

Gene Expression Testing to Predict Coronary Artery Disease

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Blood tests for gene expression have been reported to discriminate between cases of obstructive coronary artery disease (CAD) and healthy controls. This testing has been proposed to help predict obstructive CAD in patients who present with chest pain or other suggestive symptoms, or in asymptomatic patients who are at high risk of CAD.

MEDICAL POLICY CRITERIA

Gene expression testing to predict coronary artery disease is considered **investigational** for all indications.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. [Genetic Testing for Familial Hypercholesterolemia](#), Genetic Testing, Policy No. 11
2. [Measurement of Lipoprotein-Associated Phospholipase A2 \(Lp-PLA2\) in the Assessment of Cardiovascular Risk](#), Laboratory No. 63

BACKGROUND

Heart disease is the leading cause of death for both men and women. About 610,000

Americans die from heart disease each year, which translates to about one in every four deaths. Coronary heart disease is the most common type of heart disease, killing more than 370, 0000 people annually.^[1] Individuals with signs and symptoms of obstructive coronary artery disease (CAD), the result of a chronic inflammatory process that ultimately results in progressive luminal narrowing and acute coronary syndromes, may be evaluated with a variety of tests according to prior risk. Coronary angiography is the gold standard for diagnosing obstructive CAD, but it is invasive and associated with a low but finite risk of harm. Thus, coronary angiography is recommended for patients at a high risk of CAD according to history, physical findings, electrocardiogram, and biomarkers of cardiac injury.^[2]

For patients initially assessed at low-to-intermediate risk, observation and noninvasive diagnostic methods, which may include imaging methods such as coronary computed tomographic angiography, may be recommended. Nevertheless, even noninvasive imaging methods have potential risks of exposure to radiation and contrast material. In addition, coronary angiography has a relatively low yield despite risk stratification recommendations. In one study of nearly 400,000 patients without known CAD undergoing elective coronary angiography, approximately 38% were positive for obstructive CAD (using the CAD definition, stenosis of 50% or more of the diameter of the left main coronary artery or stenosis of 70% or more of the diameter of a major epicardial or branch vessel that was more than 2.0 mm in diameter; result was 41% if using the broader definition, stenosis of 50% or more in any coronary vessel).^[3] Thus, methods of improving patient risk prediction prior to diagnostic testing are needed.

A CAD classifier has been developed based on the expression levels, in whole blood samples, of 23 genes plus patient age and sex. This information is combined in an algorithm to produce a score from 1 to 40, with higher values associated with a higher likelihood of obstructive CAD. The test is marketed as Corus® CAD (CardioDx, Inc.). The intended population is stable, nondiabetic patients suspected of CAD either because of symptoms, a high-risk history, or a recent positive or inconclusive test result by conventional methods.

REGULATORY STATUS

The Corus® CAD test is not a manufactured test kit and has not been reviewed by the U.S. Food and Drug Administration (FDA). Rather, it is a laboratory-developed test (LDT), offered by the Clinical Laboratory Improvement Act (CLIA)-licensed CardioDx Commercial Laboratory.

EVIDENCE SUMMARY

The focus of the following literature appraisal is on evidence related to the clinical utility of testing to:

- Provide clinically relevant information beyond that provided by traditional risk assessment measures, and
- Improve health outcomes as a result of patient management decisions compared with standard clinical evaluation techniques.

ANALYTIC VALIDITY

Assay Development

In an initial proof-of-principle study, Wingrove (2008) evaluated 27 cases with and 14 controls without angiographically defined coronary artery disease (CAD) for expression of genes that differed significantly between the two groups, selecting 50 genes.^[4] To that, the authors added 56 genes selected from relevant literature reports and evaluated expression of these 106 genes in an independent set of 63 cases and 32 controls, resulting in the selection of 14 genes that independently and significantly discriminated between groups in multivariable analysis. The significance of 11 of these 14 genes was replicated in a third set of 86 cases and 21 controls. Expression of the 14 genes was proportional to maximal coronary artery stenosis in the combined cohort of 215 patients. Limitations of this study included variable source of RNA for different cohorts (whole blood vs. separated whole blood leukocytes), small sample sizes in conjunction with large numbers of genes investigated and no apparent correction for multiple tests in significance testing, and modest discrimination between groups.

