BlueCross BlueShield of Vermont

An Independent Licensee of the Blue Cross and Blue Shield Association.

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

File Name: Nontraditional Biomarkers
File Code: 2.04VT65
Origination: 08/2026
Last Review: 09/2026
Next Review: 09/2027
Effective Date: 01/01/2027

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 (e.g., total/high-density lipoprotein cholesterol) may also be reported as part of a simple lipid panel.

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

Reference Resources

1. Ahmadi-Abhari S, Luben RN, Wareham NJ, et al. Seventeen year risk of all-cause and cause-specific mortality associated with C-reactive protein, fibrinogen and leukocyte count in men and women: the EPIC-Norfolk study. EurJ Epidemiol. Jul 2013; 28(7): 541- 50. PMID 23821244
2. Albers JJ, Slee A, O'Brien KD, et al. Relationship of apolipoproteins A-1 and B, and lipoprotein(a) to cardiovascular outcomes: the AIM-HIGH trial (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglyceride and Impact on Global Health Outcomes). J Am Coll Cardiol. Oct 22 2013; 62(17): 1575-9. PMID23973688
3. Alebna PL, Mehta A. An Update on Lipoprotein(a): The Latest on Testing, Treatment, and Guideline Recommendations. Expert Analysis, American College of Cardiology. Sep 19, 2023. https://www.acc.org/Latest-in-Cardiology/Articles/2023/09/19/10/54/AnUpdate-on-Lipoprotein-a
4. Arca M, Montali A, Pigna G, et al. Comparison of atorvastatin versus fenofibrate in reaching lipid targets and influencing biomarkers of endothelial damage in patients with familial combined hyperlipidemia. Metabolism. Nov2007; 56(11): 1534-41. PMID 17950105
5. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. Sep 10 2019; 140(11): e596-e646. PMID 30879355
6. Balagopal, PB et al. Nontraditional risk factors and biomarkers for cardiovascular disease: mechanistic, research, and clinical considerations for youth: a scientific statement from the American Heart Association. Circulation, 2011 Jun 14;123(23):2749- 69.
7. Ballantyne CM, Pitt B, Loscalzo J, et al. Alteration of relation of atherogenic lipoprotein cholesterol to apolipoprotein B by intensive statin therapy in patients with acute coronary 43 syndrome (from the Limiting UNdertreatment of lipids in ACS With Rosuvastatin [LUNAR] Trial). Am J Cardiol. Feb 15 2013; 111(4): 506-9.PMID 23237107

8. Bays HE, Dujovne CA, McGovern ME, et al. Comparison of once-daily, niacin extendedrelease/lovastatin with standard doses of atorvastatin and simvastatin (the ADvicor Versus Other Cholesterol-Modulating Agents Trial Evaluation [ADVOCATE]). Am J Cardiol. Mar 15 2003; 91(6): 667-72. PMID 12633795
9. Benn M, Nordestgaard BG, Jensen GB, et al. Improving prediction of ischemic cardiovascular disease in the general population using apolipoprotein B: the Copenhagen City Heart Study. Arterioscler Thromb Vasc Biol. Mar 2007;27(3):661-670. PMID 17170368
10. Bennet A, Di Angelantonio E, Erqou S, et al. Lipoprotein(a) levels and risk of future coronary heart disease: large-scale prospective data. Arch Intern Med. Mar 24 2008; 168(6): 598-608. PMID 18362252
11. Bennet AM, Di Angelantonio E, Ye Z, et al. Association of apolipoprotein E genotypes with lipid levels and coronary risk. JAMA. Sep 19 2007;298(11):1300-1311. PMID 17878422
12. Blake GJ, Otvos JD, Rifai N, et al. Low-density lipoprotein particle concentration and size as determined by nuclear magnetic resonance spectroscopy as predictors of cardiovascular disease in women. Circulation. Oct 8 2002;106(15):1930-1937. PMID 12370215
13. Blonde L, Umpierrez GE, Reddy SS, et al. American Association of Clinical Endocrinology Clinical Practice Guideline: Developing a Diabetes Mellitus Comprehensive Care Plan-2022 Update. Endocr Pract. Oct 2022; 28(10): 923-1049. PMID 35963508
14. Blue Cross Blue Shield Association Medical Policy Reference Manual. Biomarker Testing in Risk Assessment and Management of Cardiovascular Disease – 2.04.65. Last Reviewed August 2026. Accessed August 2026.
15. Blue Cross Blue Shield Blue Care Network of Michigan: Joint Medical Policy : Nontraditional Biomarkers in Risk Assessment and Management of Cardiovascular Disease – Policy Effective Date: 11/1/2025. Accessed 08/2026. Policy References the following resources:
16. Boekholdt SM, Arsenault BJ, Mora S, et al. Association of LDL cholesterol, non-HDL cholesterol, and apolipoprotein B levels with risk of cardiovascular events among patients treated with statins: a meta-analysis. JAMA. Mar 28 2012; 307(12): 1302-9. PMID 22453571
17. Boekholdt SM, Hovingh GK, Mora S, et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. J Am Coll Cardiol. Aug 05 2014; 64(5): 485-94. PMID25082583
18. Bolibar I, von Eckardstein A, Assmann G, et al. Short-term prognostic value of lipid measurements in patients with angina pectoris. The ECAT Angina Pectoris Study Group: European Concerted Action on Thrombosis and Disabilities. Thromb Haemost. Dec 2000; 84(6): 955-60. PMID 11154140
19. Bostom AG, Cupples LA, Jenner JL, et al. Elevated plasma lipoprotein(a) and coronary heart disease in men aged55 years and younger. A prospective study. JAMA. Aug 21 1996; 276(7): 544-8. PMID 8709403
20. Brown G, Albers JJ, Fisher LD, et al. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. N Engl J Med. Nov 08 1990; 323(19): 1289-98. PMID 2215615
21. Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and

