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# Nontraditional Biomarkers in Risk Assessment and Management of Cardiovascular Disease Corporate Medical Policy

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### Description/Summary

Various lipid and non-lipid biomarkers have been proposed as potential risk markers for cardiovascular disease (CVD). Biomarkers discussed in this policy include apolipoprotein B (apo B), apolipoprotein A1 (apo A1), apolipoprotein E (apo E), B-type natriuretic peptide, cystatin C, fibrinogen, high-density lipoprotein (HDL) subclass, leptin, low-density lipoprotein (LDL) subclass, lipoprotein (a), high sensitivity C-reactive protein (hs-CRP), and genetic biomarkers. These biomarkers have been studied as alternatives or additions to standard lipid panels for risk stratification in CVD or as treatment targets for lipid-lowering therapy.

## Policy

### Coding Information

### Click the links below for attachments, coding tables & instructions.

Attachment I

### When a service may be considered medically necessary

**Lipoprotein(a)**

Lipoprotein(a) measurement may be considered **medically necessary** for individuals who meet **at least one** of the following criteria:

- Individuals with primary severe hypercholesterolemia (LDL cholesterol greater than or equal to 190 mg/dL) or suspected familial hypercholesterolemia; **OR**
- Individuals with premature atherosclerotic cardiovascular disease (ASCVD) (i.e., diagnosis of ASCVD in men younger than 55 years of age; and in women younger than 65 years of age); **OR**

- Family history of first-degree relatives with premature (ASCVD) (i.e., first-degree male relative diagnosed with ASCVD before reaching 55 years of age; first-degree female relative diagnosed with ASCVD before reaching 65 years of age); **OR**
- Family history of first-degree relative with elevated Lp(a); **OR**
- Individuals at *very high-risk* of ASCVD to better define those who are more likely to benefit from PCSK9 (proprotein convertase subtilisin/kexin type 9 serine protease) inhibitor therapy

NOTE: *Very high-risk* includes a history of more than one major ASCVD events (e.g., history of myocardial infarction, history of ischemic stroke, recent acute coronary syndrome) or one major ASCVD event and multiple high-risk conditions (e.g., over 65 years of age, family history of hypercholesterolemia, diabetes mellitus, hypertension, chronic kidney disease, history of congestive heart failure, current smoker, etc.)

**Apolipoprotein B (apo B)**
Measurement of apolipoprotein B may be considered **medically necessary** in individuals who meet **at least one** of the following criteria:

- Established atherosclerotic cardiovascular disease
- Hypertriglyceridemia
- Diabetes mellitus
- Obesity
- Metabolic syndrome
- Other dyslipidemias (e.g., very low LDL-C)
- On lipid therapy
- To facilitate diagnosis of familial dysbetalipoproteinemia
- To facilitate diagnosis of familial combined hyperlipidemia

**High-sensitivity C-reactive protein (hs-CRP)**
High-sensitivity **C-reactive protein** testing may be considered **medically necessary** for cardiovascular risk assessment in adults without established atherosclerotic cardiovascular disease to guide decisions regarding therapeutic initiation when all of the following criteria are met:

- After quantitative risk assessment using ACC/AHA Pooled Cohort Equations to calculate *10-year risk of CVD events*, a risk-based treatment decision is uncertain

NOTE: Several tools are available to calculate *10-year risk of atherosclerotic cardiovascular disease (ASCVD)*. The following are examples:
ACC/AHA: https://tools.acc.org/ldl/ascvd_risk_estimator/index.html#!/calulate/estimator/
ClinCalc.com: https://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx

## When a service is considered investigational

Measurement of apolipoprotein(a) for all other clinical situations not meeting medical necessity criteria above is considered **investigational**.

Measurement of apolipoprotein B for all other clinical situations not meeting medical necessity criteria above is considered **investigational**.

Measurement of High-sensitivity C-reactive protein for all other clinical situations not meeting medical necessity criteria above is considered **investigational**.

Measurement of other nontraditional analytes to assess cardiovascular risk, including but not limited to apolipoprotein AI, apolipoprotein E or *APOE* genotypes, brain natriuretic peptide (BNP), fibrinogen, leptin, LDL subclass and HDL subclass is considered **investigational**.

