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## OVERVIEW

Numerous lipid and nonlipid biomarkers have been proposed as potential risk markers for cardiovascular disease. Biomarkers assessed here 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 coverage of tests filed with PLA codes (0052U-VAP Cholesterol Test), please refer to the related policy “Proprietary Laboratory Analyses (PLA).”

## MEDICAL CRITERIA

Not applicable

## PRIOR AUTHORIZATION

Not applicable

## POLICY STATEMENT

### Commercial Products

Measurement of novel lipid and non-lipid risk factors (ie, apolipoprotein B, apolipoprotein AI, apolipoprotein E, cystatin C, fibrinogen, leptin, low-density lipoprotein (LDL) subclass, high-density lipoprotein (HDL) subclass, lipoprotein[a]) are not medically necessary for Commercial products as the evidence is insufficient to determine the effects of the technology on health outcomes. This policy is applicable to Commercial Products only. For Medicare Advantage Plans see the related policy for Medicare Advantage Plans National and Local Coverage Determinations.

### Medicare Advantage Plans and Commercial Products

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 section of the Benefit Booklet, Evidence of Coverage or Subscriber Agreement for services not medically necessary.

## BACKGROUND

### Commercial Products

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 (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 therapy.

### ***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 B<sub>100</sub>, constitutes the apo B found in LDL and very-LDL. Because LDL and very-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 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**

High-density lipoprotein contains 2 associated apolipoproteins (ie, AI, AII). High-density lipoprotein 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 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, 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 the 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. 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 HDL<sub>2</sub>, the larger, less dense particles that may have the greatest degree of cardioprotection, and HDL<sub>3</sub>, which are smaller, denser particles.

An alternative to measuring the concentration of subclasses of HDL (eg, HDL<sub>2</sub>, HDL<sub>3</sub>) is a direct measurement of HDL particle size and/or number. Particle size can be measured by nuclear magnetic resonance spectroscopy or by gradient-gel electrophoresis. High-density lipoprotein 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 common 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) 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 the risk for CAD independent of the total LDL level. Also, some drugs may cause a greater shift in lipid profiles 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, the cardiac risk may be further enhanced when the particles are smaller versus larger.

### **Lipoprotein (a)**

Lipoprotein (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 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***

#### **B-Type or Brain Natriuretic Peptide**

Brain natriuretic peptide (BNP) 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.

#### **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.

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 that the technology results in an improvement in the net 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 that the technology results in an improvement in the net health outcomes. Therefore, these services are considered not medically necessary for Commercial products.

There is a Local Coverage Determination (LCD) for B-type Natriuretic Peptide (BNP) Testing that indicates:

BNP measurements may be considered reasonable and necessary when used in combination with other medical data such as medical history, physical examination, laboratory studies, chest x-ray, and electrocardiography:

- To distinguish cardiac cause of acute dyspnea from pulmonary or other non-cardiac causes. Plasma BNP levels are significantly increased in patients with CHF (Congestive Heart Failure) presenting with acute dyspnea compared with patients presenting with acute dyspnea due to other causes.
- To distinguish decompensated CHF from exacerbated chronic obstructive pulmonary disease (COPD) in a symptomatic patient with combined chronic CHF and COPD. Plasma BNP levels are significantly increased in patients with CHF with or without concurrent lung disease compared with patients who have primary lung disease.
- To establish prognosis or disease severity in chronic CHF when needed to guide therapy
- To achieve optimal dosing of guideline-directed medical therapy (GDMT) in select clinically euvolemic patients followed in a well-structured heart failure (HF) disease management program
- To guide therapeutic decision-making in individuals who have amyloidosis

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. Therefore, 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.

## **CODING**

### **Commercial Products**

The following CPT codes are not medically necessary:

**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

**83722** Lipoprotein, Direct Measurement; Small Dense LDL Cholesterol (Effective 1/1/2019)

**85384** Fibrinogen; activity

**85385** Fibrinogen; antigen

### **Medicare Advantage Plans and Commercial Products:**

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

**83880** Natriuretic peptide

## **RELATED POLICIES**

Medicare Advantage Plans National and Local Coverage Determinations Policy

Measurement of Lipoprotein-Associated Phospholipase A2 in the Assessment of Cardiovascular Risk

Propriety Laboratory Analyses (PLA)

## **PUBLISHED**

Provider Update, March 2023

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