

## Medical Coverage Policy | Biomarker Testing in Risk Assessment and Management of Cardiovascular Disease



**EFFECTIVE DATE:** 07 | 01 | 2025

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### OVERVIEW

Numerous lipid and non-lipid biomarkers have been proposed as potential risk markers for cardiovascular disease (CVD). Biomarkers assessed herein include, B-type natriuretic peptide, cystatin C, fibrinogen, high-density lipoprotein subclass, leptin, low-density lipoprotein subclass, lipoprotein(a), and lipoprotein-associated phospholipase A2 (Lp-PLA2). 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. Cardiovascular risk panels refer to different combinations of cardiac markers that are intended to evaluate the risk of CVD. There are numerous commercially available risk panels that include different combinations of lipids, noncardiac biomarkers, measures of inflammation, metabolic parameters, and/or genetic markers. Risk panels report the results of multiple individual tests, as distinguished from quantitative risk scores that combine the results of multiple markers into a single score.

This policy addresses the following test(s):

- Cystatin C, CPT Code 82610
- Fibrinogen; activity, CPT Code 85384
- Fibrinogen; antigen, CPT Code 85385
- Lipoprotein (a), CPT Code 83695
- Lipoprotein-associated phospholipase A2, (Lp-PLA2), CPT Code 83698
- Lipoprotein, blood; electrophoretic separation and quantitation, CPT Code 83700
- Lipoprotein, blood; high resolution fractionation and quantitation of lipoproteins including lipoprotein subclasses when performed (eg, electrophoresis, ultracentrifugation), CPT Code 83701
- Lipoprotein, blood; quantitation of lipoprotein particle number(s) (eg, by nuclear magnetic resonance spectroscopy), includes lipoprotein particle subclass(es), when performed, CPT Code 83704
- Lipoprotein, Direct Measurement; Small Dense LDL Cholesterol, CPT Code 83722
- MI-HEART Ceramides, Plasma (Mayo Clinic), CPT Code 0119U
- Natriuretic peptide, CPT Code 83880
- VAP Cholesterol Test (VAP Diagnostics Laboratory, Inc.), CPT Code 0052U

This policy does not address the use of a simple lipid panel, which includes a total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides. Certain calculated ratios (eg, total/high-density lipoprotein cholesterol) may also be reported as part of a simple lipid panel. Other types of lipid testing (ie, apolipoproteins, lipid particle number or particle size, lipoprotein [a]) are not considered components of a simple lipid profile.

This policy also does not address the use of panels of biomarkers in the diagnosis of acute myocardial infarction.

### MEDICAL CRITERIA

Not applicable

### PRIOR AUTHORIZATION

#### Medicare Advantage Plans and Commercial Products

There is no specific CPT coding for some testing referenced in this policy. Therefore, an Unlisted CPT code should be used (See Coding Section for details). All Unlisted genetic testing CPT codes require prior

authorization to determine what service is being rendered and if the service is covered or not medically necessary. See the Related Policies section.

**Note:** Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

## **POLICY STATEMENT**

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

#### **CPT Codes 82610, 83700, 83701 and 83704**

Measurement of the following nontraditional lipid and non-lipid biomarkers are medically necessary when filed with a covered diagnosis. See the Coding section for details.

- Lipoprotein, blood; electrophoretic separation and quantitation (CPT Code 83700)
- Lipoprotein, blood; high resolution fractionation and quantitation of lipoproteins including lipoprotein subclasses when performed (eg, electrophoresis, ultracentrifugation) (CPT Code 83701)
- Lipoprotein, blood; quantitation of lipoprotein particle number(s) (eg, by nuclear magnetic resonance spectroscopy), includes lipoprotein particle subclass(es), when performed (CPT Code 83704)
- Cystatin C (CPT Code 82610)

#### **CPT Codes 83695, 83722, 85384 and 85385**

Measurements of the following nontraditional lipid and non-lipid biomarkers are not covered for Medicare Advantage Plans and not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes.

- Lipoprotein (a) (CPT Code 83695)
- Lipoprotein, direct measurement; small dense LDL cholesterol (CPT Code 83722)
- Fibrinogen; activity (CPT Code 85384)
- Fibrinogen; antigen (CPT Code 85385)

#### **CPT Code 83698**

Measurement of lipoprotein-associated phospholipase A2 is considered not covered for Medicare Advantage Plans and not medically necessary for Commercial Products as the evidence is insufficient to determine the effects of the technology on health outcomes.

