BlueCross BlueShield of Alabama

Name of Policy:
Lipoprotein-Associated Phospholipase A2 (Lp-PLA2)

Policy #: 155
Category: Laboratory

Latest Review Date: June 2014
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Proprietary Information of Blue Cross and Blue Shield of Alabama

Description of Procedure or Service:

Lipoprotein-associated phospholipase A2 (Lp-PLA2), also known as platelet-activating factor acetylhydrolase, 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 and may have a proinflammatory role in the progression of atherosclerosis.

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 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 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.

Policy:

Measurement of lipoprotein-associated phospholipase A2 (Lp-PLA2) does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational.**

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administer benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

A large body of literature has accumulated on the utility of risk factors in the prediction of future cardiac events. The evidence reviewed for this policy statement consists of large, prospective cohort studies that have evaluated the association of lipoprotein-associated phospholipase A2 (Lp-PLA2) with cardiovascular outcomes. A smaller amount of literature is available on the utility of Lp-PLA2 as a treatment target.

The National Cholesterol Education Program (NCEP) ATP-III guidelines document notes that to determine their clinical significance, the emerging risk factors should be evaluated against the following criteria in order to determine their clinical significance:

- Significant predictive power that is independent of other major risk factors;
- A relatively high prevalence in the population (justifying routine measurement in risk assessment);
- Laboratory or clinical measurement must be widely available, well standardized, inexpensive, have accepted population reference values, and be relatively stable biologically;
- Preferable, but not necessarily, modification of the risk factor in clinical trials will have shown reduction in risk.

A 2002 TEC Assessment summarized the steps necessary to determine utility of a novel cardiac risk factor. Three steps were required:

- Standardization of the measurement of the risk factor;
- Determination of its contribution to risk assessment. As a risk factor, it is important to determine whether the novel risk factor […] independently contributes to risk assessment compared to established risk factors;
- Determination of how the novel risk assessment will be used in the management of the patient, compared to standard methods of assessing risk, and whether any subsequent changes in patient management result in an improvement in patient outcome.

Is the measurement of Lp-PLA2 standardized?

According to the FDA's Summary of Safety and Effectiveness for the diaDexus' lipoprotein-associated phospholipase A2 (Lp-PLA2) assay, the intra-assay precision for the assay was 7% coefficient of variability (CV), and the inter-assay precision was 9% CV, with a detection limit of 1.2 ng/mL. Reference intervals for the Lp-PLA2 assay were calculated from samples for 251 apparently healthy males and 174 apparently healthy females aged 40 to 70 years; the reference interval calculated from the samples (central 90%) was determined to be 120 to 342 ng/mL for females and 131 to 376 ng/mL for males. FDA concluded that the assay demonstrated acceptable analytical performance.

Is Lp-PLA2 an independent risk factor for cardiovascular disease?

Lp-PLA2 as a predictor of cardiovascular disease

Results of numerous, large-scale observational studies have examined whether Lp-PLA2 is an independent risk factor for cardiovascular disease. Some of these observational studies have been evaluated in systematic reviews and meta-analyses. A representative sample of some of the larger studies is given next.

Systematic Reviews

Several systematic reviews and meta-analyses have summarized the association between Lp-PLA2 and cardiovascular disease in general populations.

The Emerging Risk Factors Collaboration performed a patient-level meta-analysis of the association of novel lipid risk factors with cardiovascular risk. Records from 37 prospective cohort studies enrolling 165,544 participants were combined to predict cardiovascular risk over a median follow-up of 10.4 years. The authors examined the independent association of markers with cardiovascular risk and the ability to reclassify risk into clinically relevant categories. For Lp-PLA2, there were 11 studies enrolling 32,075 participants that measured this factor. Overall, Lp-PLA2 was an independent risk factor for cardiovascular events with a hazard ratio of 1.12 (95% confidence interval [CI]: 1.09-1.21) for each one standard deviation (SD) increase in Lp-PLA2 activity. There was no significant improvement in risk reclassification following the addition of Lp-PLA2 to the reclassification model, with a net reclassification improvement of 0.21 (-0.45 to 0.86). The net reclassification improvement crossing 0.0 indicates that the addition of Lp-PLA2 to the model may result in either improvement or worsening of reclassification.

