Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: Genetic Testing for Heterozygous Familial Hypercholesterolemia

Description/Background

FAMILIAL HYPERCHOLESTEROLEMIA

Familial hypercholesterolemia (FH) is an inherited disorder characterized by markedly elevated low-density lipoprotein (LDL) levels, physical exam signs of cholesterol deposition, and premature cardiovascular disease. 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.(2) Individuals with homozygous FH have extreme elevations of LDL, develop coronary artery disease (CAD) in the second or third decade, and are generally diagnosed easily.

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

Diagnosis

The diagnosis of FH relies on elevated LDL levels in conjunction with a family history of premature CAD and physical exam signs of cholesterol deposition. There is wide variability in cholesterol levels for patients with FH, and considerable overlap in levels between patients with FH and patients with non-FH. Physical exam findings can include tendinous xanthomas,

xanthelasma, and corneal arcus, but these are not often helpful in making a diagnosis. Xanthelasma and corneal arcus are common in the elderly population and therefore not specific. Tendinous xanthomas are relatively specific for FH but are not sensitive findings. They occur mostly in patients with higher LDL levels and treatment with statins likely delays or prevents the development of xanthomas.

Because of the variable cholesterol levels, and the low sensitivity of physical exam findings, there are a considerable number of patients in whom the diagnosis is uncertain. For these individuals, there are a number of formal diagnostic tools for determining the likelihood of FH.(1,8)

- Make Early Diagnosis Prevent Early Deaths 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 higher than 8 and probable FH when the score is 6 to 8.
    - The diagnosis can be made with or without genetic testing. A positive genetic test is given 8 points, which is the highest for any criterion and indicates that a positive genetic test alone is sufficient to make a definitive diagnosis.
- Simon-Broome 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 myocardial infarction or a family history of total cholesterol 290 mg/dL or higher in a first- or a second-degree relative.

Treatment

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

As with other forms of hypercholesterolemia, statins are the mainstay of treatment for FH. However, because of the degree of elevated LDL in many patients with FH, statins will not be sufficient to achieve target lipid levels. Additional medications can be used in these patients. Ezetimibe inhibits the absorption of cholesterol from the gastrointestinal tract and is effective for reducing LDL levels by up to 25% in patients already on statins.(4) The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial randomized patients with 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.(9)

The proprotein convertase subtilisin/kexin type 9 (*PCSK9*) inhibitors are the most recently approved drugs for hyperlipidemia. These medications have potent LDL-lowering properties and have been tested in patients with FH.(4,10) When added to statins, these drugs can result in additional LDL reduction of 30% to 70% and have been reported to reduce the incidence of nonfatal myocardial infarction.(4,10) Other anti-lipid medications (e.g., bile acid sequestrants, niacin) are effective at reducing LDL levels but have not demonstrated efficacy in reducing cardiovascular events when added to statins. For patients who continue to have elevated LDL levels despite maximum medical treatment, lipid apheresis is an option.

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

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

Regulatory Status

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

Medical Policy Statement

The effectiveness and clinical utility of genetic testing to confirm a diagnosis or future risk of familial hypercholesterolemia have been established. It may be considered a useful diagnostic option when indicated.

Inclusionary and Exclusionary Guidelines

Inclusions: (see Policy Guidelines for clarification)
Genetic testing to confirm a diagnosis of familial hypercholesterolemia (FH) when **ALL** of the following are met:

- A definitive diagnosis is required as an eligibility criterion for specialty medications
- The individual is in an uncertain category according to clinical criteria (personal and family history, physical exam, lipid levels). *See examples provided in Policy Guideline section.*
    - ALL of the following apply:
        - FH is suspected and evaluated against standardized diagnostic criteria
        - Criteria for a definite diagnosis are NOT met
- Alternative treatment considerations are in place for individuals who have an uncertain diagnosis of FH and a negative genetic test

