Integrating The Digital Microscope Into Clinical Practice

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Disclosure

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  – Former Co-Chairman, Subcommittee On Quality Assurance For Immunohistochemical Procedures
Diagnostic Histopathology

• Rendering A Diagnosis
  – Gross Examination
  – Microscopic Examination

• “Diagnosis”
  – Identification Of The Disease Entity

• “Prognosis”
  – Additional Information That Guides Therapy
Making A Histopathology Diagnosis

• Intellectual
  – Cognition
  – Fund Of Knowledge

• Visual
  – Human Factors
    • What Is The Impact Of The Environment On The Pathologist To Appreciate All The Factors Involved in A Complete Diagnosis
  – Image Factors
    • Is The Digital Image Equal To The Diagnostic Microscope Image

• Workflow
  – Can The Pathologist Perform The Task Without Negative Impact To Productivity?
Basic Principle Of A Microscope

Figure 5

Figure 6

Virtual Image

Sample Holder

Sample Translator

Focus Knob

Lens

Simple Magnifying Lens

Object

Retina
Unique Experiences Of Microscopes & Telescopes

- A Virtual Image Is Perceived
- Quality Of Image Is Defined By Optics
- Illumination Is A Unique Feature Of Microscopes
  - Optics Of Illumination Path
  - Light Source
  - Visualization Into A Light Source

- Immersive Environment
Ansel Adams
Cameras
Photography

- Large Format- Film
  - Image Visualized On Ground Glass
  - Composition
  - Focus
  - Complete Control Of Image Parameters
  - WYSIWYG
    - Minimal Or No Enlargement

- Digital – Point & Shoot
  - Image Displayed On A Miniature Screen
  - “Snapshot”
  - Autofocus
  - No Control Of Image Parameters
  - Viewing Environment Variable
    - TV, Digital Frame, Computer Screen
Microscope / Imaging Device
Microscopy

- Optical Microscope
  - Immersive Viewing Environment
    - Surroundings Obscured
    - Fixed Gaze
    - Controls Do Not Require Averting Gaze
  - User Controlled Image
    - “Composition”
    - User Control Of Illumination & Focus

- Digital Microscope
  - Viewing A Screen
    - Surrounding Environment
    - Ocular Activity
    - Visualize Controls
  - Predefined Image
    - Fixed Image
    - Fixed Focus
    - Limited Control Of Illumination
Pathology & Radiology

Very Different

– Observation
  • Of The Object Vs Image Of An Object

– Approaches
  • Sampling Of The Object Vs Multiple Image Of The Object

– Language
  • Look, Review, Examine Vs Read

Collision Course

– Spectroscopy
– *In Vivo* Microscopy (IVM)
Does Imaging In Cervical Cytology Provide A Framework Forward?

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<th>Diagnostic Pathology</th>
<th>Cervical Cytology</th>
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<td>• Multiple Organs</td>
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<tr>
<td>• Multiple Diagnostic Axis</td>
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<tr>
<td>• Histomorphology</td>
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<td>• Reflex To Microscope</td>
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Quality Is Everything

Quality Remains Subjective

• Tissue Quality
  – Fixation & Processing
  – Sectioning & Staining
  – Coverslipping

• Image Quality
  – Instrument
  – Software
  – Viewing Environment
A Picture Is Worth A 1000 Words

• Must Define What Is Being Observed
• Must Have A Schema Of What Information Is To Be Obtained
• Fit-For-Purpose Model
• Intended Use
  – Microscopic Examination As A Diagnostic Process

Similar Concept
Different Approach
Ends-Means-Goals
Philosophical Model Of Scientific Process
Original Purpose, Intermediate Use, Final Role

Fit-For-Purpose
Diagnostic Paradigm
Matching The Process To The Test

Intended Use
Regulatory Concept
Goal The Object Is Intended To Accomplish
Digital Microscopy

• Ends-Means-Goals
  – Ends: Digital Microscope Image
  – Means: Enablement Of High-Throughput Imaging, Image Analysis & Image Databases
  – Goals: Digital Diagnostic Pathology

• Fit-For-Purpose
  – Design Of A System To Replicate Manual Microscopy

• Intended Use
  – Development Of An Imaging System Capable Of Allowing A Pathologist To Generate A Diagnosis Equal To Manual Microscopy
Byproducts Of Imaging

