Gene Expression Testing to Predict Coronary Artery Disease

Policy # 00309
Original Effective Date: 07/20/2011
Current Effective Date: 12/21/2016

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers gene expression testing to predict coronary artery disease (CAD) for all indications, including but not limited to prediction of the likelihood of CAD in stable, nondiabetic patients to be investigational.*

Background/Overview
The expression levels of various genes in circulating white blood cell or whole blood samples have been reported to discriminate between cases of obstructive CAD and healthy controls. Multiplex gene expression testing can be combined with other risk factors to predict the likelihood of obstructive CAD in patients who present with chest pain or other suggestive symptoms, or in asymptomatic patients who are at high risk of CAD. These tests have potential to improve the accuracy of predicting CAD likelihood. A commercially available Gene Expression Score (GES) test, Corus CAD™ ‡, has been developed and validated for this purpose in nondiabetic patients.

Heart disease is the leading cause of mortality in the U.S. and together with cerebrovascular disease accounted for 31% of deaths in 2007. Individuals with signs and symptoms of obstructive CAD, the result of a chronic inflammatory process that ultimately results in progressive luminal narrowing and acute coronary syndromes, may be evaluated with a variety of tests according to prior risk. Coronary angiography is the gold standard for diagnosing obstructive CAD, but 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, even 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 one study of nearly 400,000 patients without known CAD undergoing elective coronary angiography, about 38% were positive for obstructive CAD (using the CAD definition, stenosis of 50% or more of the diameter of the left main coronary artery or stenosis of 70% or more of the diameter of a major epicardial or branch vessel that was more than 2.0 mm in diameter; result was 41% if using the broader definition, stenosis of 50% or more in any coronary vessel). Thus, methods of improving patient risk prediction prior to diagnostic testing are needed.

A CAD classifier has been developed based on the expression levels, in whole blood samples, of 23 genes plus patient age and sex. This information is combined 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 †.
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(CardioDx, Inc.). 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.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standard of the Clinical Improvement Act (CLIA). The Corus CAD test is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of these tests.

Centers for Medicare and Medicaid Services (CMS)
There are no Medicare national coverage determinations for GES testing to predict CAD. In July 2013, Palmetto GBA issued a positive local coverage decision for the Corus CAD test in patients who have typical symptoms of CAD or atypical symptoms and 1 or more CAD risk factors.

Rationale/Source

What is the technical performance of the prediction model (assay development and validation)?

Assay Development

In an initial proof-of-principle study, Wingrove et al. evaluated 27 cases with and 14 controls without angiographically defined CAD for expression of genes that differed significantly between the 2 groups, selecting 50 genes. To that the 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. Limitations of this study included variable source of ribonucleic acid (RNA) for different cohorts (whole blood vs. separated whole blood leukocytes), small sample sizes in conjunction with large numbers of genes investigated and no apparent correction for multiple tests in significance testing, and modest discrimination between groups.

Elashoff et al described final test 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 (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 (n=198) and final development of the assay was limited to nondiabetic patients. 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 (ROC) analysis in the second case-control study resulted in an area under the curve (AUC) for CAD of 0.77 (95% confidence interval [CI], 0.73 to 0.81).
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Assay Validation
The finalized assay was validated in a prospective multicenter trial, the PREDICT trial, in which blood samples were collected from nondiabetic patients (N=526) with a clinical indication for coronary angiography but no known previous myocardial infarction (MI), revascularization, or obstructive CAD. This is the same cohort from which the second assay development case-control cohort was drawn. Patients were sequentially allocated to development and validation sets. The authors defined obstructive CAD as 50% or greater stenosis in 1 or more major coronary arteries on quantitative coronary angiography, which they stated corresponded to 65% to 70% stenosis on clinical angiography. The assay AUC for CAD was 0.70±0.02 (p<0.001). In a follow-up publication, the authors evaluated Gene Expression Score (GES) performance in nondiabetic patients from the gene discovery and algorithm development cohorts in combination with the validation cohort (N=1038) and, as would be expected, found similar performance (AUC, 0.70±0.02; p<0.001).

