HER2 Update
Erin Van Winkle Grimm, MD

One out of eight women will develop breast cancer, and nearly everyone has had a family member or friend who has combated this disease. A new drug in the treatment of breast cancer is trastuzumab, known under the brand name of Herceptin®. Trastuzumab therapy targets the transmembrane tyrosine kinase receptor known as human epidermal growth factor receptor-2, or HER2, which is encoded by the HER2 gene (also known as ERBB2 and CERB-B2) found on chromosome 17. Although there is physiologic expression of HER2 in non-neoplastic breast epithelium, this gene is highly amplified in 10-25% of breast carcinomas.\(^1\text{-}^4\) The degree of HER2 amplification is both prognostic (untreated HER2-amplified cancers have a worse prognosis) and predictive (survival for HER2-amplified carcinomas improves on regimens that include trastuzumab).\(^5\)

Patients with HER2-amplified breast carcinomas who receive trastuzumab have improved clinical outcome; however, the drawbacks include side effects such as cardiotoxicity and high expense. Therefore, distinguishing which patients will benefit from this drug is essential for optimum patient care. Laboratories use two central methodologies to determine HER2 status in the US: immunohistochemistry (IHC) and fluorescence in-situ hybridization (FISH). Both methods require interpretation of the test by a pathologist. Both methods were used in initial clinical trials for trastuzumab. IHC detects tissue antigens (in this case, the HER2 transmembrane protein) by using a labeled antibody. The HercepTest™ is a FDA-approved IHC method for assessing HER2 status where the intensity of staining observed is related to the number of receptors present on the cell membrane. Staining is titrated so that cells without HER2 amplification (normal epithelium or non-amplified neoplastic epithelium) have no or minimal staining, while neoplastic cells with amplified HER2 levels have strong, circumferential membrane staining. Studies show that non-amplified cells with no staining have less than half of the receptors compared with those with HER2 gene amplification.\(^6\) A category of intermediate HER2 overexpression exists, and these cases are referred to a second methodology, usually FISH.

FISH is a method that uses fluorescent probes that bind directly to a DNA sequence. The number of signals generated is directly related to the number of HER2 gene copies. Different FISH methods are FDA approved. Some methods assess HER2 amplification solely by determining the number of HER2 signals in a cell, while others require an amplified ratio of HER2 copies when compared to another chromosome 17 locus.

Immunohistochemistry is a common technique used daily by nearly all pathology laboratories in many applications (HER2 is one application). FISH is performed by fewer laboratories and often isn’t performed daily. FISH is more time intensive and more expensive. For these reasons, assessing HER2 by IHC is preferred by most laboratories. Since HER2 overexpression is
directly related to gene amplification, one would expect the correlation between these two methods to be nearly 100%. However, there are reports of HER2 concordances below 80%.\textsuperscript{7}

Attempts to explain and decrease discordances have been made. The scoring system initially introduced with the HercepTest has been modified to increase specificity by requiring a higher degree of staining to render a positive result. The American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) teamed up to publish guideline recommendations for HER2 testing, which attempt to standardize pre-analytical and analytical variables to improve overall concordance in both IHC and FISH methods.\textsuperscript{8} The guidelines require proof of internal quality assurance, adequate validation of the assay, and ongoing proficiency testing. These guidelines require concordance of 95% with another validated HER2 test. Accepted comparisons include FISH, an outside laboratory’s IHC, or other accepted but less common HER2 testing methodologies. However, even with these improvements, some authors press for conversion of HER2 testing entirely to FISH with elimination of IHC testing.\textsuperscript{9}

Other laboratories achieve >95% concordance between IHC and FISH, and therefore they believe IHC with reflex to FISH when necessary is a valid and cost-effective testing strategy.\textsuperscript{10,11}

In summary, accurate HER2 testing is essential for quality patient care. However, no gold standard exists for HER2 testing, and pathology as a discipline is still debating the optimal testing strategy. Immunohistochemistry is the most widely used testing methodology with equivocal results reflexed for FISH testing. The ASCO/CAP HER2 guidelines published in 2007 attempt to standardize testing, and therefore, help patients receive accurate information regarding optimal treatment regimens for their breast carcinoma.

References:
