2.04.72	Gene Expression Testing in the Evaluation of Patients with Stable Ischemic Heart Disease		
Original Policy Date:	October 5, 2012	**Effective Date:**	May 1, 2020
Section:	2.0 Medicine	**Page:**	Page 1 of 22

Policy Statement

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 Corus CAD™ 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.[1] 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.[2]

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, ³50% stenosis of the diameter of the left main coronary artery or ³70% stenosis of the diameter of a major epicardial or branch vessel >2.0 mm in diameter) and 41% if using the broader definition (³50% stenosis in any coronary vessel).[3] 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.[4] 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.[5] 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 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, the estimated risk (or pretest probability) of obstructive coronary artery disease is estimated using clinical characteristics such as age, sex, type of angina symptoms, smoking, and other comorbidities (e.g., diabetes, hyperlipidemia).[2,6] The guidelines provide a table of pretest probabilities of coronary artery disease by age, sex, and type of angina adapted from the Diamond-Forrester tool.[2] For example, a woman aged 30 to 39 with nonanginal chest pain has a 4% pretest probability of coronary artery disease and a man aged 60 to 69 with typical anginal chest pain has a 94% pretest probability of coronary artery disease.

For patients initially assessed at low-risk (<10% pretest probability of obstructive coronary artery disease, no further testing is generally needed, and the patient can be observed and treated with medical therapy.[2] Patients at high-risk of obstructive coronary artery disease 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 coronary artery disease, noninvasive diagnostic methods, such as exercise or pharmacologic stress tests with or without imaging methods such as myocardial perfusion imaging, 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 coronary artery disease 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

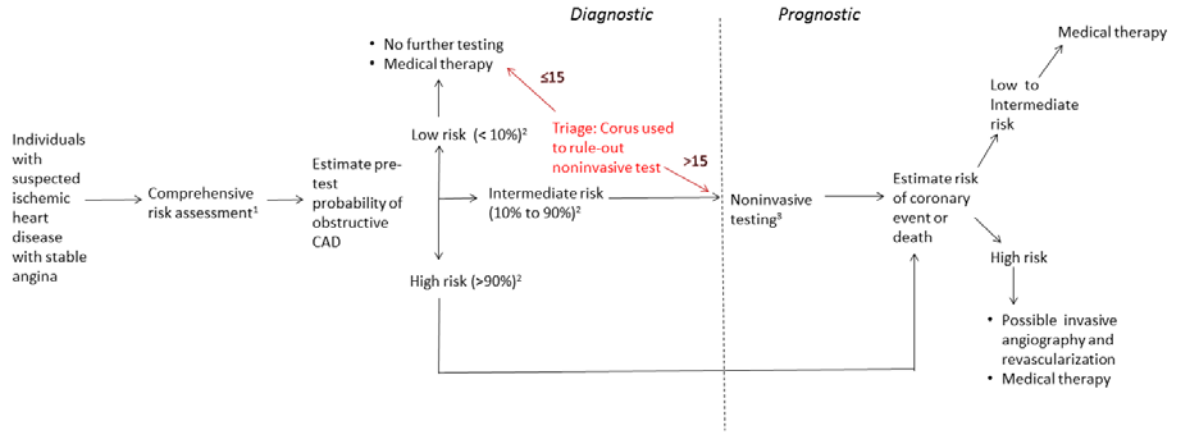
guidelines also provide risk stratification following noninvasive testing.[2,] For example, severe stress-induced left ventricular dysfunction (peak exercise left ventricular ejection fraction <45% or drop in left ventricular ejection fraction with stress ≥10%) indicates a high (>3%) annual risk of death 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 infraction; 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 infraction. 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 (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 coronary artery disease who can safely forgo referral to cardiology or advanced cardiac testing.[7,] Other studies have been performed in patients who have been referred for invasive angiography and myocardial perfusion imaging.

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 PICO was used to select literature to inform this review.

