MEDICAL POLICY

MEDICAL POLICY DETAILS	
Medical Policy Title	**Inflammatory Markers of Coronary Artery Disease Risk**
Policy Number	**2.02.15**
Category	**Technology Assessment**
Original Effective Date	**12/18/02**
Committee Approval Date	**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, 7/20/17, 06/21/18, 06/20/19, 6/18/20, 6/17/21, 06/16/22, 07/20/23**
Current Effective Date	**07/20/23**
Archived Date	**NA**
Archive Review Date	**NA**
Product Disclaimer	• *If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.* • *If a commercial product (including an Essential Plan or Child Health Plus product), 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 STATEMENT

I. Based upon our criteria and assessment of the peer-reviewed literature, including the January 2003 recommendation put forth by the American Heart Association and Centers for Disease Control and Prevention, the use *of high sensitivity C-reactive protein (hs-CRP) testing* for primary prevention in the clinical setting is considered **medically appropriate** for those 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) and who are free of non-cardiac conditions that are known to increase CRP (e.g., rheumatoid arthritis, chronic inflammatory processes).

II. Based upon our criteria and assessment of the peer-reviewed literature, all other indications for *hs-CRP testing*, aside from the indication above, are considered **not medically necessary**.

III. Based upon our criteria and assessment of the peer-reviewed literature, measurement of other inflammatory markers including but not limited to lipoprotein-associated phospholipase A_2 (Lp-PLA_2) and plasma myeloperoxidase (MPO) in the assessment of cardiovascular risk by any method has not been proven to improve health outcomes and, therefore, is considered **investigational**.

Refer to Corporate Medical Policy #11.01.03 Experimental or Investigational Services

POLICY GUIDELINES

I. 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.

II. 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-PLA_2.

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.

RATIONALE

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.

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.

Ridker PM, et al. (2003) conducted the Jupiter Trial, a randomized double-blind, placebo controlled, multicenter study that investigated whether treatment with rosuvastatin, 20 mg daily, as compared with placebo, would decrease the rate of first major cardiovascular events for healthy men and women with elevated high-sensitivity C-reactive protein levels, a calculated Framingham risk score of 10% or less, or an LDL cholesterol level of 100 mg per deciliter (2.6 mmol per liter) or lower. The observed relative reductions in the hazard ratio associated with rosuvastatin for the primary end-point were similar to those in higher-risk groups. For subjects with elevated high-sensitivity C-reactive protein levels but no other major risk factor other than increased age, the benefit of rosuvastatin was similar to that for higher-risk subjects (hazard ratio, 0.63; 95% CI, 0.44 to 0.92; P=0.01). Consequently, those individuals who are considered to be at low- to intermediate-risk (0 to 20%) of heart disease but who have an elevated hs-CRP measurement may also benefit from statin therapy. While this study shows the benefits of statin therapy, it does not address the clinical value of hs-CRP testing for individuals with low cardiovascular risk. The study was prematurely terminated before the long-term safety and efficacy of the drug therapy could be established. In addition, those patients treated with rosuvastatin demonstrated significantly higher glycated hemoglobin levels and incidence of diabetes. Additional long-term studies are needed to determine the role of hs-CRP testing in clinical management of individual with low cardiovascular risk.

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 Thrapy: 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.

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 (Brennan, 2003) 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. Results of studies have not been incorporated into clinical management.

CODES

- *Eligibility for reimbursement is based upon the benefits set forth in the member's subscriber contract.*
- *CODES MAY NOT BE COVERED UNDER ALL CIRCUMSTANCES. PLEASE READ THE POLICY AND GUIDELINES STATEMENTS CAREFULLY.*
- *Codes may not be all inclusive as the AMA and CMS code updates may occur more frequently than policy updates.*
- *Code Key: Experimental/Investigational = (E/I), Not medically necessary/ appropriate = (NMN).*

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) (*Effective 04/01/23*)
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 *(Effective 10/01/23)*

HCPCS Codes

Code	Description
No specific code(s)	

ICD10 Codes

Code	Description
E71.30	Disorder of fatty-acid metabolism, unspecified

Code	Description
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)
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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*Key Article

KEY WORDS

Cardiac disease risk, CRP, hs-CRP, Lp-PLA2, PLAC test, plasma myeloperoxidase (MPO).

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

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:

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.

[https://www.cms.gov/Regulations-and-Guidance/Guidance/Manuals/Internet-Only-Manuals-IOMs-Items/CMS019326] accessed 08/04/23.