Medical Policy
Gene Expression Testing in the Evaluation of Patients with Stable Ischemic Heart Disease

Table of Contents
- Policy: Commercial
- Policy: Medicare
- Authorization Information
- Coding Information
- Description
- Policy History
- Information Pertaining to All Policies
- References

Policy Number: 349
BCBSA Reference Number: 2.04.72
NCD/LCD: Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

Related Policies
- KIF6 Genotyping for Predicting Cardiovascular Risk and/or Effectiveness of Statin Therapy, #129
- Genotyping for 9p21 Single Nucleotide Polymorphisms to Predict Risk of Cardiovascular Disease or Aneurysm, #340

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

Gene expression testing in the evaluation of patients with stable ischemic heart disease is considered INVESTIGATIONAL for all indications, including but not limited to prediction of coronary artery disease in stable, nondiabetic patients.

Medicare HMO BlueSM and Medicare PPO BlueSM Members

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

Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000)

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
Inpatient
- For services described in this policy, precertification/preauthorization IS REQUIRED for all products if the procedure is performed inpatient.

Outpatient
For services described in this policy, see below for products where prior authorization might be required if the procedure is performed outpatient.

<table>
<thead>
<tr>
<th>Product</th>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Medicare HMO BlueSM</td>
<td>Prior authorization is not required.</td>
</tr>
<tr>
<td>Medicare PPO BlueSM</td>
<td>Prior authorization is not required.</td>
</tr>
</tbody>
</table>

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:

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>81493</td>
<td>Coronary artery disease, mrna, gene expression profiling by real-time rt-pcr of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score</td>
</tr>
</tbody>
</table>

Description

HEART DISEASE
Heart disease is the leading cause of death in the United States, accounting for approximately one-third of all deaths in people over age 35.1 The death rate is higher in men compared with women and in blacks compared with whites, but lower in Hispanic populations compared with blacks and whites. The most common form of heart disease is ischemic heart disease, also known as coronary artery disease (CAD). Angina is the first symptom of CAD in approximately 50% of patients. However, women and the elderly are more likely to present with atypical symptoms such as nausea, vomiting, gastric discomfort, or atypical chest pain, which makes diagnosis more challenging.2

Diagnosis
Patients with signs and symptoms of obstructive CAD may be evaluated with a variety of tests according to prior risk. Coronary angiography is the criterion standard for diagnosing obstructive CAD, but it is invasive and associated with a low but finite risk of harm. Coronary angiography also has a relatively low yield. In a study of nearly 400,000 patients without known CAD undergoing elective coronary angiography, approximately 38% were positive for obstructive CAD (using the CAD definition, ≥50% stenosis of the diameter of the left main coronary artery or ≥70% stenosis of the diameter of a major epicardial or branch vessel >2.0 mm in diameter) and 41% if using the broader definition (≥50% stenosis in any coronary vessel).3 Thus, methods of improving patient risk prediction before invasive coronary angiography are needed.

In an initial proof-of-principle study of the Corus CAD score in patients referred for invasive coronary angiography, Wingrove et al (2008) evaluated 27 cases (96% symptomatic) with and 14 controls without angiographically defined CAD for expression of genes that differed significantly between the 2 groups, selecting 50 genes.4 To that authors added 56 genes selected from relevant literature reports and evaluated the expression of these 106 genes in an independent set of 63 cases and 32 controls, resulting in the selection of 14 genes that independently and significantly discriminated between groups in multivariable analysis. The significance of 11 of these 14 genes was replicated in the third set of 86 cases.
and 21 controls. Expression of the 14 genes was proportional to maximal coronary artery stenosis in the combined cohort of 215 patients.

