Primary Diagnosis and the Regulatory/DICOM Landscape and How it will Impact the use of Digital Images in Pathology

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Outline

1. Review the WSI regulatory timeline in relation to FDA approval
2. Explain the technical and clinical implications of FDA approval for primary diagnosis
3. Describe the pros & cons of DICOM with regard to enterprise imaging
Drivers for Digital Pathology

**Superior Service**
- Consolidation (Core)
- Specialists (Experts)
- Reference Lab

**More Function**
- Telepathology (consultation)
- Tumor Boards
- Peer Review
- Sharing
- Education
- QA

**Better Practice**
- Image Analysis
- Load Balancing
- Easy Archiving

**Better Care**
- Efficiency
- Accuracy
- Quality
- Lower Cost

- Non-inferiority study.
- True difference in major discrepancies between WSI vs. glass slides <4%.
- **Conclusion**: Diagnostic WSI review was **not inferior** to microscope slide review.
# Meta-Analysis: Validation of WSI for Histopathological Diagnosis

Saco A et al. Pathobiology 2016; 83:89-98

<table>
<thead>
<tr>
<th>Pathology Subspecialty</th>
<th>Accuracy (Concordance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical Pathology</td>
<td>75% - 98%</td>
</tr>
<tr>
<td>Breast Pathology</td>
<td>90% - 99%</td>
</tr>
<tr>
<td>Dermatopathology</td>
<td>94% - 100%</td>
</tr>
<tr>
<td>GU Pathology</td>
<td>88% - 90%</td>
</tr>
<tr>
<td>GI Pathology</td>
<td>95%</td>
</tr>
<tr>
<td>GYN Pathology</td>
<td>96%</td>
</tr>
<tr>
<td>Pediatric Pathology</td>
<td>90% - 93%</td>
</tr>
<tr>
<td>Pulmonary Pathology</td>
<td>85% - 100%</td>
</tr>
<tr>
<td>Renal Pathology</td>
<td>84%</td>
</tr>
<tr>
<td>Cytopathology</td>
<td>89% - 97%</td>
</tr>
</tbody>
</table>
Barriers

- Technical
- Regulatory
- Cultural
- Financial
Barriers

- Technical
- Regulatory
- Cultural
- Financial
Regulatory Barriers

Regulators Scanning the Digital Scanners

January 2012
Karen Titus

The authors of this editorial call for urgent resolution and clarification to the murky regulations currently hampering WSI before the digital pathology candle burns out.

Of the FDA’s decision to regulate whole-slide imaging systems as Class III devices, Aperio president Dirk Soenksen says, “They’ve made up their mind.... You’re talking five years at the earliest when someone’s going to get approval.” How broad will Aperio’s submission be? “As broad as FDA allows,” he says.

http://www.captodayonline.com/Archives/0112/0112a_regulators.html
DPA Regulatory Task Force

• Consists of pathologists and several industry members
• Mission is to bring clarity to digital pathology regulations
• Previously centered on regulatory education and awareness
• Constant and collegial discussions with FDA
• Culminated in FDA recommendation that:
  – Industry follow the de novo regulatory pathway when pursuing approval of WSI for primary diagnosis
De Novo Classification

• Under an alternate *de novo* pathway if there is no legally marketed predicate device manufacturers may submit a direct *de novo* without a preceding 510(k)

• If *de novo* is granted for a specific device it:
  – May be “downgraded” (class II)
  – Serve as a predicate device for future 510(k) submissions
  – Can be immediately marketed
  – Class II devices are easier to modify
## WSI Regulatory Timeline

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>Commercial WSI devices</td>
<td>Digital Pathology trend started</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Validation of diagnostic applications</td>
</tr>
<tr>
<td>2009</td>
<td>FDA advisory panel</td>
<td>High risk (class III) device</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-clinical use cases expanded</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-US regulatory approval</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DPA &amp; select vendor discussions with FDA</td>
</tr>
<tr>
<td>2015</td>
<td>TPA* guideline</td>
<td>Assures manufacturers follow same standards</td>
</tr>
<tr>
<td>2017</td>
<td>FDA approval of WSI</td>
<td>For primary diagnosis in surgical pathology</td>
</tr>
</tbody>
</table>

*TPA = Technical Performance Assessment
FDA allows marketing of first whole slide imaging system for digital pathology

For Immediate Release
April 12, 2017

The U.S. Food and Drug Administration today permitted marketing of the Philips IntelliSite Pathology Solution (PIPS), the first whole slide imaging (WSI) system that allows for review and interpretation of digital surgical pathology slides prepared from biopsied tissue. This is the first time the FDA has permitted the marketing of a WSI system for these purposes.

