Medical Coverage Policy

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Atherosclerotic Cardiovascular Disease Risk Assessment: Emerging Laboratory Evaluations

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Coverage Policy

Lipoprotein-associated phospholipase A2 (Lp–PLA₂) testing (CPT® 83698) is considered medically necessary for ANY of the following individuals who are at intermediate- or high-risk for developing coronary heart disease (CHD):

- any age with at least two or more major risk factors (e.g., smoking, hypertension, family history of premature CHD, low levels of HDL cholesterol)
- age ≥ 65 years with one major risk factor
- cigarette smoking
- fasting blood glucose level of ≥ 100 mg/dl
- metabolic syndrome

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Lipoprotein-associated phospholipase A2 (Lp–PLA2) testing for ANY other indication is considered experimental, investigational or unproven.

Apolipoprotein B testing (CPT® 82172) is considered medically necessary when the individual is undergoing management for lipoprotein abnormalities and ANY of the following conditions is met:

- established coronary heart disease (CHD), as evidenced by ANY of the following:
  - previous history of myocardial infarction (MI)
  - stable or unstable angina
  - revascularization with coronary artery bypass grafting
  - percutaneous coronary angioplasty
- diabetes mellitus
- two or more major risk factors (i.e., tobacco smoking, hypertension, family history of premature CHD, low levels of HDL cholesterol, age [men ≥ 45 years, women ≥ 55 years)

Apolipoprotein B testing for ANY other indication is considered experimental, investigational or unproven.

Lipoprotein(a) enzyme immunoassay (Lp[a]) testing (CPT® 83695) is considered medically necessary for ANY of the following at-risk groups, when used to assess risk and guide treatment of lipoprotein abnormalities:

- family history of premature CHD
- genetic predisposition for hypercholesterolemia
- established atherosclerotic heart disease with a normal routine lipid profile
- hyperlipidemia refractory to therapy
- history of recurrent arterial stenosis

Lipoprotein(a) enzyme immunoassay (Lp[a]) testing for ANY other indication is considered experimental, investigational or unproven.

The following testing is considered experimental, investigational or unproven for screening, diagnosing or management of coronary heart disease:

- apolipoprotein A–1
- circulating micro RNAs
- CoEnzyme Q10
- cystatin C
- fatty acids (e.g., Omega-3, Omega-6, saturated, monounsaturated [e.g., Boston Heart Fatty Acid Balance™ test])
- growth stimulation expressed gene 2 (ST2)
- leptin and other similar type tests (e.g., adiponectin, apelin, galectin 3, resistin, retinol binding protein, visfatin)
- lipoprotein remnants, including very low density lipoprotein (VLDL) and intermediate dense lipoprotein (IDL)
- long-chain omega–3 fatty acids
- molecular lipid and/or metabolic profiling (e.g., lipidomics, metabolomics)
- osteoprotegerin
- oxidized phospholipids
- peroxisome proliferator activated receptor
- protein C
- plasma myeloperoxidase (MPO)
- pregnancy-associated plasma protein-A (PAPP-A)
• prothrombotic factors (e.g., plasminogen activator inhibitor [PAI–1], activated factor VII, tissue plasminogen activator [tPA], von Willebrand factor, factor V Leiden, protein C, antithrombin III, fibrinogen)
• quantification of lipoproteins, including any of the following:
  ➢ VLDL subclasses
  ➢ IDL subclasses
  ➢ high-density lipoprotein (HDL) subclasses (LpAI, LpAI/AII and/or HDL3, HDL2)
  ➢ low-density lipoprotein (LDL) subclass size and concentration (small and large LDL particles)
• secretory type II phospholipase A2 (sPLA₂), including isoenzymes (e.g., sPLA₂-IIA)
• serum sterols (e.g., Boston Heart Cholesterol Balance® test)
• skin cholesterol testing
• test panels/profiles that include non-standard lipoprotein and/or other emerging cardiac disease risk markers (e.g., vertical auto profile [VAP], NMR LipoProfile®, TruRisk™ Lipoprotein Particle Profile™, MIRISK VP™, Singulex® Cardiac /Inflammatory Biomarkers, Boston Heart HDL Map®, Cholesterol Balance® and Fatty Acid Balance™ Test)
• thromboxane metabolite(s) testing
• total cholesterol content in red blood cell membranes
• tumor necrosis factor alpha
• Troponin*
• homocysteine testing*

*Note: The measurement of troponin levels to assess for acute cardiac injury or homocysteine testing for evaluation of folate deficiency, homocystinuria or venous thromboembolism (i.e., unexplained thrombotic disorders) does not fall within the scope of this Cigna Medical Coverage Policy.

Overview

This Coverage Policy addresses emerging laboratory tests performed for atherosclerotic cardiovascular disease risk assessment.

General Background

Cholesterol has been proven to play a major role in the development of heart disease and contains both lipids and proteins (lipoproteins). Low density lipoprotein (LDL) is considered the primary target for lipid lowering therapy.

Determination of cardiac disease risk is based on standard, accepted risk-stratification approaches, involving determination of standard lipid profiles consisting of total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides levels.

Scientific evidence illustrates that therapies aimed at reducing LDL cholesterol levels reduce cardiovascular risk and historically various guidelines have recommended treating to LDL-cholesterol target levels. In 2013 however the recommendations of the American College of Cardiology (ACC) and American Heart Association (AHA) no longer recommend treating to specific LDL and non-HDL targets. According to the ACC/AHA guidelines (Goff, et al., 2013) evidence from randomized controlled clinical trials supporting treatment to specific targets is lacking. The emphasis for management of cardiovascular risk, in addition to a healthy lifestyle and diet, is the intensity of statin use (i.e., appropriate and maximum-tolerated statin therapies). Once an individual is placed on statin therapy follow-up LDL testing may be considered on an individual basis to monitor adherence to therapy and efficacy. Similarly, the Department of Veteran’s Affairs and Department of Defense (Va/DOD) Clinical Practice Guideline for the Management of Dyslipidemia for Cardiovascular Risk Reduction (2014) supports the use of statin therapy, adoption of healthy lifestyles, and a healthy diet for individuals with elevated cardiovascular risk.

With regards to secondary prevention the guideline does not identify any LDL-C threshold for statin therapy with subjects with known ASCVD and strongly recommends against the routine monitoring of LDL-C and non-HDL-C
goals. According to the guidelines, patients with known ASCVD should be offered treatment with a moderate dose statin, regardless of lipid levels.

While it remains that some individuals continue to have significant risk despite lowering LDL cholesterol levels, some authors contend that evaluating lipoproteins other than LDL (or non-HDL) levels may provide significant additional information regarding CVD risk for a subset of patients (e.g., those identified as “high risk” or with multiple risk factors). Risk factors other than LDL cholesterol are referred to as “emerging/novel risk factors” and include a variety of tests such as serum inflammatory markers, comprehensive lipoprotein testing, angiotensin gene testing, prothrombotic factors and other types of gene testing. Several clinical trials are underway to evaluate methods aimed at cardiovascular risk reduction, however evidence in the form of randomized controlled trials supporting that treating to target levels of emerging risk factors lowers risk is lacking. According to the 2014 Standards of Medical Care in Diabetes (2014), “some experts recommend a greater focus on non-HDL cholesterol, apolipoprotein B (apoB), or lipoprotein particle measurements to assess residual CVD risk in statin-treated patients who are likely to have small LDL particles, such as people with diabetes, but it is unclear whether clinical management would change with these measurements.”

**Determining Cardiac Risk**

**Pooled Cohort Equation:** In the 2013 the ACC/AHA published new guidelines on the assessment of cardiovascular risk (Goff, et al., 2013). Within these guidelines the ACC/AHA work group developed new equations to estimate 10-year risk and lifetime risk for developing a first atherosclerotic cardiovascular disease (ASCVD) event (i.e., nonfatal myocardial infarction, CHD death, or fatal or nonfatal stroke). The Pooled Cohort Equation is designed to assess risk and included subjects from diverse cohorts such as the Framingham Heart Study, Atherosclerosis Risk in Communities (ARIC) study, the Coronary Artery Risk Development in Young Adults (CARDIA) and the Cardiovascular Health Study (CHS) and provides sex and race specific estimates for 10-year risk for ASCVD in non-Hispanic African-American and non-Hispanic white men and women age 40-79 years. The variables included in the risk assessment include age, sex, race, total and HDL-cholesterol, systolic BP, use of blood pressure lowering medication, diabetes, and smoking status (Goff, et al 2013). Based on the results of the assessment tool a 10-year risk of < 7.5% is considered low and a 10-year risk of ≥ 7.5% is considered elevated.

An electronic version of the CV Risk Calculator using the Pooled Cohort Equation is available at [http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp](http://my.americanheart.org/professional/StatementsGuidelines/PreventionGuidelines/Prevention-Guidelines_UCM_457698_SubHomePage.jsp).

**Framingham Risk Score:** When utilizing the Framingham risk scoring tool, point scores are assigned to various risk factors and totaled. These risk factors are considered major independent cardiovascular risk factors and include the following:

- cigarette smoking
- hypertension (BP ≥ 140/90mm/Hg or on antihypertensive medication)
- low HDL cholesterol (< 40mg/dL)
- family history of premature CHD (CHD in male first-degree relative < 55 years, CHD in female first-degree relative < 65 years)
- age (men ≥ 45 years, women ≥ 55 years)

Ten-year risk percent is then determined by a point total. Framingham risk scoring divides persons with multiple risk factors into categories of 10-year risk for CHD, which are > 20%, 10-20%, or < 10%.

