MEDICAL POLICY

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Medical Policy Title	**Inflammatory Markers of Coronary Artery Disease Risk**
Policy Number	**2.02.15**
Current Effective Date	July 17, 2025
Next Review Date	July 2026

Our medical policies are based on the assessment of evidence based, peer-reviewed literature, and professional guidelines. Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract. (Link to Product Disclaimer)

POLICY STATEMENT(S)

I. The use of high sensitivity C-reactive protein (hs-CRP) testing for primary prevention in the clinical setting is considered **medically appropriate** for:

   A. Individuals who are at intermediate risk (10%-20%) of heart disease over the next 10 years by conventional risk scoring (e.g., Framingham Heart Study criteria);

   B. Individuals who are free of non-cardiac conditions that are known to increase CRP (e.g., rheumatoid arthritis, chronic inflammatory processes).

II. All other indications for hs-CRP testing, aside from the indication above, are considered **not medically necessary**.

III. Measurement of other inflammatory markers, including but not limited, to lipoprotein-associated phospholipase A2 (Lp-PLA2) and plasma myeloperoxidase (MPO) in the assessment of cardiovascular risk by any method, is considered **investigational**.

RELATED POLICIES

Corporate Medical Policy

11.01.03 Experimental or Investigational Services

POLICY GUIDELINE(S)

To be eligible for coverage of hs-CRP testing, a patient must be categorized as at a 10 to 20% higher risk (intermediate risk) than the average individual. Determination of increased risk is based on the Framingham Heart Study that identified patients who can be classified as either low, intermediate, or high risk for the cardiovascular events in the next 10 years. The classification is based on factors such as high blood pressure, high blood cholesterol, smoking, obesity, diabetes, and physical inactivity.

DESCRIPTION

High sensitivity C-reactive protein (hs-CRP) is a nonspecific, acute-phase reactant, produced by the liver as a marker of inflammatory processes. Traditionally CRP has been used to monitor inflammatory processes, such as infections or autoimmune diseases. Chronic inflammatory disorders, including autoimmune diseases and malignancies can produce persistent increases in serum CRP concentrations. Studies suggest the association of low-level chronic inflammation during

atherogenesis. The use of technologies collectively known as hs-CRP, including enzyme linked immunoabsorbent assays (ELISA) and other techniques using monoclonal antibodies, has allowed for a greater precision in detecting the lower levels of CRP that are related to chronic inflammation in otherwise healthy individuals. Results from studies indicate a correlation between hs-CRP levels and coronary artery disease. It is theorized that the increased sensitivity of an hs-CRP test should be able to detect that activity as a marker for cardiovascular disease, either current or future.

Lipoprotein-associated phospholipase A_2 (Lp-PLA_2), also known as platelet-activating factor acetylhydrolase, is an enzyme that hydrolyses 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. 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. Large, prospective studies are needed to establish whether measurement of Lp-PLA_2 biomarkers will be more predictive of cardiovascular disease (CVD) than conventional lipid risk factors.

Plasma myeloperoxidase (MPO), an abundant leukocyte enzyme, is elevated in culprit lesions that have fissured or ruptured in patients with sudden death from cardiac causes. Research suggests a mechanistic link between myeloperoxidase and both inflammation and cardiovascular disease risk. It has been proposed that elevated plasma MPO levels may be an independent predictor of endothelial dysfunction, angiographically-evident CAD and cardiac risk. There is a lack of scientific evidence regarding how measurements of MPO would affect management of individuals at risk for or patients with CVD. Large randomized controlled studies are needed to ascertain the clinical value of MPO in the management of CVD.

SUPPORTIVE LITERATURE

Use of hs-CRP in Primary Prevention of Cardiovascular Disease

Several prospective epidemiologic studies have suggested that the measurement of hs-CRP may be an independent risk factor for cardiovascular disease.

Use of hs-CRP in Secondary Prevention of Cardiovascular Disease

Scientific evidence supports the theory that hs-CRP is a strong and independent marker for future heart events in patients who have already been assessed to be at a 10 to 20% greater risk than the average individual. Based on this information, use of the hs-CRP test to further evaluate this group of patients may result in a change in treatment and/or lifestyles that could decrease the risk for future cardiac events.

