Digital Pathology - Are We There Yet?

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Disclosures

• “Employee” Of The US Federal Government
• Incoming Editor-in-Chief, *Journal of Histochemistry & Cytochemistry*, Effective January 1, 2016
• Instigator, Ad Hoc Committee On WSI, Association For Pathology Informatics
• Co-Lead, WSI Working Group
• Center For Devise & Radiological Health, Food & Drug Administration
  – Consultant, Hematology & Pathology Devices Panel
  – Collaborator, Critical Path Initiative On WSI
• Clinical and Laboratory Standards Institute
  – Member, Consensus Committee On Immunology and Ligand Assays
  – Chairholder, Subcommittee On Quality Assurance For Immunohistochemical Procedures
Lofty Goals Meet Practical Issues

Digital Pathology Has Been Promised To Bring Benefits To Patient Care, Absent Facts
Digital Pathology
Not In The Clinic Yet

• In The USA, Subject To Regulation By FDA
  – “Not Substantially Equivalent”
  – FDA Is Reactive, Not Proactive
    • Action Triggered By A Manufacturer Submission
    • Intended Use

• Self-Validation Pathway Requires Assembly By User & Validation By User
  – One User Attempted & Documented Failure
  – Other Users Were Scared Off By FDA
  – Currently Being Self-Validated For Vet-Path
What is a medical device?

- 5 MP digital camera
- Captures still images or videos
- LCD display at 320 x 240 resolution
- Three objectives with magnification from 40X-400X
- 2 built-in light sources
- 128 MB memory

A clinical intended use would make this a medical device!

Safety

Reasonable assurance, based on valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks

21 CFR 860.7(d)(1)

Effectiveness

Reasonable assurance, based on valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended use and conditions of use, when accompanied by adequate directions for use and warning against unsafe use, will provide clinically significant results

21 CFR 860.7(e)(1)

What does this mean?

- Microscope just one component of the system
- Image acquisition, processing and display new technology for this intended use
- Diagnostic for neoplastic disease
- WSI systems cannot be considered Class I exempt
WSI In The Clinic Today

What The FDA Is Silent About

• Consultation

• Frozen Section Diagnosis

• Logic: There Is Always A Review Of The Permanent Slides Under An Optimal Microscope To Ensure The Existing Standard Of Care
Getting This Right The First Time

*The FDA Rarely Allows A Muligan*

- Ultimately The Adoption Of WSI Does Not Depend On The Regulatory Issues, But A *Functional Use-Plan*

- Using A Real Clinical Paradigm
  - Real Slides, Real Images
    - Collect Based On Real World Setting
  - Define Reading Environment
  - Define Washout Period
Why Does The FDA’s Action Matter In Europe?

• RapidlyExpandedKnowledge-base
  – In Short Order Many Groups Will Move Forward To *RealWorld* Digital Pathology Workflow

• Cross-Connecting Approvals
  – Approval Is Not Just Regulatory, But Payor Driven, For Which US Experience Is A Factor

• Money
  – Substantial Investment Will Occur Based On Regulatory Approval

*In The US, All Money Is Green!*
History Of Whole Slide Imaging

• Pre-2010 – Wow, This Is Neat!
• 2012 – Pornography For Pathologist
  – All They Do Is Look At It
• 2015 – Internet Porn
  – All Around & Pretending Not To Use/Hoping Not To Get Caught
• 2016 (?) - Playboy Period
  – Limited Use Likely, Infatuation
• 2020 – Utility Comes To Pathology
  – Application Outside Using A Screen To Replicate A Microscope
Innovator Or Adopter

• Success In Digital Pathology Will Be Based On Embracing WSI To Solve Problems / Advance Patient Care
  – Pathologist Driven, Based On Need

• Application Of WSI To Current Pathology Paradigm Is Not A Viable Economic Model / Maintain The Current Standard Of Care
  – A Solution In Search Of A Problem
Cost Analysis Of Digital Pathology

*Current Practice Paradigm*

- **Negative Economic Factors**
  - Cost Of Getting Slide To Workstation
  - Rate Of Pathologist Review

- **Neutral Cost Factors**
  - Consultation Cost
  - Reporting Cost

- **Positive Economic Factors**
  - Organizing & Tracking Slides

*Current Net Cost Impact: Negative*
What Will Drive The Adoption Of Digital Pathology?

• Efficiency
  – When A Pathologist Can Sign Out More Cases By WSI Than A Microscope

• Cost Effectiveness
  – When The Cost Of Presenting Cases To The Pathologist Is Offset By the Improved Efficiency

• Work Force Needs
  – Total Available Workforce
  – Specialized Skills Workforce
When Will Digital Pathology Become A Necessity?

- **Imagers**
  - Faster & More Reliable, *Nearly There*

- **Networks, Servers & Storage**
  - Very Costly To Implement, *Currently Lacking*

- **Cockpit, Software & Workflow**
  - Many Details To Refine, But *Functional*

- **Training**
  - A Big *Unknown*

- **Utility**
  - Absolutely *Missing*
Impetus To Adopt Digital Pathology

• Implementation Is A Economic Decision

• Decision Is Not Driven By The Sign-Out Pathologist

• Decision Is Driven By:
  – Laboratory Director Chairman
  – CTO Of Hospital Or Laboratory Organization
Better, Faster, Cheaper

- Motto For Biomarker Development

- *As Good As Will Not Succeed In A Cost-Constrained Environment*
Why Do We Need Digital Pathology?