Low cardiac risk is described as having one risk factor or less; moderate cardiac risk is defined as having two risk factors and a 10-year Framingham risk of less than 10%; moderate high risk is defined as having more than two risk factors and a 10-year Framingham risk of 10–20%; persons in the high risk category have existing CHD (previous history of MI, stable or unstable angina, or revascularization with coronary artery bypass grafting or percutaneous coronary angioplasty) or a CHD risk equivalent (e.g., diabetes mellitus, abdominal aortic aneurysm, peripheral vascular disease, significant coronary artery disease, a 10-year Framingham risk that exceeds 20%)(Toth, et al., 2011). The American Heart Association also includes chronic kidney disease as a risk equivalent.
An electronic version of Framingham risk assessment tool is available through the NHLBI website under the heading “Health Assessment Tools” (http://hp2010.nhlbihin.net/atpiii/calculator.asp?usertype=pub).

**Reynolds Risk Score:** The Reynolds risk score may also be used to predict risk of future heart attack, stroke, or other major heart disease in the next ten years. In addition to age, blood pressure, cholesterol levels, and whether an individual smokes or not, the Reynolds Risk Score includes hs-CRP level and parental history of heart attack before age 60. The Reynolds risk score is based on information collected from 24,558 initially healthy women for a median of 10.2 years, and stratified risk, as well the Framingham model, for women at high and low risk. For women at intermediate risk, the Reynolds risk score more accurately reclassified women into higher or lower risk categories (Ridker, et al., 2007).

An electronic version of the Reynolds Risk Score is available at http://www.reynoldsriskscore.org/.

**Standard Lipoprotein Profile**
A standard lipoprotein profile includes total cholesterol, HDL cholesterol, and triglyceride levels in addition to a calculated LDL cholesterol level, and calculated non-HDL levels. Calculation of the LDL level is usually an indirect measurement and is estimated from measurements of total cholesterol, total triglycerides and HDL cholesterol. Guidelines and recommendations for standard lipid screening in the general population are well-established.

In some clinical situations direct LDL calculations may be considered more accurate (e.g., presence of chyomicrons, elevated triglycerides (>400 mg/dl)). However, the methods available to specifically measure LDL cholesterol have not been standardized (Brunzell, et al., 2008). In addition the ATP III recommendations do not recommend replacing calculated LDL levels for direct LDL; calculated LDL levels are recommended for those individuals without hypertriglyceridemia.

Non-HDL cholesterol represents total cholesterol minus the HDL cholesterol. It may also be referred to as the sum of all the apolipoprotein B containing lipoprotein (i.e., very low density lipoprotein [VLDL], LDL, intermediate density lipoprotein [IDL], lipoprotein [a]) levels. Among individuals with hypertriglyceridemia (i.e., triglycerides of at least 200 mg/dl), the ATP III guidelines suggest non-HDL as a secondary target of therapy, after targeting LDL cholesterol levels. Individuals with hypertriglyceridemia typically include those individuals with cardio-metabolic risk (CMR) or diabetes. The targeted level for non-HDL cholesterol is the LDL cholesterol target plus 30. Authors contend that measuring non-HDL cholesterol is more practical than directly measuring apo B, and furthermore that non-HDL is predictive of heart disease in individuals who have high triglycerides (as the triglycerides rise, so do the VLDLs). A consensus statement from the American Diabetes Association and American College of Cardiology Foundation (ADA/ACC) (Brunzell, et al., 2008) recommends the calculation of non-HDL cholesterol on all lab reports to determine cardiovascular disease risk in cardio-metabolic risk (CMR) individuals with low to moderate LDL levels. Consequently, non-HDL cholesterol may be considered an additional tool to assess cardiovascular risk in individuals whose risk is not adequately defined by LDL cholesterol alone (e.g., diabetics).

**Advanced Laboratory Evaluation**
Factors considered in the evaluation of emerging risk factors include determining the predictive power, population prevalence, and availability of laboratory testing, the standardization methods, reference values, stability, and lastly evidence confirming whether or not modification of these markers will reduce risk and ultimately lead to improved clinical outcomes for patients with cardiac risk factors. Furthermore the clinical utility of emerging risk factor testing relies on conclusive evidence the test predicts risk beyond that of current risk prediction methods (considered standard of care) and evidence supporting improved clinical outcomes, such as a reduction in CVD or events, as a result of specific management strategies.

Evidence in the existing literature indicates most emerging risk factors are not independently related to the risk of recurrent CVD (Wattanakit, et al., 2005). However, some of these risk factors may be associated with increased risk of cardiac disease in patients already at risk. Even so, it has not been proven that lowering levels is associated with a significant decrease in the incidence or mortality of heart disease. Many of the assays/tests used to determine these levels are not standardized and accuracy, sensitivity, specificity and predictive values have not been firmly established in the medical literature. Overall, when comparing predicative values of the emerging risk factors with traditional measurements, some of the emerging risk factors have predictive value that
Apolipoproteins: Lipoproteins are large complexes of molecules that transport lipids (primarily triglycerides and cholesterols) through the blood. Apolipoproteins are proteins on the surface of the lipoprotein complex that bind to specific enzymes or transport proteins on the cell membranes; this directs the lipoprotein to the proper site of metabolism.

- Apolipoprotein A–1 (apo A–1) is a lipid-binding protein that forms complexes with other proteins and lipids to form HDL particles. It is the major protein component of HDL and is usually reduced when the HDL level is low. Together, apo A–1 and apo A–2 constitute 90% of total HDL protein. Low levels of apo A–1 may be associated with an increased risk for CVD. However, testing of apo A–1 does not add any additional predictive power above a traditional HDL level. Testing for apo A–1 is often performed with apolipoprotein B and reported as a ratio (apo B: apo A–1) which may provide information regarding the cholesterol transport to and from the peripheral tissues, including the walls of arteries. Researchers suggest that the apo B: apo A–1 ratio provides a measure of atherogenic to antiatherogenic lipoprotein particles similar to that of total cholesterol to HDL cholesterol ratios and may be a better discriminator of CVD.

- Apolipoprotein B (apo B) has two forms found in humans. The most abundant form is known as large B or B–100. It is the major protein found in LDL and VLDL. While lipoprotein particles vary in their cholesterol content, each lipoprotein particle (i.e., LDL, IDL, VLDL, Lp[a]) carries one molecule. It has been suggested that apo B is a better marker of atherogenic particles than total LDL and even nonHDL levels. The assay for measuring apo B has become standardized (Brunzell, et al., 2008).
Evidence supporting apolipoprotein measurements improve overall risk prediction compared to standard lipid testing remains mixed and the clinical utility of apolipoprotein testing in the general population is debatable. For some measurements, universal standardized testing modalities are not widely available. In addition, patient-selection criteria have not been clearly established. Numerous studies have been conducted and consist of both retrospective and prospective case series, cohort studies, and randomized controlled clinical trials, including a few systematic reviews and meta-analyses. Many study populations involve large subsets of patients evaluating outcomes over several years. Some proponents report the predictive power of apolipoprotein testing (apo A–1 and apo B) is comparable to or better than traditional measurements (Gotto, et al., 2000; Luc, et al., 2002; Sniderman, et al., 2003a; Kastelein, et al., 2008; Khadem-Ansari, et al., 2009; Benderly, et al., 2009) although in other studies testing was not found advantageous (Stamper, et al., 1991; Sharrett, et al., 2001; Ingelsson, et al., 2007; Ray, et al., 2009). Additionally, some studies strongly support the association of apo B with CVD and provide evidence that apo B may have more clinical utility than conventional measurements, including LDL (Lamarche, et al., 1996; Gotto, et al., 2000; Khadem-Ansari, et al., 2009; Sierra-Johnson, et al., 2009; Gigante, et al., 2012). The literature also lends some support that the ratios of total cholesterol to HDL and of apo B: apo A–1 (atherogenic to antiatherogenic particles) are more highly correlated with severity and extent of CVD (Wallach, et al., 2007; Lau and Smith, 2009; Sierra-Johnson, et al., 2009; Song, et al., 2015). Wallach et al. (2007) however, noted that the apo B: apo A–1 ratio showed greater sensitivity/specificity for CVD than LDL-C: HDL-C ratio, HDL-C: triglyceride ratio, or any of the individual components. Although few studies have evaluated the effect of lipid lowering agents on apolipoproteins, there is some evidence to suggest a positive effect (Tani, et al., 2010; Ray, et al., 2009; Holme, et al., 2008). A meta-analysis of 25 clinical trials (12 statin, 4 fibrates, 5 niacin, 2 comparative trials, one ileal bypass) supports that statins lower apo B more than nonstatin therapies, suggesting that intensifying statins may be a preferred method to lower apo B levels compared to other treatments (Robinson, et al., 2012). Across all drug trials evaluated in this meta-analysis, apo B did not consistently improve risk prediction, although in the statin trials specifically apo B decrease did add information to LDL and non HDL for predicting coronary risk heart disease.

The ATP III guidelines do not recommend apo A–1 for routine risk assessment, and according to the guideline non-HDL serves as a surrogate for apo B. The guidelines do not define the total cholesterol: HDL ratio as a specified target of therapy; LDL remains the primary lipid lowering target.

A consensus statement from the ADA/ACC (Brunzell, et al., 2008) suggests that measurements of apo A–1 provide little clinical value beyond measurements of HDL cholesterol level. The authors also report that although not all studies agree, once LDL cholesterol is lowered, testing for apo B may more accurately identify those still at risk for cardiovascular events and to determine the need for medication.