What is the predictive ability of the test compared to alternative methods of predicting CAD?
The PREDICT trial compared the predictive accuracy of the GES measure to clinical predictors and myocardial perfusion imaging (MPI) stress testing. This was a multicenter study of 1,160 patients presenting for coronary angiography. All patients underwent GES assessment, and the outcomes used for prediction were CAD at initial angiography, and cardiac events, including revascularization, in the year following the initial angiogram.

The clinical predictor was the Diamond–Forrester clinical risk score, which had an AUC for CAD of 0.66; the combined AUC for clinical prediction and GES score was 0.72 (p=0.003). Myocardial perfusion imaging was performed on 310 patients; AUC for the assay algorithm score plus MPI versus MPI alone was 0.70 versus 0.43 (p<0.001). Sensitivity and specificity calculated for a disease likelihood of 20% were 85% and 43%, respectively, corresponding to negative and positive predictive values of 83% and 46%, respectively. The average scores for patients with and without obstructive CAD were 25 and 17, respectively; assay algorithm scores increased with increasing degree of stenosis by angiography, with score distributions overlapping considerably.

The authors conducted a reclassification analysis, in which patients were first classified by either the Diamond–Forrester clinical risk score or an expanded clinical model based on routine history and clinical evaluation, then reclassified by the assay algorithm score. The net reclassification improvement, which quantitates the difference between the proportion of patients who are correctly reclassified from an incorrect initial classification and the proportion who are incorrectly reclassified from a correct initial classification, was 20% (p<0.001) using the initial Diamond–Forrester clinical risk score and 16% (p<0.001) using the expanded clinical model.

A follow-up publication from the PREDICT trial was published in 2012. Rosenberg et al reported on the association of GES with subsequent major adverse cardiac events (MACE), including MI, stroke/TIA (transient ischemic attack), all-cause mortality, and coronary revascularization. Among 1160 patients who underwent angiography in the PREDICT trial, there were 17 total MACE events (1.5%), 15 of which occurred 30 days or more after the initial angiogram. Using a GES cutoff of 15 or less, sensitivity for diagnosis of subsequent MACE was 82% and specificity was 34%. PPVs and NPVs were 1.8% and greater.
than 99%, respectively (with an overall MACE prevalence of 1.5%). The odds ratio (OR) for having an event was increased for patients with GES greater than 15, but this result did not reach statistical significance (OR=2.41; 95% CI, 0.74 to 10.5; p=0.16).

In another follow-up publication from the PREDICT trial, Lansky and colleagues found that GES was an independent predictor of CAD in multivariate analysis with an odds ratio of 2.53 (p=0.001) in the total study population and 1.99 (p=0.001) and 3.45 (p=0.001) for males and females respectively. In this analysis MPI was not associated with any measures of CAD in the general population or when stratified by gender. For every 10-point increase in GES there was a corresponding 2 fold increase in odds of CAD, and an increase in maximum percent stenosis, the number of lesions, and total plaque volume.

Thomas and colleagues assessed the clinical validity and utility of the Corus CAD for detection of obstructive CAD in non-diabetic patients in a multicenter, prospective study (COMPASS). Obstructive CAD was defined as 50% or greater stenosis in 1 or more major coronary arteries on quantitative coronary angiography. The COMPASS population differed from the PREDICT trial by including participants who had received a referral for MPI but had not been referred for invasive coronary angiography (ICA). Peripheral blood was drawn before MPI on all participants to obtain a GES. Myocardial perfusion imaging positive participants underwent ICA based on the clinician’s judgment, and all other participants received CTA. Of the 537 enrolled patients only 431 (80.3%) were evaluable primarily due to refusal to perform ICA or CTA. Follow-up was six months after testing with clinical end-points of MACE and revascularization. Using a GES cutoff of 15 or less, sensitivity and specificity of the Corus CAD test were 89% and 52% respectively. A summary of the AUC, sensitivity, and specificity of the comparators is given in Table 1. Net reclassification improvement in predicting CAD for GES compared to MPI (site-read), MPI (Core-Lab), Diamond-Forrester classification, and Morise score was 26%, 11%, 28% and 60% respectively.

