PATHOLOGIST AGREEMENT FROM QUANTITATIVE MEASUREMENTS: A PILOT STUDY
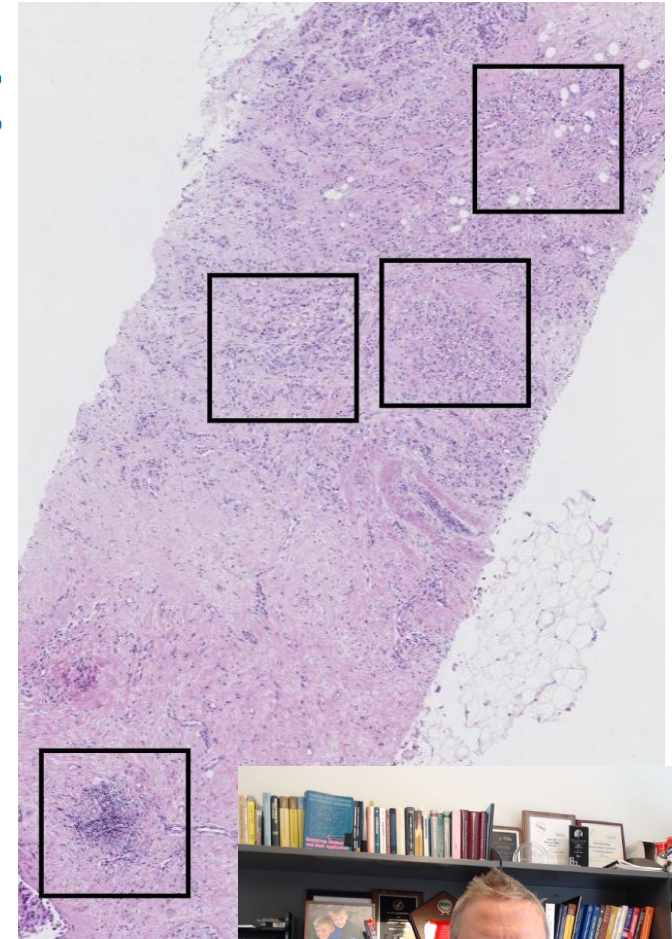
Brandon D. Gallas And Katherine Elfer

