MEDICAL POLICY – 2.04.76
Quantitative Assay for Measurement of HER2 Total Protein Expression and HER2 Dimers

Introduction

HER2 protein is a receptor that’s found on all breast cells. HER2 is a growth-promoting protein. In about one quarter of all breast cancer cases, the HER2 gene makes too many copies. All of these extra copies of the HER2 gene mean a lot of extra HER2 protein receptors are on breast cells. The extra HER2 receptors lead to breast cells that uncontrollably grow and divide. Cancer cells with higher-than-normal levels of HER2 are called HER2-positive cancers. Knowing if breast cancer is HER2-positive guides specific treatment choices. There are standard ways of determining if breast cancer is HER2-positive. Newer lab tests have been developed that try to determine HER2 status. High quality medical studies don’t show a clear connection between the information from these tests and overall health results. For this reason, these newer types of tests are considered investigational (unproven).

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

Assessment | Investigational
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HER2 status (eg, HERmark® Breast Cancer Assay) | The assessment of human epidermal growth factor receptor 2 (HER2) status by quantitative total HER2 protein expression and HER2 homodimer measurement is considered investigational.

Coding

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<th>Code</th>
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<td>CPT</td>
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<tr>
<td>0009U</td>
<td>Oncology (breast cancer), ERBB2 (HER2) copy number by FISH, tumor cells from formalin fixed paraffin embedded tissue isolated using image-based dielectrophoresis (DEP) sorting, reported as ERBB2 gene amplified or non-amplified</td>
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<td>84999</td>
<td>Unlisted Chemistry procedure</td>
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Related Information

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients. Genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may substantially alter the utilization of genetic testing and may reduce inappropriate testing. Additionally, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
Evidence Review

Description

Novel assays that quantitatively measure total human epidermal growth factor receptor 2 (HER2) protein expression and homodimers have been developed to improve the accuracy and consistency of HER2 testing.

Background

Human Epidermal Growth Factor Receptor 2

The human epidermal growth factor receptor (HER) family of receptor tyrosine kinases (EGFR/HER1, ErbB2/HER2, ErbB3/HER3, ErbB4/HER4) plays a major role in the pathogenesis of many solid tumors. In approximately 25% to 30% of breast cancers, overexpression of HER2 has been linked to shorter disease-free and overall survival, lack of responsiveness to tamoxifen antiestrogen therapy, and altered responsiveness to a variety of cytotoxic chemotherapy regimens.

Trastuzumab, a monoclonal antibody directed at the extracellular domain of HER2, has offered shorter disease-free and overall survival advantages in the metastatic and adjuvant settings in HER2-overexpressing patients, although not all patients respond. Fewer than 50% of patients with metastatic HER2-positive breast cancer show initial benefit from trastuzumab treatment, and many of those eventually develop resistance.\(^1\,\text{,}\,2\,\text{,}\,3\)

Current methodologies for the selection of HER2-positive patients include immunohistochemistry (IHC) to detect HER2 protein overexpression, and fluorescence in situ hybridization (FISH) to detect HER2 gene amplification. However, controversy still exists regarding the accuracy, reliability, and interobserver variability of these assay methods. IHC provides a semiquantitative measure of protein levels (scored as 0, 1+, 2+, 3+) and the interpretation may be subjective. FISH is a quantitative measurement of gene amplification, in which the HER2 gene copy number is counted. However, FISH, which is considered to be more quantitative analytically, is not always representative of protein expression, and multiple studies have failed to demonstrate a relation between HER2 gene copy number and response to trastuzumab. Whereas patients who overexpress HER2 protein (IHC) or show evidence of HER2
gene amplification (FISH) have been shown to experience better outcomes on trastuzumab than those scored negative by those assays, differences in the degree of expression or amplification by these methods have generally not been shown to discriminate between groups with different outcomes. IHC and FISH testing may be affected by interlaboratory variability, and neither test provides quantitative data that reflect the activation state of signaling pathways in tumors, which may limit their utility in patient selection. Most laboratories in North America and Europe use IHC to determine HER2 protein status, with equivocal category results (2+) confirmed by FISH (or more recently by chromogenic in situ hybridization).

Typically, HER2 activates signaling pathways by dimerizing with ligand-bound epidermal growth factor receptor family members such as HER1 and HER3. A HER2 ligand has not been identified, but overexpressed HER2 is constitutively active. When HER2 is pathologically overexpressed, the receptor may homodimerize and activate signaling cascades in the absence of the normal regulatory control imposed by the requirement for ligand binding of its heterodimerization partners.

A novel assay (HERmark® Breast Cancer Assay) was developed to quantify total HER2 protein expression and HER2 homodimers in formalin-fixed, paraffin-embedded tissue samples.

**Summary of Evidence**

For individuals who have breast cancer and are undergoing assessment of HER2 status who receive quantitative total HER2 protein expression and HER2 homodimer measurement, the evidence includes validation studies and retrospective analysis of the association between levels and survival outcomes. Relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Retrospective analysis using HERmark® have shown that the assay may predict a worse response to trastuzumab in certain populations. However, findings have been inconsistent, and no clear association with clinical outcomes has been shown. Additionally, cut points for defining patient groups varied across studies. Clinical utility of the HERmark® assay has not been demonstrated. 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 October 2018 did not identify any ongoing or unpublished trials that would likely influence this review.
Practice Guidelines and Position Statements

National Comprehensive Cancer Network guidelines on the treatment of breast cancer (v.3.2018) do not address the use of HERmark.\(^{21}\)

Medicare National Coverage

There is no national coverage determination.

