Measurement of Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) in the Assessment of Cardiovascular Risk

I. Description
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 (CAD) and may have a proinflammatory role in the progression of atherosclerosis.

The evidence for Lp-PLA2 testing in patients who have a risk of cardiovascular disease (CVD) includes studies of analytic validity and studies of the association of Lp-PLA2 and various CAD outcomes. Outcomes of interest include overall survival, disease-specific survival, and test validity. The studies demonstrate that Lp-PLA2 levels are an independent predictor of CVD. To improve outcomes, clinicians must have the tools to incorporate Lp-PLA2 test results into existing risk prediction models, and these models should demonstrate improved classification into risk categories that will improve treatment and health outcomes. Direct evidence for improved health outcomes with the use of Lp-PLA2 in clinical practice is lacking. Although Lp-PLA2 levels are associated with CVD risk, changes in patient management that would occur as a result of obtaining Lp-PLA2 levels in practice are not well-defined. The evidence is insufficient to determine the effects of the technology on health outcomes.

II. Criteria/Guidelines
Measurement of lipoprotein-associated phospholipase A2 (Lp-PLA2) is not covered because scientific evidence has not shown it to be effective in improving health outcomes.

III. Administrative Guidelines
The provider cannot bill or collect charges for these services unless a written acknowledgement of financial responsibility, specific to the service, is obtained from the member prior to the time services are rendered. Modifier code GA should be appended to the CPT when billing for these services.

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**Measurement of Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) in the Assessment of Cardiovascular Risk**

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

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.

**Regulatory Status**
In December 2014, FDA cleared for marketing through the 510(k) process a quantitative enzyme assay for Lp-PLA2 activity PLAC® Test for (diaDexus, San Francisco, CA). It was considered substantially equivalent to a previous version of the PLAC test (diaDexus) which was cleared for marketing in July 2003. FDA product code: NOE.

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**IV. Rationale**
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.

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:

- 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.

Analytic Validity
According to the U.S. Food and Drug Administration’s (FDA) Summary of Safety and Effectiveness for the diaDexus’ Lp-PLA2 assay, the intra-assay precision for the assay was 7% coefficient of variability (CV), and the interassay 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.

Clinical Validity
Lp-PLA2 as a Predictor of Coronary Artery Disease
Results of numerous, large-scale observational studies have examined whether Lp-PLA2 is an independent risk factor for coronary artery disease (CAD). 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 of the Association of Lp-PLA2 and CAD
Several systematic reviews and meta-analyses have summarized the association between Lp-PLA2 and CAD 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 (HR) of 1.12 (95% confidence interval [CI], 1.09 to 1.21) for each 1 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 does not result in an important magnitude of change.
Garza et al reviewed 14 observational studies enrolling 20,549 patients. This study reported the predictive ability of Lp-PLA2 levels for CVD 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 by Thompson et al 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 3 outcome measures. For every 1 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 (RR=1.10; 95% CI, 1.04 to 1.17). The authors estimated that this strength of association was similar to that seen for non–high-density lipoprotein cholesterol (HDL-C) and systolic blood pressure.

**Association of Lp-PLA2 and CAD in General Population Samples**

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**

The West of Scotland Coronary Prevention Study (WOSCOPS) was a 5-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 9 years. The case-cohort component of the study examined 2 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 nonelevated 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 (9) 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.16 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 CVD. 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.20 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. Recent studies have shown associations between Lp-PLA2 and cardiovascular events in a nonwhite multiethnic population, severity
of angiographically defined CAD in a Chinese sample, and subclinical atherosclerosis in young adults.

Some studies show that the association of Lp-PLA2 and CAD diminishes or disappears after adjustment for other risk factors. For example, Allison et al 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, a similar diminution of risk was observed. This population based study followed 520 patients for 7 years and evaluated the association between Lp-PLA2 and coronary calcification by electron beam computed tomography scan. The unadjusted OR for each SD increase in LpPLA2 was 1.6 (95% CI, 1.1 to 2.4); however, this association became nonsignificant after controlling for lipid levels.

Association of Lp-PLA2 and CAD in Specific Populations
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 1 of 2 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).

Association of Lp-PLA2 and CAD in Patients Receiving CAD Preventive Drugs
If levels of Lp-PLA2 change in response to effective CAD preventive drugs such as statins, and there is an association between CAD risk on treatment and Lp-PLA2 levels, then it is possible that measurement of Lp-PLA2 levels may be useful in monitoring treatment response. Interventional studies of antihyperlipidemic drugs (e.g., statins, fibrates, niacin) show that Lp-PLA2 levels decrease during treatment. A secondary analysis 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=3648) and at 30 days (n=3265) showed that patients randomized to atorvastatin 80 mg/d, but not pravastatin 40 mg/d, experienced a 20% reduction of Lp-PLA2 levels at 30 days. The 30-day, Lp-PLA2 level was independently associated with an increased risk of CV events. A secondary analysis from the DIACOR (Diabetes and Combined Lipid Therapy Regimen) trial demonstrated lower LpPLA2 levels (overall 16.8% reduction) after treatment compared with baseline.

