



# CIGNA MEDICAL COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject Cardiac Disease Risk  
Assessment: Emerging  
Laboratory Evaluations**

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 Magnetic Resonance Angiography (MRA)  
 Plasma Brain Natriuretic Peptide

## INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. In certain markets, delegated vendor guidelines may be used to support medical necessity and other coverage determinations. Proprietary information of CIGNA. Copyright ©2011 CIGNA

## Coverage Policy

**CIGNA covers high-sensitivity C-reactive protein (hs-CRP) testing for the assessment of coronary artery disease risk as medically necessary when BOTH of the following criteria are met:**

- Using the 10-year risk assessment tool recommended by the National Cholesterol Education Program the individual is at intermediate risk of developing coronary heart disease (CHD) (i.e., 10-year risk of 10–20%).
- The individual is metabolically stable without obvious inflammatory or infectious conditions.

**CIGNA does not cover high-sensitivity C-reactive protein (hs-CRP) testing for the following indications because it is considered experimental, investigational or unproven:**

- as a screening test in the general population
- for monitoring response to treatment of coronary artery disease risk factors

**CIGNA covers lipoprotein-associated phospholipase A2 (Lp-PLA<sub>2</sub>) testing as medically necessary, for ANY of the following individuals who are at intermediate- or high-risk for developing 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

**CIGNA covers apolipoprotein B testing as medically necessary when the individual is undergoing management for lipoprotein abnormalities and ANY of the following conditions is met:**

- The individual has clinical CHD (i.e., established CHD).
- The individual has diabetes mellitus.
- The individual does not have diabetes mellitus or known clinical CHD but has two or more major risk factors (e.g., smoking, hypertension, family history of premature CHD, low levels of HDL cholesterol).

**CIGNA covers lipoprotein(a) enzyme immunoassay (Lp[a]) testing as medically necessary for ANY of the following at-risk groups, when used to assess risk and guide treatment of lipoprotein abnormalities:**

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

**CIGNA does not cover ANY of the following testing, for screening, diagnosing or management of coronary heart disease because each is considered experimental, investigational or unproven (This list may not be all-inclusive):**

- angiotensinogen gene testing (e.g., CardiaRisk™)
- apolipoprotein A-1
- apolipoprotein E
- gene expression analysis (e.g., Corus™ CAD)
- high-density lipoprotein (HDL) subclasses (LpAI, LpAI/AII and/or HDL3, HDL2)
- homocysteine testing
- interleukin 6-174 polymorphism
- kinesin-like protein 6 (KIF6)
- lipoprotein remnants
- long-chain omega-3 fatty acids
- low-density lipoprotein (LDL) subclass size and concentration (small and large LDL particles)
- plasma myeloperoxidase (MPO)
- 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)

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## 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.

Recommendations for general screening of cardiovascular disease risk are provided by the ATP III guidelines and are considered standard of care. Overall determination of cardiac risk is based on standard, accepted risk-

stratification approaches, involving determination of standard lipid profiles consisting of total cholesterol, low density lipoprotein (LDL) and triglycerides levels. These screening and management approaches are based on traditional risk factor assessment including cholesterol/LDL, triglycerides, diet, smoking, diabetes and family and personal medical history. The National Cholesterol Education Program utilizes the Framingham risk scoring calculation, endorsed by the National Heart Lung and Blood Institute (NHLBI) and the American Heart Association (AHA) for determining 10-year coronary heart disease (CHD) risk.

There is evidence to suggest that therapies aimed at reducing LDL cholesterol levels may reduce cardiovascular risk. However, some individuals continue to have significant risk despite lowering LDL cholesterol to levels recommended by the National Cholesterol Education Program Adult Treatment Panel (NCEPA ATP III, [ATP III]). Consequently, 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 are referred to as “emerging risk factors” and include a variety of tests such as serum inflammatory markers, comprehensive lipoprotein testing, angiotensin gene testing and prothrombotic factors.

