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

BCBSA Ref. Policy: 2.04.76
Effective Date: March 1, 2018
Last Revised: Feb. 6, 2018
Replaces: N/A

RELATE MEDICAL POLICIES:
5.01.514 Herceptin® (trastuzumab) and Other HER2 Inhibitors

Select a hyperlink below to be directed to that section.

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

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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

<table>
<thead>
<tr>
<th>HER2 status (eg, HERmark® Breast Cancer Assay)</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>The assessment of human epidermal growth factor receptor 2 (HER2) status by quantitative total HER2 protein expression and HER2 homodimer measurement is considered investigational.</td>
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</table>

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>CPT</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>
</tr>
<tr>
<td>0009U</td>
<td>Unlisted Chemistry procedure</td>
</tr>
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**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**

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

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.

Herceptin® (trastuzumab), a monoclonal antibody directed at the extracellular domain of HER2, has offered significant improvement in disease-free and overall survival 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 Herceptin® (trastuzumab) treatment, and many of those eventually develop resistance.¹⁻³

Current methodologies for identifying 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 relationship between HER2 gene copy number and response to Herceptin® (trastuzumab). Whereas patients who overexpress HER2 protein (IHC) or show evidence of HER2 gene amplification (FISH) have been shown to experience better outcomes on Herceptin® (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 [CISH]).

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 (H2T) and HER2 homodimers (H2D) in formalin-fixed, paraffin-embedded (FFPE) 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 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 Herceptin® (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, and clinical trials are needed to determine the impact on clinical outcomes of patients stratified by the HERmark® assay. 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 2017 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.2.2017) do not address the use of HERmark.\textsuperscript{21}

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

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.\textsuperscript{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 (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). HERmark® Breast Cancer Assay (Monogram Biosciences) 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 this test.

References


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
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<tbody>
<tr>
<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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<tr>
<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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<tr>
<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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<tr>
<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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<tr>
<td>12/01/17</td>
<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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**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.
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

If 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, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Complaint forms are available at 800-722-1471 (TTY: 800-842-5357).

Email AppealsDepartmentInquiries@Premera.com

PO Box 91102, Seattle, WA 98111

If you believe that Premera has failed to provide these services or discriminate on the basis of race, color, national origin, age, disability, or sex. Premera 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.

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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 before 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):

لا يوجد هذا الإشعار معلومات هامة. قد يوجد هذه المعلومات باللغة العربية على مدار بواسطة Premera Blue Cross. اطلب هذه المعلومات عن طريق الاتصال بعملاء باربة Premera Blue Cross على 800-722-1471 (TTY: 800-842-5357)

Chinese (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).

Français (French):


Deutsche (German):


Italiano (Italian):


Iloko (Ilocano):


Hmoob (Hmong):


Oromoo (Cushite):


Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbe essere necessario un tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente. Chiamate 800-722-1471 (TTY: 800-842-5357).
Este aviso contiene información importante. Es posible que este aviso contenga información importante acerca de su solicitud o cobertura a través de Premera Blue Cross. Es posible que haya fechas clave en este aviso. Es posible que deba tomar alguna medida antes de determinadas fechas para mantener su cobertura médica o ayuda con los costos. Usted tiene derecho a recibir esta información y ayuda en su idioma sin costo alguno. Llame al 800-722-1471 (TTY: 800-842-5357).

Tagalog (Tagalog):

Thai (Thai):
ประกาศนี้มีข้อกำหนดสำคัญ ประกาศนี้มีข้อกำหนดสำคัญเกี่ยวกับการขอรับการช่วยเหลือของประกันสุขภาพของคุณ Premera Blue Cross และมีข้อกำหนดในการกระทำของคุณ ควรตรวจสอบข้อกำหนดในการกระทำของคุณในภาษามาก่อน ถ้าคุณมีข้อคำถามที่เกี่ยวกับประกาศนี้ โปรดติดต่อ Premera Blue Cross ที่ 800-722-1471 (TTY: 800-842-5357).

Український (Ukrainian):
Це повідомлення містить важливу інформацію. Це повідомлення може містити важливу інформацію про ваше звернення щодо страхувального покриття через Premera Blue Cross. Зверніть увагу на ключові дати, які можуть бути вказані у цьому повідомленні. Існує імовірність того, що Вам треба буде здійснити певні кроки у конкретній ситуації для того, щоб зберегти Ваше медичне страхування або отримати фінансову допомогу. У Вас є право на отримання цієї інформації та допомоги безкоштовно на Вашій рідній мові. Дозвоніться за номером телефону 800-722-1471 (TTY: 800-842-5357).

Tiếng Việt (Vietnamese):