"The system enables pathologists to read tissue slides digitally in order to make diagnoses, rather than looking directly at a tissue sample mounted on a glass slide..."
Clinical Trial

Analytical testing (assess device precision):
• Demonstrate precision, instrument-to-instrument reproducibility, and reader-to-reader reproducibility using morphological features critical to diagnosis or a differential diagnosis

Clinical study (assess system accuracy):
• Demonstrate that making a primary diagnosis with a WSI system is no non-inferior to optical microscopy using glass slides and a conventional light microscope
• Although 2000 mixed cases with 16,000 reads typically included, these studies are not really powered to test every disease
Manual Digital is non-inferior to Manual Optical for primary diagnosis in surgical pathology.
A: Image acquisition (WSI scanner)
B: Workstation (WSI display)
WSI System Implication

• Vendors are required to submit their manufactured device to the FDA as one system that encompasses the entire pixel pathway
• Technical and clinical performance of these combined subsystems in the imaging chain needs to be validated as a whole (scanner + display + IMS)
• FDA cleared system for its particular intended use is a ‘locked down’ device
• Coupling to any other subsystem does not ensure the safety and effectiveness for their intended use
• Combined set-up is referred to as a ‘closed’ system
• Labeling limitations specify that for uncertainty defer cases to conventional microscopy
FDA Approval Implications

- Following the first *de novo* reclassification, subsequent applicants will only need 510(k) clearance
- The first authorized *de novo* WSI predicate device will pave the path to show substantial equivalence for other devices
- Obtaining FDA-approval is an expensive endeavor
- Regulatory challenge remains to evaluate newer devices, possibly using tools like a phantom
- CLIA issues need to be specified when remotely diagnosing cases off site (e.g. pathologists at home or travelling)
- With approval to perform primary diagnosis using WSI, what does the business case look like?
Financial Barriers

• Expenses (direct & indirect):
  – WSI system
  – Workstations
  – IT resources
  – Data storage
  – Maintenance fees
  – Facility changes
  – Personnel
  – etc.
In a nutshell...

- Pathology and radiology aren’t equal, and the arguments for radiology’s digital transition don’t necessarily hold true for pathology’s.
- Digital pathology holds promise for image analysis and quality assessment, but other applications don’t make financial sense – yet.
Cost-Benefit Analysis

Griffin & Treanor. Histopathology. 2017; 70:134-145
Making the Move to 100 Percent Digital

LabPON is the first laboratory in the world to fully digitize its histopathology services — but how did they approach it? And has it paid off?

By Alexi Baidoshvili

Laboratory for Pathology East Netherlands

How has Digital Pathology paid off?

Business case:

– Logistical advantages
  • Streamlined processes
  • Reduced TAT

– Save $ with less staff

– Connected teams
  • Remote communication
  • Collaboration

– Diagnostic accuracy

– Dataset for deep learning

“Most people think that the biggest investment will be the scanner or the software. That’s not true. One of the biggest investments is the transition period.”
Cultural Barriers

• WSI performance is just not ready yet?
• I was trained using glass slides, not WSI?
• I am unfamiliar with “digital artifacts”.
• Using WSI is disruptive to my workflow.
• Will I have to sign out more cases now?
• Will WSI scanners eventually replace me?
• Will audit trails record what I looked at?
• Who is liable if I misdiagnose a WSI case?
What about Workflow?

