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VIRTUAL MEETING

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June 24–26

Reimagining the Future.

CELEBRATING

40 YEARS

AI in the Digital Pathology World

High-Throughput Truthing Project (HTT)

Thursday, June 25 | 8:00 am – 9:30 am

Brandon D Gallas, PhD

Division of Imaging, Diagnostics, and Software Reliability

Office of Science and Engineering Laboratories

Center for Devices and Radiological Health

FDA U.S. FOOD & DRUG ADMINISTRATION

Conflicts of Interest

- None

- The mention of any commercial products herein is not to be construed as either an actual or implied endorsement of such products by the Department of Health and Human Services.

High-throughput truthing (HTT) Collaborators

Collaboration of Volunteers

Engage stakeholders through the Alliance for Digital Pathology

Pathologists

Academia

Health Systems

Associations

Industry

Involve experts & the community.

HTT Core Collaborators

Project mgmt.

- **Sarah Dudgeon**, MPH
  - FDA/CDRH/OSEL/DIDSR

caMicroscope team

- **Ashish Sharma**, PhD
  - Emory University Department of Biomedical Informatics
- **Joel Saltz**, MD PhD
  - Dept. of Biomedical Informatics, Stony Brook Medicine
- **Nan Li**, MS
  - Dept. of Biomedical Informatics, Stony Brook Medicine

PathPresenter team

- **Matthew Hanna**, MD
  - Memorial Sloan Kettering, New York, NY
- **Rajendra Singh**, MD
  - Icahn School of Medicine at Mt Sinai
- **Krushnavadan Acharya**, MCA
  - PathPresenter

Slides and Clinical

- **Roberto Salgado**
  - Peter Mac Callum Cancer Center; GZA-ZBA Hospitals
  - International Working Group for TILs in Breast cancer
- **Denis Larismont**
  - Institut Jules Bordet

Statistics

- **Si Wen**
  - FDA/CDRH/OSEL/DIDSR
- **Manasi Sheth**
  - FDA/CDRH/OPEQ/OCEA/Biostatistics
- **Chava Zibman**
  - FDA/CDRH/OPEQ/OCEA/Biostatistics
- **Weijie Chen**, PhD
  - FDA/CDRH/OSEL/DIDSR

Committee

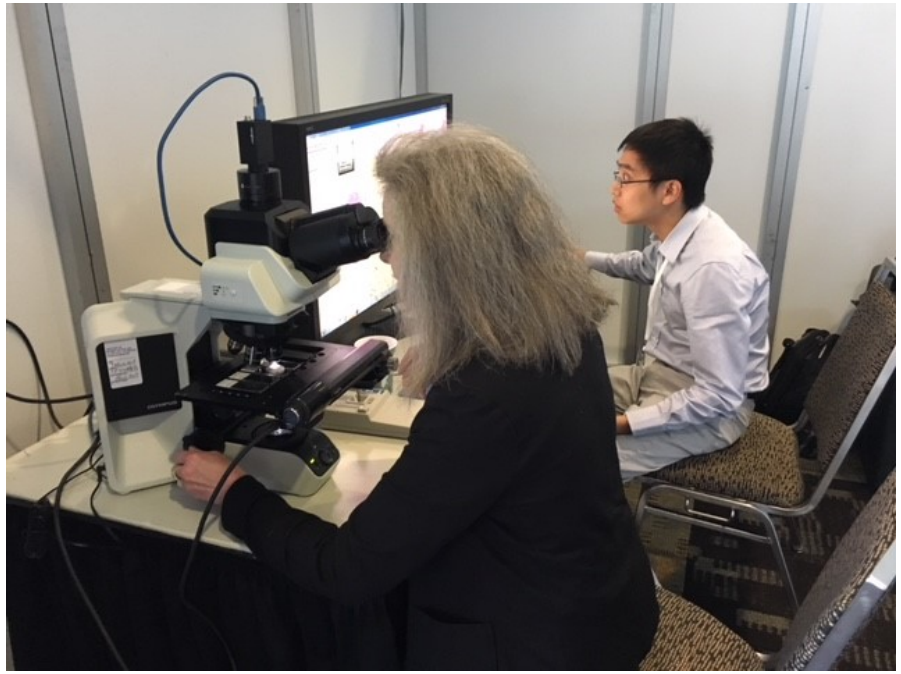
- **Mohamed Amgad**, MSc
  - Emory University School of Medicine, Atlanta, GA
- **Rajarsi Gupta**, MD, PhD
  - Renaissance School of Medicine and Dept. of Biomedical Informatics, Stony Brook Medicine
- **Steven N. Hart**, PhD
  - Mayo Clinic, Rochester, MN
- **Joe Lennerz**, MD, PhD
  - Massachusetts General Hospital, Boston, MA
- **Richard Huang**, MD, MS
  - Massachusetts General Hospital, Boston, MA
- **Anant Madabhushi**, PhD
  - Case Western Reserve University
- **Kyle J. Myers**, PhD
  - FDA/CDRH/OSEL/DIDSR

- Open door policy

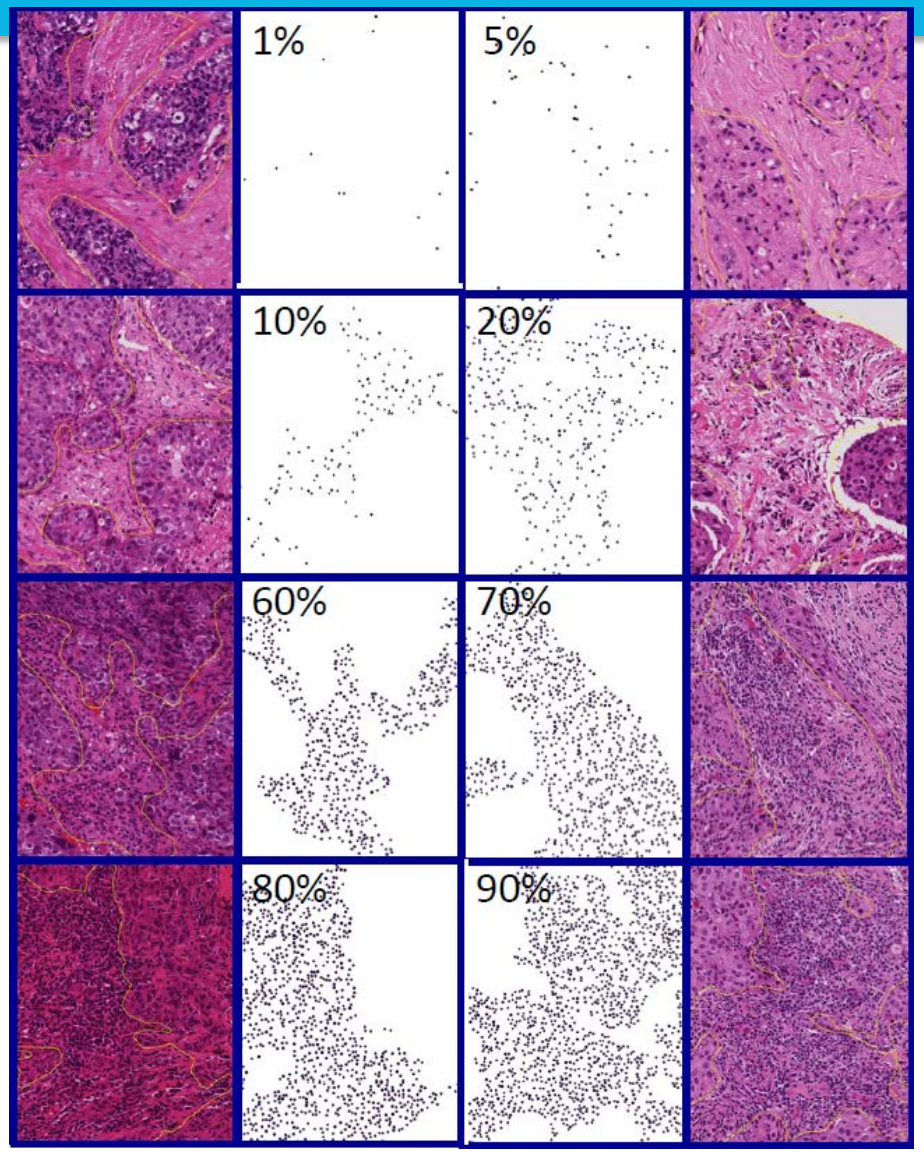
High-throughput truthing (HTT) Project

Demonstration project

- Collect multi-reader image annotations to establish biomarker truth
- Annotations support validation of an algorithm
- Pursue an FDA Medical Device Development Tool Qualification
- Application: Stromal Tumor Infiltrating Lymphocytes are prognostic in breast cancer

