (CAD) in the second or third decade, and are generally diagnosed easily.

Heterozygous FH is more common, with an estimated prevalence between 1 in 200 to 1 in 500 individuals.[3,4,5,] Some populations, such as Ashkenazi Jews and South Africans, have a higher prevalence of up to 1 in 100.[3,] For affected individuals, the burden of illness is high. Patients with FH and increased LDL cholesterol (>190 mg/dL) have a 3 times higher risk of CAD than those with increased LDL cholesterol alone.[6,] The average age for presentation with CAD is in the fourth decade for men and the fifth decade for women, and there is a 30% to 50% increase in risk for men and women in the fifth and sixth decades, respectively.[4,] Increased risk of CAD is associated with a higher rate of death associated with cardiovascular causes in patients with homozygous and heterozygous FH.[7,]

Diagnosis

The diagnosis of FH relies on elevated LDL levels in conjunction with a 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, but these are not often helpful in making a diagnosis. 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.[1, 8]

- Make Early Diagnosis Prevent Early Deaths (MEDPED) Diagnostic Criteria
  - This tool relies on a combination of total cholesterol levels, age, and family history. For example, a 20-year-old individual who has no family history is diagnosed with FH if total cholesterol is 270 mg/dL or higher. A 25-year-old individual with a first-degree relative who has FH is diagnosed with FH if total cholesterol is 240 mg/dL or higher.
  - Genetic testing is not considered as part of the diagnostic workup with this tool.
- Dutch Lipid Clinic Network Criteria
  - This tool assigns points for family history, CAD in the individual, physical exam signs of cholesterol deposition, LDL levels, and results of genetic testing. The diagnosis of definite FH is made when the score is higher than 8 and probable FH when the score is 6 to 8.
  - The diagnosis can be made with or without genetic testing. A positive genetic test is given 8 points, which is the highest for any criterion and indicates that a positive genetic test alone is sufficient to make a definitive diagnosis.
- Simon-Broome Register Criteria
  - Using these criteria, a definite diagnosis of FH is made based on total cholesterol that is greater than 290 mg/dL in adults (or LDL >190 mg/dL) together with tendinous xanthoma in the individual or a first-degree relative.
  - A definite diagnosis can also be made using cholesterol levels and a positive genetic test.
  - Probable FH is diagnosed by cholesterol levels and either a family history of premature myocardial infarction or a family history of total cholesterol 290 mg/dL or higher in a first- or a second-degree relative.

Treatment

Treatment of FH is generally similar to that for non-FH and is based on LDL levels. Treatment may differ in that the approach to treating FH is more aggressive (i.e., treatment may be initiated sooner, and a higher intensity medication regimen may be used). In adults, there are no specific treatment guidelines that indicate treatment for FH differs from the standard treatment of hypercholesterolemia. There may be more differences in children, for whom the presence of a pathogenic variant may impact the timing of starting medications.

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 not be sufficient to achieve target lipid levels. Additional medications can be used in these patients. Ezetimibe inhibits the absorption of cholesterol from the gastrointestinal tract and is effective for reducing LDL levels by up to 25% in patients already on statins.[4]

The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial randomized patients with the 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.[9]

The proprotein convertase subtilisin/kexin type 9 (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.[4,10] 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.[4,10] 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.

Genetic Markers for Familial Hypercholesterolemia

Familial hypercholesterolemia is generally inherited as an autosomal dominant condition. The primary physiologic defect in FH is the impaired ability to clear LDL from the circulation, resulting in elevated serum levels. Three genes have been identified as harboring variants associated with FH.

- The LDL receptor gene (*LDLR*) is the most common variant identified, accounting for between 60% and 80% of FH.[8,]
  - The LDL receptor binds LDL thus allowing removal of LDL from the circulation. A defect in the LDL receptor leads to reduced clearance of LDL.
  - Over 1500 different pathogenic variants have been identified in this gene.[2,8,] Characterization of the frequency and spectrum of variants is ongoing.[11,]
- The *APOB* gene accounts for approximately 1% to 5% of FH cases.[2,]
  - Apolipoprotein B is a cofactor in the binding of LDL to the LDL receptor, and variants in *APOB* lead to reduced clearance of LDL.
  - There are a limited number of variants of this gene, allowing targeted testing.
- The *PCSK9* gene accounts for approximately 0% to 3% of FH.[2,]
  - This variant results in increased PCSK9 levels, which impair the function of the LDL receptors leading to reduced clearance of LDL.
  - There are a limited number of known pathogenic variants, allowing targeted testing.