Elashoff et al (2011) described final Corus CAD score development. Investigators conducted 2 successive case-control gene expression discovery studies using samples from independent cohorts. Cases were angiographically defined as 75% or greater maximum stenosis in 1 major vessel, or 50% or greater in 2 vessels, and controls defined as less than 25% stenosis in all major vessels. Of clinical factors, diabetes had the most significant effect on gene expression; in the first case-control study in symptomatic patients (CATHGEN; N=195), expression of 42 genes in nondiabetic patients and 12 genes in diabetic patients was found to (p<0.05) discriminate significantly between cases and controls with no overlap. As a result, the second case-control study, in a subset of 198 patients from the prospective PREDICT study, and final development of the assay was limited to nondiabetic patients (62% symptomatic). The participants were 76% male and 89% white. Final variable selection comprised the expression of 20 CAD-associated genes, 3 normalization genes, and terms for age and sex. The majority of the selected genes were immune and inflammatory-related. All terms were incorporated into an algorithm that resulted in an obstructive CAD score ranging from 1 to 40.

Summary
Expression levels of various genes in circulating white blood cell or whole blood samples have been reported to discriminate between cases of obstructive coronary artery disease (CAD) and healthy controls. Multiplex gene expression testing has been combined with other risk factors to estimate the likelihood of obstructive CAD in patients who present with stable ischemic heart disease. These tests have potential to improve the accuracy of predicting CAD. A commercially available test, Corus CAD, has been developed for this purpose without diabetes or inflammatory conditions.

For individuals who have suspected stable ischemic heart disease without diabetes or inflammatory conditions who receive gene expression testing, the evidence includes retrospective case-control and prospective cohort studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, change in disease status, morbid events, and resource utilization. The diagnostic pathway for CAD includes information from a medical history, along with age and sex, stress testing, and imaging. Newer noninvasive methods are being tested, such as gene expression testing. It is not clear how the Corus CAD gene expression test fits in the current diagnostic pathway and how results would be used to change current guideline-based risk stratification before and/or after other noninvasive testing. Results of 2 validation studies (PREDICT, COMPASS) have reported that the test may improve CAD prediction beyond the Diamond-Forrester prediction model. In the COMPASS study, the sensitivity and negative predictive value of the Corus CAD score in diagnosing obstructive CAD was superior to myocardial perfusion imaging in patients referred for myocardial perfusion imaging testing. However, in that study, the reported sensitivity of myocardial perfusion imaging was considerably lower than that generally reported in the literature. Neither PREDICT nor COMPASS used the guideline definition of obstructive CAD as the reference standard. The sensitivity and negative predictive value of clinical models were not reported. An analysis of a cohort from the PROMISE trial including patients with intermediate pretest probability of obstructive CAD confirmed a high negative predictive value for the Corus CAD score. The test also has been shown to have some predictive ability of future revascularization; too few major cardiac events have been observed during the limited duration of follow-up to assess predictive ability for that outcome. Evidence for the Corus CAD score has not directly demonstrated that the test is clinically useful and a chain of evidence cannot be constructed to support its utility. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2016</td>
<td>Clarified coding information.</td>
</tr>
<tr>
<td>Date</td>
<td>Notes</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>8/2015</td>
<td>New references from BCBSA National medical policy.</td>
</tr>
<tr>
<td>7/2015</td>
<td>Local Coverage Determination (LCD):  Molecular Diagnostic Tests (MDT) (L33541) added.</td>
</tr>
<tr>
<td>5/2015</td>
<td>Local Coverage Determination (LCD):  Molecular Pathology Procedures (L34506) added. Effective immediately.</td>
</tr>
<tr>
<td>8/2014</td>
<td>BCBSA National medical policy review.  Wording modified to clarify that GES is investigational “for all indications, including but not limited to prediction of CAD likelihood in stable, nondiabetic patients. Effective 8/1/2014.</td>
</tr>
<tr>
<td>8/2013</td>
<td>New references from BCBSA National medical policy.</td>
</tr>
<tr>
<td>5/2012</td>
<td>New policy describing ongoing non-coverage.</td>
</tr>
</tbody>
</table>

**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**


