Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 5/1/25**
(See policy history boxes for previous effective dates)

Title: Measurement of Lipoprotein-Associated Phospholipase A_2 (Lp-PLA_2) and Secretory Type II Phospholipase A_2 (sPLA$_2$-IIA) in the Assessment of Cardiovascular Risk

Description/Background

LOW-DENSITY LIPOPROTEINS

Low-density lipoproteins (LDLs) have been identified as the major atherogenic lipoproteins and have long been identified by the National Cholesterol Education Project as the primary target of cholesterol-lowering therapy. An LDL particle consists 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 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 cholesterol and LDL-C. Thus, there is considerable potential to improve the accuracy of current cardiovascular risk prediction models.

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

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 measurement of proinflammatory factors as part of cardiovascular disease risk assessment.

Interest in Lp-PLA$_2$ as a possibly causal risk factor for CAD has generated development and testing of Lp-PLA$_2$ inhibitors as a new class of drugs to reduce risk of CAD. However, clinical trials of Lp-PLA$_2$ inhibitors have not shown significant reductions in CAD end points.[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.

These biomarkers have been studied as alternatives or additions to standard lipid panels for risk stratification in cardiovascular disease or as treatment targets for lipid-lowering therapy. Cardiovascular risk panels refer to different combinations of cardiac markers that are intended to evaluate the risk of cardiovascular disease. There are numerous commercially available risk panels that include different combinations of lipids, noncardiac biomarkers, measures of inflammation, metabolic parameters, and/or genetic markers. Risk panel's report the results of multiple individual tests, as distinguished from quantitative risk scores that combine the results of multiple markers into a single score.

Regulatory Status

Lp-PLA$_2$
In December 2014, the PLAC® Test (diaDexus, San Francisco, CA), 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 Food and Drug Administration in July 2003. FDA product code: NOE.

sPLA$_2$-IIA
There are several manufacturers who produce testing kits for sPLA2, including: ZEUS Scientific, antibodies-online, Biocompare, Cayman Chemical, Abcam, etc.

Medical Policy Statement

Measurement of lipoprotein-associated Phospholipase A2 (Lp-PLA$_2$) in the assessment of cardiovascular risk is considered **experimental/investigational.** While this service may be safe, its usefulness in the clinical management of atherosclerosis has not been established.

Measurement of secretory type II Phospholipase A2 (sPLA$_2$-IIA) to determine risk of cardiovascular disease is considered **experimental/investigational.** Current medical literature does not support a causal relationship between sPLA2-IIA and cardiovascular disease.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

83698 84999

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

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 (NCEP) 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 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.

Clinical Context and Test Purpose
The purpose of Lp-PLA_2 testing in patients who have risk of cardiovascular disease (CVD) is to inform, improve patient stratification using risk prediction models that alter management decisions and improve health outcomes.

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 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-PLA2 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
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).

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.[5,6,7] 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.[5] The review found Lp-PLA_2 was an independent risk factor for cardiovascular events with a hazard ratio of1.12 (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 to1.20) 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).[6] The second, smaller review (14 studies, N = 20,549) reported a pooled odds ratio of 1.60 (9% 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.[7]

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 the preceding studies showed 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-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-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.

For individuals who have risk factors for cardiovascular disease (CVD) who receive CVD risk panels, the evidence includes multiple cohorts and case-control studies and systematic reviews of these studies. Relevant outcomes are test validity, other test performance measures, change in disease status, and morbid events. The available evidence from cohort and case-control studies indicates that many of the individual risk factors included in CVD risk panels are associated with an increased risk of CVD. However, it is not clear how the results of individual risk factors impact management changes, so it is also uncertain how the panels will impact management decisions. Given the lack of evidence for the clinical utility of any individual risk factor beyond simple lipid measures, it is unlikely that the use of CVD risk panels improves outcomes. Studies that have evaluated the clinical validity of panels of multiple markers have not assessed management changes that would occur as a result of testing or demonstrated improvements in outcomes. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Group IIA Secretory Phospholipase A_2 ($sPLA_2$-IIA) and Cardiovascular Risk
Holmes et al (2013) investigated the role of secretory phospholipase A_2 ($sPLA_2$)-IIA in cardiovascular disease through a Mendelian randomization meta-analysis.[12] Nineteen general population studies (8,021 incident, 7,513 prevalent major vascular events [MVE] in 74,683 individuals) and 10 acute coronary syndrome (ACS) cohorts (2,520 recurrent MVE in 18,355 individuals) were reviewed using rs11573156, a variant in *PLA2G2A* encoding the sPLA2-IIA isoenzyme, as an instrumental variable. Higher circulating levels of $sPLA_2$-IIA mass or sPLA2

enzyme activity had been associated with increased risk of cardiovascular events. However, a causal association was not clear. There was an announcement made during the writing of the article that a phase III clinical trial of an $sPLA_2$ inhibitor (varespladib) had been stopped prematurely for lack of efficacy. The authors concluded that reduction of $sPLA_2$-IIA is unlikely to be a useful therapeutic target for prevention of cardiovascular events.