Division of Imaging, Diagnostics, Software Reliability

Office of Science and Engineering Laboratories

Center for Devices and Radiological Health

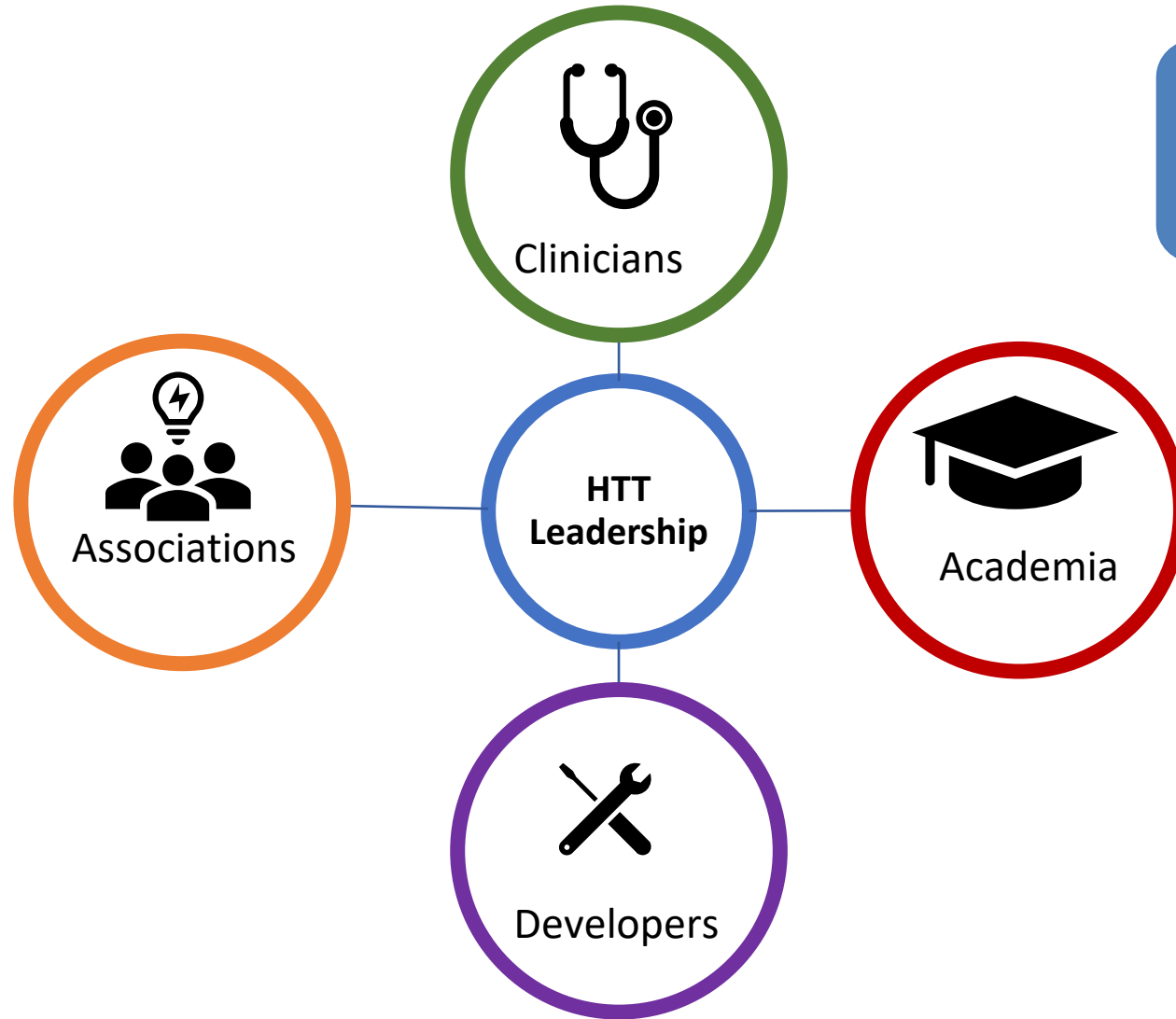U.S. Food and Drug Administration

Collaborators

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Collaboration of Volunteers

There is room for you!

Clinicians

Associations

HTT Leadership

Academia

Developers

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Outline

- Overview of the HTT project
  - High-Throughput Truthing
  - Manuscript: http://arxiv.org/abs/2010.06995

- Introduce study materials and explore data collected
  - R data package: https://github.com/DIDSR/HTT

- Introduce mean-squared differences
  - LOA: Limits of agreement

- Summary

Digital web-based data-collection interface

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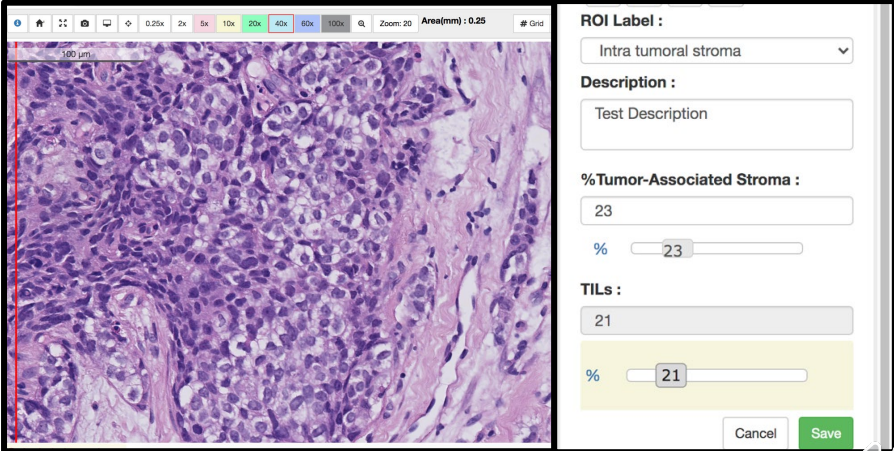
Clinical Context and Relevance

- Clinical context:
  - Breast cancer
  - Pathology Biomarker: Stromal Tumor Infiltrating Lymphocytes (sTILs)

- Clinical relevance of sTILs:
  - Prognostic for survival
  - Expected to inform patient management
  - Expected to reduce use of toxic chemotherapies

- Software as a medical device (SAMD)
  - Reduce burden on pathologist
  - Reproducible
  - Quantitative

