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The Role of Immunohistochemistry in the Era of Precision Medicine.

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Abstract.

This keynote presentation addresses some of the challenges and opportunities that the rapid growth in precision medicine presents for IHC.

Precision medicine implies precision pathology, which in turn invokes the use of a new range of advanced diagnostic tests in pathology laboratories. These new tests are variously termed “companion diagnostics,” “predictive diagnostics,” “precision diagnostics,” “theranostics,” and “advanced personalized diagnostics.” Companion diagnostics typically aim to detect “predictive biomarkers,” which are so named because the level of expression detected in a tumor may be of value in predicting the effectiveness of a particular targeted therapy for that specified tumor; hence the term companion diagnostic, where the intent is to classify patients into “responders” and “non-responders” with respect to the specified targeted therapy.

Over the past 4 decades IHC has primarily been employed to provide a broad range of “special stains” that are mostly used for identification and classification of tumors in formalin-fixed paraffin-embedded (FFPE) tissues. If success is to be measured in terms of the number of different “IHC stains” that are in daily use, then the IHC method must be judged a resounding success, for the number runs into the thousands of published IHC stains. However, the sheer scale of use, the success of the method, conceals major deficiencies in practice.

In 1998, the introduction and approval of the Her2 test as a companion diagnostic for Herceptin therapy marked the beginning of this era of precision medicine. However, the enhanced levels of performance that are required represent a real challenge for the IHC method, and the problems of poor test reproducibility encountered with early use of the HER2 test have been revisited time and time again. By analogy with ELISA in the clinical laboratory, automation of both the technical performance and the reading of IHC results for companion diagnostics is inevitable.

The expanding use of automated staining platforms, coupled with integrated QA and QC systems, effectively guarantees that reagents and protocols will be subject to increasingly rigorous validation and control processes, using closed assay systems that cannot be “tweaked” in order to produce more intense staining as a means of to compensating for a ‘weak result’ due to deficient FFPE tissue processing. In the face of poor sample preparation, the mantra—“don’t tweak the protocol; fix the fixation”—comes to mind. Also most companion diagnostics demand some degree of quantification, extending beyond the semi-quantitative manual scoring methods used in the first HER2 tests, an ongoing source of poor reproducibility of test results. Digital whole slide image analysis has made great strides with respect to the consistent and accurate reading of results and is likely to provide the intelligent microscope of the near future.

The proposition is offered that IHC can be upgraded from its use as a qualitative special stain to an accurate and reliable quantitative ‘tissue-based immunologic assay’ that would serve accurately to quantify proteins

in tissue sections (in situ proteomics), analogous to the use of the ELISA (enzyme-linked immunosorbent assay) method in the clinical laboratory. This address will argue that for the pathologist these rapidly advancing changes represent an opportunity that it will be dangerous to ignore. Molecular morphology and in situ proteomics have arrived; we just have not quite come to terms with them yet.