A number of systematic reviews have been published that summarize the observational studies on the association of Lp-PLA2 and CV disease. For example, Garza et al reviewed 14 observational studies enrolling 20,549 patients. This study reported the predictive ability of Lp-PLA2 levels for CV disease after adjustment for traditional cardiac risk factors. The combined odds ratio (OR) for an elevated Lp-PLA2 was reported as 1.60 (95% CI, 1.36 to 1.89) for the development of future cardiac events. A patient-level meta-analysis evaluated the association between Lp-PLA2 levels, CAD, stroke, and mortality. A total of 79,036 participants from 32 prospective studies were included in this report. There were significant associations found between Lp-PLA2 and all three outcome measures. For every one SD increase in Lp-PLA2 levels, the risk ratio (RR) adjusted for conventional risk factors was 1.10 (95% CI, 1.04 to 1.17) for CAD, 1.08 (95% CI, 0.97 to 1.20) for stroke, and 1.16 (95% CI, 1.09 to 1.24) for vascular death. There was also a significant association found between Lp-PLA2 levels and nonvascular deaths

Nonrandomized Comparative Studies of Lp-PLA2 in General Populations
Some of the representative cohort and case-control studies evaluating the association between Lp-PLA2 and cardiovascular outcomes are described next.

The West of Scotland Coronary Prevention Study (WOSCOPS) was a five-year, case control trial evaluating 6,595 men with elevated cholesterol levels and no history of a heart attack. Researchers looked at a smaller population of this study to determine if inflammatory markers such as Lp-PLA2 and high-sensitivity C-reactive protein (hsCRP) were correlated with coronary heart disease (CHD) events. The 580 men who went on to have a myocardial infarction (MI) or revascularization were compared to 1,160 age- and smoking-matched men who did not have an event. The results showed that those with the highest levels of Lp-PLA2 had twice the risk of an event compared to those with the lowest levels, even after adjustment for traditional risk factors and other inflammatory mediators.

The Atherosclerosis Risk in Communities (ARIC) study evaluated the various risk markers and their association with increased risk in a large, diverse population of more than 12,000 individuals. At enrollment in the study, patients were free of CHD and were followed up for the development of the disease for the next nine years. The case-cohort component of the study examined two inflammatory markers, Lp-PLA2 and hsCRP, in a subset of 608 cases and 740

controls. The results showed that elevated levels of Lp-PLA2 are higher in incident coronary heart disease cases. In individuals with non-elevated low-density lipoprotein (LDL) levels (less than 130 mg/dL), Lp-PLA2 levels were independently associated with CHD, even after adjustment for traditional risk factors and C-reactive protein. Koenig and colleagues reported similar results in a study of 934 apparently healthy men aged 45 to 64 who were followed up between 1984 and 1998. During this period, 97 men experienced a coronary event. Elevated levels of Lp-PLA2 appeared to be predictive of future coronary events in middle-aged men with moderately elevated total cholesterol, independent of C-reactive protein.

Ballantyne and colleagues studied Lp-PLA2 in the 12,762 apparently healthy individuals participating in the ARIC study. Mean levels of both Lp-PLA2 and C-reactive protein were higher in the 194 stroke cases; the authors concluded that Lp-PLA2 levels may provide complementary information beyond traditional risk factors in identifying those at risk for ischemic stroke. As part of the PEACE study, Lp-PLA2 levels were measured in 3,766 patients with stable CAD followed up for a median of 4.8 years. After adjustment for other baseline risk factors, patients in the highest quartile of Lp-PLA2 were 1.4 times more likely (95% confidence interval [CI]: 1.17–1.70, $p<0.001$) to experience an adverse cardiovascular outcome compared to patients in the lowest quartile. Winkler and colleagues studied 3,232 consecutive patients referred for coronary angiography and reported that Lp-PLA2 levels were an independent predictor of cardiac mortality (hazard ratio: 2.0; 95% CI: 1.4–3.1, $p<0.001$) after adjusting for established risk factors, including C-reactive protein and N-terminal b-natriuretic peptide. Persson and colleagues evaluated the relationship between Lp-PLA2 and the metabolic syndrome in 4,480 nondiabetic patients without a history of coronary artery disease (CAD). Both Lp-PLA2 (relative risk [RR]: 1.54; 95% CI: 1.07–2.24) and the metabolic syndrome (RR: 1.42; 95% CI: 1.06–1.90) were significant predictors of a first cardiac event. The combination of both elevated Lp-PLA2 and metabolic syndrome conferred a further increase in risk (RR: 1.97; 95% CI: 1.34–2.90).

The Rancho Bernardo Study enrolled 1,077 community-dwelling elderly individuals without known heart disease and followed up patients a mean of 16 years for the development of heart disease. Lp-PLA2 was an independent predictor of cardiac events, with a relative risk for patients in the second, third, and fourth quartiles of 1.66, 1.80, and 1.89, respectively, compared with the first quartile.

