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NCCN Guidelines Panel: Breast Cancer

On behalf of *LABORATORY CORPORATION OF AMERICA® Holdings and Monogram Biosciences*, I respectfully request the *NCCN Breast Cancer Guideline Panel* review the enclosed data in support of the inclusion of quantitative HER2 determinations (HERmark®), as a robust and reliable method for the assessment of HER2 status in FFPE breast cancer tumor samples.

**Specific Change:** We respectfully petition the NCCN to consider the inclusion of quantitative HER2 determinations as clinically actionable assessments of HER2-positive breast cancer. The potential roles for such an assessment are: (1) in cases of discordant or equivocal HER2 status, as assessed by routine HER2 testing (IHC, FISH), the quantitative measurements of HER2 expression by the HERmark assay can inform medically appropriate and beneficial treatment decisions; and (2) the quantitative measure of HER2 expression can identify cases of HER2-positive breast cancer that are more likely to realize treatment benefit from combined HER2-targeted treatments.

**Regulatory:** The HERmark Breast Cancer Assay is a laboratory developed test (LDT) conducted in accordance with CLIA standards and is performed in a CAP-accredited clinical reference laboratory (Monogram Biosciences, a LabCorp Specialty Testing Laboratory). Effective December 9<sup>th</sup>, 2011, HERmark® was granted coverage by Medicare (CMS – Centers for Medicare and Medicaid Services). The assessment by Palmetto GBA determined that HERmark meets the criteria for analytical and clinical validity, and clinical utility as a reasonable and necessary Medicare benefit.

**Rationale:** The accurate assessment of HER2 status is critical in determining the most appropriate and effective therapy for breast cancer patients. However, even after more than a decade of routine testing to determine HER2 status in breast cancer cases, the most sensitive and specific HER2 testing methodology remains controversial. Despite continued efforts to improve and standardize HER2 testing, discordance in HER2 test results between laboratories and across testing methodologies remain. Data from several studies support the need for more accurate and objective HER2 testing methods.<sup>1, 2, 3</sup>

**Methodology:** The HERmark® Breast Cancer Assay is a novel, yet well-established, HER2 testing method that provides quantitative measurements of HER2 protein expression in formalin-fixed, paraffin-embedded (FFPE) tissue samples. HERmark is a clinically-validated alternative test for the assessment of breast cancer HER2 status that qualifies for Medicare reimbursement.<sup>4</sup> The HERmark assay is a dual-antibody, proximity-binding immunoassay that derives quantitative measurements of HER2 protein expression. HERmark provides a continuum of HER2 measurements that range more than 1000-fold in human breast cancers and cell lines.<sup>4, 5</sup> HERmark negative, HERmark equivocal, and HERmark positive determinations are fundamentally based on comparison with central laboratory HER2 testing (IHC and ISH).<sup>5, 6</sup> Consequently, HERmark assay results demonstrate excellent concordance with conventional IHC assays conducted in central laboratories (98% for positive and negative determinations).<sup>6</sup>

**HERmark Clinical Performance:** In a 2010 study, breast cancer patients with advanced disease whose tumors were designated as HER2 positive by FISH, but HER2 negative by HERmark, experienced treatment outcomes (time to progression following trastuzumab treatment) consistent with the FISH/HERmark-negative group and in contrast to the responses of the FISH/HERmark-positive group.<sup>7</sup> The Collaborative Biomarker Study (CBS) in 2012 provided a comparison of HERmark testing with “real-world” routine HER2 testing. An analysis of overall survival indicates that 10% of breast cancer patients may be misclassified as false negative and another 10% may be misclassified as false positive by standard methods. Although the total number of patients identified as candidates for anti-HER2 treatment would not change based on this assessment, HERmark may provide a



more accurate identification of breast cancer patients that are most likely to experience favorable responses to HER2-targeted therapy.<sup>8</sup> In addition, a strong relationship has been found between quantitative HER2 expression as assessed by HERmark, but not HER2 FISH, and the risk for brain relapse in advanced HER2-positive breast cancer. Consequently, quantitative assessment of HER2 expression can inform and clinically justify refinements in therapeutic treatment strategies for selected patient populations with advanced and invasive HER2-positive breast cancer.<sup>9</sup> Lastly, in a recent retrospective analysis of the NeoALTTO phase III trial, increasing HER2 expression, as measured by HERmark, correlated with the increased benefit of supplementing trastuzumab treatment with lapatinib, compared to trastuzumab treatment alone. In tumors that expressed HER2 above the median, HER2 levels predicted response to trastuzumab and trastuzumab+lapatinib.<sup>10</sup>

The following references are submitted in support of the proposed guideline revisions. We would like to acknowledge the assistance of our scientific collaborators.

#### **HER2 Testing References**

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#### **HERmark Analytical Validation References**

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#### **Clinical Study References**

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10. M Scaltriti, P Nuciforo, I Bradbury, et al. Abstract P1-08-42: *High HER2 expression correlates with response to trastuzumab and the combination of trastuzumab and lapatinib in the NeoALTTO phase III trial*. Cancer Res., Dec 2013; 73: P1-08-42 (SABCS 2013)

Sincerely,



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