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

Policy # 00321
Original Effective Date: 11/16/2011
Current Effective Date: 06/14/2021

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 survival, lack of responsiveness to tamoxifen antiestrogen therapy, and altered responsiveness to a variety of cytotoxic chemotherapy regimens.

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

Policy # 00321
Original Effective Date: 11/16/2011
Current Effective Date: 06/14/2021

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 HER2protein 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 (HERmar®‡ Breast Cancer Assay) was developed to quantify total HER2 protein expression and HER2homodimers in formalin-fixed, paraffin-embedded tissue samples. On the HERmark®‡ website, the manufacturer described the test as "a novel HER-2 testing alternative to identify candidates for HER2-targeted therapy," and did not clearlytarget use for any particular

breast cancer subpopulations (e.g., those with equivocal and/or discordant IHC/FISH tests).However, the HERmark Breast Cancer Assay was discontinued by the manufacturer (Monogram Biosciences) in September 2020 because "the standard of care no longer warrants anything but the FISH or IHC assays" (MonogramBiosciences, oral communication, November 2020).

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

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. However, the HERmark Breast Cancer Assay, the sole assay included in this review, was discontinued by the manufacturer in September 2020 (Monogram Biosciences, oral communication, November 2020). 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 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 that the technology results in an improvement in the net health outcome.

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

Policy # 00321
Original Effective Date: 11/16/2011
Current Effective Date: 06/14/2021

Supplemental Information

Practice Guidelines and Position Statements
American Society of Clinical Oncology and College of American Pathologists In 2018, the American Society of Clinical Oncology (ASCO) and College of American Pathologists (CAP) published a clinical practice guideline focused update on HER2 testing in breast cancer. The guidance updated 2013 ASCO/CAP recommendations. The guideline recommends "All newly diagnosed patients with breast cancer must have a HER2 test performed. Patients who then develop metastatic disease must have a HER2 test performed in a metastatic site, if tissue sample is available." For "acceptable (immunohistochemistry [IHC] and in situ hybridization [ISH]) tests," the guideline states: "Should preferentially use an U.S. Food and Drug Administration approved IHC, brightfield ISH, or fluorescent in situ hybridization (FISH) assay."

National Comprehensive Cancer Network
National Comprehensive Cancer Network guidelines on the treatment of breast cancer (v.6.2020) 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 2020 did not identify any ongoing or unpublished trials that would likely influence this review.

References

1. Blue Cross and Blue Shield Association, Medical Policy Reference Manual, "Quantitative Assay for Measurement of HER2 Total Protein Expression and HER2 Dimers", 2.04.76, Archived February 2021.
2. Arteaga CL, O'Neill A, Moulder SL, et al. A phase I-II study of combined blockade of the ErbB receptor network with trastuzumab and gefitinib in patients with HER2 (ErbB2)-overexpressing metastatic breast cancer. Clin Cancer Res. Oct 01 2008; 14(19): 6277-83. PMID 18829509
3. de Alava E, Ocana A, Abad M, et al. Neuregulin expression modulates clinical response to trastuzumab in patients with metastatic breast cancer. J Clin Oncol. Jul 01 2007; 25(19): 2656-63. PMID 17602072
4. Piccart M, Lohrisch C, Di Leo A, et al. The predictive value of HER2 in breast cancer. Oncology. 2001; 61 Suppl 2: 73-82. PMID 11694791
5. Shi Y, Huang W, Tan Y, et al. A novel proximity assay for the detection of proteins and protein complexes: quantitation of HER1 and HER2 total protein expression and homodimerization in formalin-fixed, paraffinembedded cell lines and breast cancer tissue. Diagn Mol Pathol. Mar 2009; 18(1): 11-21. PMID 19214113
6. Lipton A, Kostler WJ, Leitzel K, et al. Quantitative HER2 protein levels predict outcome in fluorescence in situ hybridization-positive patients with metastatic breast cancer treated with trastuzumab. Cancer. Nov 15 2010; 116(22): 5168-78. PMID 20661914
7. Toi M, Sperinde J, Huang W, et al. Differential survival following trastuzumab treatment based on quantitative HER2 expression and HER2 homodimers in a clinic-based cohort of patients with metastatic breast cancer. BMC Cancer. Feb 23 2010; 10: 56. PMID 20178580
8. Bates M, Sperinde J, Kostler WJ, et al. Identification of a subpopulation of metastatic breast cancer patients with very high HER2 expression levels and possible resistance to trastuzumab. Ann Oncol. Sep 2011; 22(9): 2014- 2020. PMID 21289364
9. Joensuu H, Sperinde J, Leinonen M, et al. Very high quantitative tumor HER2 content and outcome in early breast cancer. Ann Oncol. Sep 2011; 22(9): 2007-2013. PMID 21285132