Genetic testing to determine future risk of familial hypercholesterolemia when **ALL** of the following are met:

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

Exclusions:

- Genetic testing to confirm diagnosis of heterozygous FH for all other situations not listed above
- Genetic testing of adults who are close relatives of individuals with FH to determine future risk, other than the above

Policy Guidelines:

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

This policy applies only to testing of individuals with uncertain diagnosis of familial hypercholesterolemia (FH) and thereby are unlikely to have homozygous variants in genes transmitted in autosomal dominant fashion. Testing individuals with severe presentation at high risk of homozygous variants maybe necessary for guiding testing and management of unaffected relatives. That is, when there is a clinical diagnosis of FH but no known pathogenic variant in the family, it is necessary to test an index case to determine variant status.

The definition of an “uncertain” diagnosis of familial hypercholesterolemia (FH) is not standardized. However, available diagnostic tools provide guidance on when a diagnosis is

and is not definitive. When FH is suspected and evaluated against standardized diagnostic criteria, it can be interpreted that the individual is in an “uncertain” category when criteria for a definitive diagnosis are not met. Here are some examples of certain criteria not being met:

- Dutch Lipid Clinic Criteria. A score of greater than 8 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 myocardial infarction or total cholesterol of at least 290 mg/dL in a first- or a second-degree relative.
- Make Early Diagnosis Prevent Early Death (MEDPED) Diagnostic Criteria. These criteria provide a yes/no answer for whether an individual has FH, based on family history, age, and cholesterol levels. An individual who meets criteria for FH can be considered to have definitive FH; however, there is no “possible” or “probable” category that allows assignment of an “uncertain” category.

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

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

GENETICS NOMENCLATURE UPDATE

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

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

Table PG1. Nomenclature to Report on Variants Found in DNA

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

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

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

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

GENETIC COUNSELING

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.

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81401 81405 81406

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

FAMILIAL HYPERCHOLESTEROLEMIA

Clinical Context and Test Purpose

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

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

Populations

The relevant population of interest are 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 following practice is currently being used to make decisions about managing FH: standard clinical workup without genetic testing.

Outcomes

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

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

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

Study Selection Criteria

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

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

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

Review of Evidence
A number of larger studies have assessed clinical validity and are shown in Table 1.(12-16) These cohorts included sample sizes ranging from 254 to 6015 patients with definite or suspected FH. The largest and most recent of these studies was conducted in the United States; the remaining studies were conducted in different countries 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 exome sequencing of 46,321 adults from a single health system.(17) The test had low sensitivity (2%) and high specificity (99%), complicated by reliance on an incomplete electronic medical record for retrospective clinical diagnosis by the Dutch Lipid Clinic Network diagnostic criteria. This study also revealed that of the 215 patients found to have genetic variants in the *LDLR*, *PCSK9*, and *APOB* genes, only 25% met criteria for a clinical diagnosis of FH. Patients with relevant variants had higher low-density lipoprotein (LDL)–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.(14-17) Unlike the other studies that included both definite and suspected FH cases, Diakou et al (2011), who reported a substantially higher sensitivity of 66.5%, only included patients with definite FH.(12) Abul-Husn et al (2016), who reported a substantially lower sensitivity of 1%, relied on an incomplete medical record for clinical diagnosis of FH.(17) Four studies used the Dutch Lipid Clinic Network criteria to categorize individuals as definite, probable, or possible FH.(13,15,18,19) The proportion of individuals testing positive for FH varied by category. In the definite FH category, the sensitivity ranged from 30.2% to 70.3%. This is in the same range as the 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%).(12)

