

High-Throughput Truthing (HTT) Project Data Collection Tutorial VTA: Visual TIL Assessment

**HTT aims to create a validation dataset for AI/ML medical devices,
through the use case TILs in Breast Cancer.**

**This tutorial was prepared in partnership with the International
Immuno-Oncology Biomarker Working Group - 2020**

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 - **VTA**: Visual TIL Assessment
 - **TIL**: Tumor-infiltrating lymphocyte
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 - **eeDAP**: Evaluation Environment for Digital and Analog Pathology
 - Digital
 - **CaMicroscope**
 - **PathPresenter**

Aim of this tutorial

- To provide operational data-collection instructions to pathologists (HTT study participants)
- To provide a demonstration of hardware and software used in the HTT project
 - Evaluation Environment for Digital and Analog Pathology (eeDAP)
 - CaMicroscope
 - PathPresenter
- Prerequisite: Clinical Training on VTA
 - *Standardized evaluation of Tumor-Infiltrating Lymphocytes (TIL) in Breast Cancer for daily clinical and research practice or clinical trial setting: A tutorial prepared by the **International Working Group for TIL in breast cancer** – 2014. Denkert, C., Salgado, R., Demaria, S.*
 - Access the clinical training here:
<https://ncihub.org/groups/eedapstudies/wiki/HighThroughputTruthingYear3/File:TutorialWebsiteAdapted29012020.pdf>
 - For Freely available online Training-tool, see www.tilsinbreastcancer.org
 - For any query, please contact Roberto Salgado –Roberto@salgado.be-

Data-Collection Tasks

- There are two modes of data collection: **microscope-mode** or a **digital-mode**
- You will be presented a sequence of **Regions of Interest (ROI)**.
- For each ROI, please complete three tasks:

Task 1 – Label the ROI

Task 2 – Record % Tumor-Associated Stroma

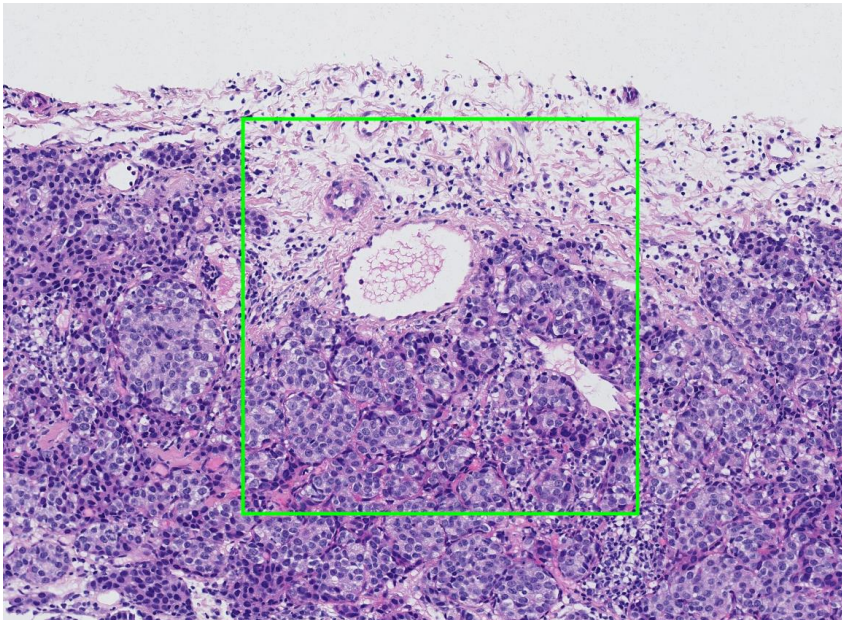
Task 3 – Record % TILs

- There are approximately **80 ROIs per batch**, 10 ROIs per slide and 8 slides.

ROI: Region of Interest

Digital ROI:

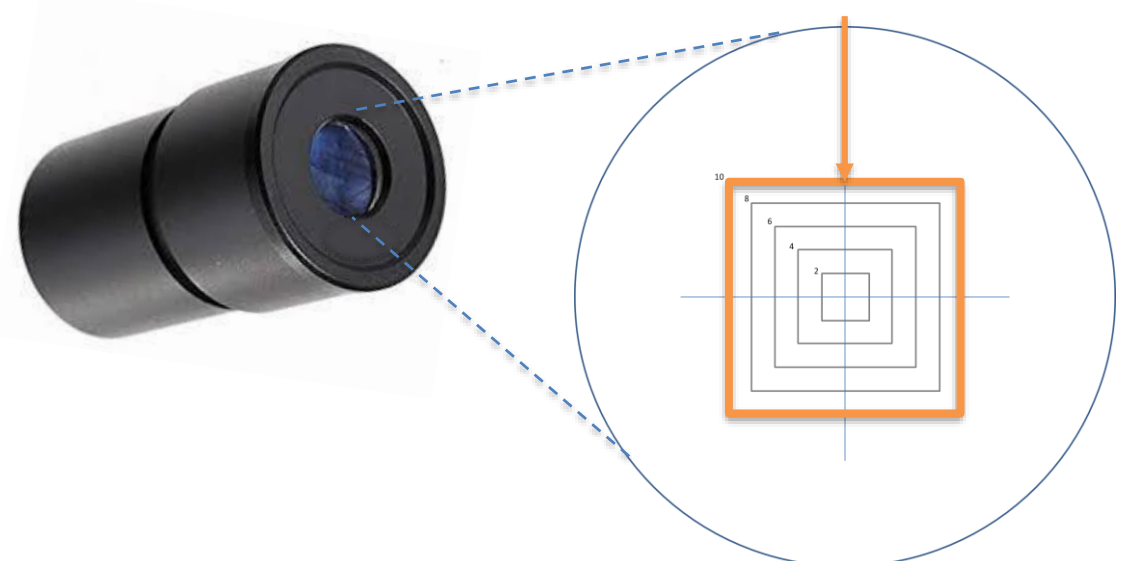
- The bounding box is digitally marked on the whole slide image (WSI)



Microscope ROI:

- There is a reticle in the eyepiece showing the bounding box

Use the outermost bounding box.
* 500 um x 500 um at 20X



Reticle Schematic

Data Collection: **Task 1 – Label the ROI**

Intra-tumoral stroma

Stroma within the limits of the cancer (NOT intra-epithelial TILs)

Eligible for
Visual TIL
Assessment
(VTA)

