2.04.32	Measurement of Lipoprotein-Associated Phospholipase A_2 in the Assessment of Cardiovascular Risk		
Original Policy Date:	October 30, 2015	**Effective Date:**	February 1, 2022
Section:	2.0 Medicine	**Page:**	Page 1 of 10

Policy Statement

Measurement of lipoprotein-associated phospholipase A_2 (Lp-PLA2) is considered **investigational**.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Measurement of lipoprotein (a) enzyme is a distinct laboratory test. Measurement of lipoprotein (a) enzyme is addressed in Blue Shield of California Medical Policy: Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease.

Coding

The following PLA code may be used:

- **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

The following CPT code is specific for this test:

- **83698**: Lipoprotein-associated phospholipase A_2 (Lp-PLA2)

Description

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2), also known as platelet-activating factor acetylhydrolase, is an enzyme that hydrolyzes phospholipids and is primarily associated with low-density lipoproteins. Accumulating evidence has suggested that Lp-PLA_2 is a biomarker of coronary artery disease and may have a proinflammatory role in the progression of atherosclerosis.

Related Policies

- Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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 (FDA) through the 510(k) process for Lp-PLA_2 activity. It was considered substantially equivalent to a previous version of the PLAC® Test (diaDexus), which was cleared for marketing by the FDA in July 2003. FDA product code: NOE.

Rationale

Background

Low-Density Lipoproteins

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-PLA_2), 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-PLA_2 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 pro-inflammatory factors as part of cardiovascular disease risk assessment.

Interest in Lp-PLA_2 as a possible causal risk factor for CAD has generated the development and testing of Lp-PLA_2 inhibitors as a new class of drugs to reduce the risk of CAD. However, clinical trials of Lp-PLA_2 inhibitors have not shown significant reductions in CAD endpoints.[1,2,3] Furthermore, assessment of Lp-PLA_2 levels has not been used in the selection or management of subjects in the clinical trials.

Literature Review

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.

Lipoprotein-Associated Phospholipase A_2 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 several systematic reviews, of

prospective cohort studies that have evaluated the association between lipoprotein-associated phospholipase A_2 (Lp-PLA_2) and cardiovascular outcomes.

The National Cholesterol Education Program ATP-III guidelines have indicated that to determine the clinical significance of Lp-PLA_2, the emerging risk factors should be evaluated against the following criteria[4]:

- 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 measurements must be widely available, well-standardized, inexpensive, have accepted population reference values, and be relatively stable biologically.
- Preferably, but not necessarily, modification of the risk factor in clinical trials will have shown a reduction in risk.

A Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment (2002) summarized the steps necessary to determine the utility of a novel cardiac risk factor.[5] The following 3 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-PLA_2 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-PLA_2 improve the net health outcome for individuals at risk for CVD?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals at risk for coronary artery disease (CAD).

Interventions

The relevant intervention of interest is testing for Lp-PLA_2 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 CAD, stroke, and mortality. The development of CVD typically occurs over many years or decades.

Study Selection Criteria

For the evaluation of clinical validity of Lp-PLA_2 testing, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard

- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described

Clinically Valid

Lipoprotein-Associated Phospholipase A_2 as a Predictor of Coronary Artery Disease

Results of numerous, large-scale observational studies have examined whether Lp-PLA_2 is an independent risk factor for CAD. These observational studies have been analyzed in several systematic reviews.[6,7,8] The largest, conducted by The Emerging Risk Factors Collaboration (2012), included 37 cohort studies and performed a patient-level meta-analysis of the association between novel lipid risk factors and cardiovascular risk over a median follow-up of 10.4 years in patients without CVD.[6] The review found Lp-PLA_2 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-PLA_2 activity based on 11 studies (N=32075). However, there was no significant improvement in risk reclassification following the addition of Lp-PLA_2 to the reclassification model, with a net reclassification change of 0.21 (95% CI, -0.45 to 0.86).

Two other systematic reviews reported similar results. One review of 32 studies (N=79036) found for every 1 standard deviation increase in Lp-PLA_2 levels, the relative risk 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, following adjustment for traditional risk factors. There was also a significant association between Lp-PLA_2 levels and nonvascular deaths (RR 1.10; 95% CI, 1.04 to 1.17).[7] The second, smaller review (14 studies, N = 20,549) reported a pooled odds ratio of 1.60 (95% CI, 1.36 to 1.89), adjusted for traditional cardiac risk factors, for the development of future cardiac events with elevated Lp-PLA_2 levels.[8]

Section Summary: Clinically Valid

Several large meta-analyses found consistent evidence that Lp-PLA_2 level is an independent predictor of CAD. Based on these reviews, it is less clear the degree to which Lp-PLA_2 improves on existing CAD prediction models regarding clinically important magnitudes of reclassification.

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-PLA_2 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 studies have shown that Lp-PLA_2 level is an independent risk factor for CAD, clinical utility depends on whether the use of Lp-PLA_2 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-PLA_2 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-PLA_2 levels improves health outcomes.

