

# High-Throughput Truthing (HTT): Pathologist Agreement from a Pilot Study

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Office of Science and Engineering Laboratories

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U.S. Food and Drug Administration

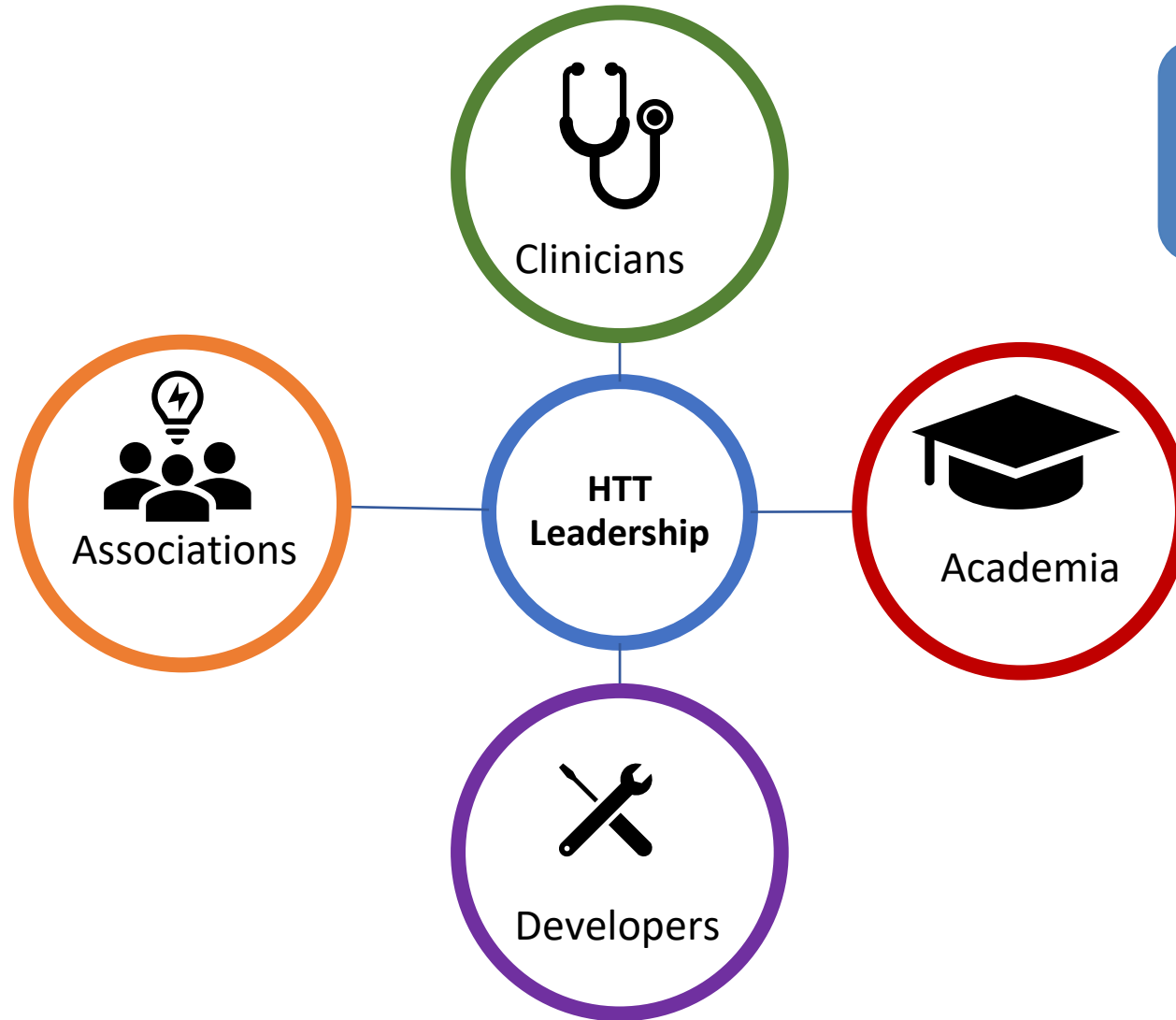


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# Collaboration of Volunteers



There is room for you!

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# DISCLOSURE

In the past 12 months, **I have not** had any significant financial interest or other relationship with the manufacturers of the products or providers of the services that will be discussed in my presentation.

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# Outline

- Overview of the HTT project
  - High-Throughput Truthing
- Explore the Data
- Questions and Current Work
- Next steps
- Conclusions

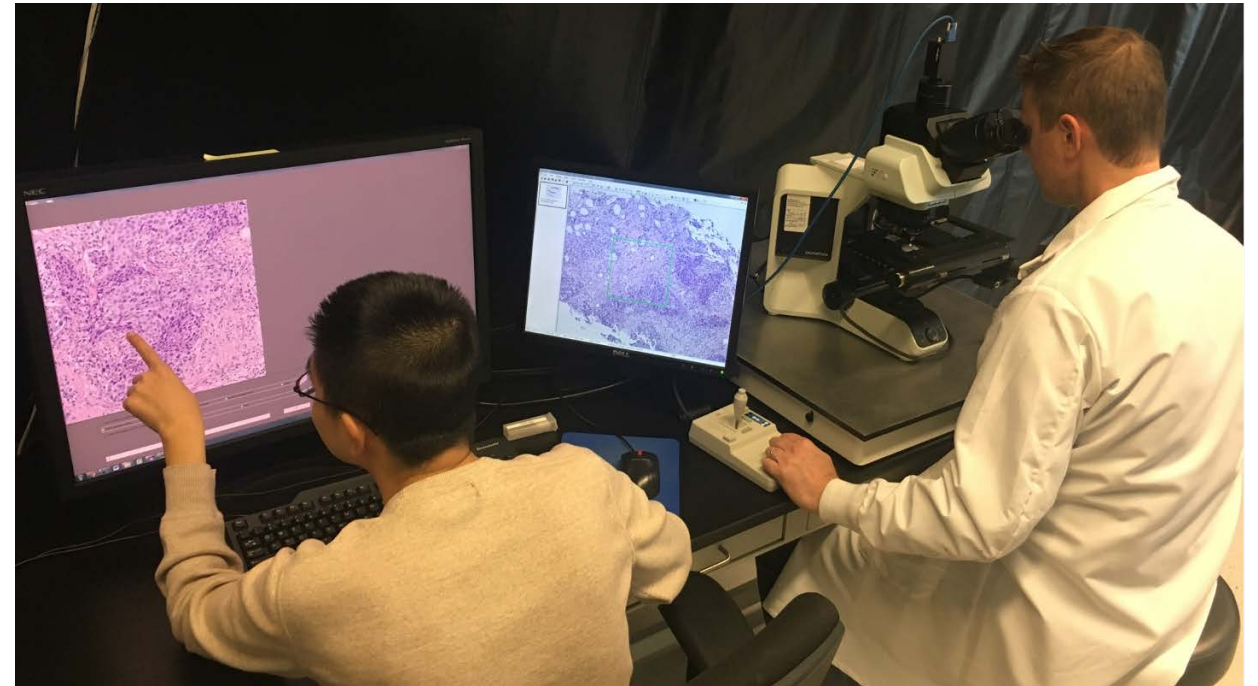
Work in  
progress

# Overview of the HTT project

- Clinical Application and Relevance
- Regulatory Deliverable
- Validation Data and Methods
- Standardized Evaluations of a Quantitative Biomarker
  
- Project description accepted for publication at the Journal of Pathology Informatics
  - S. N. Dudgeon *et al.*, “A Pathologist-Annotated Dataset for Validating Artificial Intelligence: A Project Description and Pilot Study,” *arXiv:2010.06995 [eess, q-bio]*, vol. Accepted for publication by the Journal of Pathology Informatics, Oct. 2020, Accessed: Oct. 29, 2020. [Online]. Available: <http://arxiv.org/abs/2010.06995>

# Clinical Application and Relevance

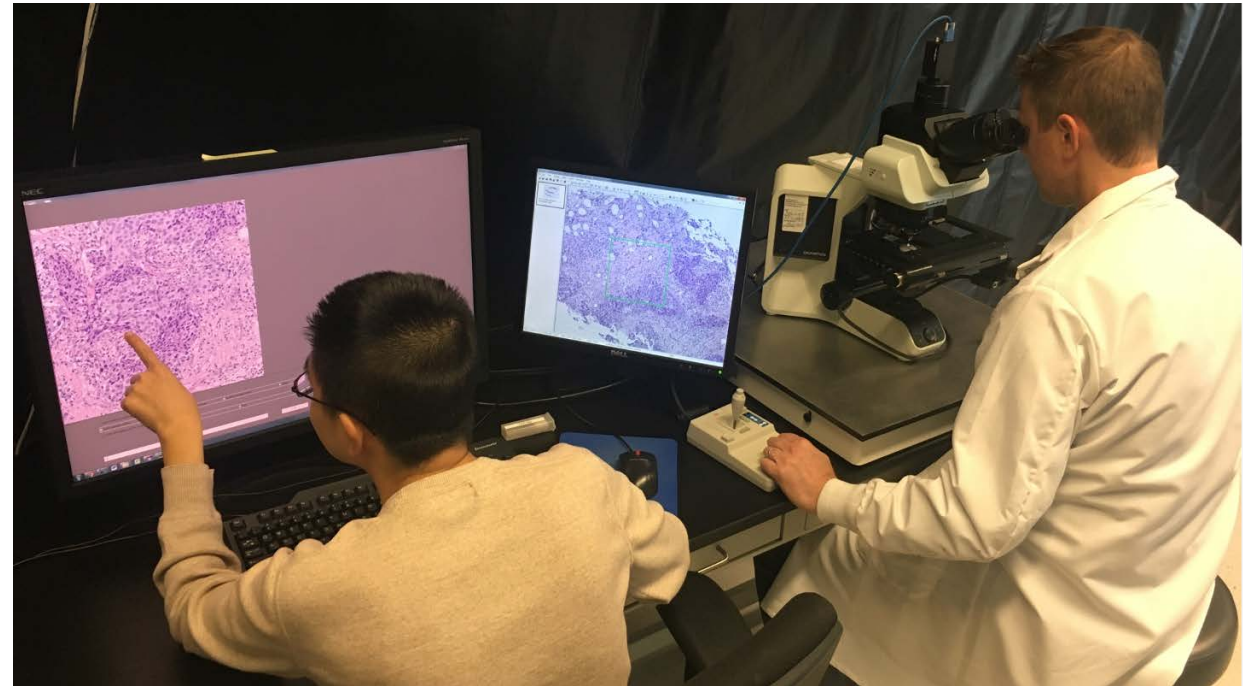
- Clinical application:
  - Stromal Tumor Infiltrating Lymphocytes (sTILs) in breast cancer
- Clinical relevance of sTILs:
  - Prognostic for survival
  - Expected to inform patient management
  - Expected to reduce use of toxic chemotherapies
- Software as a medical device (SAMM)
  - Reduce burden on pathologist
  - Reproducible
  - Quantitative



