



COLLEGE of AMERICAN
PATHOLOGISTS

Quantitative Image Analysis of HER2 Immunohistochemistry for Breast Cancer

CAP Guideline Update and Review of Draft
Recommendations

Marilyn M. Bui, MD, PhD, FCAP

May 22, 2017

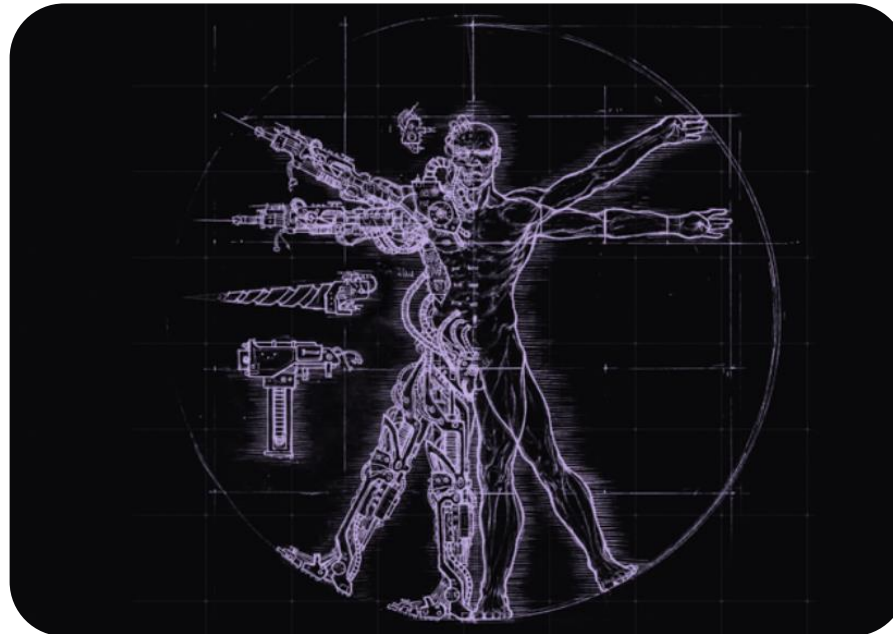
Disclosures



- **There is no financial disclosure or conflict of interest.**
- **The presentation represents my personal and professional opinion only.**
- **Member of Digital Pathology Association Board of Directors & Executive Committee, Editorial Board member of Journal of Pathology Informatics, Member of Association of Pathology Informatics, CAP Digital Pathology Committee and contributing editor of CAP Digital Pathology Resource Guide 2014-2017, Chair of the CAP Pathology and Laboratory Quality Center Expert Panel of the HER2 IHC Quantitative Image Analysis guideline.**

Outline

- Introduce quantitative image analysis (QIA)
- Discuss some of the challenges of QIA and HER2 IHC for breast cancer interpretation and reporting
- Review draft recommendations from CAP guideline on HER2 IHC QIA in progress



Introduction

**Quantitative image analysis (QIA) =
Quantitative extraction of meaningful
information from images**



QIA is a powerful advantage of digital pathology

- **When the slides are digitalized, they can be numerically analyzed using computer algorithms.**
- **Algorithms can be used to automate the manual counting of structures, or for classifying the condition of tissue, like algorithms used in grading tumors.**
- **This could reduce human error and improve accuracy of diagnoses.**

The power of image analysis

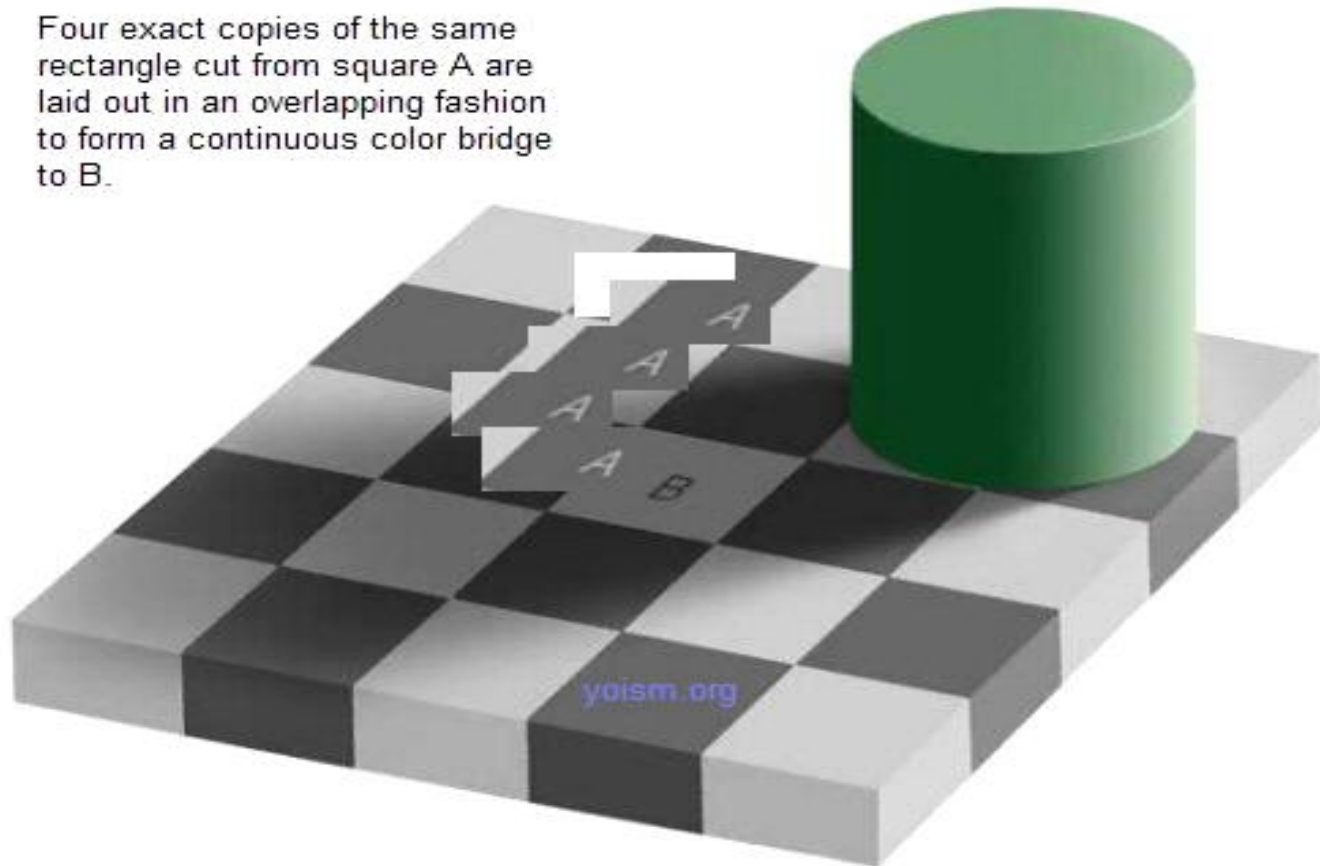
Four exact copies of the same rectangle cut from square A are laid out in an overlapping fashion to form a continuous color bridge to B.

Reliable

Measurable

Repeatable

Quantifiable



Benefits of image analysis

- **Better accuracy (more precise quantitative measurements)**
- **Standardization (more reproducible results, especially for intermediate categories & complex scoring systems)**
- **Automation (reduce time consumption for pathologists, especially for performing mundane tasks like counting)**
- **Enhanced efficiency (triage cases – eg, weed out negative cases)**
- **CAD (eg, help pathologists find, diagnose & grade disease like cancer)**
- **Enable big data projects (eg, image analysis for biomarker discovery)**



Current state of QIA

- **Advancements in genomics, computing and imaging technology have spurred new opportunities to use QIA in diagnostic medicine**
- **Current shift from research to clinical applications, especially in diagnostic testing**
- **Diagnostic pathology transition from qualitative (descriptive, analog) to quantitative (automated) science**
- **Precision medicine currently demands precision diagnostics**
- **Most widely employed clinical diagnostic algorithms are for breast cancer biomarkers (ER, PR, HER2, Ki-67 and p53)**



Image analysis tools

Software Type	Image Format Compatibility	Technical Knowledge Level	Customization Level	Features	Examples
Basic Science Image Analysis	Most Image Formats	Moderate	High	Variety of measurement tools Access to image processing tools Some automation	Image Pro Premier Metamorph ImageJ/FIJI Cell Profiler
Slide Scanner Based	Limited Image Formats	Low	Low-Moderate	Direct access to images Access to common algorithms US IVD for HER2/ER Pattern recognition Batch processing Designed for Digital Pathology	Roche/Ventana Leica/Aperio 3D Histech HALO PathXL TissueMark
Digital Pathology Inspired	Most Image Formats	Moderate	Moderate	Workflow based Easily adjustable parameters Batch processing Pattern recognition Access more feature data Designed for Digital Pathology	InForm, Visiopharm Definiens Tissue Studio
Algorithm Based	Most Image Formats	High	High	Fully customizable Unique algorithms Even more feature data Batch processing	MatLab Visiopharm Definiens Developer

