OVERVIEW
Lipoprotein-associated phospholipase A2 (Lp-PLA2), is an enzyme that hydrolyzes phospholipids and is primarily associated with low-density lipoproteins (LDLs). Accumulating evidence has suggested that Lp-PLA2 is a biomarker of coronary artery disease (CAD) and may have a proinflammatory role in the progression of atherosclerosis.

PRIOR AUTHORIZATION
Not Applicable.

POLICY STATEMENT
BlueCHiP for Medicare and Commercial:

Measurement of lipoprotein-associated phospholipase A2 (Lp-PLA2) and measurement of novel lipid risk factors (i.e., apolipoprotein B, apolipoprotein A-I, apolipoprotein E, LDL subclass, HDL subclass, lipoprotein[a]) is considered not medically necessary as there is insufficient peer-reviewed scientific literature that demonstrates that the procedure/service is effective.

MEDICAL CRITERIA
None.

BACKGROUND
Low-density lipoproteins (LDL) have been identified as the major atherogenic lipoproteins and have long been identified by the National Cholesterol Education Project (NCEP) as the primary target of cholesterol-lowering therapy. LDL particles consist of a surface coat composed of phospholipids, free cholesterol, and apolipoproteins, surrounding an inner lipid core composed of cholesterol ester and triglycerides. Traditional lipid risk factors such as low-density lipoprotein-cholesterol (LDL-C), while predictive on a population basis, are weaker markers of risk on an individual basis. Only a minority of subjects with elevated LDL and cholesterol levels will develop clinical disease, and up to 50% of cases of coronary artery disease (CAD) occur in subjects with ‘normal’ levels of total and LDL cholesterol. Thus, there is considerable potential to improve the accuracy of current cardiovascular risk prediction models.

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

Apolipoprotein B. Apolipoprotein B (apo B) is the major protein moiety of all lipoproteins except for high-density lipoprotein (HDL). The most abundant form of apo B, large B or B-100, constitutes the apo B found in LDL and very-low-density lipoproteins (VLDL). Since both LDL and VLDL each contain one molecule of apolipoprotein B, measurement of apo B reflects the total number of these atherogenic particles, 90% of
which are LDL. Since LDL particles can vary both in size and in cholesterol content, for a given concentration of LDL-C, there can be a wide variety of both size and numbers of LDL particles. Thus, it has been postulated that apo B is a better measure of the atherogenic potential of serum LDL than is LDL concentration. Two basic techniques are used for measuring LDL particle concentration. Particle size can be determined by gradient gel electrophoresis, or direct measurement of the number of LDL particles can be performed using nuclear magnetic spectroscopy. Nuclear magnetic resonance (NMR) spectroscopy is based on the fact that lipoprotein subclasses of different size broadcast distinguishable NMR signals. Thus NMR can quantify the number of LDL particles of a specific size (i.e., small dense LDL) and can provide a measurement of the total number of particles.

**Apolipoprotein A-I.** HDL contains two associated apolipoproteins, i.e., A-I and A-II. HDL particles can also be classified by whether they contain apolipoprotein A-I (apo A-I) only or whether they contain both apo A-I and apolipoprotein A-II (A-II). All lipoproteins contain apo A-I, and some also contain apo A-II. Since all HDL particles contain apo A-I, this lipid marker can be used as an approximation for HDL number, similar to the way apo B has been proposed as an approximation of the LDL number. Direct measurement of apo A-I has been proposed as more accurate than the traditional use of HDL level in evaluation of the cardioprotective, or “good,” cholesterol. In addition, the ratio of apolipoprotein B (apo B)/apo A-I has been proposed as a superior measure of the ratio of proatherogenic (i.e., “bad”) cholesterol to anti-atherogenic (i.e., “good”) cholesterol.

