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

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Replaces 2.04.72

Policy

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 the likelihood of CAD in stable, nondiabetic patients.

Related Policies

2.04.509 Cardiovascular Risk Panels

Policy Guidelines

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual’s family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Coding

<table>
<thead>
<tr>
<th>CPT</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<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>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
<tr>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
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Description
Heart disease is the leading cause of death in the United States.(1) 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.(2) 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 one study of nearly 400,000 patients without known CAD undergoing elective coronary angiography, approximately 38% were positive for obstructive CAD (using the CAD definition, stenosis of ≥50% of the diameter of the left main coronary artery or stenosis of ≥70% of the diameter of a major epicardial or branch vessel that was >2.0 mm in diameter; result was 41% if using the broader definition, stenosis of ≥50% in any coronary vessel).(3) Thus, methods of improving patient risk prediction before diagnostic testing 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.(4) 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.(5) 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, 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™ (CardioDx, Palo Alto, CA). 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.

**Regulatory Status**

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™ (CardioDx, Palo Alto, CA) test is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

**Scope**

Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject...
to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.

## Benefit Application

Some Plans may have contract or benefit exclusions for genetic testing.

## Rationale

This policy was created in June 2011 and updated annually with searches of the MEDLINE database. The most recent update with literature review covers the period through December 5, 2016.

Validation of the clinical use of any genetic or gene expression test focuses on 3 main principles: (1) analytic validity, which refers to the technical accuracy of a test in detecting a mutation that is present or in excluding a mutation that is absent; (2) clinical validity, which refers to the diagnostic performance of a test (sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and (3) clinical utility (i.e., how the results of a diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes).

### Analytic Validity

We did not identify any studies evaluating the analytic validity of the Gene Expression Score (GES) test.

### Clinical Validity

A GES was validated in the prospective multicenter PREDICT study in which blood samples were collected from 526 nondiabetic patients with a clinical indication for coronary angiography but no known previous myocardial infarction (MI), revascularization, or obstructive coronary artery disease (CAD; 71% symptomatic), (6) This is the same cohort from which the second assay development case-control cohort was drawn. (5) Patients were sequentially allocated to development and validation sets. Investigators 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 area under the curve (AUC) for CAD was 0.70±0.02 (p<0.001). In a 2014 follow-up publication, Investigators evaluated 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). (7)

PREDICT compared the predictive accuracy of the GES measure with clinical predictors and myocardial perfusion imaging (MPI) stress testing. (5,6,8) This was a multicenter study of 1,160 patients (development and validation cohorts combined) presenting for coronary angiography (71% symptomatic). All patients underwent GES assessment. Outcomes of interest were CAD at initial angiography and cardiac events, including revascularization, in the year after 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 was 0.72 (p=0.003). MPI was performed on 310 patients (27%); 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 (NPV) and positive predictive values (PPV) of 83% and 46%, respectively. 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. 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.

In 2012, Rosenberg et al. published a follow-up report from PREDICT 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 1,160 patients who underwent angiography in PREDICT, 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 PREDICT, Lansky et al. (2012) found that GES was an independent predictor of CAD in multivariate analysis with ORs of 2.53 (p=0.001) for 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 sex. For every 10-point increase in GES, there was a corresponding 2-fold increase in odds of CAD and increases in maximum percent stenosis, number of lesions, and total plaque volume.

Thomas et al. (2013) assessed the clinical validity and utility of the Corus CAD™ for detection of obstructive CAD in symptomatic, nondiabetic 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 patient sample differed from the PREDICT sample by including patients who had received a referral for MPI but had not been referred for invasive coronary angiography (ICA). Peripheral blood was drawn from all participants before MPI to obtain a GES. MPI-positive participants underwent ICA based on the clinician’s judgment, and all other participants received coronary computed tomography angiography (CTA). Of 537 enrolled patients, only 431 (80%) were evaluable primarily due to refusal to undergo ICA or CTA. Follow-up was 6 months after testing, with clinical endpoints 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 comparators is given in Table 1. Net reclassification improvement in predicting CAD for GES compared with 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(10)a

<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.

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

Voros et al. (2014) pooled results from PREDICT and COMPASS to compare GES with computed tomography (CT) imaging for detecting plaque burden (coronary artery calcium [CAC]), and luminal stenosis. (11) 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 (SD) age was 57 (11) 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 (e.g., 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 PPV and 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 (e.g., survival, morbidity), and lack of comparison with CAC and CTA for predicting these outcomes (i.e., incremental predictive value of GES was not assessed).