Final test development is described by Elashoff (2011).^[5] The authors 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 one major vessel, or 50% or greater in two vessels, and controls defined as less than 25% stenosis in all major vessels. Of clinical factors, diabetes had the most significant effect on gene expression; in the first case-control study (n = 195), the expression of 42 genes was found to significantly (p<0.05) discriminate between cases and controls in nondiabetic patients and of 12 genes in diabetic patients, with no overlap. As a result, the second case-control study (n = 198) and final development of the assay was limited to nondiabetic patients. The final selection of variables consisted of the expression of 20 CAD-associated genes and three normalization genes plus terms for age and sex, all incorporated into an algorithm that results in an obstructive CAD score ranging from 1 to 40. Receiver-operating characteristic (ROC) analysis in the second case-control study resulted in an area under the curve (AUC) for CAD of 0.77 (95% confidence interval [CI] 0.73 to 0.81).

Additional studies which demonstrate an association between gene expression scores and CAD have been identified; however, these studies did not evaluate the clinical validity or utility of testing, limiting conclusions regarding the predictive or beneficial nature of gene expression scores in patients at increased risk for CAD.^[6]

Assay Validation

The finalized assay was validated in a prospective multicenter trial, the PREDICT trial, in which blood samples were collected from nondiabetic patients (n=526) with a clinical indication for coronary angiography but no known previous myocardial infarction (MI), revascularization, or obstructive CAD.^[7] 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 authors defined obstructive CAD as 50% or greater stenosis in one or more major coronary arteries on quantitative coronary angiography, which they stated corresponds to approximately 65% to 70% stenosis on clinical angiography. The assay AUC for CAD was 0.70 +/- 0.02 (p<0.001).

CLINICAL VALIDITY

PREDICT Trial

The PREDICT trial compared the predictive accuracy of the gene expression score (GES) measure to clinical predictors and myocardial perfusion imaging (MPI) stress testing.^[5,7,8] This

was a multicenter study of 1,160 patients presenting for coronary angiography. All patients underwent GES assessment, and the outcomes used for prediction were coronary artery disease (CAD) at initial angiography, and cardiac events, including revascularization, in the year following the initial angiogram.

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

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

A follow-up publication from the PREDICT trial, published in 2012, reported on the association of GES with subsequent major adverse cardiac events (MACE), including MI, stroke/TIA (transient ischemic attack), all-cause mortality, and coronary revascularization.^[8] There were 17 total MACE events (1.5%), 15 of which occurred 30 days or longer after the initial angiogram. Using a GES cutoff of 15 or less, the sensitivity for diagnosis of subsequent MACE was 82% and the specificity was 34%. The positive predictive value and negative predictive value was 1.8% and greater than 99%, respectively. The odds ratio for having an event was increased for patients with a GES of greater than 15 at 2.41, but this result did not reach statistical significance (95% CI 0.74 to 10.5, $p=0.16$).

In another follow-up publication from the PREDICT trial, Lansky (2012) found that GES was an independent predictor of CAD in multivariate analysis with an odds ratio of 2.53 ($p=0.001$) in the total study population and 1.99 ($p=0.001$) and 3.45 ($p=0.001$) for males and females, respectively.^[9] In this analysis MPI was not associated with any measures of CAD in the general population or when stratified by gender. For every 10-point increase in GES there was a corresponding two-fold increase in odds of CAD, and an increase in maximum percent stenosis, the number of lesions, and total plaque volume. In a five-year follow-up of the PREDICT cohort indicated mean GES scores changed from 20.3 to 19.8.^[10]

