



COLLEGE of AMERICAN  
PATHOLOGISTS

# Quantitative Image Analysis of HER2 Immunohistochemistry for Breast Cancer

## Guideline from the College of American Pathologists

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\*Inactive guidelines are no longer updated with systematic literature reviews, but the recommendations may still be useful for educational, informational, or historic purposes.

# Outline

- Introduction
- Key questions addressed and main findings
- Guideline development process
- Guideline statements (recommendations)
- Conclusion

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# Introduction

- In the United States (US), breast cancer is the most common type of cancer in women and human epidermal growth factor receptor 2 (HER2) testing is standard of care.
- Although HER2 testing can be performed qualitatively, the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) HER2 guideline acknowledges that quantitative image analysis (QIA) can be used to achieve consistent interpretation of HER2 immunohistochemistry (IHC).<sup>1</sup>

# Introduction, continued

- The CAP developed an evidence-based guideline to help laboratories that use QIA for diagnostic purposes achieve accurate, reproducible HER2 IHC results for breast cancer.<sup>2</sup>
- Overarching question: “What procedural principles must be followed in order to assure that HER2 IHC QIA is accurate and reproducible?”
  - Assuming that the slide has been properly stained and is appropriate for QIA

# Key questions addressed

- 1. What equipment validation and daily performance monitoring is needed?**
- 2. What training of staff and pathologists is required?  
What are the competency assessments needs over time?**
- 3. How does one select or develop an appropriate algorithm for interpretation?**
- 4. How does one determine the performance of the image analysis?**
- 5. How should image analysis be reported?**

# Main findings

- QIA and its procedures must be validated before implementation, followed by regular maintenance and ongoing evaluation of quality control and quality assurance.
- Laboratories should validate their QIA results for clinical use by comparing them to an alternative, validated method(s) such as HER2 fluorescence in situ hybridization (FISH) or consensus images for HER2 immunohistochemistry (IHC).
- HER2 QIA performance, interpretation, and reporting should be supervised by pathologists with expertise in QIA and those involved with using the technology should be trained.

# Guideline development process

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# CAP Pathology and Laboratory Quality Center for Evidence-based Guidelines: guideline life cycle





# Guideline development process

- The CAP formed an expert panel to systematically review the relevant literature and to establish recommendations using the National Academy of Medicine standards for developing trustworthy clinical practice guidelines.<sup>3</sup>
- The scope was to provide recommendations for improving reproducibility, precision, and accuracy in the interpretation of HER2 IHC where QIA is employed.

# Expert panel members

- Marilyn Bui, MD, PhD, FCAP, chair
- Kimberly Allison, MD, FCAP
- Elizabeth Chlipala, BS, HTL(ASCP)  
QIHC
- M. Elizabeth Hammond, MD, FCAP
- Andrea Kahn, MD, FCAP
- Anant Madabhushi, PhD
- Liron Pantanowitz, MD, FCAP
- Michael Riben, MD, FCAP
- Mohamed E. Salama, MD, FCAP
- Rachel Stewart, DO, PhD, FCAP
- John E Tomaszewski, MD, FCAP



Portion of the expert panel

## CAP Staff

- Nicole E. Thomas, MPH, CT(ASCP)<sup>cm</sup>,  
Senior Manager, Center Guideline  
Development
- Carol Colasacco, MLIS, SCT(ASCP),  
Medical Librarian Specialist

# Advisory panel

- **An advisory panel was also developed to assist the expert panel in developing the project scope and reviewing the guideline recommendations and manuscript.**
  - Kenneth Bloom, MD, FCAP
  - Stephen Hewitt, MD, PhD, FCAP
  - Richard Levenson, MD
  - David Rimm, MD, PhD, FCAP
  - Mogens Vyberg, MD

# Systematic evidence review

- Identify key questions
- Literature search
  - Studies from January 2006 – January 2017
- Extract relevant data (outcomes selected a priori)
- Develop proposed recommendations
- Open comment period
- Considered judgment process
  - Consider risks and benefits, costs, regulatory requirements, patient and/or laboratory preferences, etc.