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# Regulatory Deliverable

- **Regulatory Science Question**
  - How can we use pathologist annotations to support SaMD validation?
- **Deliverables**
  - Validation data
  - Methods
- **Pursue Regulatory Deliverable:**
  - Medical Device Development Tool (MDDT)



<https://www.fda.gov/medical-devices/science-and-research-medical-devices/medical-device-development-tools-mddt>

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# Validation Data and Methods

## Data

- Multiple sites
- Represents defined population
- Reproducible protocol
- Proficient Pathologists

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# Validation Data and Methods

## Data

- Multiple sites
- Represents defined population
- Reproducible protocol
- Proficient Pathologists

## Methods

- Interchangeability
- Quantitative biomarker
  - Quantitative agreement
- Human evaluation of a quantitative biomarker
  - Rank-based agreement
  - Qualitative agreement

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# Validation Data and Methods

## Quantitative Agreement Endpoint:

*MSD = Mean-Squared Deviation*

- Algorithm-pathologist agreement

$$\text{MSD} = E \left[ (Y_{kl} - X_{jkl})^2 \right]$$

Score from SaMD

Score from pathologist  $j$

Same case  $k$  and location  $l$

- Pathologist-pathologist agreement

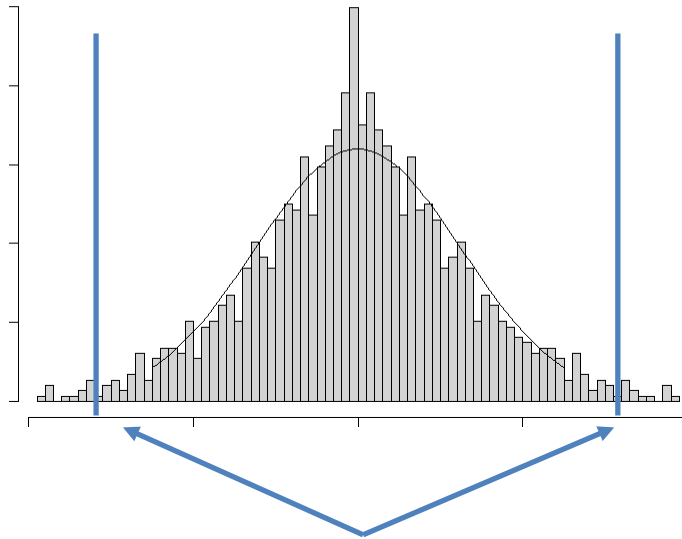
$$\text{MSD} = E \left[ (X_{j'kl} - X_{jkl})^2 \right]$$

Score from pathologists  $j$  and  $j'$

Same case  $k$  and location  $l$

# Validation Data and Methods

Distribution of differences between pathologists



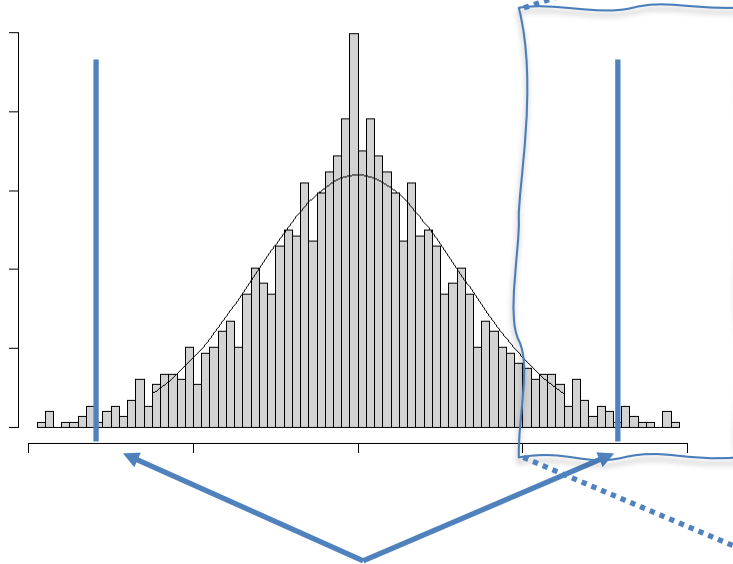
## Limits of agreement

Observed differences will be within the LOA  
~95% of the time

- Limits of agreement are proportional to
  - Standard deviation
  - Square root of MSD

# Validation data and methods

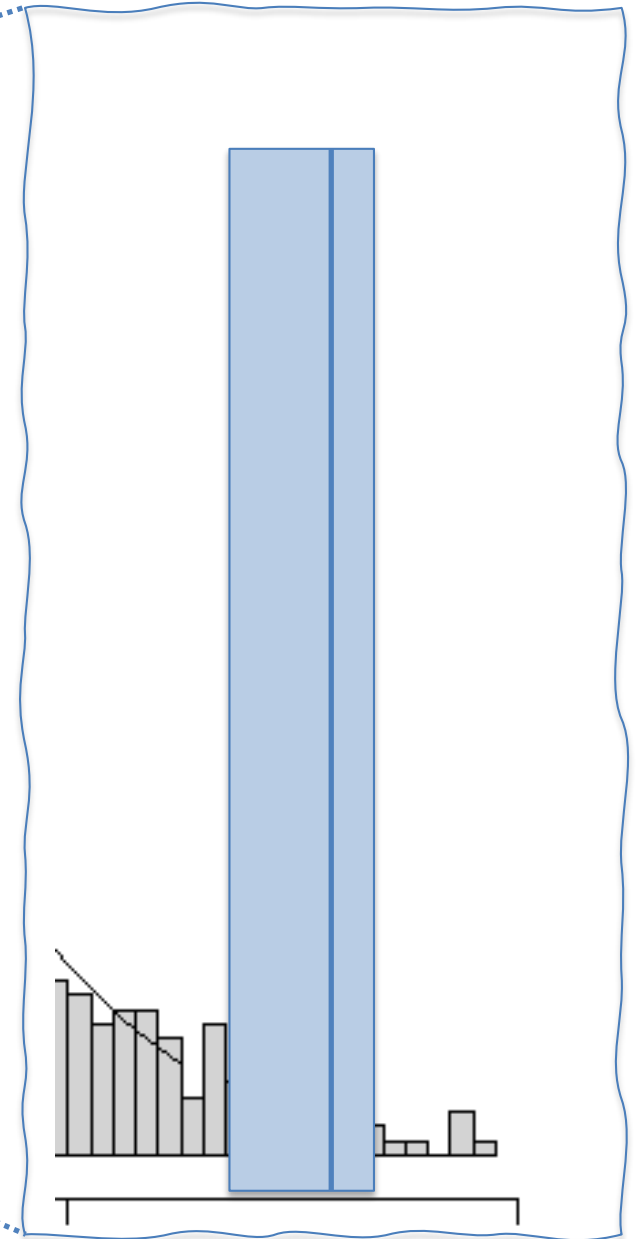
Distribution of differences between pathologists



- Confidence interval for reference panel LOA (not symmetric)

## Limits of agreement

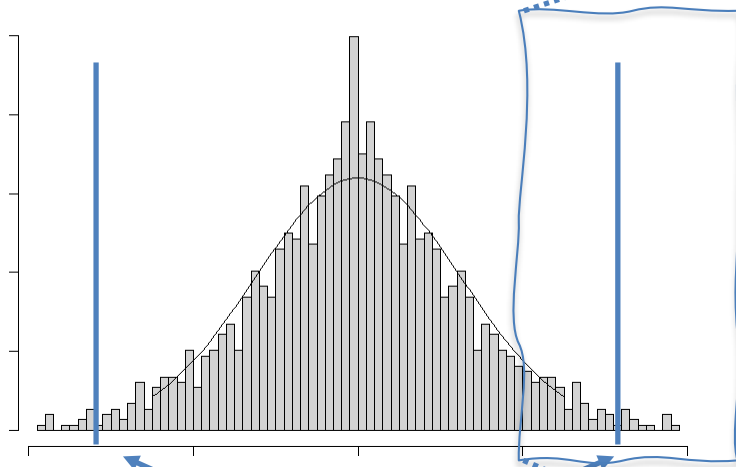
Observed differences will be within the LOA ~95% of the time



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# Validation Data and Methods

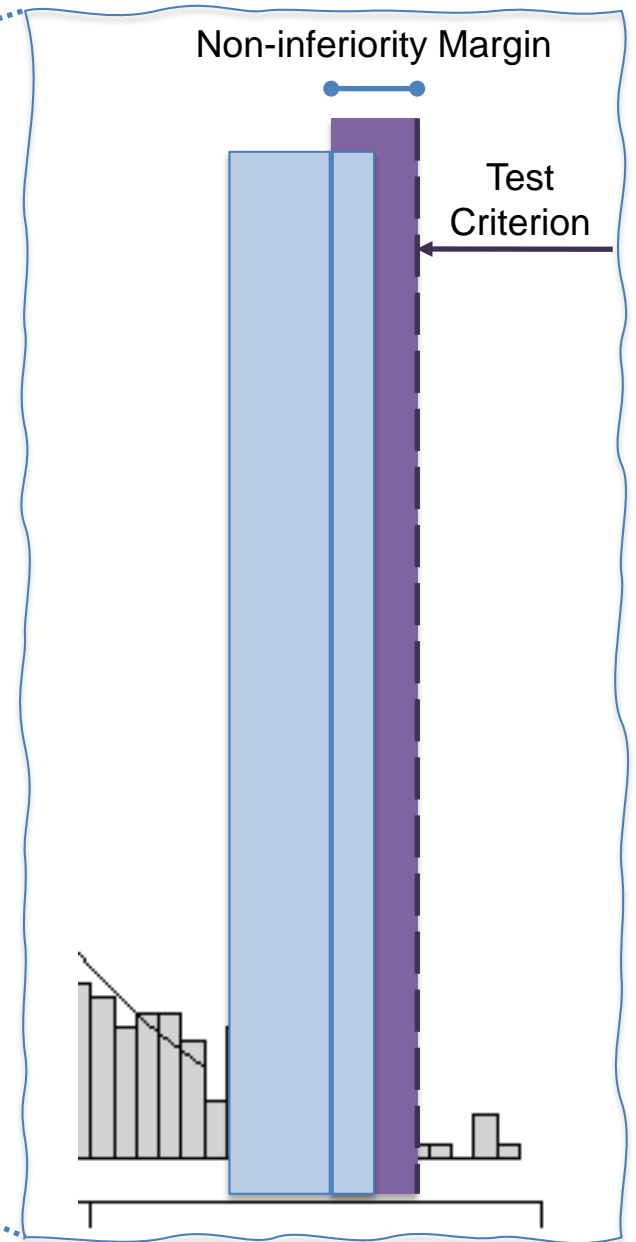
Distribution of differences between pathologists



- Clinically tolerable non-inferiority margin – 5% ?

