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 (CAD) in stable, nondiabetic patients.

**Policy Guidelines**

**Genetic Counseling**
Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

**Coding**
There is a specific CPT code for the CorusCAD™ test:
- 81493: 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

Other similar tests would be reported with the following unlisted CPT code:
- 81599: Unlisted multianalyte assay with algorithmic analysis

**Description**
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 the 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.

**Related Policies**
- KIF6 Genotyping for Predicting Cardiovascular Risk and/or Effectiveness of Statin Therapy

**Benefit Application**
Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.
Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**Regulatory Status**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service. Laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. The Corus® CAD test (CardioDx, Palo Alto, CA) is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

**Rationale**

**Background**

**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. 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.

**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 400000 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). 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. 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 the final Corus CAD score development. Investigators conducted two 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 (CATHeterization GENetics; n=195), expression of 42 genes in nondiabetic patients and 12 genes in diabetic patients were 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 Personalized Risk Evaluation and Diagnosis in the Coronary Tree 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.

**Literature Review**

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

**Gene Expression Testing for Suspected Stable Ischemic Heart Disease**

**Clinical Context and Test Purpose**

The joint guidelines by the American College of Cardiology Foundation (2012) and 6 other medical associations on the diagnosis of stable ischemic heart disease provides details on the diagnostic pathway for evaluation and treatment of heart disease. The pathway is summarized in Figure 1 and in the following paragraphs. When patients present with signs and symptoms of obstructive coronary artery disease (CAD), the estimated risk (or pretest probability) of obstructive CAD is estimated using clinical characteristics such as age, sex, type of angina symptoms, smoking, and other comorbidities (e.g., diabetes, hyperlipidemia). The guidelines provide a table of pretest probabilities of CAD by age, sex, and type of angina adapted from the Diamond-Forrester tool. For example, a woman age 30 to 39 with nonanginal chest pain has a 4% pretest probability of CAD and a man age 60 to 69 with typical anginal chest pain has a 94% pretest probability of CAD.

For patients initially assessed at low-risk (<10% pretest probability of obstructive CAD), no further testing is generally needed, and the patient can be observed and treated with medical therapy. Patients at high-risk of obstructive CAD may proceed to coronary angiography if the symptoms or findings suggest a high-risk lesion.

The classification of intermediate risk varies in the literature but is frequently defined as a pretest probability between 10% and 90%. In patients with an intermediate pretest probability of obstructive CAD, noninvasive diagnostic methods, such as exercise or pharmacologic stress tests with or without imaging methods such as myocardial perfusion imaging (MPI), or coronary computed tomographic angiography may be recommended. The noninvasive testing used depends on patient characteristics such as the ability to exercise, electrocardiographic results, and other comorbidities as well as local expertise, availability of the testing modality, and patient preference. Some noninvasive imaging methods have potential risks of exposure to radiation and contrast material. After noninvasive testing, patients initially classified as having an intermediate pretest probability of obstructive CAD are further risk-stratified based on the estimated risk of coronary event or death using clinical data and results of noninvasive testing. The American College Cardiology Foundation (2012) joint guidelines also provide risk stratification following noninvasive testing. For example, severe stress-induced left ventricular...
dysfunction (peak exercise left ventricular ejection fraction <45% or drop in left ventricular ejection fraction with stress ≥10%) indicates a high (>3%) annual risk of death or myocardial infarction; a 1-mm ST-segment depression occurring with exertional symptoms indicates an intermediate (1% to 3%) annual risk of death or myocardial infarction; and a normal stress or no change of limited resting wall motion abnormalities during stress indicates a low-risk (<1%) annual risk of death or myocardial infarction. Patients at high-risk of coronary event or death following noninvasive testing may proceed to coronary angiography.

CardioDx, the manufacturer of the gene expression score (GES; Corus CAD), has stated the test “complements and improves the current noninvasive assessment” of suspected obstructive coronary artery disease. The manufacturer-supported registry collects data in the primary care setting and a decision impact study using registry data has suggested that the test may be used to identify stable, nonacute outpatients presenting with symptoms suggestive of obstructive CAD who can safely forgo referral to cardiology or advanced cardiac testing. Other studies have been performed in patients who have been referred for invasive angiography and MPI.

The question addressed in this evidence review is: Does gene expression testing in patients with stable ischemic heart disease improve the net health outcome compared with standard clinical evaluation?

The following PICOTS were used to select literature to inform this review.

