Image Analysis in Current Clinical Practice

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OBJECTIVES

• Current benefits & problems with image analysis
• Types of algorithms & image analysis workflow
• Impact of pre-, analytical & post-analytical variables
• Recommendations for widespread adoption

ACCME/Disclosures

Dr. Pantanowitz consults for Omnyx
Introduction

- Image analysis is the “holy grail” of digital pathology
- Promise of computer aided diagnosis (CAD)
- Transition from qualitative (descriptive) to quantitative science
- Precision medicine demands precision diagnostics
- Limited image analysis tools available for routine clinical practice
- Regulatory issues, with most for Research Use Only (RUO)
- CPT code 88361 marginally justifies IHC using image analysis
- In this digital pathology era (WSI), pathologists need to understand the field of image analysis (applications, benefits, limitations)

Benefits of Image Analysis

- Better accuracy (more precise measurements)
- Standardization (more reproducible results)
- Automation (reduce time consumption for pathologists)
- Enhance efficiency (triage cases - weed out negative cases)
- CAD (help pathologists find, diagnose & grade cancer)
- Enable Big Data approach (images for biomarker discovery)

Today’s Obstacles

- Limited practical apps (killer apps needed)
- Lack of availability (iTunes concept needed)
- Interoperability (work on all image formats)
- Reliability of algorithms (measure the right things, variables)
- Black box apps (deep learning, no transparency, no modifications)
- Speed (ROI vs. WSI, automation, computational needs)
- Integrated platforms (seamless digitization, analysis & reporting)
- Workflow disruption (non-billable “extra” work)
- Complex apps (highplex analysis, fluorescence, serial sections, co-registration)
- Not easy to set-up & use (pathologists are not computer scientists)
- Lack of standardization (stain/color variation, ROI approach, validation)

HER2/neu by IHC (IA) vs FISH

Sarode VR et al. Arch Path Lab Med 2015; 139:922-8

![Graph showing comparison between Automated Cellular Imaging System (ACIS) and Ventana Imaging System (VIAS) for HER2/neu analysis.](image)
HER2/neu by IHC (IA) vs FISH

Sarode VR et al. Arch Path Lab Med 2015; 139:922-8

High False+ Rate

Assay standardization
Proper tissue handling
Better IA

Automated Cellular Imaging System (ACIS)
Ventana Imaging System (VIAS)

Types of Algorithms

1. Identify rare events (e.g. screening for microorganisms)
2. Quantitative measurements
   - Score biomarkers (e.g. ER, PR, Her2/neu, Ki67, CD34, PD-L1)
   - Tissue measurements (e.g. mitotic counts, quantify fibrosis/steatosis)
3. Analyze spatial patterns and feature distribution (e.g. neuroscience)
4. Automated grading (of tumors)
5. CAD (e.g. prostate cancer diagnosis, detect Barrett’s esophagus with dysplasia)
6. Discovery of new prognostic markers (e.g. immunoscore, stromal response)
7. Workflow (smart) algorithm (e.g. triage cases, automate downstream steps like LCM)
8. Miscellaneous (research & novel) algorithms (e.g. TMA, 3D image reconstruction)

The Killer App

- Much better than others
- Popular technology
- For users everywhere
- Provides real value

Image Analysis Tools

- Specialized image analysis software platforms
  - Often stand-alone packages
  - Simplify algorithm development (out-of-the-box solutions)
    - e.g. Visiopharm, Definiens, Indica Labs, PerkinElmer
  - WSI scanner vendor companion software
    - e.g. Virtuoso from Roche, Leica’s Genie and Ariol
Image Analysis Workflow

No Optimization

Ex vivo Digitization

Stand-alone Modules
Image Analysis Workflow

Pre-imaging | Imaging | Post-imaging | Clinical outcome

No Optimization | Ex vivo Digitization | Stand-alone Modules | No Feedback

Variables

- Quality of image analysis data can be affected by variables:
  - Pre-analytical (e.g. staining, image acquisition, scanner)
  - Analytical (e.g. algorithm, ROI, heterogeneity, artifacts)
  - Post-analytical (e.g. computer processing)

