



Evaluating Computational Pathology at the US FDA and Related Research

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Scientific Evaluation of Computational Pathology and Related Research

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Outline



Evaluating Computer Aids in Radiology at the FDA

- What about computational pathology?

My Research in Pathology

- eeDAP: Evaluation Environment for Digital and Analog Pathology
- eeDAP Studies
 - Compare scanners to microscope
 - Pathologist microscope viewing behavior
 - Measure registration accuracy
- CDRH Medical Device Development Tool program (MDDT)
 - eeDAP
 - Annotating Images to validate algorithms

Medical Device Classification



- Risk-Based Paradigm
 - Medical devices are classified and regulated according to their degree of risk to the public
- Intended Use / Indications for Use (IFU)



Some Submission Types for Medical Devices



- **510(k) Premarket Notification**
 - Path to market for the majority of medical devices
 - Requires determination that a new device is substantially equivalent to a legally marketed device (**predicate device**)
 - Guidance: <https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarket submissions/premarketnotification510k/ucm134572.htm>
- **Premarket Approval (PMA)**
 - Class III devices
 - Demonstrate reasonable assurance of safety and effectiveness
 - Very device specific
 - Standalone submission
 - No comparison to a predicate
 - Guidance: <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketApprovalPMA/ucm050289.htm>

Some Submission Types for Medical Devices



- **De Novo**
 - Novel devices that have not previously been classified are by default Class III (and hence, PMA devices)
 - De novo is a petition for down-classification (Class III to typically Class II)
 - De novo petition proposes “Special Controls” that would be needed to assure the safety and effectiveness of the device
 - A granted de novo establishes a new device type, a new regulation, and necessary general (and special) controls
 - Once the de novo is granted, the device is eligible to serve as a predicate
 - All subsequent class II followers can use it as a predicate in their 510(k) submissions
- Guidance: <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080197.pdf>



Q-Submissions

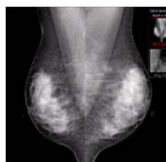
- Informal interaction with FDA (usually non-binding)
 - Pre-Submissions
 - Informational Meeting
 - Early Collaboration Meeting
 - ...
- Help avoid delays in device submission or repeating clinical studies
- Sponsors are encouraged to engage early with the FDA through the pre-submission mechanism
 - “Here’s the indications for use we’re thinking about and here’s the type of supporting data we are planning to collect”
- Guidance:
<https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf>

Algorithm Types in Medical Imaging

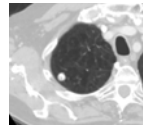


Examples from Radiology

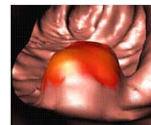
- Quantitative imaging (QI)
 - Lesion Volume
 - Lung density
 - Uptake model parameters
- Computer-aided detection (CADe)
 - Find pathology
 - Various paradigms, e.g., sequential or concurrent reading
- Computer-aided diagnosis (CADx)
 - Presence/absence of disease
 - Severity, stage, prognosis, response to therapy
 - Recommendation for intervention
- Computerized detection and or diagnosis
 - Some images are not seen by radiologists at all
- Many other possibilities



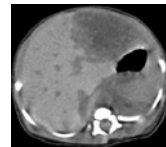
Breast



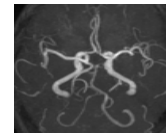
Lung



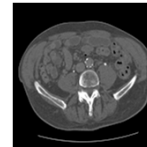
Colon



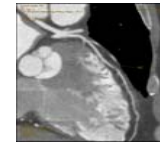
Liver



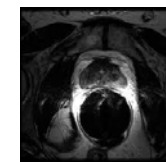
Brain



Urinary T.



Heart



Prostate

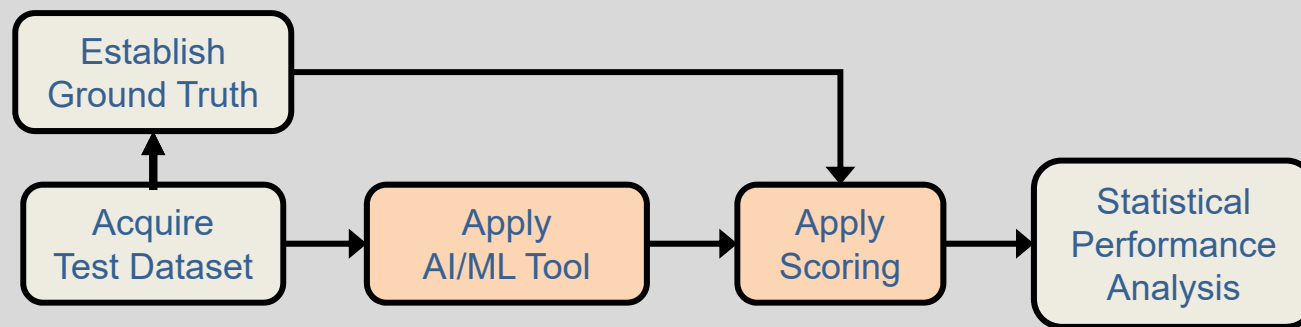
Core Content of 510(k) Submissions for computer aids in (Radiology)



- Find a predicate
- Description
 - Indications for use
 - Patient and clinician population
 - Clinical workflow
 - Imaging system and protocols
- Technological Characteristics
 - Algorithm design and function
 - Processing steps
 - Features
 - Models and classifiers
 - Training paradigm
- Imaging modality
 - Manufacturer and Model
 - Imaging parameters and techniques
- Databases: Training and Testing
 - Must be Independent
- Reference standard
- Assessment
 - Depends on algorithm type
 - Stand Alone
 - Clinical Performance: reader in-the-loop

Standalone performance

- Performance of algorithm by itself, independent of any interaction with user
 - Intrinsic functionality of device

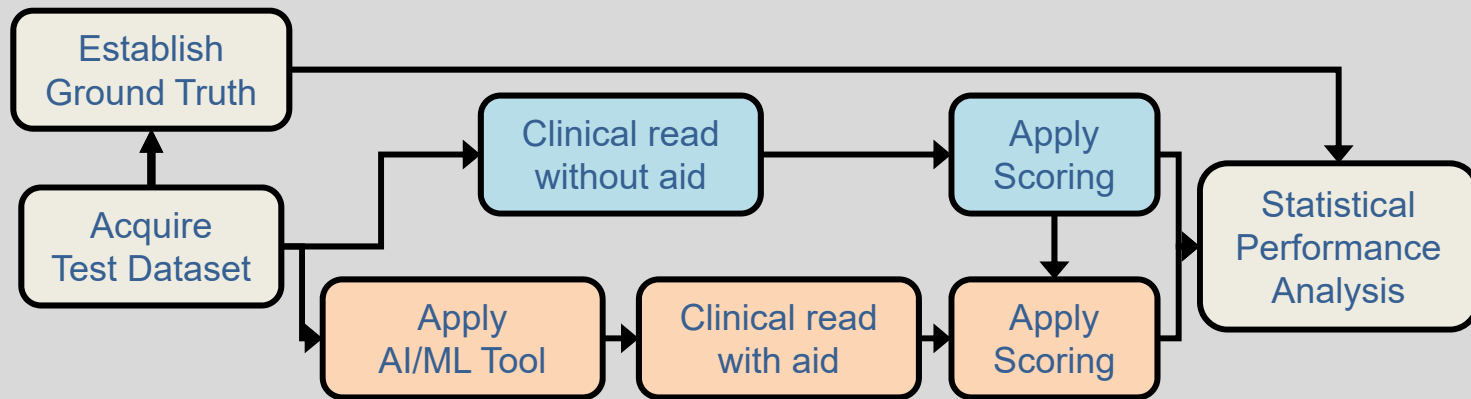


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Clinical: Reader performance