Rosenson randomized 55 hyperlipidemic subjects with metabolic syndrome to fenofibrate or placebo. Fenofibrate treatment was associated with a 13% reduction in Lp-PLA2 compared with placebo. Saougos et al studied the effect of 3 lipid-lowering agents, rosvustatin, ezetimibe, and fenofibrate, on Lp-PLA2 levels. All 3 agents significantly lowered Lp-PLA2 levels; fenofibrate also selectively increased HDL associated Lp-PLA2 levels.

Although Lp-PLA2 levels respond to CAD preventive drugs, some studies have shown that Lp-PLA2 levels do not correlate with subsequent CAD risk in treated patients. At least 2 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 subjects 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 2587 patients treated with high-dose atorvastatin or placebo. Atorvastatin reduced Lp-PLA2 levels in 2587 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.

**Section Summary Clinical Validity**
A large consistent body of evidence establishes that Lp-PLA2 levels are an independent predictor of CAD. Relatively few studies have examined the degree to which Lp-PLA2 improves upon existing CAD prediction models in terms of clinically important magnitudes of reclassification.

Levels of Lp-PLA2 decrease substantially following treatment with anti-lipid medications, including statins. However, in treated patients Lp-PLA2 may no longer be associated with risk of CAD, and thus not be useful as a measure of treatment response.

**Clinical Utility**
Although the preceding studies show that Lp-PLA2 as an independent risk factor for CAD, clinical utility depends on the capability of Lp-PLA2 to improve upon existing models of CAD prediction, and then to translate to differences in treatment which result in improved patient outcomes. Establishing improved outcomes compared to existing prediction models could be demonstrated with clinical trials, but the expected difference in outcomes would probably be so small that the sample size of the trial would be impractically large. Decision modelling could estimate differences in patient outcomes due to improved reclassification of risk. A robust validated model using Lp-PLA2 to predict CAD outcomes needs to exist in order for physicians to use the test to manage patients. However, the relative treatment benefit of CAD preventive drugs has been demonstrated to be largely constant over the full spectrum of risk, so that improved risk stratification may provide little incremental population benefit compared to simply lowering the risk threshold for treatment.

**Section Summary: Clinical Utility**
No studies were identified which evaluate whether a testing strategy that uses Lp-PLA2 levels improves health outcomes. Changes in patient management that could potentially occur with a strategy using Lp-PLA2 levels are not well-established. Studies that directly evaluate patient management changes and/or health outcome improvements are needed to conclude that the use of Lp-PLA2 measurement has efficacy in cardiovascular diseases. Alternatively, robust decision modelling studies may demonstrate clinically important changes in health outcomes by incorporating Lp-PLA2 into CAD prediction models. Groups such as the American Heart Association have often incorporated results from decision models to inform their guidelines, when the data underlying the models is robust.
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8

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in November 2015 did not identify any ongoing or unpublished trials that would likely influence this review.

Summary of Evidence
The evidence for lipoprotein-associated phospholipase A2 (Lp-PLA2) testing in patients who have a risk of cardiovascular disease (CVD) includes studies of analytic validity and studies of the association of Lp-PLA2 and various coronary artery disease outcomes. Outcomes of interest include overall survival, disease specific survival, and test validity. The studies demonstrate that Lp-PLA2 levels are an independent predictor of CVD. To improve outcomes, clinicians must have the tools to incorporate Lp-PLA2 test results into existing risk prediction models, and these models should demonstrate improved classification into risk categories that will improve treatment and health outcomes. Direct evidence for improved health outcomes with the use of Lp-PLA2 in clinical practice is lacking. Although Lp-PLA2 levels are associated with CVD risk, changes in patient management that would occur as a result of obtaining Lp-PLA2 levels in practice are not well-defined. The evidence is insufficient to determine the effects of the technology on health outcomes.

Practice Guidelines and Position Statements
American College of Cardiology Foundation and American Heart Association
The American College of Cardiology Foundation and American Heart Association published joint guidelines on the assessment of cardiovascular risk in asymptomatic patients in 2013. Lp-PLA2 testing is not mentioned in this recent guideline, which is a change from the previous guideline published in 2010. In this prior guideline, Lp-PLA2 was given a IIb recommendation for assessing cardiovascular risk in intermediate-risk asymptomatic adults.

American Association of Clinical Endocrinologists
The American Association of Clinical Endocrinologists published guidelines for the management of dyslipidemia and prevention of atherosclerosis in 2012. These guidelines made the following recommendations for Lp-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).

European Society of Cardiology and Other Societies
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).
Measurement of Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) in the Assessment of Cardiovascular Risk

U.S. Preventive Services Task Force Recommendations
No U.S. Preventive Services Task Force recommendations for the measurement of Lp-PLA2 have been identified.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

V. Important Reminder
The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

This Medical Policy has been developed through consideration of the medical necessity criteria under Hawaii’s Patients’ Bill of Rights and Responsibilities Act (Hawaii Revised Statutes §432E-1.4), generally accepted standards of medical practice and review of medical literature and government approval status. HMSA has determined that services not covered under this Medical Policy will not be medically necessary under Hawaii law in most cases. If a treating physician disagrees with HMSA’s determination as to medical necessity in a given case, the physician may request that HMSA reconsider the application of the medical necessity criteria to the case at issue in light of any supporting documentation.

VI. 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.
6. Koenig W, Khuseyinova N, Lowel H et al. Lipoprotein-associated phospholipase A2 adds to risk prediction of incident coronary events by C-reactive protein in apparently healthy


