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)
- 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
- 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. 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 Criteria. A score of 8 or greater on the Dutch Lipid Clinic criteria is considered definitive FH. Scores between 3 and 7 are considered “possible” or “probable” FH. The latter 2 categories can be considered to represent “uncertain” FH
- Simon-Broome 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 >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 coronary artery disease or total cholesterol of at least 290 mg/dL in a first- or a second-degree relative
- MEDPED (Make Early Diagnosis Prevent Early Death) 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 exists a lack of coordination for patients with different types of medical insurance.

Eligibility for specialty medicines (e.g., PCSK9 inhibitors) may require a definitive diagnosis of FH. The labeled indications for these agents state they are indicated 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**

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

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

**Genetic Counseling**

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further,
Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

**Coding**

Analyses related to this testing are listed under the following CPT tier 2 molecular pathology codes:

- **Under code 81401**: APOB (apolipoprotein B) (e.g., familial hypercholesterolemia type B), common variants (e.g., R3500Q, R3500W)
- **Under code 81405**: LDLR (low density lipoprotein receptor) (e.g., familial hypercholesterolemia), duplication/deletion analysis
- **Under code 81406**: LDLR (low density lipoprotein receptor) (e.g., familial hypercholesterolemia), full gene sequence
- PCSK9 (proprotein convertase subtilisin/kexin type 9) (e.g., familial hypercholesterolemia), full gene sequence

The Ambry Genetics FHNext panel, for example, includes all 4 of the analyses above so it would be reported with codes 81401, 81405, and 2 units of 81406.

**Description**

Familial hypercholesterolemia (FH) is an inherited disorder characterized by markedly elevated low-density lipoprotein levels, physical exam signs of cholesterol deposition, and premature cardiovascular disease. FH 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.

**Related Policies**

- N/A

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the 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 mandates [e.g., Federal Employee Program (FEP)] prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**Regulatory Status**

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

Epidemiology of 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. FH 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 1:1,000,000.1 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.2,3 Some populations, such as Ashkenazi Jews and South Africans, have a higher prevalence of up to 1 in 100.2 For affected individuals, the burden of illness is high. Patients with FH and increased LDL cholesterol (>190 mg/dL) have a three times higher risk of CAD than those with increased LDL cholesterol alone.4 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.3 Increased risk of CAD is associated with a higher rate of death associated with cardiovascular causes in patients with homozygous and heterozygous FH.5

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.6

- Make Early Diagnosis Prevent Early Deaths Program Diagnostic Criteria (MEDPED)
  - 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 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 8 or higher 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 Registry Criteria
  - Using these criteria, a definite diagnosis of FH is made based on total cholesterol 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 CAD 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 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 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 vs statins alone, and reported that cardiovascular events were reduced for patients treated with combination therapy.

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. 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 FH**

FH 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.
  - 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. Characterization of the frequency and spectrum of variants is ongoing.
- The APOB gene accounts for approximately 1% to 5% 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.
  - There are a limited number of variants of this gene, allowing targeted testing.
- The PCSK9 gene accounts for approximately 0% to 3% of FH.
  - 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. 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
This evidence review will address BCBSA genetic testing categories 1a (diagnostic testing of an individual’s germline to benefit the individual) and 3 (testing of an asymptomatic individual to determine future risk of disease) (see Appendix Table 1 for all BCBSA genetic testing categories). Validation of the clinical use of any genetic test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent; (2) clinical validity, which refers to the diagnostic performance of the test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (i.e., 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). The following is a summary of the key findings to date.

Familial Hypercholesterolemia
Clinical Context and Test Purpose
The purpose of genetic testing for familial hypercholesterolemia (FH) is to diagnose patients with homozygous or heterozygous FH.

The questions addressed in this evidence review are: (1) Is there evidence that genetic testing for FH has clinical validity?; and (2) Does genetic testing for FH change patient diagnosis and prognosis in a way that improves outcomes as a result of genetic testing?

The following PICOTS were used to select literature to inform this review.

Patients
The relevant population of interest includes patients within 4 categories. In patients who have signs and 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 comparator of interest is standard clinical workup without genetic testing.

Outcomes
The potential beneficial outcomes of primary interest would be a diagnosis of FH prompting appropriate and timely interventional strategies (e.g., statins, 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 under treatment.

Timing
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.