Figure 1. Diagnostic Pathway



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 gene expression score 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 coronary artery disease. A score of less than 15 has been used to indicate a low-risk of obstructive coronary artery disease.
Blood for the test is collected using a routine blood draw and stored between 2° and 10°C for up to 1 day before shipping to the CardioDx Commercial Laboratory, which is certified by Clinical Laboratory Improvement Amendments (CLIA) 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 coronary artery disease (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 coronary artery disease is coronary angiography with obstructive coronary artery disease 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.[8] 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 and negative likelihood ratio are key test performance characteristics.
The time period of interest for measuring the diagnostic performance is the time to obstructive coronary artery disease 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 coronary artery disease.[9]

Review of Evidence
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.

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).

Characteristics and results of clinical validity studies evaluating the performance of the Corus CAD score for diagnosing obstructive coronary artery disease are shown in Tables 1 and 2. Four studies reported the performance characteristics for Corus CAD for diagnosing obstructive

coronary artery disease. Voora et al (2017), (PROMISE) was the largest study and it used the American Heart Association definition for obstructive coronary artery disease.[10] In this population of patients referred for nonurgent, noninvasive testing, the sensitivity was 73% (95% confidence interval, 64% to 81%), the negative likelihood ratio was 0.56 (95% confidence interval, 0.42 to 0.77), and the negative predictive value was 94% (95% confidence interval, 92% to 96%). The Rosenberg et al (2010), (Personalized Risk Evaluation and Diagnosis In the Coronary Tree [PREDICT])[11] and Thomas et al (2013),(Coronary Obstruction Detection by Molecular Personalized Gene Expression [COMPASS])[12] studies used a broader definition of obstructive coronary artery disease and enrolled few patients at intermediate risk (18% and 17%, respectively) based on clinical risk prediction rules. The sensitivities were 85% (95% confidence interval, 79% to 90%) and 89% (95% confidence interval, 78% to 95%) in PREDICT and COMPASS, respectively while the negative predictive value rates were 83% (95% confidence interval, 77 to 89) and 96% (95% confidence interval, 93% to 99%). The thresholds used to identify obstructive coronary artery disease were not clear in Ladapo et al (2017).[7] 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 infraction, revascularization, or obstructive coronary artery disease (71% symptomatic).[11]This is the same cohort from which the second assay development case-control cohort was drawn.[5] Patients were sequentially allocated to development and validation sets. The development cohort was 58% male and 87% white. The validation cohort is described in the tables. Investigators defined obstructive coronary artery disease 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 gene expression score test with clinical predictors and myocardial perfusion imaging 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.[13]

In another follow-up from PREDICT, Lansky et al (2012) found that the Corus CAD score was an independent predictor of coronary artery disease in multivariate analysis, with odds ratios of 2.53 (p=0.001) for the total study population and 1.99 (95% confidence interval, 1.35 to 2.96; p=0.001) and 3.45 (95% confidence interval, 1.97 to 5.91; p=0.001) for males and females, respectively.[14] In this analysis, myocardial perffusion imaging was not associated with any measures of coronary artery disease 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 coronary artery disease in symptomatic, nondiabetic patients without inflammatory conditions in a multicenter, prospective study, COMPASS.[12] Obstructive coronary artery disease 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 myocardial perfusion imaging but had not been referred for invasive coronary angiography. Myocardial perfusion imaging positive participants underwent invasive coronary angiography based on clinician judgment, and all other participants received coronary computed tomographic 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 myocardial perfusion imaging (core-lab) in this population were also provided as follows: sensitivity, 36% (95% confidence interval, 24% to 50%); specificity, 90% (95% confidence interval, 87% to 93%); positive predictive value, 41% (95% confidence interval, 28% to 56%); and negative predictive value, 88% (95% confidence interval, 84% to 92%). The sensitivity of myocardial perfusion imaging in COMPASS was lower than generally reported in the literature.