Preventative methods should target each major risk factor. If left untreated each has the potential to produce CVD. For individuals that are considered high risk because of multiple risk factors, intense modification of more than one risk factor is typically required to maximize risk reduction. For example, the risk for developing CVD is increased in the presence of cardiometabolic syndrome; individuals with cardiometabolic risk (CMR) factors have a high lifetime risk for CVD. Cardiometabolic risk factors include a cluster of modifiable risk factors and markers such as obesity, insulin resistance, hyperglycemia, hypertension, inflammatory markers, and dyslipidemia.

### **Cardiac Risk**

**Framingham Risk Score:** When utilizing the Framingham risk scoring tool, point scores are assigned to various risk factors (e.g., age, total cholesterol, smoking, high density lipoprotein (HDL) level, and systolic blood pressure) and totaled. 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%.

The National Cholesterol Education Program Adult Treatment Panel (Adult Treatment Panel III, [ATP III]) guidelines focus on multiple risk factors and use the Framingham risk calculation to identify certain patients for more intense treatment. In general, low cardiac risk is described as no risk factors or one risk factor; moderate cardiac risk is defined as two risk factors and a 10-year Framingham risk of less than 10%; moderate high risk is defined as 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., 2007). According to the National Heart Lung and Blood Institute (NHLBI), an update to the ATP guidelines is currently under development.

An electronic version of Framingham risk assessment tool is available through the NHLBI website under the heading “Health Assessment Tools” (<http://hp2010.nhlbinet.net/atp3/calculator.asp?usertype=pub>).

**Reynolds Risk Score:** A newer model, the Reynolds risk score is also designed 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, however, 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/>.

### **Basic Lipoprotein Profile**

A lipoprotein profile generally includes total cholesterol, HDL cholesterol, and triglyceride levels in addition to a calculated LDL cholesterol level. Calculation of the LDL level is usually an indirect measurement and is estimated from measurements of total cholesterol, total triglycerides and HDL cholesterol.

In some clinical situations (e.g., presence of chylomicrons, elevated triglycerides [ $>400$  mg/dl]), indirect LDL calculation may not be considered accurate (i.e., underestimated) and direct LDL calculations may be considered more appropriate. However, the direct methods available to measure LDL cholesterol are not standardized (Brunzell, et al., 2008) and the ATP III recommendations do not favor replacing calculated LDL levels for direct LDL. Calculated LDL levels are considered sufficient and accurate 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 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**

The significance of “emerging” risk factors continues to be evaluated against the same criteria used to establish the significance of what are considered “major” risk factors. Scientific evaluation of emerging risk factors include determining predictive power, population prevalence, the availability of laboratory testing, standardization methods, reference values, stability, and 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. The potential 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; accuracy, sensitivity, specificity and predictive values have not been firmly established in the medical literature. In general, when comparing predictive values of the emerging risk factors with traditional measurements, some of the emerging risk factors have predictive value that is considered comparable, although some are not as predictive. For several of these emerging risk factors there is no consensus among authors towards identifying targeted therapy and if targeted therapy reduces risk and improves clinical outcomes when compared to the traditional evaluation and therapy. As a result, there is little agreement among authors regarding recommendations for performing any of the emerging cardiac risk factors as part of the routine risk assessment for the general population or for those who may be at high risk.

**High-Sensitivity C-Reactive Protein (hs-CRP):** High-sensitivity C-reactive protein is a test that indicates acute inflammation by measuring the concentration of a protein in the serum. It has also been referred to as ultra-sensitive C-reactive protein. It is a special type of protein produced by the liver and is excreted in small amounts within six hours of an acute inflammatory reaction. Hs-CRP may be elevated in conditions including, but not limited to: rheumatic fever, rheumatoid arthritis, systemic vasculitis, myocardial infarction and acute pancreatitis.

