Creation of a Pixel Pipeline and The Need for Image Analysis To Improve Workflow and Increase Adoption of Digital Pathology for Clinical Use
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Disclosure of Relevant Financial Relationships
Dr. Evans declares he has no conflict(s) of interest to disclose.

Overview
- WSI telepathology at University Health Network
  - how we started
  - how we have expanded our use of the technology - based on whole slide imaging (WSI)
  - enabling sub-specialty pathology
- How image analysis would benefit a department in which WSI has been used for diagnostic work since 2006.

Do UHN pathologists still use microscopes?
- Yes
  - 80% is done with glass slides and a microscope
  - 20% of my service work is done by WSI
- WSI is used for clinical purposes on a regular basis by less than half of UHN pathologists
  - new applications are slowly coming online
- We are living the adoption challenges!
Value Proposition of Telepathology at UHN

- Full departmental consolidation at TGH in early 2006
- No regular on-site pathologist at TWH as of 2004

TWH Frozen Sections: Challenges
- Single pathologist traveling from TGH to TWH
- Inefficient - traveling and waiting
- Disruptive to regular workflow at TGH
- Delays in regular sign-out affecting other UHN patients
- No consultation on difficult cases
- Potential to affect TWH surgical patients

Facilitating Multi-Site Sub-Specialty Pathology
- Move slides?
- Move pathologists?
- Telepathology?
- Expanding list of clinical applications at UHN:
  - Frozen sections (2004-present)
  - Consultation - local and international
  - Supporting transplant pathology programs
  - Quality assurance
  - Primary diagnosis (2012 - present)

TWH Robotic System: November 2004-October 2006
- 350 frozen sections
- Slow (~10 minutes/slide)

TWH Whole-Slide Imaging: October 2006-Present
- >4000 frozen sections/3500 patients
- >90% from neurosurgery
- 0-2% discrepancy rate
- 14-16 minute total turnaround time
- <1-5% deferral rate
- 2 pathologists review all deferrals

Intra-Operative Consultations: Work Flow for Single Block Frozen Sections
- 10-12 minutes
- 1-3 minutes
Why Has This Worked at UHN?

- Started with a single clearly-defined application
  - neurosurgical frozen sections
- Uncomplicated frozen section work flow
- Long development period with due diligence
  - 18 months from initial meetings to go-live
  - time to build confidence and trust
- Implementation team
- Standard Operating Procedure (SOP)

Image Quality: The Importance of Good Histology

Poor slides = Poor image quality

20x scans – ask for 40x when necessary

Episodes of Mid-Case System Failure

- 11 episodes (0.2% of cases to date) requiring a pathologist to go to TWH
  - Small pale pieces of tissue (x2)
  - Excess mounting media (x1)
  - Burned out light bulb (x1)
  - Calibration errors (x5)
    - faded H&E test slides
    - aging light bulb

System Failure: Plan B

- Pathologist informs surgeon and goes to TWH if issue not resolved in 5 minutes
- A second pathologist works with the TWH histotechnologist in case the issue is resolved.

Frozen Section Telepathology: Remote Sites
Timmins and District Hospital (TADH)

- General community hospital
- > 10,000 surgical pathology accessions/year
- UHN assumed medical leadership of TADH labs in 2006
- Pathologist staffing
  - 1 on-site at any given time
  - 1 week per month – no on-site pathologist
  - 150 frozen sections per year
  - Tissue identification/intra-operative staging

Kingston General Hospital (Queen’s University)

- Academic pathology department
- Neuropathology frozen sections (1-5 per week)
- 1 staff neuropathologist to cover all frozen sections
- Need for back-up during vacation, CME leave, etc
- UHN pathologists given limited consulting privileges
  - remote access to EPR/diagnostic imaging
  - remote access to KGH LIS

Transplant Telepathology at UHN

- Orthotopic liver transplant program
- ~ 600 post-transplant biopsies/year
  - 2 – 5 urgent biopsies/week (same day or next morning results)

Practical Issues:
- 2 liver pathologists
- Both can be off-site at once - annual USCAP meeting
- Need for continuity of highly-specialized reporting

Primary Diagnosis By WSI

- First diagnosis made on scanned slide images (H&E, special stains/immunohistochemistry)
- Diagnostic information becomes part of the patient record
- Treatment decisions to be made based on this information

Digital Pathology Guidelines

- American Telemedicine Association (2014)
- Royal College of Pathologists in Britain (2013)
- Canadian Association of Pathologists (2013)
- College of American Pathologists WSI Validation (2013)
- Others (Japan 2005)

Self-Validation Studies: What is Learned?

