Genetic Testing in the Evaluation of Patients With Stable Ischemic Heart Disease

Policy #    00309
Original Effective Date:  07/20/2011
Current Effective Date:  12/19/2018

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

Note: KIF6 Genotyping for Predicting Cardiovascular Risk and/or Effectiveness of Statin Therapy is addressed separately in medical policy 00284.

Note: Genotyping for 9p21 Single-Nucleotide Polymorphisms to Predict Risk of Cardiovascular Disease or Aneurysm is addressed separately in medical policy 00299.

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

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

Background/Overview

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 400,000 patients without known CAD undergoing elective coronary angiography, approximately 38% were positive for obstructive CAD (using the CAD definition, ≥50% stenosis of the diameter of the left main coronary artery or ≥70% stenosis of the diameter of a major epicardial or branch vessel >2.0 mm in diameter) and 41% if using the broader definition (≥50% stenosis in any coronary vessel). 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 final Corus CAD score development. Investigators conducted 2 successive case-control gene expression discovery studies using samples from independent cohorts. Cases were angiographically defined as 75% or greater maximum stenosis in 1 major vessel, or 50% or greater in 2 vessels, and controls defined as less than 25% stenosis in all major vessels. Of clinical factors, diabetes had the most significant effect on gene expression; in the first case-control study in symptomatic patients (CATHGEN; N=195), expression of 42 genes in nondiabetic patients and 12 genes in diabetic patients was found to (p<0.05) discriminate significantly between cases and controls with no overlap. As a result, the second case-control study, in a subset of 198 patients from the prospective PREDICT study, and final development of the assay was limited to nondiabetic patients (62% symptomatic). The participants were 76% male and 89% white. Final variable selection comprised the expression of 20 CAD-associated genes, 3 normalization genes, and terms for age and sex. The majority of the selected genes were immune and inflammatory-related. All terms were incorporated into an algorithm that resulted in an obstructive CAD score ranging from 1 to 40.

**FDA or Other Governmental Regulatory Approval**

**U.S. Food and Drug Administration (FDA)**

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service. Laboratory-developed tests 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.

**Centers for Medicare and Medicaid Services (CMS)**

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.
Rationale/Source
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 2012 joint guidelines by the American College of Cardiology Foundation 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 (eg, 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 angina 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 2012 American College Cardiology Foundation 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 that 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.

To evaluate the utility of the test, an explication of how the test would be integrated into the current diagnostic pathway is needed. The manufacturer’s website is not explicit on how the test fits into the current pathway. Several potential scenarios are possible, some of which are listed as follows and shown in red in Figure 1:

1. the test could be used as an add-on test with existing clinical risk assessment tools to estimate the pretest probability of obstructive CAD;
2. after initial risk stratification, the test could be used in intermediate-risk patients as a triage test to identify patients who do not need a referral for additional noninvasive testing;
3. after initial risk stratification, the test could be used in intermediate-risk patients as an add-on test with other noninvasive testing to estimate the risk of coronary artery events; or
4. after initial risk stratification, the test could be used in intermediate-risk patients as a replacement test for other noninvasive testing to estimate the risk of coronary artery events;
5. the test could be used in patients at low or intermediate risk of coronary event following noninvasive testing as a triage test for whom doubts remain regarding the need for referral for invasive angiography.

Note that each scenario has a unique PICOTS formulation. The general formulation is described below. A more complete PICOTS discussion is only possible with explicit information on how the test should be used.

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.
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Page 5 of 23

Patients
The intended population is 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 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 might be Corus CAD score alone, Corus CAD score added to current risk prediction models, or Corus CAD score added to results from noninvasive testing, depending on exactly how the test fits into the diagnostic pathway.
Comparators
The comparator would be clinical risk prediction models that estimate the pretest probability of obstructive CAD (eg, Diamond-Forrester) or noninvasive testing, depending on exactly how the test fits into the diagnostic pathway.

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.

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, American Heart Association, and Society for Cardiovascular Angiography and Interventions.

In scenario 1 in Figure 1, interest is an improvement in the calculation of pretest probability with an add-on test and reclassification of patients into low, intermediate, or high-risk of obstructive CAD.

In scenario 2 (ie, 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.

In scenarios 3 and 4, interest is an improvement in the calculation of the probability of cardiovascular events and reclassification of patients into low, intermediate, and high risk of cardiac events either as an add-on (scenario 3) or replacement to noninvasive testing (scenario 4).