# Systematic evidence review results



- 376 articles identified for title/abstract review
- 148 articles submitted for full text review
- 39 articles underwent data extraction and quality assessment analysis
- 9 articles informed the guideline statements
- 11 final guideline statements
  - 7 recommendations
  - 4 expert consensus opinions

# Open comment period

- **March 6 – March 27, 2017; 11 draft recommendations presented**
- **156 participants; 180 written comments**
  - **5 draft recommendations achieved more than 90% agreement**
  - **4 draft recommendations achieved more than 80% agreement**
  - **2 draft recommendations received more than 70% agreement**

# Definition of strength of recommendations

Grades for Strength of Recommendations		
Designation	Recommendation	Rationale
<b>Strong Recommendation</b>	Recommend for or against a particular practice (Can include “must” or “should”)	Supported by convincing (high) or adequate (intermediate) quality of evidence and clear benefit that outweighs any harms
<b>Recommendation</b>	Recommend for or against a particular practice (Can include “should” or “may”)	Some limitations in quality of evidence (adequate [intermediate] or inadequate [low]), balance of benefits and harms, values, or costs but panel concludes that there is sufficient evidence and/or benefit to inform a recommendation
<b>Expert Consensus Opinion</b>	Recommend for or against a particular practice (Can include “should” or “may”)	Serious limitations in quality of evidence (inadequate [low] or insufficient), balance of benefits and harms, values or costs, but panel consensus is that a statement is necessary
<b>No Recommendation</b>	No recommendation for or against a practice	Insufficient evidence or agreement of the balance of benefits and harms, values, or costs to provide a recommendation

# Guideline statements

INACTIVE\*

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# Guideline statement 1

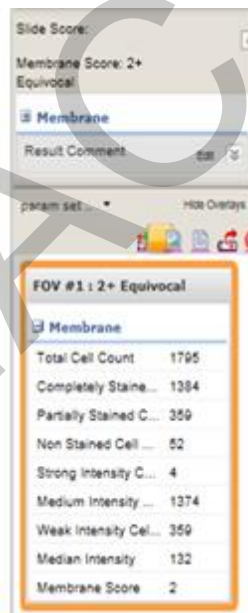
- ***Expert Consensus Opinion.*** – Laboratories that choose to implement QIA for HER2 IHC interpretation for clinical testing should select a QIA system that is validated for diagnostic interpretation. The final reporting schema should be consistent with the ASCO and the CAP guideline “Recommendations for Human Epidermal Growth Factor 2 Testing in Breast Cancer.”

# Rationale for statement 1

- **The goal of QIA is to detect and quantify HER2 membranous immunohistochemical staining of invasive breast cancer cells.**
- **Not all algorithms are designed to specifically quantify the correct staining. Therefore, for clinical use, laboratories should favor using a Food and Drug Administration (FDA)- approved system and/or algorithms.**
- **As with any new system in the laboratory used for diagnostic purposes, validation is required.**

# Rationale for statement 1, continued

- Preferably, laboratories should use a scoring system that matches the scoring system of the ASCO/CAP HER2 guideline
  - score 0 and 1+ = negative
  - score 2+ = equivocal
  - score 3+ = positive



Slide Score:  
Membrane Score: 2+  
Equivocal

Membrane

Result Comment

param set... Hide Overlays

FOV #1 : 2+ Equivocal	
Membrane	
Total Cell Count	1795
Completely Stained...	1384
Partially Stained C...	359
Non Stained Cell	52
Strong Intensity C...	4
Medium Intensity	1374
Weak Intensity Cel...	359
Median Intensity	132
Membrane Score	2