Some analysts have suggested that the utility of CRP measurements in assessing cardiovascular risk is unproven and requires further study (Danesh, et al., 2004; Korn and Eddy, 2003). However, most studies support hs-CRP testing and indicate that the higher the hs-CRP levels, the higher the risk for developing a heart attack. According to the AHA, normal ranges of hs-CRP and the associated risk are as follows:

- If the hs-CRP level is lower than 1.0 mg/L, the person has a low risk of developing cardiovascular disease.

- If the hs-CRP is between 1.0 and 3.0 mg/L, the person has an average risk.
- If the hs-CRP is higher than 3.0 mg/L, the person has a high risk.

Published evidence in the medical literature supports that increased levels of hs-CRP are associated with increased risk for CVD, sudden death and peripheral arterial disease (Ridker, et al., 2000; Pearson, et al., 2003; Yin, et al., 2004; Labarrere and Zaloga, 2004). Results of large-scale studies such as the Multiple Risk Factor Intervention Study (MRFIT), Physicians Health Study, and Women's Health Study demonstrate elevated hs-CRP levels to be a risk predictor of primary MI and stroke in men and cardiovascular events in women. High-sensitivity C-reactive protein is the only inflammatory marker that can be used as an independent cardiovascular risk factor (AHA/Center for Disease Control and Prevention [CDC], 2003).

Hs-CRP is indicated for screening of CVD in the clinical setting for individuals who are at intermediate risk (10–20%) of heart disease over the next 10 years using global risk assessment, and who are without an obvious inflammatory or infectious condition and are metabolically stable (Pearson, et al., 2003). In addition, hs-CRP may be performed as an optional adjunct for assessing risk in patients who have already undergone traditional risk assessment. In high-risk patients who have a 10-year risk of greater than 20%, the patients already qualify for intensive medical intervention, and hs-CRP testing would not be necessary. In patients identified as low risk (less than 10% per 10 years), hs-CRP levels would be unlikely to result in a high-risk level. The hs-CRP measurements should be used in conjunction with an overall assessment of the patient's CVD risk and comprehensive treatment guideline recommendations. All other indications for hs-CRP testing would not be medically necessary.

Evidence in the medical literature does suggest reduction of CRP may play a role in the prevention of cardiovascular events. Several methods of reducing CRP levels have been reported and may include diet-induced weight loss, reducing insulin resistance, statin therapy and fibric acid derivatives (Labarrere and Zaloga, 2004). In particular, investigators are evaluating the effects of statins on the reduction of CRP levels. One group of authors reported that statin therapy reduced inflammatory markers in hypercholesterolemic patients; the action was limited to patients whose markers were  $\geq 2.0$ mg/L at baseline (Horiuchi, et al., 2010). Authors have reported that the relevance of lowering CRP levels may be similar to that of lowering LDL levels, although this potential benefit has not been firmly established. In one randomized controlled trial, Ridker and colleagues (2005) reported that patients who have low CRP levels after statin therapy have better clinical outcomes (less recurrent myocardial infarction and death) than those who have higher CRP levels, regardless of the resultant LDL cholesterol level.

**Angiotensinogen Gene (AGT):** Individuals with an inherited mutation in the AGT gene are more likely to become hypertensive and to experience more severe forms of the disease earlier in life. AGT polymorphism may be associated with increased risk of cardiovascular disease and increased responsiveness to angiotensin converting enzyme (ACE) inhibitor therapy, salt restriction and weight loss. Analysis of the gene may have potential to help individualize therapy by determining the patient's responsiveness to certain types of antihypertensive interventions. Evidence in the peer-reviewed, published scientific literature is insufficient to support the clinical utility of this testing and does not support that the detection of AGT leads to improvement of clinical outcomes in patient management. One test that identifies mutation of the AGT gene is CardiaRisk™ (Myriad Genetics, Salt Lake City).