In scenario 5 (ie, a triage “rule in” test), the test would need to identify a group of patients with low or intermediate risk of cardiovascular events based on other available information who should be referred for invasive angiography; therefore, the specificity, positive predictive value (PPV) and positive 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.
Simplifying Test Terms
There are 3 core characteristics for assessing a medical test. Whether imaging, laboratory, or other, all medical tests must be:

- Technically reliable
- Clinically valid
- Clinically useful.

Because different specialties may use different terms for the same concept, we are highlighting the core characteristics. The core characteristics also apply to different uses of tests, such as diagnosis, prognosis, and monitoring treatment.

Diagnostic tests detect presence or absence of a condition. Surveillance and treatment monitoring are essentially diagnostic tests over a time frame. Surveillance to see whether a condition develops or progresses is a type of detection. Treatment monitoring is also a type of detection because the purpose is to see if treatment is associated with the disappearance, regression, or progression of the condition.

Prognostic tests predict the risk of developing a condition in the future. Tests to predict response to therapy are also prognostic. Response to therapy is a type of condition and can be either a beneficial response or adverse response. The term predictive test is often used to refer to response to therapy. To simplify terms, we use prognostic to refer both to predicting a future condition or to predicting a response to therapy.

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).

Diagnostic Performance
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. Relevance, design and conduct gaps in the studies are described in Tables 3 and 4. The studies are also briefly described 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. 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. 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% confidence interval [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. The COMPASS sample base differed from the PREDICT sample by including patients who had received a referral for MPI but had not been referred for invasive coronary angiography. MPI-positive participants underwent invasive coronary angiography based on clinician judgment, and all other participants received coronary computed tomography angiography. Of 537 enrolled patients, only 431 (80%) were evaluable, primarily due to refusal to undergo invasive coronary angiography or coronary computed tomographic angiography. The performance characteristics for MPI (core-lab) in this population were also provided as follows: sensitivity, 36% (95% CI, 24% to 50%); specificity, 90% (95% CI, 87% to 93%); PPV, 41% (95% CI, 28% to 56%); and NPV, 88% (95% CI, 84% to 92%). The sensitivity of MPI in COMPASS was lower than generally reported in the literature. Ladapo et al (2013) reported simulation analyses demonstrating how referral bias could have influenced the performance characteristics that have been reported in the literature.

Voora et al (2017) evaluated the Corus CAD score in a cohort from the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial funded by National Heart, Lung, and Blood Institute. PROMISE was a randomized controlled trial (2015) that enrolled 10,003 outpatients who were randomized to functional (ie, exercise, echocardiographic, or nuclear stress testing) or anatomic (ie, computed tomography angiography [CTA]) diagnostic testing. Patients were symptomatic and at increased risk for CAD based on age and/or the presence of CAD risk factors, and presented with symptoms suggestive of obstructive CAD. An ancillary analysis of PROMISE patients was supported in part by the manufacturer and included 2370 PROMISE patients without diabetes who were not on anti-inflammatory medications and who had samples in the biorepository of sufficient quality for analysis. The definition of obstructive CAD was 70% or more stenosis in a major coronary artery or 50% or more left main stenosis using CTA data.

Ladapo et al (2017) evaluated the Corus CAD score 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. The report 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.

Voora et al (2017) evaluated the Corus CAD score in a cohort from the Prospective Multicenter Imaging Study for Evaluation of Chest Pain (PROMISE) trial funded by National Heart, Lung, and Blood Institute. PROMISE was a randomized controlled trial (2015) that enrolled 10,003 outpatients who were randomized to functional (ie, exercise, echocardiographic, or nuclear stress testing) or anatomic (ie, computed tomography angiography [CTA]) diagnostic testing. Patients were symptomatic and at increased risk for CAD based on age and/or the presence of CAD risk factors, and presented with symptoms suggestive of obstructive CAD. An ancillary analysis of PROMISE patients was supported in part by the manufacturer and included 2370 PROMISE patients without diabetes who were not on anti-inflammatory medications and who had samples in the biorepository of sufficient quality for analysis. The definition of obstructive CAD was 70% or more stenosis in a major coronary artery or 50% or more left main stenosis using CTA data.