**Figure 1. Diagnostic Pathway**

Patients
The intended population are patients with suspected ischemic heart disease with stable angina. The manufacturer states that appropriate patients are those who do not have diabetes, without systemic infectious or systemic inflammatory conditions, and who are not currently taking steroids, immunosuppressive agents, or chemotherapeutic agents. The intended use population might be all such patients or a subset of them identified by risk stratification, depending on exactly how the test fits into the diagnostic pathway.

Interventions
A GES classifier (Corus CAD) 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. A score of less than 15 has been used to indicate a low risk of obstructive CAD.
Blood for the test is collected using a routine blood draw and stored between 2°C and 10°C for up to 1 day before shipping to the CardioDx Commercial Laboratory, which is certified by Clinical Laboratory Improvement Amendments and accredited by the College of American Pathologists. The results are available within a few days.

The intervention of interest for assessing validity would be Corus CAD score added to current risk prediction models.

Comparators
The comparator would be clinical risk prediction models alone that estimate the pretest probability of obstructive CAD (e.g., Diamond-Forrester). Noninvasive testing would be a comparator for determining whether a patient would be referred for coronary angiography.

The reference standard for diagnosing obstructive CAD is coronary angiography with obstructive CAD defined as any stenosis 50% or greater in the left main coronary artery or 70% or greater in any other coronary artery according to joint guidelines from the American College of Cardiology Foundation, the American Heart Association, and the Society for Cardiovascular Angiography and Interventions. However, this is also an imperfect reference standard for the outcome of a cardiac event.

Outcomes
Beneficial outcomes resulting from a true-negative test result are avoiding unnecessary subsequent testing. Harmful outcomes resulting from a false-positive test result are unnecessary noninvasive and invasive testing or receiving unnecessary treatment. Harmful outcomes resulting from a false-negative test result are increased risk of cardiovascular events and death.

In Figure 1, (i.e., a triage “rule-out” test), the test would need to identify precisely a group of patients that could safely forgo additional noninvasive testing; therefore, the sensitivity, negative predictive value (NPV) and negative likelihood ratio are key test performance characteristics.

Timing
The time period of interest for measuring the diagnostic performance is the time to obstructive CAD diagnosis. For assessing cardiovascular outcomes, 2.5 years is consistent with the PROspective Multicenter Imaging Study for Evaluation of chest pain (PROMISE) trial, which compared diagnostic strategies for CAD.

Setting
The test has been evaluated in the outpatient and primary care settings as well as in patients referred for advanced cardiac testing.

Review of Evidence
There are three core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:
- Technically reliable
- Clinically valid
- Clinically useful

Technical Reliability
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).
Gene Expression Testing in the Evaluation of Patients with Stable Ischemic Heart Disease

Characteristics and results of clinical validity studies evaluating the performance of the Corus CAD score for diagnosing obstructive CAD are shown in Tables 1 and 2. Four studies reported the performance characteristics for Corus CAD for diagnosing obstructive CAD. Voora et al (2017), (PROMISE) was the largest study and it used the American Heart Association definition for obstructive CAD. In this population of patients referred for nonurgent, noninvasive testing, the sensitivity was 73% (95% confidence interval [CI], 64% to 81%), the negative likelihood ratio was 0.56 (95% CI, 0.42 to 0.77), and the NPV was 94% (95% CI, 92% to 96%). The Rosenberg et al (2010), (PREDICT) and Thomas et al (2013), (COMPASS) studies used a broader definition of obstructive CAD and enrolled few patients at intermediate risk (18% and 17%, respectively) based on clinical risk prediction rules. The sensitivities were 85% (95% CI, 79% to 90%) and 89% (95% CI, 78% to 95%) in PREDICT and COMPASS, respectively while the NPV rates were 83% (95% CI, 77 to 89) and 96% (95% CI, 93% to 99%). The thresholds used to identify obstructive CAD were not clear in Ladapo et al (2017). The studies are described in more detail in the following paragraphs.

Corus CAD score was validated in the prospective multicenter PREDICT study (2010) in which blood samples were collected from 526 nondiabetic patients who did not have systemic infectious or inflammatory conditions and who were not receiving immunosuppressive or chemotherapeutic agents with a clinical indication for coronary angiography but no known previous myocardial infarction, revascularization, or obstructive CAD (71% symptomatic). 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 development cohort was 58% male and 87% white. The validation cohort is described in the tables.

In another follow-up from PREDICT, Lansky et al (2012) found that the Corus CAD score was an independent predictor of CAD in multivariate analysis, with odds ratios (ORs) of 2.53 (p = 0.001) for the total study population and 1.99 (95% CI, 1.35 to 2.96; p = 0.001) and 3.45 (95% CI, 1.97 to 5.91; 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.