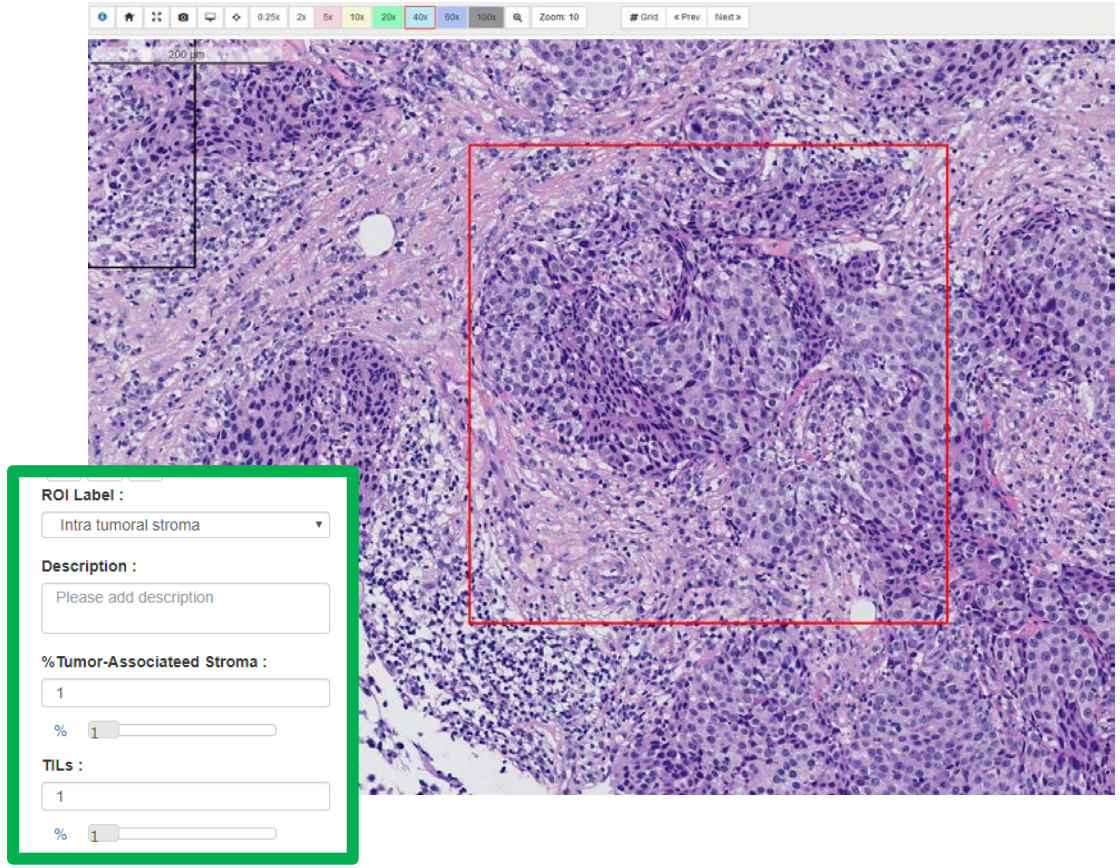


Standardized Annotations Yield a Biomarker



- Quantitative Biomarker
- Density: 0-100

Standardized Annotations Yield a Biomarker



- Pathologist
  - Takes time
  - Requires training
  - Noisy
  - Board Certification
- Algorithm
  - Fast
  - Requires training
  - Reproducible
  - Regulatory permission

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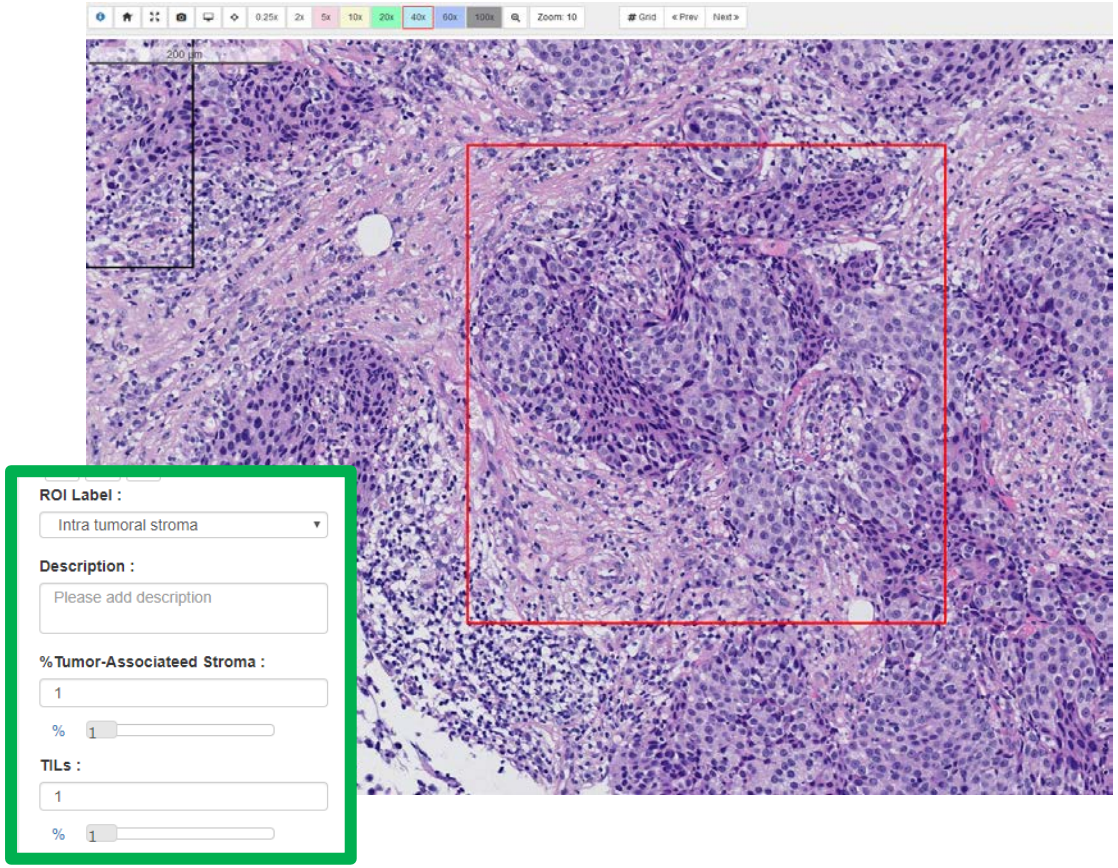

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  - Takes time
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Literature
Examples with truth
(feedback)

- Algorithm
  - Fast
  - Requires training
  - Reproducible
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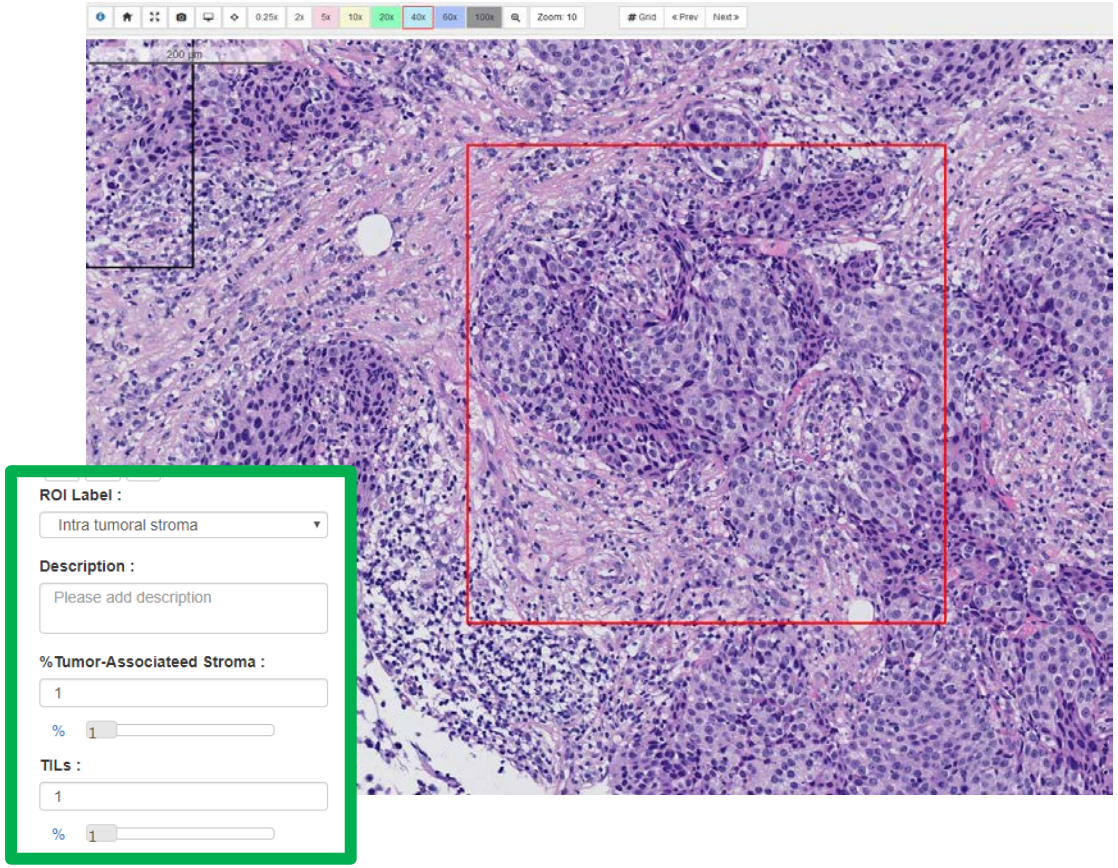
~~Literature~~
Examples with truth
(feedback)

Standardized Annotations Yield a Biomarker



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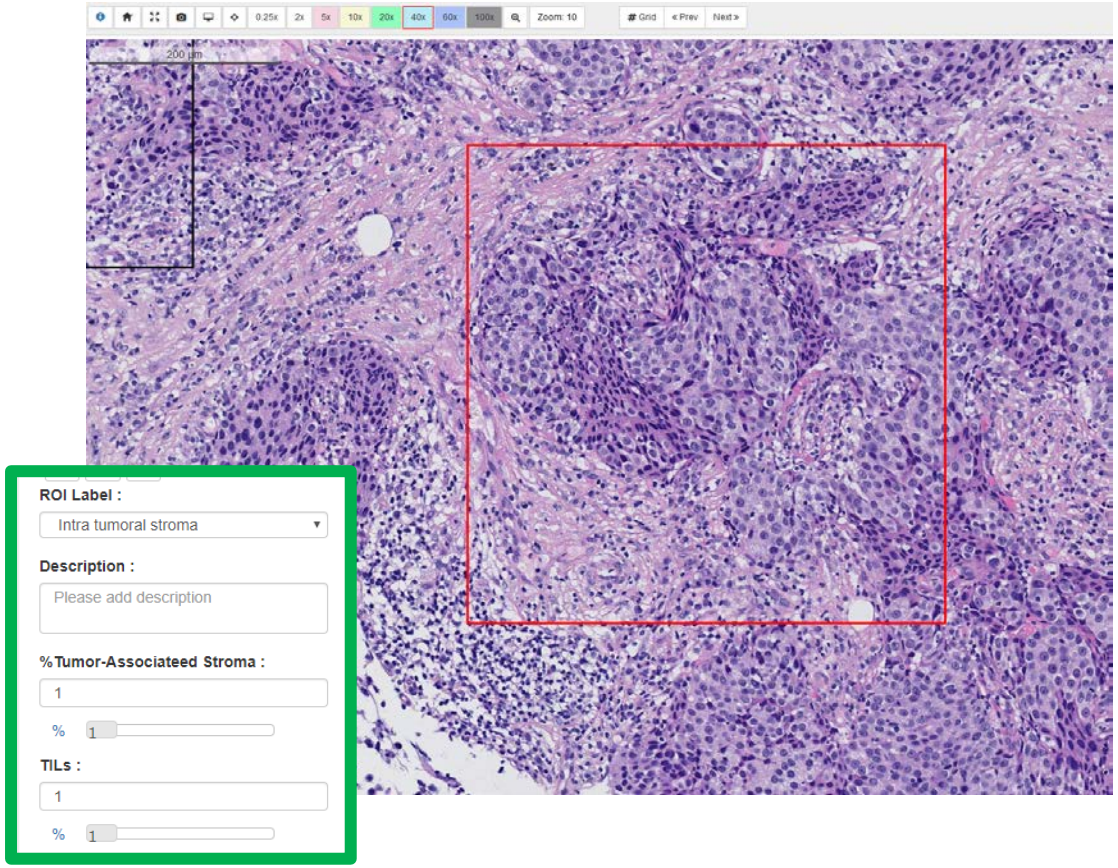
"Truth by pathologist"
Reduce and Account for Pathologist Variability