Pre-Analytical Variables

- Tissue handling (collection, fixation, processing)
- Slide preparation (section thickness, artifacts like folds)
- Stain variation (assay platform, color variation)
- Image acquisition (scanner difference, compression, etc.)
Scanning Variability

WSI Scanner Reproducibility
Keay et al. J Pathol Inform 2013, 4:19

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

Impact of Image Parameters on Results?
- N = 55 patients
- Invasive breast carcinoma
- Serially altered:
  - Brightness, contrast, compression & blurring
- Analyzed same ROI

Image Compression

Acknowledgment: C Liu, Y Huang, G Rohde, H Guo
Impact of Adjusting Parameters on HER2 Scores

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Brightness</th>
<th>Contrast</th>
<th>Compression</th>
<th>Blurring</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 score change</td>
<td>Decreases with increased illumination</td>
<td>Increases with greater contrast</td>
<td>Decreases with higher compression ratio</td>
<td>Decreases with increased blurring</td>
</tr>
<tr>
<td>HER2 score with greatest impact value</td>
<td>Score 1</td>
<td>Score 3</td>
<td>Score 3</td>
<td>Score 3</td>
</tr>
<tr>
<td>Value with least impact on HER2 score</td>
<td>±5%</td>
<td>Gamma: 1</td>
<td>Compression ratio: 200</td>
<td>Radius: 1 pixel</td>
</tr>
</tbody>
</table>

Analytical Variables

- Algorithms may be limited by file format
- Measurements vary with different algorithms
- Analyze regions of interest (ROI) vs. WSI
- Tumor heterogeneity (e.g. “hotspots”)
- Artifacts (tissue folds, air bubbles, crushed tissue, overlapping cells)
- Counting errors (e.g. cells between frames)
- Resolution (e.g. app built at 40x inferior at 20x)
Tissue Artifacts

Slide Artifacts

From M Combrinck

Tumor Heterogeneity

Comparison of Algorithms

Post-Analytical Variables

- Computational demands (downtime)
- Stand-alone systems (workstations, offline use)
- Workflow disruption (error prone, time consuming)

The Ideal Algorithm

Platforms

Stand-alone  Integrated
New CAP Guideline
Quantitative Image Analysis for HER2 IHC

Draft scope: To provide recommendations for improving reproducibility, precision, & accuracy in the interpretation of HER2 immunohistochemical (IHC) where quantitative image analysis (QIA) is employed.

Draft 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 image analysis?
5. How should image analysis be reported?

Panel Members
Expert Panel
- Marilyn Bui, MD, PhD, chair
- Liron Pantanowitz, MD
- Mohamed E. Salama, MD
- Michael Riben, MD
- Elizabeth Chlipala, BS, HTL
- John E Tomaszewski, MD
- Anant Madabhushi, PhD
- Christina Lacchetti, MHSc

Advisory Panel
- M. Elizabeth Hammond, MD
- David Rimm, MD, PhD
- Kenneth J. Bloom, MD
- Richard Levenson, MD

CAP Staff
- Nicole E. Thomas, MPH, CT(ASCP)cm
- Carol Colasacco, SCT(ASCP), MLIS, AHIP

Conclusion
- Image analysis has great potential for clinical pathology practice.
- Algorithms should not just replicate what we do, but do a better job.
- We need more approved algorithms than those being currently used (e.g. breast cancer biomarker quantification). (FDA, CE IVD)
- Widespread adoption requires better integration, simplified workflow, and reimbursement for this work.
- Studies that actually demonstrate that algorithms make a difference clinically are important.
- Need to integrate image-based machine learning with larger (omics) datasets.
Conclusion

• Just because an algorithm gives an answer, doesn't mean it's correct.
• Several variables can cause under/over scoring.
• Pathologist oversight of image analysis is critical.
• “A fool with a tool is still a fool” (Ken Bloom).
• Safe use of image analysis for routine work requires lab calibration, validation and guidelines.
• Unlikely that machine vision will completely replace traditional (morphologic) pathology (but, I’d be happy to eat my words).