Ladapo et al (2017) evaluated the Corus CAD score 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. The report 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.
### Table 1. Clinical Validity Study Characteristics of the Corus CAD Score for Diagnosing Obstructive CAD

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Population</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>
<tbody>
<tr>
<td>Rosenberg et al (2010)</td>
<td>Referred for ICA</td>
<td>Prospective</td>
<td>≥50% stenosis in ≥1 major coronary arteries by quantitative CA</td>
<td>14.75</td>
<td>Blood samples drawn before CA</td>
<td>Yes</td>
<td>• PREDICT study validation cohort&lt;br&gt;• Funded by manufacturer</td>
</tr>
<tr>
<td>Thomas et al (2013)</td>
<td>Referred for MPI stress testing</td>
<td>Prospective</td>
<td>≥50% stenosis in ≥1 major coronary arteries by quantitative CA or CCTA</td>
<td>15</td>
<td>Blood samples drawn before MPI and CA</td>
<td>Yes</td>
<td>• COMPASS study&lt;br&gt;• Funded by manufacturer</td>
</tr>
<tr>
<td>Voora et al (2017)</td>
<td>Referred for nonurgent, noninvasive testing for suspected CAD</td>
<td>Nonconcurrent, prospective</td>
<td>≥70% stenosis in a major coronary artery or ≥50% left main stenosis using CCTA</td>
<td>15</td>
<td>Blood samples drawn before CA</td>
<td>Yes</td>
<td>• PROMISE trial funded by NHLBI&lt;br&gt;• PROMISE ancillary analysis funded by manufacturer</td>
</tr>
<tr>
<td>Ladapo et al (2017)</td>
<td>Evaluated in primary care and referred for advanced cardiac testing</td>
<td>Prospective</td>
<td>Cardiac stress test or ICA (thresholds NR)</td>
<td>15</td>
<td>Blood samples drawn before further testing</td>
<td>NR</td>
<td>• PRESET registry&lt;br&gt;• Funded by manufacturer</td>
</tr>
</tbody>
</table>

CA: coronary angiography; CAD: coronary artery disease; CCTA: coronary computed tomographic angiography; ICA: invasive coronary angiography; MI: myocardial infarction; MPI: myocardial perfusion imaging; NHLBI: National Heart, Lung, and Blood Institute; NR: not reported.

*In all studies, patients were nondiabetic, without inflammatory conditions, and were not receiving immunosuppressive or chemotherapeutic agents.
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>Reference standard: ≥50% stenosis in ≥1 major coronary arteries by quantitative CA</td>
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<tr>
<td>Rosenberg et al (2010)</td>
<td>649</td>
<td>525</td>
<td>• Insufficient sample volume RNA yield: 43</td>
<td>37% (79 to 90)</td>
<td>85 (38 to 49)</td>
<td>43 (1 to 2)</td>
<td>46 (77 to 89)</td>
<td>0.70</td>
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<td></td>
<td></td>
<td></td>
<td>• Genomic DNA: 78</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
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<td>• Quality control analysis: 2</td>
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<td></td>
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<td></td>
<td></td>
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<td>• Unknown: 1</td>
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<tr>
<td>Thomas et al (2013)</td>
<td>537</td>
<td>431</td>
<td>• Refused CTA after negative MPI: 90</td>
<td>15% (78 to 95)</td>
<td>89 (47 to 57)</td>
<td>52 (19 to 30)</td>
<td>24 (93 to 99)</td>
<td>0.79</td>
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<td></td>
<td></td>
<td></td>
<td>• Other incomplete data: 16</td>
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<tr>
<td>Reference standard: ≥70% stenosis in a major coronary artery or ≥50% left main stenosis using CCTA</td>
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<td></td>
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<tr>
<td>Voora et al (2017)</td>
<td>2370</td>
<td>1137</td>
<td>Did not have site-read CTA data</td>
<td>10% (64 to 81)</td>
<td>73 (45 to 51)</td>
<td>48 (11 to 17)</td>
<td>14 (92 to 96)</td>
<td>0.63</td>
<td></td>
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<tr>
<td>Reference standard: cardiac stress test or ICA (thresholds NR)</td>
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<tr>
<td>Ladapo et al (2017)</td>
<td>126</td>
<td>84</td>
<td>Testing results not available</td>
<td>12% (59 to 100)</td>
<td>100 (10 to 28)</td>
<td>18 (7 to 25)</td>
<td>14 (66 to 100)</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

AUC: area under the curve; CA: coronary angiography; CAD: coronary artery disease; CI: confidence interval; CCTA: coronary computed tomography angiography; CTA: computed tomography angiography; ICA: invasive coronary angiography; MPI: myocardial perfusion imaging; NPV: negative predictive value; NR: not reported; PPV: positive predictive value.

a CIs not reported in publication; calculated based on data provided.