#### **CPT Code 83880**

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.

#### **Other Cardiovascular Disease Testing – CPT Codes 0119U, 0052U and 81479**

Cardiovascular disease risk panels, consisting of multiple individual biomarkers intended to assess cardiac risk (other than simple lipid panels), are considered not covered for Medicare Advantage Plans and not medically

necessary for Commercial Products as the evidence is insufficient to determine the effects of the technology on health outcomes.

### **Commercial Products**

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L. §27-19-81 described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information.

### **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**

#### **Simple Lipid Panel**

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

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

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

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

#### **Cardiovascular Disease**

Cardiovascular disease (CVD) remains the single largest cause of morbidity and mortality in the developed world. Mortality from CVD has accounted for 1 in 4 deaths in the United States, and there are numerous socio-economic factors that affect CVD mortality rates. Lower-income, race, age, and behavioral factors all have a significant impact on health outcome disparities associated with CVD.

As a result, accurate prediction of CVD risk is a component of medical care that has the potential to focus on and direct preventive and diagnostic activities. Current methods of risk prediction in use in general clinical care are not highly accurate and, as a result, there is a potential unmet need for improved risk prediction instruments.

Experts recommend formal genetic counseling for individuals who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some individuals; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

#### **Risk Assessment**

Although treatment for elevated coronary disease risk with statins targets cholesterol levels, selection for treatment involves estimation of future coronary artery disease (CAD) risk using well-validated prediction models that use additional variables.

Components of CVD risk include family history, cigarette smoking, hypertension, and lifestyle factors such as diet and exercise. Also, numerous laboratory tests have been associated with CVD risk, most prominently lipids such as low-density lipoprotein (LDL) and high-density lipoprotein (HDL). These clinical and lipid factors are often combined into simple risk prediction instruments, such as the Framingham Risk Score. The Framingham Risk Score provides an estimate of the 10-year risk for developing cardiac disease and is currently used in clinical care to determine the aggressiveness of risk factor intervention, such as the decision to treat hyperlipidemia with statins.

Many additional biomarkers, genetic factors, and radiologic measures have been associated with an increased risk of CVD. Over 100 emerging risk factors have been proposed as useful for refining estimates of CVD risk. Some general categories of these potential risk factors are as follows:

**Lipid Markers.** In addition to LDL and HDL, other lipid markers may have predictive ability, including the apolipoproteins, lipoprotein (a) (Lp[a]), lipid subfractions, and/or other measures.

**Inflammatory Markers.** Many measures of inflammation have been linked to the likelihood of CVD. High-sensitivity C-reactive protein (hs-CRP) is an example of an inflammatory marker; others include fibrinogen, interleukins, and tumor necrosis factor.

**Metabolic Syndrome Biomarkers.** Measures associated with metabolic syndromes, such as specific dyslipidemic profiles or serum insulin levels, have been associated with an increased risk of CVD.

**Genetic markers.** A number of variants associated with increased thrombosis risk, such as the 5,10-methylene tetrahydrofolate reductase (MTHFR) variant or the prothrombin gene variants, have been associated with increased CVD risk. Also, numerous single nucleotide variants have been associated with CVD in large genome-wide studies.

### **Risk Panel Testing**

CVD risk panels may contain measures from 1 or all of the previous categories and may include other measures not previously listed such as radiologic markers (carotid medial thickness, coronary artery calcium score). Some CVD risk panels are relatively limited, including a few markers in addition to standard lipids. Others include a wide variety of potential risk factors from a number of different categories, often including both genetic and nongenetic risk factors. Other panels are composed entirely of genetic markers.

Some examples of commercially available CVD risk panels are as follows:

**CV Health Plus Genomics™ Panel (Genova Diagnostics):** prothrombin; factor V Leiden; fibrinogen; HDL; HDL size; HDL particle number; homocysteine; LDL; LDL size; LDL particle number; Lp(a); lipoprotein-associated phospholipase A2 (Lp-PLA2); MTHFR gene; triglycerides; very-low-density lipoprotein (VLDL); VLDL size; vitamin D; hs-CRP.

**CV Health Plus™ Panel (Genova Diagnostics):** fibrinogen; HDL; HDL size; HDL particle number; homocysteine; LDL; LDL size; LDL particle number; lipid panel; Lp(a); Lp-PLA2; triglycerides; VLDL; VLDL size; vitamin D; hs-CRP.