Tumor with NO intervening stroma

Densely packed tumor with no stroma, regardless of immune infiltrate

Invasive margin

Typically 1mm, contains edge of malignant cell nests

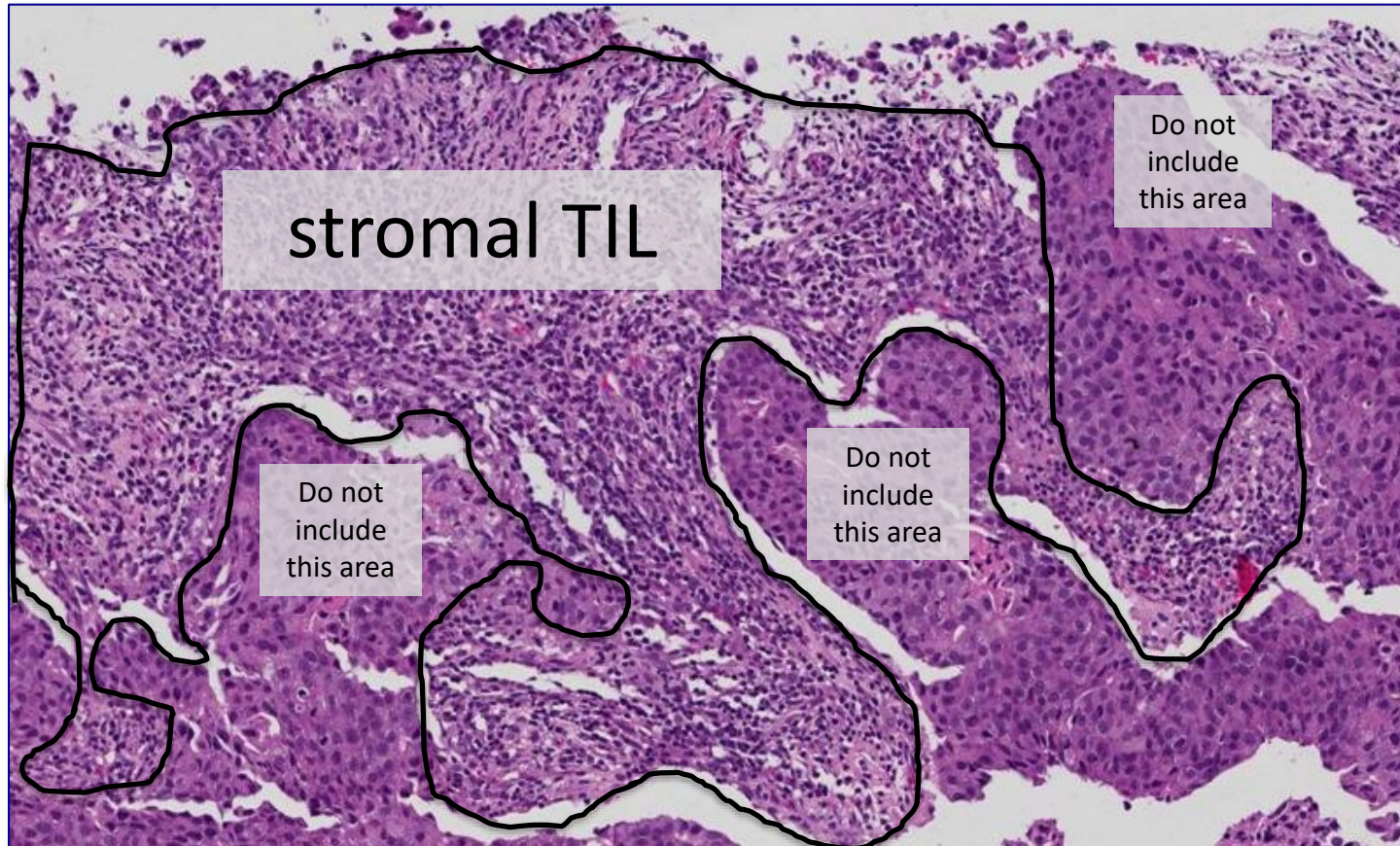
Eligible for
Visual TIL
Assessment
(VTA)

Other regions

Necrosis, fibrosis, or other areas of granulocytic infiltrate

Data Collection: **Task 2** – **Record % Tumor-Associated Stroma**

- Assess the area of the ROI which contains tumor-associated stroma and record it as a percent (%) of the total area of the ROI



This example ROI might be labeled
50-70% Tumor-Associated Stroma

Data Collection: **Task 3 – Record % TILs**

- Evaluate eligible ROIs for percent stromal TIL density (% TILs) and record using the sliding bar or numeric entry box on the digital user interface.

tumor with no/minimal
immune cells

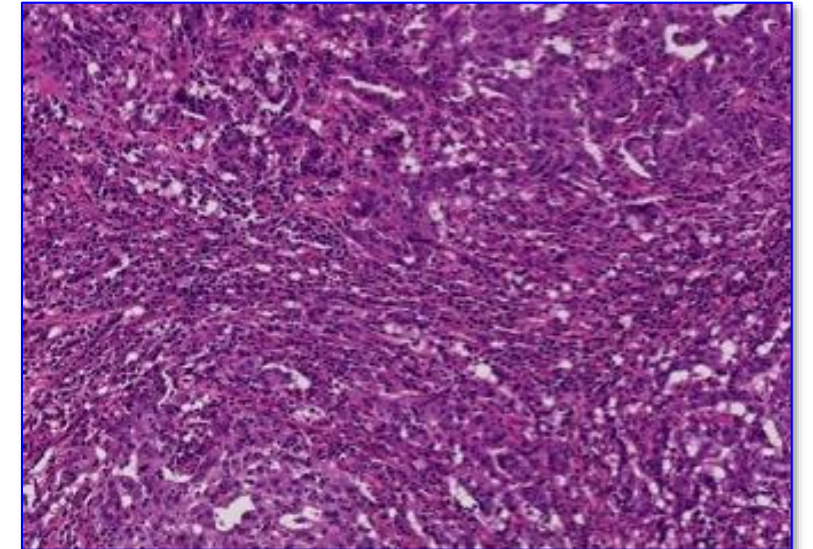
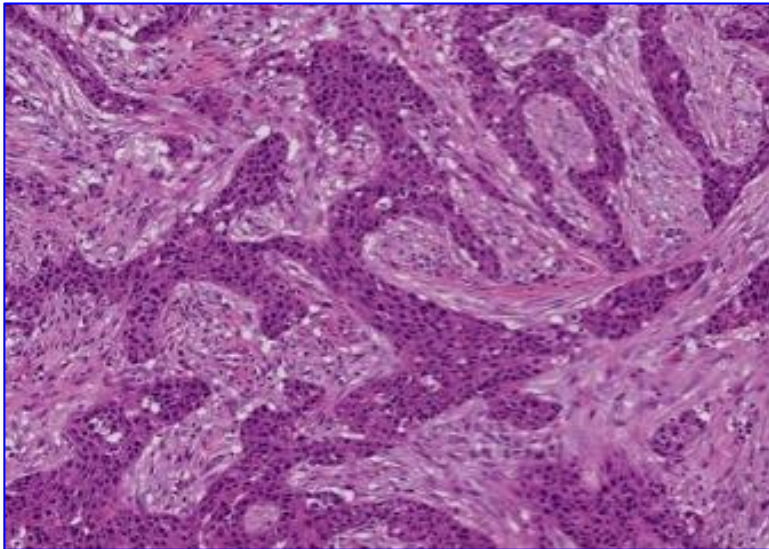
0-10% stromal TILs