In 2013, Ladapo et al reported simulation analyses demonstrating how referral bias could have influenced the performance characteristics that have been reported in the literature.[15,] Voora et al (2017) evaluated the Corus CAD score in a cohort from the PROMISE trial funded by National Heart, Lung, and Blood Institute.[10,] PROMISE was a randomized controlled trial (RCT; 2015) that enrolled 10,003 outpatients who were randomized to functional (i.e., exercise, echocardiographic, or nuclear stress testing) or anatomic (i.e., computed tomographic angiography) diagnostic testing.[16,] Patients were symptomatic and at increased risk for coronary artery disease based on age and/or the presence of coronary artery disease risk factors, and presented with symptoms suggestive of obstructive coronary artery disease. An ancillary analysis of PROMISE patients was supported in part by the manufacturer and included 2,370 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 coronary artery disease was 70% or more stenosis in a major coronary artery or 50% or more left main stenosis using computed tomographic angiography data.

Several studies have evaluated Corus CAD in a cohort of patients from A Registry to Evaluate Patterns of Care Associated with the Use of Corus CAD in Real World Clinical Care Settings(PRESET) 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 coronary artery disease without history of myocardial infraction or revascularization, diabetes, suspected acute myocardial infraction, 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 coronary artery disease in 84 patients.[7,] 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 coronary artery disease, showing higher referral rates for patients with a higher Corus CAD score.[17,18,]

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

Study	Study Population[a]	Design	Reference Standard for Obstructive CAD	Threshold Score for Positive Corus CAD Score Test	Timing of Reference and Corus CAD Score Tests	Blinding of Assessors	Comment
Rosenberg et al (2010)[11,] PREDICT	• Referred for ICA • Mean age, »60 y • 90% White • 43% women 48% low 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

	18% intermediate risk, 34% high risk						
Thomas et al (2013)[12], COMPASS	• Referred for MPI stress testing • Mean age, 56 y • 89% White· 48% women58% low risk, 17% intermediate risk, 25% high risk	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
Voora et al (2017)[10],PROMISE	• Referred for nonurgent, noninvasive testing for suspected CAD • Median age, »60 y • 91% White • 53% women	Nonconcurrent, prospective	≥70% stenosis in a major coronary artery or ≥50% left main stenosis using CCTA	15	Blood samples drawn before CA	Yes	• PROMISE trial funded by NHLBI • PROMISE ancillary analysis funded by manufacturer
Ladapo et al (2017)[7], PRESET	• Evaluated in primary care and referred for advanced cardiac testing • Proportion of women among those referred for advanced testing not reported	Prospective	Cardiac stress test or ICA (thresholds NR)	15	Blood samples drawn before further testing	NR	• PRESET registry • Funded by manufacturer

CA: coronary angiography; CAD: coronary artery disease; CCTA: coronary computed tomographic angiography; COMPASS: Coronary Obstruction Detection by Molecular Personalized Gene Expression; ICA: invasive coronary angiography;
MPI: myocardial perfusion imaging; NHLBI: National Heart, Lung, and Blood Institute; NR: not reported; PREDICT: Personalized Risk Evaluation and Diagnosis In the Coronary Tree;

PRESET: A Registry to Evaluate Patterns of Care Associated with the Use of Corus CAD in Real World Clinical Care Settings;
PROMISE: PROspective Multicenter Imaging Study for Evaluation.
[a] 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