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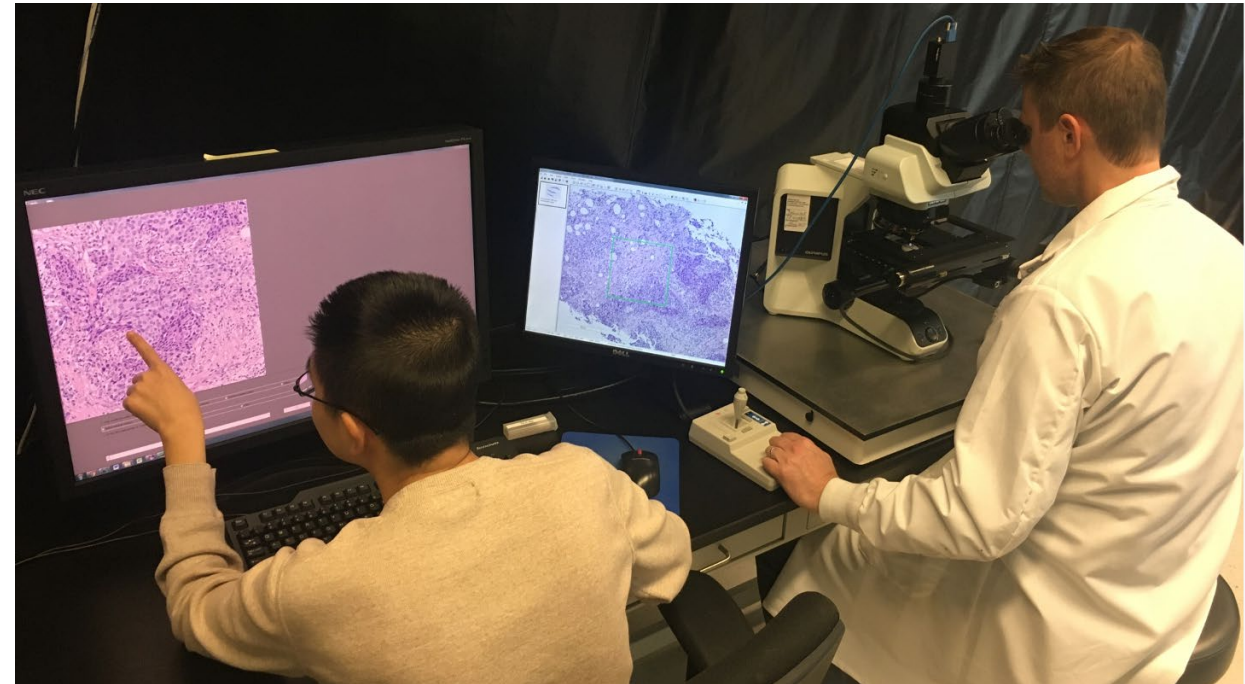
Clinical Context and Relevance

- Deliverables
  - Reference standard data from pathologists
  - Methods to validate algorithms

- Pursue Qualification of Deliverables:
  - Medical Device Development Tool (MDDT) … an FDA program

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

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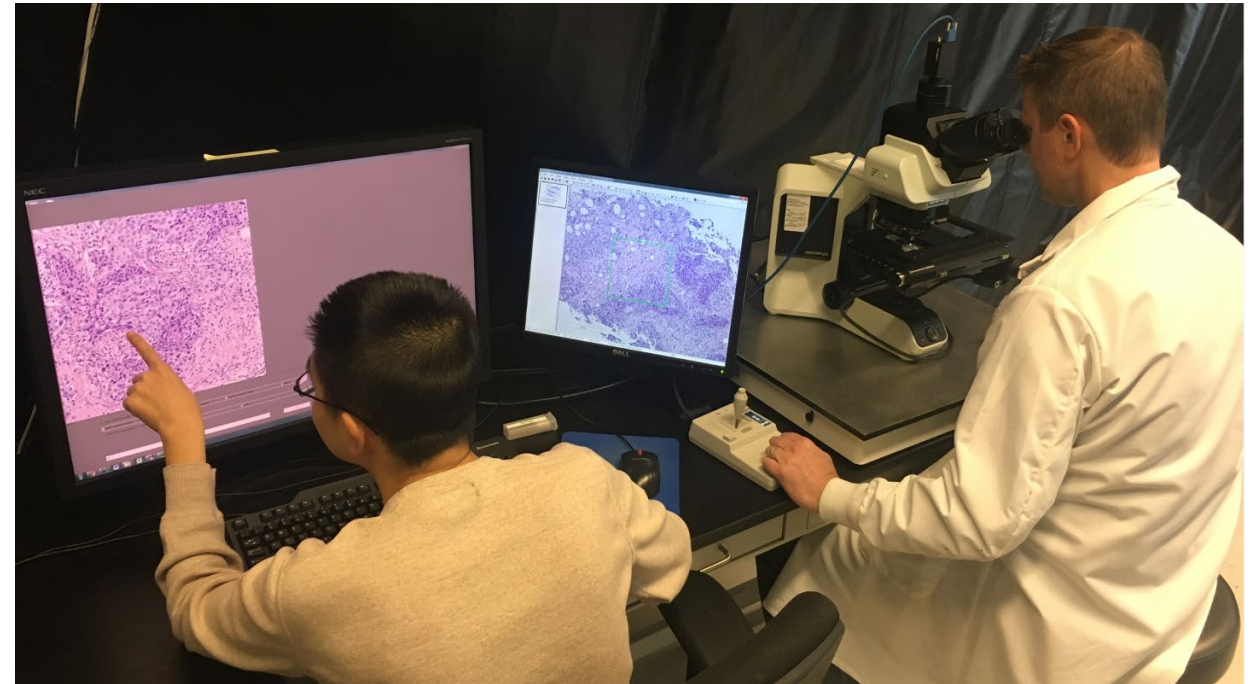
Standardized Evaluations of a Quantitative Biomarker

- ## Pathologist Evaluation

  - Density Estimates of percent stromal Tumor Infiltrating Lymphocytes (sTILs)

    $$0\% - 100\%$$

    $$\frac{Area\ of\ TILs\ in\ stroma}{Area\ of\ stroma}$$

- 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.

