Measurement of Lipoprotein-Associated Phospholipase A<sub>2</sub> in the Assessment of Cardiovascular Risk

**POLICY**

Measurement of lipoprotein-associated phospholipase A<sub>2</sub> is considered **investigational**.

**POLICY GUIDELINES**

Measurement of lipoprotein (a) enzyme is a distinct laboratory test. Measurement of lipoprotein (a) enzyme is addressed in evidence review 2.04.65, and genetic testing for lipoprotein (a) variants is addressed in evidence review 2.04.70.

**Coding**

Effective July 1, 2018, there is a new PLA code: 0052U (Lipoprotein, blood, high resolution fractionation and quantitation of lipoproteins, including all five major lipoprotein classes and subclasses of HDL, LDL, and VLDL by vertical auto profile ultracentrifugation).

**BENEFIT APPLICATION**

**BlueCard/National Account Issues**

State or federal mandates (eg, Federal Employee Program) may dictate that certain U.S. Food and Drug Administration-approved devices, drugs, or biologics may not be considered investigational, and thus these devices may be assessed only by their medical necessity.

**BACKGROUND**

**Low-Density Lipoproteins**

LDLs have been identified as major atherogenic lipoproteins and have long been identified by the National Cholesterol Education Project 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, 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 low-density lipoprotein cholesterol.

**Treatment**

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 A$_2$ (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. Recognition that atherosclerosis represents, in part, an inflammatory process has created considerable interest in the measurement of proinflammatory factors as part of cardiovascular disease risk assessment.

Interest in Lp-PLA2 as a possible causal risk factor for CAD has generated development and testing of Lp-PLA2 inhibitors as a new class of drugs to reduce the risk of CAD. However, clinical trials of Lp-PLA2 inhibitors have not shown significant reductions in CAD endpoints.$^{1,2,3}$ Furthermore, assessment of Lp-PLA2 levels has not been used in the selection or management of subjects in the clinical trials.

**Regulatory Status**

In December 2014, the PLAC® Test (diaDexus), a quantitative enzyme assay, was cleared for marketing by the U.S. Food and Drug Administration through the 510(k) process for Lp-PLA2 activity. It was considered substantially equivalent to a previous version of the PLAC® Test (diaDexus), which was cleared for marketing by the Food and Drug Administration in July 2003. Food and Drug Administration product code: NOE.

**RATIONALE**

This evidence review was created in October 2003 and has been updated regularly with searches of the MEDLINE database. The most recent literature update was performed through October 1, 2018.

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

**Lp-PLA2 and Cardiovascular risk**

A large body of literature has accumulated on the utility of risk factors in the prediction of future cardiac events. The evidence assessed for this review consists of large, prospective cohort studies that have evaluated the association between lipoprotein-associated phospholipase A$_2$ (Lp-PLA2) and cardiovascular outcomes.

The National Cholesterol Education Program ATP-III guidelines have indicated that to determine the clinical significance of Lp-PLA2, the emerging risk factors should be evaluated against the following criteria$:^4$: 

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**Original Policy Date:** October 2003  
**Page:** 2
• 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 a reduction in risk.

A TEC Assessment (2002) summarized the steps necessary to determine the utility of a novel cardiac risk factor. The following three steps were required:

• Standardize the measurement of the risk factor.

• Determine 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 with established risk factors.

• Determine how the novel risk assessment will be used in the management of the patient, compared with standard methods of assessing risk, and whether any subsequent changes in patient management result in an improvement in patient outcome.

Clinical Context and Test Purpose

The purpose of Lp-PLA2 testing in patients who have a risk of cardiovascular disease (CVD) is to inform, improve patient stratification using risk prediction models that alter management decisions and improve health outcomes.

The question addressed in this evidence review is: Does testing for Lp-PLA2 improve the net health outcome for individuals at risk for CVD?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest are individuals at risk for CAD.

Interventions

The relevant intervention of interest is testing for Lp-PLA2 as a biomarker of CAD.

Comparators

The following practice is currently being used to manage CAD risk: standard assessment of cardiovascular risk.