The National Academy of Clinical Biochemistry Laboratory (the Academy of the American Association for Clinical Chemistry) established medical practice guidelines for emerging biomarkers for primary prevention of cardiovascular disease (Myers, et al., 2009). These guidelines support apo B testing and apo B: apo A–1 ratio measurement as alternatives to non-HDL cholesterol and total cholesterol: HDL cholesterol ratio; however the workgroup acknowledged manufacturers of the assays should establish traceability to accepted standards to assure reliable and comparable results.

The College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines on assessment of cardiovascular risk do not support advanced lipid testing of apo B; according to the guideline recommendations the contribution of apo B to risk assessment for a first ASCVD event is uncertain at present (Goff, et al., 2013).

The ACC/AHA recommendations published in 2013 considered Apo-B as a new risk marker, however the workgroup concluded that the contribution of Apo B to risk assessment for first ASCVD event is uncertain (Goff, et al., 2013).

Guidelines for the management of dyslipidemias published by the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) (Capitano, et al., 2016) support apo B testing as an alternative risk marker for individuals with combined hyperlipidemias, diabetes, metabolic syndrome or chronic kidney disease. According to the guidelines apoB can be considered as an equivalent to non-HDL-C when available (Class IIa, Level C recommendation).
Lipoprotein(a) levels are not widely available (Grundy, et al., 1999) although therapy generally includes more

The 2016 National Lipid Association (NLA) published “Recommendations for Patient Centered Management of Dyslipidemia”. Within these recommendations, the NLA notes Apo-B is an optional, secondary lipid target for treatment. However, the NLA Expert Panel favors non-HDL over Apo-B because it is universally available, does not require any additional expense, and because apo-B has not consistently been superior to non-HDL in predicting risk. Regarding biomarkers for “on-treatment” the NLA panel notes the following (Bays, et al., 2016):

- Apo B is a potential marker of residual ASCVD risk because apo B may remain elevated in some individuals who have attained their treatment goals for non–HDL-C and LDL-C, as may occur in patients with elevated triglyceride and lower HDL-C levels.
- If apo B is used as an optional target for treatment, goals are < 90 mg/dL for primary prevention and < 80 mg/dL for those with very high risk.
- Measurement of apo B is generally not recommended until the patient has been treated to his or her goal levels for atherogenic cholesterol.

The American Association of Clinical Endocrinologists (AACE) supports performance of apo B levels to assess the success of LDL-C-lowering therapy (Jellinger, et al., 2017).

**High Density Lipoprotein (HDL) Subclass/Particle (LpAI, LpAI: All):** HDL can be classified by the apolipoprotein content (LpAI, LpAll), by size (small and large), by density (HDL2, HDL3), and by surface charge (pre-beta, alpha and pre-alpha). For example, regarding apolipoprotein content, HDL particles containing apo AI (LpAI) carries only apo AI on its surface whereas apo All (LpAl:LpAll) carries both apo AI and apo All on its surface. Total HDL (HDL-C) reflects the cholesterol content within all HDL subclass particles and is the risk indicator most commonly used in cardiac risk assessment. Various types of HDL subclass tests are being proposed to provide information regarding CVD risk in addition to total cholesterol, HDL cholesterol and low-density lipoprotein cholesterol. It has been suggested that HDL subclasses may be more closely associated with risk than is total HDL and may provide additional risk information for those individuals identified as low- or intermediate-risk by standard lipoprotein tests.

HDL subclass testing may be performed by methods using various separation techniques such as nuclear magnetic resonance (NMR), gradient gel electrophoresis (GGE), and ultracentrifugation.

Consistent with the ATP III panel, the literature does not support improved clinical outcomes with the use of HDL subclass testing, and it has not been recommended as a routine measurement of cardiac risk. A consensus statement by the ACC and the ADA (Brunzell, et al., 2008) indicates that measurements of HDL subfractions (or apo A-1) appear to provide little clinical value beyond measurements of HDL cholesterol. Currently, there is lack of evidence to support HDL subclass testing in the screening, diagnosis or management of dyslipidemia and/or CVD.

**Lipoprotein Remnants:** According to the ATP III publication, lipoprotein remnants, including intermediate density lipoproteins (IDLs) and VLDLs have been shown to be atherogenic. They are triglyceride-rich lipoproteins, and elevated triglycerides have been identified as an independent risk factor of CVD. The lipoprotein remnant particles may penetrate the arterial wall more easily than larger lipoproteins. The panel concluded that studies are limited, and measurement with specific assays for lipoprotein remnants cannot be recommended for routine practice.

**Lipoprotein(a) Enzyme Immunoassay (Lp[a]):** Lipoprotein(a) is a low-density, lipoprotein-like particle that may have atherogenic potential. It has been proposed by several authors to represent a link between atherosclerosis and atherothrombosis. Structurally, it is very similar to plasminogen, and may specifically compete with plasminogen in fibrinolysis by inhibiting the activation of plasminogen to plasmin, increasing the potential of plaque development and possible blockage. Research has shown it accumulates in atherosclerotic lesions; however, the actual process remains unclear. Lp(a) concentrations are genetically determined and not influenced by age, physical activity or diet. A standardized international reference material has been developed and is accepted by the World Health Organization Expert Committee on Biological Standardization and the International Federation of Clinical Chemistry and Laboratory Medicine. In general, lipoprotein(a) levels above 30mg/dl are considered elevated with levels > 50 considered high risk. Treatments specifically aimed at reducing lipoprotein(a) levels are not widely available (Grundy, et al., 1999) although therapy generally includes more
aggressive management. Niacin and estrogen have been shown to lower blood levels of Lp(a). Guidelines recommending intervention based on Lp(a) levels are limited, although according to the National Academy of Clinical Biochemistry Laboratory Practice Guidelines (Myers, et al., 2009) when both Lp(a) and LDL cholesterol are highly increased an attempt can be made to lower the Lp(a) value by lowering the increased LDL cholesterol.

While screening in the general population for routine risk assessment is not recommended, testing may be helpful for those individuals already known to be at high risk. There are some advocates for Lp(a) who recommend assessment for persons with a strong family history of premature CVD or those with genetic causes of hypercholesterolemia (e.g., familial hypercholesterolemia). According to the ATP III, an elevation of Lp(a) may raise an individual’s risk to a higher level and the ATP III accepts testing for Lp(a) as an option for these selected persons. The consensus statement from the ADA/ACC (Brunzell, et al., 2008) also supports testing of Lp(a) in select individuals. Brunzell et al. reported that lipoprotein(a) predicts CVD and there is little evidence that insulin resistance or diabetes influence lipoprotein(a) concentrations. According to the consensus statement, the clinical utility of routine measurement of Lp(a) is unclear, although more aggressive control of other lipoprotein parameters may be warranted in those with high concentrations of Lp(a).

The NACBL guidelines (Myers, et al., 2009) support Lp(a) testing if the risk is intermediate and there is uncertainty regarding management with statins or aspirin, or if there is a strong family history of premature CVD/genetic predisposition.

The College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines (Greenland, et al., 2010) did not find Lp(a) testing to be of benefit in cardiovascular risk assessment in asymptomatic individuals.

Guidelines for the management of dyslipidemias published by the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) support Lp(a) testing for individuals with high CVD risk or a strong family history of premature atherothrombotic disease (Catapano, et al., 2016).

Within the American Association of Clinical Endocrinologists (AACE) 2017 guidelines for management of dyslipidemia and prevention of cardiovascular disease the AACE acknowledges testing for lipoprotein (a) is not generally recommended, although the AACE notes “it may provide useful information to ascribe risk in Caucasians with ASCVD, those with an unexplained family history of early ASCVD, or those with unknown family history such as adopted individuals” (Jellinger, et al., 2017).

Lipoprotein-Associated Phospholipase A2 (Lp–PLA2): Lp–PLA2 belongs to the family of phospholipase A2 enzymes. Evidence has suggested Lp–PLA2 plays a role in atherosclerosis, and it has been proposed that Lp–PLA2 testing may aid in detecting CVD risk. Lp–PLA2 is a marker of inflammation produced primarily in macrophages and bound to LDL. Lp–PLA2 is commonly measured by the diaDexus PLAC™ test (diaDexus, Inc., South San Francisco, CA) an enzyme-linked imunoabsorbant assay (ELISA) test, and must be run in a CLIA (Clinical Laboratory Improvement Act) certified high-complexity laboratory.

It has been identified in some clinical trials (West of Scotland Coronary Prevention Study [Packard, et al., 2000] and Atherosclerosis Risk in Communities Study [Ballantyne, et al., 2003]) that patients with elevated levels of Lp–PLA2 had increased risk of cardiovascular disease (Moriarty and Gibson, 2005). Wallach (2007) suggests increased Lp–PLA2 with low LDL-C increases risk of heart disease by two times and that increased Lp–PLA2 with high CRP increases risk of heart disease by three times. The ATP III guidelines do not include measurement of Lp–PLA2 although several studies have been published since the initial recommendations. Corson et al. (2008) reported that Lp-PLA2(2) should be considered an important cardiovascular risk marker whose utility is as an adjunct to the major risk factors to adjust absolute risk status and thereby modify low-density lipoprotein cholesterol goals. The recent ADA/ACC consensus statement (Brunzell, et al., 2008) does not address the use of Lp–PLA2 levels for determining CVD risk. Davidson et al. (2008), an expert consensus panel, evaluated how Lp–PLA2 might be used for determining CVD risk and concluded that testing is not recommended for the general population or for persons who are at low risk. However, the panel does recommend testing in moderate- or high-risk persons to further stratify risk. In the authors’ opinion, many high-risk persons taking statins have significant residual risk identifiable with Lp–PLA2 testing. Therefore, the panel defined a simplified approach to determining criteria for testing of persons who are at least moderate-risk for CHD and includes the following individuals:
any age with two major risk factors
- age ≥ 65 years with one major risk factor
- cigarette smoking
- fasting blood glucose ≥ 100 mg/dl
- metabolic syndrome

Lp-PLA₂ levels greater than 200 mg/dl warrants risk reclassification and reduction of LDL levels. The authors suggest annual testing for individuals with levels greater than 200 mg/dl. The evidence reviewed by the panel lends some support to further stratify risk in select individuals and there is some evidence in the published medical literature that statin drugs and fibrates may reduce Lp-PLA₂ levels. Treatment for elevated Lp-PLA₂ is targeted at lowering LDL levels.

