MEDICAL POLICY

Excellus

SUBJECT: INFLAMMATORY MARKERS OF CORONARY ARTERY DISEASE RISK	EFFECTIVE DATE: 12/18/02 REVISED 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
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- ***If the member's subscriber contract excludes coverage for a specific service it is not covered under that contract. In such cases, medical policy criteria are not applied.***
- ***Medical policies apply to commercial and Medicaid products only when a contract benefit for the specific service exists.***
- ***Medical policies only apply to Medicare products when a contract benefit exists and where there are no National or Local Medicare coverage decisions for the specific service.***

POLICY STATEMENT:

I. Based on our 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)* for primary prevention in the clinical setting is considered **medically necessary** for those individuals who are at intermediate risk (10% - 20%) of heart disease over the next ten years by conventional risk scoring (e.g., Framingham Heart Study criteria). Individuals must be free of non-cardiac conditions that are known to increase CRP (e.g., rheumatoid arthritis, chronic inflammatory processes).

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

Refer to Corporate Medical Policy #2.02.29 Cardiovascular Disease Risk Assessment - Laboratory Evaluation of Lipids.

Refer to Corporate Medical Policy #11.01.03 regarding Experimental or Investigational Services.

POLICY GUIDELINES:

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

II. The Federal Employees Health Benefit Program (FEHBP/FEP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

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 high-sensitivity CRP (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 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 high-sensitivity CRP (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.

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.

RATIONALE:

Several of the high-sensitivity C-reactive protein 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.

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:
Currently no clinical studies have evaluated how knowledge of hs-CRP levels should influence current management strategies, such as diet, weight control, or cholesterol-lowering therapies in patients with cardiovascular disease and whether such management changes would reduce the subsequent incidence of future cardiovascular events.

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 10 - 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 and both groups followed up prospectively to determine the benefits and harms of the screening.

Recommendation of AHA/CDC (American Heart Association/Centers for Disease Control) regarding the role of hs-CRP measurements in clinical practice (2003): The strongest recommendation by the CHD/AHA suggests that the results of hs-CRP may help identify patients at intermediate risk (10%-20% risk of CHD per 10 years) who may benefit from primary prevention of CVD. It is estimated that some 30%-40% of the population may fall into this intermediate risk group. If the results of the hs-CRP measurement are considered high, patients may then be offered various interventions, frequently including the initiation of statin therapy. Therefore, the use of hs-CRP as one component of a risk assessment tool may ultimately result in considerably more patients being placed on lifelong drug therapy.

Ridker PM, et al. conducted a randomized double-blind, placebo controlled, multicenter study (the Jupiter Trial) which 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 low to

intermediate risk (0–20%) of heart disease but with an elevated hs-CRP measurement may also benefit from statin therapy. While this study shows 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. Further 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). 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 ARIC (Atherosclerosis Risk in Communities) 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 PROVE IT-TIMI 22 (PRavastatin Or atorVastatin Evaluation and Infection Therapy - Thombolysis In Myocardial Infarction) 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 DIACOR (Diabetes and Combined Lipid Therapy Regimen) 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. To do this requires guidelines that incorporate emerging risk factors into existing risk prediction models and that 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 therefore alter 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.

Currently, PrognostiX Inc. (Cleveland Clinic, Cleveland, Ohio), is the only company to have an FDA approved ELISA test kit for plasma MPO concentration. The product is known as CardioMPO and is intended for use in conjunction with clinical history, ECG and cardiac biomarkers to evaluate patients that present with chest pain. It operates using the sandwich ELISA method.

Several studies have assessed the value of plasma myeloperoxidase (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: Number Description

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:	83698 **(E/I)**	Lipoprotein-associated phospholipase A_2, (Lp-PLA_2)
	83876 **(E/I)**	Myeloperoxidase (MPO)
	86141	High sensitivity, C-reactive protein (hs-CRP)

HCPCS:	No specific code(s)	
ICD9:	272	Disorders of lipid metabolism (code range)
	410-414	Ischemic heart disease (code range)
	440	Atherosclerosis (code range)
	V12.5	Personal history of disease of the circulatory system
	V17.3-17.4	Family history of ischemic heart disease or other cardiovascular disease
ICD10:	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-E88.2	Lipodystrophy or Lipomatosis, not elsewhere classified (code range)
	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 (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 WORDS:

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

CMS COVERAGE FOR MEDICARE PRODUCT MEMBERS

There is currently no National (NCD) or Local Coverage Determination (LCD) for High Sensitivity C-Reactive Protein Testing (hsCRP) and Lipid Testing.