Image analysis tools

- **Examples of whole slide image analysis:**
 - **Positive pixel count**

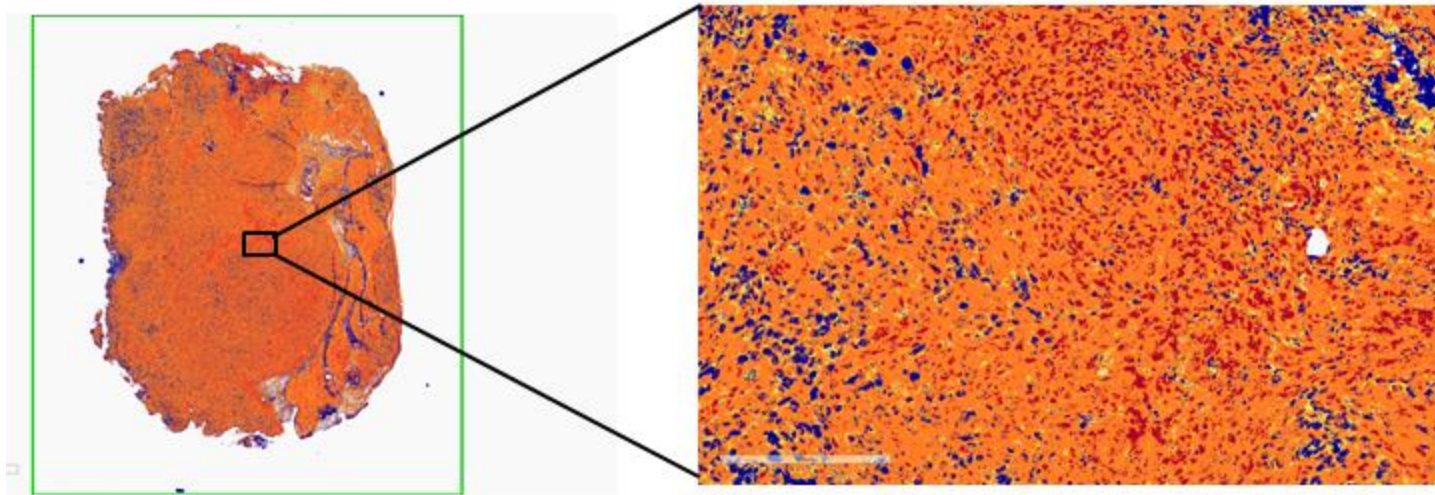


Image analysis tools

- **Examples of whole slide image analysis:**
 - **Nucleus analysis**

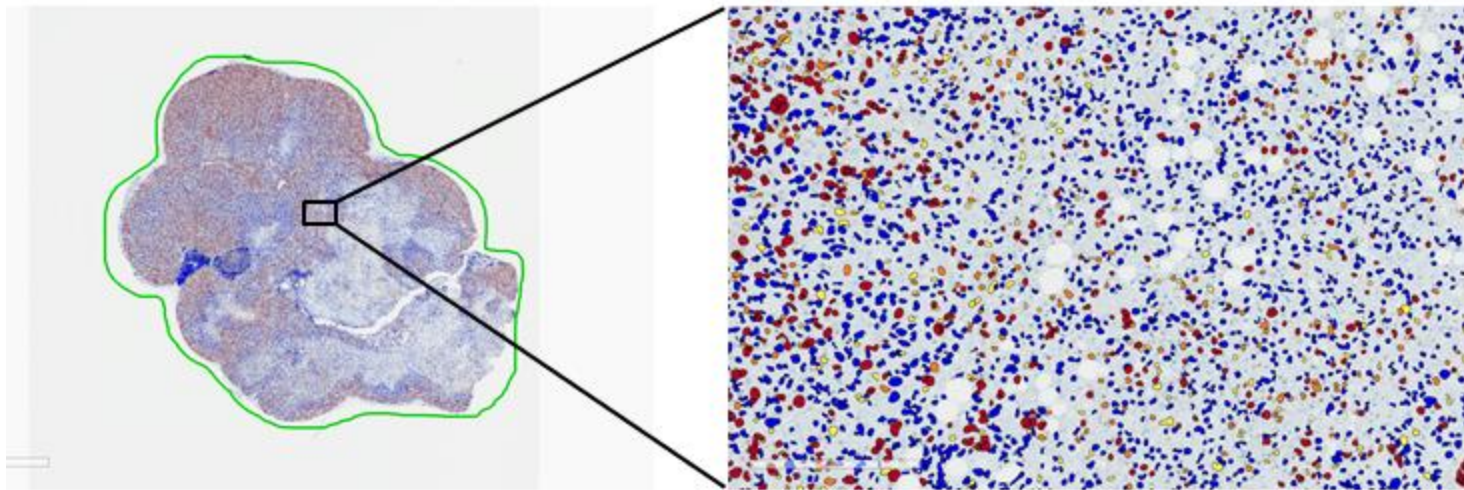


Image analysis tools

- **Examples of whole slide image analysis:**
 - **Cytoplasm analysis**

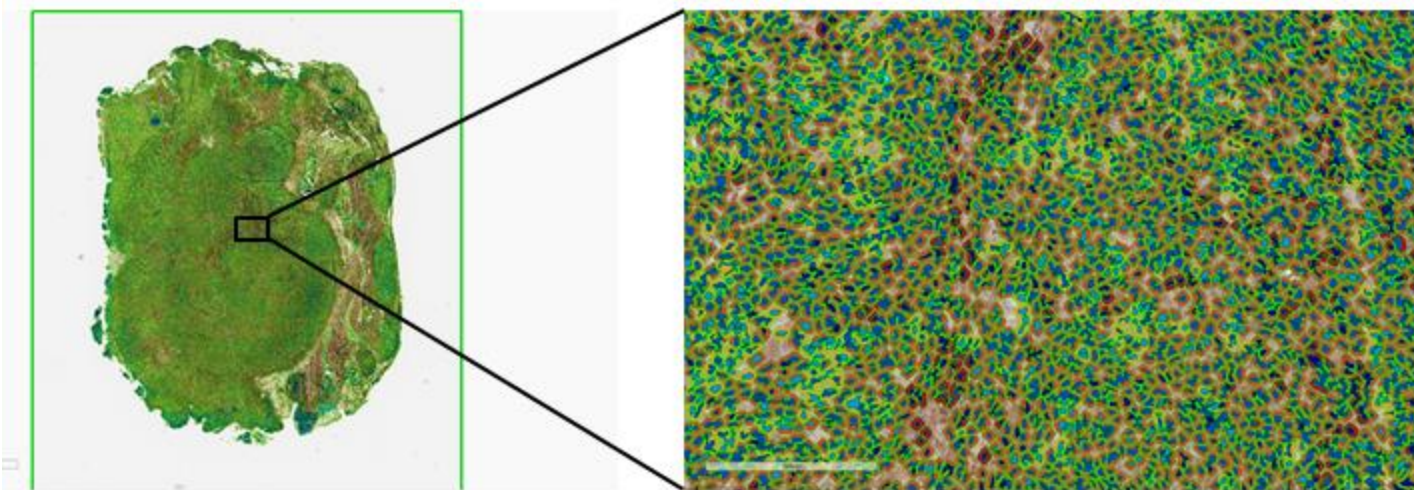
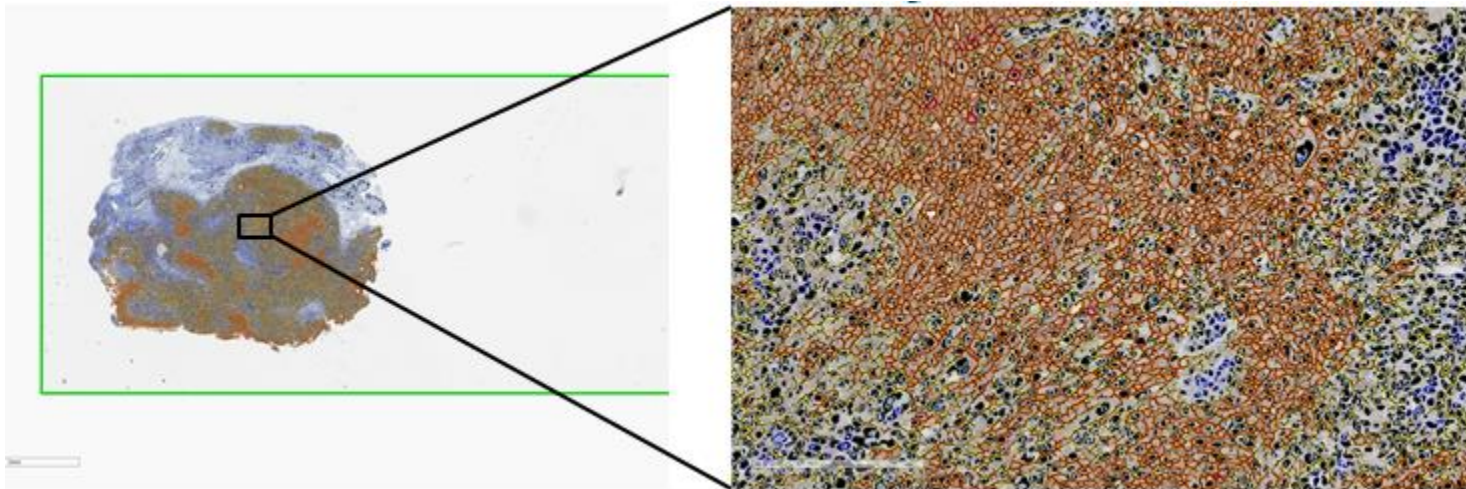