The College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines (Greenland, et al., 2010) reported lipoprotein-associated phospholipase A2 (Lp-PLA2) might be reasonable for cardiovascular risk assessment in intermediate-risk asymptomatic adults.

The American Association of Clinical Endocrinologists (AACE) guidelines for management of dyslipidemia and prevention of atherosclerosis (Jellinger, et al., 2017) supports measuring Lp-PLA₂ when it is necessary to further stratify a patient’s CVD risk, especially in the presence of systemic highly sensitive CRP elevations.

**Secretory Type II Phospholipase A₂:** Secretory type II phospholipase A₂ also belongs to the family of phospholipase A₂ enzymes, distinct from Lp-PLA₂, and is purported to be associated with increased risk of CAD, similar to CRP when sPLA₂ levels are elevated. It is an acute phase protein for which plasma levels rise during inflammatory conditions such as infection, septic shock and Rheumatoid Arthritis (RA) (Niessen, et al., 2003). Theoretically the atherogenic mechanism of sPLA₂ consists of the release of various lipid mediators at the site of lipoprotein retention in the arterial wall which may subsequently trigger a local inflammatory cellular response. In addition, in arterial tissue it may directly modify the LDL particles to become more atherogenic. While there are different forms of the enzyme (e.g., sPLA₂-IIA, sPLA₂-III, sPLA₂-V and sPLA₂-X) that may promote atherosclerosis, the assay for sPLA₂ activity does not distinguish between isoenzyme types (Holmes, et al., 2013). A small number of studies have evaluated the utility of sPLA₂ and consist mainly of published reviews, case series, observational studies, a prospective case-control study, and few randomized controlled trials (Kugiyama, et al., 1999; Kovanen, Pentikainen, 2000; Liu, et al., 2003; Boekholdt, et al., 2005; O'Donoghue, et al, 2011; Lind, et al., 2012). The results of some studies tend to support an association of increased cardiovascular risk when sPLA₂ levels are elevated in individuals with stable CAD (Kugiyama, et al., 1999; Liu, et al., 2003; Koenig, et al., 2009; O'Donoghue, et al., 2011). Published evidence also lends some support that the magnitude of the association is similar to hsCRP and CAD risk (Boekholdt, et al., 2005, O'Donoghue, et al., 2011). Holmes et al. (2013) conducted a Mendelian randomization meta-analysis of 19 general population studies and 10 acute coronary syndrome cohorts to evaluate a causal relationship of sPLA₂ enzyme activity or sPLA₂-IIA mass to cardiovascular events. The authors identified a single nucleotide polymorphism (SNP) in PLA2G2A (rs11573156) that had a large and specific effect on circulating sPLA₂-IIA mass and a small-to-modest effect on sPLA₂ enzyme activity, although no association was found between rs11573156 and incident, prevalent or recurrent major vascular events (MVE). In the authors opinion higher sPLA₂-IIA mass or sPLA₂ enzyme activity may be a consequence and not a cause of atherosclerosis. The authors concluded that reducing sPLA₂-IIA mass is unlikely to be a useful therapeutic goal for preventing cardiovascular events. While some evidence suggests sPLA₂ may play a role in the development of CAD additional clinical studies are needed to firmly establish a causal relationship in the pathogenesis of CAD, how it compares with other established markers of risk, and the clinical utility for predicting CAD risk and reducing morbidity.

**Low Density Lipoprotein (LDL) Subclass (Small and Large LDL Particles):** LDL subclass testing has been proposed as a source of quantitative and qualitative LDL information. These tests provide the number of LDL particles, measure of particle size and concentrations of subclasses including IDL, subclasses of HDL, and subclasses of VLDL. It has been reported that a discrepancy between the quantity of LDL particles and the serum level of total LDL may represent a significant source of unrecognized cardiovascular risk. While the underlying mechanism of how LDL subclass particles relate to CVD has not been established, one theory is that although small LDL particles carry less cholesterol compared to large LDL particles, the small LDL particles can
be more easily deposited into the intima and lead to atherosclerosis. Even though LDL cholesterol levels may be normal, an elevation of small, dense LDL particles may be associated with CVD, and is commonly seen in individuals with elevated triglycerides levels and low HDL cholesterol levels (also reflective of conditions such as obesity and insulin-resistance–related cardiometabolic risk) (Brunzell, et al., 2008).

Determining LDL particle concentration has been the focus of recent research; authors propose determining LDL particle concentration (i.e., number of LDL particles) would be the more precise marker for determining risk, particularly when the LDL cholesterol and LDL particle concentration are not concordant.

LDL particles can be measured by several techniques, including ultracentrifugation, gradient gel electrophoresis, nuclear magnetic resonance spectroscopy (NMR) and high pressure liquid chromatography (HPLC).

Within a technology assessment report the CTAF (2008) noted that there were no studies addressing whether or not treated LDL particle levels affected clinical outcomes.

The ATP III guidelines do not support measurement of small LDL particles in routine practice, although if particles are evaluated their use is best indicated for atherogenic dyslipidemia and metabolic syndrome. In combination with elevated triglycerides or low HDL, increased small LDL particles in high risk persons may be treated with nicotinic acid or fibric acid as part of lipid lowering therapy.

The Endocrine Society Clinical Guidelines (Rosenzwieg, et al., 2008) for primary prevention of cardiovascular disease and type 2 diabetes mellitus in patients at metabolic risk does not support LDL particle measurement for evaluating cardiovascular risk. According to the Endocrine Society LDL cholesterol is the primary target of lipid lowering therapy and non HDL is considered a secondary target.

According to the ADA/ACC consensus statement (Brunzell, et al., 2008), measuring LDL particles using NMR may be more accurate, and “many cross sectional and prospective studies show LDL particle number is a better discriminator of risk than is LDL cholesterol.” However, the authors state there is a lack of data confirming the accuracy of the method and question whether its CVD predictive power is consistent across various ethnicities, ages, and conditions that affect lipid metabolism. Consistent with the ADA/ACC consensus, Ip et al. (2009) reported that even with evidence to support a higher LDL particle number predicts incident CVD, evidence is lacking to support the clinical utility of adding LDL subfractions to the traditional risk factors. Furthermore, the authors noted that LDL subfraction testing will only be clinically useful if treatments, based on the results of testing, improve clinical outcomes.

According to a report from the AHRQ regarding LDL subfraction (subclass) measurement, it has yet to be determined if cardiac disease risk assessment and treatment decisions would be improved by adding LDL subclass measurements (AHRQ, 2008). Furthermore, the AHRQ report states that there is not yet a standard method subfraction measurement that can be used as a reference standard, has been demonstrated to be superior to other methods, or has been demonstrated to be accurate and reliable.

The NACBL guidelines (Myers, et al., 2009) do not support LDL subclass testing; according to the guideline the analyses of the existing studies are generally not adequate to show added benefit when compared to standard risk assessment for primary prevention.

In 2009 the Lipoproteins and Vascular Diseases Division of the American Association for Clinical Chemistry (AACC) published a report in which they reviewed the studies for apoB and LDL particle measurement. The authors noted that superiority of apoB or LDL particle measurement has been demonstrated in prospective studies when compared to LDL cholesterol measurement for the assessment of risk. As a result, the group recommends that apoB and alternate measures of LDL particle concentration be included in future NCEP and other various guidelines for cardiac risk. Until that time however it is reasonable to include both apoB (and LDL particle concentration) and LDL to assess related risk until apoB becomes more widely recognized. The authors acknowledged although measuring LDL particle concentration is appropriate in high risk individuals, target concentrations need to be determined through additional data. Until that time, they recommend using cutoff points similar to that of LDL (i.e., 20th percentile according to Framingham). A result of < 1100 nmol/L would
equate to LDL < 100 mg/dL and a particle concentration of <1400 nmol/L would equate to a LDL < 130 (Contois, et al., 2009).

The College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines (Greenland, et al., 2010) indicate evidence that more advanced lipid testing such as LDL-P concentration has predictive capacity beyond standard lipid measurements in asymptomatic individuals is lacking (Greenland, et al., 2010).

Otvos et al. (2011) used data from the Multi-Ethnic Study of Atherosclerosis (MESA) (n=6814) to evaluate differences between LDL cholesterol and particle concentration and their relationship to incident cardiac events among those with concordant and discordant levels. Individuals were followed for an average of 5.5 years; incident cardiac disease included myocardial infarction, coronary heart disease death, angina, stroke, stroke death, other atherosclerotic or cardiovascular death. Both LDL and LDL particles were associated with incident disease overall; when the levels disagreed only the LDL particle was associated with incident CVD. A consistent relationship was noted with intima media thickness and LDL particle rather than with LDL.

