

# Protocol

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

(20476)

<b>Medical Benefit</b>		<b>Effective Date:</b> 07/01/13	<b>Next Review Date:</b> 03/15
<b>Preauthorization</b>	No	<b>Review Dates:</b> 03/12, 03/13, 03/14	

*The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. **Preauthorization is not required but is recommended if, despite this Protocol position, you feel this service is medically necessary.** Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

### Description

Novel assays that quantitatively measure total HER2 protein expression and homodimers have been developed in an effort to improve the accuracy and consistency of HER2 testing.

#### Background

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. (1)

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+, 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 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. (2) 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]).

Normally, 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 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.

#### *Regulatory Status*

The U.S. Food and Drug Administration (FDA) does not regulate in-house or “home brew” tests for HER2 tests developed and used at unique or individual laboratory sites.

The HERmark assay has been validated according to the specifications prescribed by the Clinical Laboratory Improvement Amendments (CLIA) and is performed in a College of American Pathologists-certified clinical reference laboratory at Monogram Biosciences.

#### **Policy (Formerly Corporate Medical Guideline)**

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

#### **Medicare Advantage**

For Medicare Advantage this may be considered a **medically necessary** test on a paraffin-embedded breast cancer tissue sample.

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Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this Protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

#### **References**

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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3. Monogram biosciences announces HER2:HER3 heterodimer and HER3/PI3K VeraTag™ assays are now available for use in development of cancer therapeutics: November 11, 2008. Available online at: <http://www.businesswire.com/news/home/20081111005841/en/Monogram-Biosciences-Announces-HER2HER3-Heterodimer-HER3PI3K-VeraTag>. Last accessed August 2013.
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13. National Comprehensive Cancer Network (NCCN). Breast cancer (V.3.2013). Available online at: [http://www.nccn.org/professionals/physician\\_gls/pdf/breast.pdf](http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf). Last accessed August, 2013.
14. Medicare Local Carrier Noridian Healthcare Solutions, LLC, (Jurisdiction-Northern, California) Local Coverage Determination (LCD): Molecular Diagnostic Tests (MDT) (L33541), Revision Effective Date for services performed on or after 11/01/2013.