Differences in the methodology of these studies might have affected reported sensitivities. The populations are derived from different countries and are comprised mostly of patients from tertiary referral centers. Different populations, especially those seen in primary care, might have different rates of variants. The type and number of variants tested for, and the methods of testing, also varied. For example, for low-density lipoprotein receptor (*LDLR*) variants, some studies used a defined set of known pathogenic variants while other studies searched for any variants and reported both known and unknown variants. There were also differences in the method for making a clinical diagnosis; it is also important to note that different diagnostic criteria might have resulted in different populations. Future studies may report on additional genes associated with FH (i.e., *STAP1*), and on copy number variation. Sensitivity and specificity have not been reported in large cohort studies for these tests.(18)

Table 1. Clinical Validity of Genetic Testing for Familial Hypercholesterolemia

Study	Location	N	Genes Tested (Variants)	Sensitivity for FH, % (n/N)				Specificity for FH, % (n/N)
				Definite	*Probable*	*Possible*	*Overall*	
Hedegaard et al (2023)[19,]	Denmark	1243	*LDLR* *APOB* *PCSK9*	41.3 (19/46)	31.8 (34/107)	19.0 (97/511)	27.9 (350/ 1243)	-
Abul-Husn et al (2016)[17,]	U.S.	50,726	*LDLR* (n=29) *APOB* (n=2) *PCSK9* (n=4)	30.2 (16/53)[a]	7.0 (35/497)	1.2 (68/5465)	2.0 (119/ 6015)	99.8 (40174/ 40270)
Hooper et al (2012)[13,]	Australia	343	*LDLR* (n=18) *APOB* (n=2) *PCSK9* (n=1)	70.3 (90/128)	29.5 (26/88)	10.8 (12/111)	37.3 (128/ 343)	-
Palacios et al (2012)[14,]	Spain	5430	*LDLR* (any) *APOB* (n=1) *PCSK9* (n=4)	-	-	-	41.4[b] (2246/ 5430)	-
Tichy et al (2012)[16,]	Czech Republic	2239	*LDLR* (any) *APOB* (n=1)	-	-	-	35.7[c] (800/ 2239)	-
Diakou et al (2011)[12,]	Greece	254	*LDLR* (n=10) *APOB* (n=1) *PCSK9* (n=1) *ARH* (n=1)	66.5 (169/254)[a]	-	-	66.5 (169/ 254)[a]	100 (40/40)
Taylor et al (2010)[15,]	U.K.	635	*LDLR* (n=18) *APOB* (n=1) *PCSK9* (n=1)	56.3 (107/190)	-	28.4 (112/394)	34.5 (219/ 635)	-

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

Section Summary: Clinically Valid

Evidence on clinical validity includes cohorts 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 (RCTs).

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

Chain of Evidence

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

Diagnostic Testing of Patients with Signs and/or Symptoms of Familial Hypercholesterolemia
An indirect chain of evidence can provide evidence of clinical utility if all the links in the chain of evidence are intact. The chain of evidence for 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 with Signs and/or Symptoms of Familial Hypercholesterolemia who are Eligible for Specialty Medications
In the first scenario, in which a patient is eligible for specialty medications after definitive diagnosis with FH, a chain of evidence supporting genetic testing can be constructed. For patients who are in an uncertain category by clinical criteria, a positive genetic test will confirm the diagnosis of FH. These patients will then be eligible for specialty medications (e.g., *PCSK9* inhibitors) and these medications will be initiated in patients who have uncontrolled lipid levels despite treatment with statins and/or other agents. Management changes that occur as a result of genetic testing are initiation of effective medications (e.g., PCSK9 inhibitors). In patients who have uncontrolled lipid levels despite treatment with standard medications, these drugs have been demonstrated to improve outcomes.(20,21)

Section Summary: FH Testing for Those with Signs and/or Symptoms of Familial Hypercholesterolemia who are Ineligible for Specialty Medications
In the second scenario, encompassing all other diagnostic situations, a sufficient chain of evidence cannot be constructed. It is uncertain whether management changes occur as a result of genetic testing in other situations; therefore, it is not possible to conclude that management changes occur that improve outcomes. It is possible that clinicians may intensify treatment following a diagnosis of FH, such as switching to a more potent statin, increasing the

statin dose, or 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 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 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.