tumor with intermediate/
heterogeneous infiltrate

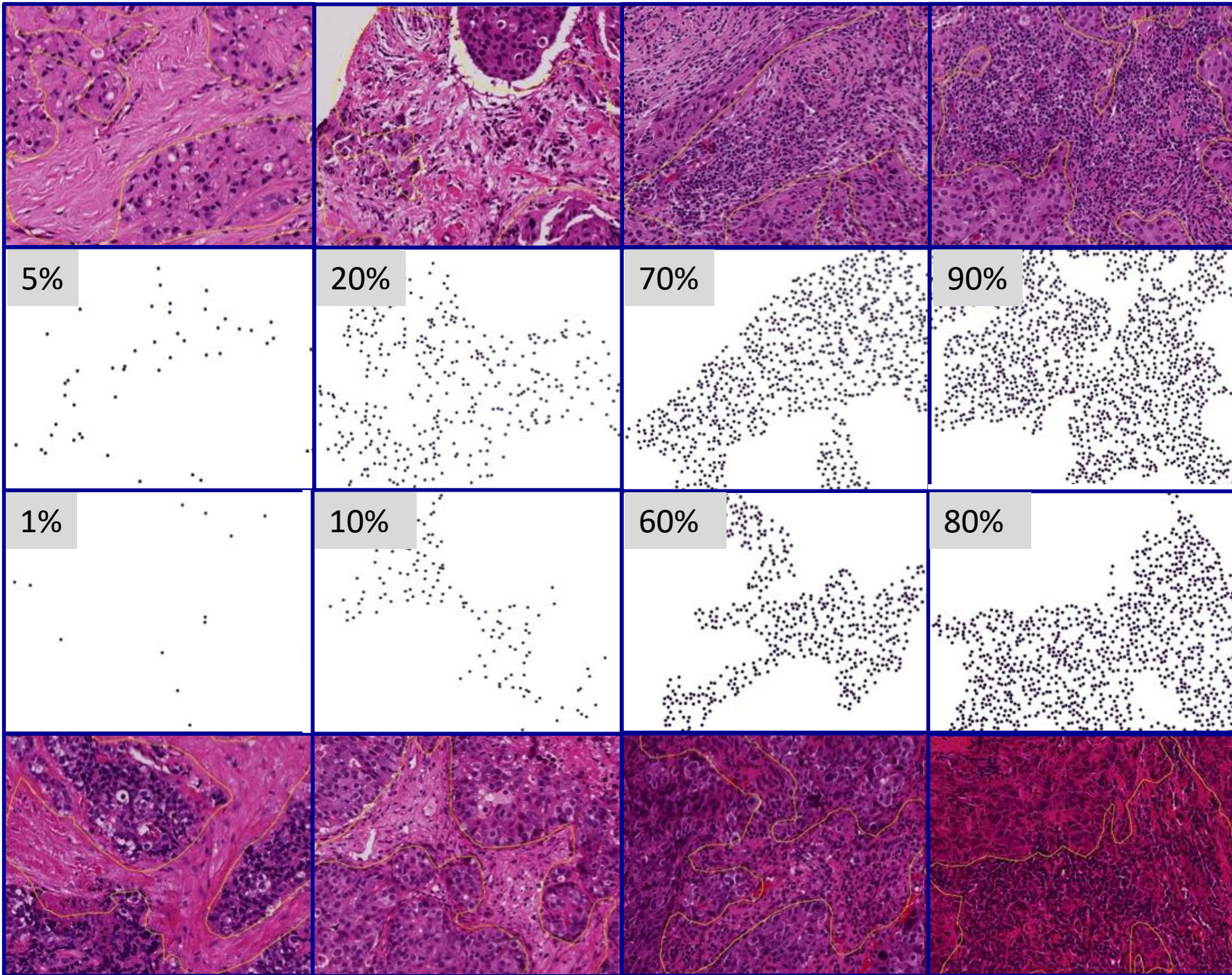
10-40% stromal TILs

tumor with high
immune infiltrate

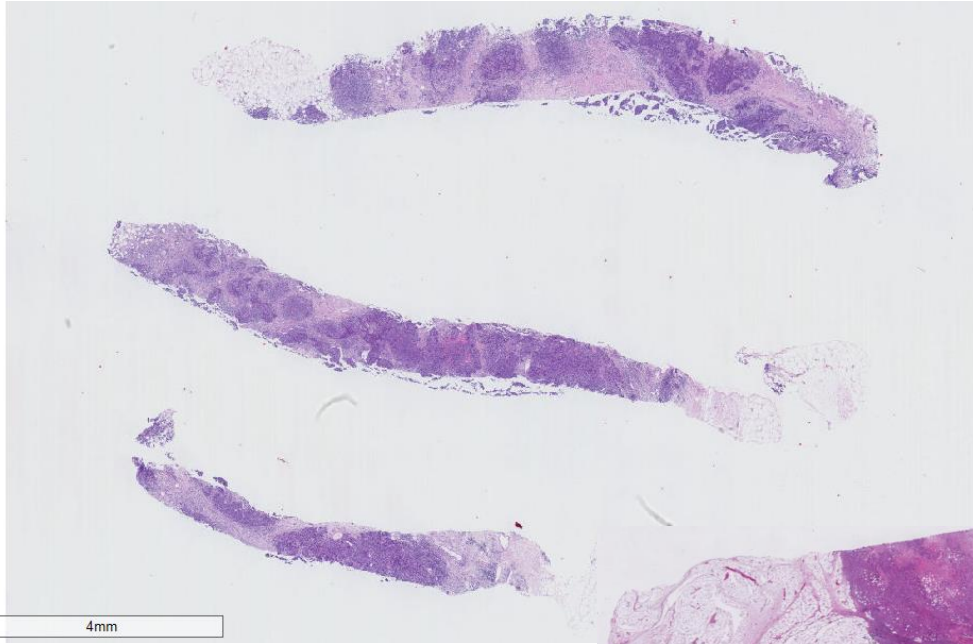
40-90% stromal TILs



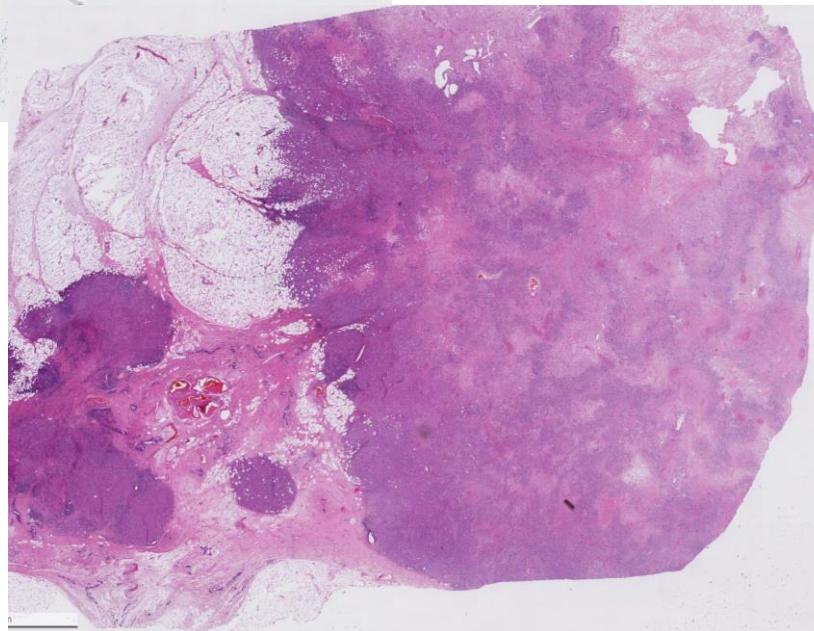
Example VTAs



Slides and Images for Evaluation



- Needle core biopsies of ductal breast carcinomas w/ H&E stain
- Each sample = unique patient.
- Hormone status and other IHC/orthogonal test outcomes unavailable.