Image analysis tools

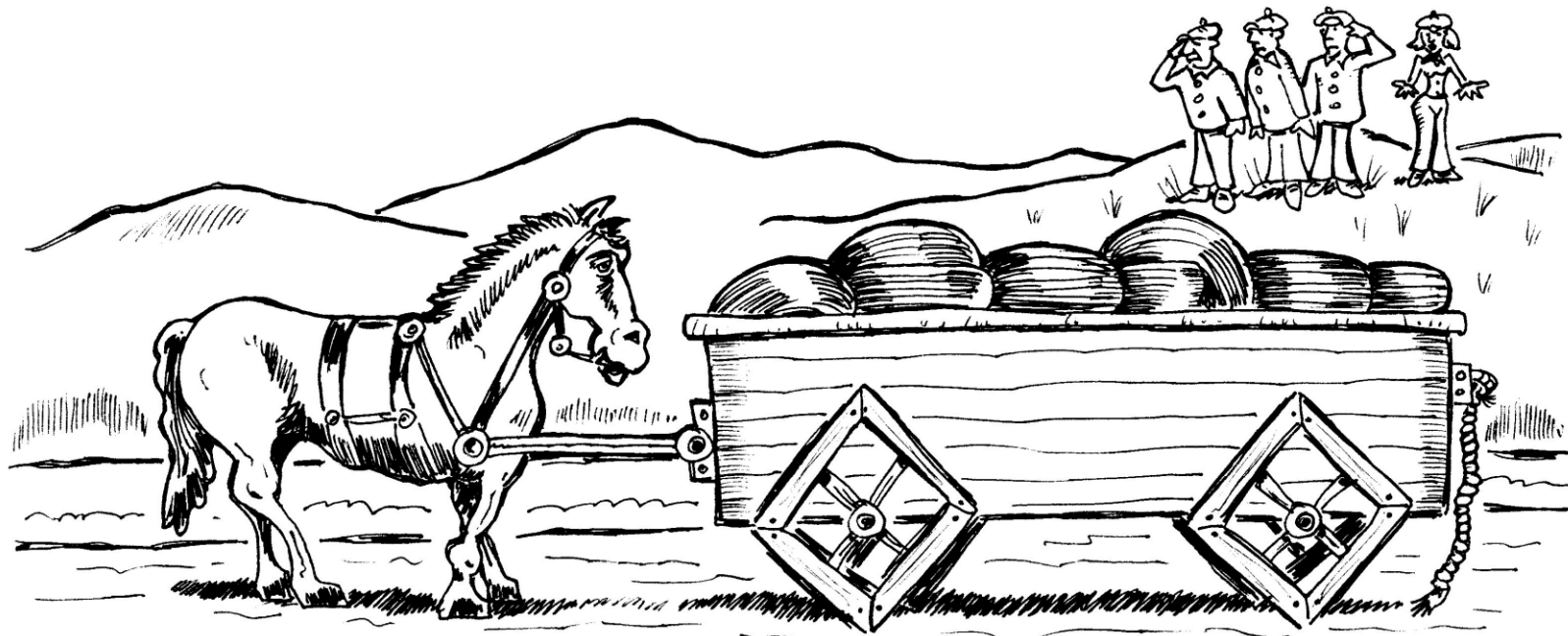
- **Examples of whole slide image analysis:**
 - **Membrane**



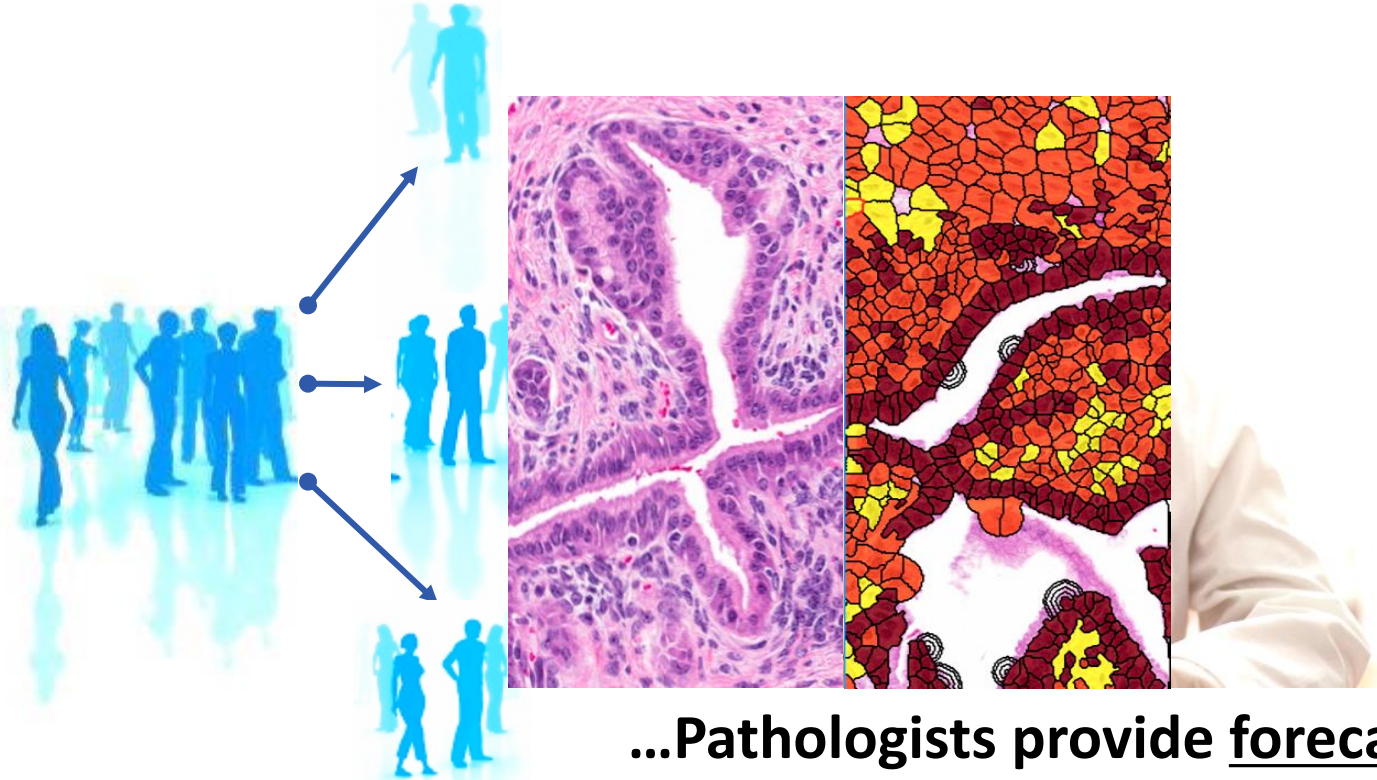
Algorithms for QIA

RESEARCH	CLINICAL
Many apps	Limited algorithms
Modifiable parameters	Locked down apps
Lab developed tests	Approved (FDA)
Research environment	Regulated lab (CLIA)
Continuous data	Discrete results
Variable output	Match manual scores
Researchers	Pathologist oversight
Financial benefit	Questionable ROI (CPT code)
Stand-alone system	Integrated workflow
Widespread use	Slow adoption

Challenges



A patient's medical journey begins with their diagnosis...



...Pathologists provide forecast of

Diagnosis

Prognosis

Therapeutic selection &

Prediction of response

HER2



ASCO/CAP HER2 guideline

American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer

Antonio C. Wolff, M. Elizabeth H. Hammond, Jared N. Schwartz, Karen L. Hagerly, D. Craig Allred, Richard J. Cote, Mitchell Dowsett, Patrick L. Fitzgibbons, Wedad M. Hanna, Amy Langer, Lisa M. McShane, Soonmyung Paik, Mark D. Pegram, Edith A. Perez, Michael F. Press, Anthony Rhodes, Catharine Sturgeon, Sheila E. Taube, Raymond Tubbs, Gail H. Vance, Marc van de Vijver, Thomas M. Wheeler, Daniel F. Hayes

• Purpose.—To develop a guideline to improve the accuracy of human epidermal growth factor receptor 2 (HER2) testing in invasive breast cancer and its utility as a predictive marker.

Methods.—The American Society of Clinical Oncology and the College of American Pathologists (CAP) convened an expert panel, which conducted a systematic review of the literature and developed recommendations for optimal HER2 testing performance. The guideline was reviewed by selected experts and approved by the board of directors for both organizations.