Setting
Ordering and interpreting genetic testing may be complex and is best done by experienced specialists experienced in lipid disorders. Most patients are likely to be tested in an outpatient setting. Referral for genetic counseling is important for the explanation of genetic disease, heritability, genetic risk, test performance, and possible outcomes.
Analytic Validity
No published evidence on the analytic validity of genetic testing for FH was identified. Kassner et al (2014) reported that the analytic validity is “close to 100%,” but no empirical data were presented or referenced.9

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 1.10-14 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 United States; the remaining studies were conducted in different countries 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 (DLCN) criteria.

The largest cohort, studied by Abul-Husn et al (2016), focused on genetic testing through exome sequencing of 46,321 adults from a single health system.15 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)-C levels (p<0.001) with an increased risk of both general coronary artery disease (CAD; odds ratio [OR], 2.6; p<0.001) and premature CAD (OR=3.7, p<0.001). Weaknesses of this study included 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 the studies in Table 1 ranged from 1% to 66.5%, with 4 studies clustering in the 34.5% to 41.2% range.11-14 Unlike the other studies that included both definite and suspected FH cases, Diakou, which reported a substantially higher sensitivity of 66.5%, only included patients with definite FH. Abul-Husn, which reported a substantially lower sensitivity of 1%, relied on an incomplete medical record for clinical diagnosis of FH. Three studies used the DLCN criteria to categorize individuals as definite, probable, or possible FH.11,13,15 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 2011 Diakou 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%-29.5%).10

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 low-density lipoprotein (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 method for making a clinical diagnosis; it is also important to note that 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 been reported in large cohort studies for these tests, as of yet.16
Table 1. Clinical Validity of Genetic Testing for FH

<table>
<thead>
<tr>
<th>Study (Year)</th>
<th>Location</th>
<th>N</th>
<th>Genes Tested (Variants)</th>
<th>Sensitivity for FH</th>
<th>Specificity for FH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Definite Probable Possible Overall</td>
<td></td>
</tr>
<tr>
<td>Diakou (2011)</td>
<td>Greece</td>
<td>254</td>
<td>LDLR (n=10) APOB (n=1) PCSK9 (n=1) ARH (n=1)</td>
<td>66.5% (169/254) a</td>
<td>– – 66.5% (169/254) a 100% (40/40)</td>
</tr>
<tr>
<td>Hooper (2012)</td>
<td>Australia</td>
<td>343</td>
<td>LDLR (n=18) APOB (n=2) PCSK9 (n=1)</td>
<td>70.3% (90/128) 29.5% (26/88) 10.8% (12/111)</td>
<td>– – 37.3% (128/343) –</td>
</tr>
<tr>
<td>Palacios (2012)</td>
<td>Spain</td>
<td>5430</td>
<td>LDLR (any) APOB (n=1) PCSK9 (n=4)</td>
<td>– – –</td>
<td>41.4% (2246/5430) –</td>
</tr>
<tr>
<td>Taylor (2010)</td>
<td>U.K.</td>
<td>635</td>
<td>LDLR (n=18) APOB (n=1) PCSK9 (n=1)</td>
<td>56.3% (107/190) – 28.4% (112/394)</td>
<td>34.5% (219/635) –</td>
</tr>
<tr>
<td>Tichy (2012)</td>
<td>Czech Republic</td>
<td>2239</td>
<td>LDLR (any) APOB (n=1)</td>
<td>– – –</td>
<td>35.7% (800/2239) –</td>
</tr>
<tr>
<td>Abul-Husn (2016)</td>
<td>U.S. 50,726</td>
<td>6</td>
<td>LDLR (n=29) APOB (n=2) PCSK9 (n=4)</td>
<td>30.2% (16/53) a 7.0% (35/497) 1.2% (68/5465)</td>
<td>2.0% (119/6015) 99.8% (40,174/40,270)</td>
</tr>
</tbody>
</table>

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. Six moderate-to-large cohorts were reviewed, from the United States and Europe. A wide range of clinical sensitivity was reported (range, 2%-66.5%). The sensitivity is higher in patients with definite FH (range, 30%-70%). In patients with probable or possible FH, the sensitivity is low (range, 1.2%-30%). Two studies reported clinical specificity (range, 99.8%-100%).

