Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 5/1/24**
(See policy history boxes for previous effective dates)

Title: Myeloperoxidase (MPO) Immunoassay for Cardiac Disease Risk

Description/Background

Acute coronary syndrome (ACS) is a broad term that describes a collection of symptoms associated with myocardial ischemia, which can range from acute myocardial infarction to unstable angina.

Evaluation of a patient with chest pain for possible ACS in the emergency department includes obtaining a history, a physical examination, ECG monitoring, and laboratory values which include cardiac biomarker levels of troponins and imaging studies. Additional cardiac biomarkers that provide prognostic data may include B-type natriuretic peptide (BNP) and C-reactive protein.

Diagnosis of ACS relies heavily on biomarkers that become elevated following heart muscle necrosis. For this reason, intense research continues into the development and clinical investigation of sensitive biomarkers that do not depend on the presence of irreversible myocardial damage.

Myeloperoxidase (MPO) is an enzyme found in white blood cells. There is some evidence that suggests there are mechanistic links between myeloperoxidase and both inflammation and cardiovascular disease. It has been proposed that MPO could predict early risk for myocardial infarction and could also predict the risk for other major adverse cardiac events in individuals with chest pain in the following 30-day and 6-month periods.

Regulatory Status

The U.S. Food and Drug Administration (FDA) has approved several myeloperoxidase immunoassay systems. Examples of such assays include the PrognostiX CardioMPO™

Enzyme Immunoassay (received FDA 510(k) clearance in 2005; updated 2008) and the Dimension MPO Flex® reagent cartridge (received FDA 510(k) clearance in 2008).

Medical Policy Statement

Myeloperoxidase (MPO) immunoassay to assess cardiac disease risk is experimental/ investigational. The clinical utility of myeloperoxidase (MPO) immunoassay to assess cardiac disease risk has not been demonstrated. The peer reviewed medical literature has not shown that a MPO level has sufficient diagnostic accuracy to provide clinically relevant information when compared to other available diagnostic studies.

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.):

83876

Rationale

Khan et al (2020) discuss the several types of tissue injuries and the pathogenesis of several other major chronic diseases such as rheumatoid arthritis, cardiovascular diseases, liver diseases, diabetes, and cancer that have been reported to be linked with Myeloperoxidase (MPO)-derived oxidants. Although myeloperoxidase assays have been extensively reported in the literature, a consensus for the standard assay has not been established. MPO substrates are the same as substrates for general peroxidase. In addition to this myoglobin and hemoglobin also show some peroxidase activity which interferes with the results. Within the studies, no comparisons have been made between the different myeloperoxidase assays, thus standardization and validation are needed to confirm the results. Flow cytometry, immunohistochemistry, or cytochemical staining may detect myeloperoxidase. A commercially available enzyme-linked immunosorbent assay (ELISA) kit is the most common method of MPO measurement. Oxygen and nitrogen production are involved in the MPO antibacterial activities. Myeloperoxidase also plays a role in the chemical modifications of different lipoproteins, protein nitrosylation, tyrosyl radical formation, and dityrosine crosslinking, etc. Myeloperoxidase has gained attention as a biomarker due to its potential role in a number of inflammatory diseases. Authors concluded that future research is needed with standardized MPO assays in order to understand the reference range of MPO in specified diseases.