Thomas et al (2013) assessed the clinical validity and utility of the Corus CAD score for detection of obstructive CAD in symptomatic, nondiabetic patients without inflammatory conditions 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, which they stated corresponded to 65% to 70% stenosis on clinical angiography. PREDICT compared the predictive accuracy of the GES test with clinical predictors and MPI stress testing. A 2014 follow-up publication, including patients from the gene discovery and algorithm development cohorts in combination with the validation cohort (n=1038), reported similar performance.

In another follow-up from PREDICT, Lansky et al (2012) found that the Corus CAD score was an independent predictor of CAD in multivariate analysis, with odds ratios (ORs) of 2.53 (p = 0.001) for the total study population and 1.99 (95% CI, 1.35 to 2.96; p = 0.001) and 3.45 (95% CI, 1.97 to 5.91; 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.

Voora et al (2017) evaluated the Corus CAD score in a cohort from the PROMISE trial funded by National Heart, Lung, and Blood Institute. PROMISE was a randomized controlled trial (2015) that enrolled 10003 outpatients who were randomized to functional (i.e., exercise,
Several studies have evaluated Corus CAD in a cohort of patients from the PRESET (A Registry to Evaluate Patterns of Care Associated with the Use of Corus CAD in Real World Clinical Care Settings) registry. The PRESET registry is funded by the manufacturer. This registry enrolled patients from 21 primary care practices in the United States between August 2012 and August 2014. Patients had nonacute chest pain and typical or atypical symptoms of obstructive CAD without history of myocardial infarction or revascularization, diabetes, suspected acute myocardial infarction, high-risk unstable angina pectoris, New York Heart Association class III or IV heart failure symptoms, cardiomyopathy with an ejection fraction of 35% or less, severe cardiac valvular diseases, current systemic infectious or inflammatory condition, or recent treatment with an immunosuppressive or chemotherapeutic agent. A report by Ladapo et al (2017) is primarily focused on physician decision-making but includes a table of the Corus CAD score and advanced cardiac testing results for obstructive CAD in 84 patients. Therefore, those data are included in the following tables. Subsequent reports focused on adults aged 65 and older (n=176) and women of all ages (n=288) with stable symptoms suggestive of obstructive CAD, showing higher referral rates for patients with a higher Corus CAD score.

### Table 1. Clinical Validity Study Characteristics of the Corus CAD Score for Diagnosing Obstructive CAD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population^a</th>
<th>Design</th>
<th>Reference Standard for Obstructive CAD</th>
<th>Threshold Score for Positive Corus CAD Score Test</th>
<th>Timing of Reference and Corus CAD Score Tests</th>
<th>Blinding of Assessors</th>
<th>Comment</th>
</tr>
</thead>
</table>
| Rosenberg et al (2010)^12, PREDICT | Referred for ICA  
- Mean age, >60 y  
- 90% White  
- 43% women  
48% low risk, 18% Intermediate Risk, 34% high risk | Prospective | ≥50% stenosis in ≥1 major coronary arteries by quantitative CA | 14.75 | Blood samples drawn before CA | Yes | · PREDICT study validation cohort  
· Funded by manufacturer |
| Thomas et al (2013)^13, COMPASS | Referred for MPI stress testing  
- Mean age, 56 y  
- 89% White  
- 48% women | Prospective | ≥50% stenosis in ≥1 major coronary arteries by quantitative CA or CCTA | 15 | Blood samples drawn before MPI and CA | Yes | · COMPASS study  
· Funded by manufacturer |
### Table 2. Clinical Validity Results of the Corus CAD Score for Diagnosing Obstructive CAD

<table>
<thead>
<tr>
<th>Study</th>
<th>Initial N</th>
<th>Final N</th>
<th>Excluded Samples</th>
<th>Prevalence of Obstructive CAD</th>
<th>Sensitivity (95% CI), %</th>
<th>Specificity (95% CI), %</th>
<th>PPV (95% CI), %</th>
<th>NPV (95% CI), %</th>
<th>AUC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenberg et al (2010)[12] PRE DI C T</td>
<td>649</td>
<td>525</td>
<td>Insufficient sample volume RNA yield: 43</td>
<td>37%</td>
<td>85 (79 to 90)a</td>
<td>43 (38 to 49)a</td>
<td>46 (41 to 52)a</td>
<td>83 (77 to 89)a</td>
<td>0.70 (NR)</td>
</tr>
</tbody>
</table>