COMPASS Trial

Thomas (2013) assessed the clinical validity and utility of the Corus® CAD for detection of obstructive CAD in a multicenter, prospective study (COMPASS).^[11] Obstructive CAD was defined as 50% or greater stenosis in one or more major coronary arteries on quantitative coronary angiography. The COMPASS population differed from the PREDICT trial by including participants who had received a referral for myocardial perfusion imaging but had not been referred for invasive coronary angiography (ICA). Peripheral blood was drawn before MPI on

all participants to obtain a GES. MPI positive participants underwent ICA based on the clinician's judgment, and all other participants received computed tomographic angiography (CTA). Of the 537 enrolled patients only 431 (80.3%) were evaluable primarily due to refusal to perform ICA or CT-angiography. Follow-up was six months after testing with clinical end-points of MACE and revascularization. Using a GES cutoff of 15 or less, sensitivity and specificity of the Corus® CAD test were 89% and 52% respectively. Net reclassification improvement in predicting CAD for GES compared to MPI (site-read), MPI (Core-Lab), Diamond-Forrester classification, and Morise score was 26%, 11%, 28% and 60% respectively. At one year follow-up the mean cut-off GES score increases from 15.9 to 17.3, corresponding to a 2.5% increase in obstructive CAD likelihood.^[10] Changes in cardiovascular medications did not alter the GES score.

Twenty-eight adverse events were observed which included 25 revascularizations within 30 days, two MACE, and one further revascularization. Twenty-five out of 26 patients with revascularization and both MACE patients had high GES (>15). The authors found that GES was associated with MACE and revascularization in a logistic regression model ($p=0.0015$) with a sensitivity of 96% and NPV of 99% at a score threshold of ≤ 15 . The GES test was also correlated with maximum percent stenosis ($r = 0.46$, $P<0.001$).

PROMISE Trial

A study by Voora (2017) utilized samples from the PROMISE trial to assess the relationship between GES, and CAD.^[12] The PROMISE randomized trial ($n = 10,003$) was designed to compare functional testing (i.e. stress or exercise testing) to CTA as an initial diagnostic strategy in patients with symptoms indicating possible CAD.^[13] Exclusion criteria included known CAD, recent acute coronary syndrome, and other forms of heart disease. The GES study included samples from 2,370 non-diabetic patients from the 3,742 available PROMISE samples. Of these, 45% had a GES score of 15 or greater. Among those with CTA data ($n = 1,137$), a high GES score (using a cutpoint of 15) was significantly associated with obstructive CAD (OR 2.5, 95% CI 1.6 to 3.8, $p<0.0001$). A high score was also associated with a composite endpoint of death, MI, hospitalization for unstable angina, and revascularization. However, the only component individually associated with the GES score was revascularization.

PREDICT and COMPASS Combined Results

Voros (2014) pooled results from PREDICT and COMPASS to compare GES with computed tomography (CT) imaging for detecting plaque burden (coronary artery calcium [CAC]), and luminal stenosis.^[14] Six hundred ten patients, 216 from PREDICT (19% of enrolled patients) and 394 from COMPASS (73% of enrolled patients), who had undergone CAC scoring, CTA, and GES were included. Mean (standard deviation, SD) age was 57 (11) years; 50% were female, and approximately 50% used statin medication. Prevalence of obstructive CAD ($\geq 50\%$ stenosis) was 16% in the PREDICT cohort (patients referred for coronary angiography) and 13% in the COMPASS cohort (patients referred for MPI). In linear regression analyses, GES was statistically significantly correlated with CAC ($r=0.50$), the number of arterial segments with any plaque ($r = 0.37$), overall stenosis severity ($r=0.38$), and maximum luminal stenosis ($r=0.41$) (all $p<0.01$), but strength of correlations was modest. Several GES cutoffs were explored (e.g., to maximize diagnostic accuracy). For detecting luminal stenosis of 50% or greater, GES PPV and NPV were 0.23 and 0.95, respectively. For detecting clinically significant CAC (≥ 400), GES PPV and NPV were 0.14 and 0.97, respectively. Limitations of

the study included lack of clinical outcomes (e.g., survival, morbidity), and lack of comparison with CAC and CTA for predicting these outcomes (i.e., incremental predictive value of GES was not assessed).