Table 1. Summary of Gene Expression Score, Myocardial Perfusion Imaging, and Clinical Factor Algorithms for Detecting Obstructive CAD

<table>
<thead>
<tr>
<th>Variable</th>
<th>GES</th>
<th>MPI (site-read)</th>
<th>MPI (core-lab)</th>
<th>Diamond-Forrester</th>
<th>Morise</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>431</td>
<td>431</td>
<td>371</td>
<td>430</td>
<td>431</td>
</tr>
<tr>
<td>ROC AUC (95% CI),</td>
<td>0.79 (0.72 to 0.84)</td>
<td>0.59 (0.54 to 0.65)</td>
<td>0.63 (0.57 to 0.70)</td>
<td>0.69 (0.62 to 0.75)</td>
<td>0.65 (0.59 to 0.74)</td>
</tr>
<tr>
<td>Sensitivity (95% CI), %</td>
<td>89 (78 to 95)</td>
<td>27 (17 to 40)</td>
<td>36 (24 to 50)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Specificity (95% CI), %</td>
<td>52 (47 to 57)</td>
<td>92 (88 to 94)</td>
<td>90 (87 to 93)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>NPV (95% CI), %</td>
<td>96 (93 to 99)</td>
<td>88 (84 to 91)</td>
<td>88 (84 to 92)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>PPV (95% CI), %</td>
<td>24 (19 to 30)</td>
<td>35 (22 to 51)</td>
<td>41 (28 to 56)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>NRI, %</td>
<td>NA</td>
<td>26</td>
<td>11</td>
<td>28</td>
<td>60</td>
</tr>
<tr>
<td>ROC AUC for GES and second modality combined (95% CI)</td>
<td>NA</td>
<td>0.81 (0.76 to 0.86)</td>
<td>0.81 (0.76 to 0.87)</td>
<td>0.79 (0.73 to 0.85)</td>
<td>0.81 (0.75 to 0.89)</td>
</tr>
</tbody>
</table>

CAD: coronary artery disease; CI: confidence interval; GES: Gene Expression Score; MPI: myocardial perfusion imaging; NA: not applicable; NPV: negative predictive value; NR: not reported; NRI: net reclassification improvement; PPV: positive predictive value; ROC AUC: area under the receiver-operator characteristic curve.

Obstructive CAD was defined as ≥50% stenosis in ≥1 major coronary arteries on quantitative coronary angiography.
Twenty-eight adverse events were observed which included 25 revascularizations within 30 days, 2 MACE, and 1 further revascularization. Twenty-five of the 26 patients with revascularization and both MACE patients had high GES (>15). The authors found that GES was associated with MACE and revascularization in a logistic regression model (p=0.0015) with a sensitivity of 96% and NPV of 99% at a score threshold of ≤15. The GES test was also correlated with maximum percent stenosis (r=0.46, P<0.001).

In a follow-up study to evaluate biological variation over time, Daniels et al (2014) drew second blood samples from 192 COMPASS participants (36%) 1 year after the original study. In 19 patients who had cardiac events, including revascularization, between blood draws, mean change in GES score was 1.1 points. In 173 patients without cardiac events, mean change was 1.4 points, from 15.9 to 17.3, corresponding to a 2.5% increase in predicted risk of obstructive CAD. On logistic regression, approximately half of the increase was due to increased patient age. Lack of paired second anatomic studies limits interpretation of these findings.