Why did the HTT project elect this use case?

Clinical: TILs are an exciting biomarker in precision medicine. Recently found to be a potential for ubiquitous cancer treatment, TILs, represent an avenue for treatment or treatment response measurement. Particularly those found in biopsy samples could lessen chemo burden carried by some patients.

Technical: TILs represent a computer-identifiable feature-level annotation. Carcinomas of the breast provide heterogenous backgrounds for ample object variability.

Data Collection Systems



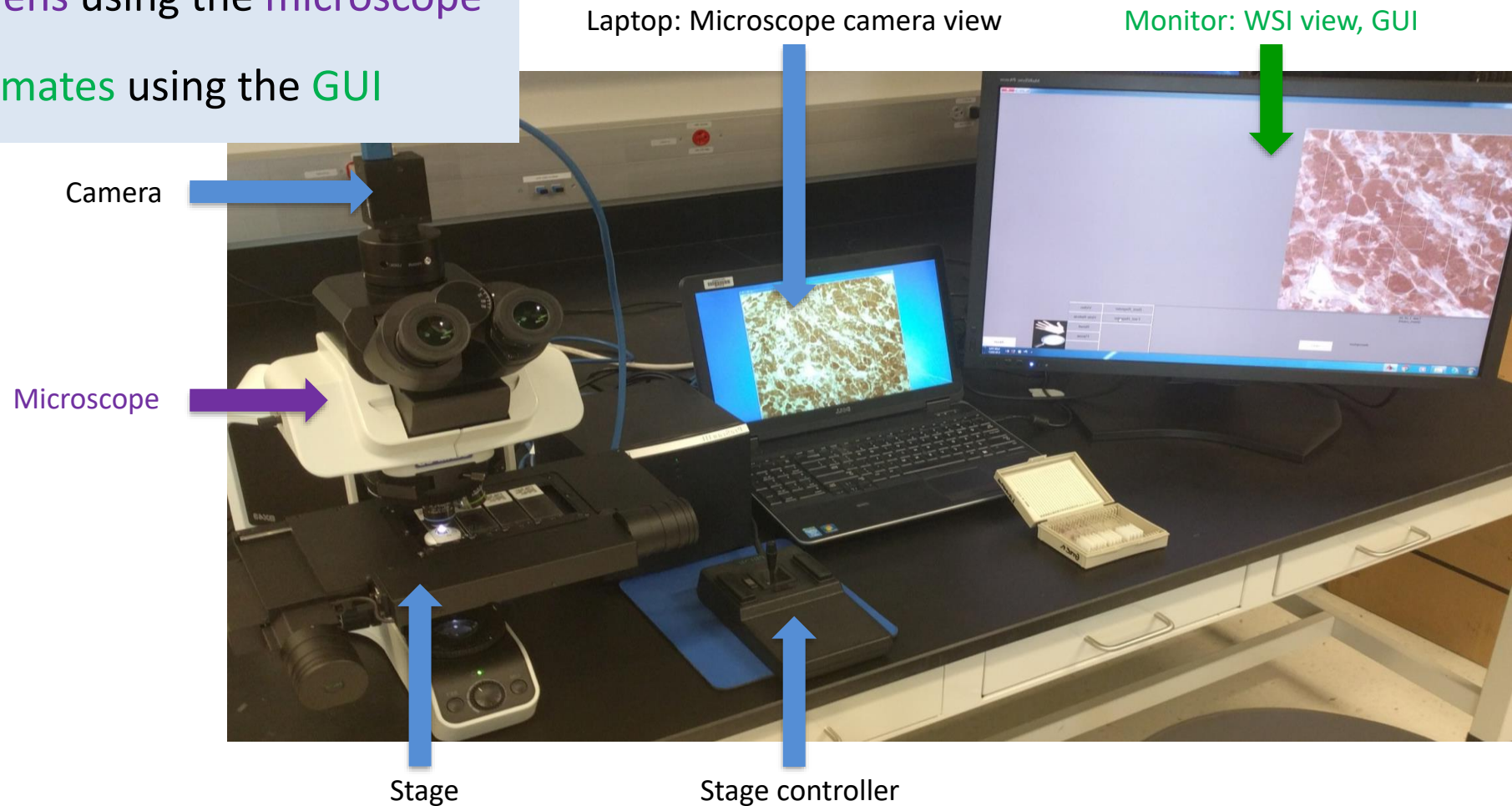
Microscope Platform: eeDAP

<https://ncihub.org/groups/eedapstudies/wiki/HighthroughputTruthingYear2>

Data Collection Systems

eeDAP is comprised of hardware and software components.

Evaluate specimens using the microscope
record estimates using the GUI



Data Collection Systems



Always evaluate at **20x**



You **CAN** switch the microscope objective for context, **without moving the stage**, in microscope mode.



DO NOT adjust the microscope location during the study.

Data Collection Systems



Digital Platforms:
caMicroscope

<http://htt.camicroscope.org/>

Data Collection Systems

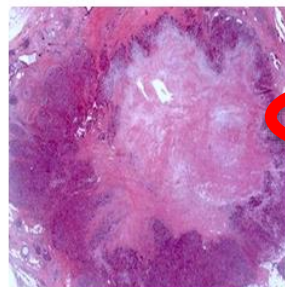
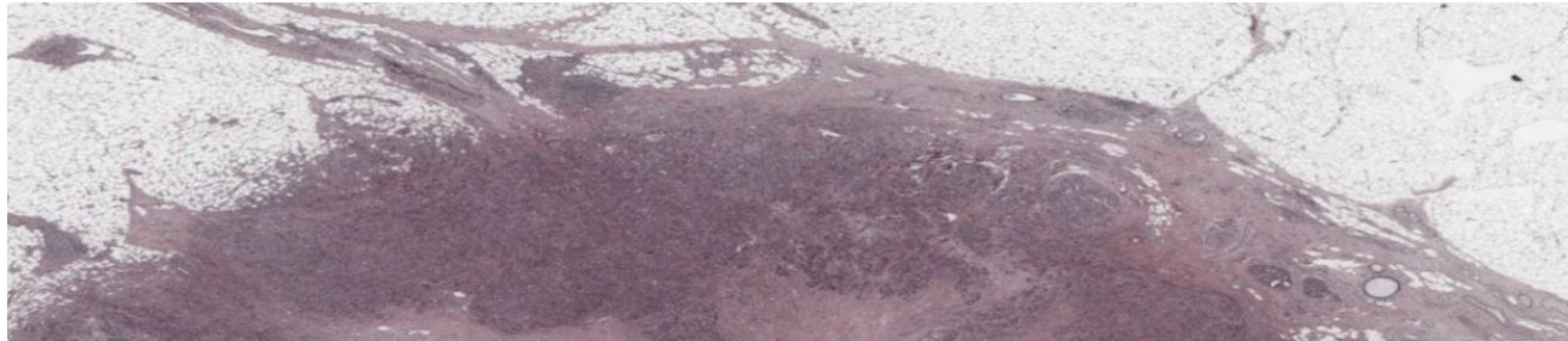


Digital Platforms:
CaMicroscope

Sign in with your **Google** account

HTT ROI ANNOTATION

HTT ROI Annotation is a tool to view, label, and annotate biomedical images.