**Apolipoproteins:** Lipoproteins are large complexes of molecules that transport lipids (primarily triglycerides and cholesterol) 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. Typically, testing for apo A–1 is 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 that are 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. The assay for measuring apo B has become standardized (Brunzell, et al., 2008).
- Apolipoprotein E (apo E) modulates the metabolism of the highly atherogenic apolipoprotein B (apo B) containing lipoproteins. It is a protein constituent of VLDL and chylomicrons. Apo E binds to the cell surface receptors and is a polymorphic gene with several phenotypes. It is proposed that apo E testing may provide additional risk information for those patients currently identified as low- or intermediate-risk by standard lipoprotein test and risk factor assessment. However, there is no uniform standard for analyzing the relationship of apo E genotypes or phenotypes to CVD risk.

Data supporting apolipoprotein measurement improves 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 (Stampfer, et al., 1991; Sharrett, et al., 2001; Ingelsson, et al., 2007; Ray, et al., 2009). Moreover, 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;). The literature also lends some support that the ratios of total cholesterol to HDL and of apo B: apo A-1 are more highly correlated with severity and extent of CVD (Wallach, et al., 2007; Lau and Smith, 2009; Sierra-Johnson, et al., 2009). 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).

There is insufficient evidence in the peer-reviewed, scientific literature to support the use of apo E testing for the screening, diagnosis or management of CVD.

The ATP III guidelines do not recommend apo A-1 for routine risk assessment, apo E is not addressed in the guideline, and according to the guideline non-HDL serves as a surrogate for apo B. Furthermore, at this time 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. Apo E is not addressed in the consensus statement.

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 manufacturers of the assays should establish traceability to accepted standards to assure reliable and comparable results.

**Corus™ CAD Gene Expression:** Gene expression has been investigated as a diagnostic tool for evaluating individuals with cardiovascular disease. One such test, the Corus CAD gene expression, is a CLIA certified blood test that integrates expression levels of 23 genes and theoretically predicts the likelihood that an individual has obstructive CAD. According to the manufacturer, Corus CAD is intended for non-diabetic individuals with stable chest pain and no previous history of cardiac disease. The test provides a single objective score (0-40) which corresponds to a percent chance an individual has obstructive CAD. The score is derived from the expression levels of 23 genes and other characteristics that are related to inflammation of the coronary arteries. The manufacturer suggests that test results are helpful to rule out obstructive CAD and consequently, to determine whether or not other diagnostic tests are necessary. Evidence in the published peer-reviewed scientific literature evaluating gene expression, in particular the Corus CAD test, is lacking and the clinical utility of gene expression testing has not been established. Sensitivity and predictive values have not been clearly defined for the Corus CAD and the impact of test results on disease management has not been demonstrated. Furthermore, the American Heart Association, the American College of Cardiology and the ATP III treatment guidelines do not provide information regarding gene expression testing.

**High Density Lipoprotein (HDL) Subclass (LpAI, LpAI/II and/or HDL3, HDL2):** The HDL subclass test is a whole-plasma blood test that determines the HDL subclass pattern for an individual. The total HDL cholesterol is the risk indicator most commonly used in cardiac risk assessment. The HDL subclasses are often determined by gradient-gel electrophoresis (GGE). HDL subclass testing is 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. According to 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. Currently, there is lack of evidence to support HDL subclass testing in the screening, diagnosis or management of dyslipidemia and/or CVD. A consensus statement by the ACC and the ADA (Brunzell, et al., 2008) state that measurements of HDL subfractions (or apo A-1) appear to provide little clinical value beyond measurements of HDL cholesterol.

**Homocysteine:** Homocysteine is an amino acid that is normally found in the body. Several vitamins, including folic acid, B<sub>6</sub>, and B<sub>12</sub> aid in the metabolism of homocysteine. The proposed mechanism 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 contributing to atherosclerosis. Elevated plasma levels have been demonstrated in patients with CVD. Elevated levels have also been shown to increase risk even in the presence of desirable lipids and lipid subfractions (Daly, et al., 2009). Patients with homocystinuria, a rare recessive disease, have elevated plasma levels and accelerated premature vascular disease.