<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>
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<td></td>
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</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 CT angiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</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>

Table 2. Performance of Gene Expression Score and Diamond-Forrester Classification for Coronary Artery Plaque Burden and Luminal Stenosis: PREDICT and COMPASS Pooled Analysis (11)

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.

* Long-term outcomes are generally excellent in patients with zero CAC and substantially worse in patients with CAC >400.

Section Summary

The GES is correlated with the presence of CAD. 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 symptomatic patients. In that study, 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 guidelines on MPI, sensitivity was estimated at 87% to 89%.(12) This raises the question of whether accuracy of MPI in the COMPASS study was representative of that seen in current clinical care or whether the spectrum of patients referred for MPI in the study was representative. Given the imperfect sensitivity and specificity of GES, and the known diagnostic characteristics of standard noninvasive tests for patients with stable ischemic heart
disease, the diagnostic characteristics of GES do not by themselves obviously demonstrate that patient outcomes would be improved compared to standard diagnostic workup.

**Clinical Utility**

The clinical utility of the GES test would be established by demonstrating improved outcomes in patients managed with the test compared to patients managed without it, preferably in randomized controlled trials. Patients managed without the GES test should be evaluated according to established guidelines for the noninvasive evaluation of patients with stable ischemic heart disease.(2)

Studies examining patient outcomes of GES testing have either analyzed changes in physician management as an outcome or have not performed a rigorous comparative trial evaluating patient outcomes.

The IMPACT-CARD study (2013) compared a prospective cohort with matched historical controls to evaluate whether the GES test altered the cardiologist’s evaluation and clinical management of CAD.(13) CAD was categorized by the authors as no CAD (0% stenosis), CAD (≤50% stenosis) or CAD (>50% stenosis). Eighty-eight patients were enrolled and 83 included in the final analysis. The matched cohort comprised 83 patients selected with similar distributions of age, sex, and clinical risk factors, and had been evaluated at a participating clinic within the past 3 to 30 months. 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).

IMPACT-PCP (2014) evaluated whether having the GES altered primary care providers' diagnostic evaluation and clinical management of stable, nonacute, nondiabetic patients presenting with CAD symptoms.(14) 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. Diagnostic testing plans were changed for 58% of patients, with reductions in testing intensity more common (64%) than increases (34%; p<0.001). No study-related MACE were observed in 247 (98%) patients who had at least 30 days of follow-up.

The REGISTRY 1 study (2015) assessed the impact of having GES on patient management decisions by examining the association between GES test results and post-test referral patterns.(15) 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.

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).(16) Mean age of this cohort was 58 years; mean systolic and diastolic blood pressure were 129 mm Hg and 79 mm Hg, respectively; most patients 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 1.) Events per GES risk group were not reported.

**Section Summary**

The studies of GES testing do not provide evidence of the clinical utility of this testing. Although physicians may have made management decisions based on results of GES testing, it is unknown whether the management decisions led to improved patient outcomes. There are no rigorous studies comparing outcomes for patients managed with GES testing versus alternative methods for stable ischemic heart disease. It is not clear that the
diagnostic characteristics of GES, as established in the studies of clinical validity, would translate to improved patient outcomes through a chain of evidence.

Summary of Evidence
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 coronary artery disease (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 Gene Expression Score (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.

Practice Guidelines and Position Statements

American Heart Association
In 2012, the American Heart Association (AHA) released a policy statement on genetics and cardiovascular disease. Gene expression testing is not specifically mentioned. Generally, AHA supported recommendations issued in 2000 by a now defunct Advisory Committee to the U.S. Department of Health and Human Services, which stated: “No test should be introduced in the market before it is established that it can be used to diagnose and/or predict a health-related condition in an appropriate way.”

American College of Cardiology Foundation et al
The 2012 joint guidelines of the American College of Cardiology Foundation and 6 other medical societies for the diagnosis and management of patients with stable ischemic heart disease did not mention the Gene Expression Score (GES). The 2014 update to these guidelines also did not mention GES.

U.S. Preventive Services Task Force Recommendations
Not Applicable.

Medicare National Coverage
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.

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in December 2016 did not identify any ongoing or unpublished trials that would likely influence this review.