Clinical Utility

Diagnostic Testing

There is no direct evidence on the clinical utility of genetic testing for FH. An indirect chain of evidence is thus constructed and can provide evidence of clinical utility if all the links in the chain of evidence are intact. The chain of evidence for two scenarios requiring diagnostic testing for FH is laid out below.

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.

FH 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. 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: FH Testing for Those 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 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.\(^{17,18}\)

**Section Summary: FH Testing for Those 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 referral 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 for Future Risk of Disease**

There is no direct evidence on the clinical utility of genetic testing for FH. A chain of evidence is thus constructed and 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 are laid out below.

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.

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.

Cascade screening for FH has been evaluated in a national screening program from the Netherlands.\(^{19}\) 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 used in the United States.
Penetrance for all of the 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.

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

Section Summary: Adults with a Close Relative Who Has a Diagnosis of FH
In the first scenario, in which an adult has a close relative with a diagnosis of FH, a sufficient 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 FH
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, 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 were able to reduce LDL levels in pediatric patients. These medications are further known to decrease cardiovascular events in adult patients with hypercholesterolemia; therefore, initiation of these medications in patients at high risk of atherosclerotic disease will improve outcomes.

Section Summary: Clinical Utility
There is a lack of direct evidence for clinical utility; as a result, specific 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 are intact, and clinical utility is demonstrated. In other situations, there are gaps in the chain of 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.

For testing individuals to determine future risk of disease, in adults there are gaps in the chain of indirect evidence that preclude conclusions on clinical utility. Genetic testing is superior to standard risk stratification, but treatment decisions are made primarily on LDL levels, and the establishment of definite FH will not change treatment recommendations. For children, a chain of evidence establishes that clinical utility is present. Screening will begin at different ages for children at risk for FH compared with the general population, and treatment with statins will be initiated earlier once a diagnosis of FH is made. Therefore, for children of individuals with a known pathogenic variant in the family, targeted genetic testing will improve outcomes.

Summary of Evidence
For individuals who have signs and/or symptoms of FH when a definitive diagnosis is required to establish eligibility for specialty medications or 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 accuracy and validity, other test performance measures, symptoms, change in disease status, and morbid events. No published empirical 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 for clinical utility is lacking. The clinical utility of genetic testing was evaluated through 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., 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 a meaningful improvement in the net health outcome.

- All other situations. Clinical utility of testing for diagnosis cannot be demonstrated through a chain of evidence in other situations. 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 the effects of the technology on health outcomes.

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 case series and cross-sectional studies. Relevant outcomes include test accuracy and validity, other test performance measures, symptoms, change in disease status, and morbid events. No published empirical 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 for clinical utility is lacking. Clinical utility was evaluated through 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 levels and will not differ for patients with a diagnosis of FH. The evidence is insufficient to determine the effects of the technology on health outcomes.

- 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 a meaningful improvement in the net health outcome.
Supplemental Information
Practice Guidelines and Position Statements

National Lipid Association Expert Panel
Recommendations on the diagnosis and screening for familial hypercholesterolemia (FH) were developed by the National Lipid Association Expert Panel on Familial Hypercholesterolemia and published in 2011.22 The following recommendations relevant to genetic testing were included:

• "Formal clinical diagnosis of FH can be made by applying any one of several validated sets of criteria [U.S. Make Early Diagnosis Prevent Early Death (MEDPED), Dutch Lipid Clinic Network, Simon-Broome Registry]. It should be noted that LDL [low-density lipoprotein] cholesterol cut points usually vary with age…
• Genetic screening for FH is generally not needed for diagnosis or clinical management but may be useful when diagnosis is uncertain.
• Identification of a causal mutation may provide additional motivation for some patients to implement appropriate treatment.
• Importantly, a negative genetic test does not exclude FH, since approximately 20% of clinically definite FH patients will not be found to have a mutation despite an exhaustive search using current methods…
• Cascade screening involves testing lipid levels in all first-degree relatives of diagnosed FH patients.
• As cascade screening proceeds, newly identified FH cases provide additional relatives who should be considered for screening.
• Cascade screening is the most cost-effective means of finding previously undiagnosed FH patients and is also cost-effective in terms of cost per year of life saved. General population screening of a young population (before age 16) is similarly cost-effective in terms of cost per year of life saved, given that effective cholesterol treatment is begun in all those identified."