A systematic review (2019) of cascade screening included 6 studies of genetic cascade testing and 4 studies of biochemical testing.(22) Due to the constraints associated with cascade screening noted below, none of the included studies were conducted in the United States. The review found similar diagnostic yield with genetic (44.3%) and biochemical (45.2%) testing, but the new cases identified per index case by genetic testing was nearly 6 times larger than cases identified by biochemical testing (2.42 versus 0.42 cases). Results favoring new case identification with genetic testing were consistent when excluding 1 outlier study (1.37 versus 0.42 cases).

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

The "Is Family screening Improved by Genetic Testing in FH" ("I FIGhT FH") randomized controlled trial (2021) conducted in the United States and published after the systematic review compared cascade screening uptake in adult relatives following proband genetic testing or usual care (lipid testing) for diagnosis of FH.(24) Of 240 enrolled probands, only 43 relatives enrolled in the trial (0.2relatives per proband). The trial did not find a difference in cascade screening uptake among relatives whether the proband was diagnosed with FH using genetic testing or usual care (0.2 vs. 0.1 relatives per proband; p=.14) nor was there a difference between group in relatives diagnosed with FH as a results of cascade screening (0.1 vs. 0.1 new cases per index case; p=.27). Results of this study may be limited due to the low participation rate by relatives eligible for cascade screening. In addition, the low rate of FH

diagnosis following cascade screening is in contrast to the results in the previously discussed systematic review. However, none of the studies in the systematic review provided a direct comparison of genetic testing with usual care.

Cascade screening for FH has been evaluated in a national screening program from the Netherlands in a large study not included in the systematic review.(25) This program was initiated at a time when cholesterol screening was recommended for the general population. The addition of cascade screening for FH led to more than 9000 additional individuals diagnosed with FH. The rate of statin use increased in this population from an estimate of 39% prior to initiation of the program to 85% after full implementation. While cascade screening is likely to improve outcomes, it requires an infrastructure that allows access to the entire population, and that is not likely to be feasible when only a limited population is available for screening. As a result of these barriers, cascade screening has not been widely used in the 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 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,(26) and treatment with statins will begin earlier than if FH was not diagnosed. For the general population, lipid screening should begin at approximately 10 years of age. However, for children of individuals with FH, screening should begin sooner, and management changes, consisting of lifestyle modifications and/or medications, should begin as soon as possible. Management changes that occur in children are primarily the initiation of effective medications (e.g., statins, PCSK9 inhibitors). A Cochrane meta-analysis by Vuorio et al (2017) found moderate quality evidence that statins were able to reduce LDL levels in pediatric patients.(27) 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. The 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 using a chain of evidence in the following situations:

- *When a definitive diagnosis of FH is required to establish eligibility for specialty medications.* A chain of evidence demonstrates that clinical utility is present. For patients who are in an uncertain diagnostic category, a positive genetic test can confirm the diagnosis of FH and establish eligibility for specialty medications. Specialty medications (e.g., proprotein convertase subtilisin/kexin type 9 [PCSK9] inhibitors) have known efficacy in patients with FH and uncontrolled lipid levels despite treatment with statins and/or other medications. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.
- *All other situations.* Clinical utility of testing for diagnosis cannot be demonstrated through a chain of evidence 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 that the technology results in an improvement in the net health outcome.