- Assessment of clinicians' performance utilizing the device
 - Many possible study designs
 - Prospective/retrospective
 - Multi-reader multi-case designs



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Radiology CADe Guidances

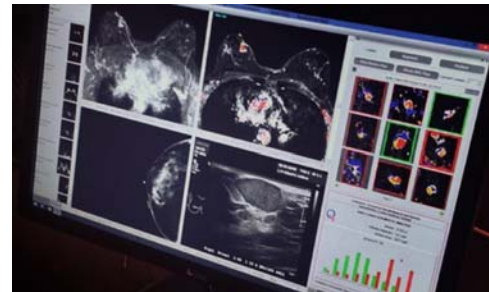
- Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data – Premarket Notification [510(k)] Submissions
 - <http://www.fda.gov/RegulatoryInformation/Guidances/ucm187249.htm>
- **Clinical Performance Assessment:** Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Approval (PMA) and Premarket Notification [510(k)] Submissions
 - <http://www.fda.gov/RegulatoryInformation/Guidances/ucm187277.htm>
- Software as a Medical Device (SAMd): Clinical Evaluation
 - <https://www.fda.gov/medicaldevices/digitalhealth/softwareasamedicaldevice/default.htm>
- **Roadmap for other algorithm types**

Predicates in Radiology



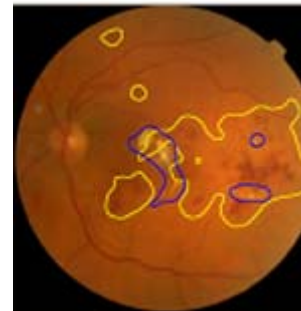
Special controls generally follow CADe guidance

- CADx: QuantX
 - DEN170022 (7/2017)
 - POK: computer-assisted diagnostic software for lesions suspicious for cancer
- CADe + CADx: OsteoDetect
 - DEN180005 (5/2018)
 - QBS: radiological computer assisted detection/diagnosis software for fracture
- Triage: ContaCT
 - DEN170073 (2/2018)
 - QAS: radiological computer-assisted triage and notification software
- Automatic Detection: IDx-DR
 - DEN180001 (4/2018)
 - PIB: diabetic retinopathy detection device



<https://www.quantinsights.com/>

<https://www.slashgear.com/osteodetect-ai-tool-finds-wrist-fractures-gets-fda-approval-28532138/>



<https://www.eyediagnosis.net/idx-dr>



<https://www.viz.ai/viz-lvo/>

Interoperability vs. Specialization

Lessons from Radiology



- First submission often tied to specific system
 - Expand indications over time
 - New imaging system
 - Algorithm updates/improvements
 - Expand indications via
 - New 510k
 - PMA Supplement
 - Device and performance familiarity may allow for less burdensome methods
- Less burdensome methods
- Studies with fewer readers or cases
 - Reuse cases for evaluating test performance
 - Re-acquire digital images with alternate systems
 - Stand-alone performance only
 - No statistical hypothesis test
 - Technical arguments

What About Algorithms in Pathology?

- History does not exist
- de Novo for first of kind algorithms (devices)
- Some issues may kick an algorithm (device) up to Class III
 - Indications tied to a therapy
- Submission contents
 - Core elements described previously
 - Several issues unique to pathology

Issues Unique To Pathology

- Discussed during (pre-) submission process
- Primary Diagnosis
- Ground truth
 - Decision/annotation
 - Patient, Slide
 - ROI, Cell
- Stains & color
- Compression
- Multiple magnification levels
- Other issues ...

What About Algorithms in Pathology?



- Automated hematology analyzers (differential cell counters)
- Chromosome analyzers
- FISH enumeration systems
- Urine sediment analyzers
- Automated microscope and imaging system for gynecologic cytology
- Immunohistochemistry **image analysis** (HER2/neu, ER, PR, etc.)
- More expected given the Philips WSI scanner de Novo (DEN160056)

Hardware with software component
Not all imaging
Not all 510k

GenASIs HiPath IHC Family (K140957)



- 510k database: Quick search “IHC”
 - <https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>
- Indications for use:
 - The GenASIs HiPath IHC Family provides image capture, management, analysis, and viewing of specific immunohistochemically stained slides. It is intended for in vitro diagnostic use as an **aid to the pathologist** in the **display, detection, counting, review and classification** of tissues and cells of clinical interest based on particular morphology, color, intensity, size, pattern and shape:
 - HER2, PR, ER, Ki67

GenASIs HiPath IHC Family (K140957)



- Four predicates for the four different antibodies
 - K111543: Virtuoso System for IHC HER2 (4B5)
 - K111869: Virtuoso System for IHC PR (1E2)
 - K130515: Virtuoso System for IHC ER (SP1)
 - K111755: Virtuoso System for IHC Ki67 (30-9)
- Image and Region Of Interest (ROI) selected by the pathologist
- Device Components: Microscope, CCD color camera, PC, keyboard, Mouse, Color Monitor, X-Y stage and rack for loading 1 glass slide.
- Differences with predicates largely based on image acquisition
 - CCD on microscope versus slide scanner

Other Virtuoso 510k's expand indications to different

- Stainer platform
- Scanner

PMA for Cytology with Computer Aid

FDA

- Gynecologic Cytology Imaging Systems
 - Cytyc/Hologic ThinPrep Imaging System (P020002)
 - Becton Dickinson/TriPath FocalPoint Guided Screening System
 - Papanicolaou Stain
 - Detection algorithm, neural network
 - Images not saved
 - Cytologist reviews locations with microscope



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Computer Aids in Radiology



- R2 ImageChecker (P970058)
 - The ImageChecker M1000 is a computer system intended to identify and mark regions of interest on routine screening mammograms to bring them to the attention of the radiologist after initial reading has been completed. Thus, the system assists the radiologist in minimizing observational oversights by identifying areas on the original mammogram that may warrant a second review.