## Limits of agreement

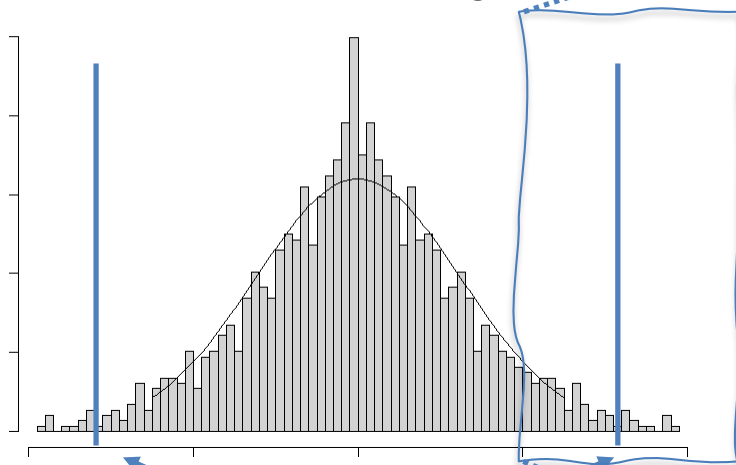
Observed differences will be within the LOA ~95% of the time



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# Validation Data and Methods

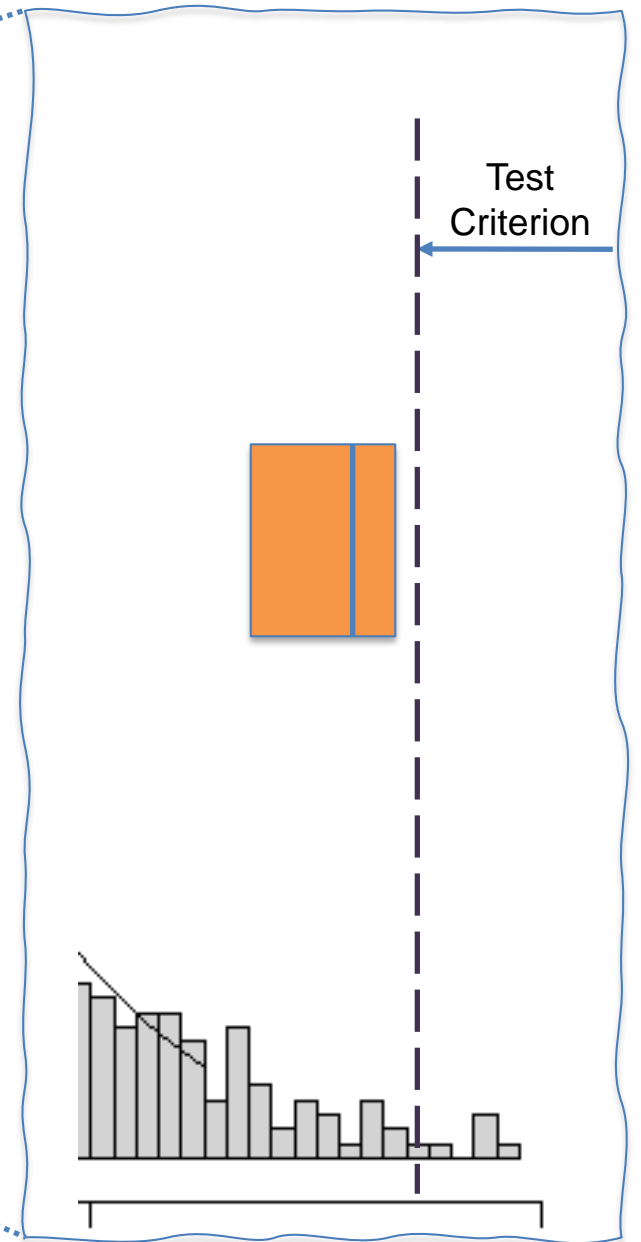
Distribution of differences between pathologists



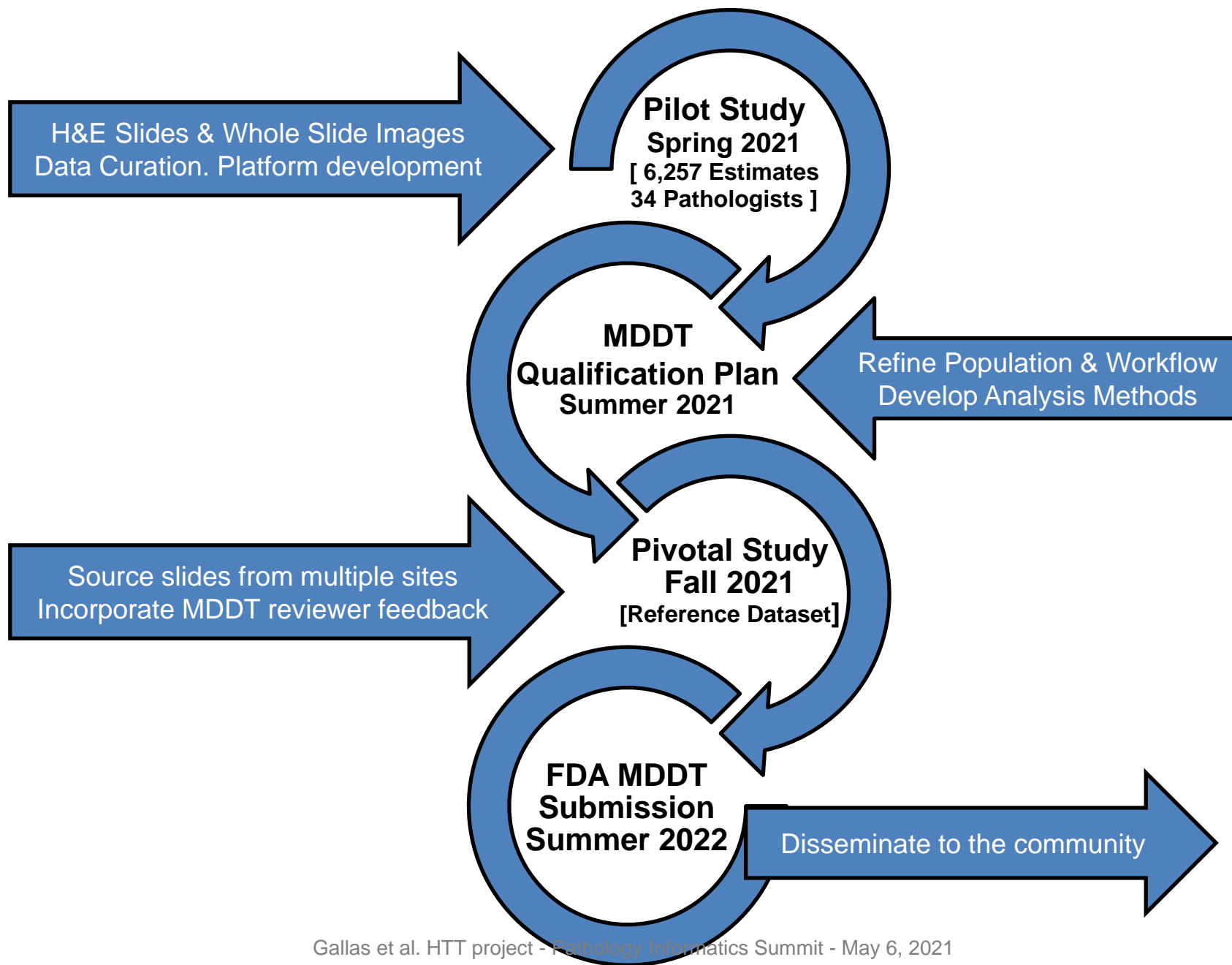
- Confidence interval of the algorithm-pathologist LOA
  - Compare to test criterion

## Limits of agreement

Observed differences will be within the LOA ~95% of the time



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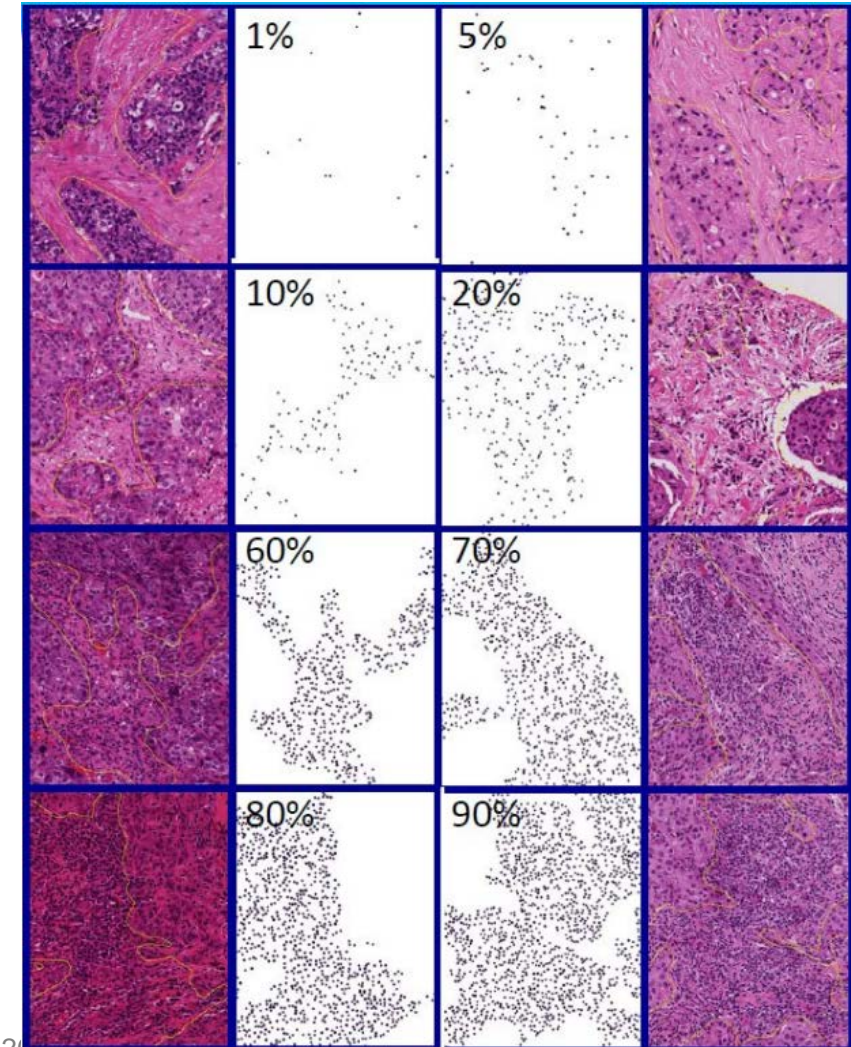