b The performance characteristics for MPI (core-lab) in this population were also provided: sensitivity, 36% (95% CI, 24% to 50%); specificity, 90% (95% CI, 87% to 93%); PPV, 41% (95% CI, 28% to 56%); and NPV, 88% (95% CI, 84% to 92%).
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>
<th>Duration of Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenberg et al (2010)</td>
<td>2. Test use in current diagnostic pathway unclear</td>
<td>None noted</td>
<td>2. Used broad obstructive CAD definition</td>
<td>3. Diagnostic performance characteristics not provided for clinical risk models; performance characteristics by sex not provided</td>
<td>None noted</td>
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<td></td>
<td>4. Study only includes patients referred for ICA</td>
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<td></td>
<td>5. Racial minorities were not well-represented</td>
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<tr>
<td>Thomas et al (2013)</td>
<td>2. Test use in current diagnostic pathway unclear</td>
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<td>5. Racial minorities were not well-represented</td>
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<tr>
<td>Voora et al (2017)</td>
<td>2. Test use in current diagnostic pathway unclear</td>
<td>None noted</td>
<td>3. Performance characteristics for comparators not provided</td>
<td>3. Diagnostic performance characteristics calculated based on data provided; performance characteristics not provided for clinical risk models; performance characteristics by sex not provided</td>
<td>None noted</td>
</tr>
<tr>
<td></td>
<td>5. Racial minorities were not well-represented</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ladapo et al (2017)</td>
<td>2. Test use in current diagnostic pathway unclear</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>None noted</td>
</tr>
<tr>
<td></td>
<td>5. Study population is subpopulation of intended use</td>
<td></td>
<td></td>
<td></td>
<td></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
6. Classification thresholds not defined
7. Version used unclear
8. Not version currently in clinical use
9. Not compared to credible reference standard
10. Not compared to other tests in use for same purpose
11. Study does not directly assess a key health outcome
12. Evidence chain or decision model not explicated
13. Key clinical validity outcomes not reported (sensitivity, specificity, predictive values)
14. Reclassification of diagnostic or risk categories not reported
15. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests)
16. Follow-up duration not sufficient with respect to natural history of disease (TP, TN, FP, FN cannot be determined)

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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenberg et al (2010)</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)</td>
<td>None noted</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>
</tr>
<tr>
<td>Voora et al (2017)</td>
<td>None noted</td>
<td>None noted</td>
<td>None noted</td>
<td>None noted</td>
<td>None noted</td>
<td></td>
</tr>
<tr>
<td>Ladapo et al (2017)</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 (ie, 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.

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Net reclassification for the Corus CAD score compared with other tests for the diagnosis of obstructive CAD was performed in Rosenberg et al (2010) and Thomas et al (2013) and are shown in Table 5 below. In Rosenberg (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 (2013), Corus CAD scores were categorized as low (≤15), intermediate (16-27), and high (≥28). The Diamond-Forrester and Morise scores were categorized as low (<15%), medium (≥15 to ≤50%), or high likelihood (≥50%). It was not clear how the cutoffs were chosen in Thomas (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>
<thead>
<tr>
<th>Author (Year)</th>
<th>Net Reclassification Improvement* for Corus CAD score vs Second Modality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Myocardial Perfusion Imaging</td>
</tr>
<tr>
<td></td>
<td>Site-Read 21% (NR)</td>
</tr>
<tr>
<td>Rosenberg et al (2010)</td>
<td>p &lt;&lt;0.001</td>
</tr>
<tr>
<td>Thomas et al (2013)</td>
<td>26% (NR)</td>
</tr>
</tbody>
</table>

CI: confidence interval; NR: not reported.

Voros et al (2014) pooled results from PREDICT and COMPASS to compare Corus CAD score with computed tomography imaging for detecting plaque burden (coronary artery calcium [CAC]), and luminal stenosis. Six hundred ten patients, 216 from PREDICT (19% of enrolled patients) and 394 from COMPASS (73% of enrolled patients), who had undergone CAC scoring, CTA, and Corus CAD score were included. Mean age was 57 years; 50% were female, and approximately 50% used statin medication. Prevalence of obstructive CAD (≥50% stenosis) was 16% in the PREDICT cohort (patients referred for coronary angiography) and 13% in the COMPASS cohort (patients referred for MPI). In linear regression analyses, Corus CAD scores statistically and 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 the strength of the correlations was modest. Several Corus CAD score cutoffs were explored (eg, to maximize diagnostic accuracy). Results using a cutoff of 15 points are shown in Table 6. For detecting luminal stenosis of 50% or greater, the Corus CAD score PPV and NPV were 23% and 95%, respectively. For detecting clinically significant CAC (≥400), the Corus CAD score PPV and NPV were 14% and 97%, respectively. Limitations of the study included a lack of clinical outcomes (eg, survival,
morbidity) and lack of comparison with CAC and CTA for predicting these outcomes (ie, incremental Corus CAD score predictive value was not assessed).