Outcomes

The primary outcomes of interest are the development of CVD such as coronary artery disease, stroke, and mortality.

Timing

The development of CVD typically occurs over many years or decades.

Setting
Asymptomatic patients are typically evaluated by primary care physicians. Symptomatic patients are referred to cardiology.

**Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

**Clinically Valid**

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

**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 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**

The Emerging Risk Factors Collaboration (2012) performed a patient-level meta-analysis of the association between novel lipid risk factors and cardiovascular risk. Results from 37 prospective cohort studies enrolling 165544 participants were combined to predict cardiovascular risk over a median follow-up of 10.4 years. Reviewers examined the independent association of markers with cardiovascular risk and the ability to reclassify risk into clinically relevant categories. For Lp-PLA2, 11 studies (n=32075 participants) 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 to 1.21) for each 1 standard deviation 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 (95% CI, -0.45 to 0.86). The fact that the net reclassification improvement crossed 0.0 indicates that the addition of Lp-PLA2 to the model did not result in an important magnitude of change.

A patient-level meta-analysis by Thompson et al (2010) evaluated the association among Lp-PLA2 levels, CAD, stroke, and mortality. A total of 79036 participants from 32 prospective studies were included in this review. Significant associations were found between Lp-PLA2 and all three outcome measures. For every 1 standard deviation increase in Lp-PLA2 levels, the relative risk (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 between Lp-PLA2 levels and nonvascular deaths (RR=1.10; 95% CI, 1.04 to 1.17). Reviewers estimated that this strength of association was similar to that seen for non-high-density lipoprotein cholesterol (HDL-C) and systolic blood pressure.

Garza et al (2007) reviewed 14 observational studies enrolling 20549 patients. This systematic review reported the predictive ability of Lp-PLA2 levels for CVD after adjustment for traditional cardiac risk factors. The combined odds ratio for an elevated Lp-PLA2 level was reported as 1.60 (95% CI, 1.36 to 1.89) for the development of future cardiac events.

**Association Between 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 was a 5-year, case-control trial evaluating 6595 men with elevated cholesterol levels and no history of a heart attack.\textsuperscript{13} As reported by Packard et al (2000), study researchers looked at a smaller population of this study to determine if inflammatory markers such as Lp-PLA2 and high-sensitivity C-reactive protein (CRP) correlated with coronary heart disease (CHD) events. The 580 men who went on to have a myocardial infarction or revascularization were compared with 1160 age- and smoking-matched men who did not have an event. Results showed those with the highest levels of Lp-PLA2 had twice the risk of an event compared with those with the lowest levels, even after adjustment for traditional risk factors and other inflammatory mediators.

The Atherosclerosis Risk in Communities study (2004) evaluated the various risk markers and their association with increased risk in a large, diverse population of more than 12000 people.\textsuperscript{10} At enrollment, patients were free of CHD and were followed for the development of the disease for the next nine years. The case-cohort component of the study examined 2 inflammatory markers, Lp-PLA2, and high-sensitivity CRP, in a subset of 608 cases and 740 controls. Results showed that elevated levels of Lp-PLA2 were higher in incident CHD cases. In people with nonelevated low-density lipoprotein levels (<130 mg/dL), Lp-PLA2 levels were independently associated with CHD, even after adjustment for traditional risk factors and CRP. Koenig et al (2004) reported similar results in a study of 934 apparently healthy men ages 45 to 64 who were followed between 1984 and 1998.\textsuperscript{11} During this period, 97 men experienced a coronary event. Elevated Lp-PLA2 levels appeared to be predictive of future coronary events in middle-aged men with moderately elevated total cholesterol, independent of CRP levels.

Ballantyne et al (2005) studied Lp-PLA2 in the 12762 apparently healthy subjects participating in the Atherosclerosis Risk In Communities study.\textsuperscript{12} Mean levels of both Lp-PLA2 and CRP were higher in the 194 stroke cases; the authors concluded that Lp-PLA2 levels might provide complementary information beyond traditional risk factors in identifying those at risk for ischemic stroke.