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# Standardized Evaluations of a Quantitative Biomarker

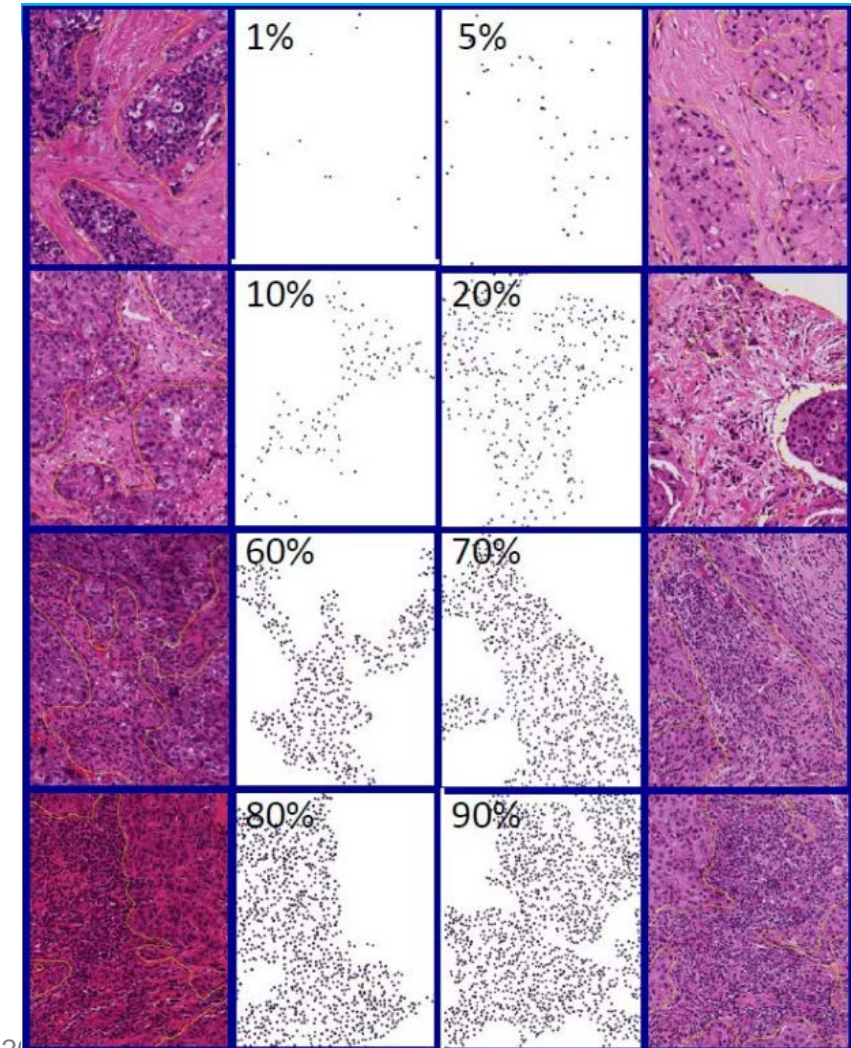
- Pathologist Evaluation
  - Density Estimates percent stromal Tumor Infiltrating Lymphocytes (sTILs) 0%-100%
  - Density Estimates percent stroma 0%-100%
- R. Salgado *et al.*, “The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: **recommendations** by an International TILs Working Group 2014,” *Ann. Oncol.*, vol. 26, no. 2, pp. 259–271, Feb. 2015, doi: [10.1093/annonc/mdu450](https://doi.org/10.1093/annonc/mdu450).



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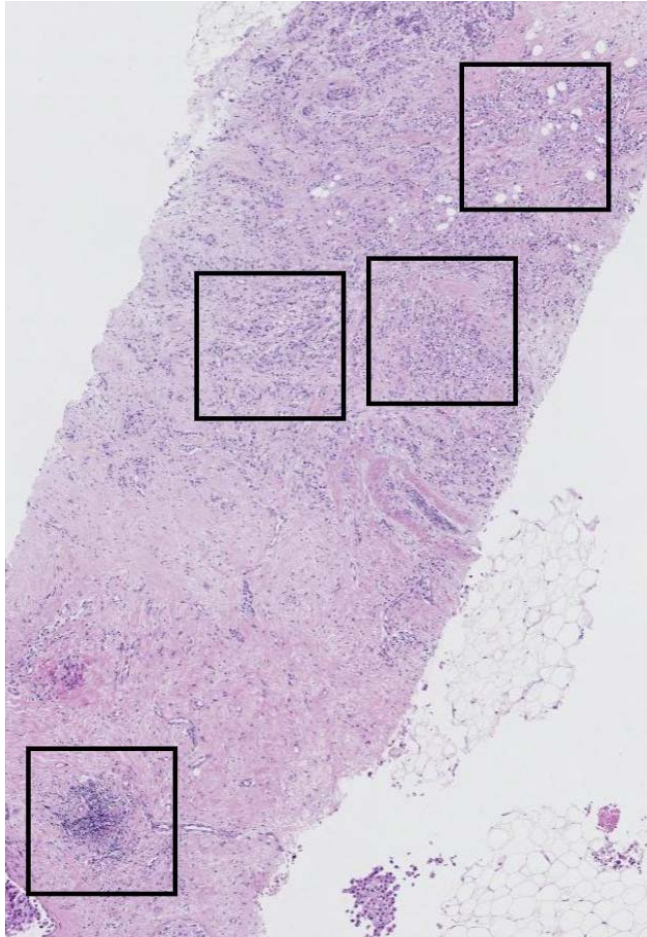
# Standardized Evaluations of a Quantitative Biomarker

- “Required” training included a 13-minute video
  - Training not monitored
- “Optional” training included
  - Link to the recommendations
  - Project overview (video)
  - Platform operation overview (video)



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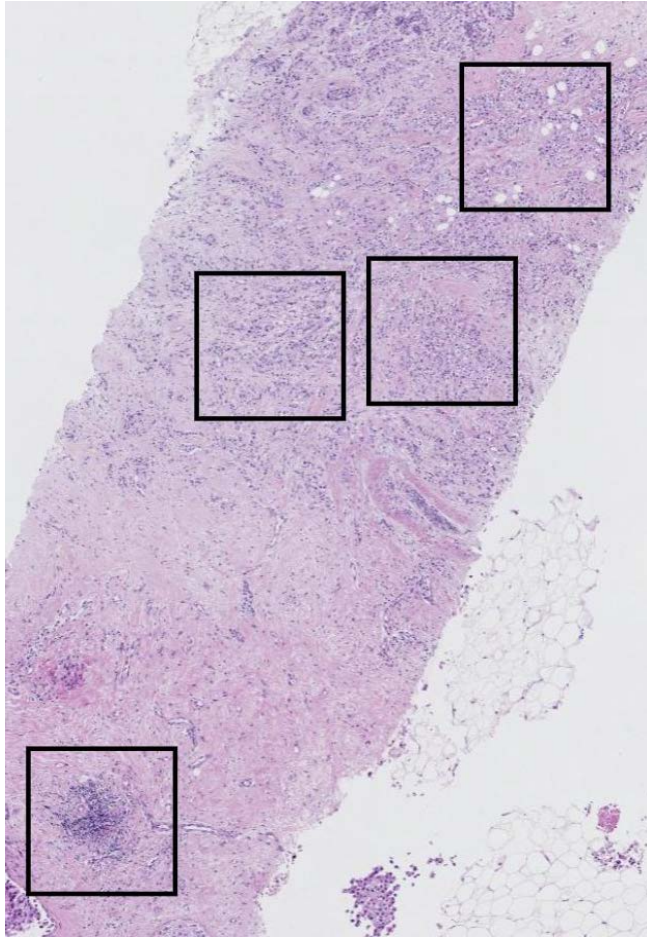
# Pre-select Regions of Interest (ROIs)



- **Intra-tumoral stroma**  
(Tumor-associated stroma)
  - Select ~3 ROIs
- **Invasive margin**  
(Tumor-stroma transition)
  - Select ~2 ROIs
- **Tumor with no intervening stroma**
  - Select ~2 ROIs, if possible
- **Other regions**
  - Select ~3-4 ROIs

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# Pilot Study Materials



- **64** Hematoxylin & Eosin Slides
  - “40X” Imaging (0.23 um/pixel)
- **10** ROIs per Slide
- **640** ROIs Total
  - 8 batches of 8 slides
- **500 um x 500 um** squares