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R2 ImageChecker Submission History



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1998

Approval of Original submission

1. Hardware changes and minor bugs and enhancements

1999

2. Performance change

3. Post approval study protocol

4. New marker (correlated masses)

5. Alternative film digitizer

2000

6. Performance change

7. Label change with respect to efficacy

8. New marker (subtle vs. obvious masses)

2001

9. New marker (subtle vs. obvious calcifications)

10. Indications expanded from screening to diagnosis

11. Indications expanded to digital images (GE Senographe 2000)

2002

12. Label change with respect to efficacy

13. Transparent marker (see image under marker)

14. Label change

2003

15. New Manufacturing facility

16. Choice of new operating points (high and low sensitivity), operates on analog and GE FFDM images, operates on GE FFDM images "formatted for presentation", reduces false-negatives of oversized malignant calcification clusters

17. Alternative film digitizer

18. Indications expanded to Fischer Senoscan FFDM

2003

19. Indications expanded to Hologic Selenia FFDM

2005

20. Indications expanded to include Siemens Novation FFDM

21. More operating points

2006

22. Change label to include specificity (previously it was sensitivity and false marks per image)

2007

24. New manufacturing facility

20012

25. Algorithm updates and indications expanded to GE Senograph Essential

2014

26. Indications expanded to C-view images Hologic Selenia Dimensions (Tomosynthesis) system

2016

27. New manufacturing facility



My Research and Projects

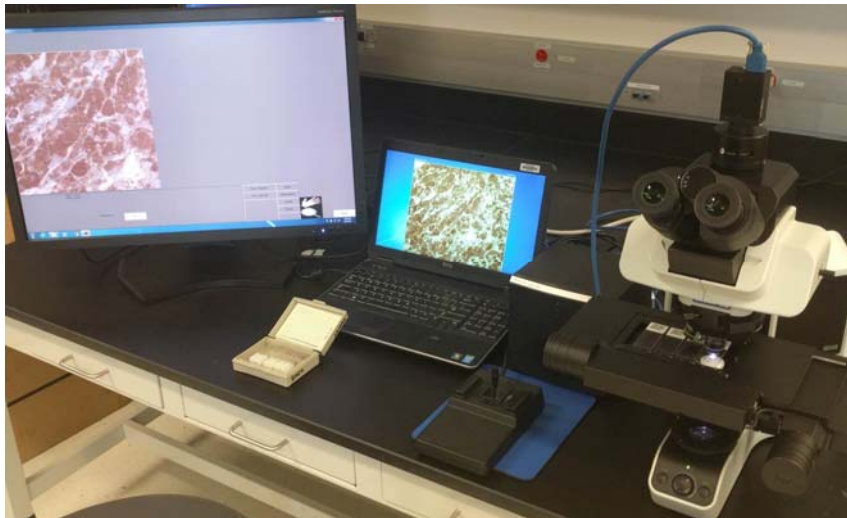
- eeDAP: Evaluation Environment for Digital and Analog Pathology
- eeDAP Studies
 - Compare scanners to microscope
 - Pathologist microscope viewing behavior
 - Measure registration accuracy
- MDDT: Medical Device Development Tool
 - CDRH program
 - eeDAP
 - Annotating Images to validate algorithms

eeDAP:



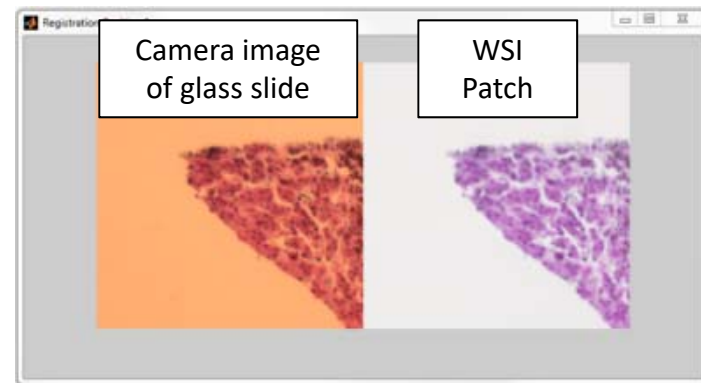
Evaluation Environment for Digital and Analog Pathology

Monitor, Computer, motorized stage with joystick, microscope with mounted camera, reticle in eyepiece



<https://github.com/DIDSR/eeDAP>

- Register glass slide and WSI
- Allow pathologists to evaluate same fields of view on microscope and WSI



eeDAP:

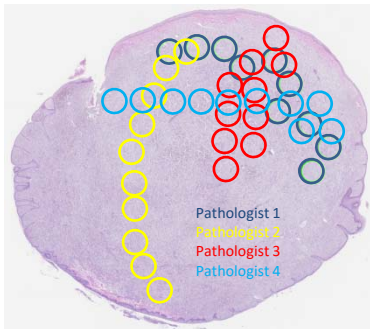


Removes search from technology evaluation

- eeDAP can eliminate location variability for faster and more precise results.

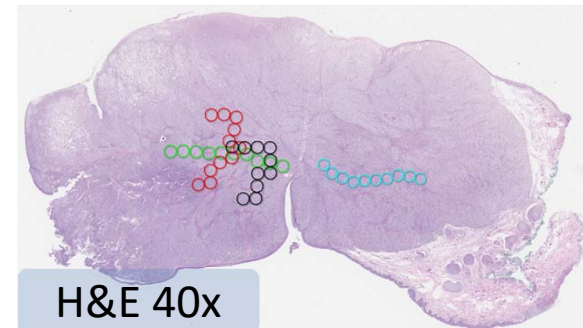
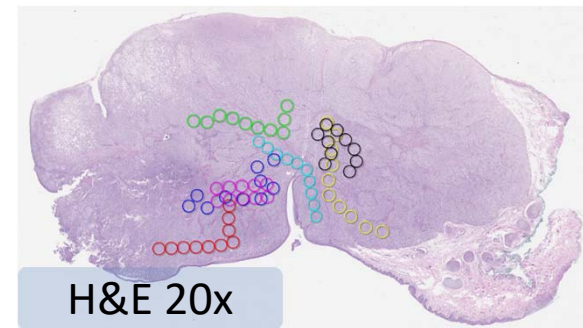
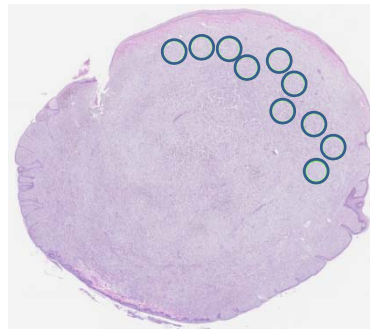
Clinical practice

Pathologists choose
Fields of View to evaluate



Technology Evaluation

All pathologists evaluate
same Fields of View



Compare scanners to microscope

Install, Demo, Train at Memorial Sloan Kettering



Study Design

- 4 slides from Mark Simpson at NCI
 - HE: canine oral melanoma
- 10 ROIs per slide from tumor
 - ROI = 800 x 800 pixels @ 0.25um/pixel
= 200um x 200um
= 17% of the entire FOV (0.24 mm²)
- Task: Mark and count mitotic figures (MF)
- eeDAP integrates ImageScope
 - Show ROIs
 - Mark cells