Evaluate performance
Requires truth

Standardized Annotations Yield a Biomarker



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- Algorithm
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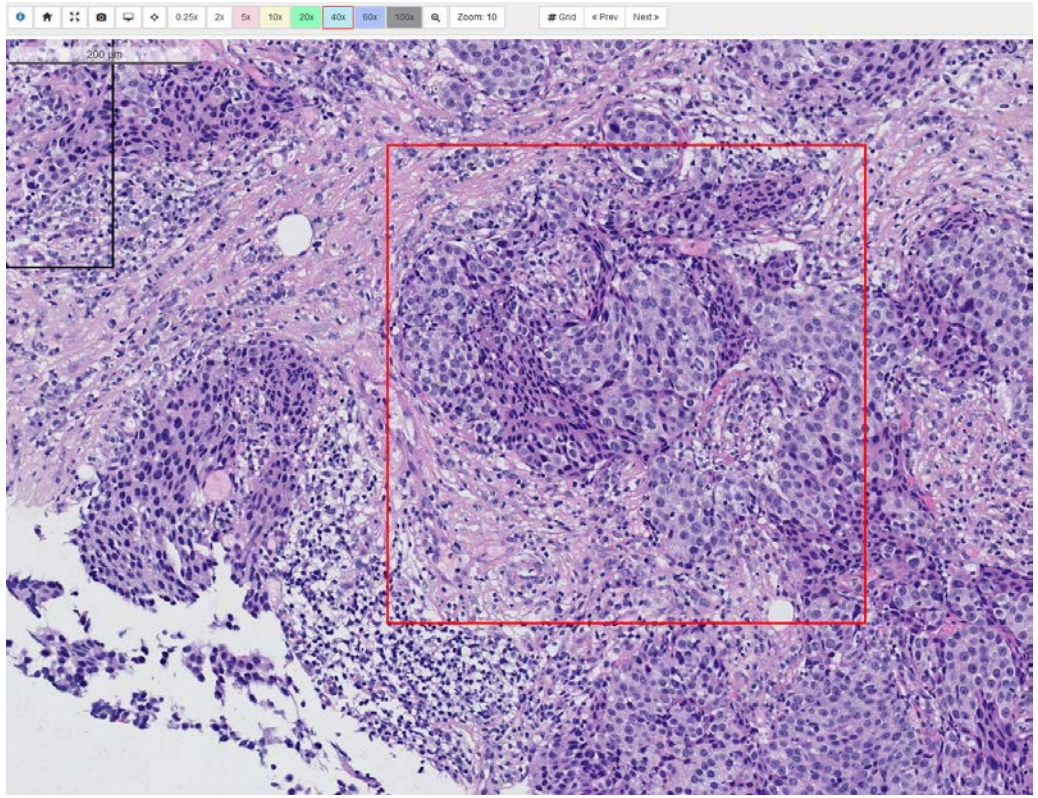
  - Requires training
  - Reproducible
  - Regulatory permission

"Truth by pathologist"

- Additional training
- Multiple pathologists per region / image
- Sophisticated analysis

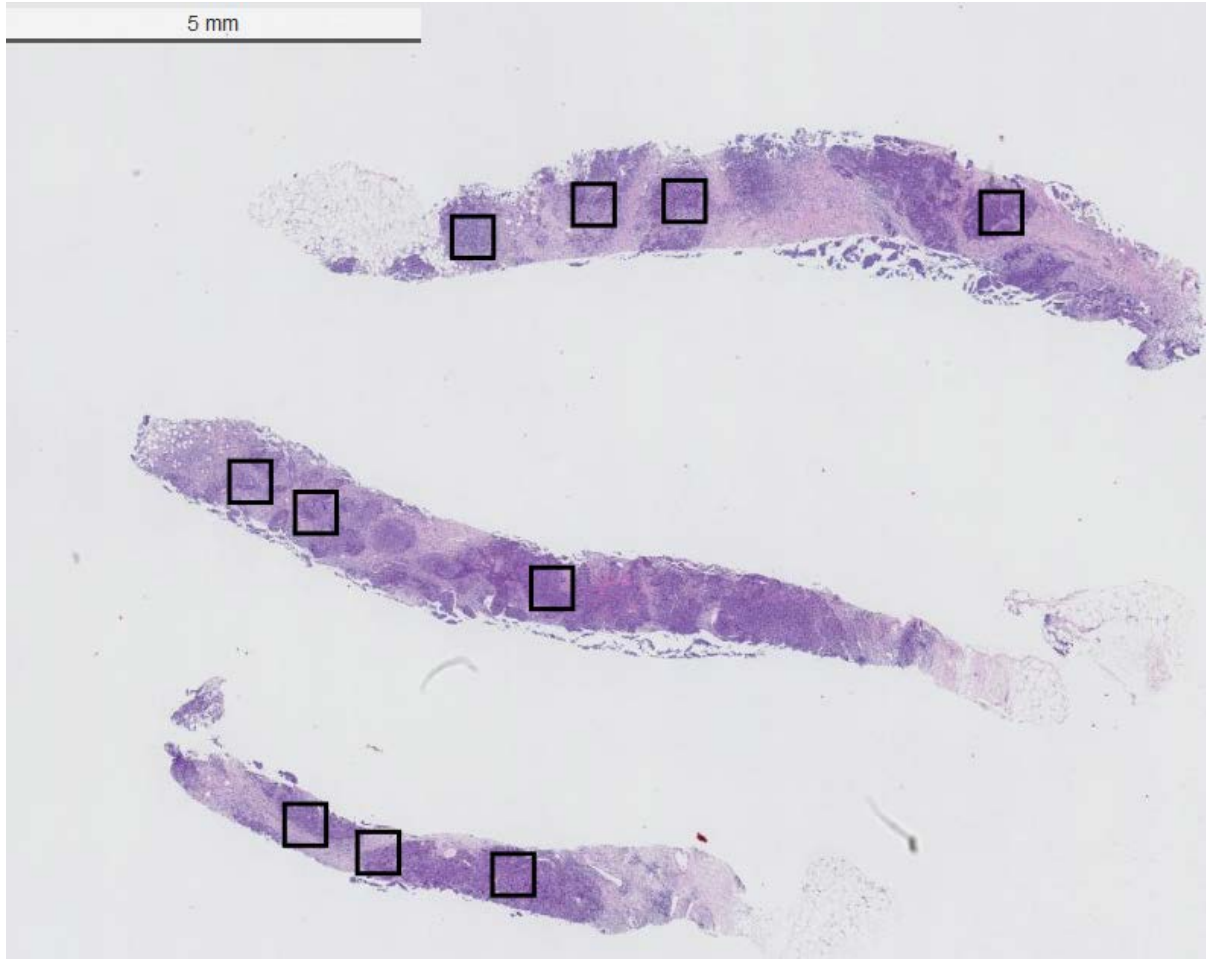
Evaluate performance
Requires truth

Patch to Whole Slide Image



- Zoom Out

Whole Slide Images: Digital Scans of Glass slides

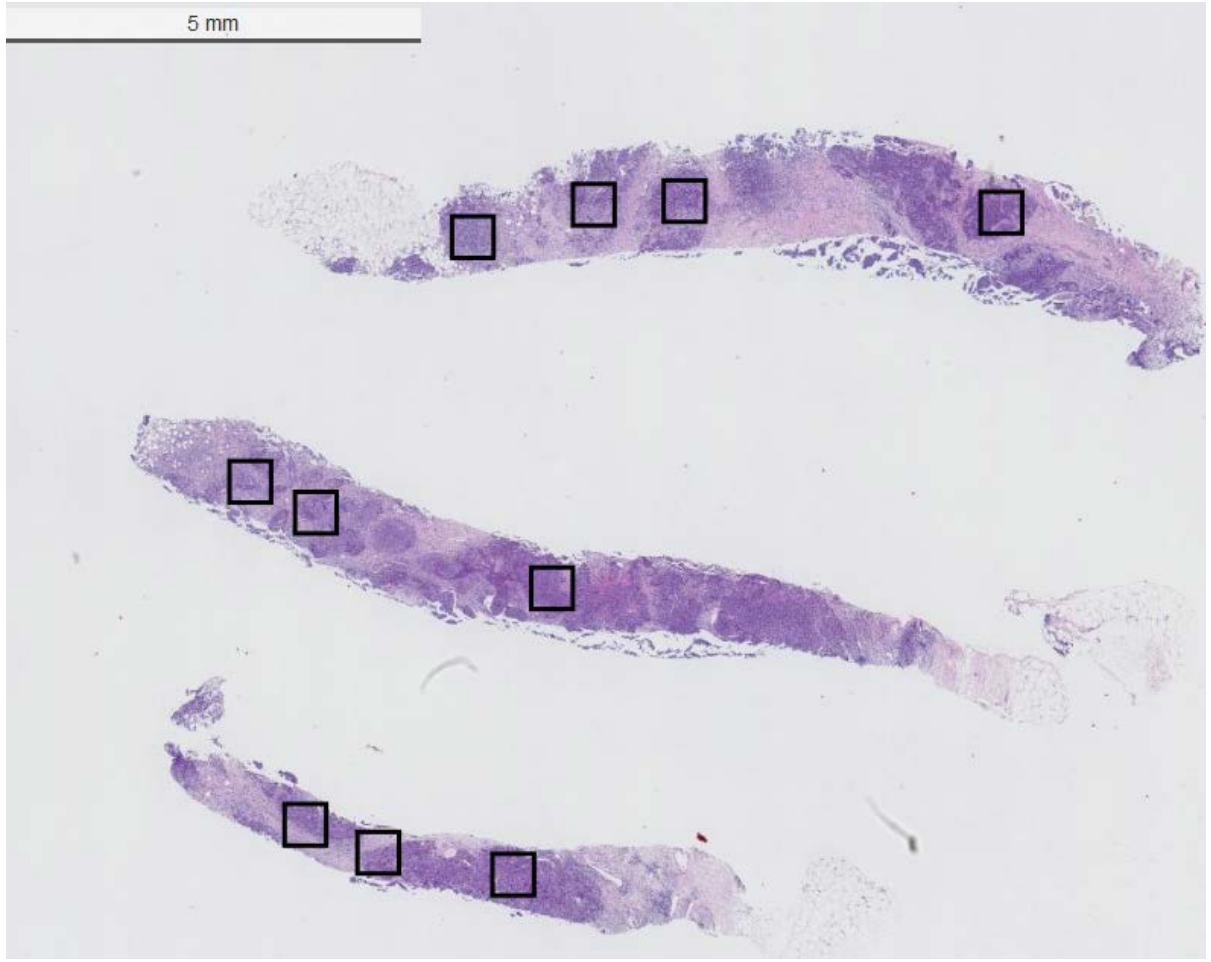


- Breast Cancer Biopsies
- Square Regions of Interest control the evaluation areas