Voros et al (2013) pooled results from PREDICT and COMPASS to compare GES with CT imaging for detecting plaque burden (coronary artery calcium [CAC]), and luminal stenosis. Six hundred ten patients, 216 from PREDICT (19% of enrolled patients) and 394 from COMPASS (73% of enrolled patients), who had undergone CAC scoring, CTA, and GES were included. Mean standard deviation (SD) age was 57 years; 50% were female, and approximately 50% used statin medication. Prevalence of obstructive CAD (≥50% stenosis) was 16% in the PREDICT cohort (patients referred for coronary angiography) and 13% in the COMPASS cohort (patients referred for MPI). In linear regression analyses, GES was statistically significantly correlated with CAC (r=0.50), the number of arterial segments with any plaque (r=0.37), overall stenosis severity (r=0.38), and maximum luminal stenosis (r=0.41) (all p<0.01), but strength of correlations was modest. Several GES cutoffs were explored (eg, to maximize diagnostic accuracy). Results using a cutoff of 15 points are shown in Table 2. For detecting luminal stenosis of 50% or greater, GES positive predictive value (PPV) and negative predictive value (NPV) were 0.23 and 0.95, respectively. For detecting clinically significant CAC (≥400), GES PPV and NPV were 0.14 and 0.97, respectively. Limitations of the study included lack of clinical outcomes (eg, survival, morbidity), and lack of comparison with CAC and computed tomography angiography (CTA) for predicting these outcomes (ie, incremental predictive value of GES was not assessed).

Table 2. Performance of Gene Expression Score and Diamond-Forrester Classification for Coronary Artery Plaque Burden and Luminal Stenosis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>GES ROC AUC (95% CI)</th>
<th>Diamond-Forrester ROC AUC (95% CI)</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque burden</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAC &gt;0</td>
<td>0.75 (0.71 to 0.79)</td>
<td>0.65 (0.61 to 0.69)</td>
<td>0.71</td>
<td>0.62</td>
<td>0.65</td>
<td>0.68</td>
</tr>
<tr>
<td>CAC ≥400</td>
<td>0.75 (0.68 to 0.82)</td>
<td>0.61 (0.53 to 0.69)</td>
<td>0.84</td>
<td>0.49</td>
<td>0.14</td>
<td>0.97</td>
</tr>
<tr>
<td>Luminal stenosis by CTA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>≥50%</td>
<td>0.75 (0.70 to 0.80)</td>
<td>0.65 (0.59 to 0.71)</td>
<td>0.84</td>
<td>0.51</td>
<td>0.23</td>
<td>0.95</td>
</tr>
<tr>
<td>≥70%</td>
<td>0.75 (0.67 to 0.83)</td>
<td>0.63 (0.53 to 0.73)</td>
<td>0.90</td>
<td>0.48</td>
<td>0.08</td>
<td>0.99</td>
</tr>
</tbody>
</table>

CI: confidence interval; CAC: coronary artery calcium; CTA: computed tomography angiography; GES: Gene Expression Score; NPV: negative predictive value; PPV: positive predictive value; ROC AUC: area under the receiver-operator characteristic curve.
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Long-term outcomes are generally excellent in patients with zero CAC and substantially worse in patients with CAC >400.

Section Summary
Results of the PREDICT and COMPASS studies established that GES has predictive ability for CAD. The PREDICT and COMPASS studies reported that GES is superior to the Diamond-Forrester model and to MPI for predicting CAD. However, there are several limitations to the evidence on comparative predictive accuracy. In the PREDICT study, the assay algorithm score discriminated cases from controls significantly better than the Diamond–Forrester clinical score by AUC analysis; however it did not discriminate better than an expanded clinical model without family history or electrocardiogram (AUC, 0.745 vs 0.732, respectively; p=0.089). Additionally, neither Diamond–Forrester clinical risk score nor the expanded clinical model included family history or electrocardiogram results, which might increase accuracy of the initial classification and decrease the net reclassification improvement observed. Furthermore, the Diamond-Forrester model is a simple prediction rule that is not commonly used in clinical care. The Framingham risk score would be a more relevant comparator that is part of contemporary clinical care. Finally, modest correlations of GES with coronary artery plaque burden and luminal stenosis in the absence of clinical outcomes are of uncertain clinical significance.

The COMPASS study compared GES with results from MPI stress testing. In that trial, sensitivity of MPI was low at 27%. This is considerably lower than is routinely reported in the literature. For example, in a meta-analysis performed in support of American College of Cardiology/American Heart Association (ACC/AHA) guidelines on MPI, sensitivity was estimated at 87% to 89%. This raises the question of whether accuracy of MPI in the COMPASS study was representative of that seen in current clinical care. Also, the comparison of overall accuracy of GES with MPI testing does not establish that clinical decisions would be changed, specifically whether patients with a positive MPI could safely forego further invasive testing based on a low GES.

