Medical Policy

**Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease**

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**Policy Number:** 283
BCBSA Reference Number: 2.04.65

NCD/LCD:
- National Coverage Determination (NCD) for Lipid Testing (190.23)
- Local Coverage Determination (LCD): B-type Natriuretic Peptide (BNP) Testing (L33573)
- Local Coverage Determination (LCD): MolDX: Biomarkers in Cardiovascular Risk Assessment (L36129)

Related Policies
- Measurement of Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) in the Assessment of Cardiovascular Risk, #558
- Gene Expression Testing to Predict Coronary Artery Disease, #349
- Genetic Testing for Lipoprotein-a Variants as a Decision Aid for Aspirin Treatment, #339
- KIF6 Genotyping for Predicting Cardiovascular Risk and or Effectiveness of Statin Therapy, #129
- Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease, #016
- Genotyping for 9p21 Single Nucleotide Polymorphisms to Predict Risk of Cardiovascular Disease or Aneurysm, #340

**Policy**

**Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity**

Measurement of novel lipid and nonlipid risk factors (i.e., apolipoprotein B, apolipoprotein A-I, apolipoprotein E, B-type natriuretic peptide, cystatin C, fibrinogen, leptin, LDL subclass, HDL subclass, lipoprotein[a]) as an adjunct to LDL cholesterol in the risk assessment and management of cardiovascular disease is **INVESTIGATIONAL**.

The use of panels that include lipid and non-lipid cardiovascular risk markers is considered **NOT MEDICALLY NECESSARY**.
Medicare HMO BlueSM and Medicare PPO BlueSM Members

Medical necessity criteria and coding guidance can be found through the link below.

National Coverage Determination (NCD) for Lipid Testing (190.23)

Medical necessity criteria and coding guidance for Medicare Advantage members living in Massachusetts can be found through the links below.

Local Coverage Determination (LCD): B-type Natriuretic Peptide (BNP) Testing (L33573)

Local Coverage Determination (LCD): MolDX: Biomarkers in Cardiovascular Risk Assessment (L36129)

For medical necessity criteria and coding guidance for Medicare Advantage members living outside of Massachusetts, please see the Centers for Medicare and Medicaid Services website for information regarding your specific jurisdiction at https://www.cms.gov.

Prior Authorization Information
Pre-service approval is required for all inpatient services for all products. See below for situations where prior authorization may be required or may not be required for outpatient services.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Outpatient</th>
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<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
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<tr>
<td>This is not a covered service.</td>
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<tr>
<td>Commercial PPO and Indemnity</td>
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<tr>
<td>This is not a covered service.</td>
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<tr>
<td>Medicare HMO BlueSM</td>
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<tr>
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<tr>
<td>Medicare PPO BlueSM</td>
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<tr>
<td>No</td>
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CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The following codes are included below for informational purposes only; this is not an all-inclusive list.

The following CPT codes are considered investigational for Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity:

<table>
<thead>
<tr>
<th>CPT codes</th>
<th>Code Description</th>
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<tbody>
<tr>
<td>82610</td>
<td>Cystatin C</td>
</tr>
<tr>
<td>83695</td>
<td>Lipoprotein A</td>
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</table>
Numerous lipid and nonlipid biomarkers have been proposed as potential risk markers for cardiovascular disease. This policy will focus on those lipid markers that have the most evidence in support of their use in clinical care. The lipid markers assessed are apolipoprotein B, apolipoprotein A-1, apolipoprotein E, LDL subclass, HDL subclass, and lipoprotein A.

**Apolipoprotein B.** Apolipoprotein B (apo B) is the major protein moiety of all lipoproteins except for high-density lipoprotein (HDL). It has been postulated that apo B is a better measure of the atherogenic potential of serum low density lipoproteins (LDL) than is LDL concentration.

**Apolipoprotein A-I.** Apolipoprotein A-I (apo A-1) can be used as an approximation for HDL number, similar to the way apo B has been proposed as an approximation of the LDL number. Direct measurement of apo A-I has been proposed as more accurate than the traditional use of HDL level in evaluation of the cardioprotective, or “good,” cholesterol.