Elevated homocysteine levels are not classified as major cardiac disease risk factors according to the AHA, although some authors have suggested supplemental B vitamins as a method of treatment for elevated levels in hopes of reducing cardiac risk. Recommendations for homocysteine testing as a cardiac risk factor are not consistent. Davidson et al. (2008) reported in a consensus statement that biomarkers, including homocysteine, have been evaluated as factors that may be considered in the evaluation of persons with lipoprotein abnormalities, although their independent predictive power and clinical utility are still unclear. According to the ATP III guidelines, homocysteine testing may be considered an option in selected cases (e.g., for patients with a strong family history of premature coronary heart disease [CHD] in an otherwise low-risk patient).

Some authors have suggested that lowering high levels of homocysteine with diet or vitamin supplements can decrease one's cardiac risk. Nonetheless, other authors have reported routine testing is not recommended (Giacobbe, et al, 2004; Splaver, et al., 2004; Linton and Fazio, 2003) and that it is not known if lowering homocysteine levels will reduce cardiovascular morbidity and mortality (Mangoni and Jackson, 2002; Grundy, et al., 1999). Cesari et al. (2005) reported in a literature review that since homocysteine lowering therapy with folate supplementation is innocuous and inexpensive, it has been proposed to assess levels in high-risk patients and to treat those with elevated levels; however, the evidence does not indicate treatment will decrease cardiovascular risk in short-term follow-up studies. Lonn et al. (2006) conducted a randomized controlled clinical trial to assess whether the supplementation of folic acid, vitamins B<sub>6</sub>, and B<sub>12</sub> 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 B<sub>12</sub>, and vitamin B<sub>6</sub> 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 B<sub>12</sub> or vitamin B<sub>6</sub> 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 B<sub>12</sub> 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 B<sub>6</sub>, B<sub>9</sub> or B<sub>12</sub>, 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 (Marti-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 outcomes.

Overall, evidence suggesting improved clinical outcomes, such as reduced cardiac risk, as a result of lowering homocysteine levels with treatment is lacking. Patient selection criteria and target levels or safe levels of homocysteine have not been clearly defined. At present, 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. Further randomized controlled clinical trials are needed to support the potential benefit of lowering homocysteine levels.

**Interleukin 6–174 Polymorphism:** Interleukin 6 is an inflammatory cytokine that is believed to play a role in the acute phase response and inflammatory cascade similar to C-reactive protein. One polymorphism, –174, has been reported to be of specific importance (Lieb, et al., 2004). However, evidence regarding the relationship between interleukin 6–174 and cardiovascular disease has not been consistently demonstrated in the peer-reviewed, published scientific literature. The results of some studies show an association between plasma levels and cardiovascular disease (Ridker, et al., 2000; Bermudez, et al., 2002) and, in other studies, authors have reported it is not a suitable marker for coronary heart disease and that significant associations have not been found (Sukhija, et al., 2007; Sie, et al., 2006; Lieb et al., 2004). The limitations of the overall body of published evidence preclude the ability to draw strong conclusions on the clinical utility of interleukin 6–174 testing at this time.

**Kinesin-like protein 6 (KIF6):** Kinesin-like protein 6 is a protein involved in intracellular transport expressed in many tissues and cell types. Theoretically, variants of KIF6 (719Arg allele) may be a risk factor associated with CVD, in particular with myocardial infarction. While the role of KIF6 in CVD is not clearly established in the peer-reviewed scientific literature, there are a few studies that support an association with CVD (Shiffman, et al., 2008a; Bare, et al., 2007; Shiffman, et al., 2008b; Iakoubova, et al., 2008). Furthermore, preliminary evidence has shown that high dose statin therapy compared with standard dose reduced the risk of death or major cardiovascular events in patients who were carriers of the gene (Iakoubova, et al., 2008). However, further studies are needed to clearly define the functional effect of the gene, the effect KIF6 has on CVD, and to determine how testing impacts medical management strategies and improves clinical outcomes.