FDA.gov   JSM 2021, Medical Devices and Diagnostics Speed Session, Gallas and Elfer, Pathologist Agreement

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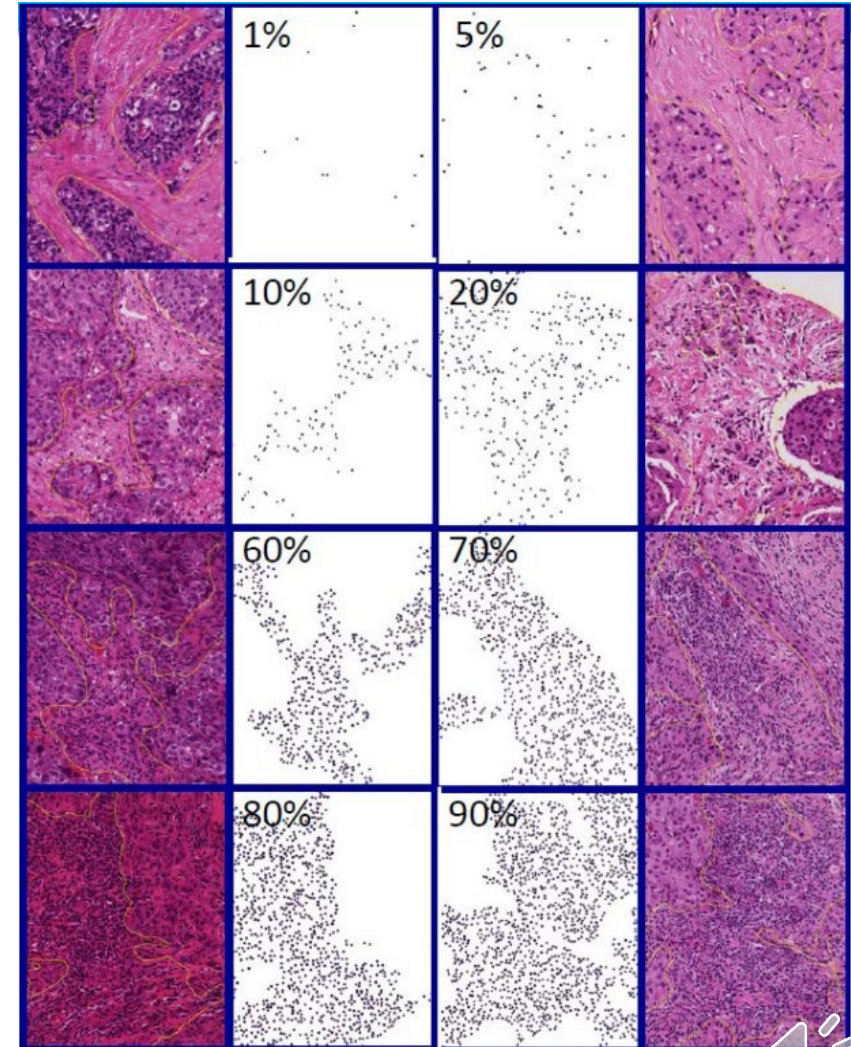
Evaluation Platforms

- **Digital**
  - caMicroscope
  - PathPresenter

- **Microscope**
  - eeDAP
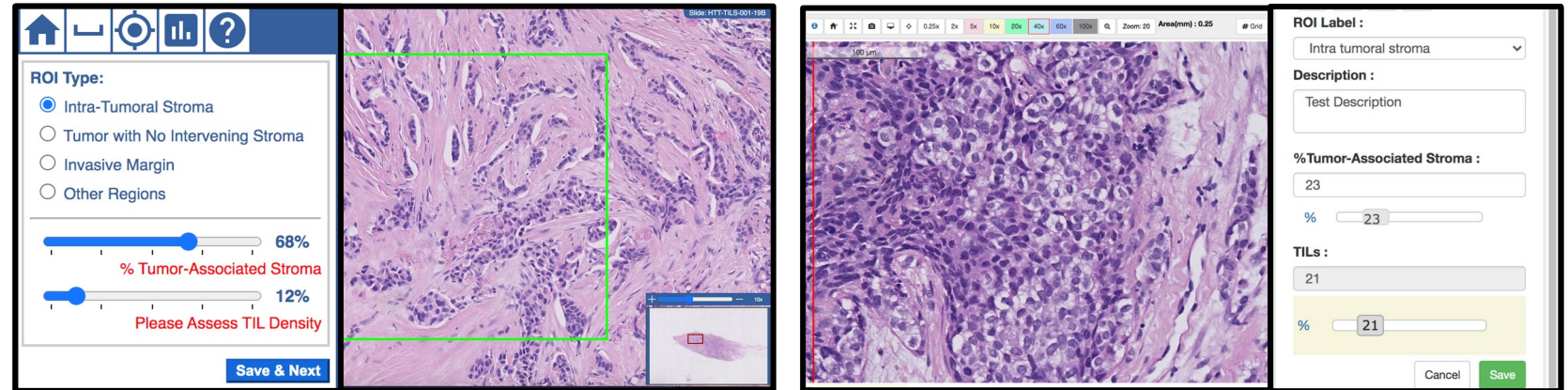
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caMicroscope (Digital)

