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

Introduction

RNA (ribonucleic acid) is a molecule found in all of our cells. There are three types of RNA, and all three play a role in making proteins in the body. Gene expression testing looks at the activity of RNA in a specific tissue or bodily fluid. Gene expression testing has been used to evaluate patients with heart disease and also to try to predict which people will develop heart disease. Medical studies have not shown that gene expression testing is useful in taking care of patients. For this reason, gene expression testing is considered to be unproven (investigational).

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be 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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<td>Unlisted molecular pathology procedure</td>
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Related Information

N/A

Evidence Review

Background

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 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.

**Description**

**Heart Disease**

Heart disease is the leading cause of death in the United States, accounting for approximately one-third of all deaths in people over age 35. The death rate is higher in men compared with women and in blacks compared with whites, but lower in Hispanic populations compared with blacks and whites. The most common form of heart disease is ischemic heart disease, also known as coronary artery disease (CAD).

Angina is the first symptom of CAD in approximately 50% of patients. However, women and the elderly are more likely to present with atypical symptoms such as nausea, vomiting, gastric discomfort, or atypical chest pain, which makes diagnosis more challenging.

**Diagnosis**

Patients with signs and symptoms of obstructive CAD may be evaluated with a variety of tests according to prior risk. Coronary angiography is the criterion standard for diagnosing obstructive CAD, but it is invasive and associated with a low but finite risk of harm. Coronary angiography also has a relatively low yield. In a study of nearly 400,000 patients without known CAD undergoing elective coronary angiography, approximately 38% were positive for obstructive CAD (using the CAD definition, ≥50% stenosis of the diameter of the left main coronary artery or ≥70% stenosis of the diameter of a major epicardial or branch vessel >2.0 mm in diameter) and 41% if using the broader definition (≥50% stenosis in any coronary vessel). Thus, methods of improving patient risk prediction before invasive coronary angiography are needed.

In an initial proof-of-principle study of the Corus CAD score in patients referred for invasive coronary angiography, Wingrove et al (2008) evaluated 27 cases (96% symptomatic) with and 14 controls without angiographically defined CAD for expression of genes that differed significantly between the 2 groups, selecting 50 genes. To that authors added 56 genes selected from relevant literature reports and evaluated the expression of these 106 genes in an independent
set of 63 cases and 32 controls, resulting in the selection of 14 genes that independently and significantly discriminated between groups in multivariable analysis. The significance of 11 of these 14 genes was replicated in the third set of 86 cases and 21 controls. Expression of the 14 genes was proportional to maximal coronary artery stenosis in the combined cohort of 215 patients.

Elashoff et al (2011) described final Corus CAD score development. Investigators conducted 2 successive case-control gene expression discovery studies using samples from independent cohorts. Cases were angiographically defined as 75% or greater maximum stenosis in 1 major vessel, or 50% or greater in 2 vessels, and controls defined as less than 25% stenosis in all major vessels. Of clinical factors, diabetes had the most significant effect on gene expression; in the first case-control study in symptomatic patients (CATHGEN; N=195), expression of 42 genes in nondiabetic patients and 12 genes in diabetic patients was found to (p<0.05) discriminate significantly between cases and controls with no overlap. As a result, the second case-control study, in a subset of 198 patients from the prospective PREDICT study, and final development of the assay was limited to nondiabetic patients (62% symptomatic). The participants were 76% male and 89% white. Final variable selection comprised the expression of 20 CAD-associated genes, 3 normalization genes, and terms for age and sex. The majority of the selected genes were immune and inflammatory-related. All terms were incorporated into an algorithm that resulted in an obstructive CAD score ranging from 1 to 40.