Study	Initial N	Final N	Excluded Samples	Prevalence of Obstructive CAD	Sensitivity (95% CI), %	Specificity (95% CI), %	PPV (95% CI), %	NPV (95% CI), %	AUC (95% CI)
Reference standard: ≥50% stenosis in ≥1 major coronary arteries by quantitative CA									
Rosenberg et al (2010)[11], PREDICT	649	525	• Insufficient sample volume • RNA yield: 43 • Genomic DNA: 78 • Quality control analysis: 2 • Unknown: 1	37%	85 (79 to 90)[a]	43 (38 to 49)[a]	46 (41 to 52)[a]	83 (77 to 89)[a]	0.70 (NR)
Thomas et al (2013)[12], COMPASS	537	431	• Refused CTA after negative MPI: 90 • Other incomplete data: 16	15%	89 (78 to 95)[b]	52 (47 to 57)[b]	24 (19 to 30)[b]	96 (93 to 99)[b]	0.79 (0.72 to 0.84)
Reference standard: ≥70% stenosis in a major coronary artery or ≥50% left main stenosis using CCTA									
Voora et al (2017)[10], PROMISE	2370	1137	• Did not have site-read CTA data	10%	73 (64 to 81)[a]	48 (45 to 51)[a]	14 (11 to 17)[a]	94 (92 to 96)[a]	0.63 (0.57 to 0.68)
Reference standard: cardiac stress test or ICA (thresholds NR)									
Ladapo et al (2017)[7], PRESET	126	84	• Testing results not available	12%	100 (59 to 100)[a]	18 (10 to 28)[a]	14 (7 to 25)[a]	100 (66 to 100)[a]	NR

AUC: area under the curve; CA: coronary angiography; CAD: coronary artery disease; CI: confidence interval; CCTA: coronary computed tomography angiography; COMPASS: Coronary Obstruction Detection by Molecular Personalized Gene Expression;
CTA: computed tomography angiography; ICA: invasive coronary angiography; MPI: myocardial perfusion imaging; NPV: negative predictive value; NR: not reported; PPV: positive predictive value; PREDICT: Personalized Risk Evaluation and Diagnosis In the Coronary Tree.
PRESET: A Registry to Evaluate Patterns of Care Associated with the Use of Corus CAD in Real World Clinical Care Settings; PROMISE: PROspective Multicenter Imaging Study for Evaluation.
[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%).

Relevance, design and conduct limitations in the studies are described in Tables 3 and 4.

Table 3. Relevance Limitations for Clinical Validity Studies of the Corus CAD Score for Diagnosing Obstructive CAD

Study	Population	Intervention	Comparator	Outcomes	Duration of Follow-Up
Rosenberg et al (2010)[11], PREDICT	2. Test use in current diagnostic pathway unclear4. Study only includes patients referred for ICA and only 18% of patients were at intermediate risk5. Racial minorities were not well-represented	None noted	2. Used broad obstructive CAD definition	3. Diagnostic performance characteristics not provided for clinical risk models; performance characteristics by sex not provided	None noted
Thomas et al (2013)[12], COMPASS	2. Test use in current diagnostic pathway unclear4. Only 17% of patients were at intermediate risk5. Racial minorities were not well-represented	None noted	2. Used broad obstructive CAD definition	3. Diagnostic performance characteristics not provided for clinical risk models performance characteristics by gender not provided	None noted
Voora et al (2017)[10], PROMISE	2. Test use in current diagnostic pathway unclear5. Racial minorities were not well-represented	None noted	3. Performance characteristics for comparators not provided	3. Diagnostic performance characteristics calculated based on data provided; performance characteristics not provided for clinical risk models; performance characteristics by sex not provided	None noted
Ladapo et al (2017)[7], PRESET	2. Test use in current diagnostic pathway unclear	None noted	1. Thresholds for diagnosis not given	3. Diagnostic performance characteristics not provided for clinical risk models; performance characteristics by sex not provided	None noted
Key	1. Intended use population unclear2. Clini	1. Classification thresholds not defined2. Versi	1. Classification thresholds not	1. Study does not directly assess a key health outcome2. Evidence	1. Follow-up duration not

	cal context for test is unclear3. Stud y population unclear4. Stud y population not representative of intended clinical use5. Study population is subpopulation of intended use	on used unclear3. Not version currently in clinical use	defined2. No t compared to credible reference standard3. N ot compared to other tests in use for same purpose	chain or decision model not explicated3. Key clinical validity outcomes not reported (sensitivity, specificity, predictive values)4. Reclassifica tion of diagnostic or risk categories not reported5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests)	sufficient with respect to natural history of disease (TP, TN, FP, FN cannot be determine d)