Another study evaluated the discriminatory ability of Lp-PLA2 for incident CHD in 421 cases and 800 controls from the Nurses' Health Study. Lp-PLA2 was a significant predictor of CHD after adjustment for traditional risk factors with a RR of 1.75 (95% CI, 1.09 to 2.84). It also added significantly to the discriminatory ability, as judged by an increase in the area under the curve from 0.720 without Lp-PLA2 to 0.733 with Lp-PLA2, and improved the net reclassification improvement index for discriminating between patients with and without CHD ($p=0.004$).

Other studies have correlated Lp-PLA2 levels with different parameters of CV disease. Multiple publications have reported that Lp-PLA2 levels are associated with characteristics of "vulnerable atherosclerotic plaques," both in the coronary and in the carotid arteries. Subsequent publications also found an association between Lp-PLA2 levels and plaque rupture and fibrous cap thickness

in patients with acute coronary syndrome. Muller et al reported that Lp- PLA2 levels are associated with low fractional flow reserve on cardiac catheterization in 197 patients with stable CAD. Tehrani et al evaluated the association between Lp-PLA2 levels and the protective effect of high-density lipoprotein-cholesterol (HDL-C) on incident CHD among 3888 adults with known cardiovascular disease. Among patients with the highest tertile of Lp- PLA2, the relationship between HDL-C and incident CHD was attenuated, although there was no consistent association of higher levels of Lp-PLA2 with CHD risk across HDL-C categories.

Most, but not all, observational studies reported a positive association of Lp-PLA2 with cardiovascular outcomes. Allison and colleagues studied 508 patients with peripheral vascular disease followed for an average of 6.7 years. While there was a modest univariate association of Lp-PLA2 with cardiovascular events, this association disappeared after adjustment for established risk factors. In the Rotterdam Coronary Calcification Study, similar results were reported. This population-based study followed 520 patients for seven years and evaluated the association between Lp-PLA2 and coronary calcification by electron-beam computed tomography scan. The unadjusted odds ratio (OR) for each standard deviation (SD) increase in Lp-PLA2 was 1.6 (95% CI: 1.1–2.4); however, this association became nonsignificant after controlling for lipid levels.

Nonrandomized Comparative Studies of Lp-PLA2 in Subpopulations

Some studies have specifically evaluated Lp-PLA2 as a risk factor in the diabetic population. For example, Saremi et al performed a substudy of the Veterans Affairs Diabetes trial (VADT) examining risk factors that predicted the progression of coronary artery calcification over an average of 4.6 years of follow-up. Lp-PLA2 mass was one of two significant independent predictors that remained (p=0.01) after adjustment for standard risk factors. Hatoum et al evaluated Lp-PLA2 as a risk factor for incident coronary heart disease in 1,517 diabetic patients enrolled in the Health Profession Follow-Up Study. After adjustment for standard risk factors, the RR for incident CHD for the upper quartile of Lp-PLA2 activity compared to the lower quartile was 1.39 (95% CI: 1.01-1.90, p=0.03).

Section Summary

There is a large amount of evidence establishing that Lp-PLA2 levels are an independent predictor of cardiovascular risk factors, physiologic measures of cardiac disease, and CV events. This association has been demonstrated in a variety of clinical populations, in people both with and without CV disease. The evidence on the ability of Lp-PLA2 to reclassify patients into clinically relevant categories is less convincing, with the largest patient-level meta-analysis reporting no significant improvement.

Lp-PLA2 as treatment target

Interventional studies involving Lp-PLA2 suggest that the level of Lp-PLA2 is modifiable by antihyperlipidemics (statins, fibrates, and niacin). An ad hoc study of the PROVE IT TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis In Myocardial Infarction) trial, in which Lp-PLA2 levels were measured at baseline (n=3,648) and at 30 days (n=3,265) and patients were followed up for a mean of 24 months for death, MI, unstable angina, revascularization, or stroke, suggested that patients randomized to atorvastatin 80 mg/day, but not pravastatin 40 mg/day, experienced a 20% reduction of Lp-PLA2 levels at 30 days,

independent of other cardiac risk factors. The 30-day, Lp-PLA2 level was independently associated with an increased risk of cardiovascular events. Another ad hoc study from the DIACOR (Diabetes and Combined Lipid Therapy Regimen) trial demonstrated improved Lp-PLA2 levels (overall 16.8% reduction) compared to baseline, with no difference found between treatment groups among the 300 patients with diabetes and mixed dyslipidemias randomized to either fenofibrate 160 mg/day, simvastatin 20 mg/day, or both, for 12 weeks.