Results.—Approximately 20% of current HER2 testing may be inaccurate. When carefully validated testing is performed, available data do not clearly demonstrate the superiority of either immunohistochemistry (IHC) or in situ hybridization (ISH) as a predictor of benefit from anti-HER2 therapy.

Recommendations.—The panel recommends that HER2 status should be determined for all invasive breast cancer. A testing algorithm that relies on accurate, reproducible assay performance, including newly available types of brightfield ISH, is proposed. Elements to reliably reduce assay variation (for example, specimen handling, assay exclusion, and reporting criteria) are specified. An algorithm

The human epidermal growth factor receptor 2 gene *ERBB2* (commonly referred to as *HER2*) is amplified in approximately 18% to 20% of breast cancers.¹ *ERBB2* is the official name provided by the HUGO Gene Nomen-

defining positive, equivocal, and negative values for both HER2 protein expression and gene amplification is recommended: a positive HER2 result is IHC staining of 3+ (uniform, intense membrane staining of > 30% of invasive tumor cells), a fluorescent in situ hybridization (FISH) result of more than 6 *HER2* gene copies per nucleus, or a FISH ratio (*HER2* gene signals to chromosome 17 signals) of more than 2.2; a negative result is an IHC staining of 0 or 1+, a FISH result of less than 4.0 *HER2* gene copies per nucleus, or a FISH ratio of less than 1.8. Equivocal results require additional action for final determination. It is recommended that to perform HER2 testing, laboratories

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JOURNAL OF CLINICAL ONCOLOGY ASCO SPECIAL ARTICLE

Recommendations for Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Update

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ABSTRACT

Purpose To update the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guideline recommendations for human epidermal growth factor receptor 2 (HER2) testing in breast cancer to improve the accuracy of HER2 testing and to define its utility as a predictive marker in invasive breast cancer.

Methods ASCO/CAP convened an Update Committee that included coauthors of the 2007 guideline to conduct a systematic literature review and update recommendations for optimal HER2 testing.

Results The Update Committee identified others and areas requiring clarification to improve the accuracy of HER2 testing by immunohistochemistry (IHC) or in situ hybridization (ISH). The guideline was reviewed and approved by both organizations.

Recommendations The Update Committee recommends the HER2 status (HER2 negative or positive) be determined in all patients with invasive breast cancer or ductal breast cancer on the basis of one or more HER2 test results (negative, equivocal, or positive). Testing criteria define HER2-positive status when low (scoring within an assay of lower than expected) or no (scoring at or below expected) and heterogeneous staining is observed on protein immunohistochemistry (IHC) or gene amplification (FISH) copy number or HER2/CEP17 ratio by FISH based on counting of at least 20 cells within the area. If results are equivocal (neither clearly negative nor clearly positive), testing should be performed using an alternative assay (ie, of bright-field testing) using a validated assay. If results seem discordant with other histopathologic findings, laboratories should demonstrate high concordance with a validated HER2 test using an appropriate set of specimens. Testing must be performed in a laboratory accredited by CAP or another accrediting entity. The Update Committee urges patients and health systems to cooperate to ensure the highest quality testing.

This guideline was developed through a collaboration between the American Society of Clinical Oncology and the College of American Pathologists and has been submitted prior to publication and content in both *Journal of Clinical Oncology* and the *Annals of Pathology & Laboratory Medicine* (Copyright © 2013 American Society of Clinical Oncology and College of American Pathologists). All rights reserved. No part of this document may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without written permission by American Society of Clinical Oncology or College of American Pathologists.

INTRODUCTION

In 2007, a joint ASCO/CAP guideline¹ was published that defined the testing criteria for HER2 testing in breast cancer. In 2013, ASCO and CAP convened an Update Committee to conduct a formal and comprehensive

- HER2 status must be determined in all patients with invasive breast cancer.
- In the US, recommend using an assay that has received FDA approval, although a CLIA-certified laboratory may choose instead to use a LDT.
- If results are equivocal (revised criteria), reflex testing should be performed using an alternative assay (IHC or ISH).
- Must ensure that interpretation and reporting guidelines for HER2 testing are followed.

Accepted for publication September 27, 2016; published online ahead of print at <http://jco.allenpress.com> on December 11, 2016.

From the College of American Pathologists, Northfield, Ill and the American Society of Clinical Oncology, Alexandria, Va. Antonio C. Wolff, M. Elizabeth H. Hammond, Jared N. Schwartz, and Daniel F. Hayes are American Society of Clinical Oncology/College of American Pathologists Expert Panel co-chairs.

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ASCO/CAP HER2 guideline

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Purpose. To update the American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guideline recommendations for human epidermal growth factor receptor 2 (HER2) testing in breast cancer to improve the accuracy of HER2 testing and to allow for a predictive marker in invasive breast cancer.

Methods. ASCO/CAP convened an Update Committee that included coauthors of the 2007 guideline to conduct a systematic literature review and update recommendations for optimal HER2 testing.

Results. The Update Committee identified others and areas requiring clarification to improve the accuracy of HER2 testing by immunohistochemistry (IHC) or in situ hybridization (ISH). The guideline was reviewed and approved by both organizations.

Recommendations. The Update Committee recommends the HER2 status (HER2 negative or positive) be determined in all patients with invasive breast cancer or suspected breast cancer on the basis of one or more HER2 test results (negative, equivocal, or positive). Testing criteria define HER2 positive status when on staining within an area of at least 10% of invasive cells, or a gene amplification ratio (copy number of *ERBB2/17*) ratio by ISH based on counting of at least 20 cells within the area. If results are equivocal (equivocal IHC staining or FISH ratio of 1.8 to 2.2), a confirmatory test is required. If results are discordant with other diagnostic findings, laboratories should demonstrate high concordance with a validated HER2 test to ensure the highest quality testing.

This guideline was developed through a collaboration between the American Society of Clinical Oncology and the College of American Pathologists and has been endorsed jointly by the American Society of Clinical Oncology and the American College of Pathology & Laboratory Medicine (ASCO/ACCP) 2013 American Society of Clinical Oncology and College of American Pathologists. All rights reserved. No part of this document may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without written permission by American Society of Clinical Oncology or College of American Pathologists.

INTRODUCTION

In 2007, a joint guideline recommended that human epidermal growth factor receptor 2 (HER2) testing be performed in all patients with invasive breast cancer to determine eligibility for trastuzumab therapy. In 2013, ASCO and CAP convened an Update Committee to conduct a formal and comprehensive

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- HER2 status must be determined in all patients with invasive breast cancer.
- In the US, recommend using an assay that has received FDA approval, although a CLIA-certified laboratory may choose instead to use a LDT.
- If results are equivocal (revised criteria), reflex testing should be performed using an alternative assay (IHC or ISH).
- Must ensure that interpretation and reporting guidelines for HER2 testing are followed.
- Image analysis can be used to achieve consistent interpretation.
- However, a pathologist must confirm the image analysis result.
- Image analysis procedures must be validated before implementation.
- Image analysis equipment, just as other laboratory equipment, must be calibrated and subjected to regular maintenance and internal quality control evaluation.

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Digital image analysis outperforms manual biomarker assessment in breast cancer

Gustav Stålhammar^{1,2}, Nelson Fuentes Martinez^{1,3}, Michael Lippert⁴, Nicholas P Tobin⁵, Ida Mølholm^{4,6}, Lorand Kis⁷, Gustaf Rosin¹, Mattias Rantalainen⁸, Lars Pedersen⁴, Jonas Bergh^{1,5,9}, Michael Grunkin⁴ and Johan Hartman^{1,5,7}

¹Department of Oncology and Pathology, Karolinska Institutet, Stockholm, Sweden; ²St Erik Eye Hospital, Stockholm, Sweden; ³Södersjukhuset, Stockholm, Sweden; ⁴Visiopharm A/S, Hoersholm, Denmark; ⁵Cancer Center Karolinska, Stockholm, Sweden; ⁶Department of Applied Mathematics and Computer Science, Technical University of Denmark, Kongens Lyngby, Denmark; ⁷Department of Clinical Pathology, Karolinska University Hospital, Stockholm, Sweden; ⁸Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden and ⁹Department of Oncology, Karolinska University Hospital, Stockholm, Sweden

- In conclusion, the system for DIA evaluated here was in most aspects a superior alternative to manual biomarker scoring.
- It also has the potential to reduce time consumption for pathologists, as many of the steps in the workflow are either automatic or feasible to manage without pathological expertise.