- WSI can be used for making accurate and complete diagnoses
- What needs to be optimized in the histopathology laboratory to facilitate digital sign out
- Limitations
  - cases that require re-scanning
  - cases to scan at 40X
  - cases requiring deferral to glass slide review
  - 5%
Image Analysis and Adoption of Digital Pathology

3/22/2017

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Image Analysis and Adoption of Digital Pathology

Primary Diagnosis Telepathology
(Live as of November 2012)

• regional cancer center
• 25,000 surgical cases per year
• 300-400 slides per day sent to UHN

WSI is an enabler:
1. Cost
2. Delayed TAT
3. Risks
   • lost/broken slides

Primary Diagnosis Telepathology
(October 2012 - present)

• 9,700 cases (52,000 slides) scanned for primary diagnosis

Phased Implementation Strategy

• Start with most experienced users
  • GU, endocrine, liver, head and neck
  • placentas, miscellaneous orthopaedic cases
• Attempt to scan all cases for these groups
• Review digital slides and sign out
  • request glass slides whenever it is required to sign out a given case

Secure
Private
Network
Central
Server
Local
Server
UHN
Data Center
Pathologist
Routine scanning at 20x

WSI: Primary Diagnosis

• October 2012 - present
• 9,700 cases (52,000 slides) scanned for primary diagnosis

Spectrum of GU Cases

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Deferral to Glass Slides: 5-10% of Cases

- **Difficult or unusual cases** especially where there is a high likelihood a case will be sent out for glass slide review by another pathologist.
- "It's slower than glass and I'm too busy" - if the pathologist has a large volume of cases to report.
- Performing diagnostic activities that are currently difficult or cannot be performed using WSI:
  - counting mitoses per high power field basis
  - identifying micro calcifications on breast biopsies by polarized light microscopy
- **Suboptimal image quality** in an area of potential diagnostic importance - a minor reason for deferral.

Example of a Case Deferred to Glass

47 year-old male, 6 cm right inguinal mass, "lipoma"

Growing Pains So Far

1. IT infrastructure/bandwidth
2. Viewer stability and reduced viewing speeds
3. Scanner issues
4. WSI-LIS interface and barcode issues
   - all cases are primarily accessed via the LIS
   - no flexibility for organizing electronic worklists
5. Mixed glass slide-WSI workflow

Hybrid Glass Slide - WSI Workflow

- Worrisome cellularity with mitoses (some atypical)
- Spindle cell lipoma/mammary-type myofibroblastoma
- De-differentiated liposarcoma
- Required IHC and molecular work-up (MDM2 FISH) not available at Lakeridge Health Oshawa

Summary of Clinical Use of WSI at UHN

- We have used computer screens the same way we use microscopes:
  - visual interpretation of H&E morphology
  - visual interpretation of immunohistochemistry
- Our WSI system works for those who use it - improvements on several fronts are needed to increase adoption
- Enter the need for a "pixel pipeline" with image analysis!
Image Analysis and Adoption of Digital Pathology

Pixel Pipelines

- Graphics card components that process pixel information to accelerate image processing tasks.
- Sequence of steps from digitizing a slide to final diagnosis with complete and robust prognostic information
- Doing what human eyes cannot do with WSI, glass slides or a microscope
  - "It's slower than glass and I'm too busy"
  - "Digital pathology is the future of pathology - and always will be"

Image Analysis: Software Tools To Help Pathologists (Not Replace Us)

- Intended goals:
  - allow the pathologist to act as the final interpreter
  - not field selection technologist
  - more robust biomarker quantitation
    - oncologists and patients like reports with hard numbers
- Use cases we have discussed at UHN

Ki-67/MIB-1

- Clinical Applications
  - neuroendocrine tumors
  - neuropathology - adjunct for grading gliomas and meningiomas
  - lymphoma
- Translational Research Applications
  - breast cancer - additional prognostic information over grading?
  - prostate cancer - active surveillance patient selection?

Ki-67 Labeling Index

- Visual inspection/ hot-spot detection
  - time consuming and error prone

Mitotic Figure Counting: H&E

- Potential confounders for visual counting:
  - thick sections
  - over-staining
  - apoptotic bodies
Multiplex Immunofluorescence

- Biopsy with limited lesional tissue
- Requires an immunohistochemistry panel (5-10 stains)
- Lesional tissue is exhausted from the block
- Can the panel be run on one single paraffin section?
  - hyperplexing (60 or more markers)

Pathologist Time & Motion Study: Glass Slide Review (Stratman et al)

- Concept of “pCAD”
  - Automated, systematic slide review, pre-annotated slides
  - Construct a report as slides are reviewed
  - Reduce the time spent on non-diagnostic work
Need for adequately-powered training sets (large number of exemplars)
- Machine learning with iterative improvement

How To Make The Pixel Pipeline a Reality

- Do it yourself (?)
- Partner with companies who focus on:
  - streamlining workflow in digital pathology - complete digitization
  - dependable IT support - continuous system monitoring
  - managing large volumes of digital data
  - development of clinically relevant algorithms
  - creative business models

Summary

- WSI telepathology at University Health Network
  - enabling sub-specialty pathology
  - how we started
  - how we have expanded our use of the technology
- How image analysis would help pathologists who have been using WSI for diagnostic work since 2006.

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