• Telepathology
  – Consultative
  – After-hours/Remote Diagnosis

• Electronic Archives
  – Panel Review
    • Classification Consensus
  – Teaching
  – Meta-Analysis
Unique Issues In Evaluation Of Digital Diagnostic Microscopy

- Clinical Use
  - Every User Is A Unique Beast

- Antecedent Status Of Microscope
  - FDA Has No Oversight Over The Diagnostic Microscope
    - Evolution Of Microscopes
    - Diversity Of Microscopes In Clinical Use

- Lack Of Calibrators
  - Objects
  - Contrast Agents

- Metrics Of Equivalence
  - Diagnosis Is Not Based On Examination Of A Single Image
    - Multiple Sections/Images
    - Adjunctive Stains
Breaking Down An Image Into Information

Recognition    Interpretation    Qualification
Histopathology

• Histomorphology
  – What Cells?

• Cytomorphology
  – Where In The Cell?

• Immunomorphology
  – Where Are Specific Proteins?
“Stains”

- **Contrast Agents**
  - Binding Based On A Chemical Reaction/Property
  - Direct Deposition
- **Immuno-recognition**
  - Antibody Binds Epitope
  - Antibody Is Detected By Means Of A Label

- **Stains**
  - Absorption Of Color
  - Obey Beer-Lambert Law
    - Concentration Correlates With Absorption
- **Light Scattering**
  - DAB
  - Silver Impregnations
Pathologic “Diagnosis”

- **Diagnosis**
  - Definition Of A Tissue-based Disease Process
  - Presence/Localization Of Disease Process
- **Decision Making (Prognosis/Prediction)**
  - Correlation Of A Finding With Action/Response
    - Cyto-/Histo- Morphology
    - Immunohistochemistry
Diagnostic Microscopy

• “You Either Know It, Or You Don’t, The Image Won’t Make A Difference”
  – Given An Adequate Image, Modality Does Not Matter

• “May I Have The Slides Please, I Would Like To Study This”
  – The Experience Of Using A Microscope Is Essential For Reaching A Diagnosis
  – Unperceivable Elements Of Microscopy Are Important For Some Diagnosis
Diagnosis

- The Constellation Of Histomorphology & Cytomorphology Based On Pattern Recognition
- The Human Eye & Mind Are Terrifyingly Accurately Fast Accurate & Fast
- Immunohistochemistry Improves Discrimination Or Provides Verification Of The Findings
“Decision Making” Microscopy

• Is It Malignant?
  – What Tumor Is It?

• How Bad Is It?
  – What Is Its Molecular Phenotype?

• What Is The Status Of The Margins?

• Is There:
  – Lymphovascular Invasion?
  – Lymph Node Metastasis?
Prognosis & Prediction Of Response

• Histopathology
  – Interpretation Of The Histomorphology & Cytomorphology To Predict Behavior
    • Well, Moderately, Poorly Differentiated
    • Sarcomatoid Features
      – Correlation With P53 Mutations In Wilms Tumor

• Immunopathology
  – Calibrated Molecular Assay
  – Quantified Presence Of A Molecule Correlated With An Outcome
When Is Good, Good Enough?
Validation Of Digital Diagnostic Pathology

• 95% Concordance
  – 1 in 20 Error
• 99% Concordance
  – 1 in 100 Error
• Can This Be Weighted For Different Kinds Of Diagnosis?
  – Maligant
  – Rare

• Suggested Approaches:
  – By Stain
  – By Organ System
  – By Disease Process

• Potential Advancements:
  – 40X Imaging
  – Z-stack Imaging
When Is Good, Good Enough?
Validation Of Digital Diagnostic Pathology

• You Either Know It Or You Don’t
• What Are The Dark-spaces Of Microscopy - Where It Matters?
  – Lymphocytes
  – Cytology
  – Liver
    • Feathery Degeneration Of Hepatocytes
  – Kidney
    • Isovolumetric Vacuolization
Is A Digital Image Equal To An Image Observed By A Human At The Microscope?