Current selection by pathologist:

- Areas in tumor (~50%)
- Areas in tumor margin (~20%)
- Other (~30%)

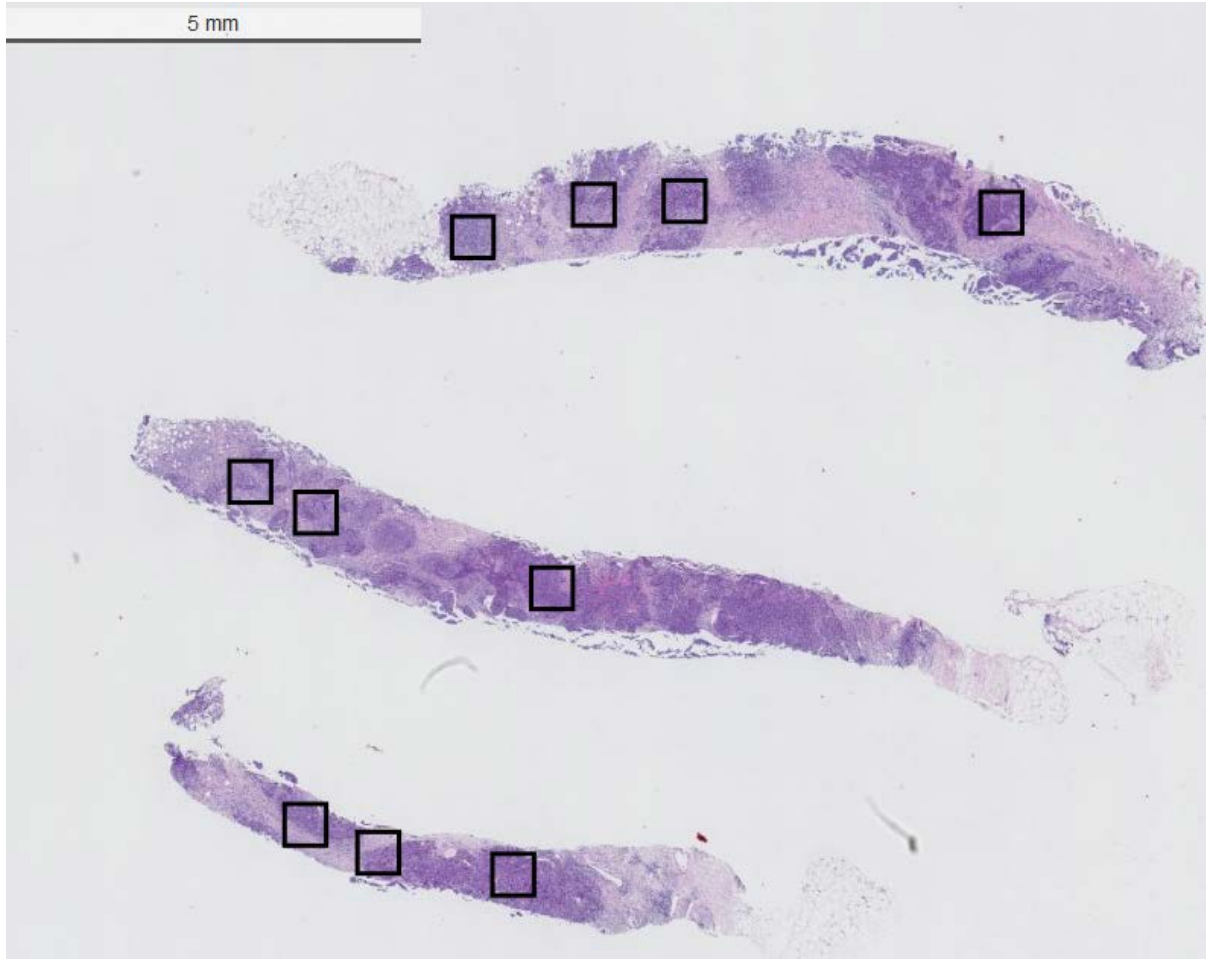
Whole Slide Images: Digital Scans of Glass slides



- Breast Cancer Biopsies
- Square Regions of Interest control the evaluation areas

Study to prepare the study.
Cover the range of scores.

Whole Slide Image to Patient



- Zoom Out

Patients

Subgroup Description		Planned for MDDT?
Age	<40 years old	Yes
	40-60 years old	Yes
	>60 years old	Yes
Breast Cancer Subtypes	Luminal A	Maybe
	Luminal B	Maybe
	Triple-negative	Yes
	HER2 positive	Maybe
	Normal-like	Maybe
Breast Cancer Stages	0	Yes
	I	Yes
	II	Yes
	III	Yes
	IV	Yes
Patients After Therapy	Therapy 1	No
	Therapy 2	No
	Therapy 3	No

TILs always look the same.
Background “context” looks different.

- Regulatory submission
- Define the patient population
- HTT project can’t afford to sample and annotate all subgroups
- Algorithm manufacturer responsible for gaps

Pathology vs. Radiology

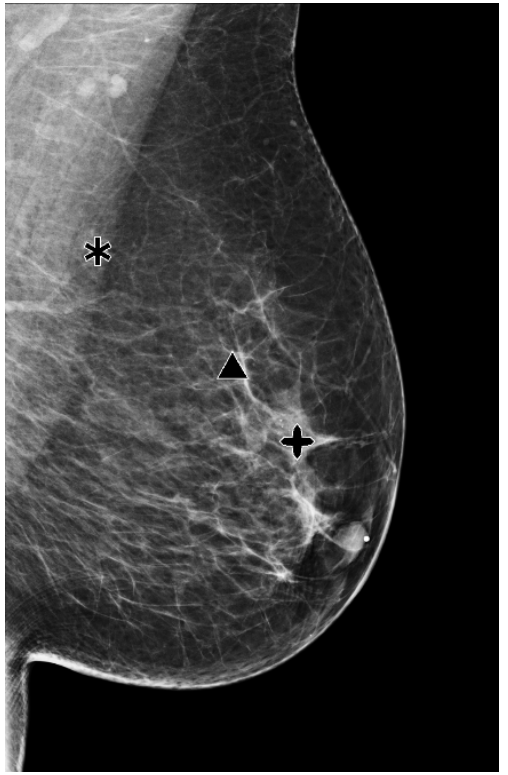
Truth for pathology is challenging

- Pathology images much larger
  - Truthing more burdensome … more area!

Focus on regions of interest

- Radiology truth often established by pathology evaluation of biopsy …

Agreement with multiple pathologists



http://www.hologic.ca/image-analytics#overlay-context=closeup-peerview-cad

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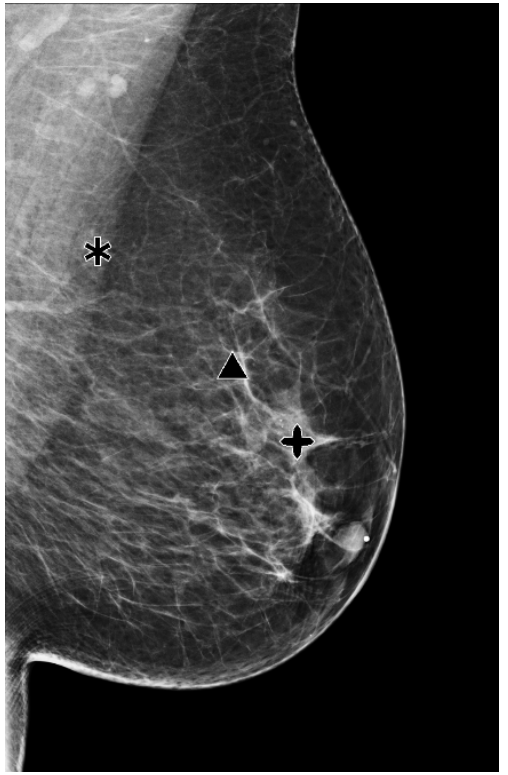
Agreement with multiple pathologists

- Alternate tissue stains
  - Done on adjacent tissue or requires restaining

Not the same tissue
Can damage the tissue



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- Pathology images much larger
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Focus on regions of interest

- Radiology truth often established by pathology evaluation of biopsy …

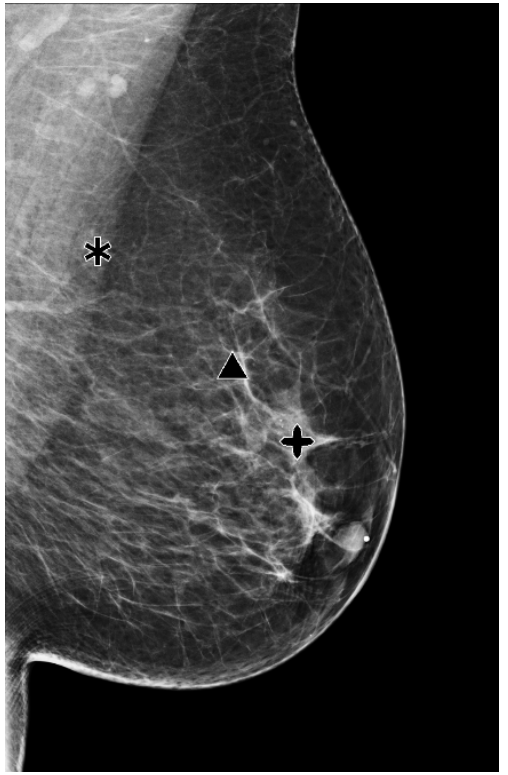
Agreement with multiple pathologists

- Alternate tissue stains
  - Clear and restain or adjacent tissue

Not the same tissue

Can damage the tissue

- Outcomes
  - Complicated to coordinate
  - Cost time and money
  - Several steps removed from tissue