Khine et al (2017) conducted a study examining the association between serum myeloperoxidase (MPO)/high-density lipoprotein (HDL) particle ratio and incident cardiovascular events in a multi-ethnic population. Levels of MPO, HDL-C, and HDL particle concentration (HDLp) by NMR were measured at baseline in 2924 adults free of cardiovascular disease. The associations of MPO/HDLp with incident atherosclerotic cardiovascular disease (ASCVD) (first non-fatal myocardial infarction, non-fatal stroke, coronary revascularization, or cardiovascular disease [CVD] death) and total CVD were assessed in Cox proportional-hazards models adjusted for traditional risk factors. The median follow-up period was 9.4 years. Adjusted for sex and race/ethnicity, MPO/HDLp was associated directly with body mass index, smoking status, high-sensitivity C-reactive protein, and interleukin 18, and inversely with age, HDL-C levels, HDL size, and PON1 arylesterase activity, but not with cholesterol efflux. In fully adjusted models, the highest versus lowest quartile of MPO/HDLp was associated with a 74% increase in incident ASCVD (aHR, 1.74, 95% CI 1.12-2.70) and a 91% increase in total incident CVD (aHR, 1.91, 95% CI 1.27-2.85). The study found Increased MPO indexed to HDL particle concentration (MPO/HDLp) at baseline was associated with increased risk of incident CVD events in a population initially free of CVD over the 9.4-year study period.

Ma et al (2016) compared the values between MPO and hs-CRP for predicting major adverse cardiovascular events (MACEs) in patients with coronary heart disease (CHD). Two hundred and 1 patients with acute coronary syndrome (ACS) and 210 controls (without ACS) participated in the study. Variables of MPO, hs-CRP, metabolic parameters, anthropometrics and lifestyle habits were collected and analyzed. Incidences of MACEs were investigated during a 4-year follow-up period in 285 CHD patients. The study found patients with ACS had significantly higher concentrations of MPO and hs-CRP than patients with non-ACS. Compared to hs-CRP, MPO had more correlations strongly with ACS-related risk factors of TG, HDL-C and LDL-C in ACS patients. Prospective study demonstrated that the incidences of MACEs associated significantly with elevated MPO baseline concentration and high hs-CRP baseline concentration. These findings suggest that MPO may have some advantages over hs-CRP for predicting MACEs. Additionally, elevated baseline MPO and hs-CRP concentrations appear to be significantly associated with MACEs in CHD patients. Despite the research findings, this study is limited by being a single site study with a short follow-up and MACEs too small to perform multivariate analysis.

Kacprzak et al (2016) reported on a study evaluating whether elevated MPO is a predictor of long-term adverse cardiac events in patients with ST-segment elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention (pPCI). Data for 127 patients with STEMI was evaluated. Plasma levels of MPO collected on admission and the 3rd-4th day of hospitalization were measured by ELISA method. C-reactive protein (CRP) and N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) were also determined. All patients were followed-up prospectively for the occurrence of major adverse cardiovascular events (MACE) defined as unscheduled coronary revascularization procedure, stroke, reinfarction or all-cause death. After 14 months follow-up, 20 % of the patients developed MACE. The authors reported, elevated MPO levels collected on days 3 and 4 of STEMI were the predictor of death, reinfarction, need for coronary revascularization and all adverse events together. In multivariate analysis, MPO and CRP levels assessed on the 3^{rd}-4^{th} day of hospitalization revealed to be significant predictors of MACE. MPO demonstrated to be significantly better predictor of MACE than NT-proBNP level.

Baseri et al (2013) evaluated the association between the plasma MPO levels and angiographic severity of coronary artery disease (CAD) in patients with the stable CAD. Sixty-eight patients who had documented CAD with angiography and 66 subjects who had normal angiography were selected as case and the control groups for this study, respectively. Gensini scoring system was used for evaluation of severity of coronary artery stenosis. Plasma MPO and C-reactive protein (CRP) levels of both case and control groups were determined. Plasma MPO levels and CRP levels were significantly higher in CAD patients ($P < 0.001$), and plasma levels of MPO and CRP were correlated with Gensini scores. The authors concluded that the plasma MPO levels increase in patients with stable CAD, and it can be used as a diagnostic factor to predict the coronary artery atherosclerosis severity in stable CAD patients. However, the authors added that "it needs further widespread investigations to achieve an accurate cut point."

