PATHOLOGIST AGREEMENT FROM QUANTITATIVE MEASUREMENTS: A PILOT STUDY
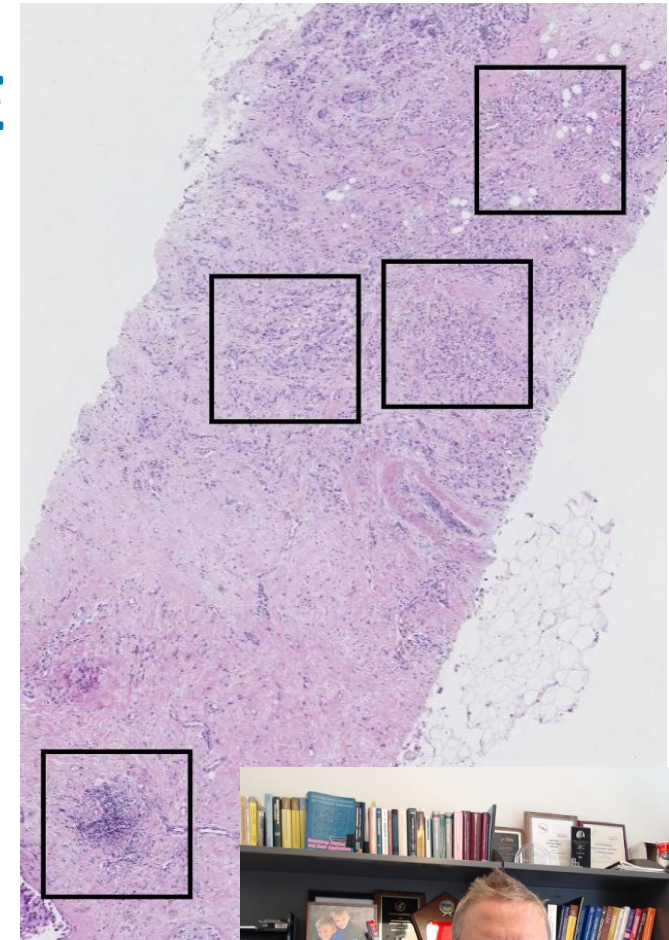
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U.S. Food and Drug Administration

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

- Biomarker Evaluation by an Algorithm
  - Reduce burden on pathologist
  - Reproducible
  - Quantitative
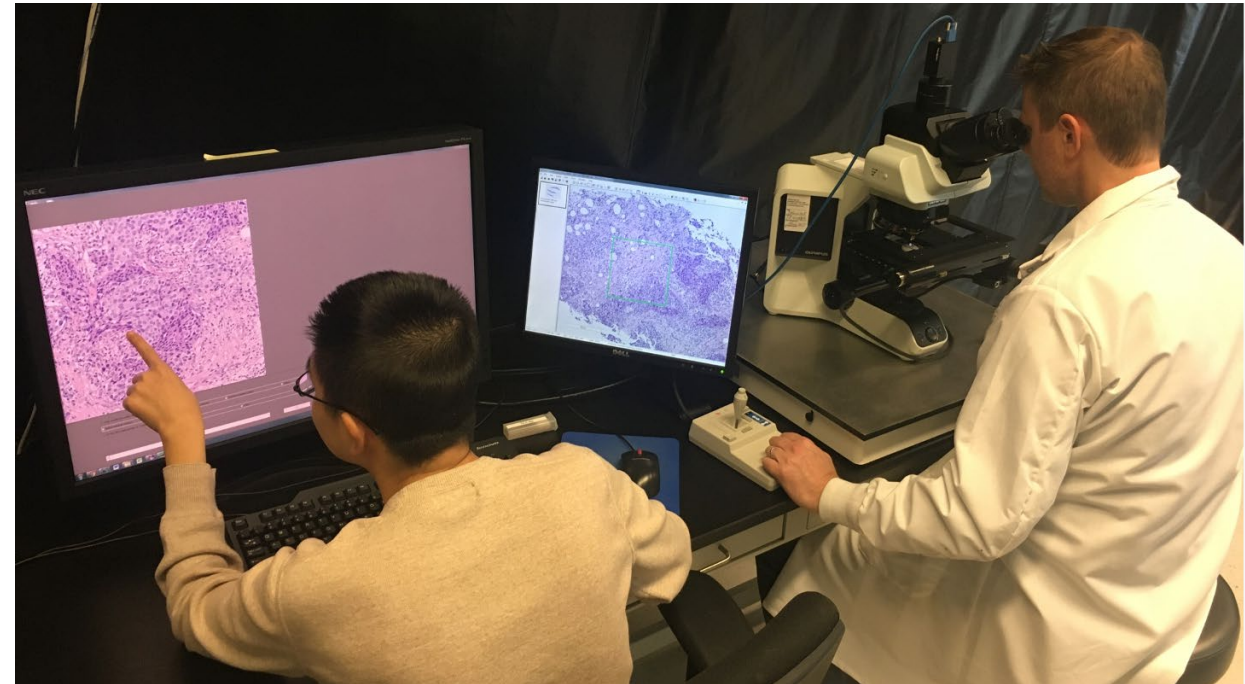
- Deliverables
  - Reference standard data from pathologists
  - Methods to validate a quantitative algorithm

