



MASSACHUSETTS

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Medical Policy

Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease

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Policy Number: 283

BCBSA Reference Number: 2.04.65

NCD/LCD:

- National Coverage Determination (NCD) for Lipid Testing (190.23)
- Local Coverage Determination (LCD): B-type Natriuretic Peptide (BNP) Testing (L33573)
- Local Coverage Determination (LCD): MoIDX: Biomarkers in Cardiovascular Risk Assessment (L36129)

Related Policies

- Cardiovascular risk panels, #[664](#)
- Measurement of Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) in the Assessment of Cardiovascular Risk, #[558](#)
- Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease and Venous Thromboembolic Disease, #[016](#)

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity

Measurement of novel lipid and nonlipid risk factors (i.e., apolipoprotein B, apolipoprotein A-I, apolipoprotein E, B-type natriuretic peptide, cystatin C, fibrinogen, leptin, LDL subclass, HDL subclass, lipoprotein[a]) as an adjunct to LDL cholesterol in the risk assessment and management of cardiovascular disease is [INVESTIGATIONAL](#).

The use of panels that include lipid and non-lipid cardiovascular risk markers is considered [NOT MEDICALLY NECESSARY](#).

Medicare HMO BlueSM and Medicare PPO BlueSM Members

Medical necessity criteria and coding guidance can be found through the links below.

[National Coverage Determinations \(NCDs\)](#)

National Coverage Determination (NCD) for Lipid Testing (190.23)

Note: To review the specific NCD, please remember to click “accept” on the CMS licensing agreement at the bottom of the CMS webpage.

Medical necessity criteria and coding guidance for **Medicare Advantage members living in Massachusetts** can be found through the links below.

[Local Coverage Determinations \(LCDs\) for National Government Services, Inc.](#)

Local Coverage Determination (LCD): B-type Natriuretic Peptide (BNP) Testing (L33573)

Local Coverage Determination (LCD): MoIDX: Biomarkers in Cardiovascular Risk Assessment (L36129)

Note: To review the specific LCD, please remember to click “accept” on the CMS licensing agreement at the bottom of the CMS webpage.

For medical necessity criteria and coding guidance for **Medicare Advantage members living outside of Massachusetts**, please see the Centers for Medicare and Medicaid Services website at <https://www.cms.gov> for information regarding your specific jurisdiction.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	This is not a covered service.
Commercial PPO and Indemnity	This is not a covered service.
Medicare HMO Blue SM	Prior authorization is not required .
Medicare PPO Blue SM	Prior authorization is not required .

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following CPT codes are considered investigational for **Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity**:

CPT Codes

CPT codes:	Code Description
82610	Cystatin C
83695	Lipoprotein A
83700	Lipoprotein, blood; electrophoretic separation and quantitation

83701	Lipoprotein, blood; high resolution fractionation and quantitation of lipoproteins including lipoprotein subclasses when performed (eg, electrophoresis, ultracentrifugation)
83704	Lipoprotein, blood; quantitation of lipoprotein particle number(s) (eg, by nuclear magnetic resonance spectroscopy), includes lipoprotein particle subclass(es), when performed
83880	Natriuretic peptide
85384	Fibrinogen; activity
85385	Fibrinogen; antigen
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

Description

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. LDL particles consist 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 (LDL-C), while predictive on a population basis, are weaker markers of risk on an individual basis. Only a minority of subjects with elevated LDL and cholesterol levels will develop clinical disease, and up to 50% of cases of coronary artery disease (CAD) occur in subjects with "normal" levels of total and LDL-C. Thus, there is considerable potential to improve the accuracy of current cardiovascular risk prediction models.

Other non-lipid markers have been identified as being associated with cardiovascular disease (CVD), including B-type natriuretic peptide, cystatin C, fibrinogen, and leptin. These biomarkers may have a predictive role in identifying CVD risk or in targeting for therapy.

Lipid Markers

Apolipoprotein B

Apolipoprotein B (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 lipoproteins (VLDL). Because LDL and VLDL each contains 1 molecule of apo B, 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 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 LDL concentration.

