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

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.

OBJECTIVE

The objective of this evidence review is to determine whether gene expression testing in patients with stable ischemic heart disease improves the net health outcome compared with standard clinical evaluation, including established noninvasive testing.

POLICY STATEMENT

Gene expression testing in the evaluation of patients with stable ischemic heart disease is considered investigative for all indications, including but not limited to prediction of coronary artery disease in stable, nondiabetic patients.

The policies contained in the FEP Medical Policy Manual are developed to assist in administering contractual benefits and do not constitute medical advice. They are not intended to replace or substitute for the independent medical judgment of a practitioner or other health care professional in the treatment of an individual member. The Blue Cross and Blue Shield Association does not intend by the FEP Medical Policy Manual, or by any particular medical policy, to recommend, advocate, encourage or discourage any particular medical technologies. Medical decisions relative to medical technologies are to be made strictly by members/patients in consultation with their health care providers. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that the Blue Cross and Blue Shield Service Benefit Plan covers (or pays for) this service or supply for a particular member.
BENEFIT APPLICATION

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient’s existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA 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

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. The 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 two validation studies (PREDICT, COMPASS) have reported the test may improve CAD prediction beyond the Diamond-Forrester prediction model. In the COMPASS study, the sensitivity and NPV of the Corus CAD score in diagnosing obstructive CAD was superior to MPI in patients referred for MPI testing. However, in that study, the reported sensitivity of MPI 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 and had relatively few patients at intermediate risk based on clinical prediction rules. The sensitivity and NPV 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 NPV 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

The AHA(2012) released a policy statement on genetics and cardiovascular disease. 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.”

The AHA (2017) 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 joint guidelines of the American College of Cardiology Foundation (2012) and 6 other medical societies for the diagnosis and management of patients with stable ischemic heart disease did not mention the gene expression score. The 2014 update to these guidelines also did not mention the gene expression score.

**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 (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.

**REFERENCES**


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<th>Date</th>
<th>Action</th>
<th>Description</th>
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<td>September 2018</td>
<td>New policy</td>
<td>Gene expression testing in the evaluation of patients with stable ischemic heart disease is considered investigational for all indications.</td>
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<tr>
<td>June 2019</td>
<td>Replace policy</td>
<td>Policy updated with literature review through January 30, 2019; references added. Policy statement unchanged.</td>
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