Commentary: Guideline for Performing Human Epidermal Growth Factor Receptor 2 Immunohistochemistry Quantitative Image Analysis well

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Summary

Biomarker testing in breast cancer is an important activity for pathology laboratories and the patients they serve. A recent guideline[1] from the College of American Pathologists (CAP) provides timely guidance on implementing and performing quantitative image analysis (QIA) for human epidermal growth factor receptor 2 (HER2) for breast cancer. This document provides a nice complement to the recently updated joint CAP/American Society of Clinical Oncology (ASCO) guideline related to HER2 testing in breast cancer[2] for those laboratories using or contemplating QIA for HER2. The text sets out 11 guideline statements, 7 based on CAP accreditation requirements and 4 based on expert consensus opinion. While QIA can be affected by variables in all three phases of testing (preanalytic, analytic, and postanalytic), the guidelines mainly concern the analytic and postanalytic issues. Specific issues addressed include validation, reproducibility, training, ongoing quality monitoring, and verification of the final results by a knowledgeable pathologist.

To my knowledge, this is a first evidence-based guideline focused on quantitative digital image analysis in the clinical practice of pathology. In a 2016 survey, over 20% of responding laboratories reported using some type of QIA. The Digital Pathology Association recently published an introduction to digital image analysis,[3] and we can reasonably expect the use of QIA to grow along with the clinical adoption of digital pathology. With many other image analysis tools already available and even more on the horizon, it is important to have informed guidance like this concerning relevant clinical assays.

Comments

Taken together, these 11 guideline statements provide a good framework for laboratories to ensure that their QIA process is sufficient to produce reproducible and reliable results. The first and second guidelines address validation, stating that a QIA system for HER2 immunohistochemistry (IHC) should be validated appropriately by comparison to an alternate-validated method. They go on to give specific guidance for a minimum number of cases to be used in various situations, comparison methods, and agreement thresholds which are summarized in a useful table.

The next two recommendations address reproducibility. Given that so many factors can affect QIA performance, it is imperative that laboratories specifically evaluate reproducibility in their particular conditions. A key part of most current systems is manual selection of regions of interest (ROIs) for automated analysis. Laboratories are encouraged to develop procedures for standardized procedures for selection of ROIs which can be used for training and competency assessment of operators, including pathologists. It is important to develop these procedures prior to performing the method validation studies since those studies should reflect real-world usage of the system.

The guidelines also address how to handle changes to a QIA system that might have clinical impact, which is something that may not always be considered before implementing a new system. Another helpful table lists seven types of changes and gives guidance on appropriate actions to take. Most types of changes listed require revalidation, which is an important point since revalidations require planning to execute well and laboratories may want to customize their revalidation to account for different types of changes to the system.

Another area which the guidelines address is the retention of QIA results and algorithm metadata. This is a complex issue given all the potential types of metadata that can be generated. While the paper does not provide definitive recommendations in this area, it does provide a good background regarding the issues and options available to laboratories, including a matrix of storage options. The question of cloud-based storage is briefly mentioned, but no recommendations are given as that is a complex topic beyond the scope of the guidelines. However, the paper does specifically state that the guidelines make no recommendations which would prohibit the use of such storage. Given that cloud-based storage is available and being used for other clinical data I see no reason why it could not be used for QIA data storage as well, as long as relevant institutional and governmental security and privacy requirements are met. The topic of data retention and storage should be considered carefully prior to implementing a QIA system.

The final two statements concern the role and responsibilities of pathologists in the QIA process. The first statement simply states that, similar to other areas of laboratory oversight, the pathologist who oversees HER2 QIA should have appropriate expertise. The next statement is more specific and concerns the pathologist who finalizes a HER2 QIA report. That pathologist needs to be knowledgeable regarding the QIA system and "visually verify" three aspects. First, that the correct ROI was

used; second, that the algorithm annotated image is acceptable; and finally, that the image analysis results are acceptable. These last two points emphasize that even though a QIA system may seem like a hands-off black box, the pathologist is a vital part of the overall process and can recognize situations where the results may not be reliable, such as when IHC staining is unacceptable or when inappropriate areas have been selected for analysis.

Overall, these guideline statements and commentary provide a much-needed consideration of how to perform clinical image analysis well. The availability of this guidance should help more laboratories utilize QIA, a desirable outcome given that at least one study has shown that QIA is a superior alternative to manual biomarker scoring in breast cancer.[4] While this publication specifically addressed HER2 IHC QIA, most of the points are widely applicable to other similar QIA processes.

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