For individuals who are adults or children and have a close relative with a diagnosis of FH who receive genetic testing to determine future risk of FH, the evidence includes a randomized controlled trial, case series and cross-sectional studies. The 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 using a chain of evidence in the following situations:

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

disease. It is recommended that the children of individuals who have a pathogenic variant initiate screening at an early age; further, the affected children should begin treatment with statins as early as possible. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

Migliara et al (2017) conducted a systematic review of guidelines on genetic testing and patient management of individuals with familial hypercholesterolemia (FH).(28) The literature search, conducted through April 2017, identified 10 guidelines for inclusion. Three of the guidelines were developed within the United States: those by the National Lipid Association,(29) International FH Foundation,(30) and American Association of Clinical Endocrinologists and American College of Endocrinology.(31) Guidance from the National Institute for Health and Care Excellence was also included in the review.(32) The quality of the guidelines was assessed using the Appraisal of Guidelines for Research and Evaluation II) instrument, with guideline quality ranging from average to good. Most guidelines agreed that genetic testing follows cholesterol testing, physical findings distinctive of FH, and highly suggestive family history of FH. Universal screening for FH was not recommended. This review highlighted the importance of genetic testing for FH in children because aggressive treatment at an earlier age may prevent premature coronary heart disease.

American Heart Association

According to a scientific statement from the American Heart Association (2020), genetic testing for cardiovascular diseases, including FH, "typically should be reserved for patients with a confirmed or suspected diagnosis of an inherited cardiovascular disease or for individuals at high a priori risk resulting from a previously identified pathogenic variant in their family" and should include taking an extensive family history.(33)

In another scientific statement focused on genetic testing for heritable cardiovascular diseases in children, the AHA (2021) notes the following:(34) "It is imperative to identify individuals with FH in childhood so that lipid-lowering therapies and lifestyle interventions can be established. Left untreated, children with FH are at high risk for atherosclerotic cardiovascular disease in early to middle adulthood attributable to the cumulative burden of elevated LDL-C levels."

American Lipid Association

Subsequent to the publication of the Migliara systematic review (2017) (26) the American Lipid Association (ALA) issued updated guidance on genetic testing for dyslipidemias, including FH (last updated September 2021).(33) Recommendations are summarized in Table 2.

Table 2. American Lipid Association Recommendations on Genetic Testing for FH

Recommendation	SOE	GOE
"Genetic testing is reasonable when heterozygous familial hypercholesterolemia is suspected but not definitively diagnosed based on clinical criteria alone."	Moderate evidence of benefit	Moderate, based on nonrandomized studies
"Cascade screening for FH either by lipid profile or genetic testing is recommended in all first-degree relatives (children and siblings) of an individual who has tested genetically positive for FH."	Strong evidence of benefit	Consensus expert opinion

FH: familial hypercholesterolemia; GOE: grade of evidence; SOE: strength of evidence

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

In 2018, the Familial Hypercholesterolemia Foundation (FHF) commissioned an expert panel through the Journal of the American College of Cardiology (JACC) to issue detailed guidelines on the use of genetic testing for FH (Table 3).(36)

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

Recommendation	SOE	GOE
"Genetic testing for FH should be offered to individuals of any age in whom a strong clinical index of suspicion for FH exists based on examination of the patient's clinical and/or family histories. This index of suspicion includes the following: children with persistent LDL-C levels ≥160 mg/dl or adults with persistent LDL-C levels ≥190 mg/dl without an apparent secondary cause of hypercholesterolemia and with at least 1 first-degree relative similarly affected or with premature CAD, or where family history is not available (e.g. adoption); children with persistent LDL-C levels ≥190 mg/dl or adults with persistent LDL-C levels ≥250 mg/dl without an apparent secondary cause of hypercholesterolemia, even in the absence of a positive family history."	Moderate evidence of benefit	Moderate, based on nonrandomized studies
"Genetic testing for FH may be considered in the following clinical scenarios: children with persistent LDL-C levels ≥160 mg/dl (without an apparent secondary cause of hypercholesterolemia) with an LDL-C level ≥190 mg/dl in at least 1 parent or a family history of hypercholesterolemia and premature CAD; adults with no pre-treatment LDL-C levels available but with a personal history of premature CAD and family history of both hypercholesterolemia and premature CAD; adults with persistent LDL-C levels ≥160 mg/dl (without an apparent secondary cause of hypercholesterolemia) in the setting of a family history of hypercholesterolemia and either a personal history or a family history of premature CAD."	Weak evidence of benefit	Consensus expert opinion
"Cascade genetic testing for the specific variant(s) identified in the FH proband (known familial variant testing) should be offered to all first-degree relatives. If first-degree relatives are unavailable, or do not wish to undergo testing, known familial variant testing should be offered to second-degree relatives. Cascade genetic testing should commence throughout the entire extended family until all at-risk individuals have been tested and all known relatives with FH have been identified."	Strong evidence of benefit	Moderate, based on randomized studies