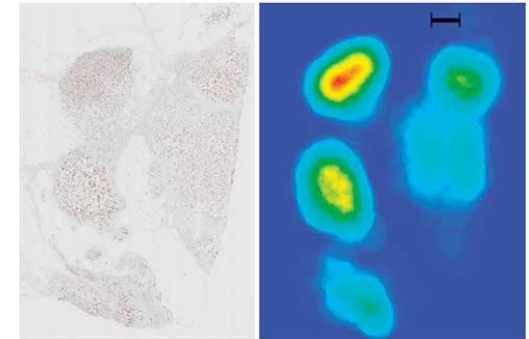
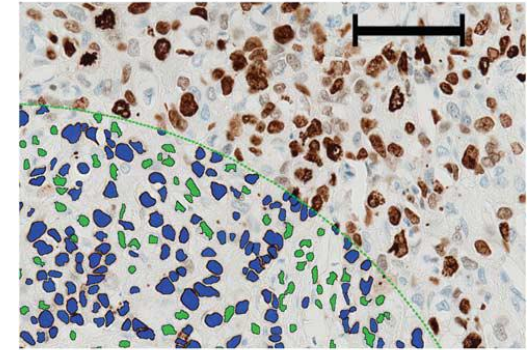
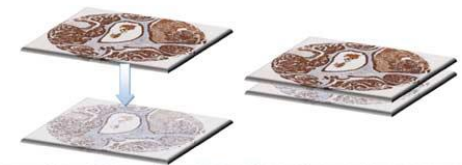


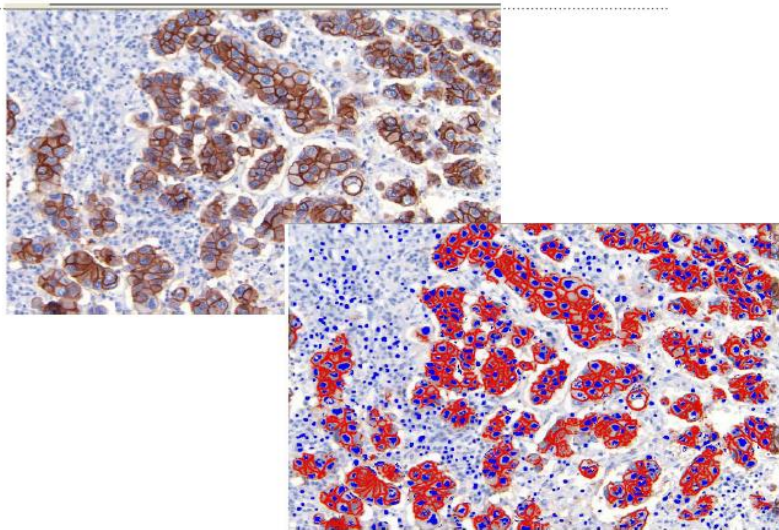
Table 2 Molecular ‘intrinsic’ breast cancer subtypes and surrogate definitions by immunohistochemical profile

<i>Intrinsic subtype</i>	<i>Surrogate IHC classification</i>
Luminal A	ER ≥ 1% and/or PR ≥ 20% and HER2 ‘negative’ and Ki67 ‘low’
Luminal B	1. ER ≥ 1% and/or PR ≥ 20% and HER2 ‘negative’ and Ki67 ‘high’ or 2. ER ≥ 1% and PR < 20% and HER2 ‘negative.’ Any Ki67 or 3. ER ≥ 1% and/or PR ≥ 1% and HER2 ‘positive.’ Any Ki67
HER2-enriched	ER < 1% and PR < 1%. HER2 ‘positive.’ Any Ki67
Basal-like	ER < 1% and PR < 1%. HER2 ‘negative.’ Any Ki67

% = Proportion of tumor cells stained with the respective biomarker. ‘Positive’ and ‘negative’ = as defined by the American Society of Clinical Oncology and College of American Pathologists recommendations for human epidermal growth factor receptor 2-testing in breast cancer.³⁰ ‘High’ and ‘low’ = as defined by each laboratory’s own reference data,^{3,6,17} with threshold generally in the range of 14–29%.^{4,5,19–21}

HER2 image algorithms

Quantitation of Results (Membrane)



Date	K-Number	Tissue - Stain	Reagent	Application
PATHIAM (Biolmagene, Sunnyvale, CA)				
FDA-approved				
2010/10	K092333	Breast - P53/Ki-67	Dako	Image Analysis
2009/02	K080910	Breast - HER2/neu	Dako ✓	Image Analysis
2007/02	K062756	Breast - HER2/neu	Dako ✓	Image Analysis (SW only)
ScanScope XT System (Aperio Technologies, Vista, CA)				
2009/08	K080564	Breast - HER2/neu	Dako ✓	Tunable Image Analysis
2008/10	K080254	Breast - PR	Dako	Reading on Monitor
2008/08	K073667	Breast - ER/PR	Dako Image Analysis	Image Analysis
2007/12	K071671	Breast - HER2/neu	Dako Reading on Monitor ✓	
2007/10	K071128	Breast - HER2/neu	Dako ✓	Image Analysis
VIAS (Tripath Imaging, Burlington, NC)				
2006/09	K062428	Breast - P53	Ventana	Image Analysis
2006/04	K053520	Breast - Ki-67	Ventana	Image Analysis
2005/08	K051282	Breast - HER2/neu	Ventana ✓	Image Analysis
2005/05	K050012	Breast - ER/PR	Ventana	Image Analysis
ARIOL (Applied Imaging, Santa Clara, CA)				
2004/03	K033200	Breast - ER/PR	Dako	Image Analysis
2004/01	K031715	Breast - HER2/neu	Dako ✓	Image Analysis
ACIS (Clariant, Aliso Viejo, CA/Chroma Vision, San Juan Capistrano, CA)				
2004/02	K012138	Breast - ER/PR	Dako	Image Analysis
2003/12	K032113	Breast - HER2/neu	Dako ✓	Image Analysis (system)
QCA (Cell Analysis, Highland Park, IL)				
2003/12	K031363	Breast - ER	Dako	Image Analysis (SW only)

Firefox | http://141.167.70...irtuoso/Login.seam | http://10.23.248.2...nversionId=21802 | +

10.23.248.25/virtuoso/PathHome.seam?conversationId=21802

Virtuoso Pathologist, General (Pathologist) Preferences Help Logout

Cases

- Assigned Cases
- All Cases
- Shared Cases
- Find Cases

Miscellaneous

- Job Queue
- Support
- About Virtuoso

Share Case Re-assign Case All

Case...	Patient	Patie...	Rece...	Type	Site	Status	Sha...	Rep...
1234	Doe, J...	123	10/2...	Breast	Venta...	In Progress		
Brea...	Patient...	8363...	10/2...	Breast	Venta...	In Progress		
S13...	John, ...	3505...	11/0...	Prostate	Venta...	In Progress		
S131...	Last, ...	5402...	11/0...	Breast	Venta...	In Progress		
SC1...	Kirk, J...	4449...	11/1...	Breast	Venta...	Signed out		

Page 1 of 1 | Displaying 1 - 5 of 5

Accession #: 1234

Patient Name: Doe, Jane
 Patient ID: 123
 Age/Gender: 58 years old Female
 Primary Tissue Type: Breast
 Received Date: 10/28/2013
 Assigned To: Pathologist, Genera
 l[path]

View Specimen

Specimens (1)