References


Appendix

N/A

History

<table>
<thead>
<tr>
<th>Date</th>
<th>Reason</th>
</tr>
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<tr>
<td>08/09/11</td>
<td>New Policy. Add to Medicine Section; Pathology/Laboratory sub-section. Policy created with literature search through April 2011; considered investigational.</td>
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<tr>
<td>05/24/12</td>
<td>Policy renumbered to 12.04.72 (previously 2.04.72) and reassigned to new Genetic Testing category. Related Policies updated; 2.04.67 and 2.04.71 renumbered to 12.04.67 and 12.04.71, respectively.</td>
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<td>08/20/12</td>
<td>Replace policy. Policy updated with literature search through April 2012; reference 6 added; no change to policy statement.</td>
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<td>01/11/13</td>
<td>Coding update. CPT codes 83890 – 83913 deleted as of 12/31/12; CPT codes 81200 – 81479 and 81599, effective 1/1/13, are added to the policy.</td>
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<tr>
<td>05/14/13</td>
<td>Update Related Policies. Add 12.04.91.</td>
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<tr>
<td>08/16/13</td>
<td>Replace policy. Policy updated with literature search through April 2013; reference 8-11 added. Rationale section reorganized and editorial changes made. No change in policy statement.</td>
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<tr>
<td>10/18/13</td>
<td>Update Related Policies. Add 2.04.509.</td>
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<tr>
<td>09/03/14</td>
<td>Annual Review. Policy statement unchanged but wording modified to clarify that GES is investigational “for all indications, including but not limited to” [prediction of CAD likelihood in stable, nondiabetic patients]. Policy updated with literature review through May 8, 2014; references 10, 13-16 added; others renumbered/removed. Policy statement revised as noted.</td>
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<td>08/11/15</td>
<td>Annual Review. Policy updated with literature review through May 20, 2015; references 7 and 16 added. Policy statements unchanged.</td>
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<tr>
<td>10/13/15</td>
<td>Annual Review. Policy updated with literature review through June 29, 2015; no new references added. Policy statements unchanged.</td>
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<tr>
<td>01/19/16</td>
<td>Coding update. New CPT code 81493, effective 1/1/16, added to policy.</td>
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<tr>
<td>06/01/16</td>
<td>Update Related Policies. Removed 12.04.67 and 12.04.71 as they were deleted; information moved to 2.04.509.</td>
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<tr>
<td>08/09/16</td>
<td>Annual Review. No change to policy statement. Literature reviewed through July 18, 2016.</td>
</tr>
<tr>
<td>03/14/17</td>
<td>Annual Review. Policy updated with literature review through December 5, 2016; references 2 and 19 added. Some references removed. Title and indication changed to “patients with stable ischemic heart disease” to be consistent with current guideline statements. Policy statements unchanged, but wording changed to reflect current terminology for indication. Removed Appendix table.</td>
</tr>
</tbody>
</table>

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2017 Premera All Rights Reserved.
**Discrimination is Against the Law**

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

**Premera:**
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201
1-800-368-1019, 800-537-7697 (TDD)
Complaint forms are available at

**Getting Help in Other Languages**

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost. Call 800-722-1471 (TTY: 800-842-5357).

**Arabic (Arabic):**


**Chinese (Chinese):**

本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或服務的重要訊息。本通知可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357).

**Creole (Kreyòl ayisyen):**

Avi sila a gen enfòmasyon enpòtan la. Avi sila a kapab enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou anpil ou tes an sètten sou pre le souvèt pou kouvèti asirans sou la osa pou yo ka ede w akèk depans yo. Se dwa w pou resewa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou pèye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

**Deutsche (German):**


**Italiano (Italian):**


**Oromoo (Cushite):**


**Français (French):**


**Italiano (Italian):**


**Deutsche (German):**


**Kreyòl ayisyen (Creole):**

Avi sila a gen enfòmasyon enpòtan la. Avi sila a kapab enfòmasyon enpòtan konsènan aplikasyon w lan oswa konsènan kouvèti asirans lan atravè Premera Blue Cross. Kapab genyen dat ki enpòtan nan avi sila a. Ou ka gen pou anpil ou tes an sètten sou pre le souvèt pou kouvèti asirans sou la osa pou yo ka ede w akèk depans yo. Se dwa w pou resewa enfòmasyon sa a ak asistans nan lang ou pale a, san ou pa gen pou pèye pou sa. Rate nan 800-722-1471 (TTY: 800-842-5357).

** Español (Spanish):**

Si desea recibir esta información y ayuda en su idioma a ningún costo, llame al 800-722-1471 (TTY: 800-842-5357).

**Português (Portuguese):**

Para obter essas informações e assistência em sua língua, gratuitamente, ligue para 800-722-1471 (TTY: 800-842-5357).

**Italiano (Italian):**

Premera Blue Cross.

The following information is important and may contain terms that are important to you.

Please read this information carefully before taking any action.

If you have questions, please call 800-722-1471 (TTY: 800-842-5357).