As a follow-up to the Holmes article, Talmud and Holmes (2015) discussed the efficacy of Mendelian randomization in validation of potential therapeutic targets before embarking on costly phase III trials.[13] The clinical trial referenced in Holmes et al was further discussed. VISTA-16 tested whether inhibition of $sPLA_2$-IIA by varespladib reduced CHD and acute coronary syndrome. At the interim analysis, the independent data and safety monitoring board reviewed submitted data and the evidence showed the drug had no effect in comparison to placebo. The trial was terminated and further assessments of varespladib for CHD prevention were abandoned. The authors concluded that despite strong biological plausibility and compelling evidence from multiple observational studies, Mendelian randomization studies failed to show evidence of causation, which was borne out in the RCT.

In 2015, Akinkuolie et al performed an analysis of the JUPITER Trial (NCT00239681).[14] The review's aim was to assess the role of $sPLA_2$-IIA in managing CVD risk in a primary prevention setting, and to assess future CVD risk relative to statin therapy. Participants with LDL cholesterol <130 mg/dL and hsCRP≥2 mg/L were randomized to rosuvastatin 20mg/day vs placebo. $sPLA_2$-IIA was quantified by sandwich-type ELISA (Cayman) in 11,269 participants before and 1 year after randomization. Cox regression was used to examine the association of $sPLA_2$-IIA with CVD. The impact of lifelong reduction in $sPLA_2$-IIA on CVD risk was assessed by Mendelian randomization analysis in 6,692 participants. The analysis concluded that while $sPLA_2$-IIA may be a measurable biomarker to assess the prognostic impact of inflammation on baseline and residual CVD risk, the results do not support $sPLA_2$-IIA as a viable pharmacological target for reducing CVD risk.

Braamscamp et al (2013) reported on a study of 187 children with familial hypercholesterolemia (FH), aged 8 to 18 years, randomized to pravastatin or placebo. At baseline, median [IQR] sPLA2-IIA mass and $sPLA_2$ activity levels were 7.2 [5.8–13.2] ng/ml and 36.4 [29.8–47.1] U/ml, respectively. Both $sPLA_2$-IIA mass and sPLA2 activity were significantly correlated with high-sensitivity C-reactive protein (r=0.33, p<.001 and r=0.386, p<.001, respectively), but not with other cardiovascular risk factors. Baseline levels of $sPLA_2$-IIA mass and $sPLA_2$ activity were not significantly associated with carotid intima-media thickness (cIMT) at baseline or at the end of follow-up. After two years, $sPLA_2$-IIA mass and $sPLA_2$ activity levels were not significantly reduced in the pravastatin group (p=.20 and p=.63, respectively), nor in the placebo group (p=.17 and p=.11, respectively). Changes from baseline did not differ between the treatment groups for $sPLA_2$-IIA mass (p=.48) and $sPLA_2$ activity (p=.88). The authors concluded that $sPLA_2$-IIA mass and $sPLA_2$ activity were not significantly associated with cIMT in our pediatric FH cohort. This could indicate that the potential predictive role of $sPLA_2$ as a biomarker of cardiovascular disease in children with FH is limited. Treatment with pravastatin did not reduce $sPLA_2$-IIA mass or $sPLA_2$ activity levels, as compared to placebo.[15] Further studies with larger samples are required to address these issues.

SUMMARY

Studies using sPLA$_2$-IIA reduction as a therapeutic target for prevention of cardiovascular events have not shown efficacy and have resulted in early termination. There is insufficient evidence of a causal relationship between sPLA$_2$-IIA and cardiovascular disease.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION

American College of Cardiology and American Heart Association

In 2019, the American College of Cardiology and American Heart Association published joint guidelines on the assessment of cardiovascular risk in asymptomatic patients.[8] Lp-PLA$_2$ testing was not mentioned in these guidelines, which was a change from 2010 guidelines.[9] In the prior guideline, Lp-PLA$_2$ was given a lib 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 (2012) published guidelines on the management of dyslipidemia and prevention of atherosclerosis.[10,11,] These guidelines made the following recommendations for LpA-PLA$_2$ testing. (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.	B	1
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 American College of Endocrinology (2017) recommended the measurement of Lp-PLA$_2$ as an additional indication of cardiovascular risk.[10] 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 risk of atherosclerotic cardiovascular disease that is provided by high-sensitivity CRP.