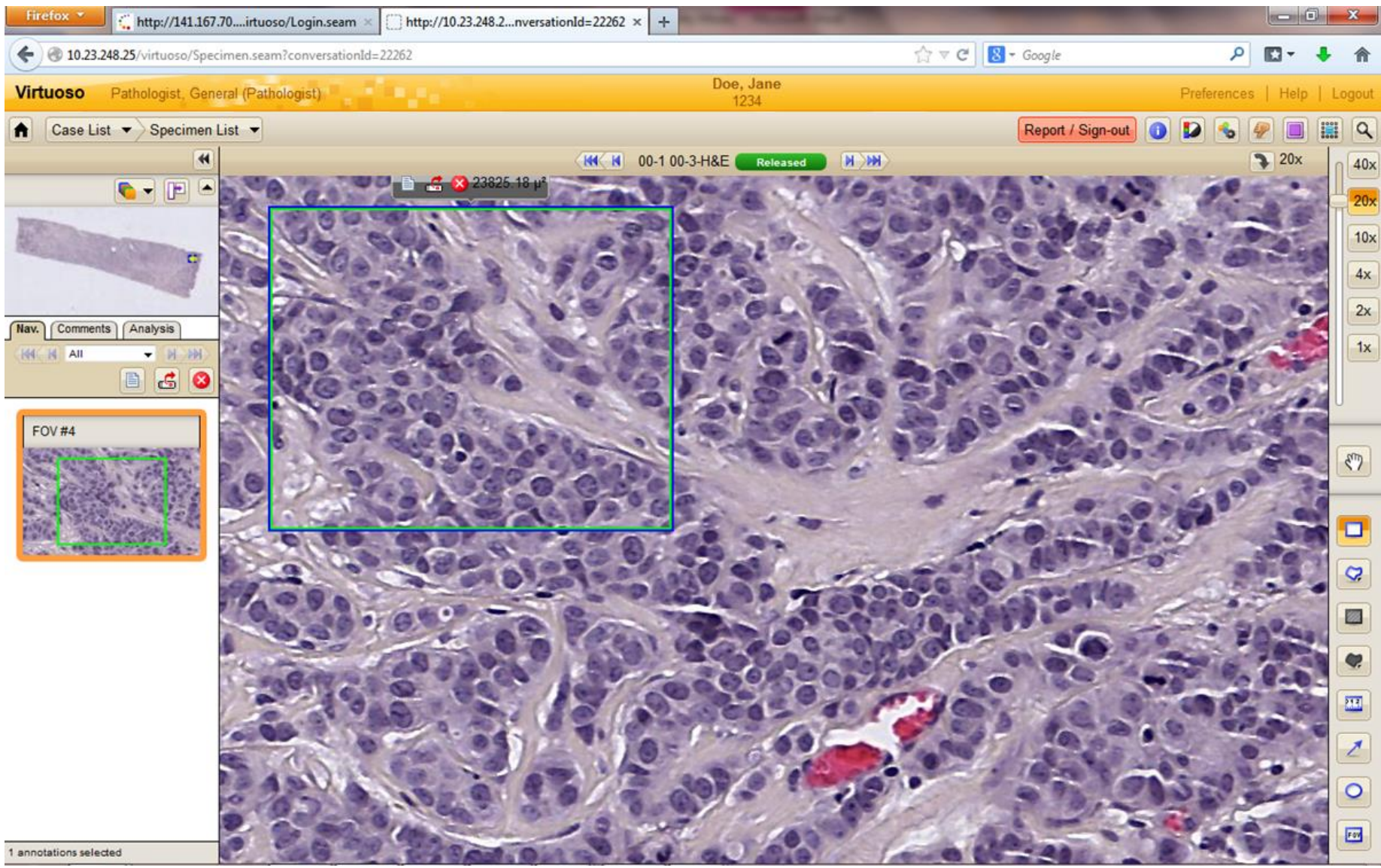
00-1 Breast In Progress

Gross Description for Specimen 00-1:

Biopsy History (3) *COMPANION ALGORITHM



Courtesy of Roche Diagnostic Corporation



Firefox | http://10.23.248.25/...onversationId=15245

10.23.248.25/virtuoso/SpecimenQC.seam?conversationId=15245

Virtuoso Histotech, General (Histotechnician) Williams, Lisa S14-98763 Preferences | Help | Logout

Specimen List

00-1 00-2-ER Imported

00-1 00-1-H&E Imported

00-1 00-2-ER Imported

00-1 00-3-PR Imported

00-1 00-4-HER2 Imported

40x 20x 10x 4x 2x 1x

No annotations have been selected.

11:02 AM 3/28/2014

Firefox | http://141.167.70...irtuoso/Login.seam | http://10.23.248.2...nversationId=21513 | 10.23.248.25/virtuoso/Specimen.seam?conversationId=21513


Virtuoso Pathologist, General (Pathologist) Patient, Unspecified BreastPanel Preferences | Help | Logout

Case List Specimen List

Report / Sign-out Save Preview Sign-out Cancel

BreastPanel 00-1

FOV Type:
 Non Analyzed Analyzed

Report Format:


Display Image Analysis Data for Specimen in Case Report:


Report Text

Comments

Clinical Indications

Specimen Diagnosis

20x 40x 10x 4x 2x 1x

Slide Score: 

Membrane Score: 2+ Equivocal
[Membrane](#)
[Result Comment](#)

FOV #1
 Membrane Score: 2+ Equivocal
[Membrane](#)

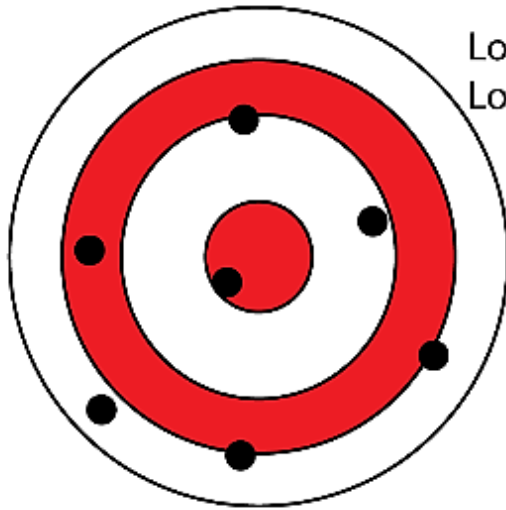
Quality AVERAGE_IMGQUALITY	
Total Cell Count	245
Completely Stained Cell Count	184
Partially Stained Cell Count	55
Non Stained Cell Count	6
Strong Intensity Cell Count	0
Medium Intensity Cell Count	67

1 annotations selected

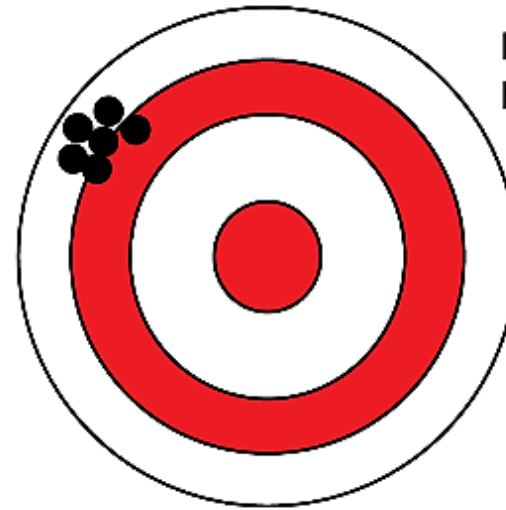
Validation

- Parameters to consider validating:
 - **System** (software, etc.)
 - **Test** (IHC platform)
 - **Pathologist** (reader)
 - **Result** (comparison)
- **Gold standard = alternative, validated method**
 - eg, FISH, another algorithm?
 - **Accuracy** (concordance/correct)

