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

File Name: gene_expression_testing_in_the_evaluation_of_patients_with_stable_ischemic_heart_disease
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Description of Procedure or Service

The 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 can be combined with other risk factors to predict the likelihood of obstructive CAD in patients who present with stable ischemic heart disease.

Heart disease is the leading cause of mortality in the U.S. Individuals with signs and symptoms of obstructive coronary artery disease (CAD) may be evaluated with a variety of tests according to prior risk. Coronary angiography is the gold standard for diagnosing obstructive CAD, but 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. 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, about 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 and 41% if using the broader definition, stenosis of 50% or more in any coronary vessel). Thus, methods of improving patient risk prediction prior to invasive coronary angiography are needed.

In an initial proof-of-principle study of the Gene Expression Score (GES) test in patients referred for invasive coronary angiography, Wingrove and colleagues (2008) evaluated 27 cases (96% symptomatic) with 14 controls without angiographically defined CAD for expression of genes that differed significantly between the 2 groups, selecting 50 genes. The authors then 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 in 21 controls. Expression of the 14 genes was proportional to maximal coronary artery stenosis in the combined cohort of 215 patients.

Elashoff and colleagues (2011) described final test development of the GES. Investigators conducted 2 successive case-control gene expression discovery studies using samples from independent cohorts. Cases were angiographically defined as 75% or greater maximum stenosis.
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in 1 major vessel, or 50% or greater in 2 vessels, and controls defined as less than 25% stenosis in all major vessels. Of clinical factors, diabetes had the most significant effect on gene expression; in the first case-control study in symptomatic patients (CATHGEN; N=195), expression of 42 genes in nondiabetic patients and 12 genes in diabetic patients was found to significantly (p<0.05) discriminate between cases and controls with no overlap. As a result, the second case-control study, in a subset of 198 patients from the prospective PREDICT study, and final development of the assay was limited to nondiabetic patients (62% symptomatic). Final variable selection comprised the expression of 20 CAD-associated genes, 3 normalization genes, and terms for age and sex, all incorporated into an algorithm that resulted in an obstructive CAD score ranging from 1 to 40. Receiver operating characteristics analysis in PREDICT resulted in an area under the curve for CAD of 0.77 (95% confidence interval, 0.73 to 0.81).

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, non-diabetic 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

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

***Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.

Policy

Gene expression testing in the evaluation of patients with stable ischemic heart disease is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Gene Expression Testing for Coronary Artery Disease is covered

Not applicable

When Gene Expression Testing for Coronary Artery Disease is not covered

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 in stable, nondiabetic patients.
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Policy Guidelines

The evidence for individuals with suspected stable ischemic heart disease without diabetes who receive gene expression testing includes retrospective case-control and prospective cohort studies. Relevant outcomes are test accuracy and validity, along with change in disease status. Results of initial validation studies report that the test may improve CAD prediction beyond that of simple prediction models such as Diamond-Forrester, but the benefit of improved prediction when added to routine clinical evaluation is uncertain. The test has also been shown to have some predictive ability for future cardiac events and revascularization. In the COMPASS study, the overall accuracy of the GES test in predicting cardiac events was superior to myocardial perfusion imaging (MPI) in patients who were referred for MPI testing. However, in that study, the reported sensitivity of MPI was considerably lower than generally reported in the literature. Also, it is unclear from the COMPASS study whether patients with a positive MPI could safely forego further testing based on a low GES.

Clinical utility of GES has not been demonstrated. Three studies with methodologic limitations reported management changes as a result of the test, but the effect of these management changes on patient outcomes is uncertain. Evidence for a significant incremental improvement in outcomes when gene expression testing is added to standard clinical evaluation is lacking. The evidence is insufficient to determine the effects of the technology on health outcomes.

CardioDX established the PRESET registry to evaluate patterns of care associated with the use of Corus® CAD in real-world clinical care settings (NCT01677156). Eligible adults were those who presented to their primary clinician's office with chest pain suggesting obstructive CAD. Patients with a history of CAD, including previous MI, New York Heart Association class 3 or 4 heart failure, or diabetes mellitus were excluded. No results published through Clinicaltrials.gov at the completion of this trial as of 10/2016.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: There is not a specific code for this test. The following codes may be submitted: 84999, 81479, 81599, G0452, 81493.

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources


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


Medical Director review 9/2011


Specialty Matched Consultant Advisory Panel review 4/2012


Medical Director review 7/2012


Specialty Matched Consultant Advisory Panel review 4/2013

Medical Director review 4/2013


Medical Director review 4/2014

Ashley EA, Hershberger RE, Caleshu C et al. Genetics and cardiovascular disease: a policy
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National Institutes of Health (NIH). Clinical Trial # NCT01677156. A Registry to Evaluate Patterns of Care Associated With the Use of Corus® CAD in Real World Clinical Care Settings. http://clinicaltrials.gov/ct2/results?term=NCT01677156&Search=Search


Specialty Matched Consultant Advisory Panel review 4/2015

Medical Director review 4/2015


Medical Director review 4/2016

For Policy titled, “Gene Expression in the Evaluation of Patients With Stable Ischemic Heart Disease”

National Institutes of Health (NIH). Clinical Trial # NCT01677156. A Registry to Evaluate Patterns of Care Associated With the Use of Corus® CAD in Real World Clinical Care Settings. http://clinicaltrials.gov/ct2/results?term=NCT01677156&Search=Search


Medical Director review 1/2017

Specialty Matched Consultant Advisory Panel review 4/2017

Medical Director review 4/2017

Policy Implementation/Update Information


5/1/12 Specialty Matched Consultant Advisory Panel review 4/2012 References updated. (mco)

8/21/12 Description section updated. Policy Guidelines updated. References updated. Medical Director review 7/2012. No changes to Policy Statement. (mco)

1/1/13 Added the following new codes to the Billing/Coding section: G0452, 81599. (mco)
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7/30/13 References updated. Policy Guidelines updated. No changes to Policy Statements. (mco)


7/29/14 “When not Covered” statement revised to state: “Gene expression testing to predict coronary artery disease is considered investigational for all indications, including but not limited to prediction of the likelihood of CAD in stable, nondiabetic patients.” References updated. Policy Guidelines updated. (mco)


7/28/15 Billing/Coding section updated to add code: 81479. References updated. (td)

10/1/15 Billing/Coding section revised to include code 81493; effective 1/1/16. Policy Guideline section revised. Policy Statement remains unchanged. References updated. (td)


2/24/17 Title changed to "Gene Expression Testing in the Evaluation of Patients With Stable Ischemic Heart Disease". Policy statement unchanged but wording updated to reflect current terminology and guidelines; Policy Guidelines and references updated. (jd)


Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.