CAD: coronary artery disease; COMPASS: Coronary Obstruction Detection by Molecular Personalized Gene Expression; FN: false negative; FP: false positive; ICA: invasive coronary angiography; PREDICT: Personalized Risk Evaluation and Diagnosis In the Coronary Tree;
PRESET: A Registry to Evaluate Patterns of Care Associated with the Use of Corus CAD in Real World Clinical Care Settings; PROMISE: PROspective Multicenter Imaging Study for Evaluation; TN: true negative; TP: true positive.

Table 4. Study Design and Conduct Limitations for Clinical Validity Studies of the Corus CAD Score for Diagnosing Obstructive CAD

Study	Selection	Blinding	Delivery of Test	Selective Reporting	Completeness of Follow-Up	Statistical
Rosenberg et al (2010)[11], PREDICT	None noted	None noted	None noted	None noted	None noted	1. CIs not reported, calculated based on data provided
Thomas et al (2013)[12], COMPASS	None noted	None noted	None noted	None noted	2. 90 patients with negative MPI refused CTA and were excluded; no description of these patients was provided	None noted
Voora et al (2017)[10], PROMISE	None noted	None noted	None noted	None noted	None noted	1. CIs not reported, calculated based on data provided 2. No comparison to noninvasi

						ve testing provided
Ladapo et al (2017)[7]. PRESET	None noted	1. Blinding not reported	None noted	None noted	None noted	1. CIs not reported, calculated based on data provided 2. No comparison to noninvasive testing provided
Key	1. Selection not described2. Selection not random nor consecutive (ie, convenience)	1. Not blinded to results of reference or other comparator tests	1. Timing of delivery of index or reference test not described2. Timing of index and comparator tests not same3. Procedure for interpreting tests not described4. Expertise of evaluators not described	1. Not registered2. Evidence of selective reporting3. Evidence of selective publication	1. Inadequate description of indeterminate and missing samples2. High number of samples excluded3. High loss to follow-up or missing data	1. CIs and/or p values not reported2. No statistical test reported to compare to alternatives

CAD: coronary artery disease; CI: confidence interval; COMPASS: Coronary Obstruction Detection by Molecular Personalized Gene Expression; CTA: computed tomography angiography; MPI: myocardial perfusion imaging; PREDICT: Personalized Risk Evaluation and Diagnosis In the Coronary Tree; PRESET: A Registry to Evaluate Patterns of Care Associated with the Use of Corus CAD in Real World Clinical Care Settings; PROMISE: PROspective Multicenter Imaging Study for Evaluation.

Net reclassification for the Corus CAD score compared with other tests for the diagnosis of obstructive coronary artery disease was performed in Rosenberg et al (2010)[11], and Thomas et al (2013)[12], 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 coronary artery disease. Myocardial perfusion imaging 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 (≤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 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 Versus Other Modalities for Diagnosing Obstructive CAD

Author (Year)	**Net Reclassification Improvement[a] for Corus CAD score vs. Second Modality (95% CI)**				
	Myocardial Perfusion Imaging				
	Site-Read	*Core-Lab*	*Diamond-Forrester*	*Morise*	*Expanded Clinical Model*

Rosenberg et al (2010)[11], PREDICT	21% (NR)	NR	20% (NR)	NR	16% (NR)
p	<0.001		<0.001		<0.001
Thomas et al (2013)[12], COMPASS	26% (NR)	11% (NR)	28% (NR)	60% (NR)	NR
p	NR	NR	NR	NR	NR

CI: confidence interval; NR: not reported; CAD: coronary artery disease; COMPASS: Coronary Obstruction Detection by Molecular Personalized Gene Expression; PREDICT: Personalized Risk Evaluation and Diagnosis In the Coronary Tree.
[a] Net reclassification improvement quantifies the difference between the proportion of patients correctly reclassified from an incorrect initial classification and the proportion incorrectly reclassified from a correct initial classification.