CAD: coronary artery disease; FH: familial hypercholesterolemia; GOE: grade of evidence; LDL-C: low-density lipoprotein cholesterol; SOE: strength of evidence

International Atherosclerosis Society

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

National Heart, Lung, and Blood Institute

Recommendations from an expert panel on cardiovascular health and risk reduction in children and adolescents were published in 2011.(38) The report contained the following recommendations (see Table 4).

Table 4. National Heart, Lung, and Blood Institute Recommendations on Cardiovascular Health and Risk Reduction in Children and Adolescents

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

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

U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS

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

A Task Force evidence report, conducted by Lozano et al (2016), evaluated lipid screening in children and adolescents to detect familial hypercholesterolemia.(40) This report stated that genetic screening for FH was beyond the scope of the report. Further, the report stated that "because implementing this approach [cascade screening] in the 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."

ONGOING AND UNPUBLISHED CLINICAL TRIALS

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

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT01960244	Study of Awareness and Detection of Familial Hypercholesterolemia (CASCADE-FH)	5000	Dec 2025
NCT04370899	Early Detection of Familial Hypercholesterolemia in Children (DECOPIN)	400	Jan 2023
Unpublished			
NCT03253432	INTegrating Active Case-finding With Next-generation Sequencing for Diagnosis Through Electronic Medical Records (IN-TANDEM): Familial Hypercholesterolemia Pilot Study	378 (actual)	Nov 2018

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

Government Regulations
National:

National Coverage Determination (NCD) for Lipid Testing (190.23), Effective Date of this Version 1/1/2005, Implementation Date 3/11/2005

Indications and Limitations of Coverage

The medical community recognizes lipid testing as appropriate for evaluating atherosclerotic cardiovascular disease. Conditions in which lipid testing may be indicated include:

- Assessment of patients with atherosclerotic cardiovascular disease.
- Evaluation of primary dyslipidemia.
- Any form of atherosclerotic disease, or any disease leading to the formation of atherosclerotic disease.
- Diagnostic evaluation of diseases associated with altered lipid metabolism, such as: nephrotic syndrome, pancreatitis, hepatic disease, and hypo and hyperthyroidism.
- Secondary dyslipidemia, including diabetes mellitus, disorders of gastrointestinal absorption, chronic renal failure.
- Signs or symptoms of dyslipidemias, such as skin lesions.
- As follow-up to the initial screen for coronary heart disease (total cholesterol + HDL cholesterol) when total cholesterol is determined to be high (>240 mg/dL), or borderline-high (200-240 mg/dL) plus 2 or more coronary heart disease risk factors, or an HDL cholesterol, <35 mg/dl.

To monitor the progress of patients on anti-lipid dietary management and pharmacologic therapy for the treatment of elevated blood lipid disorders, total cholesterol, HDL cholesterol and LDL cholesterol may be used. Triglycerides may be obtained if this lipid fraction is also elevated or if the patient is put on drugs (for example, thiazide diuretics, beta blockers, estrogens, glucocorticoids, and tamoxifen) which may raise the triglyceride level.
When monitoring long term anti-lipid dietary or pharmacologic therapy and when following patients with borderline high total or LDL cholesterol levels, it may be reasonable to perform the lipid panel annually. A lipid panel at a yearly interval will usually be adequate while measurement of the serum total cholesterol or a measured LDL should suffice for interim visits if the patient does not have hypertriglyceridemia.