Measurement of lipoprotein-associated phospholipase $A_2$ is considered **investigational**.

Cardiovascular disease risk panels, consisting of multiple individual analytes intended to assess cardiac risk (other than simple lipid panels, see Policy Guidelines section), are considered **investigational**.

## Background

**LOW-DENSITY LIPOPROTEINS AND CARDIOVASCULAR DISEASE**

Low-density lipoproteins (LDLs) have been identified as the major atherogenic lipoproteins and have long been identified by the National Cholesterol Education Project as the primary target of cholesterol- lowering therapy. An LDL particle consists of a surface coat composed of phospholipids, free cholesterol, and apolipoproteins surrounding an inner lipid core composed of cholesterol ester and triglycerides. Traditional lipid risk factors such as LDL-cholesterol (LDLC), while predictive on a population basis, are weaker markers of risk on an individual basis. Only a minority of individuals with elevated LDL and cholesterol levels will develop clinical disease, and up to 50% of cases of coronary artery disease (CAD) occur in those with ”normal” levels of total cholesterol and LDL-C. Thus, there is considerable potential to improve the accuracy of current cardiovascular risk prediction models. To assess CVD risk, especially when LDL alone does not fully explain risk (e.g., in metabolic syndrome, diabetes mellitus, or residual risk despite statin use), other lipid biomarkers are useful.

### Lipid Markers

**Apolipoprotein B**
Apolipoprotein (Apo) B is the major protein moiety of all lipoproteins except for high-density lipoprotein (HDL). The most abundant form of apo B, large B or B100, constitutes the apo B found in LDL and very-low density LDL. Because LDL and very-low density LDL each contain 1 molecule of apo B, the measurement of apo B reflects the total number of these atherogenic particles, 90% of which are LDL. Because LDL particles can vary in size and in cholesterol 4 content, for a given concentration of LDL-C, there can be a wide variety in size and numbers of LDL particles. Thus, it has been postulated that apo B is a better measure of the atherogenic potential of serum LDL than the LDL concentration.

**Apolipoprotein AI**
High-density lipoprotein contains 2 associated apolipoproteins: (i.e., apo AI, apo AII). High-density lipoprotein particles can also be classified by whether they contain apo AI only or they contain both apo AI and apo-AII. Because all HDL particles contain apo AI, this lipid marker can be used as an approximation for HDL number, similar to the way apo B has been proposed as an approximation of the LDL number.

Direct measurement of apo AI concentrations has been proposed as more accurate than the traditional use of HDL level in the evaluation of cardioprotective, or "good," cholesterol. In addition, the ratio of apo B/apo AI has been proposed as a superior measure of the ratio of proatherogenic (i.e., "bad") cholesterol to anti-atherogenic (i.e., "good") cholesterol.

**Apolipoprotein E**
Apolipoprotein E is the primary apolipoprotein found in very-low density LDLs and chylomicrons. Apolipoprotein E is the primary binding protein for LDL receptors in the liver and is thought to play an important role in lipid metabolism. The Apolipoprotein E (APOE) gene is polymorphic, consisting of 3 epsilon alleles (e2, e3, and e4) that code for 3 protein isoforms, known as E2, E3, and E4, which differ from one another by 1 amino acid. These molecules mediate lipid metabolism through their different interactions with LDL receptors. The genotype of apo E alleles can be assessed by gene amplification techniques, or the APOE phenotype can be assessed by measuring plasma levels of apo E.

It has been proposed that various APOE genotypes are more atherogenic than others and that APOE measurement may provide information on risk of CAD beyond traditional risk factor measurement. It has also been proposed that the APOE genotype may be useful in the selection of specific components of lipid-lowering therapy, such as drug selection. In the major lipid-lowering intervention trials, including trials of statin therapy, there is considerable variability in response to therapy that cannot be explained by factors such as compliance. The APOE genotype may be a factor that determines an individual's degree of response to interventions such as statin therapy.

**High-Density Lipoprotein Subclass**
High-density lipoprotein particles exhibit considerable heterogeneity, and it has been proposed that various subclasses of HDL may have a greater role in protection from atherosclerosis. Particles of HDL can be characterized based on size or density and/or on apolipoprotein composition. Using size or density, HDL can be classified into HDL2, the larger, less dense particles that may have the greatest degree of cardio-protection, and HDL3, which are smaller, denser particles.