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Pilot Study Materials
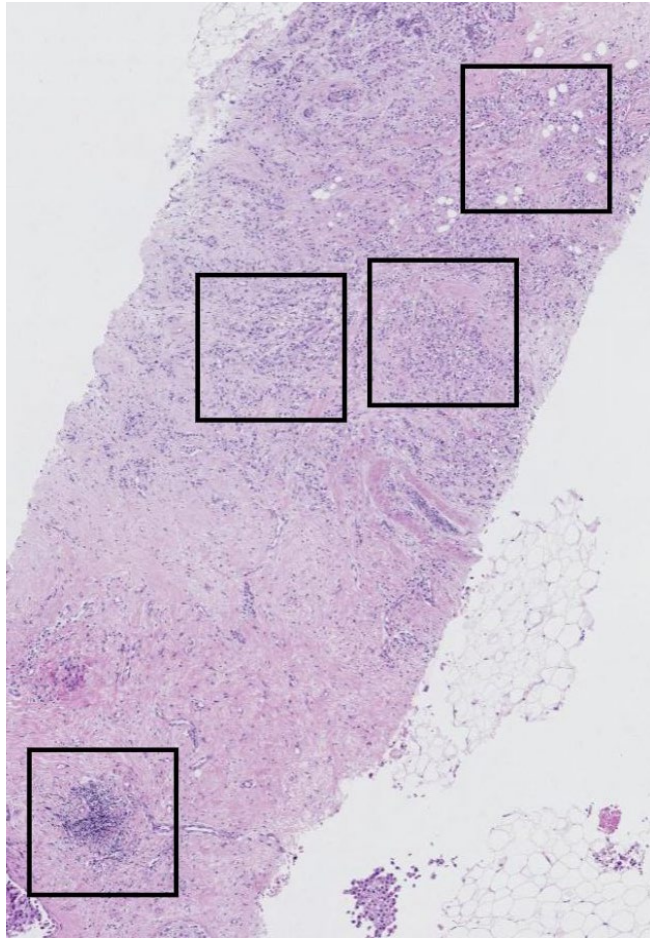
- **64** Hematoxylin & Eosin Slides
  - "40X" Imaging (0.23 um/pixel)

- **10** ROIs per Slide (pre-selected by protocol)
  - 500 um x 500 um squares

- **640** ROIs Total
  - 8 batches of 8 slides

Pilot study:
No patient
information or
meta-data

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R Data Package: It's live!

- ## https://github.com/DIDSR/HTT
  - User manual on GitHub release page and via R `help` command

- ## Annotation data: `pilotHTT`

caseID == ROI
Encodes the image name and the ROI info

```
> str(HTT::pilotHTT)
'data.frame':    7292 obs. of  18 variables:
 $ batch            : Factor w/ 8 levels "FDA-HTT-batch001",
 $ WSI              : Factor w/ 64 levels "HTT-TILS-001-03B.
 $ caseID           : Factor w/ 640 levels "HTT-TILS-001-03B.
 $ readerID         : Factor w/ 27 levels "pathologist2899",
 $ modalityID       : Factor w/ 3 levels "camic","pathp",..:
 $ score            : num  NA 5 10 NA 5 5 1 5 NA NA ...
 $ experience       : num  100 100 100 100 100 100 100 100 10
 $ experienceResident: num  100 100 100 100 100 100 100 100 10
 $ labelROI         : Factor w/ 4 levels "Intra-Tumoral Stro
 $ VTA              : logi  FALSE TRUE TRUE FALSE TRUE TRUE
 $ percentStroma    : num  NA NA NA NA NA NA NA NA NA NA ...
 $ densityTILs      : num  NA 5 10 NA 5 5 1 5 NA NA ...
 $ createDate       : POSIXct, format: "2020-02-18 21:48:38"
 $ viewerWidth      : num  NA NA NA NA NA NA NA NA NA NA ...
 $ viewerHeight     : num  NA NA NA NA NA NA NA NA NA NA ...
 $ viewerMag        : num  NA NA NA NA NA NA NA NA NA NA ...
 $ task             : Factor w/ 3 levels "doVTA_caMicro_v1.0
 $ inputFileName    : chr  NA NA NA NA ...
```