the American College of Cardiology Foundation. Diabetes Care. Apr 2008;31(4):811-822. PMID 18375431
22.Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus statement from the American Diabetes Association and the American College of Cardiology Foundation. Diabetes Care. Apr 2008; 31(4): 811-22. PMID 18375431
23. Buckley DI et al. Review C-reactive protein as a risk factor for coronary heart disease: a systematic review and meta-analyses for the U.S. Preventive Services Task Force. Ann Intern Med. 2009 Oct 6; 151(7):483-95.
24.Campos H, Moye LA, Glasser SP, et al. Low-density lipoprotein size, pravastatin treatment, and coronary events. JAMA. Sep 26 2001; 286(12): 1468-74. PMID 11572739
25.Carmena R, Roederer G, Mailloux H, et al. The response to lovastatin treatment in patients with heterozygous familial hypercholesterolemia is modulated by apolipoprotein E polymorphism. Metabolism. Jul 1993; 42(7): 895-901. PMID 8345800
26.Chiodini BD, Franzosi MG, Barlera S, et al. Apolipoprotein E polymorphisms influence effect of pravastatin on survival after myocardial infarction in a Mediterranean population: the GISSI-Prevenzione study. Eur Heart J. Aug2007; 28(16): 1977-83. PMID 17567623
27.Ciftdoğan DY, Coskun S, Ulman C, et al. The association of apolipoprotein E polymorphism and lipid levels in children with a family history of premature coronary artery disease. J Clin Lipidol. Jan-Feb 2012; 6(1): 81-7. PMID22264578
28. Clarke R, Emberson JR, Parish S, et al. Cholesterol fractions and apolipoproteins as risk factors for heart disease mortality in older men. Arch Intern Med. Jul 9 2007;167(13):1373-1378. PMID 17620530
29.Clarke R, Peden JF, Hopewell JC, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med. Dec 24 2009; 361(26): 2518-28. PMID 20032323
30.Cole, Thomas G. et al. Association of Apolipoprotein B and Nuclear Magnetic Resonance Spectroscopy-Derived LDL Particle Number with Outcomes in 25 Clinical Studies: Assessment by the AACC Lipoprotein and Vascular Diseases Division Working Group on Best Practices. Clinical Chemistry, 59 (5) p.752-70, May 2013.
31.Cook, NR et al. The effect of including C-reactive protein in cardiovascular risk prediction models for women. Ann Intern Med. 2006 Jul 4;145(1):21-9.
32.Curry SJ, Krist AH, Owens DK, et al. Risk Assessment for Cardiovascular Disease With Nontraditional Risk Factors: US Preventive Services Task Force Recommendation Statement. JAMA. Jul 17 2018; 320(3): 272-280.PMID 29998297
33.Danesh J, Lewington S, Thompson SG, et al. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant metaanalysis. JAMA. Oct 12 2005; 294(14): 1799-809. PMID 16219884
34.de Andrade M, Thandi I, Brown S, et al. Relationship of the apolipoprotein E polymorphism with carotid artery atherosclerosis. Am J Hum Genet. Jun 1995; 56(6): 1379-90. PMID 7762561
35.Di Angelantonio E, Gao P, Pennells L, et al. Emerging Risk Factors Collaboration: Lipidrelated markers and cardiovascular disease prediction. JAMA. Jun 20 2012;307(23):2499-2506. PMID 22797450
36. Di Angelantonio, E et al. The Emerging Risk Factors Collaboration: C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis. Lancet, 2010; 375: 132–40.