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Evaluation Platforms

- **Digital**
  - caMicroscope
  - PathPresenter

- **Microscope**
  - eeDAP

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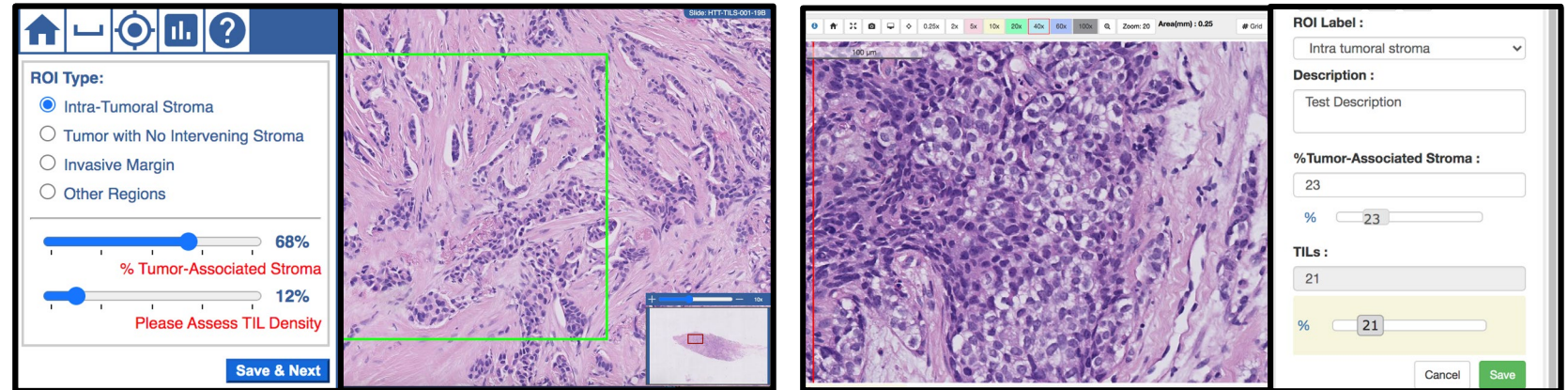
Pilot Study Materials
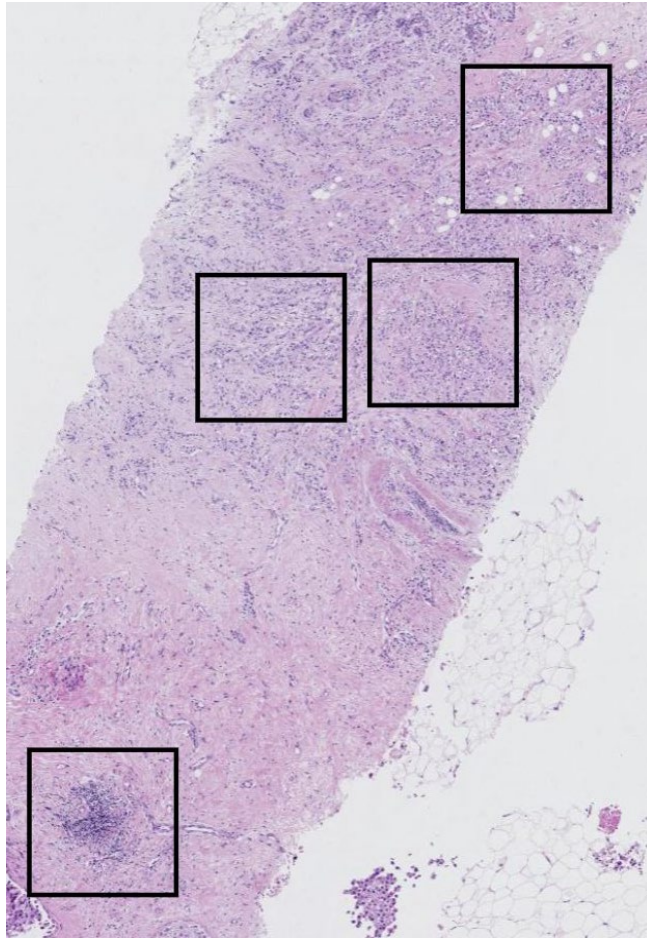
- **64** Hematoxylin & Eosin Slides
  - "40X" Imaging (0.23 um/pixel)