caseID	readerID	modalityID	labelROI	percentStroma	densityTILs
HTT-TILS-001-11B.ndpi_x124700.2190_y17272.2190	unknown5139	camic	Other Regions	NA	NA
HTT-TILS-001-11B.ndpi_x112500.2190_y34683.2190	unknown5139	camic	Intra-Tumoral Stroma	NA	5
HTT-TILS-001-11B.ndpi_x124179.2190_y13060.2190	unknown5139	camic	Intra-Tumoral Stroma	NA	10
HTT-TILS-001-11B.ndpi_x127215.2190_y12508.2190	unknown5139	camic	Other Regions	NA	NA

R Markdown File: Demonstrate Data and Analyses

- ## Pathology Informatics Presentation

  - **PDF:** https://ncihub.org/groups/eedapstudies/wiki/Presentation2021:PathologyInformaticsSummitHTTproject

  - **R Markdown:** https://github.com/DIDSR/HTT/tree/main/inst/extra/20210505-PathologyInformatics
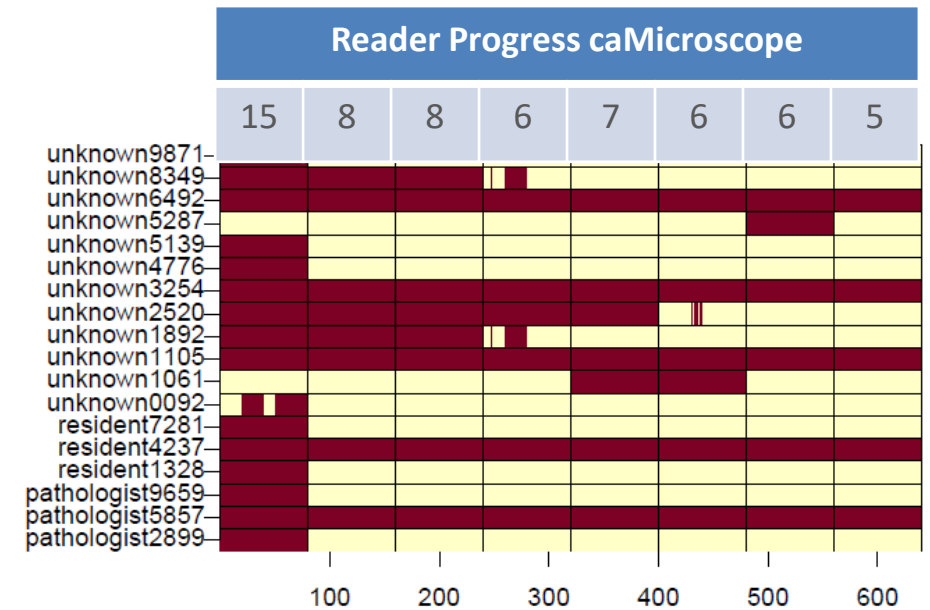
- Data Collected:
  - Each tick mark is an observation
  - Vertical lines partition the data by batch

- Hit target
  - 5 readers per ROI
  - Total observations: 7292
  - Total pathologists: 35