**Apolipoprotein E.** Apolipoprotein E (apo E) is the primary apolipoprotein found in very-low-density lipoproteins and chylomicrons. Apo E is the primary binding protein for LDL receptors in the liver and is thought to play an important role in lipid metabolism. It has been proposed that various apo E genotypes are more atherogenic than others and that apo E measurement may provide information on risk of coronary artery disease above traditional risk factor measurement.

**LDL subclass.** Two main subclass patterns of LDL, called A and B, have been described based on particle size. LDL size has also been proposed as a potentially useful measure of treatment response. Lipid-lowering treatment decreases total LDL and may also induce a shift in the type of LDL, from smaller, dense particles to larger particles. It has been proposed that this shift in lipid profile may be beneficial in reducing risk for coronary artery disease (CAD) independent of the total LDL level.

**HDL subclass.** It has been proposed that various subclasses of HDL may have a greater role in protection from atherosclerosis.

**Lipoprotein A.** Lipoprotein (a) (lp[a]) is a lipid-rich particle similar to LDL. Approximately 20% of patients with CAD have elevated levels of lp (a). Therefore, it has been proposed that levels of lp (a) may be an independent risk factor for CAD.

**Summary**

Numerous non-traditional lipid measurements have been proposed for use in improving risk prediction for cardiovascular disease, including apo B, apo A-1, the ratio of apo B/apo A-1, apo E, lipoprotein A, and subclasses of LDL and HDL. In general, there is evidence that these markers provide some incremental accuracy in risk prediction. However, it has not been established that the incremental accuracy provides clinically important information beyond that of traditional lipid measures. Furthermore, no study has provided high-quality evidence that measurement of markers leads to changes in management that improve health outcomes.
Some markers, e.g. apo B, have also been proposed as treatment targets for lipid-lowering therapy. While some evidence supports that they may be accurate in predicting residual risk for patients on lipid-lowering therapy, there is no high-quality evidence that these markers lead to health outcome improvements when used in place of traditional lipid targets, such as LDL. Because of the deficiencies in the literature around these issues, the use of these novel lipid risk markers in both the risk assessment and management of CAD is investigational.

**Policy History**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tr>
<td>1/2017</td>
<td>New references added from BCBSA National medical policy.</td>
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<td>1/2017</td>
<td>Clarified coding information for the 2017 code changes.</td>
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<tr>
<td>6/2016</td>
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<td>11/2015</td>
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<td>7/2015</td>
<td>Clarified coding information</td>
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<tr>
<td>11/2014</td>
<td>National Coverage Determination (NCD) for Lipid Testing (190.23) added.</td>
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<tr>
<td>3/2013</td>
<td>Updated to add non-covered code 83701.</td>
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<tr>
<td>5/2/2011</td>
<td>Revised date.</td>
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<tr>
<td>11/1/2010</td>
<td>Medical Policy #283 effective describing on-going non-coverage.</td>
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**Information Pertaining to All Blue Cross Blue Shield Medical Policies**

Click on any of the following terms to access the relevant information:
- Medical Policy Terms of Use
- Managed Care Guidelines
- Indemnity/PPO Guidelines
- Clinical Exception Process
- Medical Technology Assessment Guidelines

**References**


76. Superko HR, Berneis KK, Williams PT, et al. Gemfibrozil reduces small low-density lipoprotein more in normolipemic subjects classified as low-density lipoprotein pattern B compared with pattern A. Am J Cardiol. Nov 1 2005;96(9):1266-1272. PMID 16253595


86. Rosenson RS, Otvos JD, Freedman DS. Relations of lipoprotein subclass levels and low-density lipoprotein size to progression of coronary artery disease in the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC-I) trial. Am J Cardiol. Jul 15 2002;90(2):89-94. PMID 12106834


92. Ridker PM, Hennekens CH, Stampfer MJ. A prospective study of lipoprotein(a) and the risk of myocardial infarction. JAMA. Nov 10 1993;270(18):2195-2199. PMID 8411602