When monitoring long term anti-lipid dietary or pharmacologic therapy and when following patients with borderline high total or LDL cholesterol levels, it may be reasonable to perform the lipid panel annually. A lipid panel at a yearly interval will usually be adequate while measurement of the serum total cholesterol or a measured LDL should suffice for interim visits if the patient does not have hyper-triglyceridemia.

Any one component of the panel or a measured LDL may be reasonable and necessary up to 6 times the first year for monitoring dietary or pharmacologic therapy. More frequent total cholesterol HDL cholesterol, LDL cholesterol and triglyceride testing may be indicated for marked elevations or for changes to anti-lipid therapy due to inadequate initial patient response to dietary or pharmacologic therapy. The LDL cholesterol or total cholesterol may be measured 3 times yearly after treatment goals have been achieved.

Electrophoretic or other quantitation of lipoproteins may be indicated if the patient has a primary disorder of lipoid metabolism.

Effective January 1, 2005, the Medicare law expanded coverage to cardiovascular screening services. Several of the procedures included in this NCD may be covered for screening purposes subject to specified frequencies. See 42 CFR 410.17 and section 100, chapter 18, of the Claims Processing Manual, for a full description of this benefit.

Limitations
Lipid panel and hepatic panel testing may be used for patients with severe psoriasis which has not responded to conventional therapy and for which the retinoid etretinate has been prescribed and who have developed hyperlipidemia or hepatic toxicity. Specific examples include erythrodermia and generalized pustular type and psoriasis associated with arthritis.

Routine screening and prophylactic testing for lipid disorder are not covered by Medicare. While lipid screening may be medically appropriate, Medicare by statute does not pay for it. Lipid testing in asymptomatic individuals is considered to be screening regardless of the presence of other risk factors such as family history, tobacco use, etc.

Once a diagnosis is established, one or several specific tests are usually adequate for monitoring the course of the disease. Less specific diagnoses (for example, other chest pain) alone do not support medical necessity of these tests.

When monitoring long term anti-lipid dietary or pharmacologic therapy and when following patients with borderline high total or LDL cholesterol levels, it is reasonable to perform the lipid panel annually. A lipid panel at a yearly interval will usually be adequate while measurement of the serum total cholesterol or a measured LDL should suffice for interim visits if the patient does not have hypertriglyceridemia.

Any one component of the panel or a measured LDL may be medically necessary up to six times the first year for monitoring dietary or pharmacologic therapy. More frequent total cholesterol HDL cholesterol, LDL cholesterol and triglyceride testing may be indicated for marked elevations or for changes to anti-lipid therapy due to inadequate initial patient response to dietary or pharmacologic therapy. The LDL cholesterol or total cholesterol may be measured three times yearly after treatment goals have been achieved.

If no dietary or pharmacological therapy is advised, monitoring is not necessary.

When evaluating non-specific chronic abnormalities of the liver (for example, elevations of transaminase, alkaline phosphatase, abnormal imaging studies, etc.), a lipid panel would generally not be indicated more than twice per year.

Local:

Wisconsin Physician Services Local Coverage Determination
LCD Title: MolDX: Biomarkers in Cardiovascular Risk Assessment (L36523)
Effective Date: For services performed on or after 3/21/24

Under preventative services, Medicare Part B covers the basic lipid panel (total cholesterol, high density lipoprotein-cholesterol (HDL-C), triglycerides, and low-density lipoprotein-

cholesterol (LDL-C) for cardiovascular (CV) disease screening, every 5 years when ordered by a doctor.

NCD 190.23 covers lipid panel testing for symptomatic patients for evaluating atherosclerotic CV disease, to monitor the progress of patients on anti-lipid dietary management and pharmacologic therapy for various lipid disorders.