PLEASE SIGN IN WITH YOUR GOOGLE
ACCOUNT



Sign in with Google

Data Collection Systems



Digital Platforms:
CaMicroscope

Read and respond to the
Participant Consent Form

Participant Consent Form

1 of 2 Automatic Zoom

INFORMED CONSENT TO PARTICIPATE IN A RESEARCH STUDY CONDUCTED BY THE U.S. FOOD AND DRUG ADMINISTRATION

Title: High-throughput truthing of microscope slides to validate artificial intelligence algorithms analyzing digital scans of same slides

Principal Investigator: Dr. Brandon Gallas, FDA

You are being asked to participate in a research study as a pathologist performing assessments of archived tumor slides. The following information is being given to you to explain the study purpose, what you will be asked to do as a participant, and the potential risks and benefits. You are encouraged to ask questions before deciding to participate, or at any time during the course of the study.

I Accept The Terms of Consent Form. [Download Consent Form](#)

CONTINUE DECLINE

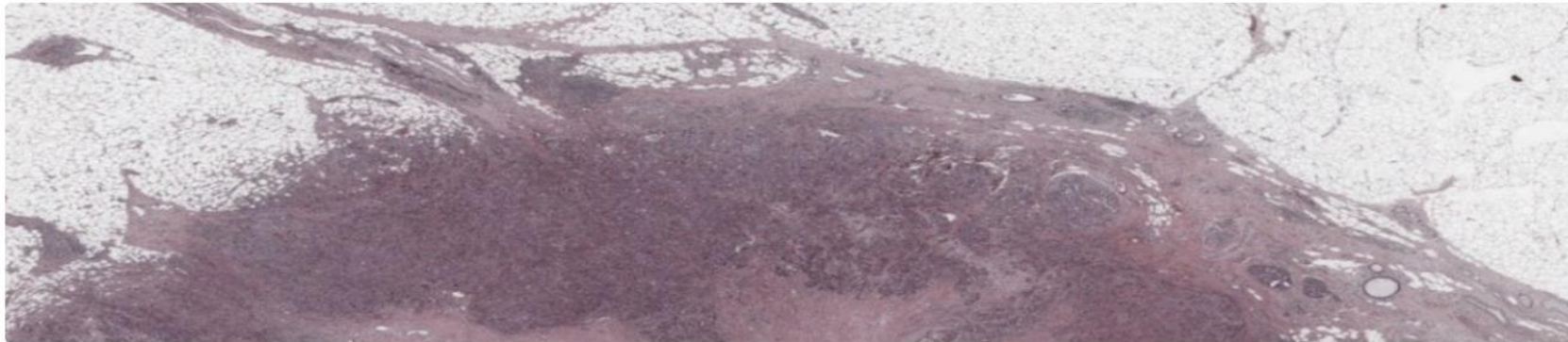
Data Collection Systems



Digital Platforms:
CaMicroscope

HTT ROI ANNOTATION

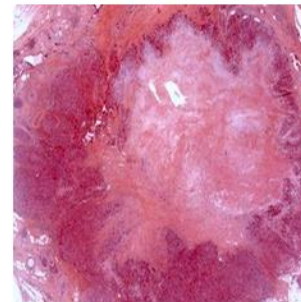
HTT ROI Annotation is a tool to view, label, and annotate biomedical images.



STEP 1: PARTICIPANT SURVEY

We want to learn more about you. Please take the time to complete this survey. (Please ignore if already done)

TAKE THE SURVEY



STEP 2: ANNOTATION

Participants randomly pick up a ROI and annotate on it.

PICK & ANNOTATE

Take the **Participant Survey**

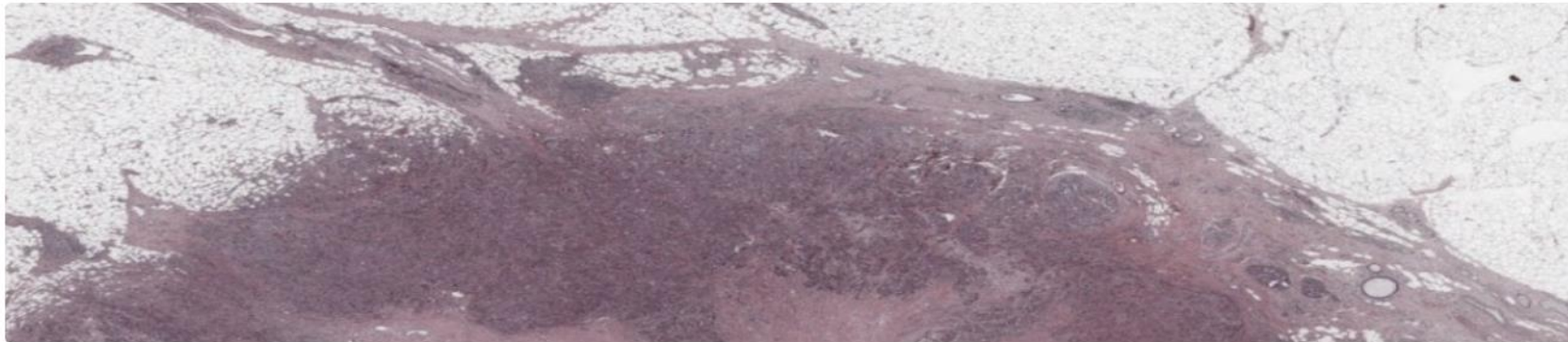
Data Collection Systems



Digital Platforms:
CaMicroscope

HTT ROI ANNOTATION

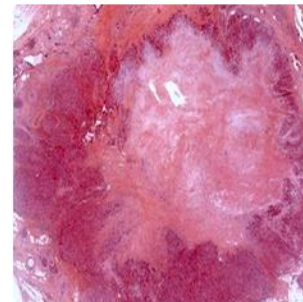
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STEP 1: PARTICIPANT SURVEY

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TAKE THE SURVEY



STEP 2: ANNOTATION

Participants randomly pick up a ROI and annotate on it.