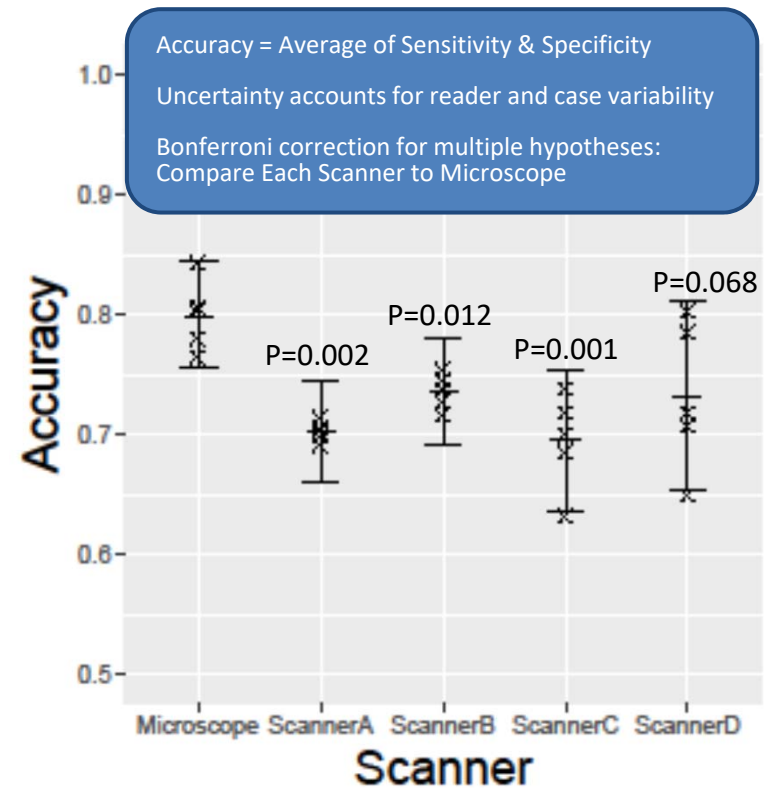
Compare scanners to microscope



- High-throughput reader study
- Same microscope frame ... 14 heads!
- Stage mounts fine
- Camera mounts fine

Compare scanners to microscope

- Four scanners and microscope
- Five study pathologists
 - 157 candidate MFs
- Three truthing pathologists
- True MFs
 - Start with candidates unanimously identified on microscope
 - Add candidates determined to be true MFs
 - Truthing panel
 - Group setting
 - Digital microscope (VisionTek)

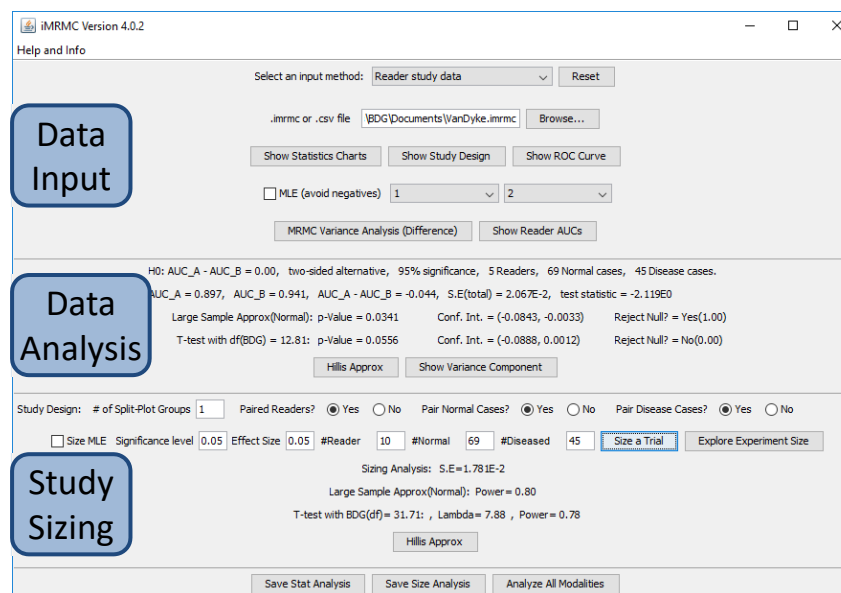


iMRMC:



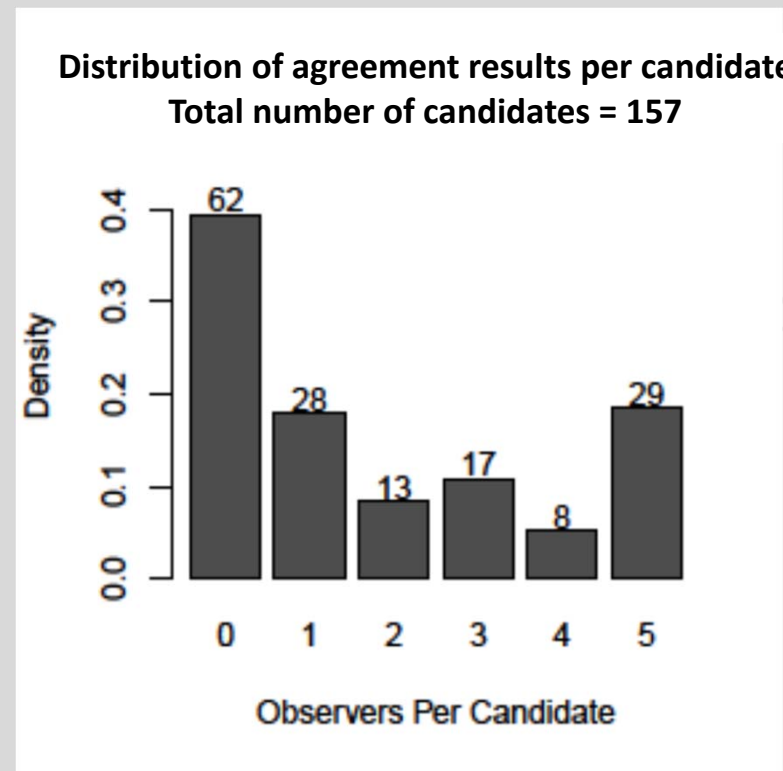
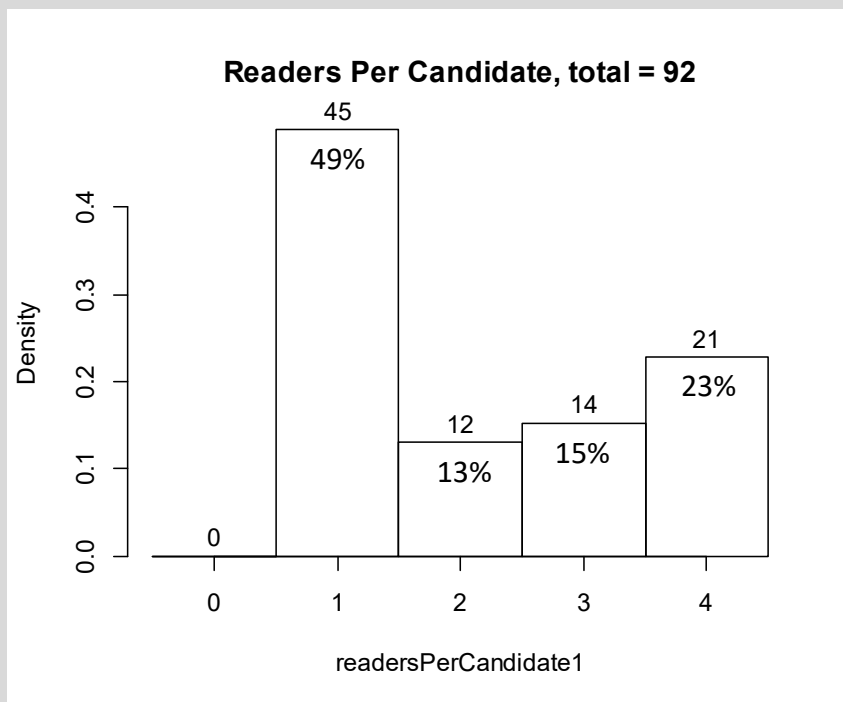
Statistical Analysis Tool for Reader Studies