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.

ONGOING AND UNPUBLISHED CLINICAL TRIALS
A search of ClinicalTrials.gov did not identify any ongoing or unpublished trials that would likely influence this review.

Government Regulations
National:
There is no national coverage determination (NCD).

Local:
Wisconsin Physicians Service Insurance Corporation
Local Coverage Determination (LCD): MolDX: Biomarkers in Cardiovascular Risk Assessment (L36523)
Original effective date 6/16/2016; Revision effective date 03/21/2024
[NOTE: due to the length of the LCD, only portions related to this policy are included]

Coverage Indications, Limitations, and/or Medical Necessity
This policy denies coverage for **all CV risk assessment panels**, except the basic lipid panel, for symptomatic (with signs and symptoms) patients with suspected or documented CV disease because panel testing is not specific to a given patient's lipid abnormality or disease. The policy indicates the medical indication(s) based on published scientific articles and consensus guidelines for individual lipid biomarkers that may be covered to characterize a given lipid abnormality or disease, to determine a treatment plan or to assist with intensification of therapy. Each individual lipid biomarkers must be specifically ordered and the reason for the test order documented in the patient's medical record. The policy denies coverage for all **non-lipid** biomarkers when used for CV risk assessment including but not limited to, biochemical, immunologic, hematologic, and genetic biomarkers for CV risk assessment regardless of whether ordered in a panel or individually.

The following biomarkers, when they are included in a CV risk assessment panel, are non-covered:
- Lipoprotein subclasses;
- LDL particles;
- Intermediate density lipoproteins;
- High density lipoprotein AI9LpAI and AI/AII;
- Lipoprotein(a);
- Apolipoprotein B (Apo B), Apo A-I and Apo E;
- **Lipoprotein-associated phospholipase A2 (Lp-PLA2)**
- BNP
- Cystatin C
- Thrombogenic/hematologic actors
- Interleukin-6 (IL-6), tissue necrosis factor- a (TNF- a) , plasminogen activator inhibitor-1 (PAI-1) and IL-6 promoter polymorphism
- Free fatty acids
- Visfatin, angiotensin-converting enzyme 1 (ACE2) and serum amyloid A
- Microalbumin
- Myeloperoxidase (MPO)

- Homocysteine and methylenetetrahydrofolate reductase (MTHFR) mutation testing
- Uric acid
- Vitamin D
- White blood cell count
- Long-chain omega-3 fatty acids in red blood cell membranes
- Gamma-glutamyltransferase (GGT)
- Genomic profiling including CardiaRisk angiotensin gene
- Leptin, ghrelin, adiponectin and adipokines including retinol binding protein 4 (RBP4) and resistin
- Inflammatory markers including VCAM-1, P-selectin (PSEL) and E-selectin (ESEL)
- Cardiovascular risk panels

Note #1: There is no Medicare benefit for screening CV risk assessment testing for asymptomatic (without signs or symptoms of disease) patients. Screening asymptomatic patients for cardiovascular risk is statutorily excluded by Medicare and will not be addressed in this policy.

Note #2: FDA approval/clearance means that a test/assay has analytical and clinical validity. The FDA does not review clinical utility (that the test/assay demonstrates improved patient outcomes). To meet Medicare's "reasonable and necessary" criteria for coverage, a test/assay must have proven clinical utility.

Traditional vs Non-traditional CV Risk Assessment
During the last two decades, the interest in CV biomarkers as early screening tools has risen dramatically, largely fueled by the recognition that traditional CV risk factors (diabetes, smoking, hypertension and hyperlipidemia) do not fully explain individual variation in CV risk, and by advances in genetic and molecular research. Risk assessment for determining the 10-year risk for developing coronary heart disease (CHD) is traditionally carried out using the Framingham risk score.