McCann et al (2009) conducted a prospective study of 664 patients presenting to 2 coronary care units with ischemic-type chest pain, which was conducted over 3 years, beginning in 2003. Patients were assessed on admission for clinical characteristics, electrocardiographic findings, renal function, cardiac troponin T (cTnT), markers of myocyte injury (heart fatty acid-binding protein [H-FABP] and glycogen phosphorylase BB), neurohormonal activation (N-terminal-pro-brain natriuretic peptide [NT-pro-BNP]), hemostatic activity (fibrinogen and D-dimer), and vascular inflammation (high-sensitivity C-reactive protein, myeloperoxidase, matrix metalloproteinase-9, pregnancy-associated plasma protein-A and soluble CD40 ligand). One hundred-nine patients were excluded due to improper sample collection or timing. The principal finding of this study was that cardiac events over the first year could be predicted from increased biomarkers at the time of admission in individuals with acute ischemic-type chest pain. A very low risk group was identified as those who had negative admission H-FABP and NT-pro-BNP in addition to negative peak cTnT. The highest risk group was the group with elevated peak cTnT, H-FABP and NT-pro-BNP. There was no statistically significant difference noted for any of the inflammatory biomarkers (high-sensitivity C-reactive protein, myeloperoxidase, matrix metalloproteinase-9, pregnancy-associated plasma protein-A and soluble CD40 ligand); furthermore, there were no strong correlations between the inflammatory biomarkers.

Shah et al (2009) sought to assess the diagnostic accuracy of MPO for acute decompensated heart failure (ADHF) and its prognostic value for individuals with acute dyspnea. They conducted a prospective, observational study in 5 U.S. centers, 412 patients [mean (SD) age, 58 (14) years; 39 percent women] who presented with dyspnea to the ED were enrolled and followed for 1 year. Clinical, serum/plasma biomarker [MPO, B-type natriuretic peptide (BNP), N-terminal proBNP (NT-proBNP)], and transthoracic echocardiographic data were obtained. The researchers concluded that unlike natriuretic peptides, MPO concentration was not predictive of ADHF diagnosis or 1-year mortality in a heterogeneous sample of emergency department patients with acute dyspnea. In addition, MPO concentration was not correlated with left ventricular ejection fraction or other cardiac structural abnormalities. Lastly, MPO concentrations did not provide significant prognostic information in dyspnea patients presenting to the ED, whereas natriuretic peptides, biomarkers that in part reflect cardiac-filling pressure, were significantly associated with heart failure diagnosis and 1-year mortality.

Brennan et al (2003) reported a study of 604 sequential patients presenting to the emergency department with chest pain in the October 23, 2003 issue of The New England Journal of

Medicine. The study hypothesized that since inflammation is linked to adverse outcomes in acute coronary syndromes, myeloperoxidase, which is an abundant leukocyte enzyme, could be a predictor of the risk of future cardiovascular events. The authors state that plasma myeloperoxidase levels predict cardiovascular risks independently of the levels of C-reactive protein and other markers of inflammation. In rebuttal to the authors' methodology, Dr. William D. Cayley, MD, commented in the January 29, 2004 New England Journal of Medicine that the use of a test (myeloperoxidase level) for clinical prediction also requires decisions about the sensitivity and specificity of any selected cutoff point. When the sensitivities and specificities are combined into likelihood ratios, they indicate that a positive result for creatine kinase MB isoform (CK-MB) is actually much more predictive of an adverse cardiac outcome at 30 days than is an elevated myeloperoxidase level. In addition, a negative result for myeloperoxidase does not decrease the likelihood of an adverse outcome much more than does a negative result for CK-MB. Although myeloperoxidase levels are correlated with risk, they do not yet appear to provide additional prognostic information for the evaluation of individual patients.

There is insufficient evidence in the peer reviewed medical literature regarding how measuring MPO would change patient management or improve health outcomes. There are no guidelines recommending MPO in the assessment of cardiac risk. Large, prospective, multicenter studies are needed to determine the clinical utility of MPO measurement in the management of cardiac disease.