Penetrance for all FH genes is 90% or higher.[2,] Therefore, nearly all patients found to have a pathogenic variant will eventually develop clinical disease. There is some degree of variable clinical expressivity that might be mediated by both environmental factors such as diet and exercise, and unknown genetic factors that modify gene expression.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Familial Hypercholesterolemia

Clinical Context and Test Purpose

The purpose of genetic testing for familial hypercholesterolemia (FH) is to diagnose individuals with homozygous or heterozygous FH.

The following PICO was used to select literature to inform this review.

Populations

The relevant populations of interest are patients within 4 categories. In patients who have signs and/or symptoms of FH, diagnostic testing may occur in 2 subpopulations: (1) those who are eligible for specialty medications or (2) those who are not eligible for specialty medications. In patients who have a close relative with a diagnosis of FH, diagnostic testing may occur in 2 additional subpopulations: (3) an adult, or (4) a child.

Interventions

The relevant intervention is genetic testing for FH. Commercial testing is available from numerous companies.

Comparators
The following practice is currently being used to make decisions about managing FH: standard clinical workup without genetic testing.

Outcomes
The general outcomes of interest are test validity, other test performance measures, symptoms, change in disease status, and morbid events.

The potential beneficial outcomes of primary interest would be a diagnosis of FH prompting appropriate and timely interventional strategies (e.g., statins, proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors) to prolong life.

The potential harmful outcomes are those resulting from a false test result. False-positive or false-negative test results can lead to the initiation of unnecessary treatment and adverse events from that treatment or undertreatment.

Genetic testing for FH may be performed at any point during a lifetime. The necessity for genetic testing is guided by the availability of information that alters the risk of an individual of having or developing FH.

Study Selection Criteria
For the evaluation of the clinical validity of genetic testing for heterozygous FH, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the genetic test;
- Patient/sample clinical characteristics were described;
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
A number of larger studies have assessed clinical validity and are shown in Table 1.[12,13,14,15,16,] These cohorts included sample sizes ranging from 254 to 6015 patients with definite or suspected FH. The largest and most recent of these studies was conducted in the U.S.; the remaining studies were conducted in Western Europe. All studies reported clinical sensitivity, and 2 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 criteria.

In addition, the largest cohort, studied by Abul-Husn et al (2016), focused on exome sequencing of 46321 adults from a single health system.[17,] 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 also revealed that of the 215 patients found to have genetic variants in the *LDLR*, *PCSK9*, and *APOB* genes, only 25% met criteria for a clinical diagnosis of FH. Patients with relevant variants had higher low-density lipoprotein (LDL) cholesterol levels (p<.001), with an increased risk of both general coronary artery disease (CAD; odds ratio, 2.6; p<.001) and premature CAD (odds ratio, 3.7; p<.001). Weaknesses of this study included reliance on a partially incomplete electronic medical record and an ascertainment bias due to sampling within a single health care delivery system.

The clinical sensitivity of the studies in Table 1 ranged from 1% to 66.5%, with 4 studies clustering in the 34.5% to 41.2% range.[14,15,16,17,] Unlike the other studies that included both definite and suspected FH cases, Diakou et al (2011), who reported a substantially higher sensitivity rate of 66.5%, only included patients with definite FH.[12,] Abul-Husn et al (2016), who reported a substantially lower sensitivity of 1%,

relied on an incomplete medical record for clinical diagnosis of FH.[17,] Four studies used the Dutch Lipid Clinic Network criteria to categorize individuals as definite, probable, or possible FH.[13,15,18,19,] The proportion of individuals testing positive for FH varied by category. In the definite FH category, the sensitivity ranged from 30.2% to 70.3%. This is in the same range as the Diakou et al (2011) study, 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, 1.2% to 29.5%).[12,]

Differences in the methodology of these studies might have affected reported sensitivities. The populations derived from different countries and are comprised mostly of patients from tertiary referral centers. Different populations, especially those seen in primary care, might have different rates of variants. The type and number of variants tested for, and the methods of testing, also varied. For example, for low-density lipoprotein receptor (*LDLR*) 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 methods for making a clinical diagnosis; it is also important to note that different diagnostic criteria might 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.[18,]