**Apolipoprotein E.** Apolipoprotein E (apo E) is the primary apolipoprotein found in VLDLs and chylomicrons. Apo E is the primary binding protein for LDL receptors in the liver and is thought to play an important role in lipid metabolism. The apo E gene is polymorphic, consisting of 3 alleles (e2, e3, and e4) that code for 3 protein isoforms, known as E2, E3, and E4, which differ from one another by one amino acid. These molecules mediate lipid metabolism through their different interactions with the LDL receptors. The genotype of apo E alleles can be assessed by gene amplification techniques, or the apo E phenotype can be assessed by measuring plasma levels of apo E. It has been proposed that various apo E genotypes are more atherogenic than others and that apo E measurement may provide information on risk of coronary artery disease (CAD) above traditional risk factor measurement. It has also been proposed that the apo E genotype may be useful in the selection of specific components of lipid-lowering therapy, such as drug selection. In the major lipid-lowering intervention trials, including trials of statin therapy, there is considerable variability in response to therapy that cannot be explained by factors such as compliance. Apo E genotype may be one factor that determines an individual’s degree of response to interventions such as statin therapy.

**LDL subclass.** Two main subclass patterns of LDL, called A and B, have been described. In subclass pattern A, the particles have a diameter larger than 25 nm and are less dense, while in subclass pattern B, the particles have a diameter less than 25 nm and a higher density. Subclass pattern B is a commonly inherited disorder associated with a more atherogenic lipoprotein profile, also termed “atherogenic dyslipidemia.” In addition to small, dense LDL, this pattern includes elevated levels of triglycerides, elevated levels of apolipoprotein B, and low levels of HDL. This lipid profile is commonly seen in type II diabetes and is one component of the “metabolic syndrome,” defined by the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III; ATP III) to also include high normal blood pressure, insulin resistance, increased levels of inflammatory markers such as C-reactive protein (CRP), and a prothrombotic state. Presence of the metabolic syndrome is considered by ATP III to be a substantial risk-enhancing factor for CAD.

LDL size has also been proposed as a potentially useful measure of treatment response. Lipid-lowering treatment decreases total LDL and may also induce a shift in the type of LDL, from smaller, dense particles to larger particles. It has been proposed that this shift in lipid profile may be beneficial in reducing risk for CAD independent of the total LDL level. Also, some drugs may cause a greater shift in lipid profile than others. Niacin and/or fibrates may cause a greater shift from small to large LDL size than statins. Therefore,
measurement of LDL size may potentially play a role in drug selection or may be useful in deciding to use a combination of 2 or more drugs rather than a statin alone.

In addition to the size of LDL particles, interest has been shown in assessing the concentration of LDL particles as a distinct cardiac risk factor. For example, the commonly performed test, LDL-C is not a direct measure of LDL but, chosen for its convenience, measures the amount of cholesterol incorporated into LDL particles. Since LDL particles carry much of the cholesterol in the bloodstream, the concentration of cholesterol in LDL correlates reasonably well with the number of LDL particles when examined in large populations. However, for an individual patient, the LDL-C level may not reflect the number of particles due to varying levels of cholesterol in different sized particles. It is proposed that the discrepancy between the number of LDL particles and the serum level of LDL-C represents a significant source of unrecognized atherogenic risk. The size and number of particles are interrelated. For example, all LDL particles can invade the arterial wall and initiate atherosclerosis. However, small, dense particles are thought to be more atherogenic compared to larger particles. Therefore, for patients with elevated numbers of LDL particles, cardiac risk may be further enhanced when the particles are smaller versus larger.

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

**HDL subclass.** HDL particles exhibit considerable heterogeneity, and it has been proposed that various subclasses of HDL may have a greater role in protection from atherosclerosis. Particles of HDL can be characterized based on size/density and/or on the apolipoprotein composition. Using size/density, HDL can be classified into HDL2, the larger, less dense particles that may have the greatest degree of cardioprotection, and HDL3, which are smaller, more dense particles. HDL contains 2 associated apolipoproteins, i.e., A-I and A-II. HDL particles can also be classified by whether they contain apolipoprotein A-I (apo A-I) only or whether they contain both apo A-I and apolipoprotein A-II (apo A-II). There has been substantial interest in determining whether subclasses of HDL can be used to provide additional information on cardiovascular risk compared to HDL alone.

An alternative to measuring the concentration of subclasses of HDL, such as HDL2 and HDL3, is direct measurement of HDL particle size and/or number. Particle size can be measured by NMR spectroscopy or by gradient-gel electrophoresis. HDL particle numbers can be measured by NMR spectroscopy. Several commercial labs offer these measurements of HDL particle size and number. Measurement of apo A-I has used measurement of HDL particle number as a surrogate, based on the premise that each HDL particle contains one apo A-I molecule.