Despite the Framingham risk-scoring tool, clinicians have sought non-traditional lipid and other biomarker measurements to predict CV events. The most promising biomarkers are the ones that closely correlate with the pathophysiological process of the disease. In general, there is evidence that some of these biomarkers may alter risk categorization (higher or lower) compared to traditional risk prediction, but it has not been established that changes in categorization provides clinically actionable information beyond that of traditional lipid measures. In addition, no study has provided high-quality evidence that measurement of non-traditional lipid and other biomarkers leads to changes in management that improve health outcomes.

To provide clinically useful knowledge, a biomarker should meet the following criteria:
- Adds clinical knowledge that improves patient outcomes (criteria for Medicare "reasonable and necessary");
- Provides risk information that is independent of established predictors;
- Is easy to measure and interpret in the clinical setting; and
- Is accurate, reproducible, and standardized.

Lipoprotein-Associated Phospholipase A2 (Lp-PLA2)
Lp-PLA2 is also known as platelet activating factor acetylhydrolase. This enzyme hydrolyzes phospholipids and is primarily associated with LDLs. It has been suggested that this enzyme has a proinflammatory role in the development of atherosclerosis. Studies show that Lp-PLA2 is an independent predictor of CV risk but fail to demonstrate improved health outcomes. To improve outcomes, studies must demonstrate how risk factors improve risk classification and change in physician practice to improve patient outcomes.

The NCEP ATP III panel concluded that routine measurement of inflammatory markers (including Lp-PLA2) for the purpose of modifying LDL-cholesterol goals in primary prevention is not warranted. In the 2010 ACCF/AHA guidelines for assessment of CV risk, the experts concluded "lipoprotein-associated phospholipase (Lp-PLA2) might be reasonable for cardiovascular risk assessment in intermediate risk asymptomatic adults". However, at the current time, it is not known whether Lp-PLA2 concentrations are clinically effective for motivating patients, guiding treatment, or improving outcomes.

Wisconsin Physicians Service Insurance Corporation
Local Coverage Article: Billing and Coding: MolDX: BIOMARKERS in Cardiovascular Risk Assessment (A57559)
Original Effective Date: 11/01/2019
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This article lists code 83698 as a covered code.
(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Cardiovascular Risk Panels
- Genetic Testing – Gene Expression Testing in the Evaluation of Patients with Stable Ischemic Heart Disease Lipoprotein Direct Measurement, Intermediate Density Lipoprotein (Retired)
- Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 1/9/25, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
9/1/07	7/30/07	8/29/07	Joint policy established
9/1/08	7/3/08	7/3/08	Routine maintenance
11/1/09	8/18/09	8/18/09	Routine maintenance: change in name from Measurement of Lipoprotein-associated Phospholipase (Lp-PLA2) to Lipoprotein-associated Phospholipase A2 (Lp-PLA2) in the Assessment of Cardiovascular Risk
11/1/10	8/28/10	8/17/10	Routine maintenance
11/1/11	8/16/11	8/16/11	Routine maintenance
5/1/14	2/24/14	3/3/14	Routine maintenance Policy reformatted to mirror BCBSA
3/1/16	12/10/15	12/10/15	Routine maintenance Added code 0423T
5/1/17	2/21/17	2/21/17	Routine maintenance Removed code 0423T
5/1/18	2/20/18	2/20/18	Routine maintenance
5/1/19	2/19/19		Routine maintenance Combined with “Secretory Type II Phospholipase A2 Testing” policy
5/1/20	2/18/20		Routine maintenance. Ref 41 added.
5/1/21	2/16/21		Routine maintenance
5/1/22	2/15/22		Routine maintenance Code 0423T deleted
5/1/23	2/21/23		Routine maintenance (jf) Vendor Managed: Avalon
5/1/24	2/20/24		Routine maintenance (jf) Vendor Managed: Avalon
5/1/25	2/18/25		Routine maintenance (jf) Vendor Managed: Avalon Minor Edits: o Note added under inclusionary criteria.

			○ Lp(a) measurement should be considered at least once in each adult person's lifetime to identify those with very high inherited Lp(a) levels >180 mg/dL (>430 nmol/L) who may have a lifetime risk of ASCVD equivalent to the risk associated with heterozygous familial hypercholesterolemia.

Next Review Date: 1st Qtr, 2026

BLUE CARE NETWORK BENEFIT COVERAGE POLICY: MEASUREMENT OF LIPOPROTEIN-ASSOCIATED PHOSPHOLIPASE A_2 (LP-PLA_2) AND SECRETORY TYPE II PHOSPHOLIPASE A_2 (sPLA_2-IIA) IN THE ASSESSMENT OF CARDIOVASCULAR RISK

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.