Table 1. Clinical Validity of Genetic Testing for Familial Hypercholesterolemia

Study	Location	N	Genes Tested (Variants)	Sensitivity for FH, % (n/N)				Specificity for FH, % (n/N)
				Definite	Probable	Possible	Overall	
Hedegaard et al (2023)[19,]	Denmark	1243	*LDLR* *APOB* *PCSK9*	41.3 (19/46)	31.8 (34/107)	19.0 (97/511)	27.9 (350/1243)	-
Abul-Husn et al (2016)[17,]	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)	99.8 (40174/40270)
Hooper et al (2012)[13,]	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 et al (2012)[14,]	Spain	5430	*LDLR* (any) *APOB* (n=1) *PCSK9* (n=4)	-	-	-	41.4[b] (2246/5430)	-
Tichy et al (2012)[16,]	Czech Republic	2239	*LDLR* (any) *APOB* (n=1)	-	-	-	35.7[c] (800/2239)	-
Diakou et al (2011)[12,]	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)
Taylor et al (2010)[15,]	U.K.	635	*LDLR* (n=18) *APOB* (n=1) *PCSK9* (n=1)	56.3 (107/190)	-	28.4 (112/394)	34.5 (219/635)	-

FH: familial hypercholesterolemia.
[a] Individuals with a clinical diagnosis of FH based on Williams' 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: Clinically Valid

Evidence on clinical validity includes cohorts with definite or suspected FH tested for genetic variants, and cohorts of unaffected patients tested for genetic variants. Six 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, 30% to 70%). In patients with

probable or possible FH, the sensitivity is low (range, 1.2% to 30%). Two studies reported clinical specificity (range, 99.8% to 100%).

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

There is no direct evidence on the clinical utility of genetic testing for FH.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Diagnostic Testing of Patients With Signs and/or Symptoms of Familial Hypercholesterolemia

An indirect chain of evidence can provide evidence of clinical utility if all the links in the chain of evidence are intact. The chain of evidence for 2 scenarios requiring diagnostic testing for FH is laid out below.

Familial hypercholesterolemia 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.

Familial hypercholesterolemia may be diagnosed by a clinical workup included testing of LDL levels, family history, and physical exams, but there are cases in which the diagnosis cannot be made. In some patients, there is an overlap in cholesterol levels between individuals with FH and those with other types of hypercholesterolemia; therefore, cholesterol levels cannot always distinguish between FH and non-FH. The 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.

Genetic testing in patients who have an uncertain diagnosis of FH 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.

Treatment of hyperlipidemia is primarily based on LDL levels, and the presence of FH does not affect treatment decisions apart from the LDL level. All patients with FH will have indications for statin treatment, and many will have indications for additional interventions based on the LDL response to statins. In patients whose lipid levels cannot be adequately managed with statins and/or other agents, specialty medications (e.g., PCSK9 inhibitors) may be used in patients with FH.

Section Summary: Familial Hypercholesterolemia Testing for Those With Signs and/or Symptoms of Familial Hypercholesterolemia who are Eligible for Specialty Medications

In the first scenario, in which a patient is eligible for specialty medications after definitive diagnosis with FH, a chain of evidence supporting genetic testing can be constructed. 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. Management changes that occur as a result of genetic testing are the initiation of effective medications (e.g., PCSK9 inhibitors). In patients who have uncontrolled lipid levels despite treatment with standard medications, these drugs have been demonstrated to improve outcomes.[20,21,]

Section Summary: Familial Hypercholesterolemia Testing for Those With Signs and/or Symptoms of Familial Hypercholesterolemia who are Ineligible for Specialty Medications

In the second scenario, encompassing all other diagnostic situations, a sufficient chain of evidence cannot be constructed. It is uncertain whether management changes occur as a result of genetic testing in other situations; therefore, it is not possible to conclude that management changes occur that improve outcomes. It is possible that clinicians may intensify treatment following a diagnosis of FH, such as switching to a more potent statin, increasing the statin dose, or by referring to a lipid specialist. However, these types of management changes have not been documented in the literature and have an uncertain impact on health outcomes.

Testing Individuals With a Close Relative With a Diagnosis of Familial Hypercholesterolemia for Future Risk of Disease

There is no direct evidence on the clinical utility of genetic testing for FH. A chain of evidence can provide evidence of clinical utility if all the links in the chain of evidence are intact. The chain of evidence for 2 scenarios requiring prospective testing for FH is laid out below.

Familial hypercholesterolemia 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.

The presence of a pathogenic variant in the family allows for targeted testing in relatives. Targeted testing for a known pathogenic variant has positive and negative predictive values, both approaching 100%. Risk stratification by lipid levels is less accurate because lipid levels for patients with FH overlap with lipid levels for patients with non-FH, and therefore some errors will be made in assigning a diagnosis.

A systematic review (2019) of cascade screening included 6 studies of genetic cascade testing and 4 studies of biochemical testing.[22,] Due to the constraints associated with cascade screening noted below, none of the included studies were conducted in the U.S. 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 6 times larger than cases identified by biochemical testing (2.42 vs. 0.42 cases). Results favoring new case identification with genetic testing were consistent when excluding 1 outlier study (1.37 vs. 0.42 cases).