Government Regulations

National:

There is no Medicare National Coverage Determination for myeloperoxidase immunoassay.

Local:

Wisconsin Physician Services **MolDX: Biomarkers in Cardiovascular Risk Assessment (L36523)**; original effective date 6/16/16, revision effective date 3/30/23

The following biomarkers, when they are included in a CV risk assessment panel, are non-covered:

- Myeloperoxidase (MPO)

Myeloperoxidase (MPO)

Elevated levels of myeloperoxidase, secreted during acute inflammation, are thought by some to be associated with coronary disease and predictive of acute coronary syndrome in patients with chest pain. Many studies have implicated MPO in the pathogenesis of atherosclerosis, showing that it is enriched within atheromatous plaques. Inflammatory cells recruited into the vascular wall release MPO-derived reactive oxygen species that can promote endothelial dysfunction by reducing the bioavailability of nitric oxide, generate atherogenic oxidized-LDL, and modify HDL, impairing its function in cholesterol efflux. However, at the current time there is insufficient data to demonstrate that plasma MPO can predict CHD independent of other CVD risk factors and there is no data that demonstrates how plasma MPO levels affect management of individuals at risk for or patients with CHD.

PPAR-y is a key regulator of fatty acid metabolism, promoting its storage in adipose tissue and reducing circulating levels of free fatty acids. Activation of PPAR-y has favorable effects on surrogate measures of adipocyte function, insulin sensitivity, lipoprotein metabolism, and

vascular structure and function. However clinical trials of thiazolidinedione PPAR-y activators have not provided conclusive evidence that they reduce CV morbidity and mortality.

(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
- Measurement of Lipoprotein – Associated Phospholipase A2 and Secretory Type II Phospholipase A2 in the Assessment of Cardiovascular Risk
- Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease

References

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4. Brennan, Marie-Luise, PhD, et al., "Prognostic Value of Myeloperoxidase in Patients with Chest Pain," *The New England Journal of Medicine*, Vol. 349, No. 17, October 23, 2003, pp. 1595-1604.
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12. Saenger, Amy K., PhD, and Allan S. Jaffe, MD, “The Use of Biomarkers for the Evaluation and Treatment of Patients with Acute Coronary Syndromes,” *The Medical Clinics of North America*, Vol. 91, 2007, pp. 657-681.
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14. Shah, Keyur B., et al., “Lack of Diagnostic and Prognostic Utility of Circulating Plasma Myeloperoxidase Concentrations in Patients Presenting with Dyspnea,” *Clinical Chemistry,* Vol. 55, No. 1, 2009, pp. 59-67.
15. Wisconsin Physician Services MolDX: Biomarkers in Cardiovascular Risk Assessment (L36523); original effective date 6/16/16, revision effective date 3/30/23.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 1/8/23, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/1/09	6/3/09	4/21/09	Joint medical policy established
11/1/11	8/16/11	8/16/11	Routine maintenance
1/1/13	10/16/12	10/16/12	Routine maintenance
7/1/14	4/10/14	4/15/14	Routine maintenance
7/1/15	4/24/15	5/8/15	Routine maintenance
7/1/16	4/19/16	4/19/16	Routine maintenance
5/1/17	2/21/17	2/21/17	Routine maintenance
5/1/18	2/20/18	2/20/18	• Routine maintenance • LCD added
5/1/19	2/19/19		• Routine maintenance
5/1/20	2/18/20		• Routine maintenance
5/1/21	2/16/21		• Routine maintenance
5/1/22	2/15/22		• Routine maintenance
5/1/23	2/21/23		• Routine maintenance (slp) • Vendor Managed: N/A
5/1/24	2/20/24		• Routine maintenance (slp) • Vendor Managed: N/A

Next Review Date: 1st Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: MYELOPEROXIDASE (MPO) IMMUNOASSAY FOR CARDIAC DISEASE RISK

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not covered.
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
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.