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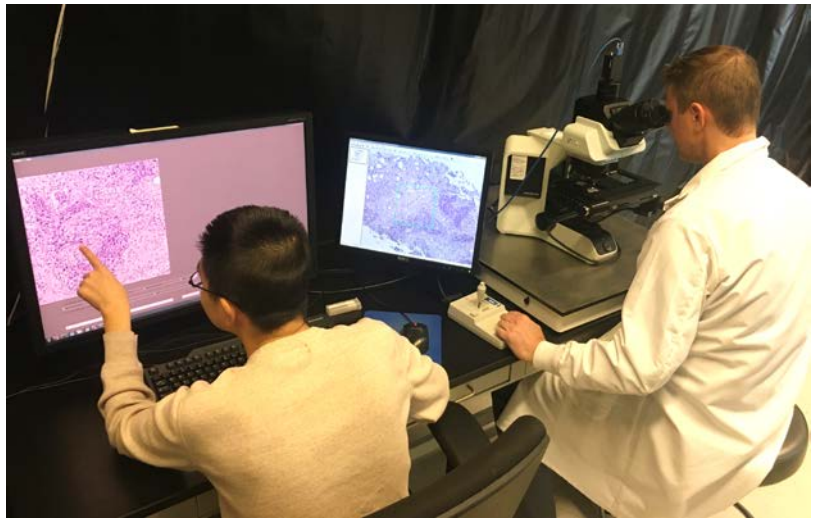
Update: Choices & Challenges

	Digital Modes		Microscope Mode
	PathPresenter	caMicroscope	eeDAP
nReaders	7	8	7
nObs at USCAP	850	300	440
nObs post USCAP	232	572	0
nObs Total	1082	872	440



Total Obs 2394

Data-collection test run

- Alliance Meeting
- USCAP Annual Meeting
- Feb. 28, 2020

Four workstations

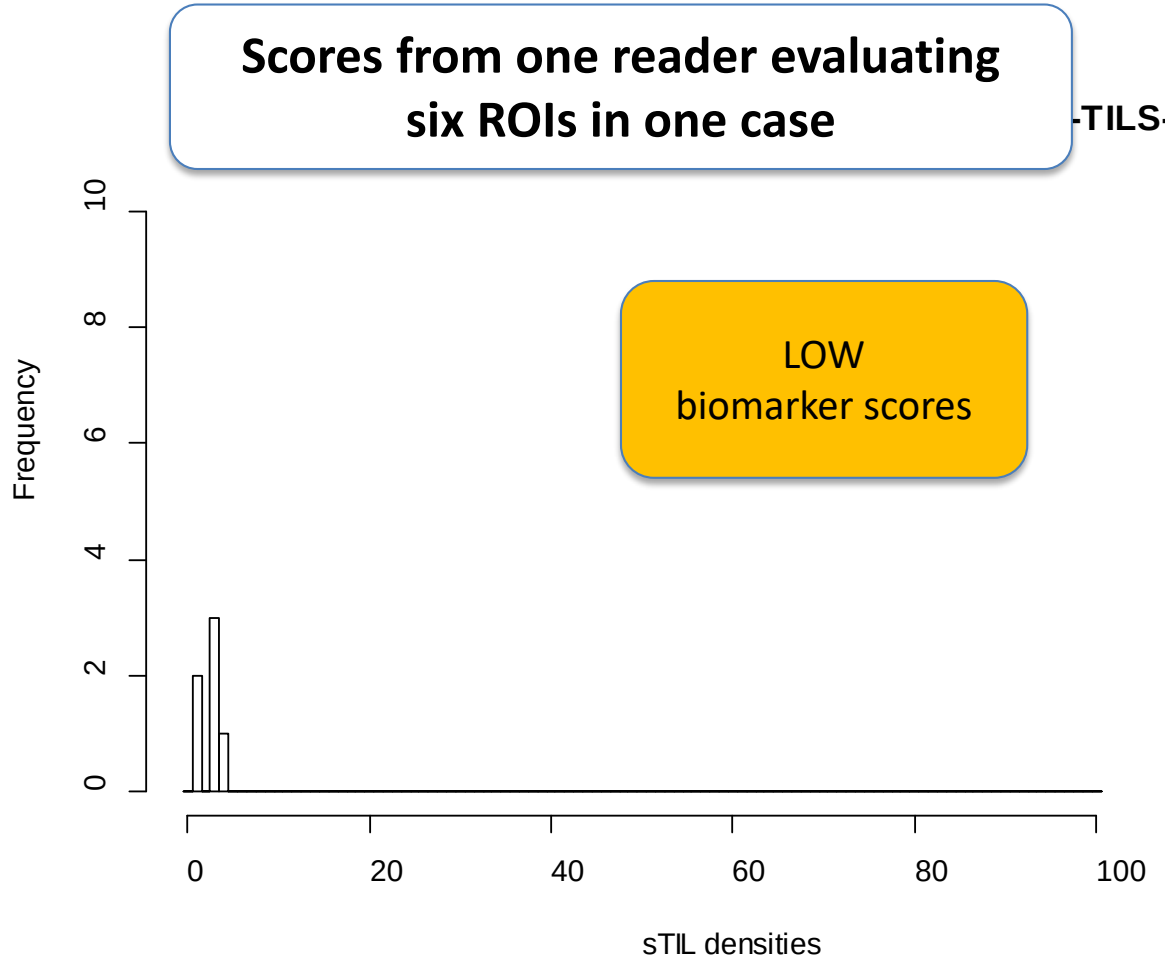
- 2 microscopes
- 2 digital platform

64 slides (balance sampling within and across specimens)

- 8 batches of 8 slides
- 10 ROIs per slide
- 30 minute sessions

What does the data look like?

- Histogram of Biomarker Scores
- Many slides yield LOW biomarker scores



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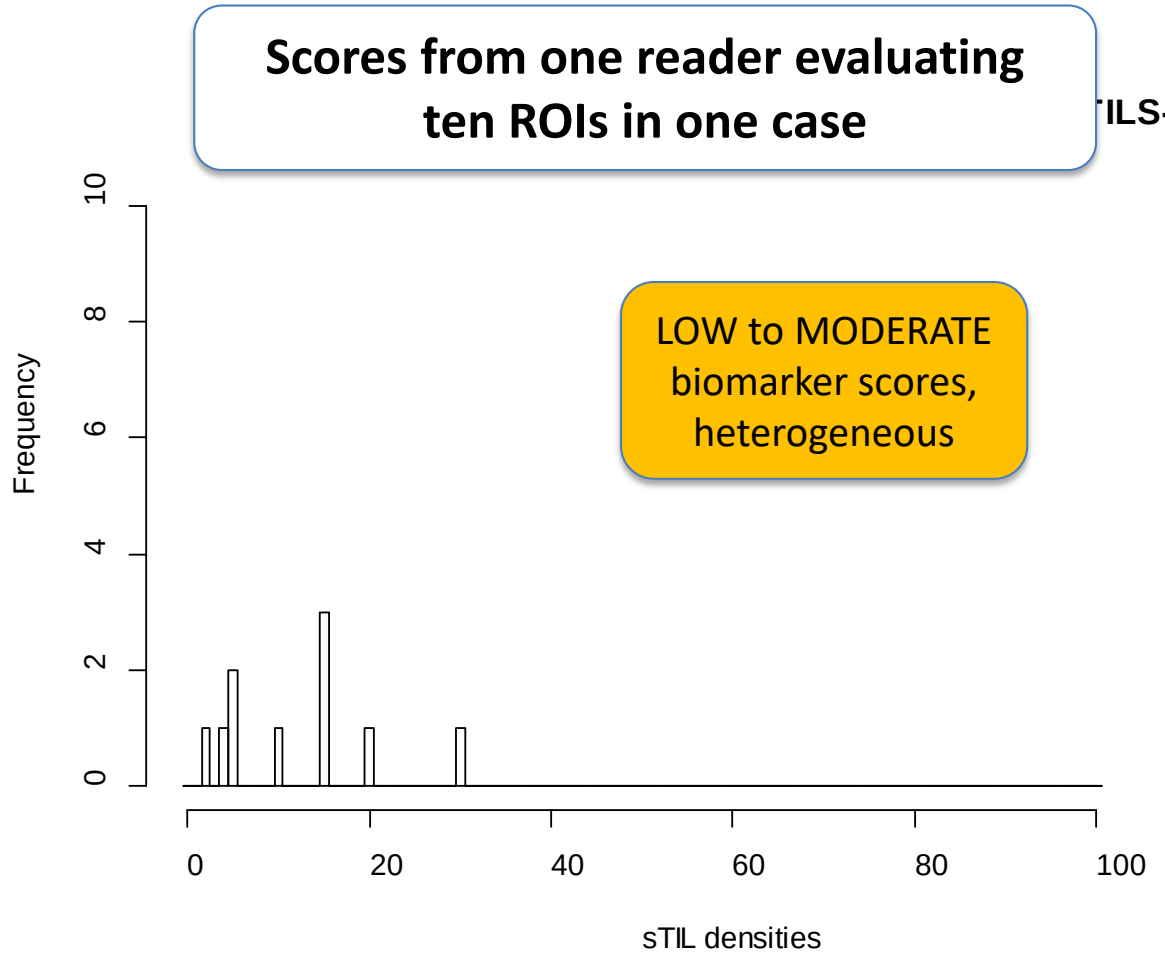
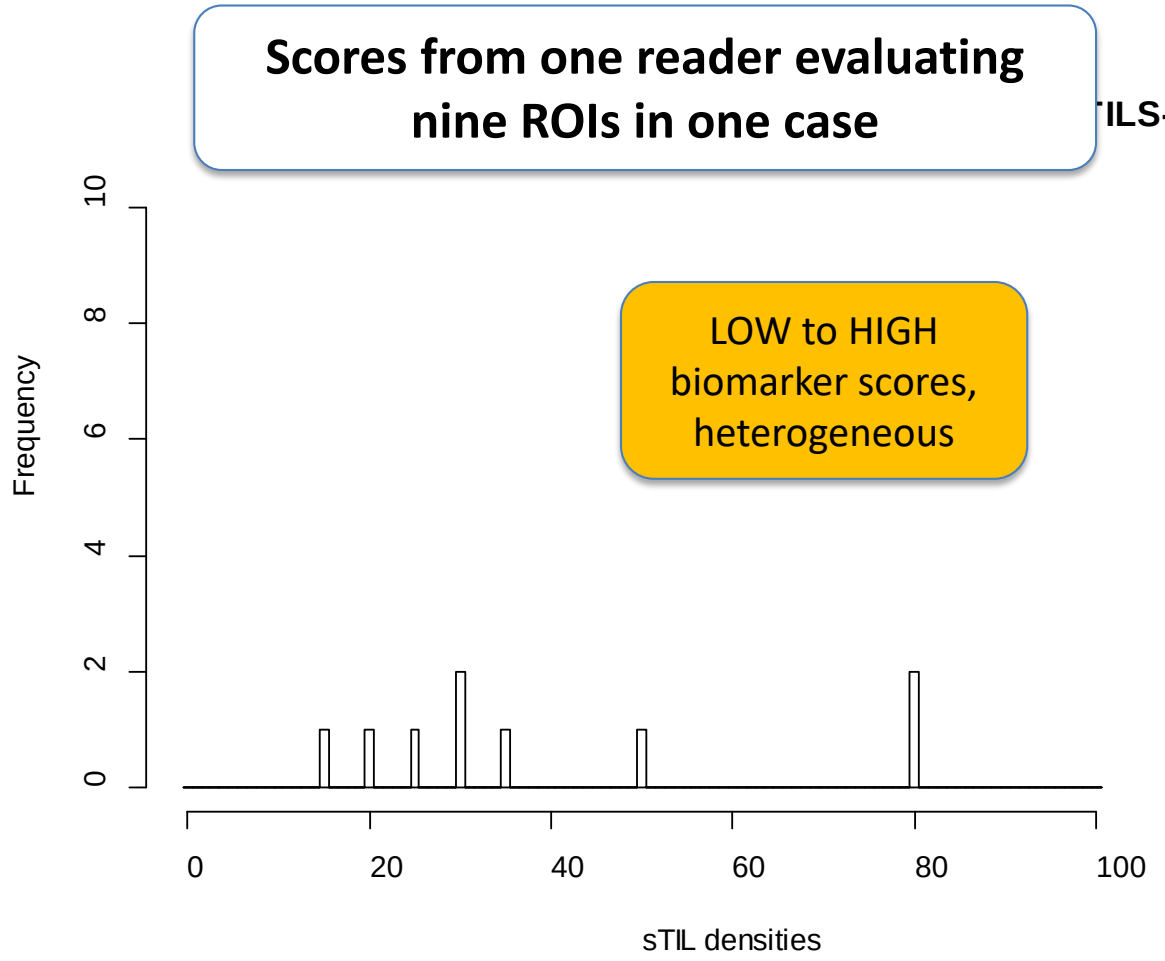
- Some slides yield LOW to MODERATE biomarker scores