- Interpretation Of Histomorphology To Render A Diagnosis Is Not Going Away
  - Cost / Speed / Information Advantage
- Integration Of “Individualized Medicine” Requires New Tools
- Evolution Of Pathology Practice
  - Reduced Number Of New Pathologist
  - Increased Demand For Pathology Services
  - Greater Specialization
Necessity Is The Mother Of Invention

- Proverb

A Business Plan Is The Father

- S M Hewitt

• Regulators Are Vilified, But Not The Real Barrier

• Digital Pathology Needs A Compelling Application To Drive Adoption
Maybe Steve Jobs Was Right

…people don't know what they want until you show it to them.

- BusinessWeek (25 May 1998)
  - Pathologists Are Limited In Their Thinking About How Pathology Must Be Performed

Why join the Navy . . . if you can be a pirate?

- Paraphrasing “Young Guns”
  - Pathologists & Diagnostic Companies Are Focused On Security, Not Innovation
  - Beware Of The Pirate In A Naval Uniform!
    - Innovation Requires A Deep Knowledge Of The Topic
    - As Noted By Commander Hewitt
Change Is Constant
Evolution Vs Revolution

- **Evolution**
  - Sequential
  - Anticipated Benefit
    - Dead Ends
- **Revolution**
  - Disruptive Change
  - Paradigm Shift
  - Rare
    - Downstream Impact Can Not Be Predicted

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**The Railroad Was Revolutionary**
- Distance Traveled Per Day
- Persons Per Vehicle

**Digital Pathology Is NOT Revolutionary (Yet)**
- View A Slide
- Current Diagnostic Features Used
Disruptive Vs Evolutionary

• Digital Pathology Is Unlikely To Be Truly Disruptive
  – Displacement Of The Pathologist?
• Digital Pathology Must Drive Evolution
  – Enable Task Not Possible With The Microscope
  – Expand The “Depth” Of Diagnosis
    • Beyond “Image Analysis”
Digital Pathology Will Transform The Pathology Environment

- Pathologist Work Space
- Histology Workspace
- Resource Demands Of Hospital
- Pre-analytic Controls
What Will A Surgical Pathologist’s Day Look Like In 2039?

• What Did It Look Like In 1989?

More Specialized       More Panels
More Volume            More Molecular
More Grading           Less Staff
More Integration
Utility In Whole Slide Imaging

*Holistic Glomerular Evaluation*

**Microscope**: Estimation, Assumes Different Lesions Are Different Glomeruli

**WSI**: A Holistic Understanding Of The Glomeruli & Nature Of Lesion Across The Glomeruli
Estimated Vs Annotated

• Linear Error In Estimation
  – Glomeruli
  – Sclerotic Glomeruli

Think Of The Glomerulus As The Denominator Of All Measurements In GN
Comprehensive Evaluation & Scoring Of Glomeruli

• Current Paradigm Of Evaluation Is Flawed
  – Poor Correlation Of Histopathology & ESRD
• A “Holistic Glomerular Evaluation” Provides Quantitative Data Concerning Histopathology
  – Rethinking Significance Of Lesions
  – Can Not Generalize To Specific Lesions
  – Follow On Study (Cure GN) Is Already Collecting Data
• Next Step – Glom Finder
  – Automated Annotation Of Glomeruli
“Black Box” Image Analysis

• Current IA Approach
  – FDA 510K Approved Algorithms
  – Mimics A Pathologist Manual Scoring
  – Reimbursement Driven

• Enabled IA Via FDA Or CLIA
  – Approach Outlined In CLSI IL28A2 (IHC)
  – Total Test Approach
  – Scoring That A Pathologist Can Not Perform
  – Tuned Relationship Of Score To Outcome
  – Supports A Different Reimbursement Model
Multiplex Immunohistochemistry & Multiplex Interpretation

• Current Approach:
  – Interpretation Of Markers One By One
  – Qualitative Scores
  – Does Not Account For Pathways
  – Outcome Analysis Complicated

• Goal:
  – Multiple Markers Generate One Outcome
  – Quantitative Scoring
  – Models Pathways
Current Paradigm

Kitano H et al. J Histochem Cytochem 2014;62:335-346
Ratiometric Approach

Kitano H et al. J Histochem Cytochem 2014;62:335-346
Computer Aided Diagnosis
AKA “Look Here!”

• Algorithms To Identify Features & Flag For Human Review
  – Take Out The Tedium

• Complex Validation Structure
  – Highly Supported By FDA

• Only Approach Envisioned That Will Substantially Improve Pathologist Efficiency
Back To The Economic Model

• Greater Value (Better)
  – More Precise Information That Improves Predictive Power Of Pathology

• Efficient Use Of Time (Faster / Cheaper)
  – Focused Workload On Task That Require The Skill Set Of A Pathologist (Decision Making)
  – Remove The Dangerous Tedium Of Review Of Negative Information
Enabling The Future Of Digital Pathology

- **Great Ideas Focused On Big Problems**
  - Opportunity For Disruptive Approaches
- **Hard Work**
  - Requires Extensive R&D
  - Requires Even More Validation
- **Money**
  - Great Ideas & Hard Work Requires Investment To Bring Products To Market
  - Think Drug Development Scale Investments
The Players Enabling Digital Pathology

- **Pathologist**
  - Provide The Ideas

- **Pathology Organizations**
  - Provide The Context & Interchange Platform

- **Regulators**
  - Provides The Guidance Of Approach

- **Vendors**
  - Funding & Product
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