Rosenson randomized 55 hyperlipidemic subjects with metabolic syndrome to fenofibrate or placebo. Fenofibrate treatment was associated with a 13% reduction in Lp-PLA2 mass compared to placebo. Saougos et al studied the effect of three lipid-lowering agents, rosuvastatin, ezetimibe, and fenofibrate, on Lp-PLA2 levels. All three agents significantly lowered Lp-PLA2 levels; fenofibrate also selectively increased HDL-associated Lp-PLA2 levels.

At least two clinical trials have examined the change in Lp-PLA2 levels in patients treated with statins versus placebo and evaluated whether the utility of Lp-PLA2 for risk stratification is modified by statin treatment. Ridker et al analyzed the changes in Lp-PLA2 levels among patients in the JUPITER trial, a randomized controlled trial (RCT) of 17,802 individuals randomized to rosuvastatin or placebo. Among patients assigned to rosuvastatin, Lp-PLA2 mass decreased by 33.8%. In the placebo group, Lp-PLA2 levels were predictive of subsequent cardiac events, but this was not true in the rosuvastatin group. In a similar analysis of the MIRACL RCT, Ryu et al analyzed 2,587 patients treated with high dose atorvastatin or placebo. Atorvastatin reduced Lp-PLA2 levels in 2,587 patients treated with high-dose atorvastatin or placebo. Atorvastatin reduced Lp-PLA2 mass by 32.1% and Lp-PLA2 activity by 29.5%. In the placebo group, Lp-PLA2 levels were predictive of adverse cardiac outcomes, but no relationship was found in the atorvastatin group. The authors estimated that treatment with statins reduced the attributable risk of death due to Lp-PLA2 by approximately 50%.

Section Summary
Levels of Lp-PLA2 decrease substantially following treatment with anti-lipid medications, including statins. However, there are not currently well-accepted thresholds for using Lp-PLA2 as a treatment target. Some studies have reported that treatment with statins eliminates the predictive ability of Lp-PLA2 as a treatment target; this may potentially reduce the potential of Lp-PLA2 for this purpose.

Will identification of Lp-PLA2 levels lead to changes in patient management, and will these changes in management lead to improved patient outcomes?
Multiple studies have identified Lp-PLA2 as an independent risk factor for CV events and CV disease and have suggested that medication treatment for hyperlipidemia is associated with changes in Lp-PLA2 levels. However, no studies were identified that addressed whether testing strategies that use Lp-PLA2 levels lead to changes in patient management.

Preliminary clinical trials of Lp-PLA2 inhibitors have been published, although none of the Lp-PLA2 inhibitors have been approved by FDA for any indication. Darapladib was the first drug of this class that was tested. In 2014, results of the STABILITY trial of darapladib were published. This study was a double-blind; placebo controlled randomized trial in which 15,828 patients with stable coronary disease were randomized to receive once-daily darapladib or placebo. Analysis

was intention-to-treat. Over a median 3.7 years of follow-up, the study's primary end point of CV death, MI, or stroke, occurred in 769/7924 (9.7%) of the darapladib group and in 819/7904 (10.4%) of those in the placebo group (HR for darapladib: 0.94; 95% CI, 0.85 to 1.03; p=0.20). Darapladib was associated with improvements in the rates of major coronary events (9.3% vs 10.3%; HR=0.90; 95% CI, 0.82 to 1.00; p=0.045) and all coronary events (14.6% vs 16.1%; HR=0.91; 95% CI, 0.84 to 0.98; p=0.02).

The Stabilization of plaques using Darapladib – Thrombolysis in Myocardial Infarction 52 (SOLID-TIMI 52) trial will enroll approximately 11,500 participants within 30 days of acute MI. Participants will be randomized to darapladib or placebo and followed for three years for the outcomes of CV death, nonfatal MI, or stroke. Results of this trial are expected to be presented in 2014.

Earlier studies compared darapladib with placebo in smaller study populations. Mohler et al randomized 959 patients with hyperlipidemia receiving atorvastatin to placebo or one of three doses of darapladib. Dose-dependent inhibition of Lp-PLA2 was noted, ranging from 43% to 66% compared with placebo. The inflammatory markers interleukin-6 and hsCRP were also reduced by 12.3% and 13%, respectively. Serruys et al randomized 330 patients with documented CAD to darapladib or placebo and reported the impact of 12 months of treatment with darapladib on Lp-PLA2 levels, hsCRP levels, and coronary plaque composition, as measured by intravascular ultrasound. This study found no difference in plaque deformability but a reduction in plaque necrotic core was reported for the darapladib group. Lp-PLA2 levels were decreased by 59%, but there were no significant differences in hsCRP levels between groups.

A second phospholipase A2 inhibitor, varespladib, is also being tested in clinical trials. The FRANCIS-ACS trial is a randomized double-blind, placebo-controlled trial of varespladib for patients with acute coronary syndrome. This trial is projected to enroll 700 patients, with follow-up for at least 24 weeks and report on the primary end point of major cardiovascular events.

Section Summary
Studies have not identified whether a testing strategy that uses Lp-PLA2 levels improves health outcomes.

Inhibitors of Lp-PLA2 have been developed and tested in clinical trials, but no trials have demonstrated an improvement in health outcomes with these inhibitors. Further phase III clinical trials are ongoing.

Summary
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 investigational.

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. One phase III clinical trial of an Lp-PLA2 inhibitor demonstrated no significant improvements in the study's primary outcome, but other trials are still in progress. Therefore, Lp-PLA2 has not demonstrated improved outcomes as a treatment target and is considered investigational for this purpose.

Practice Guidelines and Position Statements
The American College of Cardiology Foundation (ACCF) and American Heart Association (AHA) published joint guidelines on the assessment of cardiovascular risk in asymptomatic patients in 2010. The guidelines contained the following statement concerning testing for LpA-PLA2:

- Lipoprotein-associated phospholipase A2 might be reasonable for cardiovascular risk assessment in intermediate-risk asymptomatic adults. *(Class IIb recommendation; Level of Evidence B)*

The American Association of Clinical Endocrinologists (AACE) published guidelines for the management of dyslipidemia and prevention of atherosclerosis in 2012. These guidelines made the following recommendations for LpA-PLA2 testing:

- Assess markers of inflammation in patients where further stratification of risk is necessary. Highly sensitive CRP and Lp-PLA2 provide useful information in these instances and appear to be synergistic in predicting risk of CVD and stroke. *(Grade B recommendation; best level of evidence 1)*
- Measure Lp-PLA2, which in some studies has demonstrated more specificity than highly sensitive CRP [hsCRP], when it is necessary to further stratify a patient's CVD risk, especially in the presence of systemic highly sensitive CRP elevations *(Grade B recommendation; best level of evidence 2).*

In 2012, the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice issued guidelines on cardiovascular disease prevention. These guidelines include the following statements about Lp-PLA2 testing:

- LpPLA2 may be measured as part of a refined risk assessment in patients at high risk of a recurrent acute atherothrombotic event. (*Class IIb recommendation; Level of Evidence B; weak evidence).*

Key Words:
Lipoprotein-associated phospholipase A2, Lp-PLA2, PLAC test, coronary risk assessment, high-sensitivity C-reactive protein, hs-CRP, low density cholesterol, LDL

Approved by Governing Bodies:

The U.S. Food and Drug Administration (FDA) cleared for marketing an enzyme-linked immunosorbent assay (ELISA) test, the PLAC test (diaDexus, San Francisco, CA), to measure levels of Lp-PLA2. FDA product code: NOE.

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply
FEP contracts: FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT codes

83698	Lipoprotein-associated phospholipase a2, (lp-pla2)

Previous Coding:

CPT codes

83516	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen, qualitative or semiquantitative; multiple step method **(used prior to 01/01/2007)**
83520	Immunoassay, analyte, quantitative; not otherwise specified **(used prior to 01/01/2007)**

References:

1. Allison MA, Denenberg JO, Nelson JJ, et al. The association between lipoprotein-associated phospholipase A2 and cardiovascular disease and total mortality in vascular medicine patients. J Vasc Surg, Sept 2007; 46(3): 500-506.
2. Ballantyne CM, Hoogeveen RC, Bang H, et al. Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident coronary heart disease in middle-aged men and women in the Atherosclerosis Risk in Communities (ARIC) study, Circulation, February 2004; 109(7): 837-42.
3. Ballantyne CM, et al. Lipoprotein-associated phospholipase A2, high-sensitivity C-reactive protein, and risk for incident ischemic stroke in middle-aged men and women in Atherosclerosis Risk in Communities (ARIC) study. Archives of Internal Medicine, November 2005; 165(21): 2479-2484.
4. 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.
5. Brilakis ES, et al. Association of lipoprotein-associated phospholipase A2 levels with coronary artery disease, risk factors, angiographic coronary artery disease, and major adverse events at follow-up. European Heart Journal 2005; 26: 137-144.