**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. At present there is currently no international standard reference measurement for lipoprotein(a), although levels above 30mg/dl are considered elevated. Treatments specifically aimed at reducing lipoprotein(a) levels are not widely available (Grundy, et al., 1999) and in general, therapy includes more aggressive management. Niacin and estrogen have been shown to lower blood levels of Lp(a) although it has not been firmly demonstrated in the published literature that lowering lipoprotein(a) levels reduce the incidence of cardiovascular disease. Guidelines recommending intervention based on Lp(a) levels have not been clearly defined, 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 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 influences 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.

**Lipoprotein-Associated Phospholipase A2 (Lp-PLA<sub>2</sub>):** Evidence has suggested Lp-PLA<sub>2</sub> plays a role in atherosclerosis, and it has been proposed that Lp-PLA<sub>2</sub> testing may aid in detecting CVD risk. Lp-PLA<sub>2</sub> is a marker of inflammation produced primarily in macrophages and bound to LDL. Lp-PLA<sub>2</sub> is commonly measured by the diaDexus PLAC<sup>™</sup> test (diaDexus, Inc., South San Francisco, CA) an enzyme-linked immunoabsorbant 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-PLA<sub>2</sub> had increased risk of cardiovascular disease (Moriarty and Gibson, 2005). Wallach (2007) suggests increased Lp-PLA<sub>2</sub> with low LDL-C increases risk of heart disease by two times and that increased Lp-PLA<sub>2</sub> with high CRP increases risk of heart disease by three times. The ATP III guidelines do not include measurement of Lp-PLA<sub>2</sub>, although several studies have been published since the initial recommendations. Corson et al. (2008) reported that Lp-PLA(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-PLA<sub>2</sub> levels for determining CVD risk. Davidson et al. (2008), an expert consensus panel, evaluated how Lp-PLA<sub>2</sub> 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-PLA<sub>2</sub> 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-PLA<sub>2</sub> 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-PLA<sub>2</sub> levels. Nonetheless, it is not presently known whether lowering Lp-PLA<sub>2</sub> levels will decrease the incidence of coronary disease or stroke and improve clinical health outcomes. Treatment for elevated Lp-PLA<sub>2</sub> is targeted at lowering LDL 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 thrombogenesis 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 additive 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.

**Low Density Lipoprotein (LDL) Subclass (Small and Large LDL Particles):** The ATP III guidelines have identified LDL as the primary atherogenic component of total cholesterol. 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 more 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). Analytical ultracentrifugation is the methodologic standard for determining lipoprotein subfractions (Myers, et al., 2009). Ultracentrifugation measures the flotation velocity of LDL and is the gold standard, although it is only available in a few research laboratories; gradient gel electrophoresis specifies the average size of the LDL particle and is more widely available. NMR measures lipid concentration (quantity) of LDL particles (Sacks and Campos, 2003) and has been reported as the most accurate method for evaluating LDL particles (Underblakke, McBride, 2007). HPLC monitors isolated LDL subfraction by ultracentrifugation, the retention time of the LDL peak is used to calculate the LDL diameter.

There is a growing body of evidence in the medical literature that support 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 et al. (2009) reported however that risk prediction is comparable but not superior to standard lipids or immunoassay-measured apolipoproteins (Mora, et al., 2009). 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.

The effects of niacin on lipoprotein particle distribution has been studied and has been shown to reduce the number of circulating particles of the more atherogenic subtypes of LDL, despite having no effect on total LDL levels (Jafri, et al., 2009). Within a technology assessment report however, 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.

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 (or 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 point similar to that of LDL (i.e., 20<sup>th</sup> 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).

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.