The National Lipid Association (Davidson, et al., 2011) evaluated the clinical utility of inflammatory markers and advanced lipoprotein testing (i.e., C-reactive protein, lipoprotein associated phospholipase A2, apolipoprotein B, LDL article concentration, lipoprotein (a), and LDL and HDL subfractions) to improve cardiovascular risk prediction and for use as potential targets of therapy. The consensus panel identified four categories of recommendations based on their review of current published evidence and testimony from other experts in the field: recommended for routine measurement, reasonable for many patients, considered in selected patients, or not recommended. Regarding LDL particle measurement specifically, the recommendations were as follows:

- For low risk patients testing is “not recommended”.
- The panel concluded that subjects at intermediate risk (5-20%), those with a family history of CHD, and those with recurrent events all had potential for discordantly elevated LDL particles; the recommendation for testing is “reasonable for many patients.” When LDL particle concentration is discordant despite LDL or non HDL goals, consideration should be given to intensify lipid lowering therapy.
- For individuals with high risk, with known CHD, or CHD high risk equivalent the recommendation is that “testing is considered for select patients” and to treat to LDL or non HDL levels on lipid lowering therapy.

The American College of Cardiology (ACC) and American Heart Association (AHA) in collaboration with the National Heart, Lung, and Blood Institute (NHLBI) published guidelines for cardiovascular risk classification (Goff, et al., 2013) and recommendations for management of blood cholesterol levels in adults (Stone, et al., 2013). While these guidelines did include evaluation of some new risk markers (e.g., hs-CRP, ApoB, creatinine) they did not include evaluation of LDL-P as a risk marker, noting that other novel potential screening tools may be considered in future guidelines.

In 2015 an AACE task force published “Comprehensive Diabetes Management Algorithm” (Garber, et al., 2015). The algorithm includes a CVD risk factor algorithm which addresses dyslipidemia and hypertension management. Dyslipidemia management includes therapeutic lifestyle changes and CVD risk assessment using lipid evaluations; desirable values for LDL-C, Non-HDL-C, TG, TC/HDL-C, Apo B and LDL-P have been established for moderate and high risk individuals. The algorithm also includes methods to lower levels if desirable levels are not achieved. If desirable levels are not reached, the AACE recommends intensifying therapeutic lifestyle changes, and in particular for lowering Apo B and LDL-P the algorithm includes intensifying statin and/or ezetimibe and/or colesevelam and/or niacin therapy.

Guidelines for the management of dyslipidemias published by the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) do not support testing of LDL subclasses. According to the guidelines small dense LDL may be considered and emerging risk factor however it is not currently recommended for risk estimation (Catapano, et al., 2016). LDL particle subclasses are not included in the guidelines “European Consensus of Cardiovascular Disease Prevention” (Piepoli, et al., 2016).

The NLA Recommendations for Patient-Centered Management of Dyslipidemia (Bays, et al., 2016) do not recommend LDL-P testing for individuals at low risk of ASCVD. For patients at higher risk, particularly those
suspected of having discordant levels, it remains unclear if LDL-P would alter initial treatment decisions. LDL-P may be considered for select patients, including those with family history of premature ASCVD, elevated triglycerides, low HDL-levels, metabolic syndrome, DM, or recurrent ASCVD events despite disease management. Regarding biomarkers for “on-treatment”, LDL-P may be useful in some cases to monitor the course of lipid-lowering therapy.

The American Association of Clinical Endocrinologists (AACE) published guidelines for management of dyslipidemia and prevention of atherosclerosis (Jellinger, et al., 2017). Within these guidelines the panel identifies major risk factors (i.e., advanced age, high total cholesterol, high non HDL, high LDL, low HDL, DM, hypertension, cigarette smoking, family history of CAD) and those risk factors that are considered additional risk factors (i.e., obesity/abdominal obesity, family history of hyperlipidemia, small dense LDL, elevated apo B, elevated LDL particle number, fasting/postprandial hypertriglyceridemia, polycystic ovarian syndrome, dyslipidemic triad). Once initial screening for detection of cardiovascular risk has been performed utilizing lipid screening tests (fasting lipid profile, LDL, HDL, non HDL, triglycerides, apolipoproteins [apo B and/or apo B/apo A1 RATIO]) secondary causes of dyslipidemia should be excluded (i.e., glucose, thyroid, renal, liver). Additional risk factor testing may be indicated using hs CRP, Lp-PLA2, coronary artery calcification and ultrasound measurement of carotid intima media thickness for some individuals. Once initial cardiac risk has been determined, and treatment has been recommended, follow-up and monitoring of post-treatment status should include a periodic full fasting lipid panel. If optimal lipid levels are not reached following lipid lowering treatment, or if ASCVD progresses despite optimal lipid levels, advanced lipoprotein testing may be performed including nuclear magnetic resonance, gradient gel electrophoresis, ultracentrifugation, and apo B and A levels, and/or lipoprotein(a) levels to determine the size or numbers of certain lipoproteins. The guideline additionally supports the use of apolipoprotein (apo) B level and/or LDL particle concentration to refine efforts to achieve effective LDL-C lowering. However, the guidelines indicate that consistency between methods for LDL particle testing has not been established.

Evidence in the medical literature lends support that LDL particle size and concentration is associated with atherosclerosis and coronary artery disease (Cromwell and Otvos, 2006; Otvos, et al., 2006; Cromwell, et al., 2007; Mora, et al. 2007; Biswas, et al., 2008; Koba, et al., 2008, California Technology Assessment Forum [CTAF], 2008; Mora, et al., 2009). Mora and colleagues (2009) reported however that risk prediction is comparable but not superior to standard lipids or immunoassay-measured apolipoproteins. When adding LDL particle concentration or apoB to a panel that already included a total/HDL cholesterol ratio the authors noted there was no change in classification of risk. More recently, Steffen et al. (2015) published the results of cox-regression analysis of a multicenter study (MESA) evaluating associations between lipids and lipoproteins (Apo-B, ApoB/ApoA-1, LDL-PDL-P/HDL-p) to primary CHD event (n=4679). Associations between lipoprotein particle measures and CHD were attenuated after adjustment for standard lipid panel variables. Using the ACC/AHA risk calculator, ApoB/ApoA-1, and LDL-P/HDL-P were found to moderately improve the prediction of risk for future CHD events. The attenuated associations of lipoprotein particle measures however did not detect risk that was unaccounted for by the standard lipid panel, after adjustment for the lipids. The authors acknowledged additional studies are needed to confirm or refute the significance of their results.

While standards for LDL subclass categorization and optimal levels of the LDL subclasses have not yet been firmly established (Chung, et al., 2009; AHRQ, 2008), it has been suggested that when determining risk categories low risk is defined as <1000 nmol/L, intermediate risk is 1000-1599 nmol/L, and high risk is ≥ 1600 nmol/L (Contois, et al., 2009). LDL particle concentration evaluation is not recommended for low risk individuals. Whether the use of LDL particle testing in addition to LDL cholesterol testing has clinical utility, resulting in a reduction of CVD and associated events for individuals has not been demonstrated in the published literature. However, when discordant, LDL particle concentration has been shown to be the better predictor of risk. Theoretically treatment aimed at lowering LDL will lower LDL particle concentration and cholesterol content, hypothetically reducing the occurrence of adverse cardiac events. Some studies have shown that pharmacologic treatment lowers particle concentration (Rosenson, et al., 2013; Le, et al., 2013).

Although LDL particle concentration is associated with cardiac risk and published evidence lends support that for some individuals testing may be considered a more precise method of risk assessment compared with total LDL, there is insufficient published evidence that treatment aimed at lowering LDL particle concentration changes cardiac outcomes. In addition, recommendations, consensus statements and guidelines from several
Homocysteine: Homocysteine is an amino acid that is normally found in the body. Several vitamins, including folic acid, B6, and B12 aid in the metabolism of homocysteine. Total homocysteine concentration (plasma and urine) is indicated and well accepted in the medical literature for diagnosing conditions such as folate, B6, and B12 deficiencies. For these conditions levels are generally elevated. Patients with homocystinuria, a rare recessive disease, may develop accelerated premature vascular disease. Clinical manifestations of homocystinuria generally include disorders of the optical lens, osteoporosis and associated skeletal abnormalities, intellectual disabilities, psychiatric disturbances and thromboembolic disease. Treatment to normal homocysteine levels improves outcomes in individuals with homocystinuria.

Elevated levels of homocysteine may result in damage to the walls of the artery and leads to thrombus formation. Thrombus formation results in conditions such as cerebrovascular accidents, heart attacks and pulmonary embolism. Replacement of the deficient vitamins achieves normal levels. Evaluation of homocysteine levels may also be performed as part of the diagnostic work-up for dementia and other related conditions; however while in some cases levels may be elevated, testing for homocysteine levels is not generally recommended (Gingrich, Carroll; 2011, Noel, et al, 2011) and is not included in the standard evaluation of dementia (Reichman and Cummings, 2007).

The mechanisms of action for increasing an individual’s risk of CVD related to elevated levels of homocysteine is inflammatory response in the arteries, increased levels of LDL, and increased potential for thrombosis. Elevated plasma levels have been demonstrated in patients with CVD and have also been shown to increase risk even in the presence of desirable lipids and lipid subfractions (Daly, et al., 2009).

Elevated homocysteine levels are not classified as major cardiac disease risk factors according to the AHA, and published recommendations for homocysteine testing as a cardiac risk factor are not consistent. In 2008, Davidson et al. (2008) reported the predictive power and clinical utility of biomarkers, including homocysteine, in the evaluation of persons with lipoprotein abnormalities is unclear. According to the ATP III guidelines, homocysteine testing may be considered an option only in selected cases (e.g., for patients with a strong family history of premature coronary heart disease [CHD] in an otherwise low-risk patient). Furthermore, while it has been suggested lowering high levels of homocysteine with diet or vitamin supplements can decrease one’s cardiac risk, routine testing is not recommended (Cesari, et al., 2005; Giacobbe, et al, 2004; Splaver, et al., 2004; Linton and Fazio, 2003) and it is not known if lowering homocysteine levels will reduce cardiovascular morbidity and mortality (Mangoni and Jackson, 2002; Grundy, et al., 1999).