An alternative to measuring the concentration of subclasses of HDL (e.g., HDL2 and HDL3) is direct measurement of HDL particle size and/or number. Particle size can be measured by nuclear magnetic resonance (NMR) spectroscopy or by gradient-gel electrophoresis. High-density lipoprotein particle numbers can be measured by NMR spectroscopy. Several commercial labs offer these measurements of HDL particle size and number. Measurement of apo AI has used HDL particle number as a surrogate, based on the premise that each HDL particle contains a single apo AI molecule.

**Low-Density Lipoprotein Subclass**
Two main subclass patterns of LDL, called A and B, have been described. In subclass pattern A, particles have a diameter larger than 25 nm and are less dense, while in subclass pattern B, particles have a diameter less than 25 nm and a higher density. Subclass pattern B is a commonly inherited disorder associated with a more atherogenic lipoprotein profile, also termed "atherogenic dyslipidemia." In addition to small, dense LDL, this pattern includes elevated levels of triglycerides, elevated levels of apo B, and low levels of HDL. This lipid profile is commonly seen in type 2 diabetes and is one component of the "metabolic syndrome," defined by the Third Report of the Expert Panel on Detection, Evaluation, and

Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III; ATP III) to also include high normal blood pressure, insulin resistance, increased levels of inflammatory markers such as C-reactive protein, and a prothrombotic state. The presence of the metabolic syndrome is considered by Adult Treatment Panel III to be a substantial risk-enhancing factor for CAD.

Low-density lipoprotein size has also been proposed as a potentially useful measure of treatment response. Lipid-lowering treatment decreases total LDL and may also induce a shift in the type of LDL, from smaller, dense particles to larger particles. It has been proposed that this shift in lipid profile may be beneficial in reducing risk for CAD independent of the total LDL level. Also, some drugs may cause a greater shift in lipid profile than others. Niacin and/or fibrates may cause a greater shift from small to large LDL size than statins. Therefore, measurement of LDL size may potentially play a role in drug selection or may be useful in deciding to use a combination of drugs rather than a statin alone.

In addition to the size of LDL particles, interest has been shown in assessing the concentration of LDL particles as a distinct cardiac risk factor. For example, the commonly performed test for LDL-C is not a direct measure of LDL but, chosen for its convenience, measures the amount of cholesterol incorporated into LDL particles. Because LDL particles carry much of the cholesterol in the bloodstream, the concentration of cholesterol in LDL correlates reasonably well with the number of LDL particles when examined in large populations. However, for an individual patient, the LDL level may not reflect the number of particles due to varying levels of cholesterol in different sized particles. It is proposed that the discrepancy between the number of LDL particles and the serum level of LDL represents a significant source of unrecognized atherogenic risk. The size and number of particles are interrelated. For example, all LDL particles can invade the arterial wall and initiate atherosclerosis. However, small, dense particles are thought to be more atherogenic than larger particles. Therefore, for patients with elevated numbers of LDL particles, cardiac risk may be further enhanced when the particles are smaller versus larger.

**Lipoprotein (a)**
Lipoprotein (a) (Lp[a]) is a lipid-rich particle similar to LDL. The major apolipoprotein associated with LDL is Apo B; in Lp(a), however, there is an additional apo A covalently linked to apo B. The apo A molecule is structurally similar to plasminogen, suggesting that Lp(a) may contribute to the thrombotic and atherogenic basis of CVD. Levels of Lp(a) are relatively stable in individuals over time but vary up to 1,000-fold between individuals, presumably on a genetic basis. The similarity between Lp(a) and fibrinogen has stimulated intense interest in Lp(a) as a link between atherosclerosis and thrombosis. In addition, approximately 20% of patients with CAD have elevated Lp(a) levels. Therefore, it has been proposed that levels of Lp(a) may be an independent risk factor for CAD.

**Non-Lipid Markers**

Other non-lipid markers have been identified as having an association with CVD, including high sensitivity C-reactive protein, B-type natriuretic peptide, cystatin C, fibrinogen, and leptin. These biomarkers may have a predictive role in identifying CVD risk or in targeting therapy.