**CVD Inflammatory Profile (Cleveland HeartLab):** hs-CRP, urinary microalbumin, myeloperoxidase, Lp-PLA2, F2 isoprostanes.

**Applied Genetics Cardiac Panel:** genetic variants associated with CAD: cytochrome p450 variants associated with the metabolism of clopidogrel, ticagrelor, warfarin, beta-blockers, rivaroxaban, prasugrel (2C19, 2C9/VKORC1, 2D6, 3A4/3A5), factor V Leiden, prothrombin gene, MTHFR gene, APOE gene.

**Genetiks Genetic Diagnosis and Research Center Cardiovascular Risk Panel:** factor V Leiden, factor V R2, prothrombin gene, factor XIII, fibrinogen-455, plasminogen activator inhibitor-1, platelet glycoprotein

(GP) IIIA variant human platelet antigen (HPA)-1 (PLA1/2), MTHFR gene, angiotensin-converting enzyme insertion/deletion, apo B, apo E.

In addition to panels that are specifically focused on CVD risk, a number of commercially available panels include markers associated with cardiovascular health, along with a range of other markers that have been associated with inflammation, thyroid disorders and other hormonal deficiencies, and other disorders. An example of these panels is:

**Advanced Health Panel (Thorne):** total cholesterol, HDL, LDL, triglycerides, HDL ratios, non-HDL cholesterol, LDL particle number, small LDL, medium LDL, LDL pattern, LDL peak size, large HDL, apo A1, apo B, Lp(a), cortisol, hs-CRP, homocysteine, glucose, hemoglobin A1c, insulin, homeostatic model assessment for insulin resistance, free T4, free T3, thyroid-stimulating hormone, reverse T3, dehydroepiandrosterone sulfate, estradiol, follicle stimulating hormone, luteinizing hormone, sex hormone binding globulin, total testosterone, free testosterone, albumin, globulin, albumin/globulin ratio, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gammaglutamyl transferase, total bilirubin, total serum protein, blood urea nitrogen, creatinine, blood urea nitrogen/creatinine ratio, estimated glomerular filtration rate from creatinine, estimated glomerular filtration rate from cystatin C, cystatin C, fibrinogen, platelet count, white cell count, absolute neutrophils, lymphocytes, absolute lymphocytes, monocytes, absolute monocytes, eosinophils, absolute eosinophils, basophils, absolute basophils, red blood cell count, hemoglobin, hematocrit, mean platelet volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, red cell distribution width, folate, vitamin B12, vitamin D, red blood cell magnesium, calcium, carbon dioxide, chloride, potassium, sodium, ferritin, iron total iron binding capacity, omega-3 index, omega-6 to omega-3 ratio, arachidonic acid, eicosapentaenoic acid, eicosapentaenoic acid/arachidonic acid ratio, docosahexaenoic acid, free fatty acids.

### **Low-density Lipoproteins (LDLs) 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 (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 CAD occur in subjects with "normal" levels of total cholesterol 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 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***

#### **High-Density Lipoprotein (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 a 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. 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 HDL particle number as a surrogate, based on the premise that each HDL particle contains a single apo AI molecule.

### **Low-Density Lipoprotein (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.

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 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 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, the cardiac risk may be further enhanced when the particles are smaller versus larger.

### **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 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, 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.

### **Leptin**

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

### **Lipoprotein-associated Phospholipase A2**

Lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as platelet-activating factor acetylhydrolase, is an enzyme that hydrolyzes phospholipids and is primarily associated with LDLs. Accumulating evidence has suggested that Lp-PLA2 is a biomarker of CAD and may have a proinflammatory role in the progression of atherosclerosis. Recognition that atherosclerosis represents, in part, an inflammatory process has created considerable interest in the measurement of proinflammatory factors as part of cardiovascular disease risk assessment.

Interest in Lp-PLA2 as a possible causal risk factor for CAD has generated the development and testing of Lp-PLA2 inhibitors as a new class of drugs to reduce the risk of CAD. However, clinical trials of Lp-PLA2 inhibitors have not shown significant reductions in CAD endpoints. Furthermore, assessment of Lp-PLA2 levels has not been used in the selection or management of subjects in the clinical trials.

### **Regulatory Status**

Multiple assay methods for cardiac risk marker components, such as lipid panels and other biochemical assays, have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process.