Legacy Workflow:
- Accessioning / Grossing / Histology
  - Slide Creation
    - Enter Patient
    - Enter Case
    - Enter Slides
    - Stain and coverslip slides
  - Case Assembly
    - Sort slides to Cases
  - Quality Check
    - Review slide quality
    - Review case quality
  - Transport

Digital Workflow:
- Case Entry
  - Enter Patient
  - Enter Case
  - Enter Slides
- Imaging
  - Load slides
    - Generate images
    - Unload slides
- Case Assembly
  - Sort images to cases
- Quality Check
  - Review slide quality
    - Review image quality
  - Review case quality

Pathologist
# Traditional vs. Legacy Workflow

<table>
<thead>
<tr>
<th>Legacy workflow</th>
<th>Digital workflow</th>
<th>Workload of digital workflow</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accessioning</td>
<td>Accessioning</td>
<td>Same</td>
</tr>
<tr>
<td>Grossing</td>
<td>Grossing</td>
<td>Same</td>
</tr>
<tr>
<td>Histology slide creation</td>
<td>Histology slide creation</td>
<td>Same</td>
</tr>
<tr>
<td></td>
<td>Case validation in digital solution</td>
<td>More: potential duplicate step</td>
</tr>
<tr>
<td></td>
<td>Issue management/calibration</td>
<td>More: monitor against errors</td>
</tr>
<tr>
<td></td>
<td>Scanning/imaging tasks</td>
<td>More: loading/unloading slides</td>
</tr>
<tr>
<td>Case assembly (physical)</td>
<td>Case assembly (digital)</td>
<td>Equivalent (but less error prone)</td>
</tr>
<tr>
<td>Quality check (physical)</td>
<td>Quality check (digital)</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Delivery (physical)</td>
<td>Delivery (digital)</td>
<td>Less</td>
</tr>
</tbody>
</table>

Digital pathology in the diagnostic setting: beyond technology into best practice and service management

Chee Leong Cheng,¹ Puay Hoon Tan²

J Clin Pathol. 2017; 70:454-457
Enterprise Imaging

• Many institutions are implementing Enterprise Imaging
  – Include all clinical images to enhance the EHR
• Pathology is the least connected service line
  – We are at risk of becoming invisible
  – May impact allocating resources for WSI
• WSI burdens current enterprise imaging platforms
  – Are new VNAs agnostic enough for WSI?
  – Is DICOM a suitable imaging solution?
  – Are other unique solutions required?
• How will DICOM use impact the WSI regulatory process?
• Digital Imaging & Communications in Medicine
• Primarily Radiology imaging standard
• Promotes interoperability & exchange
• Working Group 26 (WG26) deals with Pathology
• Supplements dedicated to Pathology
  122 (specimen model) – related to IHE
  145 (WSI applicable) – tiled organization

IHE = Integrating the Healthcare Enterprise

Various Formats

SVS

NDPI

DICOM Conversion

PACS

HL7

LIS

MULTI-MODALITY
PATHOLOGY IMAGES
RADIOLOGY IMAGES

WADO

HTTP

Web Access to DICOM Objects
Is this the optimal way to tag WSI with the APLIS?
Will DICOM conversion change images (quality, compression ratios, annotations, z-levels)?
DICOM Conversion

WSI

Automated?
DICOM Viewer Performance

Images courtesy of Matthew Hanna
Where will be the best step to perform image analysis?
Take Home Message

- Regulatory path for digital pathology in the USA has crystalized in recent years, culminating in the FDA approval of the first WSI system for primary diagnosis in surgical pathology.
- That means WSI is no longer inferior to the light microscope!
- What about FDA approval for FS, cytology and hematology, so that labs can go “fully digital”?
- FDA approval and existing roadmap will hopefully encourage more manufacturers to enter the digital pathology field.
- WSI devices and systems will change as technology evolves, so streamlining their regulatory approval will be helpful.
- Now that the FDA regulatory hurdle seems to be removed, ROI will “still” be the biggest obstacle to surmount.
- Going digital sets the stage for the next wave of digital pathology, which is Computational Pathology (C-Path).
- Next challenge will be to resolve regulatory issues related to:
  - Use of DICOM or a related standard image file format
  - Open systems that facilitate image algorithms
  - Artificial intelligence that employs deep learning
Q&A

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