Miller et al (2022) conducted a pragmatic trial in the United States of cascade testing for FH that used direct contact between the investigators and family members.[23,] Family members of 52 FH probands with a pathogenic variant in *LDLR*, *APOB*, or *PCSK9* were offered genetic testing. Family members of 73 probands without a pathogenic variant were asked to undergo lipid testing. A total of 111 family members of individuals with a pathogenic variant underwent genetic testing, and 48 new cases were identified (43.2% yield; 0.92 new cases per index case; p=.032 and p<.001, respectively compared to the other group). Among the 63 family members of individuals without a pathogenic variant who underwent lipid testing, 17 new cases were identified (27% yield; 0.23 new cases per index case). The cascade testing uptake rate was 43.9% versus 21.4%, respectively (p<.001). The authors concluded that direct contact and coordinated genetic testing may increase cascade testing uptake and yield.

The "Is Family screening Improved by Genetic Testing in FH" ("I FIGhT FH") RCT (2021) conducted in the United States and published after the systematic review compared cascade screening uptake in

adult relatives following proband genetic testing or usual care (lipid testing) for diagnosis of FH.[24,] Of 240 enrolled probands, only 43 relatives enrolled in the trial (0.2 relatives per proband). The trial did not find a difference in cascade screening uptake among relatives whether the proband was diagnosed with FH using genetic testing or usual care (0.2 vs. 0.1 relatives per proband; p=.14) nor was there a difference between group in relatives diagnosed with FH as a results of cascade screening (0.1 vs. 0.1 new cases per index case; p=.27). Results of this study may be limited due to the low participation rate by relatives eligible for cascade screening. In addition, the low rate of FH diagnosis following cascade screening is in contrast to the results in the previously discussed systematic review. However, none of the studies in the systematic review provided a direct comparison of genetic testing with usual care.

Cascade screening for FH has been evaluated in a national screening program from the Netherlands in a large study not included in the systematic review.[25,] 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. 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 widely used in the U.S.

Penetrance for all known pathogenic variants is greater than 90%. Therefore, the presence of a pathogenic variant in an asymptomatic individual indicates a very high likelihood of developing clinical disease.

Familial hypercholesterolemia has a reasonably long presymptomatic phase in which preventive strategies can be implemented. Because the development of atherosclerotic disease is gradual and cumulative, preventive strategies initiated during the presymptomatic phase have the potential to reduce the burden of atherosclerotic disease.

Section Summary: Adults With a Close Relative Who Has a Diagnosis of Familial Hypercholesterolemia

In the first scenario, in which an adult has a close relative with a diagnosis of FH, a chain of evidence cannot be constructed. Following a definitive diagnosis of FH, it is unlikely that management changes will improve outcomes. In adults, treatment of hyperlipidemia is based on LDL levels, and the presence of FH does not affect treatment decisions apart from the LDL level. All patients with FH will have indications for statin treatment, and many will have indications for additional interventions based on the LDL response to statins.

Section Summary: Children With a Close Relative Who Has a Diagnosis of Familial Hypercholesterolemia

In the second scenario, in which a child has a close relative with a diagnosis of FH, a chain of evidence can be constructed. For children, screening for hyperlipidemia will begin at different ages if FH is present in the family,[26,] and treatment with statins will begin earlier than if FH was not diagnosed. For the general population, lipid screening should begin at approximately 10 years of age. However, for children of individuals with FH, screening should begin sooner, and management changes, consisting of lifestyle modifications and/or medications, should begin as soon as possible. Management changes that occur in children are primarily the initiation of effective medications (e.g., statins, PCSK9 inhibitors). A Cochrane meta-analysis by Vuorio et al (2017) found moderate-quality evidence that statins reduce LDL levels in pediatric patients.[27,] These medications are further known to decrease cardiovascular events in adults with hypercholesterolemia; therefore, initiation of these medications in patients at high-risk of atherosclerotic disease will improve outcomes.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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).[28,] 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,[29,] International FH Foundation,[30,] and American Association of Clinical Endocrinologists and American College of Endocrinology.[31,] Guidance from NICE was also included in the review.[32,] 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 (AHA) (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.[33,]

In another scientific statement focused on genetic testing for heritable cardiovascular diseases in children, the AHA (2021) notes the following:[34,] "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)[28,], the American Lipid Association (ALA) issued updated guidance on genetic testing for dyslipidemias, including FH (last updated September 2021).[35,] Recommendations are summarized in Table 2.