**B-type or Brain Natriuretic Peptide**
Brain natriuretic peptide (BNP, also called B-type natriuretic peptide) is an amino acid polypeptide secreted primarily by the ventricles of the heart when the pressure to the cardiac muscles increases or there is myocardial ischemia. Elevations in BNP levels reflect deterioration in cardiac loading levels and may predict adverse events. Brain natriuretic peptide has been studied as a biomarker for managing heart failure and predicting cardiovascular and heart failure risk.

**Cystatin C**
Cystatin C is a small serine protease inhibitor protein secreted from all functional cells in the body. It has primarily been used as a biomarker of kidney function. Cystatin C has also been studied to determine whether it may serve as a biomarker for predicting cardiovascular risk. Cystatin C is encoded by the CST3 gene.

**Fibrinogen**
Fibrinogen is a circulating clotting factor and precursor of fibrin. It is important in platelet aggregation and a determinant of blood viscosity. Fibrinogen levels have been shown to be associated with future risk of CVD and all-cause mortality.

**High-Sensitivity C-Reactive Protein (hs-CRP)**
High sensitivity C-reactive protein (hs-CRP) is produced in response to inflammation in the body. It is a systemic marker of inflammation that has been extensively studied and identified as an independent risk factor for coronary artery disease (CAD). A high sensitivity CRP assay can detect low levels of chronic inflammation associated with heart disease.

**Leptin**
Leptin is a protein secreted by fat cells that has been found to be elevated in heart disease. Leptin has been studied to determine if it has any relation to the development of CVD.

## Summary of Evidence

For individuals who are asymptomatic with risk of cardiovascular disease (CVD) who receive nontraditional cardiac biomarker testing (e.g., apolipoprotein B [apo B], apolipoprotein AI [apo AI], apolipoprotein E [apo E], B-type natriuretic peptide, cystatin C, fibrinogen, leptin, subclasses of low-density lipoprotein [LDL], high-density lipoprotein [HDL], and lipoprotein [a]), the evidence includes systematic reviews, meta-analyses, and large, prospective cohort studies. Relevant outcomes are overall survival, other test performance measures, change in disease status, morbid events, and medication use. The evidence from cohort studies and meta-analyses of these studies has suggested that some of these markers are associated with increased cardiovascular risk and may provide incremental accuracy in risk prediction. The evidence is sufficient to determine that apo B, hs-CRP and Lp(a) testing results in an improvement in the net health outcome.

For individuals with hyperlipidemia managed with lipid-lowering therapy who receive nontraditional cardiac biomarker testing (e.g., apo B, apo AI, apo E, apo E, HDL subclass, LDL subclass, Lp[a], BNP, cystatin C, fibrinogen, leptin), the evidence includes analyses of the intervention arm(s) of lipid-lowering medication trials. Relevant outcomes are overall survival, change in disease status, morbid events, and medication use. In particular, apo B, apo AI, and apo E have been evaluated as markers of lipid-lowering treatment success, and

evidence from the intervention arms of several RCTs has suggested that these markers are associated with treatment success. However, there is no direct evidence that using markers other that LDL and HDL as lipid-lowering treatment targets leads to improved health outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome

## Supplemental Information

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

**PRACTICE GUIDELINES AND POSITION STATEMENTS**

**National Heart, Lung, and Blood Institute**
In 2001, the National Heart, Lung, and Blood Institute's National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) issued a position statement. Apo lipoprotein B (apo B), apolipoprotein AI (apo AI), lipid subclass, and lipoprotein(a) (Lp[a]) were listed as "emerging risk factors" for cardiovascular risk assessment, without specific recommendations for how these measures should be used in clinical practice. A 2004 update to these guidelines discussed the result of clinical trials of statin therapy.

In 2013, the Institute published a systematic evidence review on managing blood cholesterol in adults. The review was used to develop joint guidelines by the American College of Cardiology (ACC) and American Heart Association (AHA) on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults (see below).

