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.

Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Testing</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene expression testing</td>
<td>Gene expression testing in the evaluation of patients with</td>
</tr>
</tbody>
</table>

Select a hyperlink below to be directed to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.
Testing

Investigational

| Evaluation of patients with stable ischemic heart disease | Stable ischemic heart disease is considered investigational for all indications, including but not limited to prediction of the likelihood of CAD in stable, nondiabetic patients. |

Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>81493</td>
<td>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</td>
</tr>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
<tr>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
</tr>
</tbody>
</table>

Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).

Related Information

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
Description

Heart disease is the leading cause of death in the United States.\(^1\) Patients with signs and symptoms of obstructive coronary artery disease (CAD) may be evaluated with a variety of tests. Coronary angiography is the criterion 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 who are at risk of having CAD according to their history, physical findings, electrocardiogram, and biomarkers of cardiac injury. For patients at low to intermediate risk, observation and noninvasive diagnostic methods, which may include imaging methods such as coronary computed tomographic angiography, may be recommended.\(^2\) Nevertheless, some 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 who underwent elective coronary angiography, approximately 38\% were positive for obstructive CAD (using the CAD definition, stenosis of ≥50\% of the diameter of the left main coronary artery or stenosis of ≥70\% of the diameter of a major epicardial or branch vessel that was >2.0 mm in diameter; result was 41\% if using the broader definition, which is stenosis of ≥50\% in any coronary vessel).\(^3\) Thus, methods of improving patient risk prediction before diagnostic testing are needed.

A CAD classifier of 23 genes plus patient age and sex has been developed based on expression levels in whole blood samples.\(^4\) 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, Palo Alto, CA). 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.

Summary of Evidence

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

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in December 2016 did not identify any ongoing or unpublished trials that would likely influence this review.

Practice Guidelines and Position Statements

American Heart Association

In 2012, the American Heart Association (AHA) released a policy statement on genetics and cardiovascular disease.\textsuperscript{17} 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.”\textsuperscript{18}

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 (GES).\textsuperscript{2} The 2014 update to these guidelines also did not mention GES.\textsuperscript{19}

**Medicare National Coverage**

There are no Medicare National Coverage Determinations for GES testing to predict CAD. In July 2013, Palmetto GBA issued a positive local coverage decision for the Corus CAD\textsuperscript{®} test in patients who have typical symptoms of CAD or atypical symptoms and 1 or more CAD risk factors.

**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 Act (CLIA). The Corus CAD\textsuperscript{™} (CardioDx, Palo Alto, CA) test 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.

**References**


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>08/09/11</td>
<td>New Policy. Add to Medicine Section; Pathology/Laboratory sub-section. Policy created with literature search through April 2011; considered investigational.</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>08/20/12</td>
<td>Replace policy. Policy updated with literature search through April 2012; reference 6 added; no change to policy statement.</td>
</tr>
<tr>
<td>01/11/13</td>
<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>
</tr>
<tr>
<td>05/14/13</td>
<td>Update Related Policies. Add 12.04.91.</td>
</tr>
<tr>
<td>08/16/13</td>
<td>Replace policy. Policy updated with literature search through April 2013; reference 8-11 added. Rationale section reorganized and editorial changes made. No change in policy statement.</td>
</tr>
<tr>
<td>10/18/13</td>
<td>Update Related Policies. Add 2.04.509.</td>
</tr>
<tr>
<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 statement revised as noted.</td>
</tr>
<tr>
<td>08/11/15</td>
<td>Annual Review. Policy updated with literature review through May 20, 2015; references 7 and 16 added. Policy statements unchanged.</td>
</tr>
<tr>
<td>10/13/15</td>
<td>Annual Review. Policy updated with literature review through June 29, 2015; no new references added. Policy statements unchanged.</td>
</tr>
<tr>
<td>01/19/16</td>
<td>Coding update. New CPT code 81493, effective 1/1/16, added to policy.</td>
</tr>
<tr>
<td>06/01/16</td>
<td>Update Related Policies. Removed 12.04.67 and 12.04.71 as they were deleted; information moved to 2.04.509.</td>
</tr>
<tr>
<td>09/01/16</td>
<td>Annual Review, approved August 9, 2016. No change to policy statement. Literature reviewed through July 18, 2016.</td>
</tr>
<tr>
<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.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>09/22/17</td>
<td>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. Policy moved to new format. No changes to policy statements.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2017 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination Is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can file a grievance in person or by mail, fax, or email. If you need help filing a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.

Call 800-722-1471 (TTY: 800-842-5357).

Arabic (Arabic):

يكون هذا الإشعار معلومات هامة. قد يكون هذا الإشارة معلومات مهمة في بعض حالات طلبي أو معلومات relevant to this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.

Call 800-722-1471 (TTY: 800-842-5357).

中文 (Chinese):

本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要訊息。本通知可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357).

037338 (07-2016)
Premera Blue Cross: This notice contains important information you may need to know about your claims or coverage. Some of the dates mentioned in this notice may be important. Please read the notice carefully. For more information, call 800-722-1471 (TTY: 800-842-5357).

Thai (Thai): ประกาศนี้อาจมีข้อมูลที่สำคัญเกี่ยวกับการขอเงินคืนค่าสุขภาพ หรือสิทธิในการรักษาสุขภาพผ่าน Premera Blue Cross. โปรดตรวจสอบข้อมูลที่สำคัญที่อาจอยู่ในหน้าของข่าวความเห็น หรือโปรดติดต่อที่ 800-722-1471 (TTY: 800-842-5357).