37. Donnelly LA, Palmer CN, Whitley AL, et al. Apolipoprotein E genotypes are associated with lipid-lowering responses to statin treatment in diabetes: a Go-DARTS study. Pharmacogenet Genomics. Apr 2008; 18(4): 279-87. PMID 18334912
38. Eichner JE, Kuller LH, Orchard TJ, et al. Relation of apolipoprotein E phenotype to myocardial infarction and mortality from coronary artery disease. Am J Cardiol. Jan 15 1993; 71(2): 160-5. PMID 8421977
39. ElSayed NA, Aleppo G, Bannuru RR, et al. 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes-2024. Diabetes Care. Jan 01 2024; 47(Suppl 1): S179-S218. PMID 38078592
40. Erqou S, Kaptoge S, Perry PL, et al. Lipoprotein(a) concentration and the risk of coronary heart disease, stroke, and nonvascular mortality. JAMA. Jul 22 2009; 302(4): 412-23. PMID 19622820
41. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. May 16 2001;285(19):2486-2497. PMID 11368702
42. Fogacci F, Cicero AF, D'Addato S, et al. Serum lipoprotein(a) level as long-term predictor of cardiovascular mortality in a large sample of subjects in primary cardiovascular prevention: data from the Brisighella Heart Study. Eur J Intern Med. Jan 2017; 37: 49-55. PMID 27553697
43. Genest J et al. 2009 Canadian Cardiovascular Society/Canadian guidelines for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease in the adult - 2009 recommendations. Can J Cardiol 2009; 25;567-79.
44. Genser B, Dias KC, Siekmeier R, et al. Lipoprotein (a) and risk of cardiovascular disease--a systematic review and meta-analysis of prospective studies. Clin Lab. 2011; 57(3-4): 143-56. PMID 21500721
45. Goff, DC et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology /American Heart Association Task Force on Practice Guidelines. Circulation; November 12, 2013.
46. Gotto AM, Jr., Whitney E, Stein EA, et al. Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). Circulation. Feb 8 2000;101(5):477-484. PMID 10662743
47. Grundy SM, Cleeman JI, Merz CN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. Jul 13 2004; 110(2): 227-39. PMID 15249516
48. Hamm, Christian W. et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). European Heart Journal (2011) 32, 2999–3054.
49. Handelsman Y, Jellinger PS, Guerin CK, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Management of Dyslipidemia and Prevention of Cardiovascular Disease Algorithm - 2020 Executive Summary. Endocr Pract. Oct 2020; 26(10): 1196-1224. PMID33471721
50. Helfand M, Buckley DI, Freeman M, et al. Emerging risk factors for coronary heart disease: a summary of systematic reviews conducted for the U.S. Preventive Services Task Force. Ann Intern Med. Oct 06 2009; 151(7):496-507. PMID 19805772