Palmetto GBA determines coverage and reimbursement for laboratories that perform molecular diagnostic testing and submit claims to Medicare in Medicare Jurisdiction E (California, Nevada, Hawaii). Palmetto GBA’s decisions apply for all molecular diagnostic tests for Medicare.

Palmetto GBA has completed an assessment of HERmark® and determined that the test meets criteria for analytic and clinical validity, and clinical utility as a reasonable and necessary Medicare benefit.\(^{22}\) Effective December 9, 2011, Palmetto GBA will reimburse HERmark® services for patients with breast cancer.

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. HERmark® Breast Cancer Assay (Monogram Biosciences) is available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by 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.

References


### History

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<th>Comments</th>
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<td>12/13/11</td>
<td>New Policy – Add to Pathology/Laboratory Section. Policy created with literature search through September 2011; considered investigational.</td>
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<td>12/19/12</td>
<td>Replace policy. Rationale updated based on a literature search through September 2012. Reference 9 added. Other references renumbered. Policy statement unchanged. Updated title in related policy 5.01.514 to include: “Other”.</td>
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<td>12/17/14</td>
<td>Annual Review. Policy updated with literature review through September 17, 2014; references 11, 14-16, and 18 added; references 3 and 17 updated. No change to policy statement.</td>
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<td>02/09/16</td>
<td>Annual Review. Policy updated with literature review through November 12, 2015; no references added; references 3 and 17 updated. No change to policy statement.</td>
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<tr>
<td>10/01/17</td>
<td>Coding update, added new CPT code 0009U. Combined both Coding sections into one under Policy Guidelines.</td>
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<td>Annual Review, approved November 9, 2017. Policy updated with literature review through October 2017; Added reference 20. No change to policy statement.</td>
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<tr>
<td>03/01/18</td>
<td>Annual Review, approved February 6, 2018. Policy updated with literature review through October 2017; references 1-3, 5, 7, and 10 added; reference 22 updated. Policy statement unchanged.</td>
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<td>03/01/19</td>
<td>Annual Review, approved February 5, 2019. Policy updated with literature review through October 2018; references 17-20 added. Policy statement unchanged.</td>
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**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). ©2019 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.
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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:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5952, 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 S09F, HHH Building
Washington, DC 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):
يوجب هذا الإشعار معلومات هامة. قد يحتوي هذا الإشعار معلومات مهمة لمكونات طبلك أو
العلاقة التي تزيد الحصول عليها من خلال
Premera Blue Cross ذاكرة هذا الإشعار وقد يحتوي معلومات عن فعالية الصحيحة والاستعمال
فقط في تغطية الكلفة. يعطى لك نسخة هذه المعلومات والمساعدة بكلام ت뭡
800-722-1471 (TTY: 800-842-5357) باللغة العربية.

Chinese (Chinese):
本通知有重要的信息。本通知可能有关於您透过Premera Blue Cross提交的申请或保险的重要讯息。本通知内可能有重要日期。您可能需要在截止日期之前採取行動。以保留您的健康保险或者費用補貼。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).

Oromo (Cushite):

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본 통지서에는 중요한 정보가 들어 있습니다. 즉 이 통지서는 귀하의 신청에 관해 그리는 Premera Blue Cross 를 통해 커버리지에 관한 정보를 표시하고 있습니다. 본 통지서에는 백신이 되는 볼파이리가 있을 수 있습니다. 귀하는 귀하의 건강 커버리지를 계속 유지하거나 비용을 절감하기 위해서 일정한 만료일까지 조치를 취해야 할 필요가 있을 수 있습니다. 귀하의 이러한 정보와 응급을 귀하의 안전과 비용 부담없이 알 수 있는 권리가 있습니다. 0800-722-1471 (TTY: 800-842-5357)로 전화하실 수 있습니다.

ไทย (Thai):
ประกาศนี้ให้ทราบว่า ข้อมูลที่สำคัญมีอยู่ในเอกสารนี้ โปรดซึ่ง Premera Blue Cross มีการส่งข้อมูลที่สำคัญเพื่อให้คุณทราบ โปรดติดต่อกับ Premera Blue Cross ที่ 800-722-1471 (TTY: 800-842-5357) เพื่อขอข้อมูลเพิ่มเติม.

Polski (Polish):

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Este aviso contém informações importantes. Este aviso poderá conter informações importantes a respeito de sua aplicação ou cobertura por meio do Premera Blue Cross. Poderão existir dados importantes neste aviso. Talvez seja necessário que você tome providências dentro de determinados prazos para manter sua cobertura de saúde ou ajuda de custos. Você tem o direito de obter esta informação e ajuda em seu idioma e sem custos. Ligue para 800-722-1471 (TTY: 800-842-5357).

Română (Romanian):

Русский (Russian):
Настоящее уведомление содержит важную информацию. Это уведомление может содержать важную информацию о вашем заявлении или страховом покрытии через Premera Blue Cross. В настоящем уведомлении могут быть указаны ключевые даты. Вам, возможно, потребуется принять меры к определенным предельным срокам для сохранения страхового покрытия или помощи с расходами. Вы имеете право на бесплатное получение этой информации и помощь на вашем языке. Звоните по телефону 800-722-1471 (TTY: 800-842-5357).

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