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

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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
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>Commercial Managed Care (HMO and POS)</th>
<th>This is not a covered service.</th>
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</thead>
<tbody>
<tr>
<td>Commercial PPO and Indemnity</td>
<td>This is not a covered service.</td>
</tr>
<tr>
<td>Medicare HMO BlueSM</td>
<td>No</td>
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<tr>
<td>Medicare PPO BlueSM</td>
<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:

CPT Codes

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<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>
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Description

Heart disease is the leading cause of death in the United States. Patients with signs and symptoms of obstructive coronary artery disease (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. Thus, coronary angiography is recommended for patients at a high prior risk of CAD according to history, physical findings, electrocardiogram, and biomarkers of cardiac injury. For patients initially assessed at low-to-intermediate risk, observation and noninvasive diagnostic methods, which may include imaging methods such as coronary computed tomographic angiography, may be recommended. Nevertheless, some noninvasive imaging methods have potential risks of exposure to radiation and contrast material. In addition, coronary angiography has a relatively low yield, despite risk stratification recommendations. 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 that was >2.0 mm in diameter and 41% if using the broader definition, ≤50%stenosis in any coronary vessel). Thus, methods of improving patient risk prediction before invasive coronary angiography are needed.

In an initial proof-of-principle study of the Gene Expression Score (GES) test 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. To that authors added 56 genes selected from relevant literature reports and evaluated 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 a 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 test development of the GES. 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 significantly (p<0.05) discriminate 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 (discussed next), and final development of the assay was limited to nondiabetic patients (62% symptomatic). Final variable selection comprised the expression of 20 CAD-associated genes, 3 normalization genes, and terms for age and sex, all incorporated into an algorithm that resulted in an obstructive CAD score ranging from 1 to 40. Receiver operating characteristic analysis in PREDICT resulted in an area under the curve for CAD of 0.77 (95% confidence interval, 0.73 to 0.81).

A CAD classifier has been developed based on expression levels derived from the previously described studies, in whole blood samples, of 23 genes plus patient age and sex. This information is used in an algorithm to produce a score from 1 to 40, with higher values associated with a higher likelihood of obstructive CAD. The test is marketed as Corus CAD. The intended population is stable, nondiabetic patients suspected of CAD either because of symptoms, a high-risk history, or a recent positive or inconclusive test result by conventional methods.

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 can be 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 Gene Expression Score (GES) test, Corus CAD, has been developed and validated for this purpose in nondiabetic patients.

For individuals who have suspected stable ischemic heart disease without diabetes who receive gene expression testing, the evidence includes retrospective case-control and prospective cohort studies. Relevant outcomes are test accuracy and validity, change in disease status. Results of initial validation studies have reported that the test may improve CAD prediction beyond that of simple prediction models (e.g., Diamond-Forrester), but the benefit of improved prediction when added to routine clinical evaluation is uncertain. The test also has been shown to have some predictive ability of future cardiac events and revascularization. In the COMPASS study, overall accuracy of the GES test in predicting cardiac events was superior to myocardial perfusion imaging (MPI) in patients referred for MPI testing. However, in that study, the reported sensitivity of MPI was considerably lower than that generally reported in the literature. Also, it is unclear from the COMPASS study whether patients with positive MPI could safely forgo further testing based on a low GES. The clinical utility of the GES has not been demonstrated. Three studies with methodologic limitations reported management changes as a result of the test, but the effect of these management changes on patient outcomes is uncertain. Evidence for a significant incremental improvement in outcomes when gene expression testing is added to standard clinical evaluation is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy History

<table>
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<tr>
<td>1/2016</td>
<td>Clarified coding information.</td>
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<tr>
<td>8/2015</td>
<td>New references from BCBSA National medical policy.</td>
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<td>7/2015</td>
<td>Local Coverage Determination (LCD): Molecular Diagnostic Tests (MDT) (L33541) added.</td>
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<tr>
<td>5/2015</td>
<td>Local Coverage Determination (LCD): Molecular Pathology Procedures (L34506) added. Effective immediately.</td>
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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.

8/2013
New references from BCBSA National medical policy.

5/2012
New policy describing ongoing non-coverage.

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


