MASSACHUSETTS

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Medical Policy

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

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Policy Number: 397

BCBSA Reference Number: 2.04.76
NCD/LCD: N/A

Related Policies

None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO Blue[SM] and Medicare PPO Blue[SM] Members

The assessment of human epidermal growth factor receptor 2 (HER2) status by quantitative total HER2 protein expression and HER2 homodimer measurement is considered **INVESTIGATIONAL**.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
Commercial Managed Care (HMO and POS)	This is **not** a covered service.
Commercial PPO and Indemnity	This is **not** a covered service.
Medicare HMO Blue[SM]	This is **not** a covered service.
Medicare PPO Blue[SM]	This is **not** a covered service.

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

CPT Codes

There is no specific CPT code for this testing.

Description

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.

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.[1,2,3]

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.[4,] 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. 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).[5]

Summary

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.

Policy History

Date	Action
1/2020	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
2/2019	BCBSA National medical policy review. Description, summary and references updated. Policy statements unchanged.
3/2018	New references added from BCBSA National medical policy.
1/2016	Local Coverage Determination (LCD): Molecular Diagnostic Tests (MDT) (L33541) removed. 1/2016.
6/2015	Local Coverage Determination (LCD): Molecular Diagnostic Tests (MDT) (L33541) added.
12/2014	New references added from BCBSA National medical policy.
9/2014	Clarified coding information.
1/2014	New references added from BCBSA National medical policy.
1/2014	Clarified coding information.
2/2013	New references from BCBSA National medical policy.
11/1/12	New policy describing ongoing non-coverage.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References

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