As part of the Patient-centered Evaluative Assessment of Cardiac Events study, Lp-PLA2 levels were measured in 3766 patients with stable CAD followed for a median of 4.8 years.\textsuperscript{13} After adjusting for other baseline risk factors, patients in the highest quartile of Lp-PLA2 were 1.4 times more likely (95% CI, 1.17 to 1.70; p<0.001) to experience an adverse cardiovascular outcome than patients in the lowest quartile. Winkler et al (2007) studied 3232 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 to 3.1; p<0.001) after adjusting for established risk factors, including CRP and N-terminal b-natriuretic peptide.\textsuperscript{14} Persson et al (2007) evaluated the relation between Lp-PLA2 and the metabolic syndrome in 4480 nondiabetic patients without a history of CAD.\textsuperscript{15} Both Lp-PLA2 (RR=1.54; 95% CI, 1.07 to 2.24) and metabolic syndrome (RR=1.42; 95% CI, 1.06 to 1.90) were significant predictors of a first cardiac event. The combination of elevated Lp-PLA2 and metabolic syndrome conferred a further increase in risk (RR=1.97; 95% CI, 1.34 to 2.90).

The Rancho Bernardo Study (2008) enrolled 1077 community-dwelling older adults without known heart disease and followed patients a mean of 16 years to assess for development of heart disease.\textsuperscript{16} Lp-PLA2 levels were an independent predictor of cardiac events, with RRs 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 (2011).\textsuperscript{17} Lp-PLA2 was a significant predictor of CHD after adjustment for traditional risk factors (RR=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, improving it 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 have also found an association between Lp-PLA2 levels and plaque rupture and fibrous cap thickness in patients with acute coronary syndrome. Muller et al (2013) reported that Lp-PLA2 levels were associated with low fractional flow reserve on cardiac catheterization in 197 patients with stable CAD. Tehrani et al (2013) evaluated the association between Lp-PLA2 levels and the protective effect of HDL-C on incident CHD among 3888 adults with known CVD. Among patients with the highest tertile of Lp-PLA2, the relation between HDL-C levels and incident CHD was attenuated, although there was no consistent association between higher levels of Lp-PLA2 and CHD risk across HDL-C categories. Recent studies have shown associations between Lp-PLA2 and cardiovascular events in a nonwhite multiethnic population, in the severity of angiographically defined CAD in a Chinese sample, and subclinical atherosclerosis in young adults.

Some studies have shown the association between Lp-PLA2 and CAD diminishes or disappears after adjustment for other risk factors. For example, Allison et al (2007) studied 508 patients with peripheral vascular disease followed an average of 6.7 years. While there was a modest univariate association between Lp-PLA2 and cardiovascular events, this association disappeared after adjusting for established risk factors. In the Rotterdam Coronary Calcification Study (2007), 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 using electron-beam computed tomography scan. The unadjusted odds ratio for each standard deviation increase in Lp-PLA2 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 (2010) performed a secondary analysis of the Veterans Affairs Diabetes Trial examining risk factors that predict 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 (2010) evaluated Lp-PLA2 as a risk factor for incident CHD in 1517 diabetic patients enrolled in the Health Profession Follow-Up Study. After adjusting for standard risk factors, the RR for incident CHD for the upper quartile of Lp-PLA2 activity compared with the lower quartile was 1.39 (95% CI, 1.01 to 1.90; p=0.03).

**Association Between Lp-PLA2 and CAD in Patients Receiving CAD Preventive Drugs**

If Lp-PLA2 levels 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 measurement of Lp-PLA2 levels may be useful in monitoring treatment response.