No patient  
information or  
meta-data

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# Evaluation Platforms

- Digital
  - caMicroscope
  - PathPresenter
  
- Microscope
  - eeDAP

We did not specify the display

We did collect the display size in pixels

# caMicroscope (Digital)

Slide: HTT-TILS-001-19B

Home, Back, Rotate, Zoom, Help icons

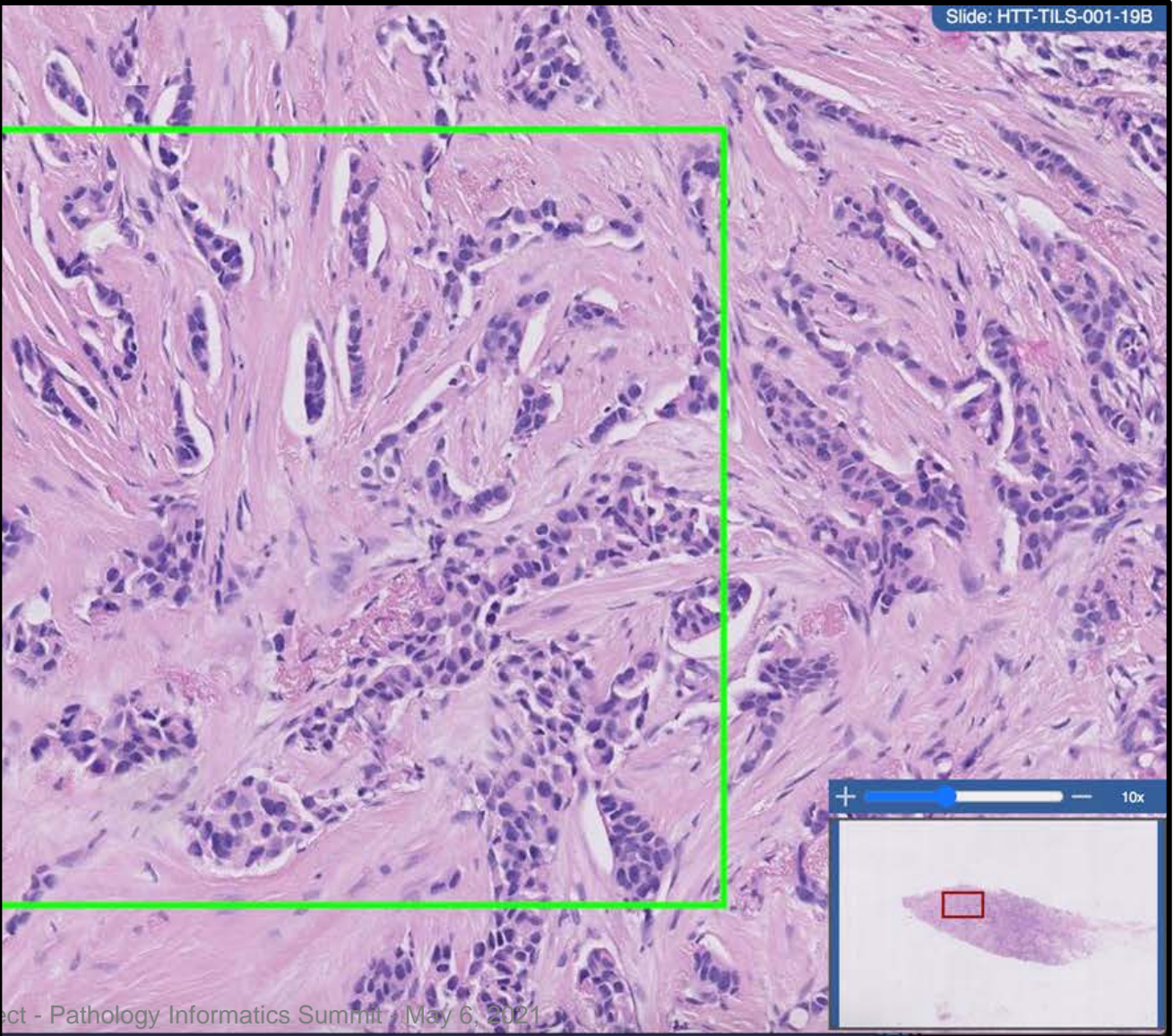
**ROI Type:**

- Intra-Tumoral Stroma
- Tumor with No Intervening Stroma
- Invasive Margin
- Other Regions

**68%**  
% Tumor-Associated Stroma

**12%**  
Please Assess TIL Density

**Save & Next**



The main image is a histology slide showing tumor tissue with a green ROI box. A 10x inset is visible in the bottom right corner.

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# PathPresenter (Digital)

The screenshot displays the PathPresenter software interface. On the left, a histology image is shown at 40x magnification, with a 100 µm scale bar. The top toolbar includes navigation icons, magnification options (0.25x, 2x, 5x, 10x, 20x, 40x, 60x, 100x), a search icon, and a zoom level of 20. The area of interest is 0.25 mm. On the right, a data entry panel is visible with the following fields:

- ROI Label :** Intra tumoral stroma
- Description :** Test Description
- %Tumor-Associated Stroma :** 23
- TILs :** 21

Each percentage field includes a slider control. The TILs field is highlighted in yellow. At the bottom right of the panel are 'Cancel' and 'Save' buttons.

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# eeDAP (Microscope)



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# PathPresenter (Digital)



Task 1 of 40  
HTT study

1. How would you label this ROI?

Intra-tumoral stroma     Tumor with NO intervening st...     Invasive margin (1mm)     Other

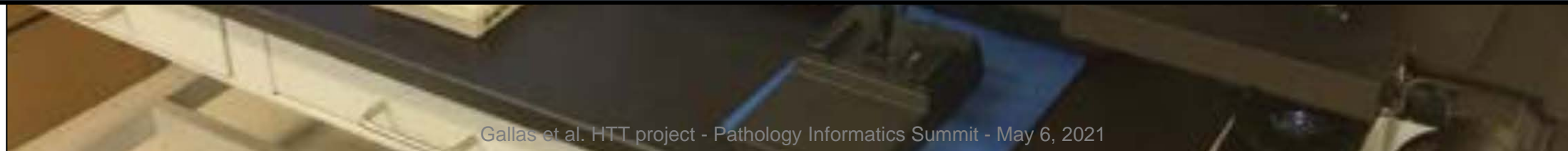
2: What is the percent (%) Tumor-Associated Stroma?

0	50	100	Score
<input type="range"/>			66

3: What is the intra-tumoral stromal TIL density?

0	50	100	Score
<input type="range"/>			66

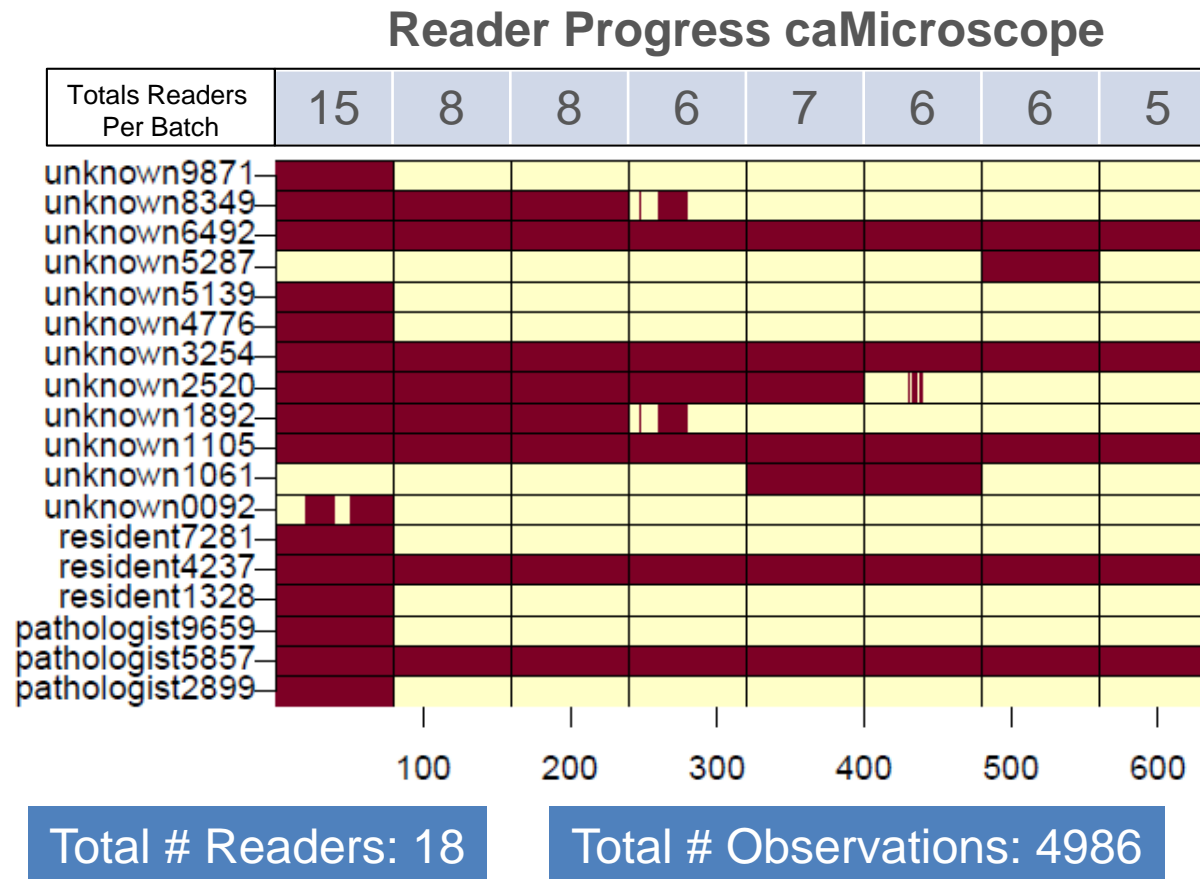
Switch to WSI thumb



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# Data Collected

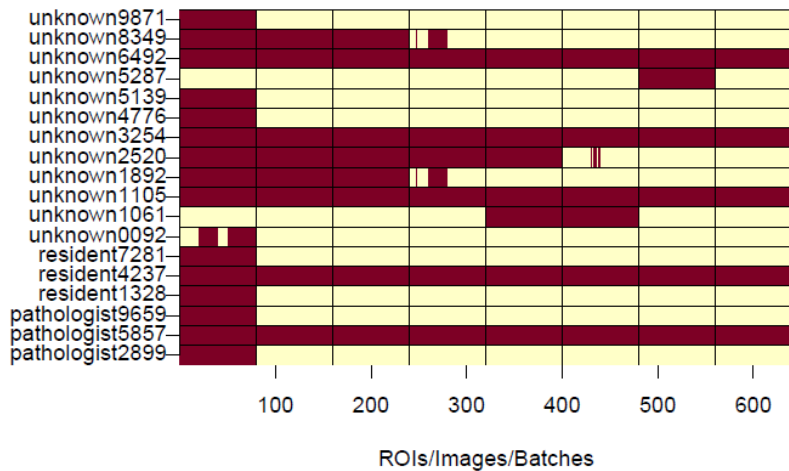
- Each tick mark is an observation
- Vertical lines partition the data by batch
- We are following up with the “unknowns” to get their experience