- MRMC analysis
 - Multiple readers
 - Multiple cases
 - Uncertainty accounts for reader and case variability
- Statistical analysis tool
 - Percent Correct
 - Area Under the ROC curve
- GitHub java application GUI
 - <https://github.com/DIDSR/iMRMC>
- CRAN R package
 - <https://cran.r-project.org/web/packages/iMRMC/index.html>



Current and previous study

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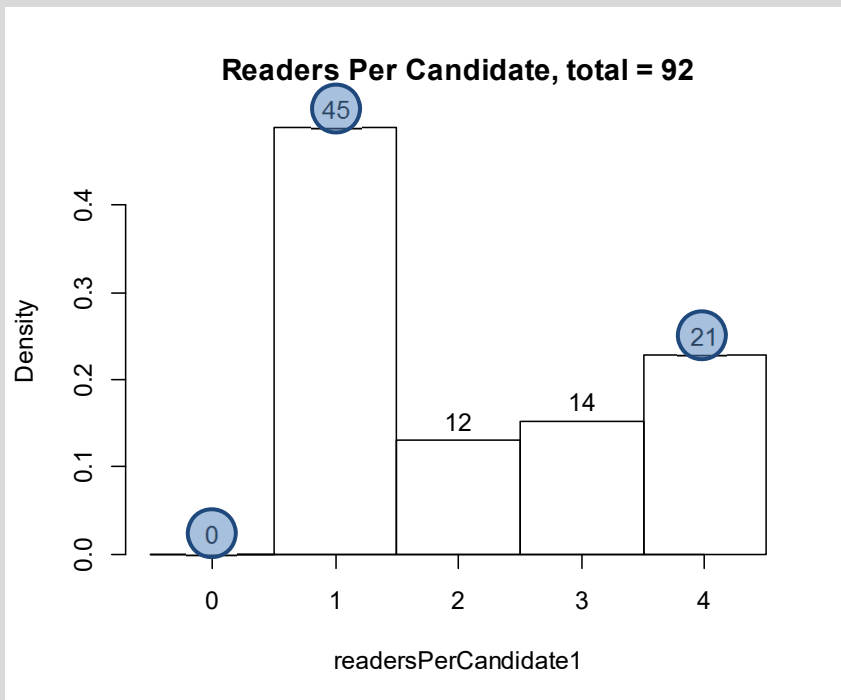
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MSKCC results

- All 5 observers detected 157 candidate mitotic cells, using all WSIs and microscopy. All counts by all observers using all observation methods are showed in Table 1. Using microscopy, 29 potential candidate mitotic cells were detected by all five observers, 8 candidates by four observers, 17 candidates by three observers, 13 candidates by two observers, 28 candidates by only one observer. The remaining 62 candidates remained undetected by microscopy; they were detected only using WSI.

Readers per Candidate

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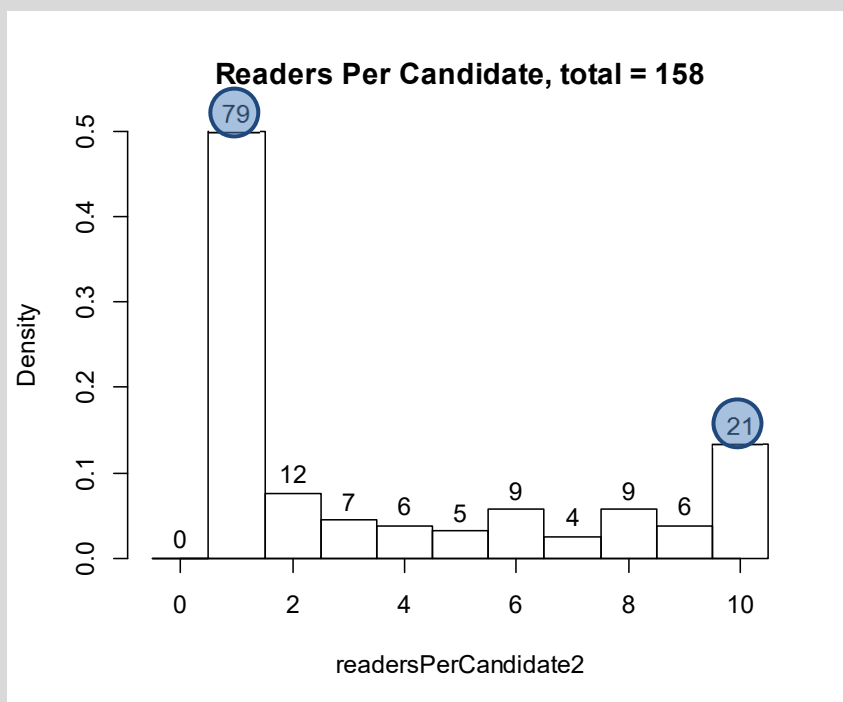
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- Do you think this is a lot of reader variability?
- $45/92 = 49\%$ marked by only one
- $21/92 = 23\%$ unanimously marked
- Build these candidates into next study: **Classification task**
- Need some low-probability candidates from ROIs with zero or one candidates -> yield 34

Readers per Candidate: Multi-head study



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- Similar characteristics as before
- $79/158 = 49\%$ marked by only one
- $21/158 = 23\%$ unanimously marked
 - 13 agree with previous, 8 new ones
- How well does AI correlate with this scoring?

Pathologist Microscope Viewing Behavior: Collaboration with Cold Spring Harbor Laboratory and Northwell Health



Original eeDAP workflow

- Register the study slides
 - Glass and WSI
- Visit locations/objects
 - Pre-determined list of “tasks”
 - ROIs ... candidate MFs
 - Evaluate each location/object
 - Perform the “task”