- **10** ROIs per Slide (pre-selected by protocol)
  - ROI: region of interest
  - 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 ...
 $ viewerHeight    : num  NA NA NA NA NA NA NA NA NA ...
 $ viewerMag       : num  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

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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)
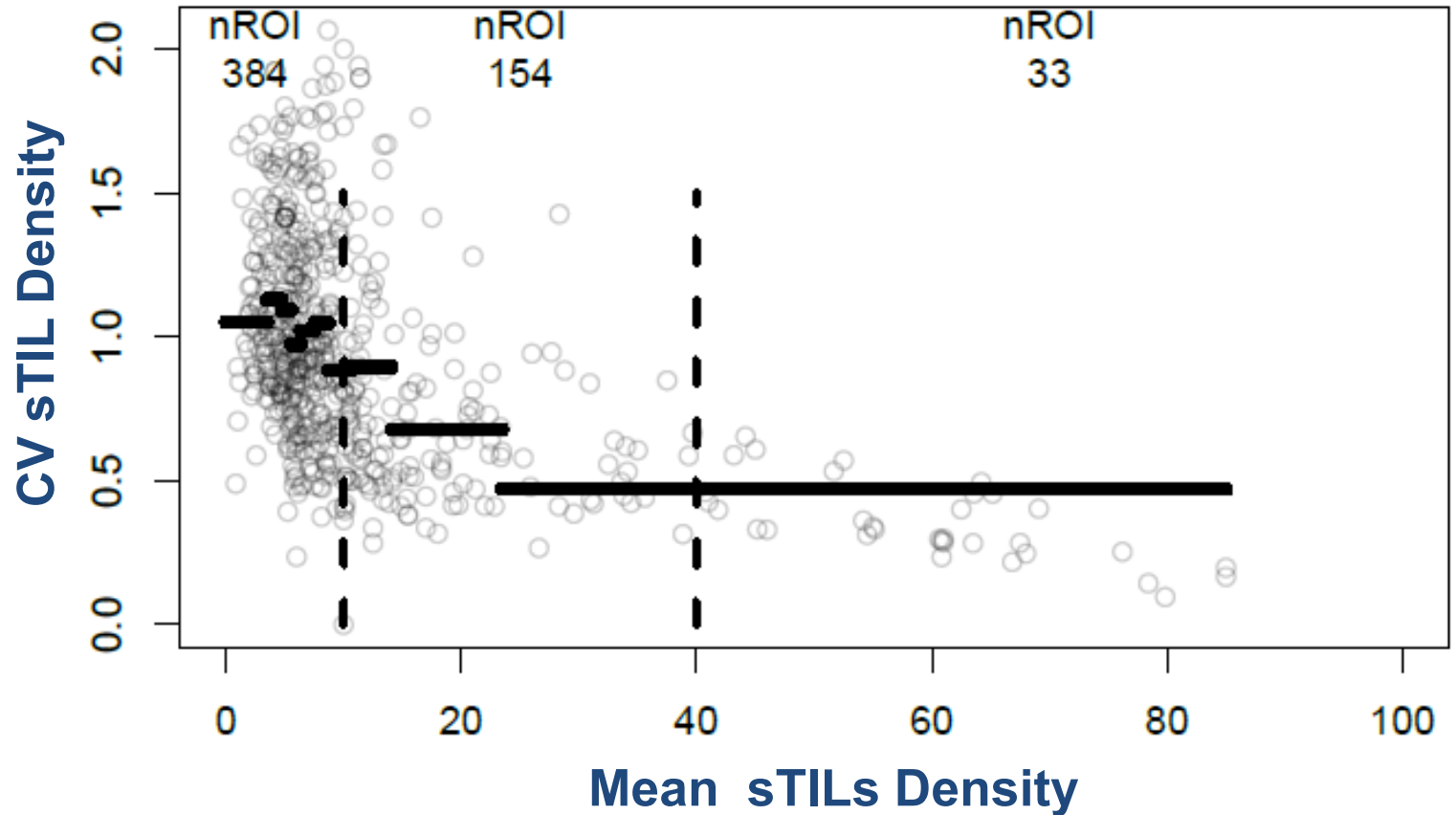
Validation Data and Methods

Quantitative Agreement Endpoint:

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

- Algorithm-pathologist agreement

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

- Pathologist-pathologist agreement

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

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

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- [DIDSR/HTT (github.com)](github.com)

- Brandon.gallas@fda.hhs.gov

- Thank you.

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