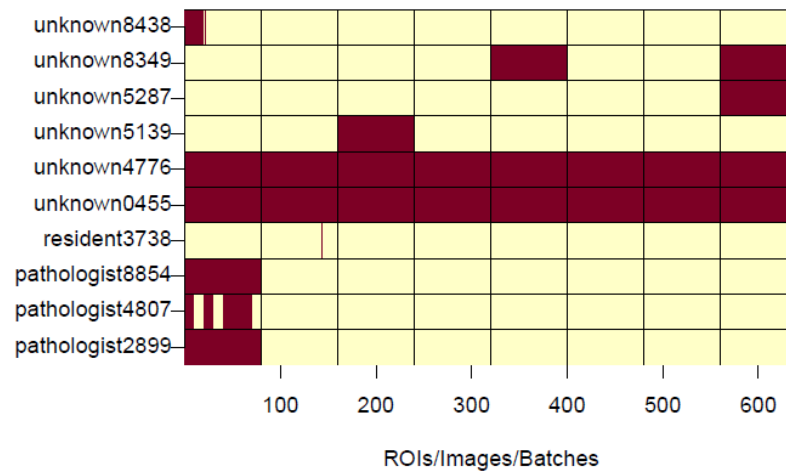
# Data Collected

- Hit target:
  - 5 readers per ROI
  - Total observations: 7,259
  - Readers: 35
- Data-collection portals still open
- Two sites planned for eeDAP data collection this summer

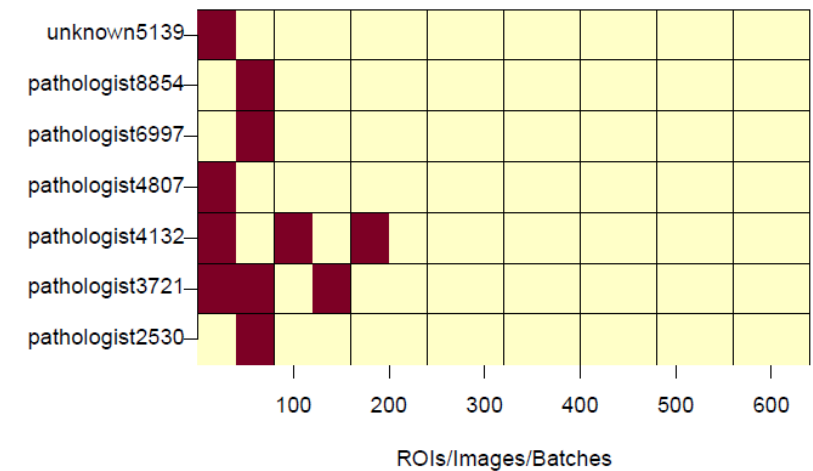
Reader Progress caMicroscope



Reader Progress PathPresenter



Reader Progress eeDAP



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# Explore the data

- R Data Package for Sharing
- **CV**: Coefficient of Variation =  $STD/Mean$
- Mean-variance relationship
- Scatter plots
- **LOA**: Limits Of Agreement

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# R Data Package

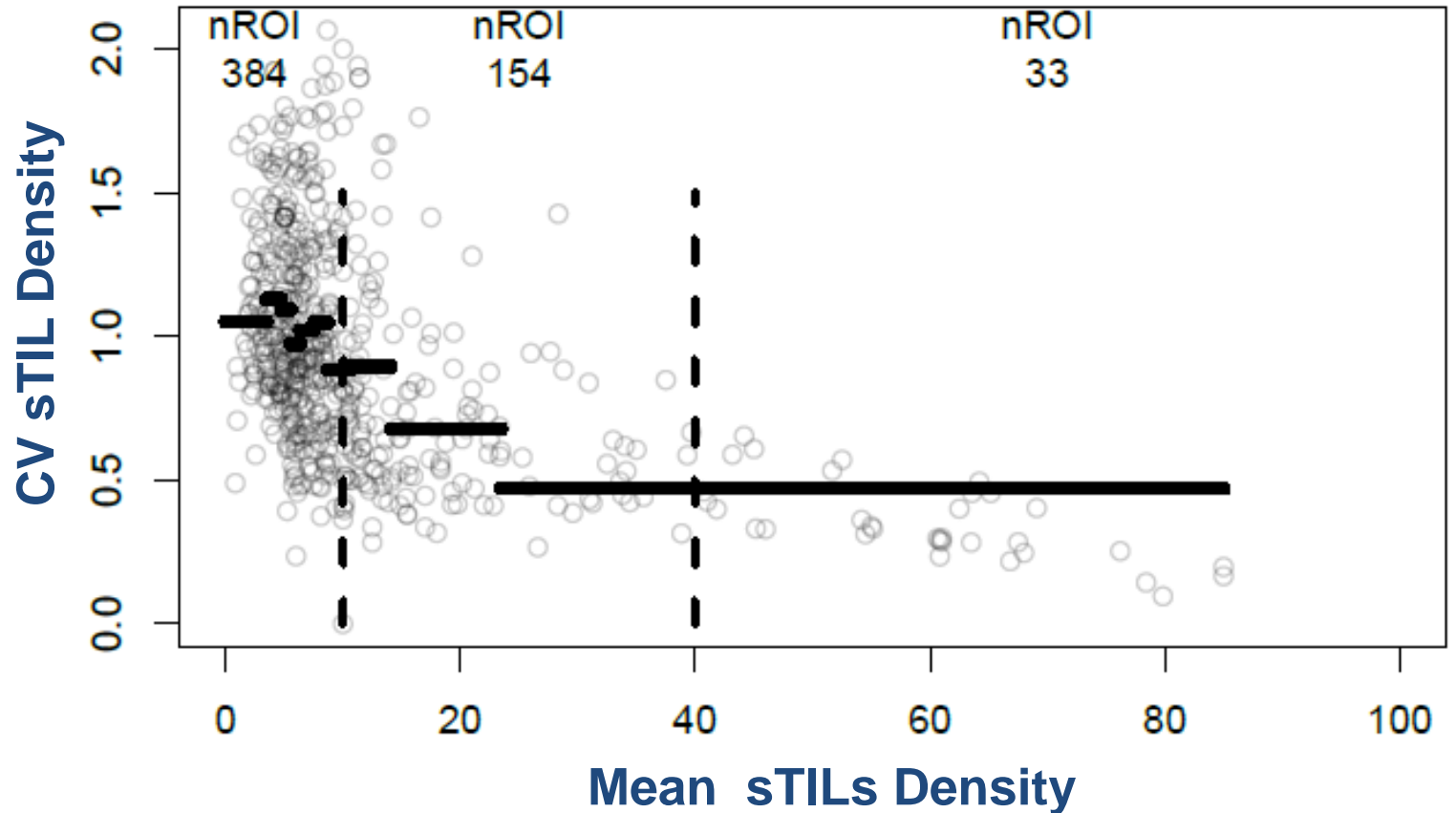
- Plan to share evaluation data summer 2021
- Use API's to pull data from platforms
- Use scripts to convert data into a standardized data frame
- Key variables:

caseID == ROI	readerID	modalityID	labelROI	percentStroma	densityTILs
HTT-TILS-001-73B.ndpi_x34892.2190_y45830.2190	unknown5287	camic	Intra-Tumoral Stroma	NA	20
HTT-TILS-001-73B.ndpi_x34892.2190_y45830.2190	pathologist5857	camic	Intra-Tumoral Stroma	39	45
HTT-TILS-001-73B.ndpi_x34892.2190_y45830.2190	resident4237	camic	Intra-Tumoral Stroma	15	20
HTT-TILS-001-73B.ndpi_x34892.2190_y45830.2190	unknown1105	camic	Intra-Tumoral Stroma	3	5
HTT-TILS-001-73B.ndpi_x34892.2190_y45830.2190	unknown6492	camic	Intra-Tumoral Stroma	20	10
HTT-TILS-001-73B.ndpi_x34892.2190_y45830.2190	unknown3254	camic	Intra-Tumoral Stroma	30	40

# CV: Coefficient of Variation = STD/Mean

- Each circle is one ROI
- Mean and CV are averages over all readers
- Horizontal lines:
  - Average CV in 10% bins of the data (57 ROIs)
- Vertical dashed lines:
  - “Clinical” bins
  - low ( $\leq 10\%$ )
  - medium ( $>10\% \ \& \ \leq 40\%$ )
  - high ( $>40\%$ )