6. Cook NR, Paynter NP, Manson JE et al. Clinical utility of lipoprotein-associated phospholipase A(2) for cardiovascular disease prediction in a multiethnic cohort of women. Clin Chem 2012; 58(9):1352-63.
7. Corsetti JP, et al. High lipoprotein-associated phospholipase A2 is a risk factor for recurrent coronary events in post-infarction patients. Clinical Chemistry, July 2006; 52(7): 1331-1338.
8. Corson MA. Darapladib: an emerging therapy for atherosclerosis. Ther Adv in Cardiovasc Dis 2010; 4(4):241-8.
9. Daniels LB, Laughlin GA, Sarno MJ, et al. Lipoprotein-associated phospholipase A2 is an independent predictor of incident coronary heart disease in an apparently healthy older population: the Rancho Bernardo Study. JACC, March 2008;51(9): 913-919.
10. Di Angelantonio E, Gao P, Pennelis L et al. Lipid-Related Markers and Cardiovascular Disease Prediction. JAMA 2012; 307(23):2499-506.
11. FDA. 510(K) Summary -- diaDexus PLAC Test. 2013. Available online at: www.accessdata.fda.gov/cdrh_docs/pdf3/K030477.pdf. Last accessed May 22, 2014.
12. Filippatos TD, Gazi IF, Liberopoulos EN, et al. The effect of orlistat and fenofibrate, alone or in combination, on small dense LDL and lipoprotein-associated phospholipase A2 in obese patients with metabolic syndrome. Atherosclerosis, August 2007; 193(2): 428-437.
13. Folsom AR. An assessment of incremental coronary risk prediction using C-reactive protein and other novel risk markers: The atherosclerosis risk in communities study. Archives of Internal Medicine, July 2006; 166(13): 1368-1373.
14. Garza CA, et al. Association between lipoprotein-associated phospholipase A2 and cardiovascular disease: A systematic review. Mayo Clinic Proceedings, February 2007; 82(2): 159-165.
15. Gerber Y, McConnell JP, et al. Lipoprotein-associated phospholipase A2 and prognosis after myocardial infarction in the community. Arteriosclerosis, Thrombosis, and Vascular Biology, November 2006; 26(11): 2517-2522.
16. Greenland P, Alpert JS, Beller GA et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2010; 56(25):e50-103.
17. Gu X, Hou J, Yang S et al. Is lipoprotein-associated phospholipase A2 activity correlated with fibrous-cap thickness and plaque volume in patients with acute coronary syndrome? Coron. Artery Dis. 2014; 25(1):10-5.
18. Hatoum IJ, Hu FB, Nelson JJ et al. Lipoprotein-associated phospholipase A2 activity and incident coronary heart disease among men and women with type 2 diabetes. Diabetes 2010; 59(5):1239-43.
19. Hatoum IJ, Cook NR, Nelson JJ et al. Lipoprotein-associated phospholipase A2 activity improves risk discrimination of incident coronary heart disease among women. Am Heart J 2011; 161(3):516-22.
20. Incorporating the PLAC test into CHD risk assessment, Clinical Laboratories Strategies, August 2003, Vol. 8, No. 9.
21. Jellinger PS, Smith DA, Mehta AE et al. American association of clinical endocrinologists' guidelines for management of dyslipidemia and prevention of atherosclerosis. Endocr Pract 2012; 18 Suppl 1:1-78.

