



Louisiana

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

Policy # 00321

Original Effective Date: 11/16/2011

Current Effective Date: 06/08/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the assessment of human epidermal growth factor receptor 2 (HER2) status by quantitative total HER2 protein expression and HER2 homodimer (H2D) measurement to be **investigational**.*

Policy Guidelines

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 alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview

Human Epidermal Growth Factor Receptor 2

The 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

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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 significant 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.

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.

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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. On the HERmark[®] website, the manufacturer describes the test as "a novel HER-2 testing alternative to identify candidates for HER2-targeted therapy," and does not clearly target use for any particular breast cancer subpopulations (e.g., those with equivocal and/or discordant IHC/FISH tests).

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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 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/Source

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.

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. The relevant outcomes are overall survival, disease-specific survival, test accuracy, and test validity. Retrospective analysis using HERmark has 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. The clinical utility of the HERmark assay has not been demonstrated. The evidence is insufficient to determine the effects of the technology on health outcomes.

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Supplemental Information

Practice Guidelines and Position Statements

National Comprehensive Cancer Network guidelines on the treatment of breast cancer (v.3.2019) do not address the use of HERmark.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, 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 assessed HERmark and determined that the test meets the criteria for analytic and clinical validity and clinical utility as a reasonable and necessary Medicare benefit. Effective December 9, 2011, Palmetto GBA will reimburse HERmark services for patients with breast cancer.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in November 2019 did not identify any ongoing or unpublished trials that would likely influence this review.

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Policy History

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11/03/2011 Medical Policy Committee review

11/16/2011 Medical Policy Implementation Committee approval. New policy.

11/01/2012 Medical Policy Committee review

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11/28/2012	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/12/2013	Medical Policy Committee review
12/18/2013	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/04/2014	Medical Policy Committee review
12/17/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
12/03/2015	Medical Policy Committee review
12/16/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/01/2016	Medical Policy Committee review
12/21/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
12/07/2017	Medical Policy Committee review
12/20/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/06/2018	Medical Policy Committee review
12/19/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
12/05/2019	Medical Policy Committee review
12/11/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/07/2020	Medical Policy Committee review
05/13/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 05/2021

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Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81479, 84999
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into

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standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
 1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
 2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
 3. Reference to federal regulations.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

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