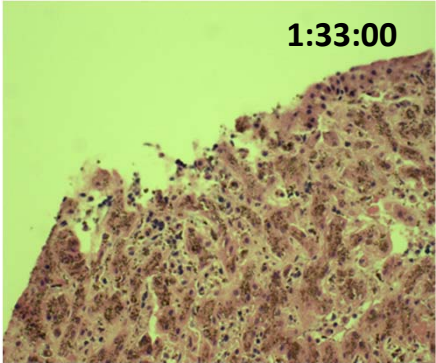
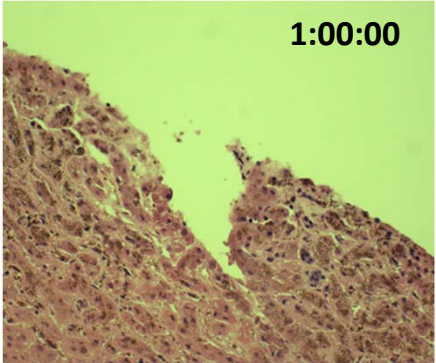
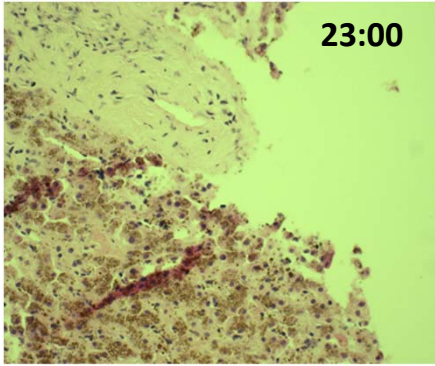
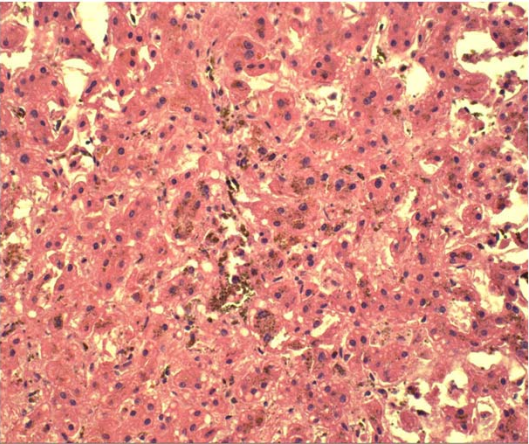
New eeDAP workflow

- Pathologist driven navigation of slides on the microscope
 - Collect main diagnosis, grade, type, etc.
 - Provide confidence ratings
- Continuously record
 - Stage position (+ mouse clicks)
 - Eyepiece camera video
 - Audio
- Registration after the fact

Pathologist Microscope Viewing Behavior: Collaboration with Cold Spring Harbor Laboratory and Northwell Health



Registration
after the fact



Video: Collecting
3 registration anchors

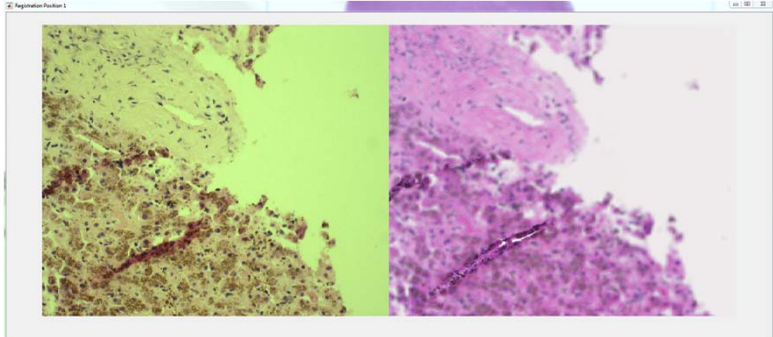
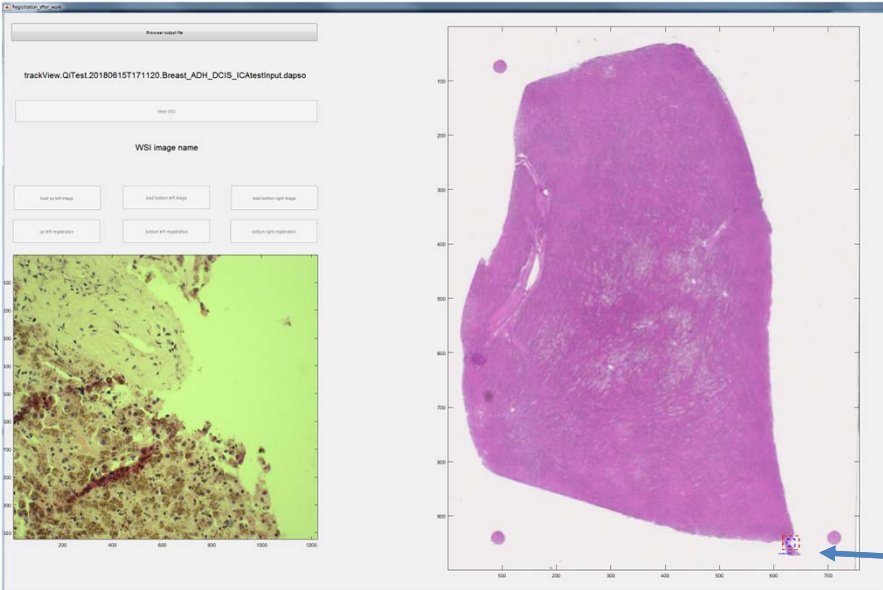


Static images:
3 registration anchors

Pathologist Microscope Viewing Behavior: Collaboration with Cold Spring Harbor Laboratory and Northwell Health