No clinical trials have been completed in which a population has been randomly allocated to hs-CRP screening compared with a control population group not allocated to hs-CRP screening with both groups followed up prospectively to determine the benefits and harms of the screening.

Duprez et al (2015) studied the association of GlycA and inflammatory biomarkers with future death and disease. A total of 6,523 subjects in the Multi-Ethnic Study of Atherosclerosis who were free of overt cardiovascular disease (CVD) and in generally good health had baseline blood analyzed for

high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6), and d-dimer. A spectral deconvolution algorithm was used to quantify GlycA signal amplitudes from automated NMRLipoProfile test spectra. Median follow-up was 12.1 years. The authors found that relative risk per SD of GlycA, IL-6, and d-dimer for total death (n = 915); for total CVD (n = 922); and for chronic inflammatory-related severe hospitalization and death (ChrIRD) (n = 1324) ranged from 1.05 to1.20, independently of covariates. In contrast, prediction from hsCRP was statistically explained by adjustment for other inflammatory variables. Only GlycA was predictive for total cancer (n = 663). Women had 7% higher values of all inflammatory biomarkers than men and had a significantly lower GlycA prediction coefficient than men in predicting total cancer. The authors concluded that GlycA derived from NMR is associated with risk for total death, CVD, and chronic inflammatory-related severe hospitalization and death, and cancer. This novel biomarker reflecting the risk of death, CVD, ChrIRD, and cancer may have the potential to improve risk assessment.

Luo et al (2022) conducted a meta-analysis that aimed to evaluate the predictive value of baseline CRP level in stable CAD patients. The endpoints of interest included cardiovascular mortality, all-cause mortality, or major adverse cardiovascular events (MACEs). The predictive value of CRP level was estimated by pooling the multivariable adjusted risk ratio with 95% confidence intervals (CI) compared the highest to the lowest CRP level. Twenty-six studies involving of 22,602 patients with stable CAD satisfied the inclusion criteria. In a comparison of the highest with the lowest CRP level, the pooled multivariable adjusted risk ratio was 1.77 (95% CI 1.60–1.96) for MACEs, 1.64 (95% CI 1.13–2.33) for cardiovascular mortality, and 1.62 (95% CI 2.62–5.12) for all-cause mortality, respectively. Subgroup analyses indicated that the values of elevated CRP level in predicting MACEs were consistently observed in each subgroup. Authors concluded, elevated baseline CRP level was an independent predictor of MACEs, cardiovascular mortality, and all-cause mortality in patients with stable CAD. Baseline CRP level can provide important predictive information in stable CAD patients.

Tajani et al (2024) performed a systematic review and meta-analysis to evaluate the relationship between the concentration of c-reactive protein (CRP) and the incidence and progression of CAC. Out of the 2545 records, 42 cross-sectional and 9 cohort studies were included in the systematic review. The meta-analysis on 12 eligible cross-sectional studies revealed no significant association between CAC and CRP [pooled odd ratios (OR): 1.03 (1.00, 1.06)]. Additionally, an insignificant association was found between CAC and CRP through meta-analysis on three eligible cohort studies [pooled OR: 1.05 (0.95, 1.15)] with no considerable heterogeneity across studies. Sensitivity analyses indicated that the meta-analysis models were robust. There was no evidence of publication bias. Based on the meta-analysis fndings, elevated levels of CRP did not emerge as a valuable prognostic maker for CAC incidence and progression prediction.

Lipoprotein-associated Phospholipase A_2 (Lp-PLA_2) as an Independent Biomarker

Current studies generally report the utility of Lp-PLA2 as an independent biomarker for coronary artery disease and recurrent cardiac events. However, Lp-PLA2 was not found to be an independent marker for subclinical atherosclerosis, and a study of the Atherosclerosis Risk in Communities (ARIC) cohort found that routine measurement of Lp-PLA2 did not improve existing risk stratification models that use traditional risk factors. Interventional studies involving Lp-PLA2 suggest that the level of Lp-PLA2 is modifiable by antihyperlipidemics. An ad hoc study of the Pravastatin or Atorvastatin

Evaluation and Infection Therapy: Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) trial concluded that the 30-day Lp-PLA2 level was independently associated with an increased risk of cardiovascular events. Another ad hoc study from the Diabetes and Combined Lipid Therapy Regimen (DIACOR) trial demonstrated improved Lp-PLA2 levels compared to baseline, with no difference found between treatment groups among 300 patients with diabetes and mixed dyslipidemias randomized to either fenofibrate, simvastatin, or both for 12 weeks.