Does use of the test lead to changes in management that improve outcomes?
The IMPACT-CARD study compared a prospective cohort with matched historical controls to evaluate whether the GES test altered the cardiologist’s evaluation and clinical management of CAD. Coronary artery disease was categorized by the authors as no CAD (0% stenosis), CAD (≤50% stenosis) or CAD (>50% stenosis). All participants were nondiabetic, had no known prior MI or revascularization, were not using steroids, immune suppressive agents or chemotherapeutic agents, and had been referred to a cardiologist for evaluation of chest pain or angina equivalent symptoms. Eighty-eight patients were enrolled and 83 included in the final analysis. The matched cohort comprised 83 patients selected with similar distributions of age, gender, and clinical risk factors, and had been evaluated at a participating clinic within the past 3 to 30 months.

In a similar but unmatched study, IMPACT-PCP evaluated whether GES altered primary care providers' diagnostic evaluation and clinical management of stable, nonacute, nondiabetic patients presenting with CAD symptoms. Nine primary care providers at 4 centers evaluated 261 consecutive patients, 251 (96%) of whom were eligible for participation. Clinicians documented their pretest impressions and recommendations for further evaluation and management on a clinical report form. All patients underwent GES testing. The primary outcome was the change in patient management between preliminary and final treatment plans.
In both studies, change in patient management was defined prospectively as an increase or decrease in intensity of the diagnostic plan. The authors defined categories of intensity in the following order: 1) no further cardiac testing or medical therapy for angina or noncardiac chest pain, 2) stress testing (with/without imaging) or CTA, or 3) ICA. GESs were divided into a high-risk group (>15) and a low-risk group (≤15). In IMPACT-CARD, diagnostic testing plans were changed for 58% of patients in the prospective cohort (95% CI, 46 to 69; p<0.001) with a greater reduction in testing intensity (39%) compared with increased testing intensity (19%). Compared with the historical control group, the prospective cohort had a 71% reduction in overall diagnostic testing (p<0.001). Results from IMPACT-PCP were similar: Diagnostic testing plans were changed for 58% of patients, with reductions in testing intensity more common than increases (64% vs 34%; p<0.001). No study-related major adverse cardiovascular events were observed in 247 patients (98%) who had at least 30 days of follow-up.

A secondary analysis of IMPACT-CARD examined testing patterns around ICA. Thirty patients, 14 from the prospective cohort and 16 from the historical cohort, who underwent ICA were included in the analysis. The authors did not find a significant difference in diagnostic yield between the 2 groups (p=0.24). No major cardiovascular adverse events were observed for either cohort during the 6-month follow-up period.

The REGISTRY 1 study assessed the impact of GES on patient management decisions by examining the association between GES test results and post-test referral patterns. Primary care practitioners at 7 centers evaluated 342 stable, nonacute, nondiabetic patients presenting with CAD symptoms. All patients underwent GES testing. Of 167 patients with low (≤15) GES, 10 (6%) were referred for further cardiac evaluation compared with 122 (70%) of 175 patients in the high GES group (p<0.001). Analysis of GES as a continuous variable showed a statistically significant change in cardiac referrals for every 10-point change in GES (adjusted OR, 13.7 [95% CI, 12.5 to 15.0]; p<0.001). Over a mean follow-up of 264 days, there were 5 major adverse cardiovascular events, 2 in the low GES group and 3 in the high GES group. Of 21 patients who underwent elective ICA, 1 (50%) of 2 in the low GES group and 8 (42%) of 19 in the high GES group had obstructive findings.