22. Johnston N, Jernberg T, et al. Improved identification of patients with coronary artery disease by the use of new lipid and lipoprotein biomarkers. American Journal of Cardiology, March 2006, Vol. 97, Issue 5.
23. Kardys I, Oei HH, et al. Lipoprotein-associated phospholipase A2 and measures of extracoronary atherosclerosis: The Rotterdam Study. Arteriosclerosis, Thrombosis, and Vascular Biology, March 2006; 26(3): 631-636.
24. Kardys I, Oei HH, Hofman A, Oudkerk M and Witteman JC. Lipoprotein-associated phospholipase A2 and coronary calcification. The Rotterdam Coronary Calcification Study. Atherosclerosis, April 2007; 191(2): 377-383.
25. Koenig W, et al. Lipoprotein-Associated phospholipase A2 adds to risk prediction of incident coronary events by C-reactive protein in apparently healthy middle-aged men from the general population. Results from the 14-year follow-up of a large cohort from southern Germany. Circulation 2004; 110(4): 1903-1908.
26. Koenig W, et al. Lipoprotein-associated phospholipase A2 predicts future cardiovascular events in patients with coronary heart disease independently of traditional risk factors, markers of inflammation, renal function, and hemodynamic stress. Arteriosclerosis, Thrombosis and Vascular Biology, July 2006; 26(7): 1586-1593.
27. Kolodgie FD, et al. Lipoprotein-associated phospholipase A2 protein expression in the natural progression of human coronary atherosclerosis. Arteriosclerosis, Thrombosis, and Vascular Biology 2006; 26: 2523-2529.
28. Kuvin JT, Dave DM, et al. Effects of extended-release niacin on lipoprotein particle size, distribution, and inflammatory markers in patients with coronary artery disease. American Journal of Cardiology, September 2006, Vol. 98, Issue 6.
29. Lanman RB, et al. Lipoprotein-associated phospholipase A2: Review and Recommendation of a clinical cut point for adults. Preventive Cardiology, Summer 2006, pp. 138-143.
30. Lind L, Simon T, Johansson L et al. Circulating levels of secretory- and lipoprotein-associated phospholipase A2 activities: relation to atherosclerotic plaques and future all-cause mortality. Eur Heart J 2012; 33(23):2946-54.
31. Liu YS, Hu XB, Li HZ et al. Association of lipoprotein-associated phospholipase A(2) with characteristics of vulnerable coronary atherosclerotic plaques. Yonsei Med J 2011; 52(6):914-22.
32. Liu CF, Qin L, Ren JY et al. Elevated plasma lipoprotein-associated phospholipase A(2) activity is associated with plaque rupture in patients with coronary artery disease. Chin Med J (Engl) 2011; 124(16):2469-73.
33. Mohler ER, 3rd, Ballantyne CM, Davidson MH, et al. The effect of darapladib on plasma lipoprotein-associated phospholipase A2 activity and cardiovascular biomarkers in patients with stable coronary heart disease or coronary heart disease risk equivalent: The results of a multicenter, randomized, double-blind, placebo-controlled study. JACC, April 2008; 51(17): 1632-1641.
34. Muhlestein JB, May HT, et al. The reduction of inflammatory biomarkers by statin, fibrate, and combination therapy among diabetic patients with mixed dyslipidemia: the DIACOR (Diabetes and Combined Lipid Therapy Regimen) study. JACC, July 2006; 48(2): 396-401.
35. Muller O, Ntalianis A, Wijns W et al. Association of biomarkers of lipid modification with functional and morphological indices of coronary stenosis severity in stable coronary artery disease. Journal of cardiovascular translational research 2013; 6(4):536-44.

36. National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Available at www.nhlbi.nih.gov/guidelines/cholesterol/atp3xsum.pdf.
37. O'Donoghue M, Morrow DA, Sabatine MS et al. Lipoprotein-associated phospholipase A2 and its association with cardiovascular outcomes in patients with acute coronary syndromes in the PROVE IT-TIMI 22 (PRavastatin Or atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction) trial. Circulation 2006; 113(14):1745-52.
38. Oei H, et al. Lipoprotein-associated phospholipase A2 activity is associated with risk of coronary heart disease and ischemic stroke, the Rotterdam Study. Circulation 2005, Vol. III, pp. 570-575.
39. Oldgren J, James SK, et al. Lipoprotein-associated phospholipase A2 does not predict mortality or new ischemic events in acute coronary syndrome patients. European Heart Journal, March 2007; 28(6): 699-704.
40. Packard Chris J, et al. Lipoprotein-associated phospholipase A_2 as an independent predictor of coronary heart disease, The New England Journal of Medicine, October 2000, Vol. 343, No. 16, pp. 1148-1155.
41. Perk J, De Backer G et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur. Heart J. 2012; 33(13):1635- 701.
42. Perrson M, et al. Elevated Lp-PLA2 levels add prognostic information to the metabolic syndrome on incidence of cardiovascular events among middle-aged nondiabetic subjects. Arterioscler Thromb Vasc Biol 2007; 27(6): 1411-1416.
43. Ridker PM, Macfadyen JG, Wolfert RL et al. Relationship of lipoprotein-associated phospholipase A2 mass and activity with incident vascular events among primary prevention patients allocated to placebo or to statin therapy: an analysis from the JUPITER trial. Clin Chem 2012; 58(5):877-86.
44. Rosenson RS. Fenofibrate reduces lipoprotein associated phospholipase A2 mass and oxidative lipids in hypertriglyceridemic subjects with the metabolic syndrome. Am Heart Journal, March 2008; 155(3): 499.e9-16.
45. Ryu SK, Mallat Z, Benessiano J et al. Phospholipase A2 enzymes, high-dose atorvastatin, and prediction of ischemic events after acute coronary syndromes. Circulation 2012; 125(6):757-66.
46. Sabatine MS, et al. Prognostic utility of lipoprotein-associated phospholipase A2 for cardiovascular outcomes in patients with stable coronary artery disease. Arterioscler Thromb Vasc Biol 2007; 27(11): 2463-2469.
47. Saougos VG, Tambaki AP, Kalogirou M, et al. Differential effect of hypolipidemic drugs on lipoprotein-associated phospholipase A 2. Arteriosclerosis, Thrombosis, and Vascular Biology 2007; 27: 2236-2243.
48. Saremi A, Moritz TE, Anderson RJ et al. Rates and determinants of coronary and abdominal aortic artery calcium progression in the Veterans Affairs Diabetes Trial (VADT). Diabetes Care 2010; 33(12):2642-7.