American College of Cardiology and American Heart Association
The American College of Cardiology and American Heart Association released recommendations on the treatment of blood cholesterol to reduce atherosclerotic disease in adults (follow-up report to Adult Treatment Recommendations from the National Cholesterol Education Panel) in 2013.23 These recommendations did not mention genetic testing. Treatment recommendations were based on LDL levels and clinical factors, and there were no separate treatment recommendations for individuals with FH.

National Heart, Lung, and Blood Institute
Recommendations from an expert panel on cardiovascular health and risk reduction in children and adolescents were published in 2011.20 The report contained the following recommendations (see Table 2).

Table 2. Recommendations on Cardiovascular Health and Risk Reduction in Children and Adolescents

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>GOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>“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.”</td>
<td>B</td>
</tr>
<tr>
<td>“TC and LDL-C levels fall as much as 10-20% or more during puberty.”</td>
<td>B</td>
</tr>
<tr>
<td>“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.”</td>
<td>D</td>
</tr>
</tbody>
</table>

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 published recommendations on lipid disorders in adults in 2008, which was archived in 2014. This publication did not make specific recommendations for genetic testing for FH.

An evidence review on lipid screening in children and adolescents to detect familial hypercholesterolemia was published in 2016. This report stated that genetic screening for FH is beyond the scope of the report. Further, it stated that “because implementing this approach [cascade screening] in the United States 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 unpublished trials that might influence this review are listed in Table 3.

Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>Study to Assess the Tolerability and Efficacy of Anacetrapib Co-administered With Statin in Participants With Heterozygous Familial Hypercholesterolemia (MK-0859-020) (REALIZE)</td>
<td>306</td>
<td>Oct 2018</td>
</tr>
<tr>
<td>NCT03253432</td>
<td>IN-TANDEM Familial Hypercholesterolemia Pilot Study</td>
<td>400</td>
<td>Dec 2018</td>
</tr>
<tr>
<td>NCT01960244</td>
<td>Study of Awareness and Detection of Familial Hypercholesterolemia (CASCADE-FH)</td>
<td>5000</td>
<td>Oct 2020</td>
</tr>
</tbody>
</table>

NCT: National Clinical Trial.

Appendix
Appendix Table 1. Categories of Genetic Testing Addressed in 2.04.139

<table>
<thead>
<tr>
<th>Category</th>
<th>Addressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Testing of an affected individual’s germline to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>1a. Diagnostic</td>
<td>X</td>
</tr>
<tr>
<td>1b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>1c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>2. Testing cancer cells from an affected individual to benefit the individual</td>
<td></td>
</tr>
<tr>
<td>2a. Diagnostic</td>
<td></td>
</tr>
<tr>
<td>2b. Prognostic</td>
<td></td>
</tr>
<tr>
<td>2c. Therapeutic</td>
<td></td>
</tr>
<tr>
<td>3. Testing an asymptomatic individual to determine future risk of disease</td>
<td>X</td>
</tr>
<tr>
<td>4. Testing of an affected individual’s germline to benefit family members</td>
<td></td>
</tr>
<tr>
<td>5. Reproductive testing</td>
<td></td>
</tr>
<tr>
<td>5a. Carrier testing: preconception</td>
<td></td>
</tr>
<tr>
<td>5b. Carrier testing: prenatal</td>
<td></td>
</tr>
<tr>
<td>5c. In utero testing: aneuploidy</td>
<td></td>
</tr>
<tr>
<td>5d. In utero testing: familial variants</td>
<td></td>
</tr>
<tr>
<td>5e. In utero testing: other</td>
<td></td>
</tr>
<tr>
<td>5f. Preimplantation testing with in vitro fertilization</td>
<td></td>
</tr>
</tbody>
</table>


**Documentation for Clinical Review**

Please provide the following documentation (if/when requested):

- 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**

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

**Coding**

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or
when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT®</td>
<td>81401</td>
<td>Molecular pathology procedure level 2</td>
</tr>
<tr>
<td></td>
<td>81405</td>
<td>Molecular pathology procedure level 6</td>
</tr>
<tr>
<td></td>
<td>81406</td>
<td>Molecular pathology procedure level 7</td>
</tr>
</tbody>
</table>

HCPCS None

ICD-10 Procedure None

ICD-10 Diagnosis All Diagnoses

**Policy History**

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

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>07/01/2016</td>
<td>BCBSA Medical Policy Adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>08/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>12/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

**Definitions of Decision Determinations**

**Medically Necessary:** A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. 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 contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.