In a follow-up study, Ladapo et al (2015) pooled results for women who participated in the IMPACT-PCP (n=140) and REGISTRY 1 (n=180) studies to evaluate the impact of GES on further cardiac evaluation (N=320). Mean age of this cohort was 58 years; mean systolic and diastolic blood pressure were 129 mm Hg and 79 mm Hg, respectively; most were white (84%) and nonsmokers (59%); and mean (SD) GES was 10 (8). Seventy-six percent of women had low GES (≤15). Referral rate for further cardiac evaluation was 4% for women with low GES (n=248) versus 83% for women with elevated GES (n=72). Overall, there were 4 MACE/revascularization events. (Median follow-up was 37 days in IMPACT-PCP and 278 days in REGISTRY I). Events per GES risk group were not reported.

Section Summary
Based on the IMPACT and REGISTRY 1 studies, management decisions may be changed as a result of GES. IMPACT-CARD was limited by comparison with historical controls, which were not well-matched to the study population, and IMPACT-PCP was an uncontrolled study. In addition, the impact of management changes in these studies is uncertain. There is no information provided on whether management changes led to beneficial effects on outcome, and it is not possible to estimate the likelihood of benefit from the
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Information given. Although REGISTER 1 followed patients for approximately 9 months, reported clinical outcomes do not indicate benefits of GES testing. Therefore, it is not possible to conclude that GES leads to changes in management that improve outcomes.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this policy are listed in Table 3.

Table 3. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td>Ongoing trials are not listed.</td>
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<td></td>
</tr>
<tr>
<td>NCT01677156 Mandarin*</td>
<td>The PRESET Registry: A Registry to Evaluate Patterns of Care Associated With the Use of Corus CAD in Real World Clinical Care Settings</td>
<td>1000</td>
<td>Sep 2015</td>
</tr>
<tr>
<td>Unpublished</td>
<td>Unpublished trials are not listed.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02158754</td>
<td>Clinician Utilization of CORUS CAD in Primary Care Provider Decision Making</td>
<td>NR</td>
<td>Jun 2015 Terminated</td>
</tr>
</tbody>
</table>

NCT: national clinical trial; NR: not reported.
* Denotes industry-sponsored or cosponsored trial.

Summary
Gene expression assays to predict the likelihood of obstructive CAD have potential to improve the accuracy of predicting CAD likelihood. A commercially available GES test, Corus CAD, has been developed and validated for this purpose in nondiabetic patients. The PREDICT study raised the possibility that this test could be used to increase the proportion of patients selected for coronary angiography who truly have disease and reduce the number of patients who might otherwise be inappropriately exposed to radiation, contrast agent, and an invasive procedure. Results of initial validation studies reported that the test may improve CAD prediction beyond that of simple prediction models such as Diamond-Forrester, but the improvement in CAD prediction when added to routine clinical evaluation is uncertain. The test also has been shown to have some predictive ability for future cardiac events and revascularization. In the COMPASS study, overall accuracy of GES in predicting cardiac events was superior to MPI in patients who were referred for MPI testing. However, in that study, reported sensitivity of MPI was considerably lower than generally reported in the literature. Also, it is unclear from the COMPASS study whether patients with a positive MPI could safely forego further testing based on a low GES.

Clinical utility of 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 is uncertain. Currently, there is no convincing evidence that the use of GES can reduce unnecessary coronary angiography. As a result, the use of GESs for predicting CAD is considered investigational.

References
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07/07/2011 Medical Policy Committee review
06/28/2012 Medical Policy Committee review
07/27/2012 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/27/2013 Medical Policy Committee review
07/17/2013 Medical Policy Implementation Committee approval. Added “for prediction of the likelihood of coronary artery disease (CAD) in stable, nondiabetic patients” to the investigational statement.
07/10/2014 Medical Policy Committee review
07/16/2014 Medical Policy Implementation Committee approval. Format revision; including, addition of FDA and or other governmental regulatory approval and rationale/source. Coverage eligibility unchanged.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
09/03/2015 Medical Policy Committee review
12/01/2016 Medical Policy Committee review.
01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes

Next Scheduled Review Date: 12/2017

Coding
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<table>
<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>81479, 81493, 84999, 81599</td>
</tr>
<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
</tr>
</tbody>
</table>

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Gene Expression Testing to Predict Coronary Artery Disease

Policy # 00309
Original Effective Date: 07/20/2011
Current Effective Date: 12/21/2016

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:

1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

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