**Lipoprotein A.** Lipoprotein (a) (lp[a]) is a lipid-rich particle similar to LDL. Apolipoprotein B is the major apolipoprotein associated with LDL; in lp[a], however, there is an additional apolipoprotein A covalently linked to the apolipoprotein B. The apolipoprotein (a) molecule is structurally similar to plasminogen, suggesting that lp(a) may contribute to the thrombotic and atherogenic basis of cardiovascular disease. Levels of lp(a) are relatively stable in individuals over time, but vary up to 1,000-fold between individuals, presumably on a genetic basis. The similarity between lp(a) and fibrinogen has stimulated intense interest in lp(a) as a link between atherosclerosis and thrombosis. In addition, approximately 20% of patients with CAD have elevated levels of lp(a). Therefore, it has been proposed that levels of lp(a) may be an independent risk factor for CAD.

There is a large body of literature evaluating lipoprotein-associated phospholipase A2 (Lp-PLA2) as a predictor of cardiovascular risk. These studies demonstrate that Lp-PLA2 is an independent predictor of
cardiovascular disease but do not demonstrate that health outcomes are improved as a result of measuring Lp-PLA2. Improved risk prediction does not by itself result in improved health outcomes. To improve outcomes, clinicians must have the tools to incorporate emerging risk factors into existing risk prediction models, and these models should demonstrate improved classification into risk categories that will lead to more appropriate treatment. These tools are not currently available to the practicing clinician for Lp-PLA2. As a result, use of Lp-PLA2 for risk stratification for cardiovascular disease is considered not medically necessary as there is no proven efficacy.

Clinical trials of Lp-PLA2 inhibitors are a new line of research with therapeutic potential. However, the available trials are preliminary, reporting only on physiologic outcomes such as reduction in high-sensitivity C-reactive protein (hsCRP), and use a pharmacologic agent that is not yet approved for use in the U.S. At least 3 Phase III clinical trials that utilize clinical outcomes as the primary endpoint(s) are currently in progress, and results from these may be available starting in 2012. Therefore, Lp-PLA2 has not demonstrated improved outcomes as a treatment target and is considered not medically necessary as there is no proven efficacy.

Numerous non-traditional lipid measurements have been proposed for use in improving risk prediction for cardiovascular disease, including apo B, apo A-1, the ratio of apo B/apo A-1, apo E, lipoprotein A, and subclasses of LDL and HDL. In general, there is evidence that these markers provide some incremental accuracy in risk prediction. However, it has not been established that the incremental accuracy provides clinically important information beyond that of traditional lipid measures. Furthermore, no study has provided high-quality evidence that measurement of markers leads to changes in management that improve health outcomes. Some markers, e.g. apo B, have also been proposed as treatment targets for lipid-lowering therapy. While some evidence supports that they may be accurate in predicting residual risk for patients on lipid-lowering therapy, there is no high-quality evidence that these markers lead to health outcome improvements when used in place of traditional lipid targets, such as LDL. Because of the deficiencies in the literature around these issues, the use of these novel lipid risk markers remains not medically necessary as there is no proven efficacy.

**COVERAGE**

Benefits may vary between groups/contracts. Please refer to the appropriate member certificate/subscriber agreement for applicable not medically necessary coverage.

**CODING**

_BlueCHiP for Medicare and Commercial:_

The following codes are considered not medically necessary:

83695, 83698, 83700, 83701, 83704

**RELATED POLICIES**

None

**PUBLISHED**

| Provider Update | Jan 2014 |
| Provider Update | Dec 2011 |
| Provider Update | Jan 2011 |
| Provider Update | Aug 2009 |
| Provider Update | Nov 2008 |
| Policy Update  | Nov 2007 |
| Policy Update  | Dec 2004 |
| Policy Update  | Oct 1999 |
REFERENCES


2. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). C-Reactive Protein as a Cardiac Risk Marker (Special Report). TEC Assessments 2002; Volume 17, Tab 23.


12. BlueCross and BlueShield Technology Evaluation Center (TEC). C-Reactive Protein as a Cardiac Risk Marker (Special Report). TEC Assessment 2002; Volume 17, Tab 23.