49. Sarlon-Bartoli G, Boudes A, Buffat C et al. Circulating lipoprotein-associated phospholipase A2 in high-grade carotid stenosis: a new biomarker for predicting unstable plaque. Eur J Vasc Endovasc Surg 2012; 43(2):154-9.
50. Serruys PW, Garcia-Garcia HM, Buszman Pawel, et al. Effects of the direct lipoprotein-associated phospholipase A2 inhibitor darapladib on human coronary atherosclerotic plaque. Circulation 2008; 118: 1172-1182.
51. STABILITY Investigators S, White HD, Held C et al. Darapladib for preventing ischemic events in stable coronary heart disease. N. Engl. J. Med. 2014; 370(18):1702-11.
52. Suckling KE. Phospholipase A2 inhibitors in the treatment of atherosclerosis: A new approach moves forward in the clinic. Expert Opin Investig Drugs, October 2009; 18(10): 1425-1430.
53. Tehrani DM, Gardin JM, Yanez D et al. Impact of inflammatory biomarkers on relation of high density lipoprotein-cholesterol with incident coronary heart disease: cardiovascular Health Study. Atherosclerosis 2013; 231(2):246-51.
54. The Lp-PLA2 Studies Collaboration, et al. Collaborative meta-analysis of individual participant data from observational studies of Lp-PLA2 and cardiovascular diseases. European Journal of Cardiovascular Prevention and Rehabilitation, February 2007; 14(1): 3-11.
55. Thompson A, Gao P, Orfei L, et al. The Lp-PLA_2 Studies Collaboration. Lipoprotein-associated phospholipase A_2 and risk of coronary disease, stroke, and mortality: Collaborative analysis of 32 prospective studies. Lancet, May 2010; 375(9725): 1536-1544.
56. Vittos O, Toana B, Vittos A et al. Lipoprotein-associated phospholipase A2 (Lp-PLA2): a review of its role and significance as a cardiovascular biomarker. Biomarkers 2012; 17(4):289-302.
57. Winkler K, Hoffmann, NM, et al. Lipoprotein-associated phospholipase A2 predicts 5-year cardiac mortality independently of established risk factors and adds prognostic information in patients with low and medium high sensitivity C-reactive protein (The Ludwigshafen Risk and Cardiovascular Health Study). Clinical Chemistry, June 2007; 53(8): 1440-7.

Policy History:

Medical Policy Group, April 2004
Medical Policy Administration Committee, April 2004
Available for comment May 17-June 30, 2004
Medical Policy Group, April 2006 **(1)**
Medical Policy Group, August 2006 **(1)**
Medical Policy Group, June 2007 **(3)**
Medical Policy Group, June 2009 **(1)**
Medical Policy Group, June 2010 **(1):** Description updated, Key Points updated, References added, no coverage change
Medical Policy Group, June 2011 **(1):** Update to Key Points and References
Medical Policy Group, June 2012 **(1):** 2012 Update to Title, Key Points and References related to MPP update; no change in policy statement
Medical Policy Panel, June 2013
Medical Policy Group, September 2013 **(1):** Update to Key Points and References; no change to policy statement

Medical Policy Panel, June 2014
Medical Policy Group, June 2014 **(1):** Update to Key Points and References; no change to policy statement

---

This medical policy is not an authorization, certification, explanation of benefits, or a contract. Eligibility and benefits are determined on a case-by-case basis according to the terms of the member's plan in effect as of the date services are rendered. All medical policies are based on (i) research of current medical literature and (ii) review of common medical practices in the treatment and diagnosis of disease as of the date hereof. Physicians and other providers are solely responsible for all aspects of medical care and treatment, including the type, quality, and levels of care and treatment.

This policy is intended to be used for adjudication of claims (including pre-admission certification, pre-determinations, and pre-procedure review) in Blue Cross and Blue Shield's administration of plan contracts.