CA: coronary angiography; CAD: coronary artery disease; CCTA: coronary computed tomographic angiography; ICA: invasive coronary angiography; MPI: myocardial perfusion imaging; NHLBI: National Heart, Lung, and Blood Institute; NR: not reported. a In all studies, patients were nondiabetic, without inflammatory conditions, and were not receiving immunosuppressive or chemotherapeutic agents.
### Table 3. Relevance Gaps for Clinical Validity Studies of the Corus CAD Score for Diagnosing Obstructive CAD

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenberg et al (2010)¹² PREDICT</td>
<td>2. Test use in current diagnostic pathway unclear 4. Study only includes patients referred for ICA and only 18% of patients were at intermediate risk 5. Racial minorities were not well-represented</td>
<td>None noted</td>
<td>2. Used broad obstructive CAD definition 3. Diagnostic performance characteristics not provided for clinical risk models; performance characteristics by sex not provided</td>
<td>None noted</td>
</tr>
<tr>
<td>Thomas et al (2013)¹³ COMPASS</td>
<td>2. Test use in current diagnostic pathway unclear 4. Only 17% of patients were at</td>
<td>None noted</td>
<td>2. Used broad obstructive CAD definition 3. Diagnostic performance characteristics not provided for clinical risk models performance characteristics by gender not provided</td>
<td>None noted</td>
</tr>
<tr>
<td>Study</td>
<td>Population</td>
<td>Intervention</td>
<td>Comparator</td>
<td>Outcomes</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------</td>
<td>-----------------------------------</td>
<td>-------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Voora et al (2017)¹¹, PROMISE</td>
<td>intermediate risk</td>
<td>None noted</td>
<td>3. Thresholds for diagnosis not given</td>
<td>3. Diagnostic performance characteristics not provided; performance characteristics not provided for clinical risk models; performance characteristics by sex not provided</td>
</tr>
<tr>
<td></td>
<td>2. Test use in current diagnostic pathway unclear</td>
<td>3. Performance characteristics for comparators not provided</td>
<td>1. Classification thresholds not defined</td>
<td>1. Study does not directly assess a key health outcome; Evidence chain or decision model not explicated; Key clinical validity outcomes not reported (sensitivity, specificity, predictive values)</td>
</tr>
<tr>
<td>Ladapo et al (2017)⁸, PRESET</td>
<td>None noted</td>
<td>1. Thresholds for diagnosis not given</td>
<td>3. Diagnostic performance characteristics not provided for clinical risk models; performance characteristics by sex not provided</td>
<td>1. Classification thresholds not defined</td>
</tr>
<tr>
<td></td>
<td>2. Test use in current diagnostic pathway unclear</td>
<td>3. Performance characteristics for comparators not provided</td>
<td>1. Classification thresholds not defined</td>
<td>1. Study does not directly assess a key health outcome; Evidence chain or decision model not explicated; Key clinical validity outcomes not reported (sensitivity, specificity, predictive values)</td>
</tr>
</tbody>
</table>

Key: 1. Intended use population unclear 2. Clinical context for test is unclear 3. Study population unclear 4. Study population not representative of intended clinical use 5. Study population is subpopulation of intended use

CAD: coronary artery disease; FN: false negative; FP: false positive; ICA: invasive coronary angiography; TN: true negative; TP: true positive.
### Table 4. Study Design and Conduct Gaps for Clinical Validity Studies of the Corus CAD Score for Diagnosing Obstructive CAD

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Blinding</th>
<th>Delivery of Test</th>
<th>Selective Reporting</th>
<th>Completeness of Follow-Up</th>
<th>Statistical Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenberg et al (2010)¹², PREDICT</td>
<td>None noted</td>
<td>None noted</td>
<td>None noted</td>
<td>None noted</td>
<td>None noted</td>
<td>1. CIs not reported, calculated based on data provided</td>
</tr>
<tr>
<td>Thomas et al (2013)¹³, COMPASS</td>
<td>None noted</td>
<td>None noted</td>
<td>None noted</td>
<td>None noted</td>
<td>2. 90 patients with negative MPI refused CTA and were excluded; no description of these patients was provided</td>
<td>None noted</td>
</tr>
<tr>
<td>Voora et al (2017)¹¹, PROMISE</td>
<td>None noted</td>
<td>None noted</td>
<td>None noted</td>
<td>None noted</td>
<td>None noted</td>
<td>1. CIs not reported, calculated based on data provided 2. No comparison to noninvasive testing provided</td>
</tr>
<tr>
<td>Ladapo et al (2017)⁸, PRESET</td>
<td>None noted</td>
<td>1. Blinding not reported</td>
<td>None noted</td>
<td>None noted</td>
<td>None noted</td>
<td>1. CIs not reported, calculated based on data provided 2. No comparison to noninvasive testing provided</td>
</tr>
</tbody>
</table>