What does the data look like?

- Histogram of Biomarker Scores
- Many slides yield LOW biomarker scores
- Some slides yield LOW to MODERATE biomarker scores
- Some slides yield LOW to HIGH biomarker scores

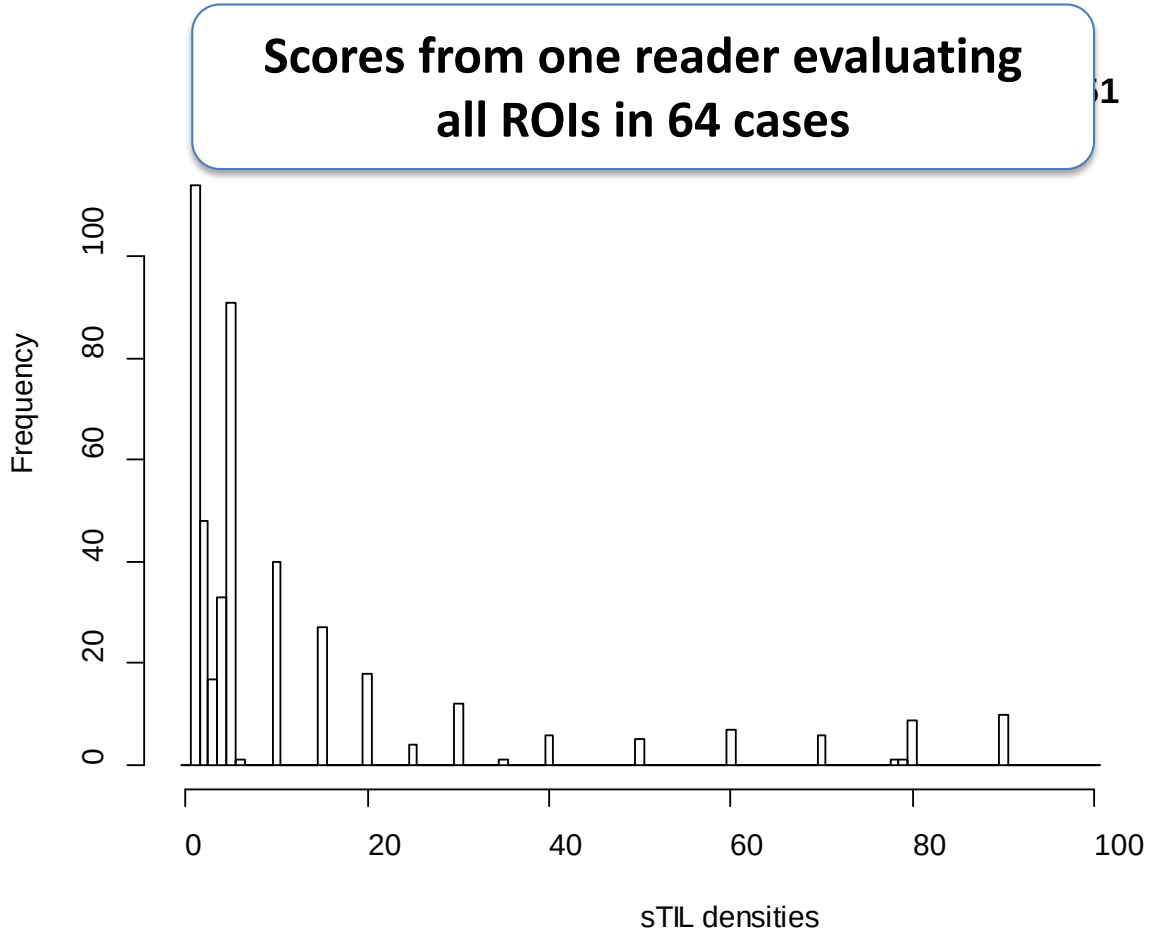


What does the data look like?

- Histogram of Biomarker Scores

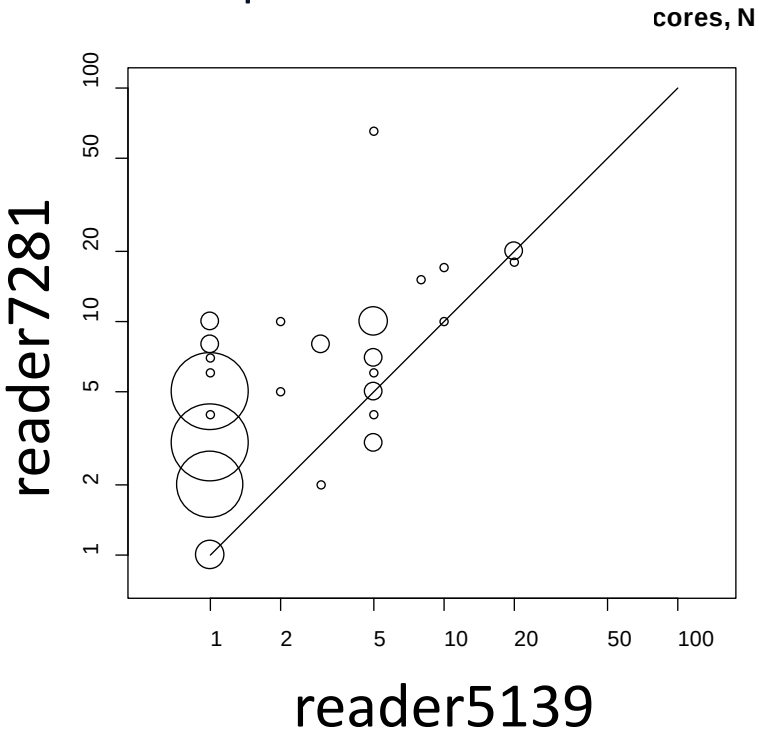
- One reader
- All 64 slides
- 10 ROIs per slide

