

## Corporate Medical Policy

### Quantitative Assay for Measurement of HER2 Total Protein Expression and HER2 Dimers

**File Name:** quantitative\_assay\_for\_measurement\_of\_her2  
**Origination:** 1/2012  
**Last CAP Review:** 3/2018  
**Next CAP Review:** 3/2019  
**Last Review:** 3/2018

#### Description of Procedure or Service

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

The HER-family of receptor tyrosine kinases (EGFR/HER1, ErbB2/HER2, ErbB3/HER3, and ErbB4/HER4) plays a major role in the pathogenesis of many solid tumors. In approximately 25-30% of breast cancers, overexpression of HER2 has been linked to shorter disease-free (DFS) and overall survival (OS), 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 significant DFS and OS 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.

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 inter-observer variability of these assay methods. IHC provides a semi-quantitative measure of protein levels (scored as 0, 1+, 2+, and 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 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 inter-laboratory 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 EGFR-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

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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, Monogram Biosciences, South San Francisco, CA) was developed to quantify total HER2 protein expression (H2T) and HER2 homodimers (H2D) in formalin-fixed, paraffin-embedded tissue samples.

## Related Policies

Trastuzumab

**\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.**

## Policy

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**The assessment of HER2 status by quantitative total HER2 protein expression and HER2 homodimer measurement is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.**

## Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

## When Quantitative Assay for Measurement of HER2 is covered

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Not applicable

## When Quantitative Assay for Measurement of HER2 is not covered

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The assessment of HER2 status by quantitative total HER2 protein expression and HER2 homodimer measurement is considered investigational.

## Policy Guidelines

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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 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.

## Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

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*Applicable codes: 0009U*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

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BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.76, 10/4/2011

Medical Director – 12/2011

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.76, 10/11/2012

Specialty Matched Consultant Advisory Panel – 3/2013

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.76, 10/10/2013

Specialty Matched Consultant Advisory Panel – 3/2014

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.76, 10/9/2014

Specialty Matched Consultant Advisory Panel- 3/2015

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.76, 12/10/2015

Specialty Matched Consultant Advisory Panel- 3/2016

Specialty Matched Consultant Advisory Panel- 3/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.76, 12/14/2017

Specialty Matched Consultant Advisory Panel- 3/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.76, 12/13/2018

## Policy Implementation/Update Information

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1/1/12 New policy. “The assessment of HER2 status by quantitative total HER2 protein expression and HER2 homodimer measurement is considered investigational.” Medical Director review 12/14/11. Notification given 1/1/2012. Policy effective 4/1/2012. (btw)

11/27/12 Reference added. (btw)

4/16/13 Specialty Matched Consultant Advisory Panel review 3/20/2013. No change to policy statement. (btw)

12/10/13 Policy Guidelines updated. Reference added. (btw)

4/15/14 Specialty Matched Consultant Advisory Panel review 3/25/2014. No change to policy statement. (btw)

11/11/14 Reference added. No change to policy statement. (lpr)

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- 4/28/15 Specialty matched consultant advisory panel review 3/25/2015. No change to policy. (lpr)
- 4/29/16 Updated Description and Policy Guidelines sections. Reference added. Specialty Matched Consultant Advisory Panel review 3/30/2016. No change to policy intent. (lpr)
- 4/28/17 Specialty Matched Consultant Advisory Panel review 3/29/2017. No change to policy statement. (lpr)
- 7/28/17 Added CPT code 0009U to the Billing/Coding section. (lpr)
- 1/12/18 Reference added. No change to policy statement.(lpr)
- 4/27/18 Specialty Matched Consultant Advisory Panel review 3/28/2018. No change to policy statement. (lpr)
- 1/15/19 Reference added. (lpr)

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Medical policy is not an authorization, certification, explanation of benefits or a contract. Benefits and eligibility are determined before medical guidelines and payment guidelines are applied. Benefits are determined by the group contract and subscriber certificate that is in effect at the time services are rendered. This document is solely provided for informational purposes only and is based on research of current medical literature and review of common medical practices in the treatment and diagnosis of disease. Medical practices and knowledge are constantly changing and BCBSNC reserves the right to review and revise its medical policies periodically.