**Key**
1. Selection not described  
2. Selection not random nor consecutive (i.e., convenience)  
3. Not blinded to results of reference or other comparator tests  
4. Timing of delivery of index or reference test not described  
5. Timing of index and comparator tests not same  
6. Procedure for interpreting tests not described  
7. Expertise of evaluators not described  
8. Not registered  
9. Evidence of selective reporting  
10. Evidence of selective publication  
11. Inadequate description of indeterminate and missing samples  
12. High number of samples excluded  
13. High loss to follow-up or missing data  
14. CIs and/or p values not reported  
15. No statistical test reported to compare to alternatives

CAD: coronary artery disease; CI: confidence interval; CTA: computed tomography angiography; MPI: myocardial perfusion imaging.

Net reclassification for the Corus CAD score compared with other tests for the diagnosis of obstructive CAD was performed in Rosenberg et al (2010)¹² and Thomas et al (2013)¹³, and are shown in Table 5 below. In Rosenberg et al (2010), the Corus CAD, Diamond-Forrester, and expanded clinical model scores were prospectively categorized as low (0% to <20%), intermediate (≥20% to <50%), or high (≥50%) risk for obstructive CAD. MPI results were categorized as negative (no defect or possible fixed or reversible defect) or positive (fixed or reversible defect). In Thomas et al (2013), Corus CAD scores were categorized as low
The Diamond-Forrester and Morise scores were categorized as low (<15%), medium (16 to ≤50%), or high likelihood (>50%). It was not clear how the cutoffs were chosen in Thomas et al (2013). As described in the Clinical Context section of this review, the pretest probability cutoffs from clinical models used for risk stratification vary in the literature, but intermediate risk frequently ranges from 10% to 90%. Net reclassification using this cutoff has not been reported.

### Table 5. Net Reclassification Index for the Corus CAD Score vs Other Modalities for Diagnosing Obstructive CAD

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Net Reclassification Improvementa for Corus CAD score vs Second Modality (95% CI)</th>
<th>Myocardial Perfusion Imaging</th>
<th>Diamond-Forrester</th>
<th>Expanded Clinical Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenberg et al (2010)12, PREDICT</td>
<td>21% (NR) &lt;0.001</td>
<td>Site-Read</td>
<td>20% (NR)</td>
<td>16% (NR)</td>
</tr>
<tr>
<td>Thomas et al (2013)13, COMPASS</td>
<td>26% (NR) &lt;0.001</td>
<td>Core-Lab</td>
<td>28% (NR)</td>
<td>60% (NR)</td>
</tr>
</tbody>
</table>

Cl: confidence interval; NR: not reported; CAD: coronary artery disease.

### Table 6. Performance of Corus CAD and Diamond-Forrester Classification for Coronary Artery Plaque Burden and Luminal Stenosis: Pooled PREDICT and COMPASS Analysis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Corus CAD AUROC (95% CI)</th>
<th>Diamond-Forrester AUROC (95% CI)</th>
<th>Sensitivity, %</th>
<th>Specificity, %</th>
<th>PPV, %</th>
<th>NPV, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque burdena</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>71</td>
<td>62</td>
<td>65</td>
<td>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>84</td>
<td>49</td>
<td>14</td>
<td>97</td>
</tr>
<tr>
<td>Luminal stenosis by CTA</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>84</td>
<td>51</td>
<td>23</td>
<td>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>90</td>
<td>48</td>
<td>8</td>
<td>99</td>
</tr>
</tbody>
</table>

Adapted from Voros et al (2014).20

AUROC: area under the receiver operating characteristic curve; CAC: coronary artery calcium; CAD: coronary artery disease; CI: confidence interval; CTA: computed tomography angiography; NPV: negative predictive value; PPV: positive predictive value.

Long-term outcomes are generally excellent for patients with CAC >0 and substantially worse for patients with CAC >400.