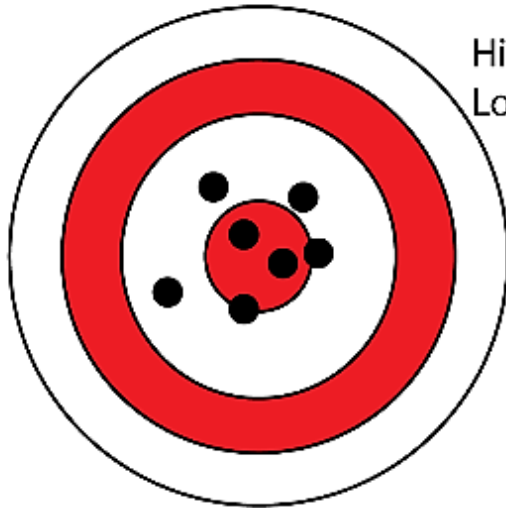




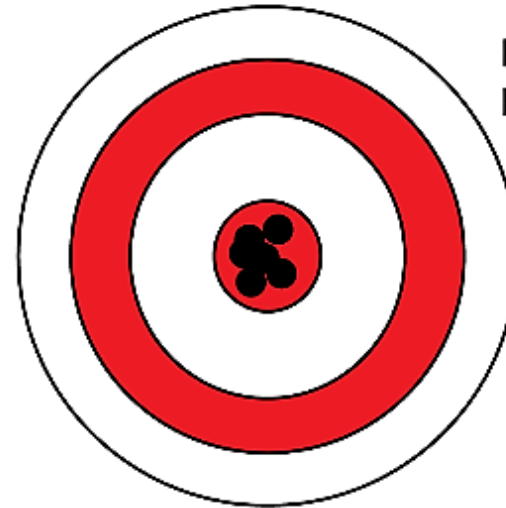
Low accuracy
Low precision



Low accuracy
High precision



High accuracy
Low precision



High accuracy
High precision

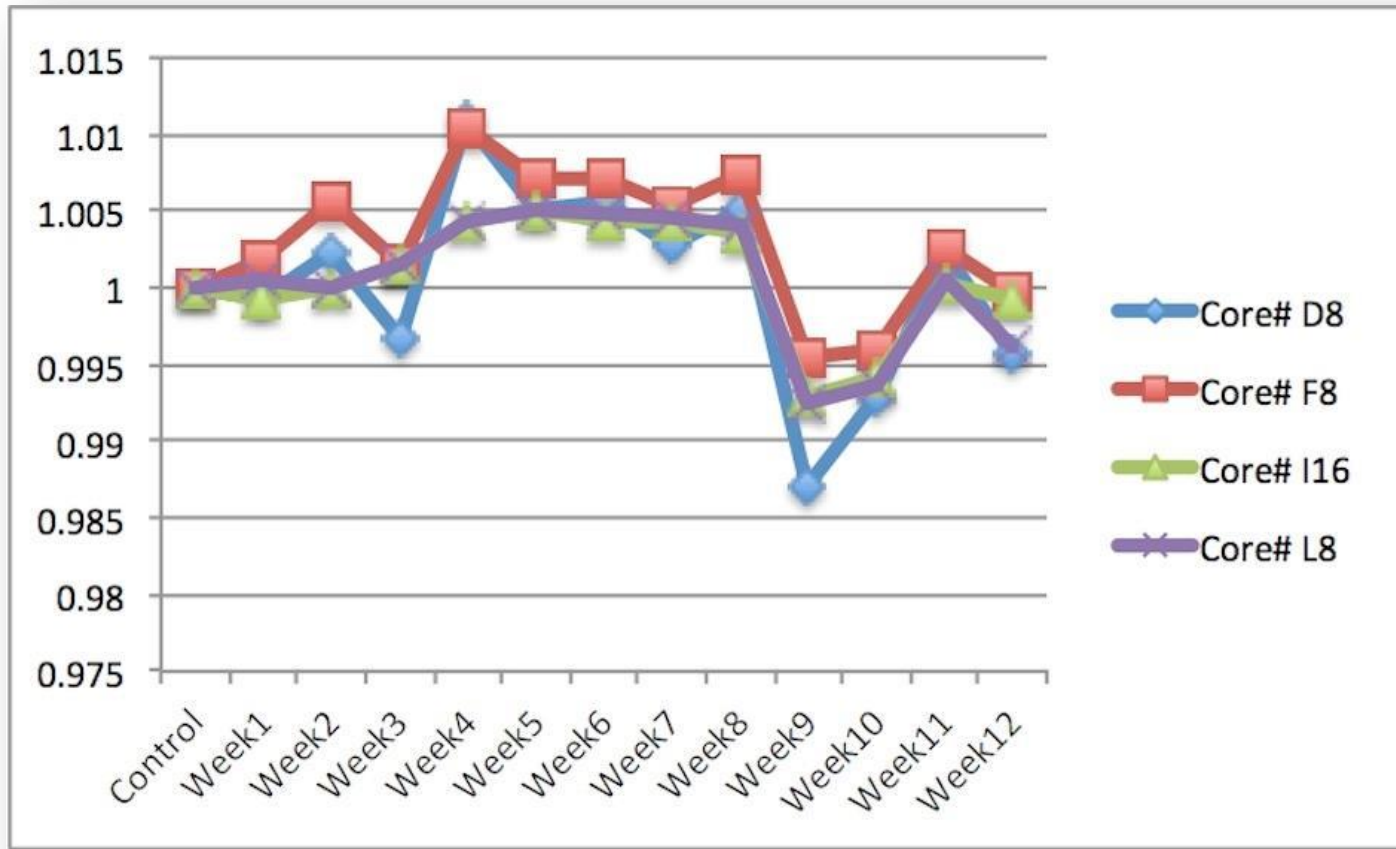
Accuracy: the closeness of a measured value to a standard or know value
Precision: the closeness of two or more measurements to each other;
precision is independent of accuracy.

Precision

- **Repeatability or reproducibility**
 - Assay variations (batches/runs)
 - Technical variations (image acquisition)
 - Operator variability (ROI selection)



Same scanner variability



WSI scanner reproducibility

- HER2/neu algorithms
 - Commercial algorithm
 - Preset parameters
- WSI from 3 scanners
- Inter-scanner variability
 - Different image properties
- Reducing discrepancies
 - Re-training (calibration)

Classifier	1+	2+	3+
Pathologist panel	21	137	83
Algorithm 1 on Aperio-CS	46	120	75
Algorithm 1 on Aperio-T2	65	101	75
Algorithm 1 on Hamamatsu	24	119	98
Algorithm 2 on Aperio-CS	13	145	83
Algorithm 2 on Aperio-T2	13	146	82
Algorithm 2 on Hamamatsu	14	149	78

HER2/neu: (Human epidermal growth factor receptor 2)

The gap in practice

- QIA has been shown to improve consistency and accuracy of interpretation than manual scoring by pathologists, but has not gained widespread acceptance
 - In 2016, of the 826 laboratories enrolled in the CAP HQIP-A mailing, 183 (22.1%) reported using QIA
- While the ASCO/CAP HER2 testing guidelines addressing the key pre-analytical and IHC related issues, there is a need of guideline for HER2 IHC QIA

CAP QIA guideline

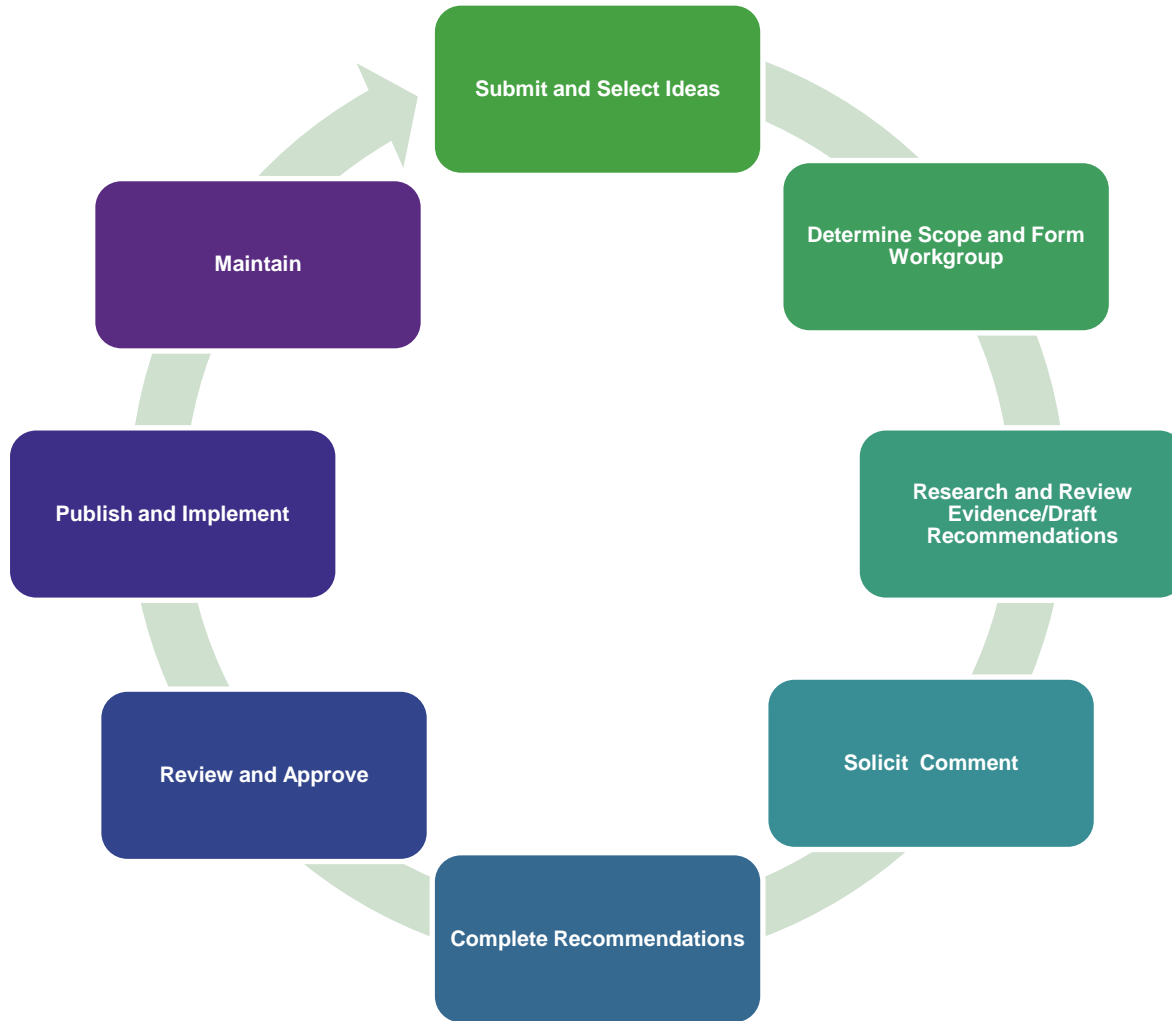
Scope:

- to provide recommendations for improving reproducibility, precision, and accuracy in the interpretation of HER2 IHC where QIA is employed

Methods:

- process follows the National Academy of Science (formerly IOM) standards for developing clinical practice guidelines
 - Built on systematic literature review
 - Draft recommendations by an expert panel with the input of an advisory panel
 - Public comment period
 - Grades provided for strength of evidence and strength of recommendation

