BlueCross BlueShield of Alabama

Name of Policy:
Genetic Testing for Heterozygous Familial Hypercholesterolemia

Policy #: 701	Latest Review Date: October 2018
Category: Laboratory	Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *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 that patient's illness, injury or disease.*

Description of Procedure or Service:

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.

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 1:160000 and 1:1000000. 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. Some populations, such as Ashkenazi Jews and South Africans, have a higher prevalence of up to 1 in 100. 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. 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. Increased risk of CAD is associated with a higher rate of death associated with cardiovascular causes in patients with homozygous and heterozygous FH.

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.

- 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. (See medical policy *#103 – Lipid Apheresis* for additional information)

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.[1]
    - 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.

Policy:

Genetic testing to confirm a diagnosis of familial hypercholesterolemia (FH) meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage **when a definitive diagnosis is required as an eligibility criterion for specialty medications (e.g., PCSK9 inhibitors)**.

Genetic testing to confirm a diagnosis of heterozygous FH does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage **for all other situations** and is considered **investigational**.

Genetic testing of adults who are close relatives of individuals with FH to determine future risk of disease does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational**.

Genetic testing of children of individuals with FH to determine future risk of disease meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage when **BOTH** of the following criteria are met:

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

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature update was performed through August 6, 2018.

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 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 four categories. In patients who have signs and symptoms of FH, diagnostic testing may occur in two 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 two 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.

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.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

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).

A number of larger studies have assessed clinical validity and are shown in Table 1. 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 Western Europe. All studies reported clinical sensitivity, and two studies reported on clinical specificity. In some cases, the analysis was stratified by the clinical likelihood of FH prior to genetic testing using the Dutch Lipid Clinic Network criteria.

In addition, 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. 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 *LDR*, *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 four studies clustering in the 34.5% to 41.2% range. 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. 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%).

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.

Table 1. Clinical Validity of Genetic Testing for FH

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

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

Section Summary: Clinical Validity

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

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.

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 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.

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 with a Close Relative with a Diagnosis of FH 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 two scenarios requiring prospective 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.

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. 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 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 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.

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 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 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 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 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 satins as early as possible. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

Practice Guidelines and Position Statements

Migliara et al (2017) conducted a systematic review of guidelines on genetic testing and patient management of individuals with familial hypercholesterolemia (FH). The literature search, conducted through April 2017, identified 10 guidelines for inclusion. Three of the guidelines were developed within the United States: those by the National Lipid Association, International FH Foundation, and American Association of Clinical Endocrinologists and American College of Endocrinology. Guidance from the National Institute for Health and Care Excellence was also included in the review. 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.

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. The report contained the following recommendations (see Table 2).

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

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

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

U.S. Preventive Services Task Force Recommendations

The U.S. Preventive Services Task Force 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."

Key Words:

Familial Hypercholesterolemia, FH, high cholesterol, genetic testing, heterozygous hypercholesterolemia, heterozygous FH, *PCSK9*

Approved by Governing Bodies:

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.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

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) – includes *APOB* (apolipoprotein B) (e.g., familial hypercholesterolemia type B), common variants (e.g., R3500Q, R3500W)
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) – includes *LDLR* (low density lipoprotein receptor) (e.g., familial hypercholesterolemia), duplication/deletion 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, cytogenomic array analysis for neoplasia) – includes *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 four of the analyses above so it would be reported with codes 81401, 81405, and 2 units of 81406.

References:

1. Abul-Husn NS, Manickam K, Jones LK, et al. Genetic identification of familial hypercholesterolemia within a single U.S. health care system. Science. Dec 23 2016; 354(6319).
2. Bilen O, Pokharel Y, Ballantyne CM. Genetic testing in hyperlipidemia. Endocrinol Metab Clin North Am. Mar 2016; 45(1):129-140.
3. Bouhairie VE, Goldberg AC. Familial hypercholesterolemia. Endocrinol Metab Clin North Am. Mar 2016; 45(1):1-16.
4. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. Jun 18 2015; 372(25):2387-2397.