### Subsection Summary: Diagnostic Performance

The diagnostic pathway for CAD includes information from medical history, along with age and sex, stress testing, and imaging. 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 two validation studies (PREDICT, COMPASS) have reported the test may improve CAD prediction beyond the Diamond-Forrester prediction model. In the COMPASS study, the sensitivity and NPV of the Corus CAD score in diagnosing obstructive CAD was superior to 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. Neither PREDICT nor COMPASS used the guideline definition of obstructive CAD as the reference standard and had relatively few patients at intermediate risk based on clinical prediction rules. The sensitivity and NPV of clinical models were not reported. An analysis of a cohort from the PROMISE trial including patients with an intermediate pretest probability of obstructive CAD confirmed a high NPV for the Corus CAD score.

The test excludes patients with diabetes, acute and chronic inflammatory conditions, and such patients are expected to be common among those being evaluated for obstructive CAD. Thus, applicability to clinical practice may be narrow. Although the test is marketed as a sex-specific test, performance characteristics by sex and age were not provided. One study reported that the Corus CAD score was associated with obstructive CAD in both men (OR=1.99; 95% CI, 1.35 to 2.96) and women (OR=3.45; 95% CI, 1.97 to 5.91). The gene selection, algorithm development, and validation studies have been performed in populations that were approximately 90% white.

Net reclassification has been reported comparing the Corus CAD score with other clinical prediction tools and MPI. While the pretest probability cutoffs from clinical models used for risk stratification vary in the literature, intermediate risk frequently ranges from 10% to 90% and net reclassification using this cutoff has not been reported.

Prognostic Performance
Publications from four of the previously described studies have reported performance of the Corus CAD score in the prognosis of cardiovascular events. Table 7 summarizes the results. Rosenberg et al (2012) published a follow-up report from PREDICT on the association between Corus CAD score and subsequent major adverse cardiac events (MACE), including myocardial infarction, stroke/transient ischemic attack, all-cause mortality, and coronary revascularization.

In Thomas et al (2013), patients were followed for 6 months after Corus CAD testing, with 420 of 431 completing follow-up. MACE (nonfatal myocardial infarction, stroke/transient ischemic attacks, or all-cause mortality) and revascularization events were recorded. Only two MACE events occurred.

Voora et al (2017) included analysis of 2370 PROMISE patients with samples in the biorepository who were followed for a median of 25 months. The association between the Corus CAD score and a composite outcome of death, myocardial infarction, revascularization, or unstable angina was statistically significant after adjustment for the Framingham Risk Score. The association was driven primarily by the revascularization component. When revascularization was removed from the composite, there was no longer a significant association between the Corus CAD score and the outcome after adjusting for the Framingham Risk Score. A low Corus CAD score was associated with a low-risk (1.6%) of revascularization and an NPV of 98% (CI not reported).

Ladapo et al (2018) and Gul et al (2019) evaluated the association between Corus CAD scores and cardiovascular events at 12 months in elderly adults (n=176) and women (n=288) from the PRESET registry. In adults 65 years of age or older the incidence of major adverse cardiovascular events or revascularization was 0% in patients with a low Corus CAD score and 10% in patients with a higher Corus CAD score (p=0.04). In the cohort of women of all ages, the incidence of major cardiac events was not statistically different between women with a low Corus CAD score (1.3%) and those with a higher Corus CAD score (4.2%, p=0.16).
Table 7. Clinical Validity Results of the Corus CAD Score for Prognosticating Cardiovascular Events

<table>
<thead>
<tr>
<th>Author</th>
<th>N</th>
<th>Event</th>
<th>Incidence</th>
<th>Sens (95% CI)</th>
<th>Spec (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
<th>Association (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenberg et al (2012)</td>
<td>1160</td>
<td>12-mo MACE(^a)</td>
<td>1.5</td>
<td>82 (NR)</td>
<td>34 (NR)</td>
<td>1.8 (NR)</td>
<td>99 (NR)</td>
<td>OR=2.41 (0.74 to 10.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12-mo MACE(^b) or revascularizations</td>
<td>25</td>
<td>86 (NR)</td>
<td>41 (NR)</td>
<td>33 (NR)</td>
<td>90 (NR)</td>
<td>OR=4.32 (3.02 to 6.25)</td>
</tr>
<tr>
<td>Thomas et al (2013)</td>
<td>420</td>
<td>6-mo revascularizations or MACE(^b)</td>
<td>6.7</td>
<td>96 (NR)</td>
<td>NR</td>
<td>NR</td>
<td>99 (NR)</td>
<td>NR</td>
</tr>
<tr>
<td>Voora et al (2017)</td>
<td>2370</td>
<td>Death, MI, or UA with median 25-mo follow-up</td>
<td>2.6</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>HR=0.98 (0.52 to 1.87)(^b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Death, MI, UA, or revascularization with median 25-mo follow-up</td>
<td>6.0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>HR=1.70 (1.10 to 2.64)(^b)</td>
</tr>
</tbody>
</table>