**American College of Cardiology**
In 2023, the American College of Cardiology (ACC) published an update on lipoprotein(a) testing guidelines, which included the following:

- Lipoprotein(a) (Lp[a]) is an independent risk factor for atherosclerotic cardiovascular disease (CVD) and calcific valvular aortic stenosis.
- Lp(a) exhibits significant race/ethnic variations, with levels highest among persons of African ancestry.
- Lp(a) levels typically do not change after 5 years of age except during times of significant inflammation, liver disease, or kidney disease; hence, levels should be interpreted cautiously during these times.
- Current guidelines support once-in-a-lifetime measurement in most individuals with increased risk of atherosclerotic CVD.
- Emerging data appear to show a strong correlation with high-sensitivity C-reactive protein levels for predicting CVD risk.

**American College of Cardiology and American Heart Association**
In 2013, the American College of Cardiology (ACC) and the American Heart Association (AHA) published guidelines on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk and the assessment of cardiovascular risk. Pooled cohort equations for estimating arteriosclerotic cardiovascular disease (ASCVD) were developed from sex- and

race-specific proportional hazards models that included covariates of age, treated or untreated systolic blood pressure level, total cholesterol and high-density lipoprotein cholesterol (HDL-C) levels, current smoking status, and history of diabetes. Additional risk factors evaluated included diastolic blood pressure, family history of ASCVD, moderate or severe chronic kidney disease, and body mass index. None of the variables significantly improved discrimination for 10-year hard ASCVD risk prediction. The ACC and AHA recommended that further research using state-of-the-art statistical techniques (including net reclassification improvement and integrative discrimination index) examine the utility of novel biomarkers when added to these new pooled cohort equations in different populations and patient subgroups. The guidelines stated that future updates might include guidance on whether on-treatment markers such as apo B, Lp(a), or low-density lipoprotein (LDL) particles are useful for guiding treatment decisions. Regarding newer risk markers after quantitative risk assessment, the guidelines stated the following: "If, after quantitative risk assessment, a risk-based treatment decision is uncertain, assessment of ≥1 of the following: family history, hs-CRP [high-sensitivity C-reactive protein], CAC [coronary artery calcium] score, or ABI [ankle-brachial index] may be considered to inform treatment decision-making" (class of recommendation IIb, level of evidence B). The guidelines did not recommend other novel cardiac risk factors or panels of cardiac risk factors.

The ACC/AHA (2019) guidelines on primary prevention of cardiovascular disease include information on appropriateness of Lp(a) level measurement stating, "a relative indication for its measurement is family history of premature ASCVD. An Lp(a) ≥50 mg/dL or ≥125 nmol/L constitutes a risk-enhancing factor, especially at higher levels of Lp(a)." The guidelines also include recommendations for apo B measurement stating, "a relative indication for its measurement would be triglyceride ≥200 mg/dL. A level ≥130 mg/dL corresponds to an LDL-C >160 mg/dL and constitutes a risk-enhancing factor."

**American Diabetes Association and American College of Cardiology Foundation**
In 2008, a consensus statement from the American Diabetes Association and the ACC Foundation addressed lipoprotein management in patients with cardiometabolic risk. This statement included specific recommendations for incorporating apo B testing into clinical care for high-risk patients and recommended that, for patients with metabolic syndrome being treated with statins, both LDL-C and apo B should be used as treatment targets, with an apo B target of less than 90 mg/dL, even if target LDL has been achieved.

This consensus statement also commented on the use of LDL particle number in patients with cardiometabolic risk and on the limitations of the clinical utility of nuclear magnetic resonance measurement of LDL particle number or size, including lack of widespread availability. The statement also noted that there is a need for more independent data confirming the accuracy of the method and whether its predictive power is consistent across various patient populations.

The American Diabetes Association 2024 Standards of Care do not discuss the use of specific novel biomarkers for cardiovascular disease and risk management.

**American Association of Clinical Endocrinologists and American College of Endocrinology**
In 2017, the American Association of Clinical Endocrinologists (AACE, now the American Association of Clinical Endocrinology) and the American College of Endocrinology (ACE) published joint guidelines on the management of dyslipidemia and the prevention of

cardiovascular diseases. The guidelines recommended that, among patients with “triglyceride (TG) concentration of greater than 150 mg/dL or HDL-C concentration of less than 40 mg/dL, the apo B or the apo B to apo AI ratio may be useful in assessing residual risk in individuals at risk for ASCVD (even when the LDL-C levels are controlled).”