This policy denies coverage for all CV risk assessment panels, except the basic lipid panel, for symptomatic (with signs and symptoms) patients with suspected or documented CV disease because panel testing is not specific to a given patient's lipid abnormality or disease. The policy indicates the medical indication(s) based on published scientific articles and consensus guidelines for individual lipid biomarkers that may be covered to characterize a given lipid abnormality or disease, to determine a treatment plan or to assist with intensification of therapy. Each individual lipid biomarkers must be specifically ordered and the reason for the test order documented in the patient's medical record. The policy denies coverage for all **non-lipid** biomarkers when used for CV risk assessment including but not limited to, biochemical, immunologic, hematologic, and genetic biomarkers for CV risk assessment regardless of whether ordered in a panel or individually.

The following biomarkers, when they are included in a CV risk assessment panel, are non-covered:

- Lipoprotein subclasses;
- LDL particles;
- Intermediate density lipoproteins;
- High density lipoprotein AI9LpAI and AI/AII;
- Lipoprotein(a);
- Apolipoprotein B (Apo B), apo A-I and apo E;
- Lipoprotein-associated phospholipase A2 (Lp-PLA2)
- BNP
- Cystatin C
- Thrombogenic/hematologic actors
- Interleukin-6 (IL-6), tissue necrosis factor- a (TNF- a), plasminogen activator inhibitor-1 (PAI-1) and IL-6 promoter polymorphism
- Free fatty acids
- Visfatin, angiotensin-converting enzyme 1 (ACE2) and serum amyloid A
- Microalbumin
- Myeloperoxidase (MPO)
- Homocysteine and methylenetetrahydrofolate reductase (MTHFR) mutation testing
- Uric acid
- Vitamin D
- White blood cell count
- Long-chain omega-3 fatty acids in red blood cell membranes
- Gamma-glutamyltransferase (GGT)
- Genomic profiling including CardiaRisk angiotensin gene
- Leptin, ghrelin, adiponectin and adipokines including retinol binding protein 4 (RBP4) and resistin
- Inflammatory markers including VCAM-1, P-selectin (PSEL) and E-selectin (ESEL)
- Cardiovascular risk panels

Note #1: There is no Medicare benefit for screening CV risk assessment testing for asymptomatic (without signs or symptoms of disease) patients. Screening asymptomatic patients for cardiovascular risk is statutorily excluded by Medicare and will not be addressed in this policy.

Note #2: FDA approval/clearance means that a test/assay has analytical and clinical validity. The FDA does not review clinical utility (that the test/assay demonstrates improved patient outcomes). To meet Medicare's "reasonable and necessary" criteria for coverage, a test/assay must have proven clinical utility.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Cardiovascular Risk Panels
- CPT Category III Codes – Noncovered Services
- Laboratory Tests-Genetic, Molecular, and Other-Experimental/Investigational Status Genetic Testing and Counseling
- Genetic Testing for Alzheimer Disease
- Genetic Testing for Specified Conditions Using Testing Panels
- Measurement Of Lipoprotein-Associated Phospholipase A_2 (Lp-PLA_2) and Secretory Type II Phospholipase A_2 (SPLA2-IIA) in the Assessment of Cardiovascular Risk
- Nontraditional Biomarkers in Risk Assessment and Management of Cardiovascular Disease

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 1/20/25, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
11/1/18	8/21/18	8/21/18	Joint policy established
7/1/19	4/16/19		Routine maintenance
7/1/20	4/14/20		Routine maintenance
7/1/21	4/20/21		Routine maintenance
7/1/22	4/19/22		Routine maintenance
7/1/23	4/18/23		Routine maintenance (slp) Vendor Managed: N/A
7/1/24	4/16/24		Routine maintenance (slp) Vendor managed: N/A
7/1/25	4/15/25		Routine maintenance (slp) Vendor managed: N/A

Next Review Date: 2nd Qtr, 2026

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GENETIC TESTING FOR HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.
- *Duplicate (back-up) equipment is not a covered benefit.*