5. Chiou KR, Charng MJ. Genetic diagnosis of familial hypercholesterolemia in Han Chinese. J Clin Lipidol. May-Jun 2016; 10(3):490-496.
6. Descamps OS, Tenoutasse S, Stephenne X, et al. Management of familial hypercholesterolemia in children and young adults: consensus paper developed by a panel of lipidologists, cardiologists, paediatricians, nutritionists, gastroenterologists, general practitioners and a patient organization. Atherosclerosis. Oct 2011;218(2):272-280.
7. Diakou M, Miltiadous G, Xenophontos SL, et al. Spectrum of LDLR gene mutations, including a novel mutation causing familial hypercholesterolaemia, in North-western Greece. Eur J Intern Med. Oct 2011; 22(5):e55-59.
8. Hooper AJ, Nguyen LT, Burnett JR, et al. Genetic analysis of familial hypercholesterolaemia in Western Australia. Atherosclerosis. Oct 2012; 224(2):430-434.
9. Hopkins PN, Toth PP, Ballantyne CM, et al. Familial hypercholesterolemias: prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. J Clin Lipidol. Jun 2011; 5(3 Suppl):S9-17.
10. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for management of dyslipidemia and prevention of cardiovascular disease - executive summary. Endocr Pract. Apr 2 2017; 23(4):479-497.
11. Khera AV, Won HH, Peloso GM, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. J Am Coll Cardiol. Jun 07 2016; 67(22):2578-2589.
12. Kassner U, Wuhle-Demuth M, Missala I, et al. Clinical utility gene card for: hyperlipoproteinemia, TYPE II. Eur J Hum Genet. Jul 2014; 22(7).
13. Leren TP. Cascade genetic screening for familial hypercholesterolemia. Clin Genet. Dec 2004; 66(6):483-487.
14. Lozano P, Henrikson NB, Dunn J, et al. Lipid screening in childhood and adolescence for detection of familial hypercholesterolemia: evidence report and systematic review for the US Preventive Services Task Force. JAMA. Aug 09 2016; 316(6):645-655.
15. Migliara G, Baccolini V, Rosso A, et al. Familial hypercholesterolemia: a systematic review of guidelines on genetic testing and patient management. Front Public Health. Oct 2017;5: 252.
16. Mundal L, Igland J, Ose L, et al. Cardiovascular disease mortality in patients with genetically verified familial hypercholesterolemia in Norway during 1992-2013. Eur J Prev Cardiol. Jan 2017; 24(2):137-144.
17. National Heart Lung and Blood Institute. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. n.d.; www.nhlbi.nih.gov/health-pro/guidelines/current/cardiovascular-health-pediatric-guidelines/summary#chap9. Accessed October 9, 2017.
18. Palacios L, Grandoso L, Cuevas N, et al. Molecular characterization of familial hypercholesterolemia in Spain. Atherosclerosis. Mar 2012; 221(1):137-142.
19. Patel RS, Scopelliti EM, Savelloni J. Therapeutic management of familial hypercholesterolemia: current and emerging drug therapies. Pharmacotherapy. Dec 2015; 35(12):1189-1203.
20. Robinson JG, Farnier M, Krempf M, et al. Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med. Apr 16 2015; 372(16):1489-1499.

21. Sabatine MS, Giugliano RP, Wiviott SD, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med. Apr 16 2015; 372(16):1500-1509.
22. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. Jul 1 2014; 63(25 Pt B):2889-2934.
23. Taylor A, Wang D, Patel K, et al. Mutation detection rate and spectrum in familial hypercholesterolaemia patients in the UK pilot cascade project. Clin Genet. Jun 2010; 77(6):572-580.
24. Tichy L, Freiberger T, Zapletalova P, et al. The molecular basis of familial hypercholesterolemia in the Czech Republic: spectrum of LDLR mutations and genotype-phenotype correlations. Atherosclerosis. Aug 2012; 223(2):401-408.
25. US Preventive Services Task Force (USPSTF). Final Recommendation Statement: Lipid Disorders in Adults (Cholesterol, Dyslipdemia): Screening. 2014; www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/lipid-disorders-in-adults-cholesterol-dyslipidemia-screening. Accessed October 9, 2017.
26. Vuorio A, Kuoppala J, Kovanen PT, et al. Statins for children with familial hypercholesterolemia. Cochrane Database Syst Rev. Jul 07 2017; 7:CD006401
27. Wang J, Dron JS, Ban MR, et al. Polygenic versus monogenic causes of hypercholesterolemia ascertained clinically. Arterioscler Thromb Vasc Biol. Dec 2016; 36(12):2439-2445.
28. Watts GF, Gidding S, Wierzbicki AS, et al. Integrated guidance on the care of familial hypercholesterolaemia from the International FH Foundation: executive summary. J Atheroscler Thromb. 2014;21(4):368-374.
29. Youngblom E, Knowles JW. Familial Hypercholesterolemia. In: Adam MP, Ardinger HH, Pagon RA, et al., eds. GeneReviews(R). Seattle, WA: University of Washington; 2014.

Policy History:

Medical Policy Panel, October 2017
Medical Policy Group, January 2018 **(3)**: New policy addressing genetic testing specific to heterozygous familial hypercholesterolemia
Medical Policy Administration Committee, February 2018
Available for comment January 20 through March 5, 2018
Medical Policy Panel, October 2018
Medical Policy Group, October 2018 **(9):** 2018 updates to key points, description, references. No changes to policy statement.