## Coefficient of Variation (n=571, caMic)

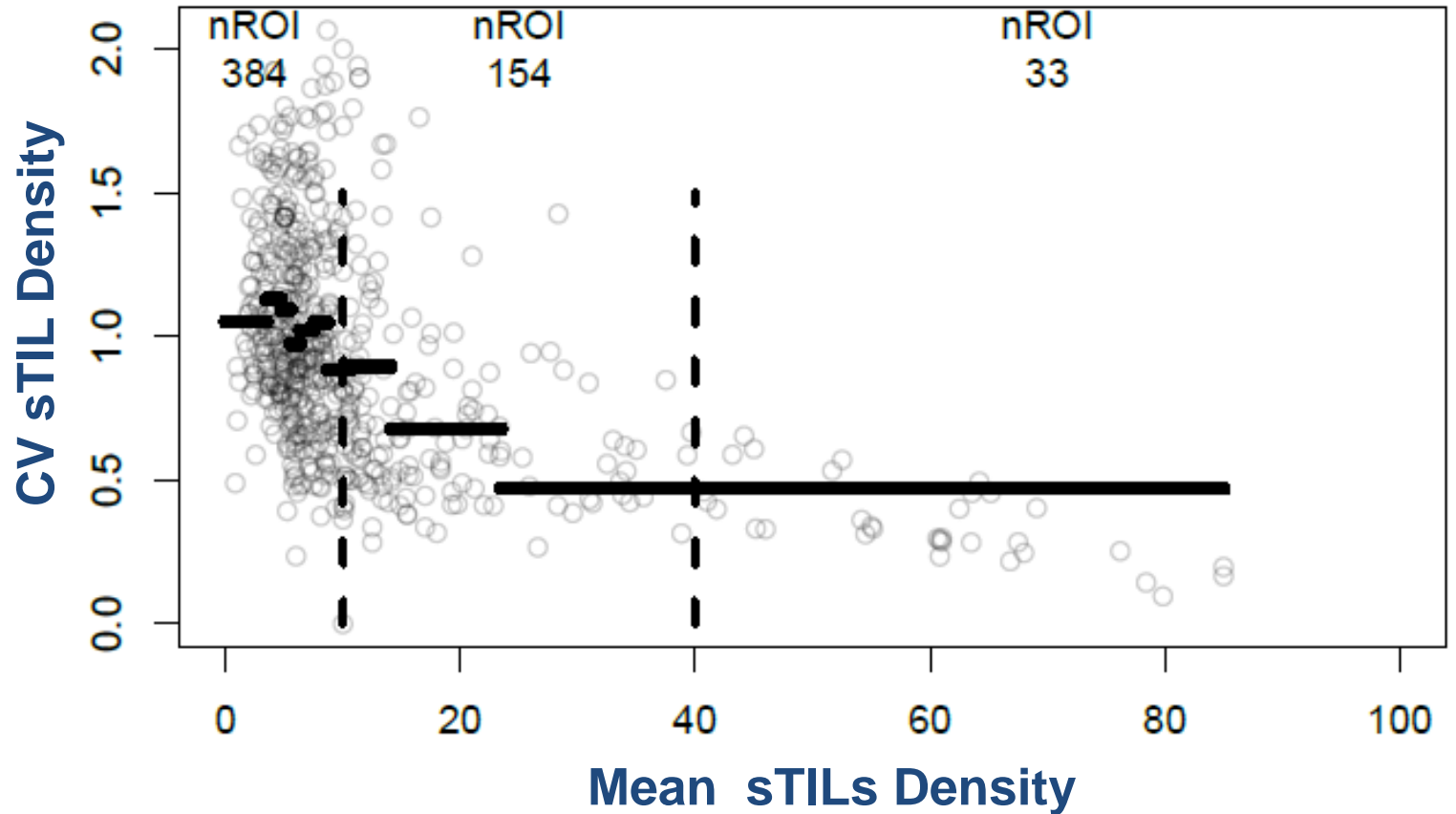


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# CV: Coefficient of Variation = STD/Mean

- Clinical Interpretation:
  - Difficult for pathologists to quantitate scores, especially below 10
- Statistical Interpretation:
  - Standard deviation is not proportional to the mean
  - What is the mean-variance relationship?

Coefficient of Variation (n=571, caMic)

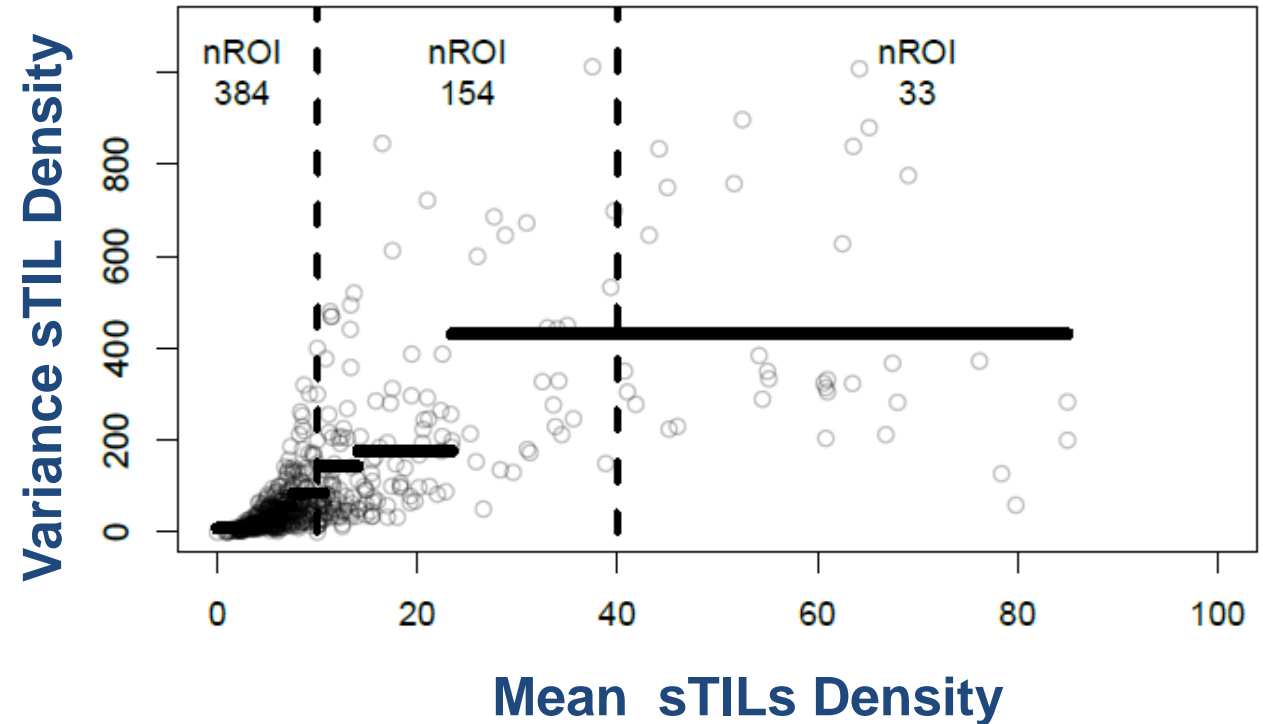


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# Mean-variance relationship

- Statistical Interpretation:
  - Variance increases with the mean
- Can't pool the data
  - Pick best readers
  - Transform the data
    - Log
    - Square-root
  - Bin the data
  - Average over ROIs per WSI
  - Ranks-based correlation

Mean-Variance (n=571, caMic)



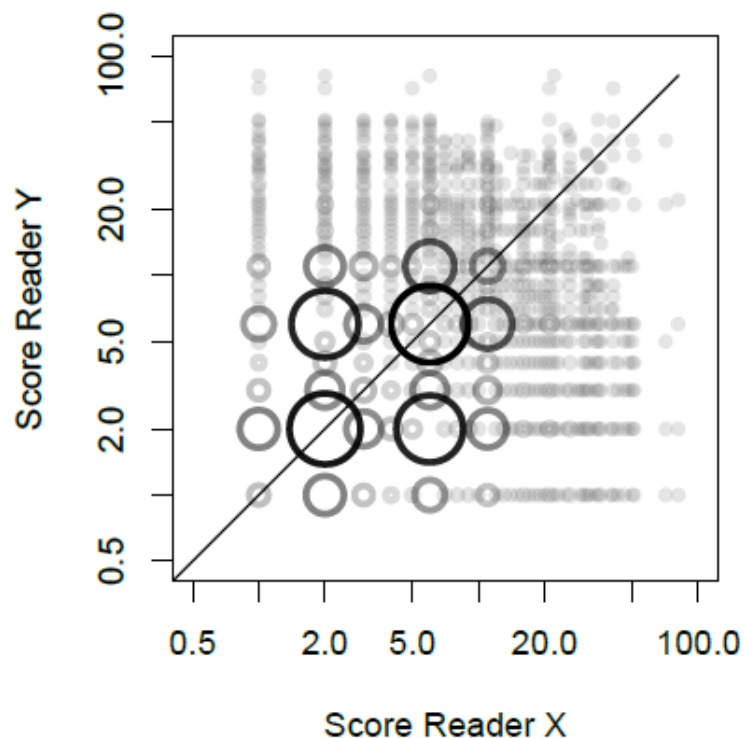


# Scatter Plots

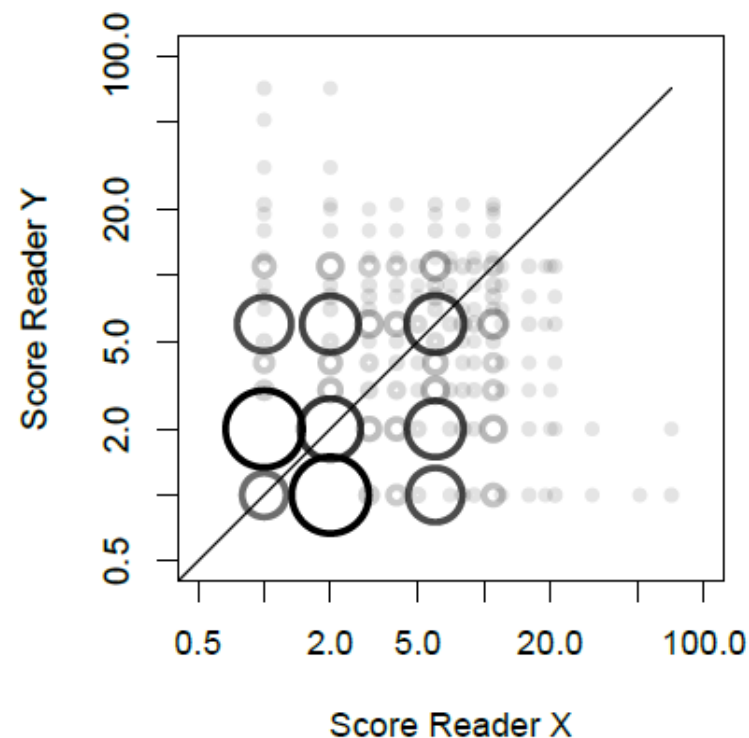
$0 \leq \text{scores} \leq 10$

**Symmetrized:** We plot (x,y) and (y,x) since we are pooling over readers and none is the reference.

Size of symbol and transparency are scaled with number of paired observations



n = 44784 , Largest symbol == 2602 observations



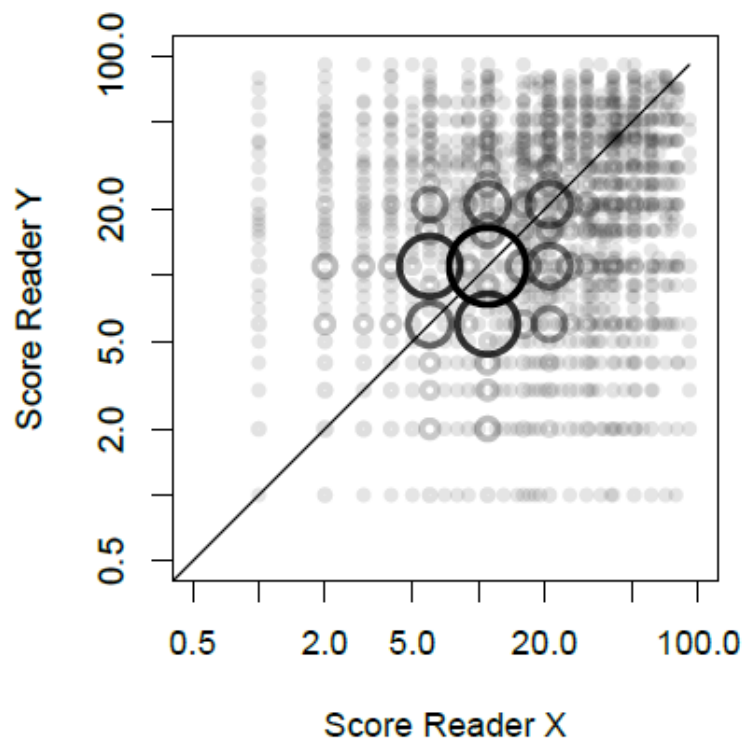
n = 4274 , Largest symbol == 343 observations