10. Duchnowska R, Biernat W, Szostakiewicz B, et al. Correlation between quantitative HER-2 protein expression and risk for brain metastases in HER-2+ advanced breast cancer patients receiving trastuzumab-containing therapy.
11. Han SW, Cha Y, Paquet A, et al. Correlation of HER2, p95HER2 and HER3 expression and treatment outcome of lapatinib plus capecitabine in her2-positive metastatic breast cancer. PLoS One. 2012; 7(7): e39943. PMID 22848366
12. Lipton A, Goodman L, Leitzel K, et al. HER3, p95HER2, and HER2 protein expression levels define multiple subtypes of HER2-positive metastatic breast cancer. Breast Cancer Res Treat. Aug 2013; 141(1): 43-53. PMID 23959396
13. Barros FF, Abdel-Fatah TM, Moseley P, et al. Characterisation of HER heterodimers in breast cancer using in situ proximity ligation assay. Breast Cancer Res Treat. Apr 2014; 144(2): 273-85. PMID 24557338
14. Montemurro F, Prat A, Rossi V, et al. Potential biomarkers of long-term benefit from single-agent trastuzumab or lapatinib in HER2-positive metastatic breast cancer. Mol Oncol. Feb 2014; 8(1): 20-6. PMID 24075779
15. Yardley DA, Kaufman PA, Huang W, et al. Quantitative measurement of HER2 expression in breast cancers: comparison with 'real-world' routine HER2 testing in a multicenter Collaborative Biomarker Study and correlation with overall survival. Breast Cancer Res. Mar 18 2015; 17: 41. PMID 25886996
16. Scaltriti M, Nuciforo P, Bradbury I, et al. High HER2 expression correlates with response to the combination of lapatinib and trastuzumab. Clin Cancer Res. Feb 01 2015; 21(3): 569-76. PMID 25467182
17. Duchnowska R, Sperinde J, Czartoryska-Arlukowicz B, et al. Predictive value of quantitative HER2, HER3 and p95HER2 levels in HER2-positive advanced breast cancer patients treated with lapatinib following progression on trastuzumab. Oncotarget. Nov 28 2017; 8(61): 104149-104159. PMID 29262628
18. Chumsri S, Sperinde J, Liu H, et al. High p95HER2/HER2 Ratio Associated With Poor Outcome in TrastuzumabTreated HER2-Positive Metastatic Breast Cancer NCCTG N0337 and NCCTG 98-32-52 (Alliance). Clin Cancer Res. Jul 01 2018; 24(13): 3053-3058. PMID 29530935
19. Camp RL, Dolled-Filhart M, Rimm DL. X-tile: a new bio-informatics tool for biomarker assessment and outcomebased cut-point optimization. Clin Cancer Res. Nov 01 2004; 10(21): 7252-9. PMID 15534099

20. Green AR, Barros FF, Abdel-Fatah TM, et al. HER2/HER3 heterodimers and p21 expression are capable of predicting adjuvant trastuzumab response in HER2+ breast cancer. Breast Cancer Res Treat. May 2014; 145(1): 33-44. PMID 24706169
21. Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. Arch Pathol Lab Med. 2007; 131(1): 18-43. PMID 19548375
22. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology: Breast cancer. Version 6.2020. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

Policy History

Original Effective Date: 11/16/2011
Current Effective Date: 06/14/2021

11/03/2011	Medical Policy Committee review
11/16/2011	Medical Policy Implementation Committee approval. New policy.
11/01/2012	Medical Policy Committee review
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

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

Policy # 00321
Original Effective Date: 11/16/2011
Current Effective Date: 06/14/2021

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.
05/06/2021	Medical Policy Committee review
05/12/2021	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 05/2022

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 2020 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.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy

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

Policy # 00321
Original Effective Date: 11/16/2011
Current Effective Date: 06/14/2021

Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

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 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.

‡ Indicated trademarks are the registered trademarks of their respective owners.

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.