Medical Coverage Policy | Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease

Blue Cross Blue Shield of Rhode Island

EFFECTIVE DATE: 01|01|2016
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OVERVIEW

Numerous lipid and nonlipid biomarkers have been proposed as potential risk markers for cardiovascular disease. The biomarkers assessed here are apolipoprotein B (apo B), apolipoprotein AI (apo AI), apolipoprotein E (apo E), B-type natriuretic peptide, cystatin C, fibrinogen, high-density lipoprotein (HDL) subclass, leptin, low-density lipoprotein (LDL) subclass, and lipoprotein A.

MEDICAL CRITERIA

Not applicable

PRIOR AUTHORIZATION

Not applicable

POLICY STATEMENT

BlueCHiP for Medicare and Commercial Products

Measurement of novel lipid and nonlipid risk factors (ie, apolipoprotein B, apolipoprotein AI, apolipoprotein E, cystatin C, fibrinogen, leptin, LDL subclass, HDL subclass, lipoprotein[a]) is considered **not medically necessary** as there is insufficient peer-reviewed scientific literature to demonstrate that the service is effective.

B type natriuretic peptide testing is covered but not separately reimbursed when used in conjunction with standard diagnostic tests, medical history and clinical findings during an evaluation of heart failure in an acute care setting or other setting (i.e. emergency department) where test results are immediately determined.

COVERAGE

Benefits may vary between groups/contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for limitations of benefits/coverage when services are not medically necessary.

BACKGROUND

LDL have been identified as the major atherogenic lipoproteins and have long been identified by the National Cholesterol Education Project (NCEP) 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 nonlipid markers have been identified as having an association with cardiovascular disease including B-type natriuretic peptide, cystatin C, fibrinogen, and leptin. These biomarkers may have a predictive role in identifying cardiovascular disease risk or in targeting for therapy,

Apolipoprotein B
Apolipoprotein B (apo B) is the major protein moiety of all lipoproteins except for 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 both LDL and VLDL each contain 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 both in size and in cholesterol content, for a given concentration of LDL-C, there can be a wide variety of both 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 is LDL concentration. Two basic techniques are used for measuring LDL particle concentration. Particle size can be determined by gradient gel electrophoresis, or direct measurement of the number of LDL particles can be performed using nuclear magnetic spectroscopy. Nuclear magnetic resonance (NMR) spectroscopy is based on the fact that lipoprotein subclasses of different size broadcast distinguishable NMR signals. Thus NMR can quantify the number of LDL particles of a specific size (ie, small dense LDL) and can provide a measurement of the total number of particles.

Apolipoprotein AI
HDL contains 2 associated apolipoproteins, ie, AI and AII. HDL particles can also be classified by whether they contain apolipoprotein AI (apo AI) only or whether they contain both apo AI and apolipoprotein AII (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 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. A

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 the 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 1 factor that determines an individual's degree of response to interventions such as statin therapy.

B-Type or Brain Natriuretic Peptide
Brain natriuretic peptide (BNP) is an amino acid polypeptide that is 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.

Additionally, there is a Local Coverage Determination (LCD) for B-type Natriuretic Peptide (BNP) Testing which states:
BNP measurements must be analyzed in conjunction with standard diagnostic tests, medical history and clinical findings. The efficacy of BNP measurement as a stand-alone test has not yet been established. Clinicians should be aware that certain conditions such as ischemia, infarction and renal insufficiency, may cause elevation of circulating BNP concentration and require alterations of the interpretation of BNP results.

Additional investigation is required to further define the diagnostic value of plasma BNP in monitoring the efficiency of treatment for CHF and in tailoring the therapy for heart failure. Therefore, BNP measurements for monitoring and management of CHF are not a covered service.

Cystatin C
Cystatin C is a small serine protease inhibitor protein that is secreted from all functional cells found throughout 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 cardiovascular risk and all-cause mortality

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/density and/or on the apolipoprotein composition. Using size/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. HDL contains 2 associated apolipoproteins, ie, AI and AII. HDL particles can also be classified by whether they contain apo AI only or whether they contain both apo AI and apo AII. There has been substantial interest in determining whether subclasses of HDL can be used to provide additional information on cardiovascular risk compared to HDL alone. An alternative to measuring the concentration of subclasses of HDL, such as HDL2 and HDL3, is direct measurement of HDL particle size and/or number. Particle size can be measured by NMR spectroscopy or by gradient-gel electrophoresis. HDL 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 measurement of HDL particle number as a surrogate, based on the premise that each HDL particle contains 1 apo AI molecule.

LDL Subclass
Two main subclass patterns of LDL, called A and B, have been described. In subclass pattern A, the particles have a diameter larger than 25 nm and are less dense, while in subclass pattern B, the 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 II diabetes and is 1 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 (CRP), 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 to use a combination of 2 or more 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, 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 compared with larger particles. Therefore, for patients with elevated numbers of LDL particles, cardiac risk may be further enhanced when the particles are smaller versus larger.

Two techniques are most commonly used for measuring LDL particle concentration, the surrogate measurement of apo B or direct measurement of the number of particles using NMR. NMR is used based on the fact that lipoprotein subclasses of different size broadcast distinguishable NMR signals. Thus NMR can directly measure the number of LDL particles of a specific size (ie, small dense LDL) and can provide a measurement of the total number of particles. Thus, NMR is proposed as an additional technique to assess cardiac risk

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 relationship with the development of cardiovascular disease.

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 apolipoprotein (a) molecule is structurally similar to plasminogen, suggesting that lp(a) may contribute to the thrombotic and atherogenic basis of cardiovascular disease. 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 levels of lp(a). Therefore, it has been proposed that levels of lp(a) may be an independent risk factor for CAD.

Numerous nontraditional lipid and other biomarker measurements have been proposed for use in improving risk prediction for cardiovascular disease, including apolipoprotein B (apo B), apolipoprotein AI (apo AI), the ratio of apo B/apo AI, apolipoprotein E (apo E), lipoprotein A, subclasses of low-density lipoprotein (LDL) and high-density lipoprotein (HDL), B-type natriuretic peptide, cystatin C, fibrinogen and leptin. In general, there is evidence that some of these markers may provide some incremental accuracy in risk prediction. However, it has not been established that the incremental accuracy provides clinically important information beyond that of traditional lipid measures. Furthermore, no study has provided highquality evidence that measurement of markers leads to changes in management that improve health outcomes. Some markers, eg, apo B, have also been proposed as treatment targets for lipid-lowering therapy. While some evidence supports that they may be accurate in predicting residual risk for patients on lipid-lowering therapy, there is no high-quality evidence that these markers lead to health outcome improvements when used in place of traditional lipid targets, such as LDL. Because of the deficiencies in the literature around these issues, the use of these novel lipid risk markers is considered not medically necessary.

CODING

BlueCHiP for Medicare and Commercial Products
The following CPT codes are considered not medically necessary:

82610 83695 83700 83701
83704 85384 85385

The following CPT code is covered but not separately reimbursed for BlueCHiP for Medicare and Commercial Products:

83880

RELATED POLICIES
Measurement of Small Low-Density Lipoprotein (LDL) Particles

PUBLISHED
Provider Update, November, 2015

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B-type Natriuretic Peptide (BNP) Testing (L26375):
https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=26375&ContrId=303&ver=58&ContrVer=1&CntrctrSelected=303*1&Cntrctr=303&s=47&DocType=Active&LCntrctr=295*1&bc=AggAAAIAAAAAAA%3d%3d&

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