Interventional studies of antihyperlipidemic drugs (eg, statins, fibrates, niacin) have shown that Lp-PLA2 levels decrease during treatment. A secondary analysis of the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infraction trial (2006), in which Lp-PLA2 levels were measured at baseline (n=3648) and 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 cardiovascular events.
2006 secondary analysis from the Diabetes and Combined Lipid Therapy Regimen trial demonstrated lower Lp-PLA2 levels (16.8% overall reduction) after treatment compared with baseline.32

Rosenson (2008) randomized 55 hyperlipidemic subjects with metabolic syndrome to fenofibrate, or placebo.33 Fenofibrate treatment was associated with a 13% reduction in Lp-PLA2 levels compared with placebo. Saougos et al (2007) studied the effect of 3 lipid-lowering agents (rosuvastatin, ezetimibe, fenofibrate) on Lp-PLA2 levels.34 All three 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 two clinical trials have examined the change in Lp-PLA2 levels in patients treated with statins versus placebo and evaluated whether the clinical utility of Lp-PLA2 levels for risk stratification is modified by statin treatment.35,36 Ridker et al (2012) analyzed the changes in Lp-PLA2 levels among patients in the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin, a randomized controlled trial of 17802 subjects allocated to rosuvastatin or placebo.35 Among the patients who received 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 Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering randomized controlled trial, Ryu et al (2012) analyzed 2587 patients treated with high-dose atorvastatin, or placebo.36 Atorvastatin reduced Lp-PLA2 levels in 2587 patients treated with high-dose atorvastatin. 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 correlation was found in the atorvastatin group. In a clinical trial by White et al (2014), patients were randomized to placebo or darapladib, an Lp-PLA2 inhibitor.37 A secondary analysis of this trial by Wallentin et al (2016) demonstrated that, although baseline Lp-PLA2 levels were associated with cardiovascular risk, there was no association between changes in Lp-PLA2 levels and outcomes.37

Section Summary: Clinically Valid

A large consistent body of evidence has established that Lp-PLA2 level is an independent predictor of CAD. Relatively few studies have examined the degree to which Lp-PLA2 improves on existing CAD prediction models regarding clinically important magnitudes of reclassification.

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

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No studies were identified that assessed the clinical utility of Lp-PLA2 test to define CAD risk.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Although the preceding studies showed that Lp-PLA2 level is an independent risk factor for CAD, clinical utility depends on whether the use of Lp-PLA2 levels improves on existing models of CAD prediction, which then translates into differences in treatment that improve patient outcomes. Establishing improved outcomes compared with 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 modeling is another approach to estimating differences in patient outcomes due to the improved reclassification of risk. A robust, validated model using Lp-PLA2 levels to predict CAD outcomes is necessary to use the test to manage patients. No studies identified evaluated whether a testing strategy that uses Lp-PLA2 levels improves health outcomes.

Section Summary: Clinically Useful

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 determine whether the use of Lp-PLA2 measurement has efficacy in CVD. Alternatively, robust decision modeling studies may demonstrate clinically important changes in health outcomes by incorporating Lp-PLA2 levels 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 are robust. Incorporation of Lp-PLA2 into decision models is necessary to demonstrate the potential clinical utility of the biomarker.

Summary of Evidence

For individuals who have a risk of cardiovascular disease who receive Lp-PLA2 testing, the evidence includes studies of the association between Lp-PLA2 and various coronary artery disease outcomes. The relevant outcomes are overall survival, disease-specific survival, and test validity. The studies have demonstrated that Lp-PLA2 levels are an independent predictor of cardiovascular disease. Although Lp-PLA2 levels are associated with cardiovascular disease risk, changes in patient management that would occur as a result of obtaining Lp-PLA2 levels in practice are not well-defined. To demonstrate clinical utility, clinicians must have the tools to incorporate Lp-PLA2 test results into existing risk prediction models that improve classification into risk categories alter treatment decisions and lead to improved health outcomes. Direct evidence for such improved health outcomes with Lp-PLA2 testing in clinical practice is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American College of Cardiology and American Heart Association

The American College of Cardiology and American Heart Association (2013) published joint guidelines on the assessment of cardiovascular risk in asymptomatic patients Lipoprotein-associated phospholipase A2 (Lp-PLA2) testing was not mentioned in these guidelines, which was a change from 2010 guidelines. In their prior guideline, Lp-PLA2 was given an IIb recommendation for assessing cardiovascular risk in intermediate-risk asymptomatic adults.