No standards for LDL subclass categorization and optimal levels of the LDL subclasses have been firmly established (Chung, et al., 2009; AHRQ, 2008). It has been suggested however 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). Whether the use of LDL particle testing in addition to LDL cholesterol testing will result in a reduction of CVD and associated events has not been demonstrated in the published literature (CTAF, 2008). When discordant, LDL particle concentration has been shown to be the better predictor of risk, and theoretically treatment aimed at lowering LDL will lower LDL particle concentration and cholesterol content. Some studies have shown that pharmacologic treatment lowers particle concentration. Published evidence supporting improved cardiovascular outcomes (i.e., reduction in cardiac events) as a result of on treatment targets is lacking. The role of LDL subclass testing remains unknown in the routine screening, diagnosis or patient management for the treatment of CVD or for those individuals defined as high risk (e.g., those with cardiometabolic risk factors, dyslipoproteinemia).

**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 predicative 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). 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.

### **Professional Societies/Organizations**

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. While using hs-CRP to screen men and women with intermediate Framingham risk would reclassify some individuals into low or high risk groups, there is insufficient evidence to determine the definitive effect on the occurrence of CHD events and CHD-related deaths.

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.

However, the AACC has 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):**

	LDL cholesterol goal (mg/dl)	Non-HDL cholesterol goal (mg/dl)	Apo B goal (mg/dl)
High-risk patients, including those with 1) known CVD or 2) diabetes plus one or more additional major CVD risk factor*	< 70	< 100	< 80
High-risk patients, including those with 1) no diabetes or known clinical CVD but two or more additional major CVD risk factors* or 2) diabetes but no other major CVD risk factors*	<100	<130	<90

\*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). Currently, there has been no update to the initial report for assessment of cardiovascular risk by use of multiple-risk factor assessment equations.

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.

### Summary

There is a growing body of evidence that continues to evaluate emerging risk factors as a method of determining or adjusting cardiovascular disease risk assessment. However, for many of these laboratory studies the added value beyond that associated with traditional testing has not been firmly established. Many of the studies do not have established reference standards and some assays are not widely available. Furthermore, despite potential improvement of predictive value for a few of these emerging risk factors, there is little agreement regarding their effect on treatment strategies and disease management. The impact this testing has on meaningful clinical outcomes such as morbidity and mortality has not yet been clearly defined. At present the American Heart Association, the American College of Cardiology and The National Cholesterol Education Program Adult Treatment Panel guidelines (ATP III) have not issued formal recommendations for many of these laboratory evaluations. Further evidence is needed to establish the clinical utility of emerging risk factor assessment in determining and monitoring cardiovascular disease risk.

## Coding/Billing Information

**Note:** This list of codes may not be all-inclusive.

**Covered when medically necessary for the assessment of coronary artery disease risk when the individual is at intermediate risk (i.e., 10 year risk of 10-20%) of developing coronary heart disease (CHD) and is metabolically stable without inflammatory or infectious conditions:**

CPT <sup>®*</sup> Codes	Description
86141	C-reactive protein; high sensitivity (hsCRP)

ICD-9-CM Diagnosis Codes	Description
272.0-272.3	Pure hypercholesterolemia
272.5	Lipoprotein deficiencies
272.7	Lipidoses
305.1	Nondependent tobacco use disorder
401.0-401.9	Essential hypertension
V17.3	Family history of ischemic heart disease
V17.49	Family history of other cardiovascular diseases

**Covered when medically necessary for an individual at intermediate- or high-risk for developing CHD:**

CPT <sup>®*</sup> Codes	Description
83698	Lipoprotein-associated phospholipase A2, (Lp-PLA2)

ICD-9-CM Diagnosis Codes	Description
250.00- 250.93	Diabetes mellitus
272.0-272.3	Pure hypercholesterolemia
272.5	Lipoprotein deficiencies
272.7	Lipidoses
277.7	Dysmetabolic Syndrome X
305.1	Nondependent tobacco use disorder
401.0-401.9	Essential hypertension
V17.3	Family history of ischemic heart disease
V17.49	Family history of other cardiovascular diseases

**Covered when medically necessary and used to assess risk and guide treatment of lipoprotein abnormalities:**

CPT <sup>®*</sup> Codes	Description
82172 <sup>†</sup>	Apolipoprotein, each

**†Note:** Covered as medically necessary when used to report evaluation of apolipoprotein B level testing. Tests for other apolipoprotein components are not covered.

