



Louisiana

Genetic Testing for Heterozygous Familial Hypercholesterolemia

Policy # 00510

Original Effective Date: 07/20/2016

Current Effective Date: 07/11/2018

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider genetic testing to confirm a diagnosis of familial hypercholesterolemia (FH) to be **eligible for coverage** when a definitive diagnosis is required as an eligibility criterion for specialty medications.

Patient Selection Criteria

Coverage eligibility for genetic testing to confirm a diagnosis of familial hypercholesterolemia (FH) will be met when:

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

Based on review of available data, the Company may consider genetic testing of children of individuals with familial hypercholesterolemia (FH) to determine future risk of disease to be **eligible for coverage**.

Patient Selection Criteria

Coverage eligibility for testing of children of individuals with familial hypercholesterolemia (FH) will be met when:

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

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

The use of genetic testing to confirm a diagnosis of familial hypercholesterolemia (FH) when patient selection criteria are not met is considered to be **investigational**.*

The use of Genetic testing to determine future risk of disease in children of individuals with familial hypercholesterolemia (FH) when patient selection criteria are not met is considered to be **investigational**.*

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Heterozygous Familial Hypercholesterolemia

Policy # 00510

Original Effective Date: 07/20/2016

Current Effective Date: 07/11/2018

Genetic testing in adults who are close relatives of individuals with familial hypercholesterolemia (FH) to determine future risk of disease is considered to be **investigational**.*

Policy Guidelines

The definition of an “uncertain” diagnosis of FH is not standardized. However, available diagnostic tools provide guidance on when a diagnosis is and is not definitive. 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, as follows:

- 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 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 mutation in the family, it is necessary to test an index case to determine mutation status. Coverage of testing an index case to benefit family members depends on contract benefit language.

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, or 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 lack of an infrastructure to identify all individuals in the cascade and a lack of coordination for patients with different types of medical insurance. Eligibility for specialty medicines (eg, 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 Food and Drug Administration (FDA) approval of these

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Heterozygous Familial Hypercholesterolemia

Policy # 00510
 Original Effective Date: 07/20/2016
 Current Effective Date: 07/11/2018

inhibitors, having a diagnosis of FH was 1 eligibility criterion. The diagnosis in these trials was based on clinical factors with or without genetic testing.

GENETICS NOMENCLATURE UPDATE

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

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

Table PG1. Nomenclature to Report on Variants Found in DNA

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

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

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

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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Heterozygous Familial Hypercholesterolemia

Policy # 00510

Original Effective Date: 07/20/2016

Current Effective Date: 07/11/2018

Background/Overview

EPIDEMIOLOGY OF 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. 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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Heterozygous Familial Hypercholesterolemia

Policy # 00510

Original Effective Date: 07/20/2016

Current Effective Date: 07/11/2018

- 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 (ie, 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 (eg, 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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Heterozygous Familial Hypercholesterolemia

Policy # 00510

Original Effective Date: 07/20/2016

Current Effective Date: 07/11/2018

- 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.

FDA or Other Governmental Regulatory Approval **U.S. Food and Drug Administration (FDA)**

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. FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)

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

Rationale/Source

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 (ie, 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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Heterozygous Familial Hypercholesterolemia

Policy # 00510

Original Effective Date: 07/20/2016

Current Effective Date: 07/11/2018

FAMILIAL HYPERCHOLESTEROLEMIA

Clinical Context and Test Purpose

The purpose of genetic testing for 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 (eg, 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 undertreatment.

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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Heterozygous Familial Hypercholesterolemia

Policy # 00510

Original Effective Date: 07/20/2016

Current Effective Date: 07/11/2018

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.

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. 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. 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 LDL-C levels ($p < 0.001$) with an increased risk of both general 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. 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

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Genetic Testing for Heterozygous Familial Hypercholesterolemia

Policy # 00510

Original Effective Date: 07/20/2016

Current Effective Date: 07/11/2018

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 (ie, *STAP1*), and on copy number variation. Sensitivity and specificity have not been reported in large cohort studies for these tests, as of yet.

Table 1. Clinical Validity of Genetic Testing for FH

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

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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Heterozygous Familial Hypercholesterolemia

Policy # 00510

Original Effective Date: 07/20/2016

Current Effective Date: 07/11/2018

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 (eg, 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 (eg, 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 (eg, 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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Heterozygous Familial Hypercholesterolemia

Policy # 00510

Original Effective Date: 07/20/2016

Current Effective Date: 07/11/2018

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. 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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Heterozygous Familial Hypercholesterolemia

Policy # 00510

Original Effective Date: 07/20/2016

Current Effective Date: 07/11/2018

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 (eg, 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%.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Heterozygous Familial Hypercholesterolemia

Policy # 00510

Original Effective Date: 07/20/2016

Current Effective Date: 07/11/2018

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 (eg, PCSK9 inhibitors) have known efficacy in patients with FH and uncontrolled lipid levels despite treatment with statins and/or other medications. The evidence is sufficient to determine that the technology results in 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.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Heterozygous Familial Hypercholesterolemia