In December 2014, the PLAC® Test (diaDexus), a quantitative enzyme assay, was cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process for Lp-PLA2 activity. It was considered substantially equivalent to a previous version of the PLAC® Test (diaDexus), which was cleared for marketing by the FDA in July 2003.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Components of testing panels, lipid, and non-lipid biomarker tests are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of these tests.

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.

For individuals who are asymptomatic with risk of cardiovascular disease (CVD) who receive nontraditional cardiac biomarker testing (eg, high-density lipoprotein [HDL] subclass, low-density lipoprotein [LDL] subclass, lipoprotein[a], cystatin C, fibrinogen), the evidence includes systematic reviews, meta-analyses, and large, prospective cohort studies. Relevant outcomes are overall survival (OS), 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. 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 outcome.

For individuals with hyperlipidemia managed with lipid-lowering therapy who receive nontraditional cardiac biomarker testing (eg, lipoprotein [a], cystatin C, fibrinogen), the evidence includes analyses of the intervention arm(s) of lipid-lowering medication trials. Relevant outcomes are OS, change in disease status, morbid events, and medication use. 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 outcome.

For individuals who have a risk of CVD who receive Lp-PLA2 testing, the evidence includes studies of the association between Lp-PLA2 and various coronary artery disease (CAD) outcomes. Relevant outcomes are OS, disease-specific survival, and test validity. The studies have demonstrated that Lp-PLA2 levels are an independent predictor of CVD. Although Lp-PLA2 levels are associated with CVD risk, changes in patient management that would occur as a result of obtaining Lp-PLA2 levels in practice are not well-defined. To demonstrate clinical utility, clinicians must have the tools to incorporate Lp-PLA2 test results into existing risk prediction models that improve classification into risk categories, alter treatment decisions, and lead to improved health outcomes. Direct evidence for such improved health outcomes with Lp-PLA2 testing in clinical practice is lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

For individuals who have risk factors for CVD who receive CVD risk panels, the evidence includes multiple cohorts and case-control studies and systematic reviews of these studies. Relevant outcomes are test validity, other test performance measures, change in disease status, and morbid events. The available evidence from cohort and case-control studies indicates that many of the individual risk factors included in CVD risk panels are associated with an increased risk of CVD. However, it is not clear how the results of individual risk factors impact management changes, so it is also uncertain how the panels will impact management decisions.



Given the lack of evidence for the clinical utility of any individual risk factor beyond simple lipid measures, it is unlikely that the use of CVD risk panels improves outcomes. Studies that have evaluated the clinical validity of panels of multiple markers have not assessed management changes that would occur as a result of testing or demonstrated improvements in outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

## **CODING**

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

The following CPT codes are medically necessary when filed with one of the covered ICD-10-CM codes, below:

- 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

### Covered ICD-10-CM

The following CPT code(s) are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products:

- 83695** Lipoprotein (a)
- 83698** Lipoprotein-associated phospholipase A2, (Lp-PLA2)
- 83722** Lipoprotein, Direct Measurement; Small Dense LDL Cholesterol
- 85384** Fibrinogen; activity
- 85385** Fibrinogen; antigen

The following CPT code is used for MI-HEART Ceramides, Plasma:

- 0119U** Cardiology, ceramides by liquid chromatography-tandem mass spectrometry, plasma, quantitative report with risk score for major cardiovascular events

The following CPT code is used for VAP Cholesterol Test:

- 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

The following CPT code(s) are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products **EXCEPT** when utilized for evaluating renal function and filed with one of the covered ICD-10-CM codes, below:

- 82610** Cystatin C

### **Covered ICD-10-CM codes:**

- N18.30 – N18.32
- T45.AX1A - T45.AX5S
- T50.904A - T50.905S
- T50.994A - T50.995S
- T65.94XA - T65.94XS
- Z52.4
- Z92.26

\*When there is no specific CPT code for a cardiovascular risk panel, the following Unlisted CPT code should be filed:

- 81479** Unlisted molecular pathology procedure

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

## 83880 Natriuretic peptide

### RELATED POLICIES

Biomarker Testing Mandate

Genetic Testing Services

Medicare Advantage Plans National and Local Coverage Determinations Policy

Non-Reimbursable Health Service Codes

Proprietary Laboratory Analyses (PLA) and Multianalyte Assays with Algorithmic Analyses (MAAA)

Unlisted Procedures

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