Some evidence in the form of randomized controlled trials do not support a treatment effect when homocysteine levels are reduced. Lonn et al. (2006) conducted a randomized controlled clinical trial to assess whether the supplementation of folic acid, vitamins B6, and B12 reduced the risk of cardiovascular disease in patients with vascular disease; the authors concluded supplementation did not reduce cardiovascular risk. Ebbing et al. (2008) conducted a randomized double-blind, controlled clinical trial to evaluate the effect of treatment with folic acid, vitamin B12, and vitamin B6 as secondary prevention in patients with coronary artery disease or aortic valve stenosis. The primary endpoint was a composite of all-cause death, nonfatal acute myocardial infarction, acute hospitalization for unstable angina and nonfatal thromboembolic stroke. Mean plasma homocysteine concentration was reduced by 30% after one year of treatment, however the trial did not support a treatment effect from folic acid/vitamin B12 or vitamin B6 on total mortality or cardiovascular events among the patients. The authors of a double-blind RCT evaluated the potential benefits and hazards of lowering homocysteine with folic acid and vitamin B12 supplementation in survivors of myocardial infarction (n=12,064) and reported that in high risk patients supplementation had no beneficial effect on major vascular events (Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine [SEARCH] Collaborative Group, 2010). The authors of a recent Cochrane review concluded that the results from available published trials suggest that there is no evidence to support the use of homocysteine lowering interventions, in the form of vitamins B6, B9 or B12, given alone or in combination, at any dosage compared with placebo or standard care, prevented cardiovascular events in participants at risk or with established CVD (Martí-Carvajal, et al., 2009).
According to the medical practice guidelines established by NACBL (Myers, et al., 2009) there is still a need for standardization of homocysteine assays and there is still no convincing evidence to recommend screening in the general population.

The USPSTF (2009) found no evidence that treating persons with a high homocysteine level improves clinical cardiovascular outcomes.

A meta-analysis of 30 RCTs (n=82,334) was conducted to assess the overall effect of folic acid supplementation on the risk of CVD, CHD or stroke (Li, et al., 2016). The average folic acid supplementation was 3.2 years, the dosage ranged from .5 to 15 mg/day, with the exception of one trial of end-stage renal disease with a dosage of 40 mg/day. Subjects had pre-existing conditions including prior CVD, renal disease, hypertension, atherosclerosis, esophageal dysplasia, and colorectal adenomas. The incident rate for stroke (20 RCTs) was 3.8% in the folic acid group compared to 4.4% in the control group, for CHD (25 RCTs) it was 7.7% in the folic acid group compared to 7.4% in the control group, and for risk of CVD (22 RCTs) it was 12.8% in the folic acid group compared to 13.4% in the control group. The authors concluded there was a 10% reduced risk of stroke and a 4% reduced risk of overall CVD with folic acid supplementation. A greater benefit for CVD was observed among participants without preexisting CVD or with lower plasma folate levels at baseline and in studies with a larger decrease in homocysteine levels. Limitations of the analysis acknowledged by the authors included the inability to completely exclude publication bias, variation in trial design, and heterogeneous definitions of CVD outcomes which may influence interpretation of results.

Evidence suggesting improved clinical outcomes of reduced cardiac risk and adverse events as a result of lowering homocysteine levels with treatment is lacking. Patient selection criteria and target levels or safe levels of homocysteine for determining cardiac risk have not been clearly defined. While there is some clinical utility for homocysteine evaluation to confirm folate deficiency there is insufficient evidence in the peer-reviewed, published scientific literature to support routine measurement of homocysteine testing for screening, diagnosing and management of CVD, for evaluation of dementia, for hypertension, or for other non-specific symptoms in general, such as shortness of breath, malaise and fatigue. Further randomized controlled clinical trials are needed to support the potential clinical utility of lowering homocysteine levels.

**Long-chain Omega–3 Fatty Acids:** Long-chain omega–3 fatty acids may be detected in the red cell membrane using gas chromatography. It has been suggested this measurement may be clinically useful as a cardiac risk factor for sudden cardiac death. Omega–3 fatty acids have been linked to various health conditions including, but not limited to, heart disease, dementia and visual performance. Furthermore, it has been reported that omega-3 fatty acid consumption, primarily eicosapentaenoic acid and docosahexaenoic acid found in fish, may have beneficial effects on several cardiovascular outcomes, including sudden death, cardiac death and stroke. Additionally, some data suggest these fatty acids have antiarrhythmic properties.

Omega–3 fatty acids benefit the heart of healthy people and those at high risk of or who have cardiovascular disease (AHA, 2006). The AHA recommends inclusion of omega–3 fatty acids in patients with stable coronary artery disease because of evidence from randomized controlled trials that omega–3 fatty acids decrease the risk of arrhythmias, decrease triglyceride levels, decrease growth rate of atherosclerotic plaque and slightly lowers blood pressure. However, more studies are needed to confirm and further define the health benefits of omega–3 fatty acid supplements for preventing a first or subsequent cardiovascular event.

Evidence in the peer reviewed published literature examining the relationship between fish consumption and risk of coronary disease or stroke consist mainly of observational studies and meta-analyses (Albert, et al., 2002; Hu, et al., 2003; Whelton, et al., 2004; He, et al., 2004; Mozaffarian, et al., 2005) and demonstrate that the n-3 fatty acids found in fish are associated with a reduced risk of CVD. The results of one meta-analysis demonstrate that dietary supplements with omega-3 fatty acids for one year or longer significantly reduced the risk of cardiovascular deaths, including sudden cardiac death, all-cause mortality, and nonfatal cardiovascular events (Marick, et al, 2009). According to the authors the benefit appeared to depend on the patient’s risk stratification; a reduction in death was associated with high risk patients and a reduction of nonfatal events was associated with moderate risk patients. Meta-regression failed to demonstrate an association between treatment effect and dose of fish oil. Based on the results of a systematic review, Hartweg et al. (2009) concluded that the main mechanism by which omega-3 may lower CVD risk in type 2 diabetic patients is by reducing thrombogensis and
improving triglyceride levels. The authors reviewed 24 trials involving 1533 participants and noted that long-term supplementation reduced CVD risk factors (i.e., triglycerides, fibrinogen, and platelet aggregation) safely, and may be added to conventional therapy while maintaining good glycemic and lipid control for this subset of individuals. However the authors acknowledged that three large clinical outcome trials evaluating omega-3 supplementation in diabetic patients have yet to publish results and therefore, the potential benefits of omega-3 supplementation in CVD risk reduction for patients with type 2 diabetes remains inconclusive.

The Agency for Healthcare Research and Quality (AHRQ) reported that a large, consistent, beneficial effect of omega–3 fatty acids was found only for triglyceride levels, and little or no effect was found for a variety of other cardiovascular risk factors and markers of cardiovascular disease (Balk, et al., 2004). The Institute for Clinical Systems Improvement (ICSI) reported dietary and non-dietary intake of n–3 polyunsaturated fatty acids may reduce overall mortality, mortality due to myocardial infarction, and sudden death in patients with stable coronary artery disease (ICSI, 2005). The ATP III guidelines do not address long chain omega-3 fatty acid levels as emerging risk factors for cardiovascular disease risk assessment, however they do acknowledge that prospective data and clinical trials suggest higher intake of omega-3 fatty acids reduce risk for coronary events or coronary mortality. The guidelines recommend higher dietary intake and supports the AHA recommendation that fish be included as part of the cardiac risk reduction diet.

Despite a correlation with cardiac risk, there is insufficient scientific evidence in the published literature regarding how measurements of omega–3 fatty acid composition would affect management and improve clinical outcomes of individuals at risk for or patients with CHD.

**Plasma Myeloperoxidase:** Plasma myeloperoxidase (MPO), an enzyme secreted by white blood cells, (inflammatory marker) may contribute to tissue injury during inflammation and promote plaque buildup in coronary arteries; preliminary research suggests a link between myeloperoxidase and both inflammation and cardiovascular disease risk. MPO can be measured by spectrophotometric assays, counter and flow cytometry as well as with other commercial methods being proposed. Although studies of MPO testing indicate a possible relationship between elevated levels and cardiac risk, its ability to improve on existing risk stratification methods is unclear (Apple, et al., 2007; Stefanescu, et al., 2008; Roman, et al., 2008). Furthermore, in the studies evaluating MPO various methods of testing were used, making comparisons difficult and reference standards have not yet been identified. The body of evidence evaluating MPO as a potential cardiac biomarker is insufficient to support an increased predictive value as compared to traditional testing or for recommending medical management based on MPO values that would improve clinical outcomes.

**Prothrombotic Factors:** Prothrombotic factors such as plasminogen activator inhibitor (PAI–1), activated factor VII, tissue plasminogen activator (tPA), von Willebrand factor, factor V Leiden, protein C, antithrombin III, and fibrinogen have been proposed as risk factors of cardiovascular disease (Linton and Fazio, 2003). It has been reported that thrombosis plays a role in acute coronary syndromes involving both platelets and coagulation factors. Nevertheless, the association between these factors and associated heart disease has not been clearly identified in the scientific literature, and authors have reported laboratory measurements are not widely available and are not standardized (Institute for Clinical Systems Improvement [ICSI], 2003). Evidence supporting clinical utility in the published peer reviewed scientific literature is lacking; measurement of prothrombotic factors as part of the routine assessment for cardiovascular risk has not been shown to improve patient outcomes. In addition, testing is not recommended by the ATP III guidelines.