Section Summary

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

The COMPASS study compared the GES score to results from MPI stress testing. In that trial, the sensitivity of MPI was low at 27%. This is a considerably lower sensitivity than is routinely reported in the literature. For example, in one meta-analysis performed in support of ACC/AHA guidelines on myocardial perfusion imaging, sensitivity was estimated at 87% to 89%.^[15] This raises the question of whether the accuracy of MPI in the COMPASS study is representative of that seen in current clinical care. Given the imperfect sensitivity and specificity of GES, and the known diagnostic characteristics of standard noninvasive tests for patients with stable ischemic heart disease, the diagnostic characteristics of GES do not obviously by themselves demonstrate that patient outcomes would be improved compared to standard diagnostic workup.

CLINICAL UTILITY

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

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

PRESET Registry

The PRESET registry was designed to evaluate the use of Corus® CAD in clinical care setting.^[16] PRESET prospectively enrolled stable, non-acute, non-diabetic patients with no

history of CAD at 21 primary care practices in the U.S. between 2012 and 2014. The patients were symptomatic and presented to these practices for evaluation of suspected obstructive CAD, and blood samples were collected during the outpatient clinic visit. Outcomes used to evaluate the impact of the test on clinical decision making focused on referrals for further cardiac testing. Patients were followed for one year for assessment of major adverse cardiac events. There were 934 patients initially enrolled, with 723 remaining after investigator site withdrawal and protocol non-compliance, and 566 patients left at follow-up. Among these 566 patients, 252 had a low GES and 314 had a high GES, using a GES cutpoint of 15. The low GES patients had a 10% referral rate for cardiac testing, while the high GES patients had a referral rate of 44%. Cardiac testing results were available for 84 patients, and none of the 13 low GES patients and 10 of the 71 high GES patients referred for testing had positive stress tests or obstructive CAD on coronary angiography. At one-year follow-up, 12 patients had had major adverse cardiovascular events: three of the patients with a low GES and nine with a high GES. Five patients had revascularization and all five had a high GES. This study was limited by a high rate of exclusion/loss to follow-up. The lack of a control group makes the contribution of the GES to clinician decision-making impossible to assess.

A similar analysis was published on a subset of PRESET registry patients aged 65 years and older that remained at follow-up (n=176).^[17] The primary outcome in this study was referral to cardiology or advanced cardiac testing within 45 days of the test. Seventy-two patients (41%) had this outcome, which was significantly associated with a high GES score (using a cutpoint of 15) in a multivariate analysis (p<0.001).

IMPACT Trial

The IMPACT-CARD study compared a prospective cohort to matched historic controls to evaluate if the GES test altered the cardiologist's evaluation and clinical management of CAD.^[18] CAD was defined by the authors as no CAD (0% stenosis), CAD (\leq 50% stenosis) and obstructive CAD (>50% stenosis). All participants were non-diabetic, had no known prior MI or revascularization, were not using steroids, immune suppressive agents or chemotherapeutic agents, and had been referred to a cardiologist for evaluation of chest pain or angina equivalent symptoms. Eighty-eight patients were enrolled, and 83 were included in the final analysis. The matched cohort was composed of 83 patients selected with similar distributions of age, gender, clinical risk factors and had been evaluated at the institution within the past 3 to 30 months.

In a similar but unmatched study, IMPACT-PCP evaluated whether GES altered primary care providers' diagnostic evaluation and clinical management of stable, nonacute, nondiabetic patients presenting with CAD symptoms.^[19] Nine primary care providers at four centers evaluated 261 consecutive patients, 251 (96%) of whom were eligible for participation. Clinicians documented their pretest impressions and recommendations for further evaluation and management on a clinical report form. All patients underwent GES testing. The primary outcome was the change in patient management between preliminary and final treatment plans.