Registration
after the fact



Camera

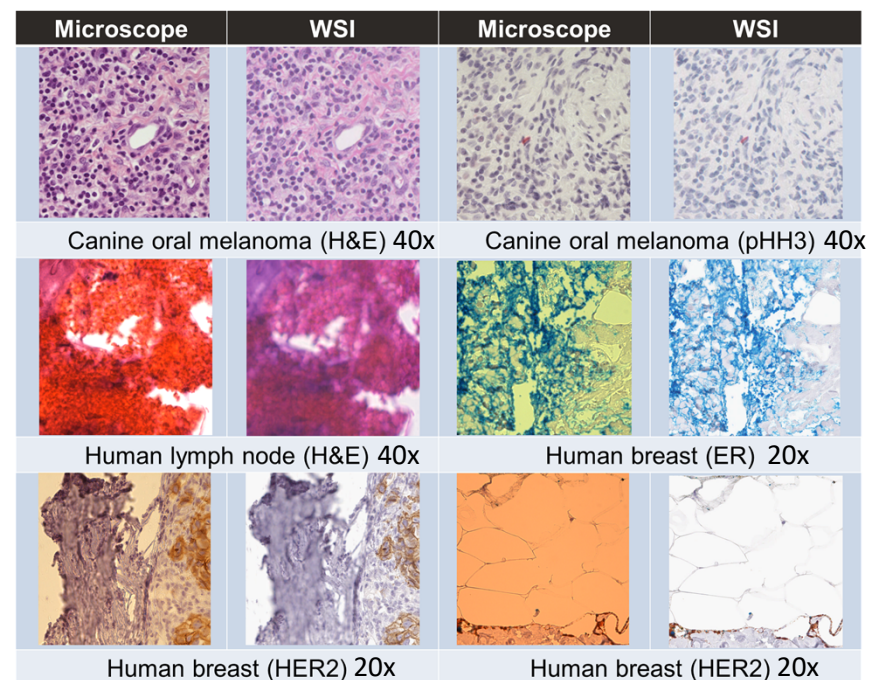
WSI

Video helps identify
where to look/register

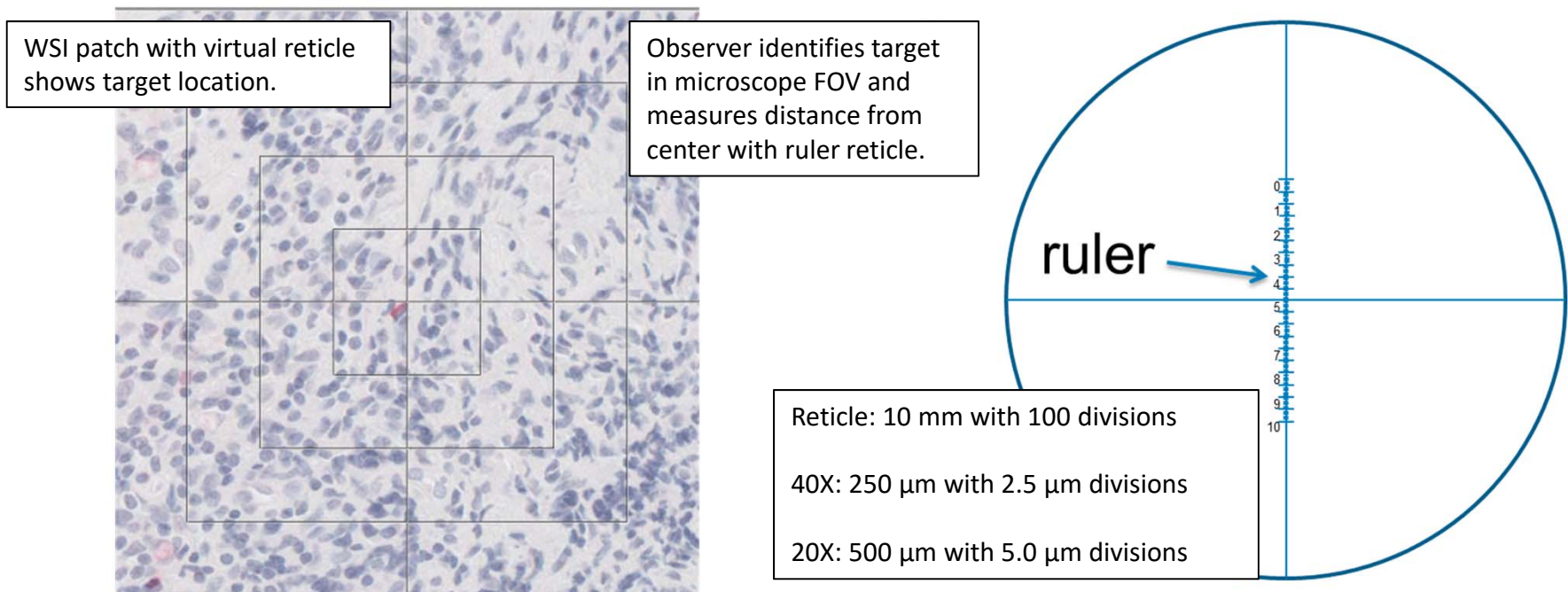
Measure eeDAP Registration Accuracy



- People ask about registration accuracy
- Pursuing an “FDA MDDT” qualification
- Global Registration (WSI and camera)
 - For each slide
 - Before data collection
 - Find and locally register 3 anchors
 - Normalized cross correlation
 - Create transformation matrix
 - Register camera and eyepiece
- Local registration
 - During data collection
 - Refinement at each ROI/object
 - Automatic, Fast, and Best options
 - Options differ by focus, size, and padding



Measure eeDAP Registration Accuracy



Measure eeDAP Registration Accuracy



FDA study

- 120 measurements
 - 6 slides
 - 10 measurements per slide
 - 2 participants (replicate study)
- Global registration
 - Mean error = 37.62 μm (~3 cells)
 - Standard Deviation = 28 μm
- Local registration after focusing
 - Better than 95% of measurements < 5 μm

CSHL study

- Designed and executed at CSHL
- Very similar results

Measure eeDAP Registration Accuracy

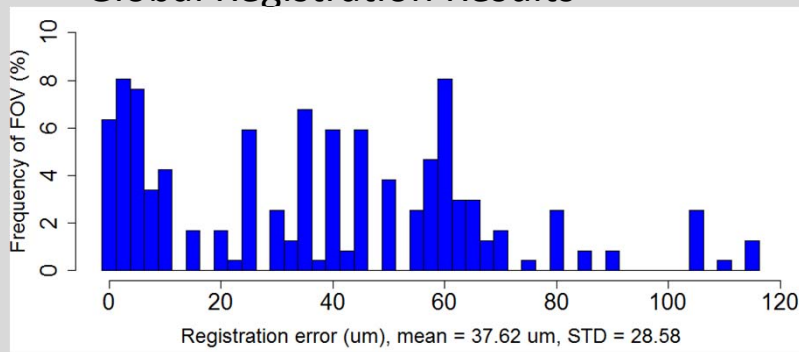


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FDA study

- 120 measurements
 - 6 slides
 - 10 measurements per slide
 - 2 participants (replicate study)

Global Registration Results



CSHL study

- 400 measurements
 - 20 slides (10 Rat H&E + 10 human H&E), scanned magnification 20X
 - 10 measurements per slide
 - 2 participants (replicate study)
- Global registration
 - Mean error = 31.35 um
- Local registration after focusing
 - Better than 95% of measurements <5um

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MDDT: Medical Device Development Tool (CDRH program)



- Definition: Method, material, or measurement used to assess the effectiveness, safety, or performance of a medical device
- Qualified for a context of use
- Facilitates submission and its review (Point to the qualification package)
- Encourages
 - Innovation
 - Collaboration
 - Chance for community to impact regulatory process
- Clinical outcome assessments
 - Surrogate outcomes
 - Patient reported outcomes
- Biomarker tests
 - Measure biological process (gold standard)
 - Measure response to intervention
- Nonclinical assessment models
 - Computational models (simulations)
 - Probes and phantoms for bench tests
 - **eeDAP!**
 - **Image databases with truth annotations**

Guidance on the web!

<https://www.fda.gov/medicaldevices/scienceandresearch/medicaldevicedevelopmenttoolsmddt/>

MDDT:



Annotating Images to validate algorithms

- Elevator Pitch:
 - Create dataset of images with truth annotations
 - To be available to algorithm developers for FDA submission (Performance Evaluation)
- Follow example of ACR
 - American College of Radiology
 - <https://www.acrdsi.org/Use-Case-Development>
- TOUCH-AI: Technology-Oriented **Use Cases** for Healthcare AI
- CERTIFY-AI: ACR Digital Science Institute validation service



MDDT:

Annotating Images to validate algorithms

ACR TOUCH-AI: Concepts and Tools

- Open framework for defining use cases
- Community-Contributed use cases
- Use cases reviewed by ACR committees
- Use cases reviewed by FDA (MDDT)
- CARDS: Computer-Assisted Reporting and Decision Support Tools for Radiologists
 - XML-based Proceduralized Definitions
 - Logic relating Common Data Elements (CDE's) to patient management
- Reference implementation
 - No-frills user interface defined by CARDS
 - Structured evaluation (inputs): check boxes, menus, numeric fields
 - Standardized report (outputs)
 - Framework for value-added vendors: PACS, VRS, AI

- Can be unique to institution
- Can be reviewed by ACR committees
- Can be reviewed by FDA (MDDT)

- “Scores” (Labels, Counts, Segmentations, Measurements, Units)
- Image-based
- Other Dx
- Cut offs

Add No-Frills Reference Viewer

MDDT:



Annotating Images to validate algorithms

ACR TOUCH-AI: Use case core contents

- Clinical implementation ([FDA: device description](#))
 - Value proposition, narrative(s), workflow description
- Considerations for dataset development ([FDA: indications for use](#))
 - ([FDA: intended imaging procedures and protocols](#))
 - ([FDA: intended patient population](#))
- Technical specifications ([CARDS, XML](#)):
 - Inputs, outputs
- Future development ([CARDS, XML](#))
 - Inputs, outputs, extensions, comparison over time



MDDT:

Annotating Images to validate algorithms

ACR CERTIFY-AI: Work In Progress

- STARD: Standards for Reporting of Diagnostic Accuracy Studies
 - Study design: prospective/retrospective, ...
 - Reader and case sampling/description
 - Reference standard: “Scores” specified in use case
 - Performance metric: stand-alone vs. reader in-the-loop
 - Analysis method: MRMC? Missing/indeterminate data? Sizing?
 - Study limitations

MDDT:



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Possible Use Cases (Tasks)

- Automated detection of breast cancer metastases in lymph node WSIs
- Classify tumor infiltrating lymphocytes and score ROIs by density of TILS
- Classify tumor bed cells, ROI cellularity
- Counting mitotic figures and scoring proliferation in H&E

My Goals (not requirements)

- Collect truth on the microscope
 - Reference standard
 - Continuous 3D object. Not digitized.
 - Pathologist familiarity
 - Not tied to specific scanner
- Collect truth from multiple pathologists
 - Acknowledge pathologist variability
 - Reduce pathologist variability
 - Account for pathologist variability
 - Number of readers depends on reader variability

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Leveraging Challenges

- (High Throughput)
- Can't do this by myself
 - Nurturing partnerships
 - Need partners to share the load
- Willing to do heavy lifting
 - Drafting/reviewing FDA proposal and submission
 - Reader study design
 - Reader study execution
 - Reader study analysis

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Leveraging Challenges

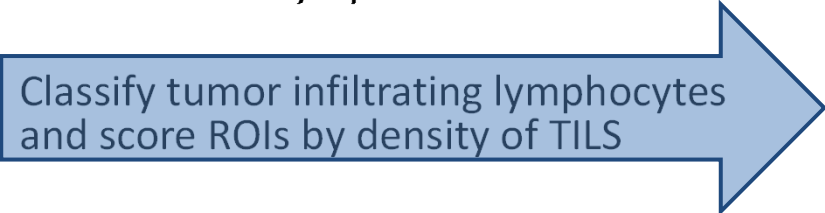
- CAMELYON 16 & 17
- Point of Contact: Jeroen van der Laak
 - Challenge Organizer
 - Radboud University Medical Center
 - Nijmegen, The Netherlands
- Starting material transfer agreement (MTA)
 - Camelyon16 glass slides
 - Algorithms available
- FDA algorithm
- MDDT Issue: Camelyon16 images and truth released

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Leveraging Challenges

- Future challenge planned
- Point of Contact: Roberto Salgado
 - Chair: International Immuno-oncology Working Group
- Large, motivated, working group with many pathologists and image sets from drug trials
- Massive Analysis and QC (MAQC) Society
 - Project: “Reproducible machine learning for pathology image analysis”

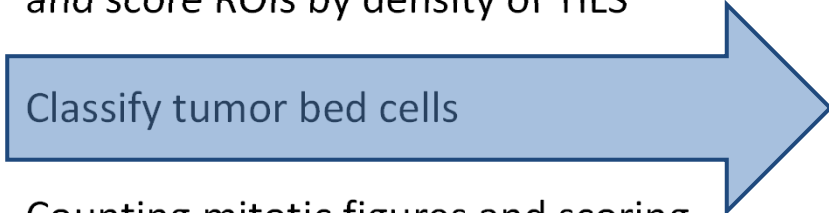
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Leveraging Challenges

- SPIE Medical Imaging conference
 - February 2019
 - The international society for optics and photonics
 - CAD and Digital Pathology tracks
- Point of Contact: FDA colleagues!
 - Sunnybrook Research Institute, University of Toronto, University of Chicago, University of Michigan, NIH/NCI, Harvard University, Stony Brook University, University of Buffalo, Western University, Fraunhofer (Medical Imaging Computing) MEVIS, Nagoya University

SPIE Medical Imaging Challenge



Hidden during presentation

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- NIH/NCI
- Harvard University
- Stony Brook University
- University of Buffalo
- Western University
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Leveraging Challenges

- Tumor Proliferation Assessment Challenge 2016 | TUPAC16
- Point of contact: Mitko Veta
 - Challenge Organizer
 - Eindhoven University of Technology (TU/e)
- No glass slides available but preparing for next challenge: breast cancer prognosis

MDDT:



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- Next up ...
- American Society for Clinical Pathology Annual Meeting (October 3)
 - Call for proposal to conduct perception studies (June 21)
 - NCI funding did not come through (September 7) ... making calls ... help?
 - Demonstrate and get experience running eeDAP in conference environment (high-throughput)
 - Offer CME for study participants
 - Sourced lung tumor tissue for TILS counting/scoring
 - Data collection: Pre-defined ROIs or Pathologist Guided?



Summary

- FDA has been evaluating computer aids in radiology for two decades
 - Core content
 - There is guidance, examples, and predicates
 - Start with limited indication ... grow indications
- FDA history with computational pathology device
 - De Novo request of Whole Slide Imaging (WSI) system for primary diagnosis was granted (PIPS, Philips, April 2017)
 - No devices on the market for that scanner/technology today
 - Request feedback on your submission plans
- eeDAP is at my research core ... it is a tool
 - Microscope is still dominant/reference modality
- Large datasets are needed for training
 - Smaller high-quality data sets are needed for testing
- Reader variability
 - Account for it in performance evaluation
 - Statistics and Truthing
- MDDT:
 - Demonstrate and get experience with data collection
 - Plan for defining use cases
 - Nurturing partnerships
 - Looking for partners to share the load



Feedback?
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Resources

- eeDAP: evaluation environment for digital and analog pathology
 - <https://github.com/DIDSR/eeDAP>
- iMRMC statistical analysis tool
 - GitHub: <https://github.com/DIDSR/iMRMC>
 - CRAN R package: <https://cran.r-project.org/web/packages/iMRMC/index.html>
- WSI Working Group
 - https://nciphub.org/groups/wsi_working_group
- MDDT: Medical Device Development Tools
 - <https://www.fda.gov/medicaldevices/scienceandresearch/medicaldevicedevelopmenttoolsmddt/>
- CADe
 - <http://www.fda.gov/RegulatoryInformation/Guidances/ucm187249.htm>
 - <http://www.fda.gov/RegulatoryInformation/Guidances/ucm187277.htm>
- Software as a Medical Device (SAMd): Clinical Evaluation
 - <https://www.fda.gov/medicaldevices/digitalhealth/softwareasamedicaldevice/default.htm>
- Requests for Feedback on Medical Device Submissions
 - <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm311176.pdf>
- De Novo Classification Process
 - <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080197.pdf>
- How to Prepare a Traditional 510(k)
 - <https://www.fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketnotifications/premarketnotification510k/ucm134572.htm>