Values are percent unless otherwise indicated. CI: confidence interval; MACE: major adverse cardiac events; MI: myocardial infarction; NPV: negative predictive value; NR: not reported; OR: odds ratio; HR: hazard ratio; PPV: positive predictive value; Sens: sensitivity; Spec: specificity; UA: unstable angina
\(^a\) MACE included MI, stroke/transient ischemic attack, all-cause mortality.
\(^b\) Adjusted for Framingham Risk Score.

Subsection Summary: Prognostic Performance

There is less evidence on the association between the Corus CAD score and cardiovascular events. The available evidence provides a preliminary indication that a Corus CAD score of 15 or less identifies a group unlikely to require revascularization within 2 years. No data was given regarding which revascularizations were planned vs emergent; e.g., information is needed describing how many revascularizations were performed to alleviate symptoms, for progression to unstable angina, or to decrease the risk of cardiac outcomes such as death, heart failure, or myocardial infarction. More data are needed on coronary events other than revascularizations. Notably, CIs for performance characteristics are lacking in these studies.

Section Summary: Clinically Valid

There is uncertainty regarding the role of the test in the diagnostic pathway. The proposed strategy for integrating the results of the test with current guidelines for risk stratification before and/or after other noninvasive testing is not clear. The diagnostic strategy incorporating the Corus CAD test should be explicitly described so that it is clear which existing data are relevant for evaluating the proposed use. Proposed changes in stratification compared with existing guidelines are needed so that net reclassification analyses compared with guideline recommended stratification can be constructed. Decision models of a strategy incorporating the Corus CAD score into the guideline recommendations would be useful.

The Corus CAD score is correlated with the presence of obstructive CAD. The PREDICT and COMPASS studies reported that the GES is superior to the Diamond-Forrester model and to MPI for predicting obstructive CAD. However, the available studies do not specify the use of the test in the guideline, recommended diagnostic pathway for stable ischemic heart disease. Therefore, it is not possible to make conclusions about clinical validity. The test provides scores that are age- and sex-specific and the manufacturer's website states the test is the “first sex-specific test for obstructive CAD”. Performance characteristics by sex and age were reported from a safety analysis of registry data. A high Corus CAD score was associated with adverse cardiac events in older adults (both men and women), but this association was not statistically significant when assessed in the cohort of women.
Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

There is no direct evidence from randomized controlled trials.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

To develop a chain of evidence or a decision model requires explication of the elements in the model and evidence that is sufficient to demonstrate each of the links in the chain of evidence or the validity of the assumptions in the decision model. A chain of evidence or decision model must be constructed so to permit comparison between a diagnostic strategy including Corus CAD testing and a strategy of no Corus CAD testing. The Corus CAD test is associated with the diagnosis of obstructive CAD. The Corus CAD test classifies patients into clinically credible diagnostic groups (low- and high-risk of obstructive CAD) that were defined a priori and evaluated in prospective studies. However, it is not clear how the test fits in the current diagnostic pathway and how results would be used to change current guideline-based risk.

Patients managed without the Corus CAD test should be evaluated according to established guidelines for the noninvasive evaluation of patients with stable ischemic heart disease. Studies examining patient outcomes of Corus CAD testing have primarily analyzed changes in physician management as an outcome.

The Investigation of a Molecular Personalized Coronary Gene Expression Test (IMPACT)-CARDiology Practice Pattern study (2013) compared a prospective cohort with matched historical controls to evaluate whether the Corus CAD test altered cardiologist evaluation and clinical management of CAD. CAD was categorized by authors as no CAD (0% stenosis), CAD with 50% or less stenosis, or CAD with more than 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 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-Primary Care Practice Pattern (PCP) (2014) evaluated whether having the Corus CAD 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 Corus CAD 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 the Corus CAD on patient management decisions by examining the association between Corus CAD results and posttest referral patterns. Primary care practitioners at 7 centers evaluated 342 stable, nonacute, nondiabetic patients presenting with CAD symptoms. All patients underwent Corus CAD testing. Of 167 patients with low (≤15) Corus CAD score, 10 (6%) were referred for further cardiac evaluation compared with 122 (70%) of 175 patients in the high Corus CAD score group (p<0.001). Over a mean follow-up of 264 days, there were 5 MACE, 2 in the low Corus CAD score group and 3 in the high Corus CAD score group. Of 21 patients who underwent elective invasive coronary angiography, 1 (50%) of 2 in the low Corus CAD score group and 8 (42%) of 19 in the high Corus CAD score 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 Corus CAD score on further cardiac evaluation (n=320). Referral rate for further cardiac evaluation was 4% for women with low Corus CAD score (n=248) vs 83% for women with elevated Corus CAD score (n=72).