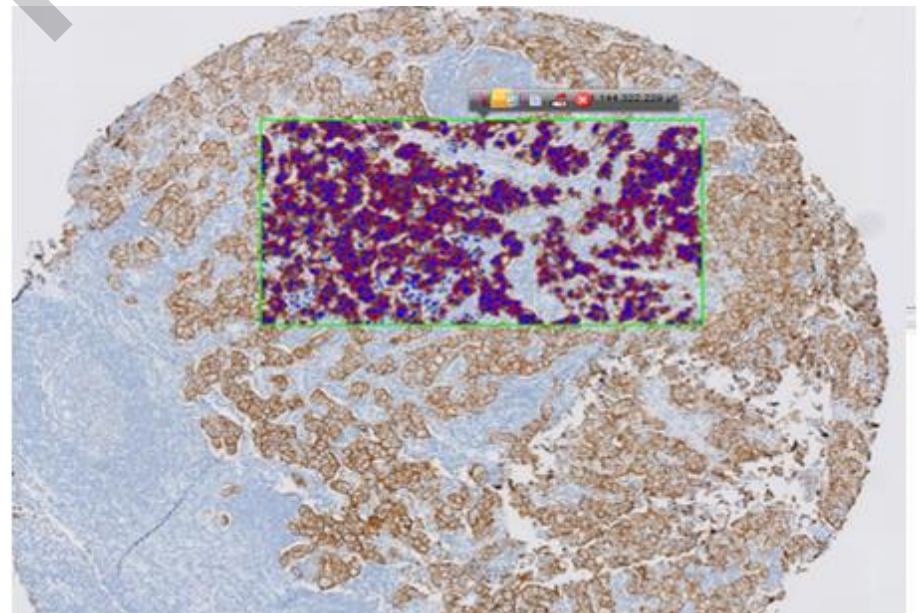


Photo courtesy of Marilyn M. Bui, MD, PhD, FCAP

## Guideline statement 2

- ***Recommendation.*** – Laboratories should validate their QIA results for clinical use by comparing them to an alternative, validated method(s) such as HER2 FISH or consensus images for HER2 IHC

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# Rationale for statement 2

- **QIA tests must be validated by comparing results to an alternative method. These may include:**
  - Comparison with manual consensus scoring of IHC cases for HER2
  - Comparison with FISH numeric chromosome counts for HER2
  - Comparison with bright-field chromogenic in-situ hybridization (CISH) numeric chromosome counts for HER2
  - Comparison with a previously validated QIA algorithm for HER2
- **The literature emphasizes the importance of performing such comparative studies in order to understand the differences in operating characteristics between manual and QIA methods.**

## Guideline statement 3

- ***Recommendation.*** – Laboratories should ensure that the results produced by a QIA system are reproducible within and between different batch analyses.

# Rationale for statement 3

- **Clinical Laboratory Improvement Amendments (CLIA) regulations stipulate that laboratories must establish and verify the performance specifications for all assays used in patient testing.**
- **As applied to QIA, this would include an assessment of intra-run and inter-run reproducibility (to establish precision)**

## Guideline statement 4

- ***Recommendation.*** – Laboratories should ensure that the results produced by a QIA system are reproducible between operators when they select regions of interest (ROI) for analysis and/or perform annotation.

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## Rationale for statement 4

- **Most QIA systems rely on operators to select regions of interest (ROIs), which can introduce interobserver variability.**
- **Laboratories are encouraged to develop documented procedures for training and selecting ROIs.**
- **Laboratories are responsible for the training of the laboratory professionals or pathologists on the ROI selection procedure.**
- **Once a procedure for the ROI selection has been developed, laboratories should validate the accuracy and precision of their procedure across a number of cases and operators prior to implementation.**

## Guideline statement 5

- ***Recommendation.*** – Laboratories should monitor and document the performance of their QIA system.

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# Rationale for statement 5

- **The CAP Anatomic Pathology Laboratory Checklist spells out the requirements for validation and includes requirements for quality control.<sup>4</sup>**
- **Laboratories should define an ongoing quality control process that monitors the results of HER2 attained by QIA along with maintaining algorithm accuracy.**
- **QIA has been associated with false-positives. Dennis et al highlighted the importance of instrument calibration to reduce false-positives.<sup>5</sup>**

## Guideline statement 6

- ***Recommendation.*** – Laboratories should have procedures in place to address changes to the QIA system that could impact clinical results.

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# Rationale for statement 6

- **The CAP All Common Checklist requires that all instruments and equipment be verified upon installation and after major maintenance or service.<sup>4</sup>**
- **Laboratory procedures for change control will provide a formal process by which changes to the QIA system are introduced and controlled in a coordinated manner. This process will assure that changes are documented and managed to prevent unintended consequences.**

## Guideline statement 7

- ***Expert Consensus Opinion.*** – The pathologist should document that results were obtained using QIA in the pathology report.