**Growth Stimulation Expressed Gene 2:** Growth stimulation expressed gene 2 (ST2, Interleukin 1 receptor like-1) (e.g., Presage® ST2 Assay, Critical Diagnostics, San Diego, CA) is a biomarker being investigated for several medical conditions, including cardiovascular disease. Authors suggest plasma ST2 is thought to identify which chronic heart failure subjects are progressing towards worsening heart failure. It has been purported testing may be indicated to establish a prognosis for congestive heart failure subjects, to guide chronic heart failure therapies, and to predict cellular rejection post cardiac transplantation. There is some evidence in the peer-reviewed scientific literature to support a correlation between elevated ST2 (i.e., >35 ug/L) and adverse cardiac outcomes (e.g., higher risk of heart failure, sudden cardiac death, and all-cause death) (Wang, et al, 2012; Kohli, et al., 2012; Shimpo, et al., 2004). However, evidence demonstrating how growth stimulation expressed gene-2 testing impacts the clinical management of subjects with congestive heart failure, the recommended frequency of testing, and resulting clinical outcomes is lacking. Furthermore, in comparison to other established measures of...
heart failure the published evidence is insufficient to support ST2 provides predictive information, alone or in combination, above that of conventional measures (e.g., standard clinical exam combined with BNP levels). Further research is needed to firmly establish the clinical utility for growth stimulation expressed gene 2 (ST2) in the management of patients with heart failure.

**Pregnancy Associated Plasma Protein-A (PAPP-A):** Pregnancy associated plasma protein-A is a circulating protein found in the serum of pregnant women. Recently, authors have asserted PAPP-A is an emerging biomarker of inflammation and plaque instability, linked to coronary artery disease and acute coronary syndrome. Evidence in the peer-reviewed published literature evaluating PAPP-A as a cardiac biomarker consists primarily of observational studies and systematic reviews (Li, et al., 2017; Leonard, et al., 2016; Nichenametla and Thomas, 2016; Wu, et al., 2016; von Haeling, et al., 2016; Parveen, et al., 2015; Li, et al., 2013; Wlazel, et al., 2013; Gururajan, et l., 2012 ); it has been reported standardization of assays has not yet been established and optimal cut-off values have yet to be determined. While some trials support a positive correlation to acute coronary events, others do not. The clinical utility of PAPP-A is unproven and additional studies are needed to validate PAPP-A as a biomarker for predicting cardiovascular events.

**Other Cardiac Risk Assessment Tests**
Several other tests, performed either alone or as part of panels, are under investigation for assessing cardiovascular and atherosclerotic risk (Berliner, et al., 2009; Creemers, et al., 2012; Pala, et al., 2012; Roysland, et al., 2012; Shah, et al., 2012; Kramer, 2013; Salgado, et al., 2013; Tashakkor, Mancini, 2013; Stegemann, et al., 2014; Rankin, et al., 2014; Hoff, et al., 2016; Laaksonen, 2016). How the results of these various tests impact risk stratification and disease management has yet to be determined. At present professional society recommendations and evidence in the published peer-reviewed scientific literature is insufficient to support clinical utility for performance of any of the following tests for the screening, diagnosing or management of coronary heart disease:

- Adiponectin
- Apelin
- Circulating micro RNAs
- Coenzyme Q10 (CoQ10)
- Cystatin C
- Fatty acid levels (e.g., Omega-3, Omega-6, monounsaturated, saturated)
- Galectin 3
- Leptin
- Osteoprotegerin
- Oxidized phospholipids
- Molecular lipid and/or metabolic profiling (e.g., lipidomics, metabolomics)
- Peroxisome proliferator activated receptor
- Protein C
- Resistin
- Retinol binding protein
- Serum sterols
- Skin cholesterol testing
- Thromboxane metabolite(s) testing
- Total cholesterol content in red blood cell membranes
- Tumor necrosis factor alpha
- Troponin, (for other than acute myocardial injury)
- Visfatin

**Professional Societies/Organizations**
Within guidelines published by the American College of Cardiology (ACC) for management of heart failure (ACC, 2013, focused update 2017) the ACC provides recommendations for biomarkers. Based on a Class IIB recommendation in addition to measurement of brain natriuretic peptide (BNP) or N-terminal pro-B-type natriuretic peptide (NP-proBNP) for risk stratification in patients with heart failure measurement of other clinically available
tests such as biomarkers of myocardial injury or fibrosis (ST2, Galectin3, hs-Troponin and others) may be considered.

In 2016 the European Guidelines on Cardiovascular Disease Prevention in Clinical Practice were updated (Piepoli, et al., 2016). Within these guidelines the committee classifies biomarkers into those that are inflammatory (e.g., high sensitivity C-reactive protein [hsCRP, fibrinogen]), thrombotic (e.g., homocysteine, lipoprotein-associated phospholipase A2), glucose and lipid-related (e.g., apolipoproteins) and organ-specific (e.g., renal, cardiac). According to the guidelines:

- Not all potentially useful circulatory and urinary biomarkers have undergone state-of-the-art assessment of their added value in CV risk prediction on top of conventional risk factors.
- Biomarkers may be useful in specific subgroups, but this has been addressed in only a limited number of studies.
- The role of metabolomics as risk factors for CVD and to improve CV risk prediction beyond conventional risk factors should be further assessed.

The American College of Cardiology (ACC) and American Heart Association (AHA) in collaboration with the National Heart, Lung, and Blood Institute (NHLBI) published guidelines for cardiovascular risk classification (Goff, et al., 2013) and recommendations for management of blood cholesterol levels in adults (Stone, et al., 2013). Regarding cardiovascular risk classification the ACC/AHA recommends the use of a Pooled Cohort Equation which takes into consideration additional variables such as age and race, in contrast to the ATP III risk classification. As part of risk factor management the ACC/AHA also considered newer risk factors such as hs-CRP, ApoB, glomerular filtration rate (GFR), microalbuminuria, family history, cardiorespiratory fitness, ankle brachial index (ABI), coronary artery calcium (CAC) scoring, or carotid intima media thickness (CIMT) and the impact of each on reclassification or contribution to risk assessment. The work group noted that none of these markers has been evaluated as a screening test in randomized controlled trials monitoring clinical events as measured outcomes. The evidence available and reviewed either did not support clinical utility or was insufficient to support any additional value for these markers. Within the management of blood cholesterol guidelines, the ACC/AHA does not define LDL cholesterol target goals and notes there were no randomized controlled trials supporting the previously recommended targets. This work group recommends using the Pooled Cohort Equation to more accurately determine risk and then initiating statin therapy to those most likely to benefit. As a result four major statin benefit groups have been identified for which statin therapy is recommended and for which the risk reduction benefit exceeds potential adverse events: individuals with clinical ASCVD, individuals with primary elevations of LDL > 190mg/dL, individuals with diabetes aged 40-75 years and LDL 70-189 mg/dL and without clinical ASCVD, or those without clinical ASCVD or diabetes with LDL 70-189 mg/dL and estimated 10-year risk of ASCVD ≥ 7.5%. In the new guidelines statin therapy is graded as either high intensity or moderate intensity. High intensity statin therapy is defined as that which is intended to reduce LDL by ≥ 50% and moderate intensity statin therapy is intended to reduce LDL by 30-50% (Stone, et al., 2013).

The American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) published guidelines for assessment of cardiovascular risk in asymptomatic individuals (i.e., apparently healthy adult) (Greenland, et al., 2010). The task force conducted a systematic review of the current scientific evidence (March 2008 – April 2010) and used evidence based methodologies to weigh the evidence which was reviewed. Level A evidence represented data from multiple randomized controlled trials or meta-analyses, level B evidence was data from a single RCT or nonrandomized trial, and level C evidence represented consensus opinion, case studies or standard of care. The recommendations were approved and endorsed by the ACCF, AHA, American Society of Echocardiography, American Society of Nuclear Cardiology, Society of Atherosclerosis Imaging and Prevention, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. The guidelines support global risk assessment in all asymptomatic adults without a clinical history of CVD (level B evidence) and obtaining a family history of atherothrombotic CVD (level B evidence). Regarding laboratory studies specifically, the guidelines recommend hs C-reactive protein (level B evidence), hemoglobin A1C (level B evidence), and Lp-PLA2 (level B evidence). The guidelines do not support genotype testing (level B evidence) or measurement of lipid parameters such as lipoproteins, apolipoproteins, particle size and density, beyond the standard fasting lipid profile (level C evidence), or natriuretic peptide testing (level B evidence).

In October 2009 the U.S Preventive Services Task Force (USPSTF) published recommendations for using nontraditional risk factors in coronary heart disease assessment (USPSTF, 2009). The recommendations are
intended for asymptomatic men and women with no history of CHD, diabetes or any CHD risk equivalent. The recommendations are based on a systematic review of the evidence of the benefits and harms, and an assessment of the net health benefit of the service. Regarding laboratory evaluations, the nontraditional risk factors included hs-CRP, leukocyte count, fasting blood glucose level, homocysteine level, and lipoprotein(a) level. The USPSTF concluded the evidence was insufficient to determine the balance between benefit and harms of using nontraditional risk factors in screening for coronary artery disease risk. There was no evidence that risk stratification with any of the nontraditional risk factors, either independently or in addition to Framingham risk scoring, reduced myocardial infarction or CVD mortality compared with risk stratification and treatment on the basis of Framingham scoring alone.