The Ladapo et al (2017) analysis of the 566 patients from the PRESET registry (described previously) evaluated the association between the Corus CAD score and cardiac referrals (referral to cardiology or further cardiac testing). Ten percent (26/252) of low Corus CAD score patients were referred vs 44% (137/314) of high Corus CAD score patients. After adjusting for age, sex, body mass index, smoking status, hypertension, and dyslipidemia, the association between Corus CAD score and referral rate remained statistically significant (OR=0.15; 95% CI, 0.10 to 0.24; p<0.001). With 1 year of follow-up, MACE and revascularizations were noted in 3 (1.2%) of 252 low Corus CAD score patients and 14 (4.5%) of 314 high Corus CAD score patients (p=0.03).

**Section Summary: Clinically Useful**

There are no rigorous studies comparing clinical outcomes for patients managed using Corus CAD testing with alternative methods for stable ischemic heart disease (i.e., no direct evidence that the test is clinically useful). Currently, it is unclear whether a chain of evidence can be constructed because of the lack of evidence on use of the test in the intermediate risk population.

**Summary of Evidence**

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. The 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 two validation studies (PREDICT, COMPASS) have reported the test may improve CAD prediction beyond the Diamond-Forrester prediction model. In the COMPASS study, the sensitivity and NPV of the Corus CAD score in diagnosing obstructive CAD was superior to 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. Neither PREDICT nor COMPASS used the guideline definition of obstructive CAD as the reference standard and had relatively few patients at intermediate risk based on clinical prediction rules. The sensitivity and NPV 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 NPV 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.

**SUPPLEMENTAL INFORMATION**

**Practice Guidelines and Position Statements**

**American Heart Association**

The AHA (2012) released a policy statement on genetics and cardiovascular disease. Gene expression testing is not specifically mentioned. Generally, the 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.”

The AHA (2017) released a scientific statement on the expressed genome in cardiovascular diseases and stroke. The statement summarized the clinical validity and utility evidence for the Corus CAD score, stating “…the Corus CAD test is a clinically available diagnostic test that has been evaluated, has been deemed to be valid and useful....”

**American College of Cardiology Foundation et al**

The joint guidelines of the American College of Cardiology Foundation (2012) and 6 other medical societies for the diagnosis and management of patients with stable ischemic heart disease did not mention the gene expression score. The 2014 update to these guidelines also did not mention the gene expression score.

**U.S. Preventive Services Task Force Recommendations**

Not applicable.

**Medicare National Coverage**

There are no Medicare national coverage determinations for Corus CAD testing to predict coronary artery disease (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 one or more CAD risk factors. In October 2015, Noridian also issued a positive local coverage decision. However, a draft noncoverage decision has been posted by Noridian with comment period open until April 2018. In 2016, Novitas Solutions issued a local coverage decision.

**Ongoing and Unpublished Clinical Trials**

A search of ClinicalTrials.gov in December 2017 did not identify any ongoing or unpublished trials that would likely influence this review.

**References**


Incorporating Age, Sex, and Gene Expression for Evaluating Women with Stable Symptoms Suggestive of Obstructive Coronary Artery Disease: Analysis from the PRESET Registry. J Womens Health (Larchmt), 2019 Jan 18. PMID 30653377.


Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms.
of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

IE
The following services may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<tr>
<td>CPT®</td>
<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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<tr>
<td></td>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
<tr>
<td>HCPCS</td>
<td>None</td>
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</tr>
<tr>
<td>ICD-10 Procedure</td>
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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/05/2012</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>08/29/2014</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
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<tr>
<td>01/01/2016</td>
<td>Coding update</td>
<td>Administrative Review</td>
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<td>01/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
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<tr>
<td>03/01/2017</td>
<td>Policy title change from “Gene Expression Testing to Predict Coronary Artery Disease” Policy revision without position change</td>
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<tr>
<td>05/01/2018</td>
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</tr>
<tr>
<td>06/01/2019</td>
<td>Policy revision without position change</td>
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</table>

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an
authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.