51. Ito H, Pacold IV, Durazo-Arvizu R, et al. The effect of including cystatin C or creatinine in a cardiovascular risk model for asymptomatic individuals: the multi-ethnic study of atherosclerosis. Am J Epidemiol. Oct 15 2011; 174(8):949-57. PMID 21880578
52. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. Endocr Pract. Apr 2017;23(Suppl 2):1-87. PMID 28437620
53. Jellinger PS, Handelsman Y, Rosenblit PD, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease. Endocr Pract. Apr 2017; 23(Suppl 2):1-87. PMID 28437620
54. Jellinger, Paul S. et al. AACE Task Force for the Management of Dyslipidemia and Prevention of Atherosclerosis Writing Committee. AACE Lipid and Atherosclerosis Guidelines, Endor Pract. 2012; 18, (suppl 1), retrieved June 2, 2021 from: https://www.aace.com/files/lipid-guidelines.pdf.
55. Kamstrup PR, Benn M, Tybjaerg-Hansen A, et al. Extreme lipoprotein(a) levels and risk of myocardial infarction in the general population: the Copenhagen City Heart Study. Circulation. Jan 15 2008; 117(2): 176-84. PMID18086931
56. Kaptoge S, White IR, Thompson SG, et al. Associations of plasma fibrinogen levels with established cardiovascular disease risk factors, inflammatory markers, and other characteristics: individual participant meta-analysis of 154,211 adults in 31 prospective studies: the fibrinogen studies collaboration. Am J Epidemiol. Oct 152007; 166(8): 867- 79. PMID 17785713
57. Kastelein JJ, van der Steeg WA, Holme I, et al. Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment. Circulation. Jun 10 2008;117(23):3002-3009. PMID 18519851
58. Kengne AP, Czernichow S, Stamatakis E, et al. Fibrinogen and future cardiovascular disease in people with diabetes: aetiological associations and risk prediction using individual participant data from nine community-based prospective cohort studies. Diab Vasc Dis Res. Mar 2013; 10(2): 143-51. PMID 22786872
59. Khera AV, Everett BM, Caulfield MP, et al. Lipoprotein(a) concentrations, rosuvastatin therapy, and residual vascular risk: an analysis from the JUPITER Trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). Circulation. Feb 11 2014; 129(6): 635-42. PMID 24243886
60. Koch W, Hoppmann P, Schomig A, et al. Apolipoprotein E gene epsilon2 /epsilon3/epsilon4 polymorphism and myocardial infarction: case-control study in a large population sample. Int J Cardiol. Mar 28 2008; 125(1): 116-7.PMID 17433475
61. Kuller L, Arnold A, Tracy R, et al. Nuclear magnetic resonance spectroscopy of lipoproteins and risk of coronary heart disease in the Cardiovascular Health Study. Arterioscler Thromb Vasc Biol. Jul 1 2002;22(7):1175-1180. PMID 12117734
62. Kulminski AM, Ukraintseva SV, Arbeev KG, et al. Health-protective and adverse effects of the apolipoprotein E epsilon2 allele in older men. J Am Geriatr Soc. Mar 2008; 56(3): 478-83. PMID 18179501
63. Kwiterovich PO. Clinical relevance of the biochemical, metabolic, and genetic factors that influence low-density lipoprotein heterogeneity. Am J Cardiol. Oct 17 2002; 90(8A): 30i47i. PMID 12419479
64. Lamarche B, Moorjani S, Lupien PJ, et al. Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Québec cardiovascular study. Circulation. Aug 011996; 94(3): 273-8. PMID 8759066

65. Lamarche B, Tchernof A, Moorjani S, et al. Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men. Prospective results from the Quebec Cardiovascular Study. Circulation. Jan 7 1997;95(1):69-75. PMID 8994419
66. Lee M, Saver JL, Huang WH, et al. Impact of elevated cystatin C level on cardiovascular disease risk in predominantly high cardiovascular risk populations: a meta-analysis. Circ Cardiovasc Qual Outcomes. Nov 2010;3(6): 675-83. PMID 20923994
67. Lee SR, Prasad A, Choi YS, et al. LPA Gene, Ethnicity, and Cardiovascular Events. Circulation. Jan 17 2017;135(3): 251-263. PMID 27831500
68. Luo J, Wang LP, Hu HF, et al. Cystatin C and cardiovascular or all-cause mortality risk in the general population: A meta-analysis. Clin Chim Acta. Oct 23 2015; 450: 39-45. PMID 26192218
69. Mach R, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS), European Heart Journal, Volume 41, Issue 1, 1 January 2020, Pages 111–188, https://doi.org/10.1093/eurheartj/ehz455
70. McQueen, Matthew J. et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. Lancet 2008; 372: 224–33.
71. Medical Services Commission. Cardiovascular disease-primary prevention. Victoria, BC: British Columbia Medical Services Commission; March 15, 2008, revised 2014. https://www2.gov.bc.ca/assets/gov/health/about-bc-s-health-care-system/bcguidelines/cvd.pdf Accessed 7/22/25.
72. Melander O, Newton-Cheh C, Almgren P, et al. Novel and conventional biomarkers for prediction of incident cardiovascular events in the community. JAMA. Jul 01 2009; 302(1): 49-57. PMID 19567439
73. Miller BD, Alderman EL, Haskell WL, et al. Predominance of dense low-density lipoprotein particles predicts angiographic benefit of therapy in the Stanford Coronary Risk Intervention Project. Circulation. Nov 01 1996; 94(9):2146-53. PMID 8901665
74. Mora S, Glynn RJ, Boekholdt SM, et al. On-treatment non-high-density lipoprotein cholesterol, apolipoprotein B, triglycerides, and lipid ratios in relation to residual vascular risk after treatment with potent statin therapy: JUPITER (justification for the use of statins in prevention: an intervention trial evaluating rosuvastatin). J Am Coll Cardiol. Apr24 2012; 59(17): 1521-8. PMID 22516441
75. Mora S, Glynn RJ, Ridker PM. High-density lipoprotein cholesterol, size, particle number, and residual vascular risk after potent statin therapy. Circulation. Sep 10 2013;128(11): 1189-1197. PMID 24002795
76. Mora S, Otvos JD, Rifai N, et al. Lipoprotein particle profiles by nuclear magnetic resonance compared with standard lipids and apolipoproteins in predicting incident cardiovascular disease in women. Circulation. Feb 24 2009;119(7):931-939. PMID 19204302
77. Mora S, Wenger NK, Demicco DA, et al. Determinants of residual risk in secondary prevention patients treated with high- versus low-dose statin therapy: the Treating to New Targets (TNT) study. Circulation. Apr 24 2012;125(16):1979-1987. PMID 22461416
78. National Heart Lung and Blood Institute. Managing Blood Cholesterol in Adults: Systematic Evidence Review From the Cholesterol Expert Panel, 2013. Bethesda, MD: National Heart, Lung, and Blood Institute; 2013.