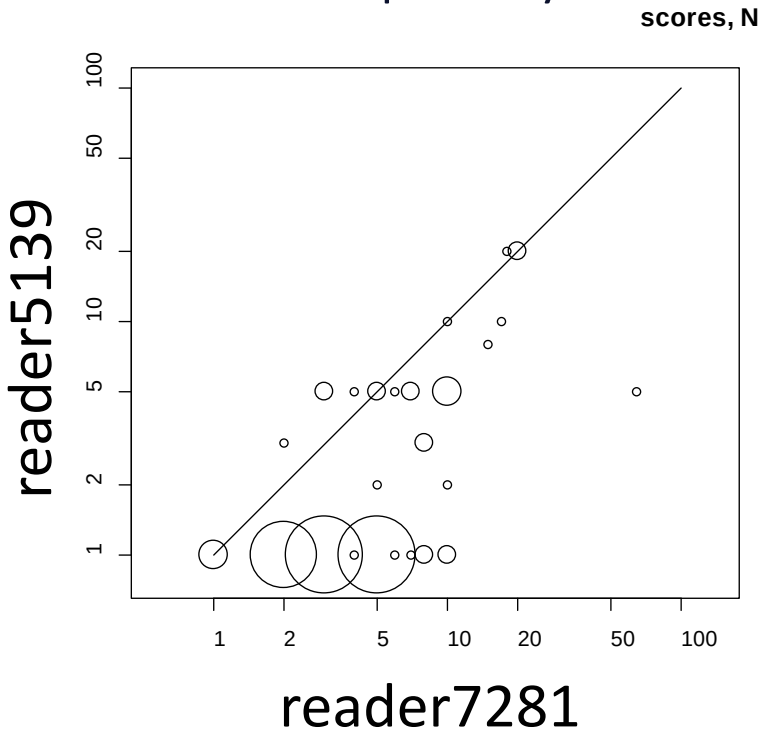
- Oversampling low scores



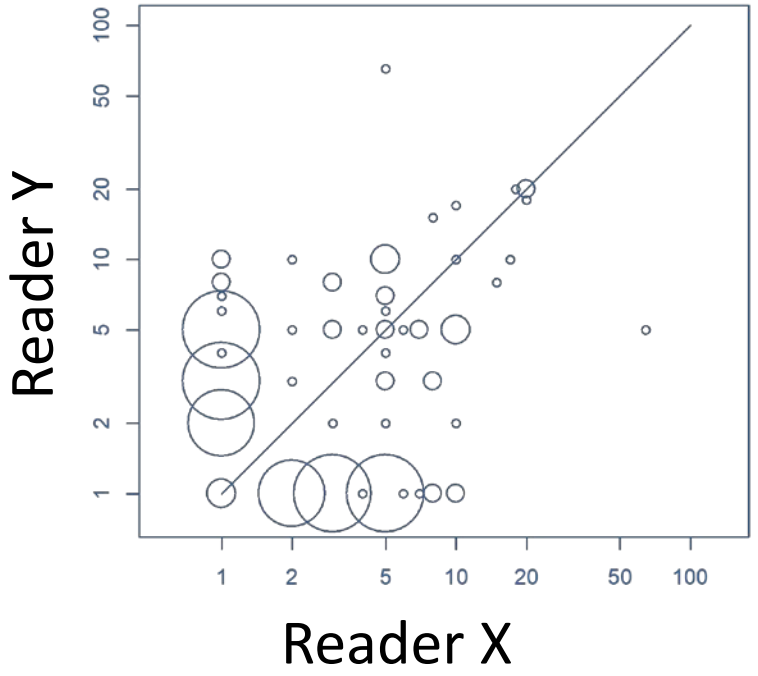
Agreement: Start with a scatter plot

- Two readers, CAmicroscope, batch001
- Plots scaled log base 10
- Circle size proportional with number of observations
- Flip reader7281 <-> reader5139 == Flip x <-> y

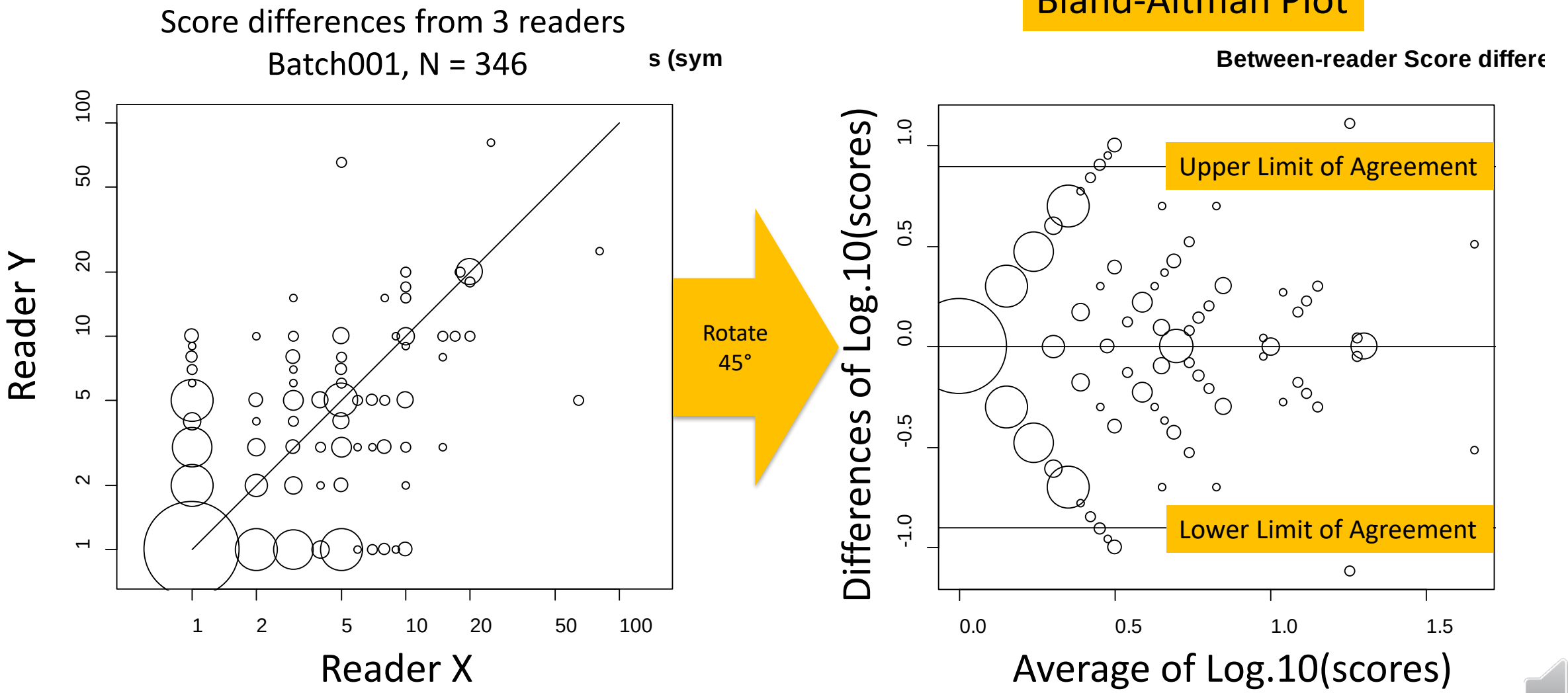




Combine to Symmetrize



Agreement: Consider all pairs of readers



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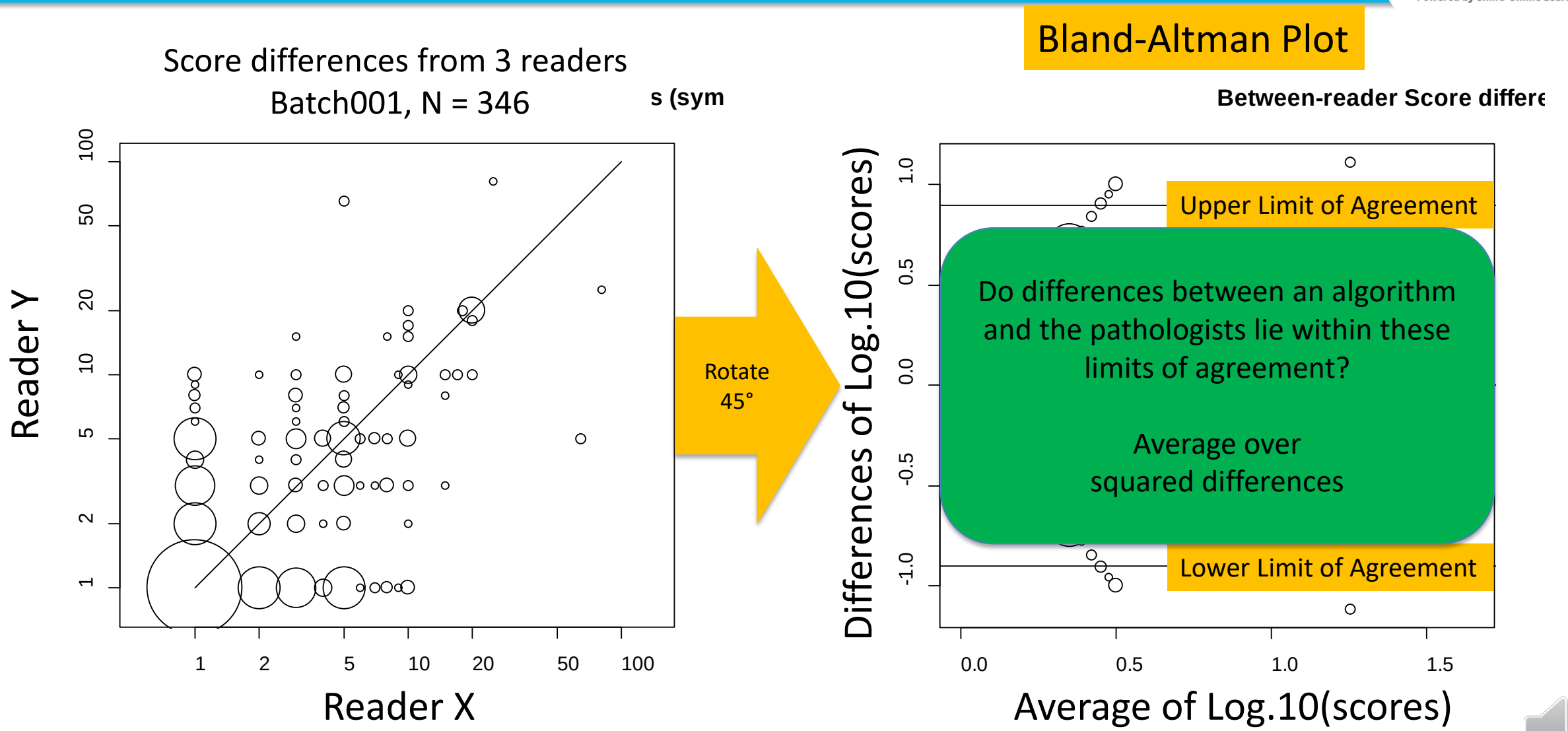

Summary

Truth by pathologists

Pathologist evaluations are noisy

Reduce variability with

- Training
- Multiple pathologists per case

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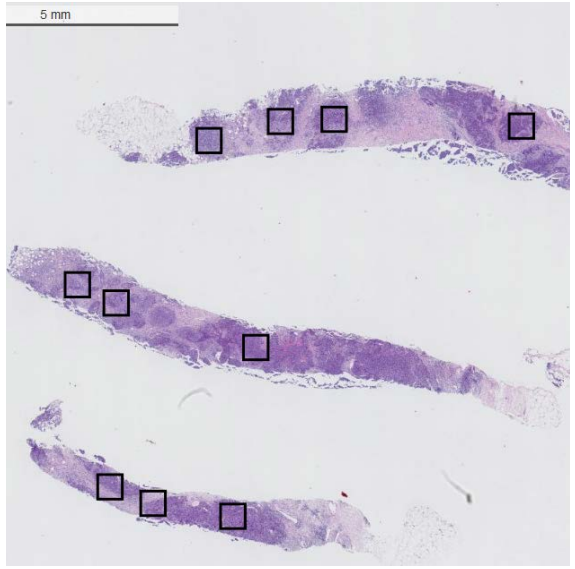