PICK & ANNOTATE

Start the study: **Pick & Annotate**

Data Collection Systems



Digital Platforms:
CaMicroscope

HOME

SIGN OUT

The image shows a grid of eight data collection system cards, labeled HTT-001 through HTT-008. Each card contains the following text:

- HTT-001**
This Is The Batch
001 of HTT-TILS-001
ROIs Evaluation
- HTT-002**
This Is The Batch
002 of HTT-TILS-002
ROIs Evaluation
- HTT-003**
This Is The Batch
003 of HTT-TILS-003
ROIs Evaluation
- HTT-004**
This Is The Batch
004 of HTT-TILS-004
ROIs Evaluation
- HTT-005**
This Is The Batch
005 of HTT-TILS-005
ROIs Evaluation
- HTT-006**
This Is The Batch
006 of HTT-TILS-006
ROIs Evaluation
- HTT-007**
This Is The Batch
007 of HTT-TILS-007
ROIs Evaluation
- HTT-008**
This Is The Batch
008 of HTT-TILS-008
ROIs Evaluation

The first card (HTT-001) is circled in red, and a red arrow points from the text below to it.

Begin with **HTT-001**, then work sequentially

Data Collection Systems



Digital Platforms:
CaMicroscope

CaMicroscope Data Table

https://wolf.cci.emory.edu//camicroscope/htt/apps/labeling/labelingSimpleAnnotationViewer.html?collectionId=5e289220f628fc6b8f7e54d0

HOME COLLECTION LIST SIGN OUT

50 entries per page Search...

ID	Name	Study	Specimen	MPP	ROIs
5e2886c7adbe1d0005170121	HTT-TILS-001-11B			0.22834699609526637	10/10 <input checked="" type="checkbox"/>
5e2886a3adbe1d0005170107	HTT-TILS-001-08B			0.22834699609526637	10/10 <input checked="" type="checkbox"/>
5e288696adbe1d00051700f7	HTT-TILS-001-12B			0.22834699609526637	10/10 <input checked="" type="checkbox"/>
5e288684adbe1d00051700e1	HTT-TILS-001-13B			0.22834699609526637	10/10 <input checked="" type="checkbox"/>
5e288681adbe1d00051700db	HTT-TILS-001-07B			0.22834699609526637	10/10 <input checked="" type="checkbox"/>
5e28866fadbe1d00051700c7	HTT-TILS-001-09B			0.22834699609526637	10/10 <input checked="" type="checkbox"/>
5e273addadbe1d000517006c	HTT-TILS-001-04B			0.22834699609526637	8/10 <input type="button" value="Open"/>
5e273994adbe1d000517002c	HTT-TILS-001-03B			0.22834699609526637	0/10 <input type="button" value="Open"/>

Showing 1 to 8 of 8 entries

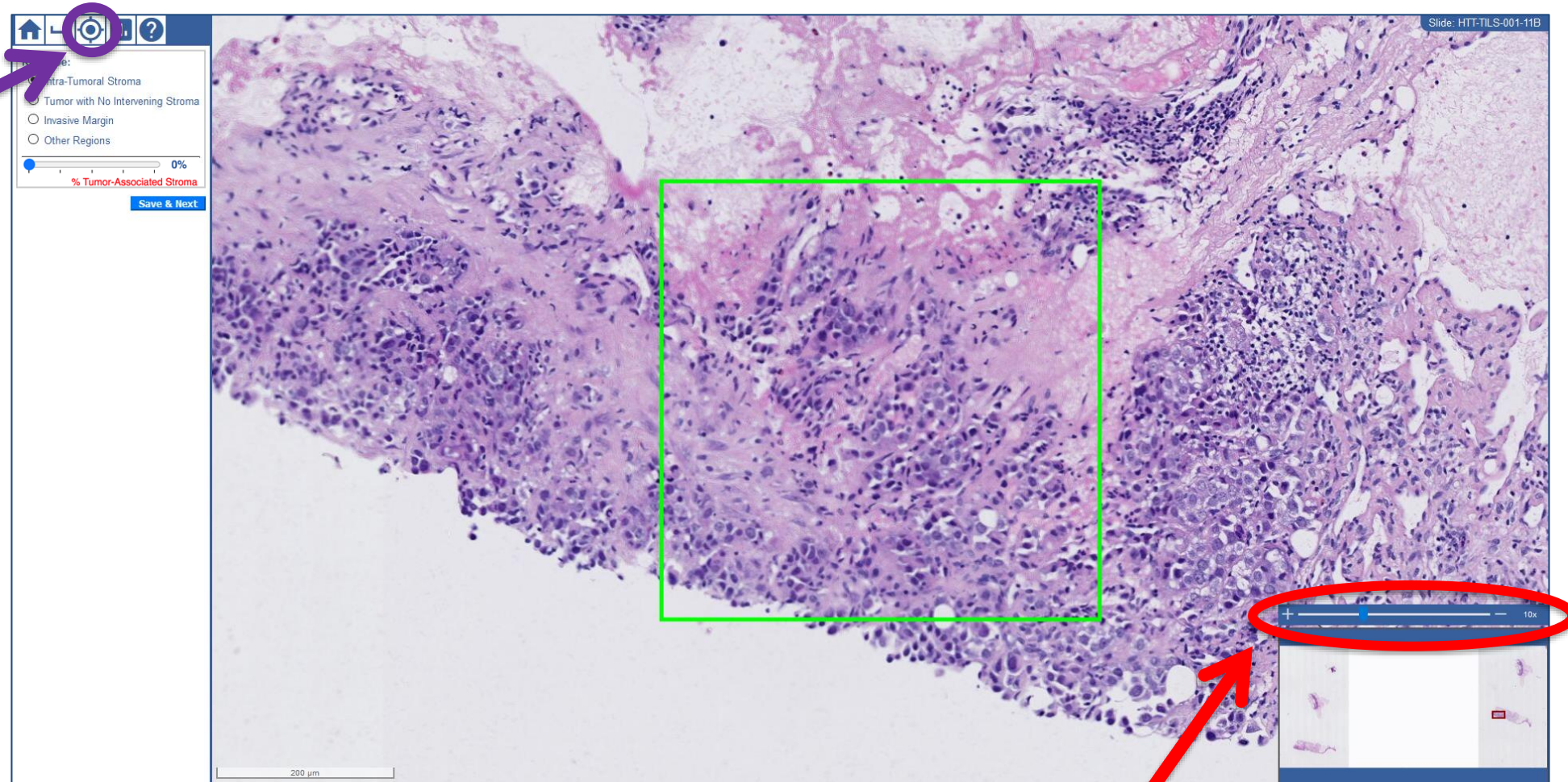
Please **complete all slides** in the batch