Section Summary: Clinically Useful
Changes in patient management that could potentially occur with a strategy using Lp-PLA_2 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-PLA_2 measurement has efficacy in CVD. Alternatively, robust decision modeling studies may demonstrate clinically important changes in health outcomes by incorporating Lp-PLA_2 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-PLA_2 into decision models is necessary to demonstrate the potential clinical utility of the biomarker.

Summary of Evidence
For individuals who have a risk of CVD who receive Lp-PLA_2 testing, the evidence includes studies of the association between Lp-PLA_2 and various CAD outcomes. Relevant outcomes are overall survival, disease-specific survival, and test validity. The studies have demonstrated that Lp-PLA_2 levels are an independent predictor of CVD. Although Lp-PLA_2 levels are associated with CVD risk, changes in patient management that would occur as a result of obtaining Lp-PLA_2 levels in practice are not well-defined. To demonstrate clinical utility, clinicians must have the tools to incorporate Lp-PLA_2 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-PLA_2 testing in clinical practice is lacking. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

Supplemental Information
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Cardiology and American Heart Association
In 2019, the American College of Cardiology and the American Heart Association published joint guidelines on the assessment of cardiovascular risk in asymptomatic patients.[9] Lp-PLA_2 testing was not mentioned in these guidelines, which was a change from 2010 guidelines.[10] In their prior guideline, Lp-PLA_2 was given a IIb recommendation for assessing cardiovascular risk in intermediate-risk asymptomatic adults.

American Association of Clinical Endocrinologists and American College of Endocrinology
In 2012, the American Association of Clinical Endocrinologists and the American College of Endocrinology published guidelines on the management of dyslipidemia and the prevention of atherosclerosis.[11,12] These guidelines made the following recommendations for Lp-PLA_2 testing (see Table 1).

Table 1. Guidelines on Dyslipidemia and Atherosclerosis

Recommendation	GOE	LOE
Assess markers of inflammation in patients where further stratification of risk is necessary. Highly sensitive CRP (hsCRP) and Lp-PLA_2 provide useful information in these instances and appear to be synergistic in predicting the risk of CVD and stroke.	A	1

Recommendation	GOE	LOE
Measure Lp-PLA_2, 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	B	2

CRP: C-reactive protein; CVD: cardiovascular disease; GOE: grade of evidence; hsCRP: high-sensitivity C-reactive protein; LOE: level of evidence; Lp-PLA_2: lipoprotein-associated phospholipase A_2.

In 2017, an update to guidelines published jointly by the American Association of Clinical Endocrinologists and the American College of Endocrinology recommended the measurement of Lp-PLA_2 as an additional indication of cardiovascular risk.[11] Citing several studies in which Lp-PLA_2 was comparable with high-sensitivity CRP as a risk predictor, the guidelines accordingly recommended the use of Lp-PLA_2 data in situations requiring a more specific evaluation of the risk of atherosclerotic cardiovascular disease that is provided by high-sensitivity CRP.

European Society of Cardiology et al
In 2016, the European Society of Cardiology and other cardiovascular disease societies issued clinical practice guidelines on cardiovascular disease prevention. [13] These guidelines included the following statement :

- Routine assessment of circulating or urinary biomarkers is not recommended for refinement of CVD risk stratification (Class IIIB recommendation)

The guideline also noted that "there is evidence of publication bias in the field of novel biomarkers of CV risk, leading to inflated estimates of strength of association and potential added value".

U.S. Preventive Services Task Force Recommendations
No U.S. Preventive Services Task Force recommendations on the use of Lp-PLA_2 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, 2021 did not identify any ongoing or unpublished trials that would likely influence this review.

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14. Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 2.04.32 (December 2021).

Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	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

Type	Code	Description
	83698	Lipoprotein-associated phospholipase A_2 (Lp-PLA2)
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
10/30/2015	Policy title change from Coronary Heart Disease (CHD) - Assessment of Emerging Risk Factors Policy revision without position change BCBSA Medical Policy adoption
03/01/2016	Policy revision without position change
02/01/2017	Policy revision without position change
02/01/2018	Policy revision without position change
02/01/2019	Policy revision without position change
02/01/2020	Annual review. No change to policy statement. Literature review updated.
02/01/2021	Annual review. No change to policy statement. Literature review updated.
02/01/2022	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) 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 the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Measurement of Lipoprotein-Associated Phospholipase A_2 in the Assessment of Cardiovascular Risk 2.04.32 **Policy Statement:** Measurement of lipoprotein-associated phospholipase A_2 (Lp-PLA2) is considered **investigational.**	**Measurement of Lipoprotein-Associated Phospholipase A_2 in the Assessment of Cardiovascular Risk 2.04.32** **Policy Statement:** Measurement of lipoprotein-associated phospholipase A_2 (Lp-PLA2) is considered **investigational**.