Results of two large-scale observational studies have suggested that Lp-PLA_2 is an independent risk factor for coronary heart disease in men. However, the key outcome of cardiac risk assessment is an improvement in health outcomes. Improved risk prediction does not by itself result in improved health outcomes. To improve outcomes, clinicians must have the tools to translate this information into clinical practice. This requires guidelines that incorporate emerging risk factors into existing risk prediction models and have been demonstrated to classify patients into risk categories with greater accuracy. Predictive models also need to be accompanied by treatment guidelines that target intervention toward patients who will get the most benefit. At present, measurements of Lp-PLA_2 are not a component of the guidelines developed by the National Cholesterol Education Program Adult Treatment Panel III.

Zhang et al (2021) performed a prospective study to investigate the association between cardiovascular disease and Lp-PLA2. A total of 823 individuals at a high risk of stroke were screened and followed at three (3), six (6), 12, and 24 months. Among the 823 participants, 286 had varying degrees of carotid artery stenosis and 18 participants had cerebrovascular events. The level of Lp-PLA2 was higher in the group with cerebrovascular events than in the group without cerebrovascular events (662.81 ±111.25 vs 559.86 ±130.05, $p < 0.001$). No statistical difference was found between the other parameters of the event group, such as HDL, LDL, and the no event group. The incidence of cerebrovascular events in the stenosis group was higher than that in the no stenosis group but no statistically significant difference was noted. The authors concluded that the level of Lp-PLA2 was positively correlated with the degree of carotid artery stenosis and predicted cerebrovascular events. The study limitations included sample size; the study follow-up time was only two (2) years, and the number of cerebrovascular events that eventually occurred was relatively small. Also of note, the study was conducted at a single center and the study population mainly included people aged > 40 years at a high risk of stroke, so the results of the study only represented a small part of the population. Furthermore, the study did not address how integrating measurements of Lp-PLA2 to clinical care alters patient management and improves clinical outcomes.

While studies have suggested that statin drugs and fibrates may reduce levels of Lp-PLA_2, it is not known whether such drug therapy in patients not already considered candidates, based on other well established risk factors would ultimately decrease the incidence of coronary heart disease. Although results of studies of Lp-PLA_2 test are promising, its biological role is not yet understood, its ability to improve on existing risk stratification methods is uncertain, and its clinical utility remains in question, particularly when compared to currently available methods for cardiovascular risk reduction. The extent to which antihyperlipidemics modify the level of Lp-PLA_2 beyond their established therapeutic use, and thereby altering cardiac outcomes, is unknown.

Risk Prediction for Stroke

While some studies have shown that levels of both Lp-PLA_2 and C-reactive protein were higher in stroke cases, improved risk prediction does not necessarily result in improved outcomes. Results of studies have not been incorporated into clinical management.

Several studies have assessed the value of MPO as a predictor of the risk of cardiovascular events in patients presenting with chest pain or acute coronary syndrome and chronic heart failure. MPO levels have also been evaluated as an inflammatory marker of future coronary artery disease (CAD) in apparently healthy individuals (Meuwesem, et al 2007). Although studies of MPO testing indicate a possible relationship between elevated levels and cardiac risk, its ability to improve on existing risk stratification methods is unclear. (Roman, et al, 2008; Stefanescu, et al, 2008). Furthermore, in the studies evaluating MPO various methods of testing were used, making comparisons difficult. The body of evidence evaluating MPO as a potential cardiac biomarker is insufficient to support an increased predicative value as compared to traditional testing or for recommending medical management based on MPO values that would improve clinical outcomes.