https://www.nhlbi.nih.gov/sites/default/files/media/docs/cholesterol-in-adults.pdf. Accessed August 23, 2022.
79. Nestel PJ, Barnes EH, Tonkin AM, et al. Plasma lipoprotein(a) concentration predicts future coronary and cardiovascular events in patients with stable coronary heart disease. Arterioscler Thromb Vasc Biol. Dec 2013;33(12): 2902-8. PMID 24092750
80. Ohira T, Schreiner PJ, Morrisett JD, et al. Lipoprotein(a) and incident ischemic stroke: the Atherosclerosis Risk in Communities (ARIC) study. Stroke. Jun 2006; 37(6): 1407-12. PMID 16675734
81. Ordovas JM, Mooser V. The APOE locus and the pharmacogenetics of lipid response. Curr Opin Lipidol. Apr 2002;13(2): 113-7. PMID 11891412
82. Osei-Hwedieh DO, Amar M, Sviridov D, et al. Apolipoprotein mimetic peptides: Mechanisms of action as anti-atherogenic agents. Pharmacol Ther. Apr 2011; 130(1): 83-91. PMID 21172387
83. Otvos JD, Jeyarajah EJ, Cromwell WC. Measurement issues related to lipoprotein heterogeneity. Am J Cardiol. Oct 17 2002;90(8A):22i-29i. PMID 12419478
84. Patel AP, Wang M, Pirruccello JP, et al. Lp(a) (Lipoprotein[a]) concentrations and incident atherosclerotic cardiovascular disease. Arterioscler Thromb Vasc Biol. 2021;42:465-474.
85. Pearson GJ, Thanassoulis G, Anderson TJ, et al. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. Volume 37, Issue 8, P1129-1150, August 2021. https://onlinecjc.ca/article/S0828-282X(21)00165-3/fulltext
86. Pearson TA et al. Markers of inflammation and cardiovascular disease. Application to clinical and public health practice. A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. AHA/CDC Scientific Statement, Circulation, 2003;107:499-511.
87. Ray KK, Cannon CP, Cairns R, et al. Prognostic utility of apoB/AI, total cholesterol/HDL, non-HDL cholesterol, orhs-CRP as predictors of clinical risk in patients receiving statin therapy after acute coronary syndromes: results from PROVE IT-TIMI 22. Arterioscler Thromb Vasc Biol. Mar 2009; 29(3): 424-30. PMID 19122170
88. Reyes-Soffer G, Ginsberg HN, Berglund L, et al. Lipoprotein(a): A genetically determined, causal, and prevalent risk factor for atherosclerotic cardiovascular disease: a scientific statement from the American Heart Association. Arterioscler Thromb Vasc Biol. 2022;42:e:48-e60.
89. Ridker PM, Buring JE, Rifai N, et al. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. JAMA. Feb 14 2007;297(6):611-619. PMID 17299196
90. Ridker PM, Danielson E, Fonseca FA, et al. JUPITER Trial Study Group. Reduction in Creactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: A prospective study of the JUPITER trial. Lancet, 2009;373(9670):1175-1182.
91. Ridker PM, Hennekens CH, Stampfer MJ. A prospective study of lipoprotein(a) and the risk of myocardial infarction. JAMA. Nov 10 1993; 270(18): 2195-9. PMID 8411602
92. Ridker PM, Rifai N, Cook NR, et al. Non-HDL cholesterol, apolipoproteins A-I and B100, standard lipid measures, lipid ratios, and CRP as risk factors for cardiovascular disease in women. JAMA. Jul 20 2005;294(3):326-333. PMID 16030277
93. Rigal M, Ruidavets JB, Viguier A, et al. Lipoprotein (a) and risk of ischemic stroke in young adults. J Neurol Sci. Jan 15 2007; 252(1): 39-44. PMID 17113602

