American Society of Clinical Oncology/College of American Pathologists Human Epidermal Growth Factor Receptor 2 Testing Clinical Practice Guideline Upcoming Modifications

Proof That Clinical Practice Guidelines Are Living Documents

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Recently, the Journal of Clinical Oncology (JCO) received a letter to the editor from Rakha et al1 about the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) Recommendations for Human Epidermal Growth Factor Receptor 2 (HER2) Testing in Breast Cancer Clinical Practice Guideline Update.2 The authors of the letter cite several areas of concern that have also been raised in communications with us, as ASCO/CAP HER2 Testing Guideline Update Steering Committee pathologist-members. Such matters are always individually addressed and often spark lively discussions among the ASCO/CAP HER2 Testing Guideline Update Steering Committee members, who are the leaders of the ASCO/HER2 Clinical Practice Guideline Update Panel.

In response to evidence cited by the Rakha et al letter and questions raised by pathologists, the Update Panel has provided a clarifying letter to the editor of JCO.3 The issues identified in the Rakha et al letter had also been raised by pathologists and are directly relevant to the dynamic nature of the guideline as a living document. For that reason, we would like to communicate directly with our colleagues about these recommendations and discuss forthcoming modifications in the HER2 Testing Guideline Update that will result. We encourage the continued engagement and feedback, which support our shared commitment to the quality of diagnostic information that pathologists provide.

Some pathologists have expressed concern about changes in the HER2 Testing Guideline Update tied to the interpretation criteria for HER2 immunohistochemistry (IHC) 2+, pointing out that original descriptions of the HER2 IHC categories had been promulgated at the time that trastuzumab was approved by the US Food and Drug Administration (FDA) with the companion diagnostic test, HercepTest (Dako, Carpinteria, California), in September, 1998.4 Pathologists had learned to interpret slides based on those definitions, and the FDA had codified them in package inserts of approved companion diagnostics from several companies, including Dako4 and Ventana Medical Systems (Tucson, Arizona). After reviewing those comments, the Update Panel unanimously agreed that it would be best to go back to the original definition of the HER2 IHC 2+ equivocal category and describe the rare cases where other patterns should be considered in the figure 1 legend of the algorithm.

The forthcoming modified legend will read as follows:

In Figure 1 (Algorithm for HER2 Testing by Immunohistochemistry [IHC]), IHC 2+ (equivocal) was described as invasive breast cancer with “circumferential membrane staining that is incomplete and/or weak/moderate and within <10% of tumor cells.” Many pathologists expressed concern that the terms “circumferential” and “incomplete” cannot be reconciled when used together. Consequently, more IHC 1+ (HER2-) tumors risk being called IHC 2+ (equivocal) and being submitted for reflex testing. The statement “circumferential membrane staining that is intense and within ≤10% of tumor cells” was also felt to refer to an unusual pattern that did not need to be specified in the main portion of the figure.

Therefore, the Update Panel will be publishing 2 revisions in figure 1. First, the definition for IHC 2+ in invasive breast cancer will now simply reflect the commonly accepted definition of “a weak to moderate complete membrane staining is observed in >10% of tumor cells.”

Second, discussions about possible uncommon IHC scenarios will be limited to the figure legend. The figure 1 legend will be partly revised to read as follows:

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Unusual staining patterns of HER2 by IHC can be encountered that are not covered by these definitions. In practice, these patterns are rare, and if encountered, should be considered IHC 2+ equivocal. As one example, some rare breast cancers (e.g., micropapillary carcinomas) show IHC staining that is moderate to intense but incomplete (basolateral or lateral) and can be found to be HER2 amplified.

The other issue raised by Rakha et al.,1 and supported by evidence they cite, concerns the need to retest excision samples when a core biopsy is HER2 negative by either IHC or in situ hybridization. The evidence suggests that although this may be useful, it should not be required. In view of the greater clinical experience confirming the high concordance in HER2 testing between core and excisional biopsies, the Update Panel will be updating Table 2 to allow the pathologist and oncologist to exercise clinical judgment and will no longer indicate that grade 3 alone suffices as a criterion for mandatory retesting. The revised language will indicate that “If the initial HER2 test result in a core needle biopsy specimen of a primary breast cancer is negative, a new HER2 test may [emphasis added] be ordered on the excision specimen.” Other criteria mentioned in Table 2 as reasons for excision testing will undergo careful scrutiny to see whether other Table 2 revisions are needed.

The Update Panel has communicated these upcoming changes in a reply to the letter to the editor of JCO.3 It responds to the original correspondence from Rakha et al.1 Revisions to the figure and table will be incorporated in a focused update of the HER2 Testing Guideline Update to be completed this year and published simultaneously by JCO and the Archives of Pathology & Laboratory Medicine. This will ensure that all the information and evidence is clearly communicated in a widely accessible, peer-reviewed document.

The letter from Rakha et al, the Update Panel’s response, and supporting materials will be available on the CAP Web site. We urge pathologists to review them with care and to continue to contribute to this work by providing feedback to the Update Panel. Your guidance is always welcome.

References