Liao et al (2025) conducted a systematic review and meta-analysis that aimed to assess the relationship between circulating factors and cognitive impairment associated with cerebral small vessel disease, especially the possibility of becoming the potential biomarkers for diagnosis. Articles published before November 2023 were searched in four databases, PubMed, Web of Science, Embase, and Cochrane Library, to identify all relevant studies reporting circulating markers in patients with cerebral small vessel disease (CSVD). Twenty-nine articles were finalized for this study. Two or more articles were meta-analyzed that were jointly considered to be circulating biomarkers of CSVD-CI and summarized a total of 4 possible biomarkers: homocysteine (Hcy), high-sensitivity C-reactive protein (hs-CRP), lipoprotein-associated phospholipase A2 (Lp-PLA2), and neurofilament protein light chain (NfL). The results revealed that patients in the CSVD-related cognitive impairment group had significantly higher levels of Hcy and hs-CRP than those in the CSVD-without cognitive impairment group, whereas there was no statistically significant difference in Lp-PLA2 and NfL between the two groups. Therefore, Hcy, hs-CRP may be considered circulating markers of cognitive impairment associated with cerebral small vessel disease.

PROFESSIONAL GUIDELINE(S)

The American Heart Association (AHA) and Centers for Disease Control and Prevention (CDC) has issued the following recommendation regarding the role of hs-CRP measurements in clinical practice (2020): it is reasonable to measure hs-CRP as an adjunct to the major risk factors to further assess absolute risk for coronary disease primary prevention. At the discretion of the physician, the measurement is considered optional, based on the moderate level of evidence (Evidence Level C). In this role, hs-CRP measurement appears to be best employed to detect enhanced absolute risk in persons in whom multiple risk factor scoring projects a 10-year CHD risk in the range of 10% to 20% (Evidence Level B). However, the benefits of this strategy or any treatment based on this strategy remain uncertain. Individuals at low risk (10% per 10 years) will be unlikely to have a high risk (20%) identified through hs-CRP testing. Individuals at high risk (20% risk over 10 years) or with established atherosclerotic disease generally should be treated intensively regardless of their hs-CRP

levels, so the utility of hs-CRP in secondary prevention appears to be more limited. In patients with stable coronary disease or acute coronary syndromes, hs-CRP measurement may be useful as an independent marker for assessing likelihood of recurrent events, including death, myocardial infarction, or restenosis after percutaneous coronary intervention. However, secondary preventive interventions with proven efficacy should not be dependent on hs-CRP levels. Further, serial testing of hs-CRP should not be used to monitor the effects of treatment.

REGULATORY STATUS

The United States Food and Drug Administration (FDA) provides oversight of laboratory developed tests, now considered medical devices under the Federal Food, Drug, and Cosmetic Act. Refer to the FDA Medical Device website. Available from: https://www.fda.gov/medical-devices [accessed 2025 Jun 20]

Several of the hs-CRP tests have received 510(k) marketing clearance from the U.S. Food and Drug Administration (FDA). In 2003, the FDA cleared for marketing an enzyme linked immunoabsorbent (ELISA) test, the PLAC test (diaDexus, San Francisco, CA) to measure levels of Lp-PLA2.

CODE(S)

- Codes may not be covered under all circumstances.
- Code list may not be all inclusive (AMA and CMS code updates may occur more frequently than policy updates).
- (E/I)=Experimental/Investigational
- (NMN)=Not medically necessary/appropriate

CPT Codes

Code	Description
83698 (E/I)	Lipoprotein-associated phospholipase A2, (Lp-PLA_2)
83876 (E/I)	Myeloperoxidase (MPO)
86141	C-reactive protein, high sensitivity, (hsCRP)
0052U (E/I)	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 (VAP Cholesterol Test, VAP Diagnostics Laboratory, Inc)
0377U (E/I)	Cardiovascular disease, quantification of advanced serum or plasma lipoprotein profile, by nuclear magnetic resonance (NMR) spectrometry with report of a lipoprotein profile (including 23 variables) (Liposcale, CIMA Sciences, LLC)

Code	Description
0415U (E/I)	Cardiovascular disease (acute coronary syndrome [ACS]), IL-16, FAS, FASLigand, HGF, CTACK, EOTAXIN, and MCP-3 by immunoassay combined with age, sex, family history, and personal history of diabetes, blood, algorithm reported as a 5-year (deleted risk) score for ACS (SmartHealth Vascular Dx, Morningstar Laboratories, LLC, SmartHealth DX)
0466U (E/I)	Cardiology (coronary artery disease [CAD]), DNA, genome-wide association studies (564856 single-nucleotide polymorphisms [SNPs], targeted variant genotyping), patient lifestyle and clinical data, buccal swab, algorithm reported as polygenic risk to acquired heart disease (CardioRisk+, Gene by Gene, ltd, Open DNA, ltd)