94. Robinson JG, Wang S, Jacobson TA. Meta-analysis of comparison of effectiveness of lowering apolipoprotein B versus low-density lipoprotein cholesterol and nonhigh-density lipoprotein cholesterol for cardiovascular risk reduction in randomized trials. Am J Cardiol. Nov 15 2012;110(10):1468-1476. PMID 22906895
95. Rosenson RS, Otvos JD, Freedman DS. Relations of lipoprotein subclass levels and low-density lipoprotein size to progression of coronary artery disease in the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I) trial. Am J Cardiol. Jul 15 2002;90(2):89-94. PMID 12106834
96. Rosenson RS, Underberg JA. Systematic review: Evaluating the effect of lipid-lowering therapy on lipoprotein and lipid values. Cardiovasc Drugs Ther. Jul 28 2013;27(5):465-479. PMID 23893306
97. Rosenson RS, Wolff DA, Huskin AL, et al. Fenofibrate therapy ameliorates fasting and postprandial lipoproteinemia, oxidative stress, and the inflammatory response in subjects with hypertriglyceridemia and the metabolic syndrome. Diabetes Care. Aug 2007; 30(8): 1945-51. PMID 17483155
98. Sarkkinen E, Korhonen M, Erkkila A, et al. Effect of apolipoprotein E polymorphism on serum lipid response to the separate modification of dietary fat and dietary cholesterol. Am J Clin Nutr. Dec 1998; 68(6): 1215-22. PMID9846849
99. Sattar N, Wannamethee G, Sarwar N, et al. Leptin and coronary heart disease: prospective study and systematic review. J Am Coll Cardiol. Jan 13 2009; 53(2): 167-75. PMID 19130985
100. Schaefer EJ, Lamon-Fava S, Jenner JL, et al. Lipoprotein(a) levels and risk of coronary heart disease in men. The lipid Research Clinics Coronary Primary Prevention Trial. JAMA. Apr 06 1994; 271(13): 999-1003. PMID 8139085
101. Schmitz F, Mevissen V, Krantz C, et al. Robust association of the APOE epsilon4 allele with premature myocardial infarction especially in patients without hypercholesterolaemia: the Aachen study. Eur J Clin Invest. Feb 2007;37(2): 106-8. PMID 17217375
102. Sharrett AR, Ballantyne CM, Coady SA, et al. Coronary heart disease prediction from lipoprotein cholesterol levels, triglycerides, lipoprotein(a), apolipoproteins A-I and B, and HDL density subfractions: The Atherosclerosis Risk in Communities (ARIC) Study. Circulation. Sep 4 2001;104(10):1108-1113. PMID 11535564
103. Shaw LJ, Polk DM, Kahute TA, et al. Prognostic accuracy of B-natriuretic peptide measurements and coronary artery calcium in asymptomatic subjects (from the Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research [EISNER] study). Am J Cardiol. Nov 01 2009; 104(9): 1245-50. PMID 19840570
104. Singh K, Chandra A, Sperry T, et al. Associations Between High-Density Lipoprotein Particles and Ischemic Events by Vascular Domain, Sex, and Ethnicity: A Pooled Cohort Analysis. Circulation. Aug 18 2020; 142(7): 657-669.PMID 32804568
105. Sirtori CR, Calabresi L, Pisciotta L, et al. Effect of statins on LDL particle size in patients with familial combined hyperlipidemia: a comparison between atorvastatin and pravastatin. Nutr Metab Cardiovasc Dis. Feb 2005; 15(1):47-55. PMID 15871851
106. Smolders B, Lemmens R, Thijs V. Lipoprotein (a) and stroke: a meta-analysis of observational studies. Stroke. Jun 2007; 38(6): 1959-66. PMID 17478739
107. Sniderman AD, Islam S, Yusuf S, et al. Discordance analysis of apolipoprotein B and non-high density lipoprotein cholesterol as markers of cardiovascular risk in the INTERHEART study. Atherosclerosis. Dec 2012;225(2):444-449. PMID 23068583
108. Sniderman, Allan et al. A Meta-Analysis of Low-Density Lipoprotein Cholesterol, NonHigh-Density Lipoprotein Cholesterol, and Apolipoprotein B as Markers of