The American Association of Clinical Chemistry (AACC) issued guidelines (Myers, et al., 2009) titled “The National Academy of Clinical Biochemistry (NACB) Laboratory Medicine Practice Guidelines”, for emerging biomarkers for primary prevention of cardiovascular disease. The guidelines were developed by a multidisciplinary expert panel after systematically reviewing available evidence and evaluating criteria of clinical usefulness, consistency of epidemiologic data, improved predictive value, independence from other factors, and available analytical methods. When possible, the recommendations were based on prospective observational studies of healthy populations. Retrospective studies or studies consisting of populations with vascular disease were only considered for secondary prevention. The strength of data was characterized using the criteria from the AHA/ACC. The guidelines supported testing of hs-CRP, Lp(a), apo B, apo B/apo A-I ratio, and chronic kidney disease including serum creatinine and microalbuminuria in specific patient populations as identified by the expert panel. The guidelines state that as a result of analytical concerns, insufficient assay standardization, and uncertainty in identifying treatment strategies testing for fibrinogen is not recommended; existing studies are not adequate to show benefit over standard risk assessment for lipoprotein subclass testing; population routine testing for small size apo A is not warranted, apo B should not be routinely measured for use in global risk assessment, the clinical application for homocysteine is uncertain, and more research should be performed to determine if BNP and NT-proBNP are useful in identifying individuals who are at increased risk of developing heart failure and might benefit from therapies for prevention.

The AACC also published a position statement from the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices for apo B testing and cardiovascular disease risk (Contois, et al., 2009). Based on the working group’s review of the available studies, rather than solely focus on LDL cholesterol, the working group supports that apo B along with LDL cholesterol is beneficial for assessing LDL-related risk until the superiority of apo B is generally recognized. The working group also stressed the need for future NCEP guidelines to address apo B and LDL particle measurement.

A consensus statement from the American Diabetes Association and the American College of Cardiology Foundation (Brunzell, et al., 2008) addressed issues surrounding the concept of global cardiometabolic risk (CMR), treatment targets, and the best approach for CVD risk reduction. The consensus panel recommended that because apo B appears to be a more sensitive index of residual CVD risk when LDL cholesterol or non-HDL cholesterol (i.e., total cholesterol minus HDL cholesterol) are < 130 mg/dl or <160 mg/dl respectively, measuring apo B using a standardized assay is warranted in patients with CMR on pharmacologic treatment; in particular, apo B levels should be used to guide adjustments of therapy.

The recommended suggested treatment goals for individuals with CMR and lipoprotein abnormalities now include apolipoprotein B levels, and are as follows:

**Table 1: Suggested treatment goals in patients with CMR and lipoprotein abnormalities (based on the panel’s consensus of evaluation of available evidence):**

<table>
<thead>
<tr>
<th></th>
<th>LDL cholesterol goal (mg/dl)</th>
<th>Non-HDL cholesterol goal (mg/dl)</th>
<th>Apo B goal (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-risk patients, including those with 1) known CVD or 2) diabetes plus one or more additional major CVD risk</td>
<td>&lt; 70</td>
<td>&lt; 100</td>
<td>&lt; 80</td>
</tr>
</tbody>
</table>
Other major risk factors (beyond dyslipoproteinemia) include: smoking, hypertension, and family history of premature CAD.

The National Cholesterol Education Program Adult Treatment Panel (Adult Treatment Panel III [ATP III]) guidelines do not recommend routine measurement of any of the emerging risk factors for the purpose of risk assessment; these tests should be used in selected persons, and only on the basis of considered clinical judgment (National Institutes of Health [NIH], 2002).

Regarding the use of conditional and predisposing risk factors in risk assessment, in 1999 the AHA and ACC reported conditional risk factors included: elevated serum triglycerides, small LDL particles, elevated serum homocysteine, elevated serum lipoprotein(a), prothrombotic factors (e.g., fibrinogen), and inflammatory markers (e.g., C-reactive protein). However, their quantitative contribution and independence of contribution to risk are not well defined, and they are not usually included in global risk assessment (ACC, 1999). Furthermore, the AHA and ACC concluded a high serum concentration of homocysteine is associated with increased risk for CHD; however, it remains to be proved in controlled clinical trials that a reduction in serum homocysteine levels will reduce the risk for CHD. Routine measures of lipoprotein (a), fibrinogen, and C-reactive protein currently are not recommended. An elevated serum lipoprotein(a) correlates with a higher incidence of CHD in some studies but not in others, and specific therapeutics to reduce lipoprotein(a) levels are not available. Additionally, the AHA and ACC stated that some investigators have suggested that an elevated lipoprotein(a) level justifies a more aggressive lowering of LDL–C. An elevated fibrinogen level is also correlated with a higher CHD incidence; however, again, no specific therapies are available, except that in smokers, smoking cessation may reduce fibrinogen concentrations. Finally, C-reactive protein is promising as a risk predictor. The preferred method for measurement appears to be a high-sensitivity test. C-reactive protein appears to be related to systemic inflammation; however, its causative role in atherogenesis is uncertain.

**Coding/Billing Information**

**Note:**
1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.

**Considered Medically Necessary when criteria in the applicable policy statements listed above are met:**

**Lipoprotein-associated phospholipase A2 (Lp-PLA2) testing**

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>83698</td>
<td>Lipoprotein-associated phospholipase A2, (Lp-PLA2)</td>
</tr>
</tbody>
</table>

**Apolipoprotein B testing**
### CPT® Codes

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
</table>
| 81401      | Molecular pathology procedure, Level 2 (eg, 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)  
  - APOB (apolipoprotein B)(eg, familial hypercholesterolemia type B)  
    common variants (eg, R3500Q, R3500W) |
| 82172      | Apolipoprotein, each |

### Lipoprotein(a) enzyme immunoassay (Lp[a]) testing

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>83695</td>
<td>Lipoprotein (a)</td>
</tr>
</tbody>
</table>

### Other Emerging Cardiac Disease Risk Factor Laboratory Tests

**Considered Experimental, investigational, or unproven when performed for screening, diagnosing or management of coronary heart disease:**

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81599†</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
<tr>
<td>82163</td>
<td>Angiotensin II</td>
</tr>
<tr>
<td>82172</td>
<td>Apolipoprotein, each</td>
</tr>
<tr>
<td>82542</td>
<td>Column chromatography, include mass spectrometry, if performed (eg, HPLC, LC, LC/MS, LC/MS-MS, GC, GC/MS-MS, GC/MS, HPLC/MS), non-drug analyte(s) not elsewhere specified, qualitative or quantitative, each specimen</td>
</tr>
<tr>
<td>82610</td>
<td>Cystatin C</td>
</tr>
<tr>
<td>82777</td>
<td>Galectin-3</td>
</tr>
<tr>
<td>83006</td>
<td>Growth stimulation expressed gene 2 (ST2, Interleukin 1 receptor like-1)</td>
</tr>
<tr>
<td>83090</td>
<td>Homocysteine</td>
</tr>
<tr>
<td>83519</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, by radioimmunoassay (eg, RIA)</td>
</tr>
<tr>
<td>83520</td>
<td>Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified</td>
</tr>
<tr>
<td>83700</td>
<td>Lipoprotein, blood; electrophoretic separation and quantitation</td>
</tr>
<tr>
<td>83701</td>
<td>Lipoprotein, blood; high resolution fractionation and quantitation of lipoproteins including lipoprotein subclasses when performed (eg, electrophoresis, ultracentrifugation)</td>
</tr>
<tr>
<td>83704</td>
<td>Lipoprotein, blood; quantitation of lipoprotein particle numbers and lipoprotein particle subclasses (eg, by nuclear magnetic resonance spectroscopy)</td>
</tr>
<tr>
<td>83719</td>
<td>Lipoprotein, direct measurement; VLDL cholesterol</td>
</tr>
<tr>
<td>83876</td>
<td>Myeloperoxidase (MPO)</td>
</tr>
<tr>
<td>84163</td>
<td>Pregnancy-associated plasma protein-A (PAPP-A)</td>
</tr>
<tr>
<td>84431</td>
<td>Thromboxane metabolite(s), including thromboxane if performed, urine</td>
</tr>
<tr>
<td>84484</td>
<td>Troponin, quantitative</td>
</tr>
<tr>
<td>84999†</td>
<td>Unlisted chemistry procedure</td>
</tr>
<tr>
<td>85230</td>
<td>Clotting; factor VII (proconvertin, stable factor)</td>
</tr>
<tr>
<td>85247</td>
<td>Clotting; factor VIII, von Willebrand factor, multimetric analysis</td>
</tr>
<tr>
<td>85300</td>
<td>Clotting inhibitors or anticoagulants; antithrombin III, activity</td>
</tr>
<tr>
<td>85303</td>
<td>Clotting inhibitors or anticoagulants; protein C, activity</td>
</tr>
<tr>
<td>85384</td>
<td>Fibrinogen; activity</td>
</tr>
</tbody>
</table>
Fibrinogen; antigen
Fibrinolytic factors and inhibitors; plasminogen activator
Long-chain (C20-22) omega-3 fatty acids in red blood cell (RBC) membranes
Secretory type II phospholipase A2 (sPLA2-IIA)

† Note: Experimental, investigational, unproven and not covered when used to report any non-covered service outlined as such in this document (e.g., MIRISK VP™, PULS Cardiac Test™).


References


120. Linton MF, Fazio S. A practical approach to risk assessment to prevent coronary artery disease and its complications. Am J Cardiol. 2003 Jul;92(1A)19i-26i.