Policy # 00510

Original Effective Date: 07/20/2016

Current Effective Date: 07/11/2018

- 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.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Genetic Testing for Heterozygous Familial Hypercholesterolemia", Policy 2.04.139, 10:2017.
2. Youngblom E, Knowles JW. Familial Hypercholesterolemia. In: Pagon RA, Adam MP, Ardinger HH, et al., eds. GeneReviews(R). Seattle (WA)2014.
3. Bouhairie VE, Goldberg AC. Familial hypercholesterolemia. *Endocrinol Metab Clin North Am*. Mar 2016;45(1):1-16. PMID 26892994
4. Patel RS, Scopelliti EM, Savelloni J. Therapeutic management of familial hypercholesterolemia: current and emerging drug therapies. *Pharmacotherapy*. Dec 2015;35(12):1189-1203. PMID 26684558
5. Bilen O, Pokharel Y, Ballantyne CM. Genetic testing in hyperlipidemia. *Endocrinol Metab Clin North Am*. Mar 2016;45(1):129-140. PMID 26893002
6. 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. PMID 26039521
7. 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). PMID 24253857
8. Diakou M, Miltiadous G, Xenophontos SL, et al. Spectrum of LDLR gene mutations, including a novel mutation causing familial hypercholesterolaemia, in North-western Greece. *Eur J Intern Med*. Oct 2011;22(5):e55-59. PMID 21925044
9. Hooper AJ, Nguyen LT, Burnett JR, et al. Genetic analysis of familial hypercholesterolaemia in Western Australia. *Atherosclerosis*. Oct 2012;224(2):430-434. PMID 22883975
10. Palacios L, Grandoso L, Cuevas N, et al. Molecular characterization of familial hypercholesterolemia in Spain. *Atherosclerosis*. Mar 2012;221(1):137-142. PMID 22244043
11. Taylor A, Wang D, Patel K, et al. Mutation detection rate and spectrum in familial hypercholesterolaemia patients in the UK pilot cascade project. *Clin Genet*. Jun 2010;77(6):572-580. PMID 20236128
12. Tichy L, Freiburger 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. PMID 22698793
13. 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. PMID 25773607
14. 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. PMID 25773378
15. Leren TP. Cascade genetic screening for familial hypercholesterolemia. *Clin Genet*. Dec 2004;66(6):483-487. PMID 15521974
16. National Heart, Lung and Blood Institute., Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. <http://www.nhlbi.nih.gov/health-pro/guidelines/current/cardiovascular-health-pediatric-guidelines/summary#chap9>. Accessed 04/05/16.
17. 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. PMID 21600530
18. 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. PMID 24239923
19. U. S. Preventive Services Task Force (USPSTF). Lipid Disorders in Adults: Screening. US Preventive Services Task Force Program 2008; www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/lipid-disorders-in-adults-cholesterol-dyslipidemia-screening. Accessed March 22, 2016.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Heterozygous Familial Hypercholesterolemia

Policy # 00510
 Original Effective Date: 07/20/2016
 Current Effective Date: 07/11/2018

20. Lozano P, Henrikson NB, Dunn J, et al. Lipid Screening in Children and Adolescents for Detection of Familial Hypercholesterolemia: A systematic evidence review for the US Preventive Services Task Force (Draft Review). US Preventive Services Task Force Publication 2016; www.uspreventiveservicestaskforce.org/Page/Document/draft-evidence-review/lipid-disorders-in-children-screening1. Accessed March 22, 2016.
21. 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). PMID 28008010
22. Vuorio A, Kuoppala J, Kovanen PT, et al. Statins for children with familial hypercholesterolemia. *Cochrane Database Syst Rev*. Jul 07 2017;7:CD006401. PMID 28685504

Policy History

Original Effective Date: 07/20/2016
 Current Effective Date: 07/11/2018
 06/30/2016 Medical Policy Committee review
 07/20/2016 Medical Policy Implementation Committee approval. New Policy
 01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
 07/06/2017 Medical Policy Committee review
 07/19/2017 Medical Policy Implementation Committee approval. No change to coverage
 07/05/2018 Medical Policy Committee review
 07/11/2018 Medical Policy Implementation Committee approval. No change to coverage
 Next Scheduled Review Date: 07/2019

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT[®]), copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81401, 81405, 81406
HCPCS	No codes
ICD-10 Diagnosis	E78.00, E78.01, Z13.6, Z13.79, Z84.81, Z83.42

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.



Louisiana

Genetic Testing for Heterozygous Familial Hypercholesterolemia

Policy # 00510

Original Effective Date: 07/20/2016

Current Effective Date: 07/11/2018

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

**Medically Necessary (or “Medical Necessity”) - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

- A. In accordance with nationally accepted standards of medical practice;
- B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
- C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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.

For these purposes, “nationally accepted standards of medical practice” means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

©2018 Blue Cross and Blue Shield of Louisiana

Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross and Blue Shield Association and incorporated as Louisiana Health Service & Indemnity Company.

No part of this publication may be reproduced, stored in a retrieval system, or transmitted, in any form or by any means, electronic, mechanical, photocopying, or otherwise, without permission from Blue Cross and Blue Shield of Louisiana.