109. Sofat R, Cooper JA, Kumari M, et al. Circulating apolipoprotein E concentration and cardiovascular disease risk: meta-analysis of results from three studies. PLoS Med. Oct 2016;13(10):e1002146. PMID 27755538
110. Stampfer MJ, Krauss RM, Ma J, et al. A prospective study of triglyceride level, lowdensity lipoprotein particle diameter, and risk of myocardial infarction. JAMA. Sep 18 1996;276(11):882-888. PMID 8782637
111. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. Jul 01 2014; 63(25 Pt B): 2889-934. PMID24239923
112. Suk Danik J, Rifai N, Buring JE, et al. Lipoprotein(a), hormone replacement therapy, and risk of future cardiovascular events. J Am Coll Cardiol. Jul 08 2008; 52(2): 124-31. PMID 18598891
113. Superko HR, Berneis KK, Williams PT, et al. Gemfibrozil reduces small low-density lipoprotein more in normolipemic subjects classified as low-density lipoprotein pattern B compared with pattern A. Am J Cardiol. Nov01 2005; 96(9): 1266-72. PMID 16253595
114. Tokuno A, Hirano T, Hayashi T, et al. The effects of statin and fibrate on lowering small dense LDL- cholesterol in hyperlipidemic patients with type 2 diabetes. J Atheroscler Thromb. Jun 2007; 14(3): 128-32. PMID 17587764
115. Toth PP, Grabner M, Punekar RS, et al. Cardiovascular risk in patients achieving lowdensity lipoprotein cholesterol and particle targets. Atherosclerosis. Aug 2014;235(2):585-591. PMID 24956532
116. Tzou WS, Douglas PS, Srinivasan SR, et al. Advanced lipoprotein testing does not improve identification of subclinical atherosclerosis in young adults: the Bogalusa Heart Study. Ann Intern Med. May 3 2005;142(9):742-750. PMID 15867406
117. Tzoulaki I, Murray GD, Lee AJ, et al. Relative value of inflammatory, hemostatic, and rheological factors for incident myocardial infarction and stroke: the Edinburgh Artery Study. Circulation. Apr 24 2007; 115(16): 2119-27.PMID 17404162
118. Vaisi-Raygani A, Rahimi Z, Nomani H, et al. The presence of apolipoprotein epsilon4 and epsilon2 alleles augments the risk of coronary artery disease in type 2 diabetic patients. Clin Biochem. Oct 2007; 40(15): 1150-6.PMID 17689519
119. van der Steeg WA, Boekholdt SM, Stein EA, et al. Role of the apolipoprotein Bapolipoprotein A-I ratio in cardiovascular risk assessment: a case-control analysis in EPIC-Norfolk. Ann Intern Med. May 1 2007;146(9):640-648. PMID 17470832
120. van Wissen S, Smilde TJ, Trip MD, et al. Long term statin treatment reduces lipoprotein(a) concentrations in heterozygous familial hypercholesterolaemia. Heart. Aug 2003; 89(8): 893-6. PMID 12860867
121. Vasunilashorn S, Glei DA, Lan CY, et al. Apolipoprotein E is associated with blood lipids and inflammation in Taiwanese older adults. Atherosclerosis. Nov 2011; 219(1): 349-54. PMID 21840004
122. Vazirian F, Sadeghi M, Kelesidis T, et al. Predictive value of lipoprotein(a) in coronary artery calcification among asymptomatic cardiovascular disease subjects: A systematic review and meta-analysis. NutrMetab Cardiovasc Dis. Nov 2023; 33(11): 2055-2066. PMID 37567791
123. Volcik KA, Barkley RA, Hutchinson RG, et al. Apolipoprotein E polymorphisms predict low density lipoprotein cholesterol levels and carotid artery wall thickness but not incident coronary heart disease in 12,491 ARIC study participants. Am J Epidemiol. Aug 15 2006;164(4):342-348. PMID 16760224