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), and luminal stenosis.[19] Six hundred ten patients, 216 from PREDICT (19% of enrolled patients) and 394 from COMPASS (73% of enrolled patients), who had undergone coronary artery calcium scoring, computed tomographic angiography, 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 myocardial perfusion imaging). In linear regression analyses, Corus CAD scores statistically and significantly correlated with coronary artery calcium (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 positive predictive value and negative predictive value were 23% and 95%, respectively. For detecting clinically significant coronary artery calcium (≥400), the Corus CAD score positive predictive value and negative predictive value were 14% and 97%, respectively. Limitations of the study included a lack of clinical outcomes (eg, survival, morbidity) and lack of comparison with coronary artery calcium and computed tomographic angiography 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

Outcome	Corus CAD AUROC (95% CI)	Diamond-Forrester AUROC (95% CI)	Sensitivity, %	Specificity, %	PPV, %	NPV, %
***Plaque burden*[a]**						
CAC >0	0.75 (0.71 to 0.79)	0.65 (0.61 to 0.69)	71	62	65	68
CAC ≥400	0.75 (0.68 to 0.82)	0.61 (0.53 to 0.69)	84	49	14	97
Luminal stenosis by CTA						
≥50%	0.75 (0.70 to 0.80)	0.65 (0.59 to 0.71)	84	51	23	95
≥70%	0.75 (0.67 to 0.83)	0.63 (0.53 to 0.73)	90	48	8	99

Adapted from Voros et al (2014).[19]
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.
[a] 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 coronary artery disease 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 2 validation studies (PREDICT, COMPASS) have reported the test may improve coronary artery

disease 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 coronary artery disease 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 coronary artery disease as the reference standard and had relatively few patients at intermediate risk based on clinical prediction rules. The sensitivity and negative predictive value of clinical models were not reported. An analysis of a cohort from the PROMISE trial including patients with an intermediate pretest probability of obstructive coronary artery disease confirmed a high negative predictive value 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 coronary artery disease. 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 coronary artery disease 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 myocardial perfusion imaging. 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 4 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, including myocardial infraction, stroke/transient ischemic attack, all-cause mortality, and coronary revascularization.[20,]

Thomas et al (2013) patients were followed for 6 months after Corus CAD testing, with 420 of 431 completing follow-up.[12,] Major adverse cardiac events (nonfatal myocardial infraction, stroke/transient ischemic attacks, or all-cause mortality) and revascularization events were recorded. Only 2 major adverse cardiac events occurred.

Voora et al (2017) included analysis of 2,370 PROMISE patients with samples in the biorepository who were followed for a median of 25 months.[10,] The association between the Corus CAD score and a composite outcome of death, myocardial infraction, 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 a negative predictive value of 98% (confidence interval 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.[17,18,] 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

Author	N	Event	Incidence	Sens (95% CI)	Spec (95% CI)	PPV (95% CI)	NPV (95% CI)	Association (95% CI)
Rosenberg et al (2012)[20.]	1160	12-mo MACE[a]	1.5	82 (NR)	34 (NR)	1.8 (NR)	99 (NR)	OR=2.41 (0.74 to 10.5)
		12-mo MACE[a] or revascularizations	25	86(NR)	41(NR)	33(NR)	90(NR)	OR=4.32 (3.02 to 6.25)
Thomas et al (2013)[12.]	420	6-mo revascularizations or MACE[a]	6.7	96 (NR)	NR	NR	99 (NR)	NR
Voora et al (2017)[10.]	2370	Death, MI, or UA with median 25-mo follow-up	2.6	NR	NR	NR	NR	HR=0.98 (0.52 to 1.87)[b]
		Death, MI, UA, or revascularization with median 25-mo follow-up	6.0	NR	NR	NR	NR	HR=1.70 (1.10 to 2.64)[b]

Values are percent unless otherwise indicated.
CI: confidence interval; CAD: coronary artery disease; 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 versus 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 infraction. More data are needed on coronary events other than revascularizations. Notably, confidence intervals 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 coronary artery disease. The PREDICT and COMPASS studies reported that the gene expression score is superior to the Diamond-Forrester model and to myocardial perfusion imaging for predicting obstructive coronary artery disease. 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. 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 RCTs. There is no direct evidence from RCTs.