- Data collection continues online and in person

Reader Progress caMicroscope							
15	8	8	6	7	6	6	5

Total # Readers: 18	Total # Observations: 4986

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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 (≤ 10%)
  - medium (>10% & ≤ 40%)
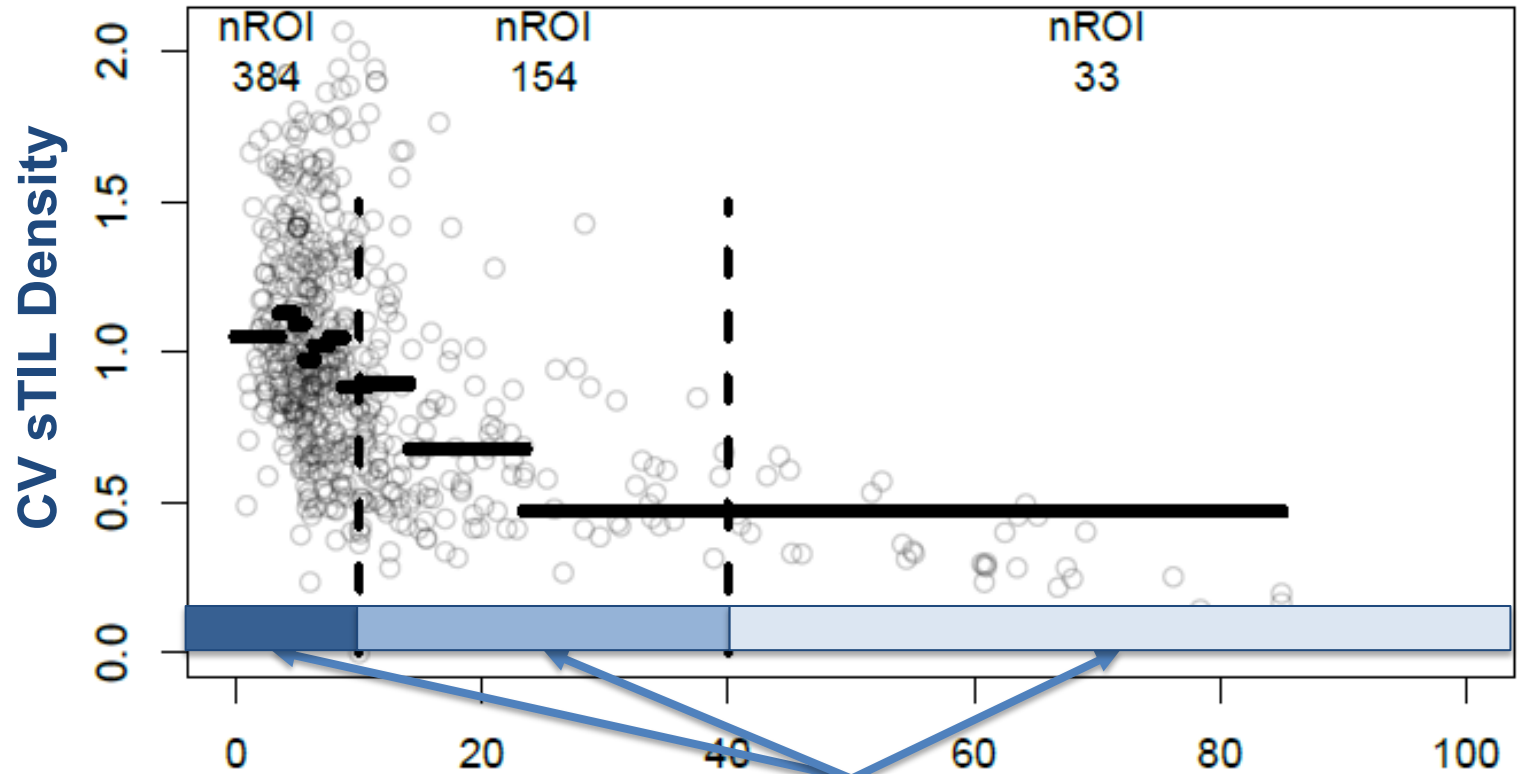 - high (>40%)

Coefficient of Variation (n=571, caMic)
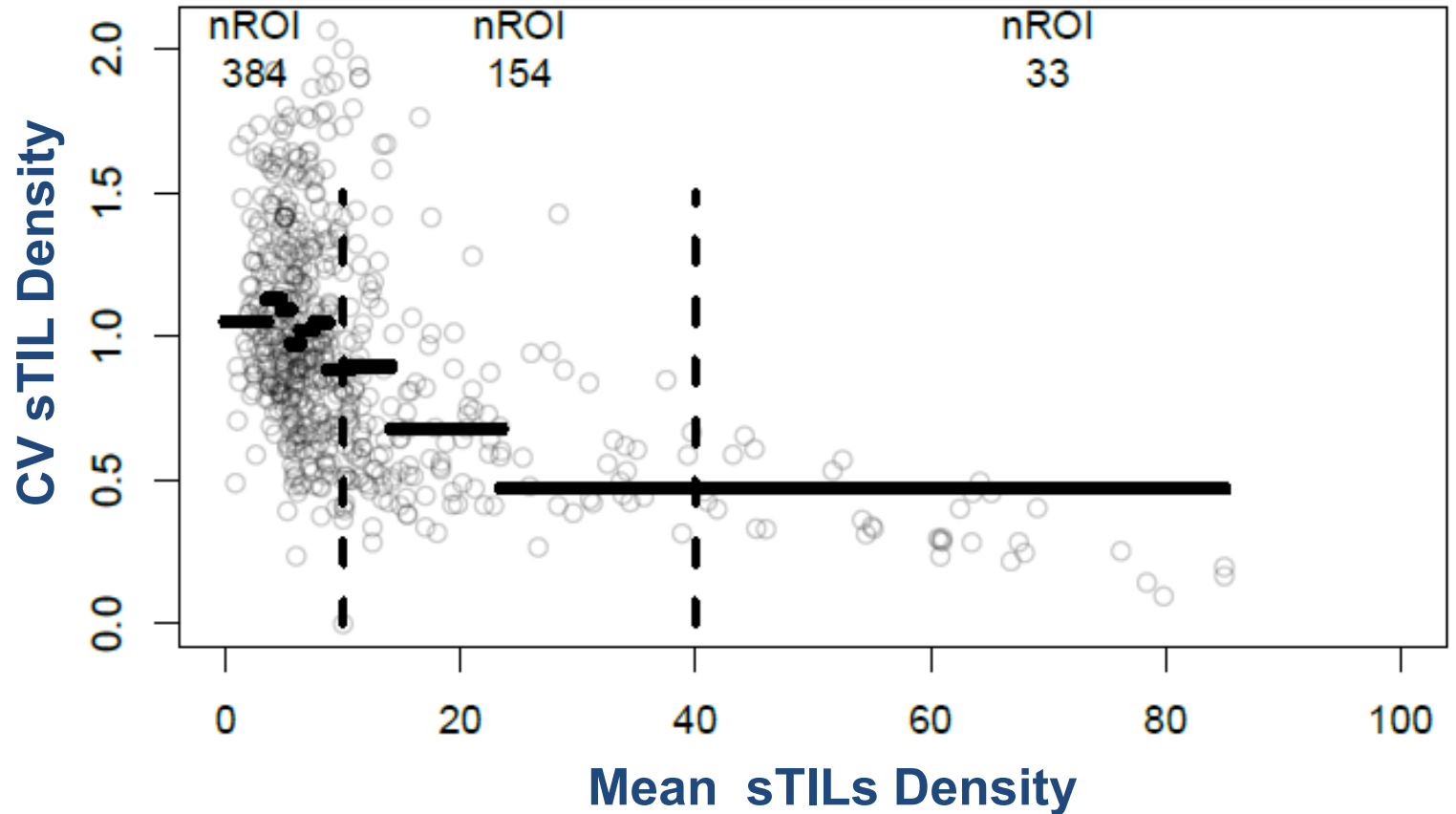
CV: Coefficient of Variation = STD/Mean