# Rationale for statement 7

- The CAP Anatomic Pathology checklist requires that the final report include the specimen sources, name of the vendor and imaging system used, the antibody clone or probe, and the detection method, as well as any limitations for the test result, if applicable (ANP.23038).<sup>4</sup>
- It is the consensus of the expert panel that HER2 QIA results be reported using the ASCO/CAP scoring schema<sup>1</sup> and that the report specify that QIA was used. Documenting that QIA was used will provide evidence for billing and quality monitoring purposes.

## Guideline statement 8

- ***Recommendation.*** – Personnel involved in the QIA process should be trained specifically in the use of the technology.



# Rationale for statement 8

- **CAP General Checklist requirement GEN.55450 requires that records be maintained for all laboratory personnel indicating that they have satisfactorily completed initial training on all instruments and methods applicable to their designated job.<sup>4</sup> GEN.55500 requires that the competency of each person performing patient testing to perform his or her assigned duties to be assessed.<sup>4</sup>**
- **A structured training about the QIA technology should ensure that personnel involved in QIA testing have consistent experience and background knowledge.**

## Guideline statement 9

- ***Expert Consensus Opinion.*** – Laboratories should retain QIA results and the algorithm metadata in accordance with local requirements and applicable regulations.

# Rationale for statement 9

- **QIA used for diagnostic purposes is a laboratory test analogous to other analytic tests performed in the clinical laboratory. As such, CLIA standards apply.**
- **While the recommendation states that QIA results and algorithm metadata be retained following local requirements and regulations, there may be reasons laboratories choose to keep the data longer.**
- **Data retention can be costly. Ideally, laboratories should consider the pros and cons prior to adopting the technology.**

# Guideline statement 10

- ***Recommendation.*** – The pathologist who oversees the entire HER2 QIA process used for clinical practice should have appropriate expertise in this area.

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# Rationale for statement 10

- **CAP Anatomic Pathology Checklist ANP.23041 requires that personnel responsible for evaluating or accepting the imaging system data must be qualified as high-complexity testing personnel.<sup>4</sup>**
- **Notwithstanding, the personnel who oversee the HER2 QIA process should have the necessary skills and problem-solving abilities to address problems that may arise if the QIA system does not function as intended and be able to supervise validation and monitor the QIA system.**

# Guideline statement 11

- ***Expert Consensus Opinion.*** – The pathologist finalizing the case should be knowledgeable in the use of the HER2 QIA system and visually verify the correct ROI was analyzed, the algorithm-annotated image produced, and the image analysis results.

# Rationale for statement 11

- While pathologists releasing or finalizing the QIA HER2 test results are not required to have advanced training in QIA, it is the panel's expert opinion that they should be familiar with the QIA system being used.
- They should also be qualified to interpret HER2 test results, which includes being familiar with the ASCO/CAP HER2 testing guideline, HER2 IHC interpretation criteria, and being able to recognize unusual or discordant results.<sup>1</sup>

# Conclusion

- **The CAP developed this guideline to help laboratories implement QIA for clinical practice.**
- **11 guideline statements, based on a systematic review of the literature and the panel's considered judgment are offered.**
- **As the literature expands, the guideline will be reviewed and updated to address new advances in the field.**



# References

- 1. Wolff AC, Hammond ME, Allison KH, et al. Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. *J Clin Oncol*. 2018;36(20):2105-2122. doi: 10.1200/JCO.2018.77.8738
- 2. Bui M, Riben MW, Allison KH, et al. Quantitative image analysis of human epidermal growth factor receptor 2 immunohistochemistry for breast cancer: guideline from the College of American Pathologists. *Arch Pathol Lab Med*. 2019;143(10):1180-1195. doi: [10.5858/arpa.2018-0378-CP](https://doi.org/10.5858/arpa.2018-0378-CP)
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- 4. College of American Pathologists. Accreditation checklists. College of American Pathologists website. <https://www.cap.org/laboratory-improvement/accreditation>. Accessed January 14, 2019.
- 5. Dennis J, Parsa R, Chau D, et al. Quantification of human epidermal growth factor receptor 2 immunohistochemistry using the Ventana Image Analysis System: correlation with gene amplification by fluorescence in situ hybridization: the importance of instrument validation for achieving high (>95%) concordance rate. *Am J Surg Pathol*. 2015;39(5):624-631. doi:10.1097/PAS.0000000000000375

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