# Scatter Plots

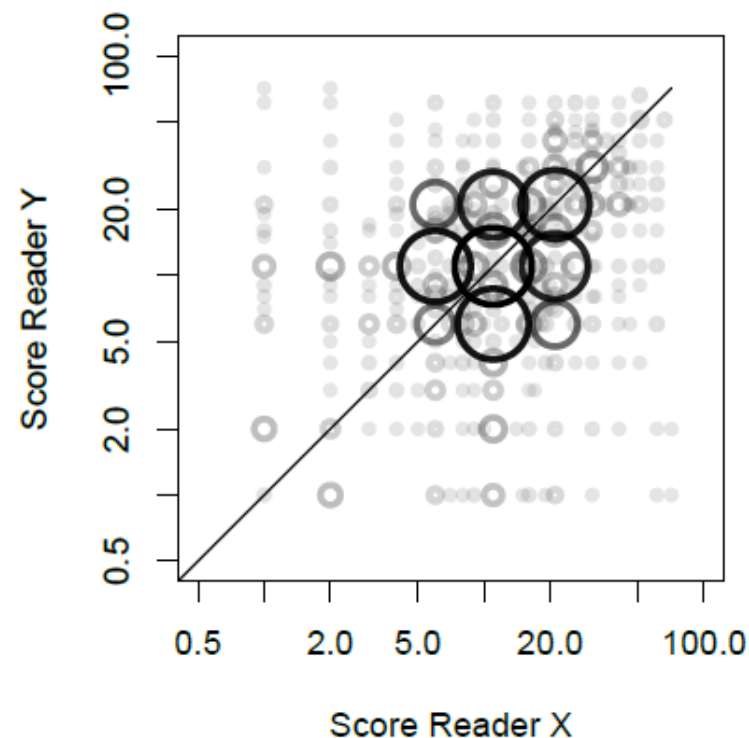
$10 < \text{scores} \leq 40$

**Symmetrized:** We plot (x,y) and (y,x) since we are pooling over readers and none is the reference.

Size of symbol and transparency are scaled with number of paired observations



n = 20080 , Largest symbol == 982 observations



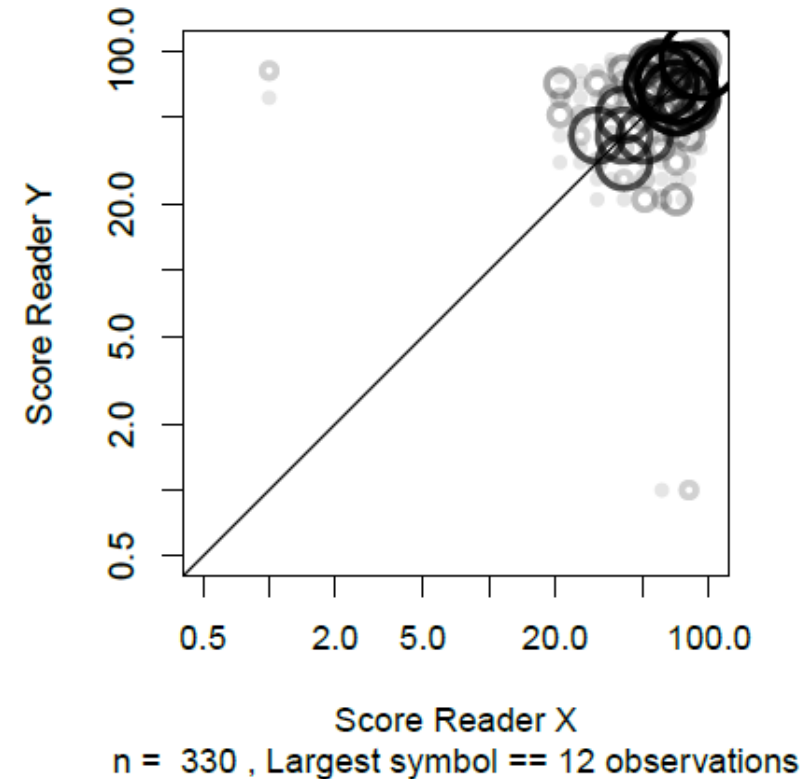
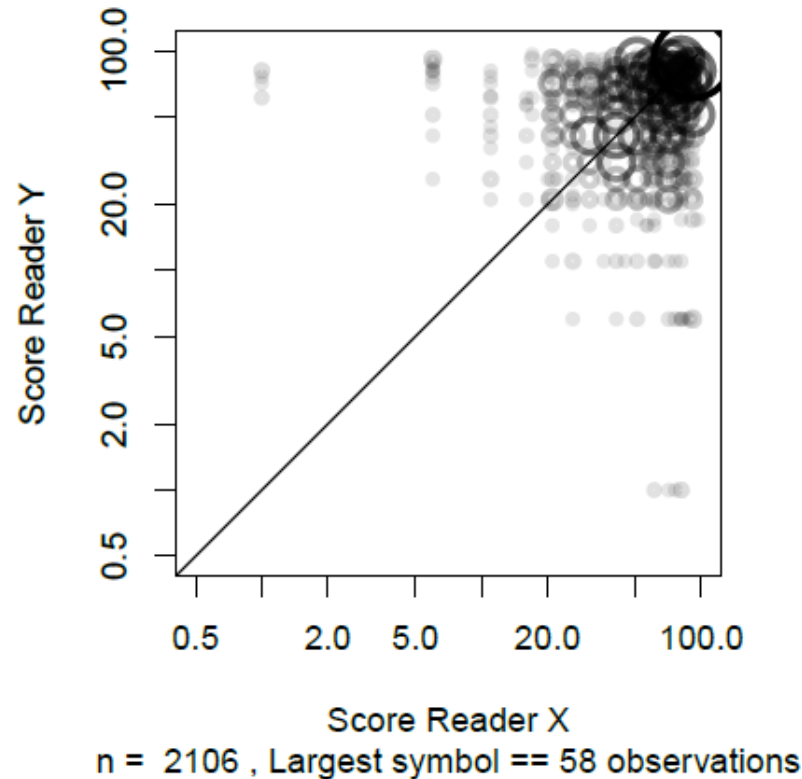
n = 1554 , Largest symbol == 70 observations

# Scatter Plots

$40 < \text{scores} \leq 100$

**Symmetrized:** We plot (x,y) and (y,x) since we are pooling over readers and none is the reference.

Size of symbol and transparency are scaled with number of paired observations



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# Limits Of Agreement

	Limits of Agreement (Point Estimates)	
	All Readers	Panel of Four
	Score differences	Score differences
$0 \leq \text{scores} \leq 10$	18.3	12.4
$10 < \text{scores} \leq 40$	38.0	27.0
$40 < \text{scores} \leq 100$	66.2	62.6

- LOA accounts for reader and case variability
- LOA reduced by 30% with panel (except for high scores)
- What's the precision of these estimates?
- Still need to account for correlations between ROIs in an image

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# Questions and Current Work

	Limits of Agreement (Point Estimates)	
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Q: Are these limits clinically acceptable?

- A: Discuss with partners and community



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# Questions and Current Work

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$40 < \text{scores} \leq 100$	66.2	62.6

Q: Are these limits clinically acceptable?

- Compare to other studies
  - Denkert et al, *\*Ring Study\**, **Modern Pathology**, 2016.

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# Questions and Current Work

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- Align with previous work



PROGNOSIS TOOL for Triple Negative Breast Cancer (TNBC)

Welcome to the online TIL and Prognosis tool for TNBC.

[tilsinbreastcancer.org](https://tilsinbreastcancer.org)

Q: Are these limits clinically acceptable?

# Questions and Current Work

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A: Find Breast Cancer experts

A: Find TIL evaluation experts

Q: How can we tighten LOAs?



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# Questions and Current Work

	Limits of Agreement (Point Estimates)	
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Q: How can we tighten LOAs?

A: Improve training

- Emphasize calibration cheat sheet
- Test with feedback.
- Proficiency test

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# Questions and Current Work

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# Questions and Current Work

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- Which pathologists are interchangeable with the panel?
- Which algorithm is interchangeable with the panel?

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# Questions and Current Work

	Limits of Agreement (Point Estimates)	
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	Score differences	Score differences
$0 \leq \text{scores} \leq 10$	18.3	12.4
$10 < \text{scores} \leq 40$	38.0	27.0
$40 < \text{scores} \leq 100$	66.2	62.6

- To Investigate:
  - Image-based assessment
  - Average ROIs per image
- To Investigate:
  - Rank-based correlation agreement metrics
  - Smaller evaluation intervals
  - Agreement Rates per Interval

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# Next Steps

- Update Pathologist Training
  - Immediate
    - Emphasize the calibration cheat sheet
  - For pivotal study
    - Test with feedback
    - Proficiency test
- Continue with pilot study
  - Collect more PathPresenter data
  - Collect microscope-mode data
  - Road trip!
  - Looking for sites and pathologists to help with data collection
- Finalize pivotal study statistical analysis plan
  - Determine study size and power
  - Simulation methods
- Get feedback from the community (including MDDT)
- Source and curate pivotal study slides
  - Looking for one or two more sites
- Plan and execute data-collection

# Conclusions

- Continue to make progress on this challenging project
  - Many thanks to all the collaborators
  - Are you interested in getting involved?
- We have collected 7,259 pathologist evaluations (and counting)
  - Building platforms and pipelines
  - Learning about pathologist agreement
  - Developing methods
- We plan to leverage the platforms, pipelines, methods, experience, **and relationships**
  - Other quantitative biomarkers
  - Other pathologist evaluations (qualitative biomarkers, marks, segmentations)

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