Data Sampling

Range of biomarker scores

Regions within an image

Images from different patient subgroups

Summary

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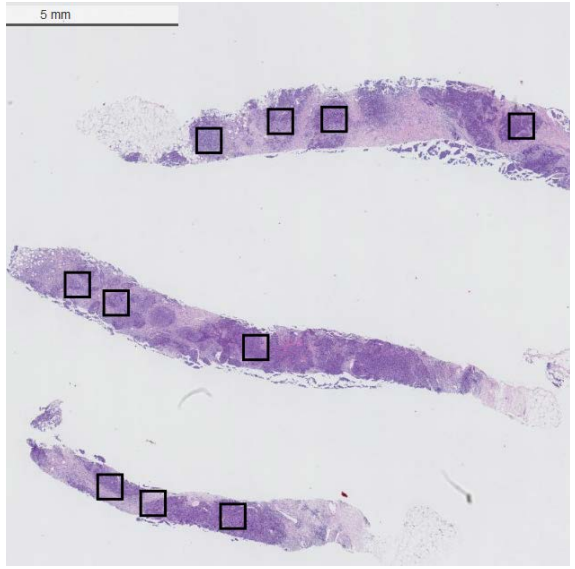

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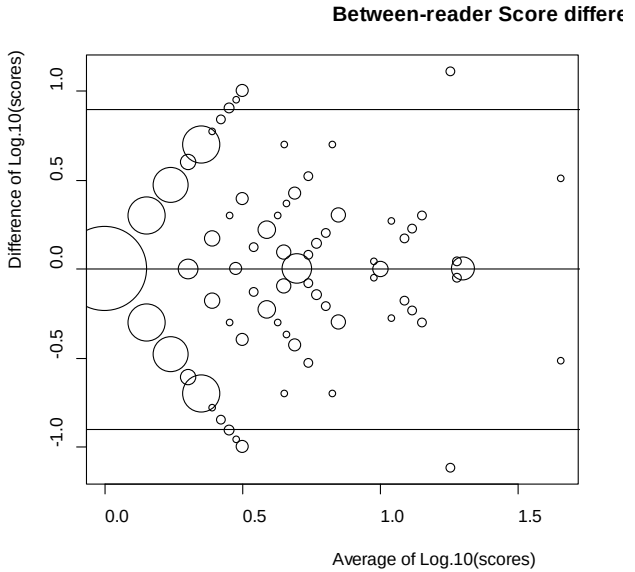


Data analysis

Account for known sources of variability and correlations

Multi-reader, multi-case analysis

Clustered and nested data

So sad. Not enough time to discuss.

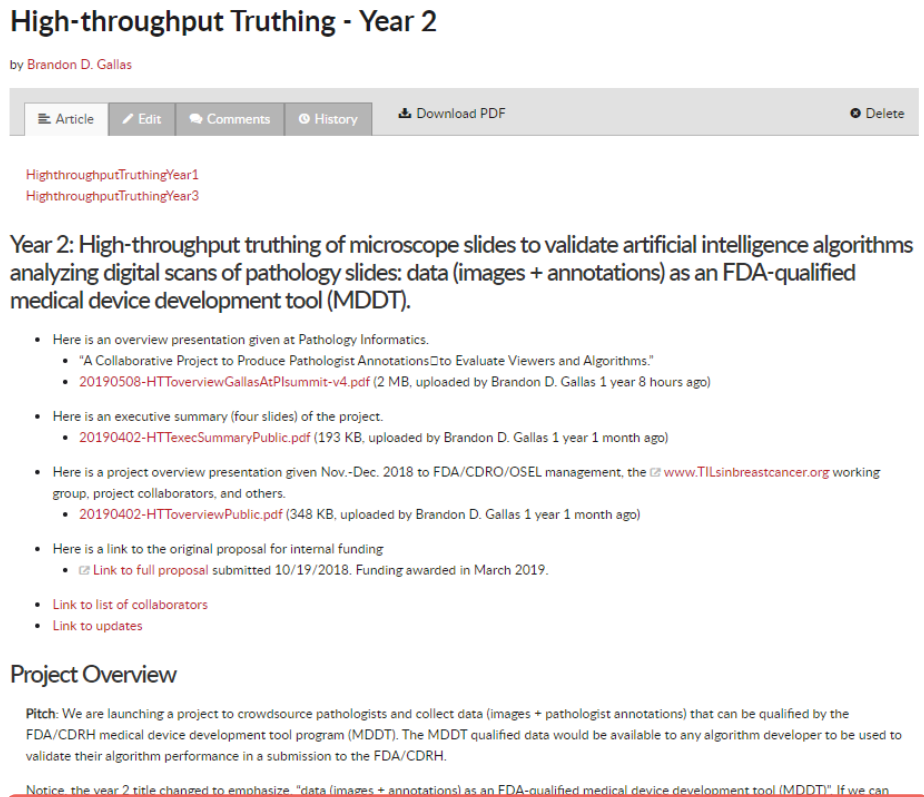
- Statistical methods
- Clinical context and use case
- FDA's Medical Device Development Tool Program
- Device advice
  - https://ncihub.org/groups/eedapstudies/wiki/DeviceAdvice

Closing

- We are collecting data to
  - Build collaborative relationships
  - Investigate methods and tools
  - Support the evaluation of AI/ML
- We hope to
  - Inform regulatory decision making
  - Improve submissions
  - Support and enable interoperability

More information

Learn about the project



High-throughput Truthing - Year 2

by Brandon D. Gallas

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HighthroughputTruthingYear1
HighthroughputTruthingYear3

Year 2: High-throughput truthing of microscope slides to validate artificial intelligence algorithms analyzing digital scans of pathology slides: data (images + annotations) as an FDA-qualified medical device development tool (MDDT).

- Here is an overview presentation given at Pathology Informatics.
  - "A Collaborative Project to Produce Pathologist Annotations to Evaluate Viewers and Algorithms."
  - 20190508-HTToverviewGallasAtPIsummit-v4.pdf (2 MB, uploaded by Brandon D. Gallas 1 year 8 hours ago)
- Here is an executive summary (four slides) of the project.
  - 20190402-HTTexecSummaryPublic.pdf (193 KB, uploaded by Brandon D. Gallas 1 year 1 month ago)
- Here is a project overview presentation given Nov.-Dec. 2018 to FDA/CDRO/OSEL management, the www.TILsinbreastcancer.org working group, project collaborators, and others.
  - 20190402-HTToverviewPublic.pdf (348 KB, uploaded by Brandon D. Gallas 1 year 1 month ago)
- Here is a link to the original proposal for internal funding
  - Link to full proposal submitted 10/19/2018. Funding awarded in March 2019.
- Link to list of collaborators
- Link to updates

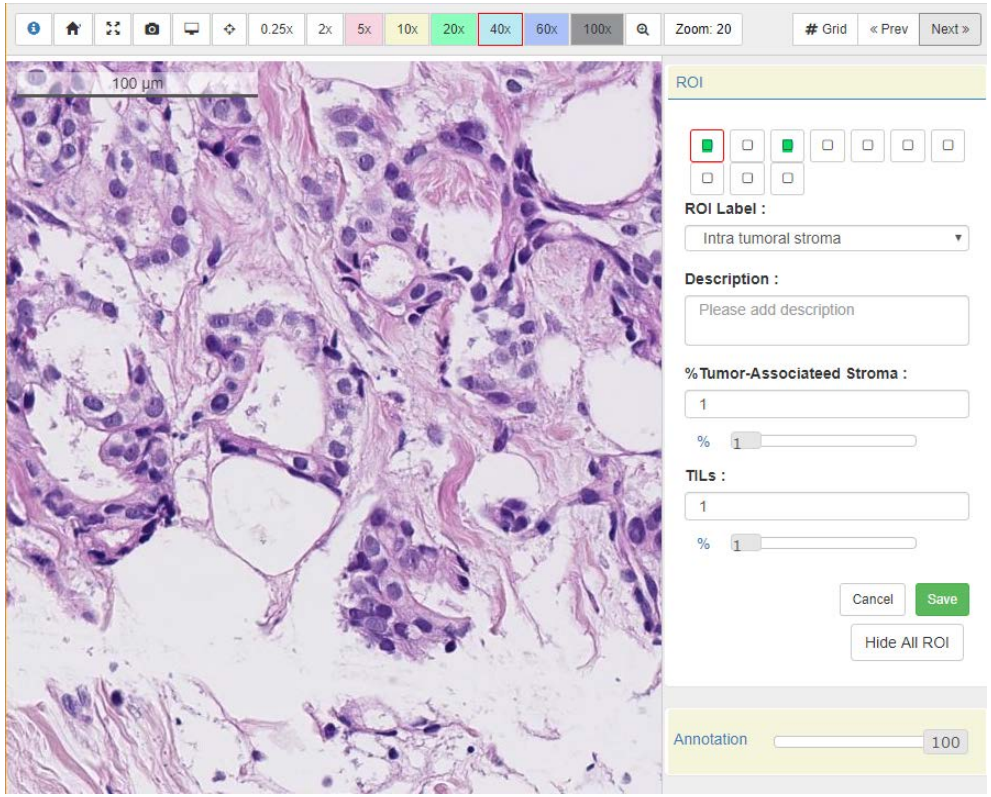
Project Overview

Pitch: We are launching a project to crowdsource pathologists and collect data (images + pathologist annotations) that can be qualified by the FDA/CDRH medical device development tool program (MDDT). The MDDT qualified data would be available to any algorithm developer to be used to validate their algorithm performance in a submission to the FDA/CDRH.

Notice, the year 2 title changed to emphasize, "data (images + annotations) as an FDA-qualified medical device development tool (MDDT)". If we can

https://nciphub.org/groups/eedapstudies/wiki/HighthroughputTruthingYear2

Participate in Data Collection



https://nciphub.org/groups/eedapstudies/wiki/HighthroughputTruthingYear3