Table 2. American Lipid Association Recommendations on Genetic Testing for Familial Hypercholesterolemia

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

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 3).[36,]

Table 3. Familial Hypercholesterolemia Foundation/Journal of the American College of Cardiology Recommendations on Genetic Testing for Familial Hypercholesterolemia

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; GOE: grade of evidence; LDL-C: low-density lipoprotein cholesterol; SOE: strength of evidence.

International Atherosclerosis Society

A 2023 guideline from the International Atherosclerosis Society includes recommendations about genetic testing as part of a best practice approach to managing FH.[37,] All patients with a phenotypic diagnosis or strong suspicion of FH should be offered genetic testing. Testing should include the following genes: *LDLR*, *APOB*, *PCSK9*, and *LDLRAP1*. Cascade testing (consisting of both phenotype and genotype testing) of all close relatives of an index case is recommended, with a focus on the specific variant(s) identified in the index case. Children should receive genetic testing at the earliest opportunity if an FH-causing variant has been identified in a parent or other first-degree relative. Reverse cascade testing (from child to parent) should be offered after a child is found to be a proband. Any potential index case should be confirmed with genetic testing. In all cases, genetic testing should include genetic counseling.

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.[38,] The report contained the following recommendations (see Table 4).

Table 4. National Heart, Lung, and Blood Institute 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: total cholesterol.

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force (2022) published recommendations on statin use for the primary prevention of cardiovascular disease in adults.[39,] This publication did not make specific recommendations for genetic testing for FH.

A Task Force evidence report conducted by Lozano et al (2016), evaluated lipid screening in children and adolescents to detect FH.[40,] 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.

Ongoing and Unpublished Clinical Trials

Some currently ongoing or unpublished trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01960244	Study of Awareness and Detection of Familial Hypercholesterolemia (CASCADE-FH)	5000	Dec 2025
NCT04370899	Early Detection of Familial Hypercholesterolemia in Children (DECOPIN)	400	Jan 2030
Unpublished			
NCT03253432	INTegrating Active Case-finding With Next-generation Sequencing for Diagnosis Through Electronic Medical Records (IN-TANDEM): Familial Hypercholesterolemia Pilot Study	378 (actual)	Nov 2018

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Comorbidities
  - Activity and functional limitations
  - Family history if applicable
  - Reason for procedure/test/device, when applicable
  - Pertinent past procedural and surgical history
  - Past and present diagnostic testing and results
  - Prior conservative treatments, duration, and response
  - Treatment plan (i.e., surgical intervention)
- Consultation and medical clearance report(s), when applicable
- Radiology report(s) and interpretation (i.e., MRI, CT, discogram)
- Laboratory results
- Other pertinent multidisciplinary notes/reports: (e.g., psychological or psychiatric evaluation, physical therapy, multidisciplinary pain management) when applicable

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed
- Procedure report(s)

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	81405	Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
07/01/2016	BCBSA Medical Policy Adoption
08/01/2017	Policy revision without position change
12/01/2017	Policy revision without position change
12/01/2018	Policy revision without position change
12/01/2019	Policy revision without position change
11/01/2025	Policy reactivated. Previously archived from 08/01/2020 to 10/31/2025.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary: Healthcare Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield of California, are: (a) consistent with Blue Shield of California medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the member; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the member's illness, injury, or disease.

Investigational or Experimental: Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

A. The technology must have final approval from the appropriate government regulatory bodies.
   - This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
   - Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
   - The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.

B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
   - The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
   - The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.

C. The technology must improve the net health outcome.
   - The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.

D. The technology must be as beneficial as any established alternatives.
   - The technology should improve the net health outcome as much as, or more than, established alternatives.

E. The improvement must be attainable outside the investigational setting.

- When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** **Blue font: Verbiage Changes/Additions**
Reactivated Policy **Policy Statement:** N/A	**Genetic Testing for Heterozygous Familial Hypercholesterolemia 2.04.139** **Policy Statement:** I. 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 **both** of the following criteria are met: A. 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) B. Alternative treatment considerations are in place for individuals who have an uncertain diagnosis of FH and a negative genetic test II. Genetic testing to confirm a diagnosis of FH is considered **investigational** in all other situations (see Policy Guidelines). III. Genetic testing of adults who are close relatives of individuals with FH to determine future risk of disease is considered **investigational** (see Policy Guidelines). IV. Genetic testing of children of individuals with FH to determine future risk of disease may be considered **medically necessary** when **both** of the following criteria are met (see Policy Guidelines): A. A pathogenic variant is present in a parent B. General lipid screening is not recommended based on age or other factors