- Difficult for pathologists to quantitate scores, especially below 10

- Standard deviation is not proportional to the mean

- Variance increases with the mean (not shown)

Coefficient of Variation (n=571, caMic)

Next
Partition the data for analysis
All readers vs. Panel

Quantitative Agreement Endpoint:

MSD = Mean-Squared Difference → square root → Limits of Agreement

- Algorithm-pathologist agreement

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

- Pathologist-pathologist agreement

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

Score from SaMD

Score from pathologist j

Score from pathologists j and j'

Same case k and location l

Same case k and location l

Quantitative Agreement Endpoint:

MSD = Mean-Squared Difference → square root → LOA: Limits of Agreement

- 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

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

$$\text{MSD} = \text{var}(X_{j'kl}, X_{jkl}) + E(X_{j'kl} - X_{jkl})^2$$

0

$$\text{MSD} = var(X_{j'kl}, X_{jkl})$$

$$LOA = 0 \pm 2\sqrt{var(X_{j'kl}, X_{jkl})}$$

FDA.gov   JSM 2021, Medical Devices and Diagnostics Speed Session, Gallas and Elfer, Pathologist Agreement   16

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Limits Of Agreement (LOA)

	Limits of Agreement (Point Estimates)	
	All Readers	Panel of Four
0 ≤ scores ≤ 10	18.3	12.4
10 < scores ≤ 40	38.0	27.0
40 < scores ≤ 100	66.2	62.6

- LOA accounts for
  - Reader and case variability
  - MRMC analysis: multi-reader, multi-case analysis

- LOA is reduced for the panel

- LOA increases with the score

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Limits Of Agreement (LOA)

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- Si Wen & Brandon Gallas (2021).
  Three-way Mixed Effect ANOVA to Estimate MRMC Limits of Agreement.
  - arXiv preprint arXiv:2107.08891
  - Submitted to Statistics in Biopharmaceutical Research.
  - GitHub Repo: https://github.com/SiWen314/ANOVA.MRMC.LOA

Limits Of Agreement (LOA)

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	All Readers	Panel of Four
0 ≤ scores ≤ 10	18.3	12.4
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- Still need to
  - Account for correlations between ROIs in an image
  - Estimate the precision of LOA estimates

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Summary

- We've provided an overview of this project
  - Dataset of pathologist annotations to validate an algorithm to evaluate sTIL density
  - Unique data collection methods, platforms, and materials
  - Explored the data
  - R data package on GitHub
  Reproducible and transparent science
  - Mean-Squared Difference endpoint

- Still need to …
  - Account for correlations between ROIs in an image
  - Estimate the precision of LOA estimates

  - **Explore** non-parametric regression (*ratio data*)
  - **Explore** ranks-based correlation (*ordinal data*)
  - **Explore** binning the data, categorical agreement (*nominal data*)

  - Size the pivotal study

- DIDSR/HTT (github.com)

- Brandon.gallas@fda.hhs.gov

- Thank you.

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