American Association of Clinical Endocrinologists et al
The American Association of Clinical Endocrinologists (2012) published guidelines on the management of dyslipidemia and prevention of atherosclerosis. These guidelines made the following recommendations for Lp-PLA2 testing (see Table 1).

### Table 1. Guidelines on Dyslipidemia and Atherosclerosis

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<thead>
<tr>
<th>Recommendation</th>
<th>GOE</th>
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<tr>
<td>Assess markers of inflammation in patients where further stratification of risk is necessary. Highly sensitive CRP (hsCRP) and Lp-PLA2 provide useful information in these instances and appear to be synergistic in predicting risk of CVD and stroke</td>
<td>B</td>
<td>1</td>
</tr>
<tr>
<td>Measure Lp-PLA2, which in some studies has demonstrated more specificity than hsCRP, when it is necessary to further stratify a patient’s CVD risk, especially in the presence of systemic highly sensitive CRP elevations</td>
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CRP: C-reactive protein; CVD: cardiovascular disease; GOE: grade of evidence; LOE: level of evidence; Lp-PLA2: lipoprotein-associated phospholipase A2.

An update to guidelines published jointly by the American Association of Clinical Endocrinologists and the American College of Endocrinology (2017) recommended the measurement of Lp-PLA2 as an additional indication of cardiovascular risk. Citing several studies in which Lp-PLA2 was comparable with high-sensitivity CRP as a risk predictor, the guidelines accordingly recommended the use of Lp-PLA2 data in situations requiring a more specific evaluation of risk of atherosclerotic cardiovascular disease that is provided by high-sensitivity CRP.

**European Society of Cardiology et al**

The European Society of Cardiology and other cardiovascular disease societies (2012) issued clinical practice guidelines on cardiovascular disease prevention. These guidelines included the following statement 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).

**U.S. Preventive Services Task Force Recommendations**

No U.S. Preventive Services Task Force recommendations on the use of Lp-PLA2 in the assessment of cardiovascular risk have been identified.

**Medicare National Coverage**

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**

A search of ClinicalTrials.gov in November 2018 did not identify any ongoing or unpublished trials that would likely influence this review.

**REFERENCES**


14. Winkler K, Hoffmann MM, Winkelmann BR, 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


33. Rosenson RS. Fenofibrate reduces lipoprotein associated phospholipase A2 mass and oxidative lipids in hypertriglyceridemic subjects with the metabolic syndrome. Am Heart J. Mar 2008;155(3):499 e499-416. PMID 18294485


Measurement of Lipoprotein-Associated Phospholipase A₂ in the Assessment of Cardiovascular Risk


| CODES |
|---|---|---|
| Codes | Number | Description |
| CPT | 83698 | Lipoprotein-associated phospholipase A2 (Lp-PLA2) |
| | 0052U | Lipoprotein, blood, high resolution fractionation and quantitation of lipoproteins, including all five major lipoprotein classes and subclasses of HDL, LDL, and VLDL by vertical auto profile ultracentrifugation |
| ICD-10-CM | | Investigational for all diagnoses |
| ICD-10-PCS | | Not applicable. No ICD procedure codes for laboratory tests. |

| POLICY HISTORY |
|---|---|---|
| Date | Action | Description |
| 06/12/14 | Replace policy | Policy updated with literature review through May 12, 2014. References 3, 21-22, 33, and 38 added. Rationale reorganized. No changes to policy statement. |
| 01/18/17 | Replace policy | Policy updated with literature review through November 8, 2016; reference 38 added. Policy statement unchanged. |
| 12/27/17 | Replace policy | Blue Cross of Idaho adopted changes as noted. Policy updated with literature review through October 16, 2017; reference 42 added. Policy statement unchanged |
| 12/20/18 | Replace policy | Blue Cross of Idaho adopted changes as noted, effective 12/20/2018. Policy updated with literature review through October 1, 2018; no references added. Policy statement unchanged. |