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Medical Policy Manual

Topic: Gene Expression Testing to Predict Coronary Artery Disease

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Section: Genetic Testing

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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

The expression levels of various genes in circulating white blood cells or whole blood samples have been reported to discriminate between cases of obstructive coronary artery disease (CAD) and healthy controls. It is theorized that multiplex gene expression testing can be combined with other risk factors to predict the likelihood of obstructive CAD in patients who present with chest pain or other suggestive symptoms, or in asymptomatic patients who are at high risk of CAD.

Background

Heart disease is the leading cause of mortality in the U.S. and, together with cerebrovascular disease, accounted for 31% of deaths in 2007.[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 prior 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.

MEDICAL POLICY CRITERIA

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

SCIENTIFIC EVIDENCE

In order to evaluate the use of gene expression testing for the management of patients at high risk for coronary artery disease, the scientific evidence must demonstrate how the results of this testing can be used to benefit patient management and impact health outcomes (i.e., clinical utility) compared with standard clinical evaluation techniques.

Literature Appraisal

What is the technical performance of the prediction model (assay development and validation)?

Assay Development

In an initial proof-of-principle study, Wingrove et al. evaluated 27 cases with and 14 controls without angiographically defined coronary artery disease (CAD) for expression of genes that differed significantly between the 2 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 et al.[5] The authors conducted 2 successive case-control gene expression discovery studies using samples from independent cohorts. Cases were angiographically defined as 75% or greater maximum stenosis in one 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 (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 3 normalization genes plus terms for age and sex, all incorporated into an algorithm that results in an obstructive CAD score ranging from 1–40. 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]: 0.73-0.81).

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.[6] This is the same cohort from which the second assay development case-control cohort was drawn.[5] Patients were sequentially allocated to development and validation sets. The authors defined obstructive CAD as 50% or greater stenosis in 1 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 ($p<0.001$).

What is the predictive ability of the test compared to alternative methods of predicting CAD?

The PREDICT trial compared the predictive accuracy of the GES measure to clinical predictors and myocardial perfusion imaging (MPI) stress testing.[5-7] This was a multicenter study of 1,160 patients presenting for coronary angiography. All patients underwent gene expression score (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 was published in 2012 that 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.[7] The PREDICT trial included 1,160 patients who underwent angiography. 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: 0.74-10.5, $p=0.16$).

In another follow-up publication from the PREDICT trial, Lansky and colleagues 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.[8] 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 2 fold increase in odds of CAD, and an increase in maximum percent stenosis, the number of lesions, and total plaque volume.

Thomas and colleagues assessed the clinical validity and utility of the Corus CAD™ for detection of obstructive CAD in in a multicenter, prospective study (COMPASS).[9] Obstructive CAD was defined as 50% or greater stenosis in 1 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 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. A summary of the AUC, sensitivity, and specificity of the comparators is given in Table 1. 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.

Twenty-eight adverse events were observed which included 25 revascularizations within 30 days, 2 MACE, and 1 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 ($r=0.46$, $P<0.001$).

Conclusion

Results of the PREDICT and COMPASS study establish that the GES score has predictive ability for CAD, however, there are several limitations to 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.

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 87-89%.[10] This raises the question of whether the accuracy of MPI in the COMPASS study is representative of that seen in current clinical care. Also, the comparison of overall accuracy of the GES score with MPI testing does not establish that clinical decisions would be changed, specifically whether patients with a positive MPI could safely forego further invasive testing based on a low GES score.

Does use of the test lead to changes in management that improve outcomes?

The IMPACT 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.[11] CAD was defined by the authors as no CAD (0% stenosis), CAD (≤50% stenosis) and 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 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. 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 (≤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%-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).

A secondary analysis 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.

Conclusion

The IMPACT study is limited by comparison with historical controls, which were not well-matched to the study population. In addition, the impact of GES results upon management decisions was not evaluated in this study and is therefore uncertain. There is no information provided on whether the management changes led to beneficial effects on health outcomes, and it is not possible to estimate the likelihood of benefit from the information given in this study. Therefore, it is not possible to conclude that the GES score leads to changes in management that improve outcomes.

Clinical Practice Guidelines

American College of Cardiology/American Heart Association

- A recent policy statement from the ACC and 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.[12]

- In joint statement, the ACC/AHA jointly state that genotype testing for coronary artery disease risk assessment in asymptomatic adults is not recommended.[13] (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 (USPSTF)

The USPSTF did not include gene expression testing in their current recommendation statement for screening for coronary heart disease.[14]

No other clinical practice guidelines or position statements from U.S. professional societies were found for screening for coronary artery disease risk.

Summary

The current evidence is insufficient to permit conclusions about the ability of gene expression scores (GES) to change patient management and improve health outcomes compared with conventional clinical evaluation or screening for coronary artery disease. Validation studies reported modest predictive ability; however testing has not been validated for the more clinically relevant population of patients being considered for angiography or treatment. Further, testing has not been validated for screening of the general population or patients who have no symptoms but are at high risk for coronary artery disease. One study with methodologic limitations reports management changes as a result of the test, but the effect of these management changes is uncertain. There has been no convincing evidence presented that the use of GES scores can reduce unnecessary coronary angiography. Therefore, gene expression testing to predict coronary artery disease is considered investigational for all indications.

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CROSS REFERENCES

Measurement of Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) in the Assessment of Cardiovascular Risk, Laboratory No. 63

CODES	NUMBER	DESCRIPTION
CPT	84999	Unlisted chemistry procedure
HCPCS	None	