ICD-9-CM Diagnosis	Description
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<b>Codes</b>	
250.00-250.93	Diabetes Mellitus
272.0-272.3	Pure hypercholesterolemia
272.5	Lipoprotein deficiencies
272.7	Lipidoses
305.1	Nondependent tobacco use disorder
401.0-401.9	Essential hypertension
414.00-414.03	Other forms of chronic ischemic heart disease
429.2	Unspecified cardiovascular disease
V17.3	Family history of ischemic heart disease
V17.49	Family history of other cardiovascular diseases

**Covered when medically necessary for an individual undergoing management for lipoprotein abnormalities:**

<b>CPT<sup>®</sup>* Codes</b>	<b>Description</b>
83695	Lipoprotein (a)

<b>ICD-9-CM Diagnosis Codes</b>	<b>Description</b>
272.0	Pure hypercholesterolemia
V17.3	Family history of ischemic heart disease
V17.4	Family history of other cardiovascular diseases

**CIGNA HealthCare does not cover ANY of the following testing, for screening, diagnosing or management of coronary heart disease because each is considered experimental, investigational, or unproven in affecting clinical outcomes (This list may not be all-inclusive):**

<b>CPT* Codes</b>	<b>Description</b>
0026T	Lipoprotein, direct measurement, intermediate density lipoproteins (IDL) (remnant lipoproteins) (Code deleted 1/1/2009. Replaced by 84999)
0111T	Long-chain (C20-22) omega-3 fatty acids in red blood cell (RBC) membranes
82163	Angiotensin II
82615	Cystine and homocystine, urine, qualitative
83090	Homocysteine
83520	Immunoassay, analyte, quantitative; not otherwise specified
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 numbers and lipoprotein particle subclasses (eg, by nuclear magnetic resonance spectroscopy)
83719	Lipoprotein, direct measurement; VLDL cholesterol
83891 <sup>††</sup>	Molecular diagnostics; isolation or extraction of highly purified nucleic acid
83892 <sup>††</sup>	Molecular diagnostics; enzymatic digestion
83898 <sup>††</sup>	Molecular diagnostics; amplification, target, each nucleic acid sequence
83909 <sup>††</sup>	Molecular diagnostics; separation and identification by high resolution technique (eg, capillary electrophoresis)
83912 <sup>††</sup>	Molecular diagnostics; interpretation and report
83914 <sup>††</sup>	Mutation identification by enzymatic ligation or primer extension, single segment, each segment (eg, oligonucleotide ligation assay (OLA), single base chain extension (SBCE), or allele-specific primer extension (ASPE))

84999 <sup>†††</sup>	Unlisted chemistry procedure
85230	Clotting; factor VII (proconvertin, stable factor)
85247	Clotting; factor VIII, von Willebrand factor, multimeric analysis
85300	Clotting inhibitors or anticoagulants; antithrombin III, activity
85303	Clotting inhibitors or anticoagulants; protein C, activity
85384	Fibrinogen; activity
85385	Fibrinogen; antigen
85415	Fibrinolytic factors and inhibitors; plasminogen activator

**††Note: Experimental, investigational, unproven and not covered when used to report angiotensinogen gene testing.**

**†††Note: Experimental, investigational, unproven and not covered when used to report Corus CAD gene expression testing or lipoprotein direct measurement , intermediate density lipoprotein (IDL).**

ICD-9-CM Diagnosis Codes	Description
V81.0	Screening for ischemic heart disease
V81.2	Screening for other and unspecified cardiovascular conditions
	All other codes

**\*Current Procedural Terminology (CPT®) ©2010 American Medical Association: Chicago, IL.**

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## Policy History

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<u>Pre-Merger Organizations</u>	<u>Last Review Date</u>	<u>Policy Number</u>	<u>Title</u>
CIGNA HealthCare	8/15/2008	0137	Cardiac Disease Risk Assessment: Emerging Laboratory Evaluations

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