CAP Center guideline life cycle



Key Questions

- 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?**

Guideline Panel Members

Advisory panel

Kenneth J. Bloom, MD

M. Elizabeth Hammond, MD

Stephen Hewitt, MD, PhD

Richard Levenson, MD

David Rimm, MD, PhD

Mogens Vyberg, MD

Staff

**Carol Colasacco, MLIS, SCT(ASCP),
Medical Librarian**

**Nicole Thomas, MPH, CT(ASCP), Sr.
Guideline Development Manager**

Expert panel

Marilyn Bui, MD, PhD, Chair

Kimberly H. Allison, MD

Elizabeth Chlipala, BS, HTL(ASCP) QIHC

M. Elizabeth Hammond, MD

Andrea Kahn, MD

Anant Madabhushi, PhD

Liron Pantanowitz, MD

Michael Riben, MD

Mohamed E. Salama, MD

Rachel L. Stewart, DO, PhD

John E. Tomaszewski, MD

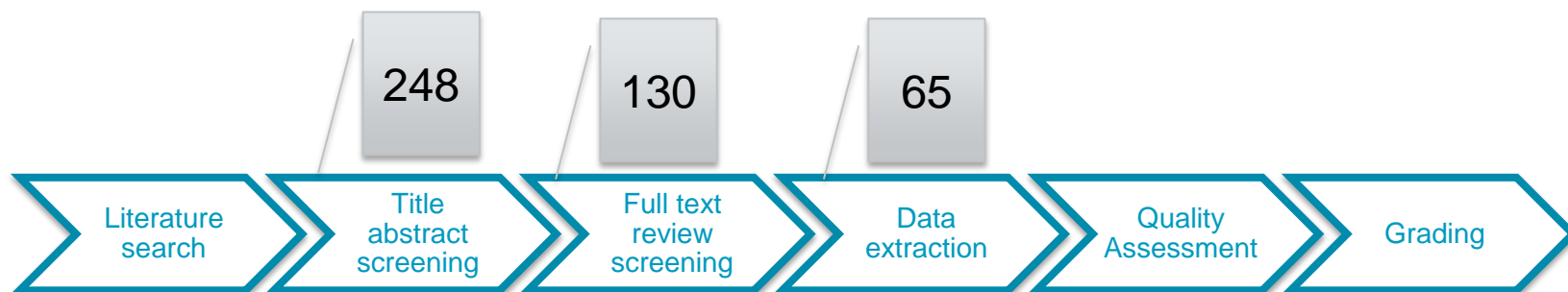
**Christina Lacchetti, MHSc, methodology
consultant**



CAP



Results of the systematic review



- 248 references for title/abstract screening
- 52% (130) included in full text screening
- 64% (65) included in data extraction

Total number of included studies to be determined after the literature refresh

Draft recommendations



- **11 draft recommendations**
 - 7 recommendations (based on laboratory accreditation requirements)
 - 4 expert consensus opinions
- **Data was difficult to synthesize**
 - Various imaging systems reported in the literature
 - Data not reported for many of the outcomes of interest

Results of comment period

- **CAP hosted a three week comment period in March 2017 for any stakeholder to provide feedback to the draft recommendations**
- **More than 150 participants and more than 180 comments received**

Draft guideline statements

1. **Laboratories should select a quantitative image analysis system for HER2 immunohistochemistry that is capable of meeting the standards for reporting as set forth by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) in the guideline “Recommendations for Human Epidermal Growth Factor 2 Testing in Breast Cancer.” – Expert Consensus Opinion**

85. 27% agree

14.73% disagree

Final statement will be revised

Draft guideline statements, continued

2. Laboratories should validate their quantitative image analysis results for clinical use by comparing them to an alternative, validated method. –

Recommendation

93.64% agree

6.36% disagree

Final statement will be revised



Draft guideline statements, continued

3. Laboratories should ensure that the results produced by a quantitative image analysis system are reproducible within and between different batch analyses. – Recommendation

95.10% agree

4.90% disagree

No revision



Draft guideline statements, continued

4. Laboratories should ensure that the results produced by a quantitative image analysis system are reproducible between operators when they select regions of interest for analysis and/or perform annotation. – Expert Consensus Opinion

89.90% agree

10.10% disagree

No revision



Draft guideline statements, continued

5. Laboratories should continuously monitor and document the performance of their quantitative image analysis system. – Recommendation

89.8% agree

10.2% disagree

Final statement will be revised



Draft guideline statements, continued

6. Laboratories should have procedures in place to address changes to the quantitative image analysis system that could impact clinical results. –

Recommendation

93.88 % agree

6.12% disagree

No revision



Draft guideline statements, continued

7. Laboratories should report that quantification was obtained by image analysis, the image analysis methods used, and at minimum, utilize the scoring schema recommended by the ASCO/CAP “Recommendations for Human Epidermal Growth Factor 2 Testing in Breast Cancer” guideline. – Expert Consensus Opinion

95.88% agree

4.12% disagree

Final statement will be revised

Draft guideline statements, continued

8. Personnel involved in the quantitative image analysis process should be trained specifically in the use of the technology. – Recommendation

92.78% agree

7.22% disagree

No revision



Draft guideline statements, continued

9. Laboratories should retain at minimum, the regions of an image that were analyzed and the metadata generated in adherence to local requirements and applicable regulations. –Expert Consensus Opinion

83.16% agree

16.84% disagree

No revision



Draft guideline statements, continued

10. A pathologist trained in QIA should oversee the entire process of quantitative image analysis used for clinical practice. – Recommendation

74.47% agree

25.53% disagree

Final statement will be revised

Draft guideline statements, continued

11. A pathologist trained in QIA must visually verify the image, the annotated image analysis output, and the algorithm results prior to finalizing the report. – Recommendation

78.72% agree

21.28% disagree

Final statement will be revised



Next steps

- **Manuscript and Methods Supplement**
 - Expected submission in August, 2017
 - Publication (early online release) estimated in October, 2017

Summary

- QIA has been shown to improve consistency and accuracy of interpretation than manual scoring by pathologists, but has not gained widespread acceptance.
- Lack of a guideline is a practical gap.
- This guideline is to provide recommendations for improving reproducibility, precision, and accuracy in the interpretation of HER2 IHC where QIA is employed.
- This is an evidence-based guideline with public input to ensure the recommendations are clinically sound, practical and implementable.



Acknowledgement

- **CAP Quality Center and member of the Expert Panel and Advisory Panel of the Quantitative Image Analysis Guideline**
- **Digital Pathology Association**
- **Moffitt Cancer Center Analytic Microscopy Core (Joseph Johnson, slides sharing and Jonathan Nguyen, file transferring)**
- **Dr. Liron Pantanowitz, slides sharing**
- **Ms. Nicole Thomas, slides preparation**

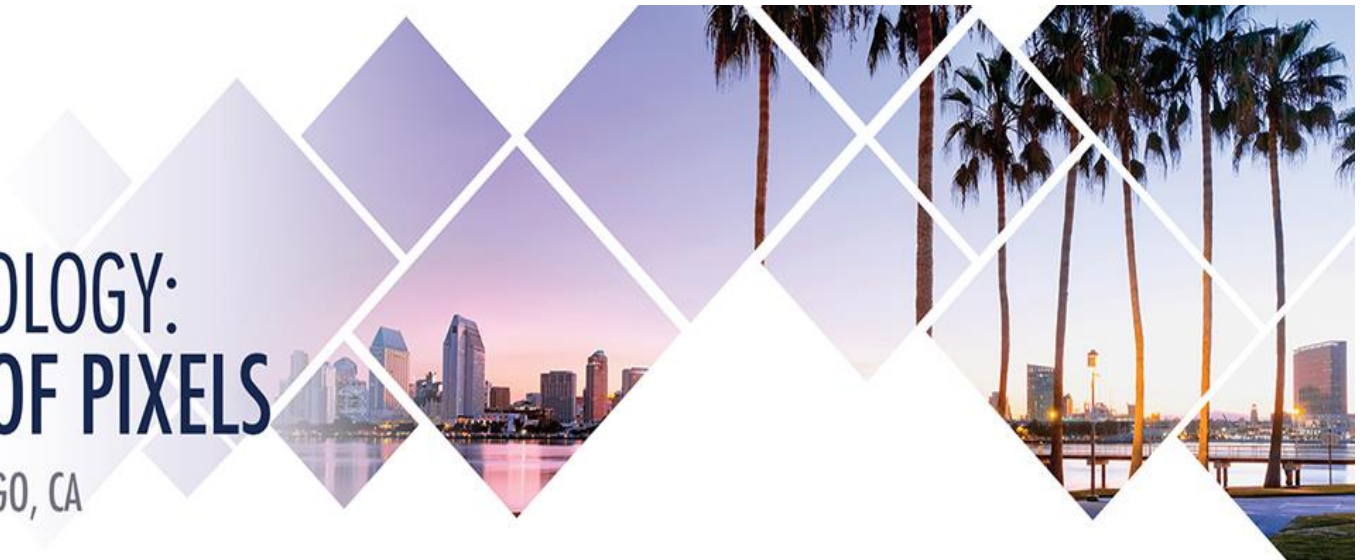


- support digital pathology education initiatives
- define best practices
- influence standards and interfaces
- organize an annual conference that addresses diverse needs within the industry

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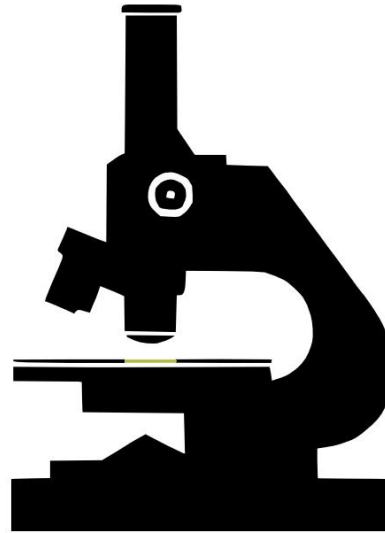
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Questions?

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