### 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 burden &lt;sup&gt;a&lt;/sup&gt;</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).*

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.

*<sup>a</sup> Long-term outcomes are generally excellent for patients with CAC >0 and substantially worse for patients with CAC >400.*

**Subsection Summary: Diagnostic Performance**

Four studies reported the performance characteristics for Corus CAD for diagnosing obstructive CAD. Because this test has higher sensitivity and NPV than specificity and PPV, we focus on the performance characteristics relevant for a test designed to rule-out obstructive CAD. The 4 clinical validity studies used different reference standards. Voora et al (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% 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 (PREDICT) and Thomas et al (COMPASS) studies used a broader definition of obstructive CAD. The sensitivity 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.

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 excludes patients with diabetes and 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 three 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 2 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).

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</td>
<td>1160</td>
<td>12-mo MACEa</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>(2012)</td>
<td></td>
<td>12-mo MACEa 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</td>
<td>420</td>
<td>6-mo revascularizations or MACEa</td>
<td>6.7</td>
<td>96 (NR)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>HR=0.98 (0.52 to 1.87)</td>
</tr>
<tr>
<td>(2013)</td>
<td></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>HR=1.70 (1.10 to 2.64)</td>
<td></td>
</tr>
<tr>
<td>Voora et al</td>
<td>2370</td>
<td>Death, MI, or UA with median 25-mo follow-up</td>
<td>6.0</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>(2017)</td>
<td></td>
<td>Death, MI, UA, or revascularization with median 25-mo follow-up</td>
<td>2.6</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>HR=1.70 (1.10 to 2.64)</td>
<td></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; eg, 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 that the test is the “the first sex-specific test for obstructive CAD”. However, performance characteristics by sex and age were not provided in the published papers.

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 IMPACT-CARD 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-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 ICA, 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.
Genetic Expression Testing in the Evaluation of Patients With Stable Ischemic Heart Disease

Policy # 00309
Original Effective Date: 07/20/2011
Current Effective Date: 12/19/2018

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 clarity on how the test results would be used to change management practices.

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. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, change in disease status, morbid events, and resource utilization. The diagnostic pathway for CAD includes information from a medical history, along with age and sex, stress testing, and imaging. Newer noninvasive methods are being tested, such as gene expression testing. It is not clear how the Corus CAD gene expression test fits in the current diagnostic pathway and how results would be used to change current guideline-based risk stratification before and/or after other noninvasive testing. Results of 2 validation studies (PREDICT, COMPASS) have reported that the test may improve CAD prediction beyond the Diamond-Forrester prediction model. In the COMPASS study, the sensitivity and negative predictive value of the Corus CAD score in diagnosing obstructive CAD was superior to myocardial perfusion imaging in patients referred for myocardial perfusion imaging testing. However, in that study, the reported sensitivity of myocardial perfusion imaging was considerably lower than that generally reported in the literature. Neither PREDICT nor COMPASS used the guideline definition of obstructive CAD as the reference standard. The sensitivity and negative predictive value of clinical models were not reported. An analysis of a cohort from the PROMISE trial including patients with intermediate pretest probability of obstructive CAD confirmed a high negative predictive value for the Corus CAD score. The test also has been shown to have some predictive ability of future revascularization; too few major cardiac events have been observed during the limited duration of follow-up to assess predictive ability for that outcome. Evidence for the Corus CAD score has not directly demonstrated that the test is clinically useful and a chain of evidence cannot be
conducted to support its utility. The evidence is insufficient to determine the effects of the technology on health outcomes.

References


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Genetic Expression Testing in the Evaluation of Patients With Stable Ischemic Heart Disease

Policy # 00309
Original Effective Date: 07/20/2011
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Policy History

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

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01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017 Medical Policy Committee review.
12/20/2017 Medical Policy Implementation Committee approval. Title changed from “Gene Expression Testing to Predict Coronary Artery Disease” to “Gene Expression Testing in the Evaluation of Patients With Stable Ischemic Heart Disease”. Indication changed to “patients with stable ischemic heart disease” to be consistent with current guideline statements. Policy statement intent unchanged, but wording changed to reflect current terminology for indication.
12/06/2018 Medical Policy Committee review
12/19/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
Next Scheduled Review Date: 12/2019

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<th>Code Type</th>
<th>Code</th>
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<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
</tr>
</tbody>
</table>

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

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

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

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Genetic Expression Testing in the Evaluation of Patients With Stable Ischemic Heart Disease

Policy # 00309
Original Effective Date: 07/20/2011
Current Effective Date: 12/19/2018

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

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