In both studies, a change in patient management was defined prospectively as an increase or decrease in intensity of the diagnostic plan. GES were divided into a high-risk group (>15) and a low risk group (\leq 15). The authors defined the categories of intensity in the following order: 1) no further cardiac testing or medical therapy for angina or non-cardiac chest pain, 2) stress testing (with/without imaging) or computed tomography coronary angiography, or 3) invasive

coronary angiography (ICA). Within the prospective cohort, the diagnostic testing plan was changed for 58% of patients (95% CI 46% to 69%, $p < 0.001$) with a greater reduction in testing intensity (39%) compared to increased testing intensity (19%). Compared to the historic control group the prospective cohort had a 71% reduction in overall diagnostic testing ($p < 0.001$). Results from IMPACT-PCP were similar: diagnostic testing plans were changed for 58% of patients, with reductions in testing intensity more common than increases (64% vs 34%; $p < 0.001$). No study-related major adverse cardiovascular events were observed in 247 patients (98%) who had at least 30 days of follow-up.

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

REGISTRY 1 Trial

The REGISTRY 1 assessed the impact of GES on patient management decisions by examining the association between GES test results and post-test referral patterns.^[20] Primary care practitioners at seven centers evaluated 342 stable, nonacute, nondiabetic patients presenting with CAD symptoms. All patients underwent GES testing. Of 167 patients with low (≤ 15) GES, 10 (6%) were referred for further cardiac evaluation compared with 122 (70%) of 175 patients in the high GES group ($p < 0.001$). Analysis of GES as a continuous variable showed a statistically significant change in cardiac referrals for every 10-point change in GES (adjusted OR 13.7, 95% CI 12.5 to 15.0, $p < 0.001$). Over a mean follow-up of 264 days, there were five major adverse cardiovascular events, two in the low GES group and three in the high GES group. Of 21 patients who underwent elective ICA, one (50%) of two in the low GES group and eight (42%) of 19 in the high GES group had obstructive findings.

IMPACT and REGISTRY 1 Trials

An analysis was conducted on the combined data of the female cohorts from the IMPACT and REGISTRY 1 trials.^[21] Information on 320 women with CAD symptoms (inclusion criteria described above) were pooled to test whether the GES was associated with referrals for further cardiac evaluation. In this analysis, women with a low GES had a referral rate of 4.0% (10/248), which was significantly lower than the rate for women with a high GES of 83.3% (60/72). Events per GES group were not reported.

Section Summary

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

PRACTICE GUIDELINE SUMMARY

AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION

The 2012 joint guidelines of the American College of Cardiology Foundation and six other medical societies for the diagnosis and management of patients with stable ischemic heart disease does not mention GES in the guideline statement.^[22] The 2014 update to these guidelines also did not mention GES.^[23]

A policy statement from the American College of Cardiology and the American Heart Association (ACC/AHA) discussed the role of genetics and cardiovascular disease treatment and diagnosis but did not address gene expression as is measured in the Corus® CAD Test.^[24]

In joint statement, the ACC/AHA indicated that genotype testing for coronary artery disease risk assessment in asymptomatic adults is not recommended.^[25] (Class III recommendation, Level of Evidence B: Sufficient evidence from multiple randomized trials or meta-analyses is available to determine that the procedure is not useful and may be harmful)

U.S. PREVENTIVE SERVICES TASK FORCE

The U.S. Preventive Services Task Force (USPSTF) did not include gene expression testing in their current recommendation statement for screening for coronary heart disease.^[26]

SUMMARY

There is not enough research to show that gene expression scores can reduce unnecessary testing and improve health outcomes for people with symptoms of coronary artery disease. There are no clinical guidelines based on research that recommend gene expression testing to predict coronary artery disease. Therefore, gene expression testing to predict coronary artery disease is considered investigational for all indications.

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CODES

Codes	Number	Description
CPT	81479	Unlisted molecular pathology procedure
	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	

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