In 2020, the AACE published an updated consensus statement on dyslipidemia and prevention of cardiovascular disease. They recommended measurement of Lp(a) in several patient populations including those with ASCVD, those with a family history of premature ASCVD and/or increased Lp(a), and individuals with a 10-year ASCVD risk of 10% or greater. Recommendations also included consideration of apo B or LDL particle measurement "based on individual patient clinical circumstances."

In 2022, the AACE published a guideline on comprehensive care plans in patients with diabetes. In addition to treatment targets for LDL-C and non-HDL-C, the guideline defines target apo B levels of <90 mg/dL, <80 mg/dL, or <70 mg/dL for patients with high, very high, and extreme risk of ASCVD. Patients receiving statins should undergo monitoring for these parameters (including apo B) every 6 to 12 weeks, and monitoring frequency can decrease after targets are achieved.

**National Lipid Association**
In 2019, the National Lipid Association issued a scientific statement on the use of Lp(a), which notes that Lp(a) measurement "is reasonable" to refine risk assessment for ASCVD events in the following populations: patients with first-degree relatives with premature ASCVD (<55 years of age for men; <65 years of age for women), patients with premature ASCVD without traditional risk factors, patients with severe hypercholesterolemia (LDL-C ≥190 mg/dL) or familial hypercholesterolemia, and patients with very high risk of ASCVD that may be candidates for proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy. Additionally, Lp(a) "may be reasonable" to measure in patients with the following: intermediate (7.5 to 19.9%) or borderline (5 to 7.4%) ASCVD risk when statin initiation is uncertain for primary prevention, inadequate response to LDL-C lowering therapy despite adherence, family history of elevated Lp(a), calcific valvular aortic stenosis, or recurrent or progressive ASCVD despite lipid-lowering therapy.

In 2021, the National Lipid Association issued a scientific statement on lipid measurements in cardiovascular disease including information on apo B, small dense LDL, and Lp(a). The authors refer to the 2019 statement for information on Lp(a), and they recommend that measurements of apo B and small dense LDL "may be reasonable at initial evaluation." Additionally, apo B measurement "is reasonable" for patients receiving lipid lowering therapy while small dense LDL measurement is "not recommended" for these patients.

**U.S. PREVENTIVE SERVICES TASK FORCE RECOMMENDATIONS**
The U.S. Preventive Services Task Force (2009) issued recommendations on the use of nontraditional risk factors for the assessment of coronary heart disease (CHD). The Task Force included lipoprotein (a) in its summary statement: “The evidence is insufficient to assess the balance of benefits and harms of using the nontraditional risk factors discussed in this statement to screen asymptomatic men and women with no history of CHD to prevent CHD events.”

The recommendation was updated in 2018 and came to the same conclusion: evidence is

insufficient to assess the benefits and harms of novel testing methods to diagnose CVD.

However, the nontraditional risk factors included in this recommendation were different than those in this evidence review.

## Policy Guidelines

A simple lipid panel is generally composed of the following lipid measures:

- Total cholesterol
- Low-density lipoprotein cholesterol
- High-density lipoprotein cholesterol
- Triglycerides

Certain calculated ratios (eg, total/high-density lipoprotein cholesterol) may also be reported as part of a simple lipid panel.

Other types of lipid testing (ie, apolipoproteins, lipid particle number or particle size, lipoprotein [a]) are not considered components of a simple lipid profile.

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### Related Policies

None applicable.

### Document Precedence

Blue Cross and Blue Shield of Vermont (Blue Cross VT) Medical Policies are developed to provide clinical guidance and are based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. The applicable group/individual contract and member certificate language, or employer's benefit plan if an ASO group, determines benefits that are in effect at the time of service. Since medical practices and knowledge are constantly evolving, Blue Cross VT reserves the right to review and revise its medical policies periodically. To the extent that there may be any conflict between medical policy and contract/employer benefit plan language, the member's contract/employer benefit plan language takes precedence.