124. Vossen CY, Hoffmann MM, Hahmann H, et al. Effect of APOE genotype on lipid levels in patients with coronary heart disease during a 3-week inpatient rehabilitation program. Clin Pharmacol Ther. Aug 2008; 84(2): 222-7.PMID 18388879
125. Waldeyer C, Makarova N, Zeller T, et al. Lipoprotein(a) and the risk of cardiovascular disease in the European population: results from the BiomarCaRE consortium. Eur Heart J. Aug 21 2017; 38(32): 2490-2498. PMID28449027
126. Walldius G, Jungner I, Holme I, et al. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. Lancet. Dec 15 2001;358(9298): 2026-33. PMID 11755609
127. Wang TJ, Larson MG, Levy D, et al. Plasma natriuretic peptide levels and the risk of cardiovascular events and death. N Engl J Med. Feb 12 2004; 350(7): 655-63. PMID 14960742
128. Willeit P, Thompson SG, Agewall S, et al. Inflammatory markers and extent and progression of early atherosclerosis: Meta-analysis of individual-participant-data from 20 prospective studies of the PROG-IMT collaboration. Eur J Prev Cardiol. Jan 2016; 23(2): 194-205. PMID 25416041
129. Wilson DP, Jacobson TA, Jones PH, et al. Use of Lipoprotein(a) in clinical practice: A biomarker whose time has come. A scientific statement from the National Lipid Association. J Clin Lipidol. May 2019; 13(3): 374-392. PMID31147269
130. Wilson PW, Jacobson TA, Martin SS, et al. Lipid measurements in the management of cardiovascular diseases: Practical recommendations a scientific statement from the national lipid association writing group. J Clin Lipidol. Published online: September 24, 2021 https://www.lipidjournal.com/article/S1933-2874(21)00245-2/fulltext Accessed 7/23/25.
131. Wilson PW, Jacobson TA, Martin SS, et al. Lipid measurements in the management of cardiovascular diseases: Practical recommendations a scientific statement from the 46 national lipid association writing group. J Clin Lipidol. Published online: September 24, 2021
132. Wilson PW, Myers RH, Larson MG, et al. Apolipoprotein E alleles, dyslipidemia, and coronary heart disease. The Framingham Offspring Study. JAMA. Dec 07 1994; 272(21): 1666-71. PMID 7966894
133. Wilson PW, Schaefer EJ, Larson MG, et al. Apolipoprotein E alleles and risk of coronary disease. A meta-analysis. Arterioscler Thromb Vasc Biol. Oct 1996; 16(10): 1250-5. PMID 8857921
134. Wu Z, Pilbrow AP, Liew OW, et al. Circulating cardiac biomarkers improve risk stratification for incident cardiovascular disease in community dwelling populations. EBioMedicine. Aug 2022; 82: 104170. PMID 35850010
135. Yang H, Guo W, Li J, et al. Leptin concentration and risk of coronary heart disease and stroke: A systematic review and meta-analysis. PLoS One. 2017; 12(3): e0166360. PMID 28278178
136. Zakai NA, Katz R, Jenny NS, et al. Inflammation and hemostasis biomarkers and cardiovascular risk in the elderly: the Cardiovascular Health Study. J Thromb Haemost. Jun 2007; 5(6): 1128-35. PMID 17388967
137. Zeng R, Xu CH, Xu YN, et al. Association of leptin levels with pathogenetic risk of coronary heart disease and stroke: a meta-analysis. Arq Bras Endocrinol Metabol. Nov 2014; 58(8): 817-23. PMID 25465603

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®	83718	Lipoprotein, direct measurement; high density cholesterol (HDL cholesterol)	Prior Approval is Not Required
CPT®	83721	Lipoprotein, direct measurement; LDL cholesterol	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

Code Type	Number	Description	Policy Instructions
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
CPT®	83719	Lipoprotein, direct measurement; VLDL 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