• Focus
• Illumination Control
  – Fixed Vs Variable Illumination
• Condenser Control
  – DAB & Silver Stains Scatter Light
  – Stains Absorb Light (Beer’s Law)
  – Kohler Illumination Generates A Higher Contrast Image Than Critical Illumination
Fit-For-Purpose Approach To Qualifying Digital Diagnostic Microscopy

• Approximation To:
  – Existing “Pre-Analytic” Elements
    • Slide & Stain
  – Existing “User-Defined” Elements
    • Focus & Illumination

• Software Solutions
  – Color & Illumination Control

• Hardware Solutions
  – Focus
  – Absorption Vs Scattering
Intended Use Approach To Qualifying Digital Diagnostic Microscopy

• Safety & Efficacy

• Can The Pathologist Obtain The Full Range Of Diagnosis For The Specimen
  – Essentially Impossible To Define
  – Restriction Disrupts Practice
  – Broad Validation Is Functionally Required
Total Test & Digital Diagnostic Pathology

• Who Defines The Specifications Of What Is Imaged?
  – Pathologist / Lab Director
    • Instrument Must Be Able To Image A Broad Spectrum Of Slide Features & Staining Conditions
      – How Would This Spectrum Of Conditions Be Defined & Tested?
  – Manufacturer Of Imaging System
    • Pathologist Must Be Able To Interpret Slides & Stains Prepared To The Specification Of The Manufacturer

• Must Samples Be Sufficient For Both Manual & Digital Microscopic Interpretation?
Safety In The Context Of Diagnostic Test

**Diagnostic Efficacy**

- Is The Treatment Of Patients Impacted By The Use Of This Test?
  - Is The Result Equal, Better Or Worse?

- “Diagnostic Drift”
  - Does A Change In *Technology* Have Long Term Consequences In The Quality Of Care?
Extending The Diagnostic Experience

Adding Tools To Microscopic Interpretation

• Special Skills
  – Pattern Recognition
  – Data Integration

• Over-rated Skills
  – Quantification Of Immunopathology

• Desired Improvements
  – Rare Event Detection
  – Tools To Ensure Entirety Of Material Is Reviewed
Computer-aided Image Analysis

- Histomorphology
  - Toxicology
- Cytomorphology
  - Cervical Cytology
- Immunohistochemistry
  - Quantification
    - Counting
    - Intensity
Digital Imaging Moving Forward

• Challenges
  – Training & Education
  – Technology Standardization/Calibration

• Promises
  – An Integrated Computerized Diagnostic Platform
  – Imaging Tools To Identify/Quantify/Classify

• Unknown
  – Action By The FDA
  – Retention Of Digital Images As Diagnostic Medium
  – Infrastructure
A Picture Is Worth A 1000 Words

• Today - Application Of A Fit-For-Purpose Approach
  – Digital Pathology Replicates The Manual Microscope

• Tomorrow – Intended Use Approach
  – Digital Pathology Adds Tools For Diagnosis, Prognosis, Prediction Of Response
How Does Digital Imaging Become Economically Viable?

• Cost Drops
  – Can Not Drop Sufficiently
  – Add-On Technology

• Economies Of Scale
  – Makes The Pathologist More Productive

• Regulatory Guidance/Imperative
  – Requires Changes To Reimbursement Model

• Revenue Generating
  – Demonstrates A Benefit To Patient Care
Conclusions

• Digital Pathology Is Not About Replicating The Microscope Experience, But Achieving An Equal Or Greater Diagnostic Benefit
  – Current Technology Does Not Replicate The Microscope
    • Numerous Features Can Be Enabled In The Digital Workflow To Provide Visualization Not Currently Feasible
  – Total Test Paradigm Would Enable Optimized “Staining” Approaches To Access The Diagnostic Features
    • May Prevent These Slides From Being Reviewed Outside Of Digital Imaging / Different Platforms
Conclusions

• Equivalency Will Be Measured At The Diagnostic Level, Not The Histologic Level
  – Diagnosis Is Based In Pattern
    • Assisted Pattern / Event Detection
  – Quantification Is-
    • Easily Matched By Non-Pathologist
    • Easily Exceeded By Software
Final Thoughts

• Current Digital Image Technology Is Not Equivalent To A Microscope At This Time

• Defining Diagnostic Equivalency Is Challenging

• Opportunity For CAD In This Space

• Introduction Of Reflex Manual Microscopy Based On Predefined Metric
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