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 a 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 coronary artery disease. The Corus CAD test classifies patients into clinically credible diagnostic groups (low- and high-risk of obstructive coronary artery disease) 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.[2,] Studies examining patient outcomes of Corus CAD testing have primarily analyzed changes in physician management as an outcome.

The Investigation of a Molecular PersonAlizedCoronary 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 coronary artery disease.[21,] Coronary artery disease was categorized by authors as no coronary artery disease (0% stenosis), coronary artery disease with 50% or less stenosis, or coronary artery disease 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 coronary artery disease symptoms.[22,] 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 major adverse cardiac events were observed in 247 (98%) patients who had at least 30 days of follow-up.

The Enhanced Assessment of Chest Pain and Related Symptoms in the Primary Care Setting Through the Use of a Novel Personalized Medicine Genomic Test (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.[23] 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 major adverse cardiac events, 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).[24] Referral rate for further cardiac evaluation was 4% for women with low Corus CAD score (n=248) versus 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).[7] Ten percent (26/252) of low Corus CAD score patients were referred versus 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 (odds ratio = 0.15; 95% confidence interval, 0.10 to 0.24; p<0.001). With 1 year of follow-up, major adverse cardiac events 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. Relevant outcomes are overall survival, disease-specific survival, test validity, change in disease status, morbid events, and resource utilization. The diagnostic pathway for coronary artery disease includes information from 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 (Personalized Risk Evaluation and Diagnosis In the Coronary Tree [PREDICT], Coronary Obstruction Detection by Molecular Personalized Gene Expression [COMPASS]) have reported that the test may improve coronary artery disease 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 coronary artery disease 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 coronary artery disease as the reference standard and had relatively few patients at intermediate risk based on clinical prediction rules. The sensitivity and negative predictive value of clinical models were not

reported. An analysis of a cohort from the PROspective Multicenter Imaging Study for Evaluation of chest pain (PROMISE) trial including patients with an intermediate pretest probability of obstructive coronary artery disease 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 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
In 2012, the American Heart Association (AHA) released a policy statement on genetics and cardiovascular disease.[25.] 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."[26.]

In 2017, the AHA released a scientific statement on the expressed genome in cardiovascular diseases and stroke.[27.] 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
In 2012, the joint guidelines of the American College of Cardiology Foundation and 6 other medical societies for the diagnosis and management of patients with stable ischemic heart disease did not mention the gene expression score.[2.] The 2014 update to these guidelines also did not mention the gene expression score.[6.]

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. In 2019, Noridian MolDX rescinded coverage of Corus CAD and issued a non-coverage determination.[28.29.]

Ongoing and Unpublished Clinical Trials
A search of ClinicalTrials.gov in January 2020 did not identify any ongoing or unpublished trials that would likely influence this review.

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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.

Type	Code	Description
CPT®	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
	81599	Unlisted multianalyte assay with algorithmic analysis
HCPCS	None	

Policy History

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

Effective Date	Action
10/05/2012	BCBSA Medical Policy adoption
08/29/2014	Policy revision without position change
01/01/2016	Coding update
01/01/2017	Policy revision without position change
03/01/2017	Policy title change from "Gene Expression Testing to Predict Coronary Artery Disease" Policy revision without position change
05/01/2018	Policy revision without position change
06/01/2019	Policy revision without position change
05/01/2020	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

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 at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 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.