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HCPCS Codes

Code	Description
Not Applicable	

ICD10 Codes

Code	Description
E71.30	Disorder of fatty-acid metabolism, unspecified
E75.21	Fabry (-Anderson) disease
E75.22	Gaucher disease
E75.240-E75.249	Niemann-Pick disease (code range)
E75.3	Sphingolipidosis, unspecified
E75.5	Other lipid storage disorders
E75.6	Lipid storage disorder, unspecified
E77.0-E77.9	Disorders of glycoprotein metabolism (code range)
E78.0-E78.9	Disorders of lipoprotein metabolism and other lipidemias (code range)
E88.1	Lipodystrophy, not elsewhere classified
E88.2	Lipomatosis, not elsewhere classified
E88.89	Other specified metabolic disorders
I20.0-I20.9	Angina pectoris (code range)

Code	Description
I21.01-I22.1	ST elevation (STEMI) myocardial infarction of anterior or inferior wall (code range)
I24.1	Dressler's syndrome
I25.110-I25.119	Atherosclerotic heart disease of native coronary artery with angina pectoris (code range)
I25.2	Old myocardial infarction
I25.700-I25.799	Atherosclerosis of coronary artery bypass graft(s) and coronary artery of transplanted heart with angina pectoris (code range)
I70.0	Atherosclerosis of aorta
I70.1	Atherosclerosis of renal artery
Z82.41	Family history of sudden cardiac death
Z82.49	Family history of ischemic heart disease and other diseases of the circulatory system
Z86.711	Personal history of pulmonary embolism
Z86.718	Personal history of other venous thrombosis and embolism
Z86.72	Personal history of thrombophlebitis
Z86.73	Personal history of transient ischemic attack (TIA), and cerebral infarction without residual deficits
Z86.74	Personal history of sudden cardiac arrest
Z86.79	Personal history of other diseases of the circulatory system

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SEARCH TERMS

Not Applicable

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Based upon our review, High Sensitivity C-Reactive Protein Testing (hsCRP) and Lipid Testing is not addressed in National or Regional Medicare coverage determinations or policies.

However, please refer to the Medicare Managed Care Manual/Chapter 4: Benefits and Beneficiary Protections (Rev.121, Issued: 04-22-16)/Section 90 National and Local Coverage Determinations/Subsection 90.4.1 MAC with Exclusive Jurisdiction over a Medicare Item or Service: 100-16 | CMS [accessed 2025 June 20]

In some instances, one Medicare A/B MAC processes all of the claims for a particular Medicare-covered item or service for all Medicare beneficiaries around the country. This generally occurs when there is only one provider of a particular item or service (for example, certain pathology and lab tests furnished by independent laboratories). In this situation, MA plans must follow the coverage policy reflected in an LCD issued by the A/B MAC that enrolled the provider and processes all the Medicare claims for that item or service.

PRODUCT DISCLAIMER

- Services are contract dependent; if a product does not cover a service, medical policy criteria do not apply.

- If a commercial product (including an Essential Plan or Child Health Plus product) covers a specific service, medical policy criteria apply to the benefit.
- If a Medicaid product covers a specific service, and there are no New York State Medicaid guidelines (eMedNY) criteria, medical policy criteria apply to the benefit.
- If a Medicare product (including Medicare HMO-Dual Special Needs Program (DSNP) product) covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.
- If a Medicare HMO-Dual Special Needs Program (DSNP) product DOES NOT cover a specific service, please refer to the Medicaid Product coverage line.

POLICY HISTORY/REVISION	
Committee Approval Dates	
12/18/02, 05/21/03, 05/19/04, 03/17/05, 01/19/06, 11/16/06, 09/20/07, 09/18/08, 02/19/09, 03/18/10, 04/21/11, 04/19/12, 04/18/13, 04/17/14, 04/16/15, 06/16/16, 07/20/17, 06/21/18, 06/20/19, 06/18/20, 06/17/21, 06/16/22, 07/20/23, 07/18/24, 07/17/25	
Date	**Summary of Changes**
07/17/25	• Annual review, policy intent unchanged.
01/01/25	• Summary of changes tracking implemented.
12/18/02	• Original effective date