### Audit Information

Blue Cross VT reserves the right to conduct audits on any provider and/or facility to ensure compliance with the guidelines stated in the medical policy. If an audit identifies instances of non-compliance with this medical policy, Blue Cross VT reserves the right to recoup all non-compliant payments.

## Administrative and Contractual Guidance

### Benefit Determination Guidance

Prior approval may be required and benefits are subject to all terms, limitations and conditions of the subscriber contract.

Incomplete authorization requests may result in a delay of decision pending submission of missing information. To be considered compete, see policy guidelines above.

NEHP/ABNE members may have different benefits for services listed in this policy. To confirm benefits, please contact the customer service department at the member's health plan.

Federal Employee Program (FEP): Members may have different benefits that apply. For further information please contact FEP customer service or refer to the FEP Service Benefit Plan Brochure. It is important to verify the member's benefits prior to providing the service to determine if benefits are available or if there is a specific exclusion in the member's benefit.

Coverage varies according to the member's group or individual contract. Not all groups are required to follow the Vermont legislative mandates. Member Contract language takes precedence over medical policy when there is a conflict.

If the member receives benefits through an Administrative Services Only (ASO) group, benefits may vary or not apply. To verify benefit information, please refer to the member's employer benefit plan documents or contact the customer service department. Language in the employer benefit plan documents takes precedence over medical policy when there is a conflict.

## Policy Implementation/Update information

| | |
|---|---|
| 09/2026 | New policy. Medical Necessity Criteria established for use of Apolipoprotein B, High-sensitivity C-reactive protein and Lipoprotein(a) for Risk Assessment and Management of Cardiovascular Disease. Measurement of other nontraditional analytes to assess cardiovascular risk and cardiovascular disease risk panels remain investigational. |

## Eligible providers

Qualified healthcare professionals practicing within the scope of their license(s).

## Approved by Blue Cross VT Medical Directors

Tom Weigel, MD, MBA
Vice President and Chief Medical Officer

Attachment I

| Code Type | Number | Description | Policy Instructions |
|---|---|---|---|
| **The following codes will be considered as medically necessary when applicable criteria have been met.** | | | |
| CPT® | 81401 | Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat) | Prior Approval is Not Required |
| CPT® | 81405 | Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis) | Prior Approval is Not Required |
| CPT® | 81406 | Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons) | Prior Approval is Not Required |
| CPT® | 82172 | Apolipoprotein, each | Prior Approval is Not Required |
| CPT® | 83695 | Lipoprotein (a) | Prior Approval is Not Required |
| CPT® | 84999 | Unlisted chemistry procedure | Prior Approval Required |
| CPT® | 86141 | C-reactive protein; high sensitivity (hsCRP) | Prior Approval is Not Required |
| **The following codes will be denied and Not Medically Necessary, Non-Covered, Contract Exclusions or Investigational.** | | | |
| CPT® | 83698 | Lipoprotein-associated phospholipase A2 (Lp-PLA2 | Investigational |
| CPT® | 83700 | Lipoprotein, blood; electrophoretic separation and quantitation | Investigational |
| CPT® | 83701 | Lipoprotein, blood; high resolution fractionation and quantitation of lipoproteins including lipoprotein subclasses when performed (e.g., electrophoresis, ultracentrifugation) | Investigational |
| CPT® | 83704 | Lipoprotein, blood; quantitation of lipoprotein particle number(s) (e.g., by nuclear magnetic resonance spectroscopy), includes lipoprotein particle subclass(es), when performed | Investigational |

| Code Type | Number | Description | Policy Instructions |
|---|---|---|---|
| CPT® | 83718 | Lipoprotein, direct measurement; high density cholesterol (HDL cholesterol) | Investigational |
| CPT® | 83719 | Lipoprotein, direct measurement; VLDL cholesterol | Investigational |
| CPT® | 83721 | Lipoprotein, direct measurement; LDL cholesterol | Investigational |
| CPT® | 83722 | Lipoprotein, direct measurement; small dense LDL cholesterol | Investigational |
| CPT® | 0052U | Lipoprotein, blood, high resolution fractionation and quantitation of lipoproteins, including all five major lipoprotein classes and subclasses of HDL, LDL, and VLDL by vertical auto profile ultracentrifugation | Investigational |
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