Summary of Evidence

For individuals who have suspected stable ischemic heart disease without diabetes or inflammatory conditions who receive gene expression testing, the evidence includes retrospective case-control and prospective cohort studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, change in disease status, morbid events, and resource utilization. The diagnostic pathway for CAD includes information from a medical history, along with age and sex, stress testing, and imaging. Newer noninvasive methods are being tested, such as gene expression testing. It is not clear how the Corus CAD gene expression test fits in the current diagnostic pathway and how results would be used to change current guideline-based risk stratification before and/or after other noninvasive testing. Results of 2 validation studies (PREDICT, COMPASS) have reported that the test may improve CAD prediction beyond the Diamond-Forrester prediction model. In the COMPASS study, the sensitivity and negative predictive value of the Corus CAD score in diagnosing obstructive CAD was superior to myocardial perfusion imaging in patients referred for myocardial perfusion imaging testing. However, in that study, the reported sensitivity of myocardial perfusion imaging
was considerably lower than that generally reported in the literature. Neither PREDICT nor COMPASS used the guideline definition of obstructive CAD as the reference standard. The sensitivity and negative predictive value of clinical models were not reported. An analysis of a cohort from the PROMISE trial including patients with intermediate pretest probability of obstructive CAD confirmed a high negative predictive value for the Corus CAD score. The test also has been shown to have some predictive ability of future revascularization; too few major cardiac events have been observed during the limited duration of follow-up to assess predictive ability for that outcome. Evidence for the Corus CAD score has not directly demonstrated that the test is clinically useful and a chain of evidence cannot be constructed to supports

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in December 2017 did not identify any ongoing or unpublished trials that would likely influence this policy.

Practice Guidelines and Position Statements

American Heart Association

In 2012, the American Heart Association (AHA) released a policy statement on genetics and cardiovascular disease. Gene expression testing is not specifically mentioned. Generally, 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.”

In 2017, AHA released a scientific statement on the expressed genome in cardiovascular diseases and stroke. 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

The 2012 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.\textsuperscript{2} The 2014 update to these guidelines also did not mention the gene expression score.\textsuperscript{6}

**Medicare National Coverage**

There are no Medicare national coverage determinations for Corus CAD testing to predict coronary artery disease (CAD). In July 2013, Palmetto GBA issued a positive local coverage decision for the Corus CAD test in patients who have typical symptoms of CAD or atypical symptoms and one or more CAD risk factors. In October 2015, Noridian also issued a positive local coverage decision. However, a draft noncoverage decision has been posted by Noridian with comment period open until April 2018. In 2016, Novitas Solutions issued a local coverage decision.\textsuperscript{26}

**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 Improvement Amendments. The Corus CAD\textsuperscript{®} (CardioDx, Palo Alto, CA) test is available under the auspices of Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical 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.

**References**


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<td>05/24/12</td>
<td>Policy renumbered to 12.04.72 (previously 2.04.72) and reassigned to new Genetic Testing category. Related Policies updated; 2.04.67 and 2.04.71 renumbered to 12.04.67 and 12.04.71, respectively.</td>
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<td>Replace policy. Policy updated with literature search through April 2012; reference 6 added; no change to policy statement.</td>
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<td>Coding update. CPT codes 83890 – 83913 deleted as of 12/31/12; CPT codes 81200 – 81479 and 81599, effective 1/1/13, are added to the policy.</td>
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<td>05/14/13</td>
<td>Update Related Policies. Add 12.04.91.</td>
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<td>08/16/13</td>
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<td>09/03/14</td>
<td>Annual Review. Policy statement unchanged but wording modified to clarify that GES is investigational “for all indications, including but not limited to” [prediction of CAD likelihood in stable, nondiabetic patients]. Policy updated with literature review through May 8, 2014; references 10, 13-16 added; others renumbered/removed. Policy</td>
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<td>04/01/17</td>
<td>Annual Review, approved March 14, 2017. Policy updated with literature review through December 5, 2016; references 2 and 19 added. Some references removed. Title and indication changed to “patients with stable ischemic heart disease” to be consistent with current guideline statements. Policy statements unchanged, but wording changed to reflect current terminology for indication. Removed Appendix table.</td>
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