Apolipoprotein AI

HDL contains 2 associated apolipoproteins (ie, AI, AII). HDL particles can also be classified by whether they contain apo AI only or they contain apo AI and apo AII. All lipoproteins contain apo AI, and some also contain 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 has been proposed as more accurate than the traditional use of HDL level in the evaluation of the 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 (ie, "bad") cholesterol to anti-atherogenic (ie, "good") cholesterol.

Apolipoprotein E

Apolipoprotein E (apo E) is the primary apolipoprotein found in VLDLs and chylomicrons. Apo 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, 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 above 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. *APOE* genotype may be a factor that determines an individual's degree of response to interventions such as statin therapy.

HDL Subclass

HDL 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 cardioprotection, and HDL₃, which are smaller, denser particles.

An alternative to measuring the concentration of subclasses of HDL (eg, HDL₂, HDL₃) is direct measurement of HDL particle size and/or number. Particle size can be measured by nuclear magnetic resonance spectroscopy or by gradient-gel electrophoresis. HDL particle numbers can be measured by nuclear magnetic resonance 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.

LDL 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 a 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. Presence of the metabolic syndrome is considered by ATP III to be a substantial risk-enhancing factor for CAD.

LDL 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 whether 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-C 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-C 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 vs larger.

Lipoprotein (a)

Lipoprotein (a) (Lp[a]) is a lipid-rich particle similar to LDL. Apo B is the major apolipoprotein associated with LDL; in Lp(a), however, there is an additional apo A covalently linked to the 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 1000-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

Brain Natriuretic Peptide

Brain natriuretic peptide (BNP) is an amino acid polypeptide secreted primarily by the ventricles of the heart when 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. BNP 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

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

Numerous lipid and non-lipid biomarkers have been proposed as potential risk markers for cardiovascular disease. Biomarkers assessed herein are those that have the most evidence in support of their use in clinical care, including apolipoprotein B (apo B), apolipoprotein AI (apo AI), apolipoprotein E (apo E), high-density lipoprotein (HDL) subclass, low-density lipoprotein (LDL) subclass, lipoprotein (a), B-type natriuretic peptide, cystatin C, fibrinogen, and leptin. These biomarkers have been studied as alternatives or additions to standard lipid panels for risk stratification in cardiovascular disease or as treatment targets for lipid-lowering therapy.

For individuals who are asymptomatic with risk of cardiovascular disease who receive novel cardiac biomarker testing (eg, apo B, apo AI, apo E, HDL subclass, LDL subclass, lipoprotein [a], B-type natriuretic peptide, cystatin C, fibrinogen, leptin), 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. In particular, apo B and apo AI have been identified as adding some incremental predictive value. However, it has not been established whether the incremental accuracy provides clinically important information beyond that of traditional lipid measures. Furthermore, no study has provided high-quality evidence that measurement of markers leads to changes in management that improve health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with hyperlipidemia managed with lipid-lowering therapy who receive novel cardiac biomarker testing (eg, apo B, apo AI, apo E, apo E, HDL subclass, LDL subclass, lipoprotein [a], B-type natriuretic peptide, 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 randomized controlled trials has suggested that these markers are associated with treatment success. However, there is no direct evidence that using markers other than LDL and HDL as a lipid-lowering treatment target leads to improved health outcomes. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy History

Date	Action
2/2019	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
7/2018	Clarified coding information.
3/2018	New references added from BCBSA National medical policy. Background and summary clarified.
1/2017	New references added from BCBSA National medical policy.
1/2017	Clarified coding information for the 2017 code changes.
6/2016	Clarified coding information.
11/2015	New references added from BCBSA National medical policy.
7/2015	Clarified coding information.
11/2014	National Coverage Determination (NCD) for Lipid Testing (190.23) added.
3/2014	BCBSA National medical policy review. Not medically necessary and investigational indications described; title changed. Effective 3/1/2014. Coverage for B-type natriuretic peptide testing for Medicare Advantage clarified. Code information clarified.
3/2013	Updated to add non-covered code 83701.
11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
5/2/2011	Revised date.

4/2011	Medical Policy Group- Cardiology and Pulmonology. No changes to policy statements.
11/1/2010	Medical Policy #283 effective describing on-going non-coverage.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

[Medical Policy Terms of Use](#)

[Managed Care Guidelines](#)

[Indemnity/PPO Guidelines](#)

[Clinical Exception Process](#)

[Medical Technology Assessment Guidelines](#)

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