Data Collection Systems



Digital Platforms:
CaMicroscope

Reset ROI view
after scrolling
and panning



Zoom & pan by using your mouse or the **sliding bar**

Data Collection Systems



Digital Platforms:
CaMicroscope

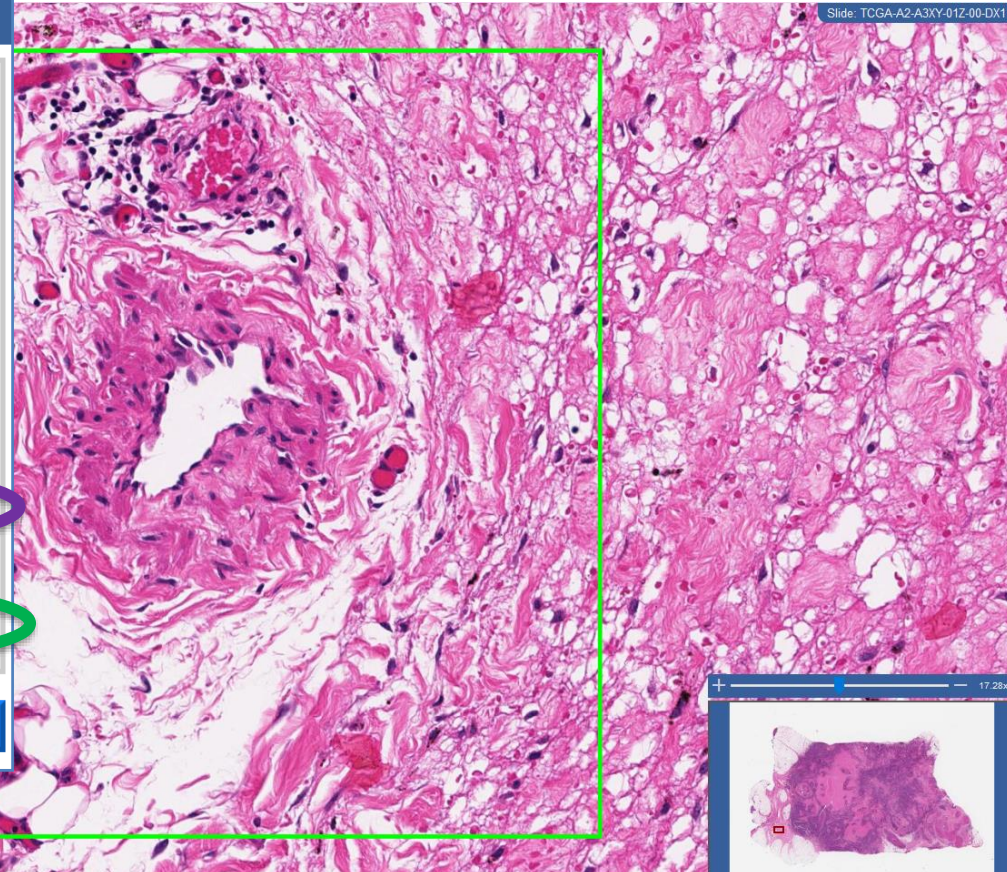
1. Select an ROI label from the list of options →

2. Verify that a Visual TIL Assessment can be conducted

3. Record TIL Density (%) →

The screenshot shows a software interface with a top navigation bar containing icons for home, back, settings, and help. Below the navigation bar is a panel with the following elements:

- ROI Type:** A dropdown menu with four radio button options:
 - Intra-Tumoral Stroma
 - Tumor with No Intervening Stroma
 - Invasive Margin
 - Other Regions
- % Tumor-Associated Stroma:** A slider control set to 31%.
- Please Assess TIL Density:** A slider control set to 60%.
- Save & Next:** A blue button at the bottom right of the panel.



Data Collection Systems



Digital Platforms:
CaMicroscope

Use the **graph** button to review examples

The screenshot displays the CaMicroscope software interface. On the left, a sidebar contains the following elements:

- Home icon, back icon, refresh icon, **graph icon** (circled in red with a red arrow pointing to it), and help icon.
- ROI Type:
 - Intra-Tumoral Stroma
 - Tumor with No Intervening
 - Invasive Margin
 - Other Regions
- Eligible for TIL Assessment
- Save button

The main window, titled "The Example Of TIL Densities", shows a 4x2 grid of image pairs. Each pair consists of a histological image on the left and a corresponding TIL density visualization on the right. The density visualizations are labeled with percentages:

1%	5%
10%	20%
60%	70%
80%	90%

Data Collection Systems



Digital Platforms:
CaMicroscope



Use the **help** button to review training documents

The screenshot displays the CaMicroscope software interface. On the left, there is a sidebar with 'ROI Type:' options: Intra-Tumoral Stroma, Tumor with No Intervening, Invasive Margin, Other Regions, and Eligible for TIL Assessment. A 'Save' button is visible below these options. The main window is titled 'Tutorial' and shows a slide with the following text:

**Standardized evaluation of
Tumor-Infiltrating Lymphocytes (TIL)
in Breast Cancer for daily clinical and
research practice or clinical trial setting**

**A tutorial prepared by the International Working
Group for TIL in breast cancer – 2014 – adapted 2020**

Carsten Denkert
Roberto Salgado
Sandra Demaria

Data Collection Systems



Digital Platforms:
CaMicroscope



Always evaluate at **20x**



You **CAN** zoom in/out and scroll through surrounding tissue in digital mode.

Data Collection Systems



Digital Platforms: **PathPresenter**

<https://ai.pathpresenter.net/Account/Home/EventView/A>

Data Collection Systems



Digital Platforms:
PathPresenter



HOME ANNOTATION JOBS ABOUT CONTACT REGISTER LOGIN

EVENT



MDDT Data Collection
Enrollment Open : 2/28/2020

[Register](#)

[TILs evaluation guidelines](#)
[HTT data-collection tutorial](#)
[Informed Consent](#)

CHECK SHORT TRAINING

MDDT Data Collection
PathPresenter AI

HOME ABOUT CONTACT REGISTER LOGIN Watch later Share

Login in AI PathPresenter

Username
example@gmail.com

Password

Remember login
(if this is a private computer)

Our other platforms

PathPresenter PathPresenter Publications

2020 ALL RIGHTS RESERVED PATH PRESENTER BACK TO HOME

Register for a new account
& consult other resources

Consult the **How-To Video**
for additional instruction

Data Collection Systems



Digital Platforms:
PathPresenter



HOME

DASHBOARD

Individual

Event Registration : MDDT Data Collection

Email

First Name **Last Name**

Password **Confirm Password**

Profession

Speciality

About You

Accept Informed Consent

Take the Participant Survey

Read and respond to the
Participant Consent Form

Data Collection Systems



Event for Jan-Batch-1

Event for Jan-Batch-2

Event for Jan-Batch-3

Event for Jan-Batch-4

Event for Jan-Batch-5

Event for Jan-Batch-6


Event for Jan-Batch-7


Event for Jan-Batch-8


Begin with **Batch-1**, then work sequentially

Data Collection Systems



 **Event for Jan-Batch-1**
Total ROI : 80
Pending Attempt :
Pending ROI to annotate : ----

 My Annotations : 0

 Visualization

Show 10 entries

Search:

FileName	Original FileName	No Of ROI's	No Of Annotations	Annotation Status	Analysis
GM1578073114208.NDPI	HTT-TILS-001-03B.ndpi	10 [Pending : 10]	0	Pending	Analysis
GM1578073114238.NDPI	HTT-TILS-001-04B.ndpi	10 [Pending : 10]	0	Pending	Analysis
GM1578073114327.NDPI	HTT-TILS-001-07B.ndpi	10 [Pending : 10]	0	Pending	Analysis
GM1578073114406.NDPI	HTT-TILS-001-08B.ndpi	10 [Pending : 10]	0	Pending	Analysis
GM1578073114431.NDPI	HTT-TILS-001-09B.ndpi	10 [Pending : 10]	0	Pending	Analysis
GM1578073114502.NDPI	HTT-TILS-001-11B.ndpi	10 [Pending : 10]	0	Pending	Analysis
GM1578073114556.NDPI	HTT-TILS-001-12B.ndpi	10 [Pending : 10]	0	Pending	Analysis
GM1578073114588.NDPI	HTT-TILS-001-13B.ndpi	10 [Pending : 10]	0	Pending	Analysis

Showing 1 to 8 of 8 entries

Previous 1 Next


[Back to DataSets](#)

[Back to Analysis Projects](#)

Please **complete all slides** in the batch

Data Collection Systems

Move through your tasks using **Next & Previous**



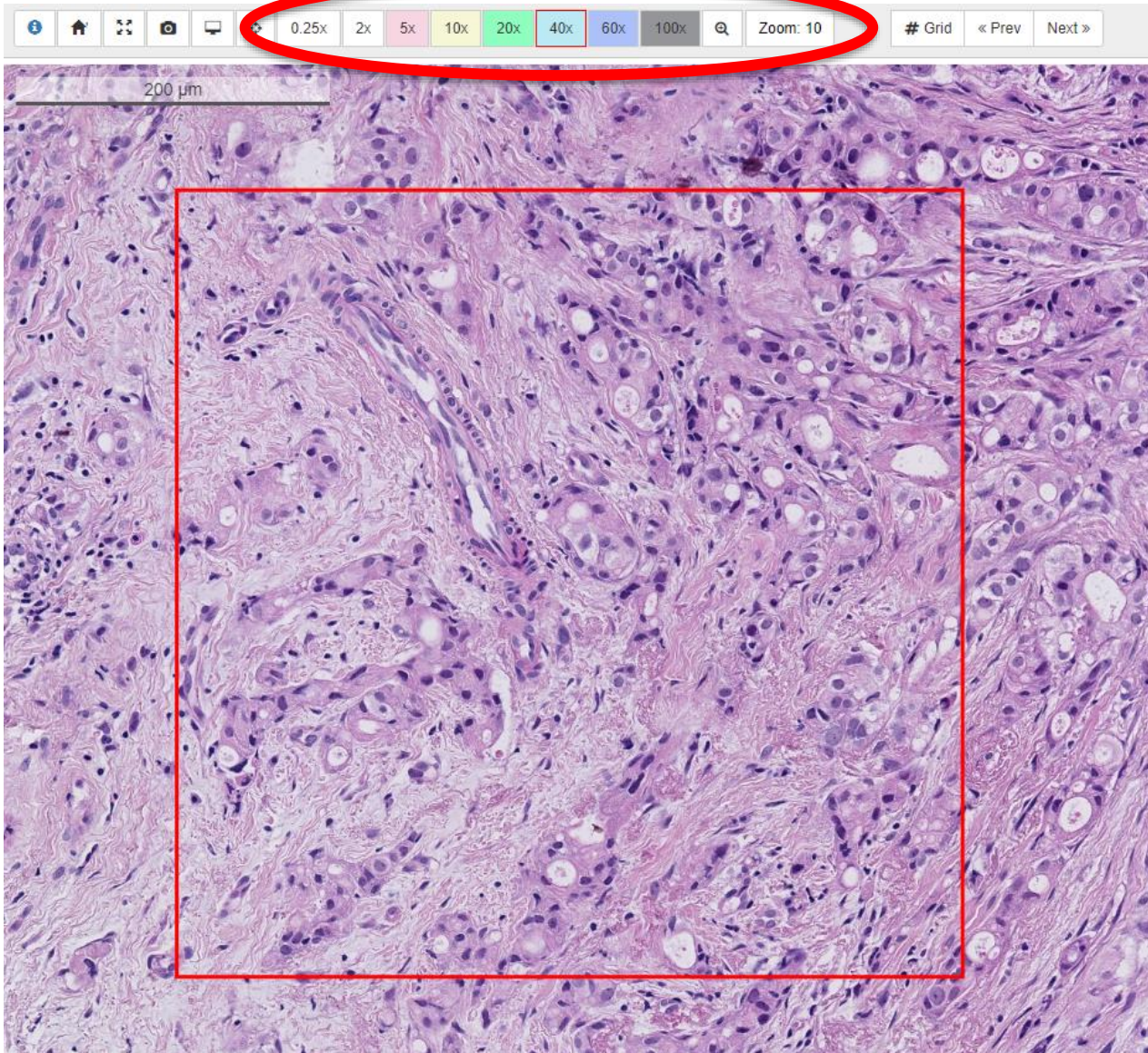
The screenshot displays the PathPresenter software interface. At the top, a toolbar includes navigation icons, zoom levels (0.25x, 2x, 5x, 10x, 20x, 40x, 60x, 100x), and a search icon. The '40x' zoom level is highlighted in red. To the right of the zoom controls, the navigation buttons '<< Prev' and 'Next >>' are circled in red. The main area shows a histology slide with a 2 mm scale bar and several black rectangular ROIs. One ROI is highlighted in red. On the right side, a task list panel is visible, containing the following sections:

- ROI**: A grid of 10 small square icons, with the first one highlighted in red.
- ROI Label**: A dropdown menu with 'Select Title' selected.
- Description**: A text input field with the placeholder 'Please add description'.
- % Tumor-Associated Stroma**: A text input field with the placeholder 'Please add tumor stroma' and a slider set to 0%.
- TILs**: A text input field with the placeholder 'Please add Tia' and a slider set to 0%.
- Buttons**: 'Cancel', 'Save', and 'Hide All ROI'.
- Annotation**: A slider set to 100.

Data Collection Systems



Digital Platforms:
PathPresenter



Zoom & pan by using your
mouse or the
magnification buttons

Data Collection Systems



The screenshot shows a histology image with a red rectangular ROI box. An overlay form titled "ROI" is positioned over the image. The form contains the following fields:

- ROI Label :** A dropdown menu with a "Select Title" label and a list of options (one is highlighted with a red box).
- Description :** A text input field with the placeholder "Please add description".
- %Tumor-Associated Stroma :** A text input field with the placeholder "Please add tumor stroma" and a slider below it.
- TILs :** A text input field with the placeholder "Please add" and a slider below it.
- Buttons:** "Cancel", "Save", and "Hide All ROI".

1. Select an **ROI label** from the list of options

2. Record **Tumor-Associated Stroma (%)** (Keyboard or Slider)

3. Record **TIL Density (%)** (Keyboard or Slider)

Data Collection Systems



Digital Platforms:
CaMicroscope



Always evaluate at **20x**



You **CAN** zoom in/out and scroll through surrounding tissue in digital mode.

Please send any **study-related** questions or comments to:

Brandon Gallas: brandon.gallas@fda.hhs.gov

Sarah Dudgeon: sarah.dudgeon@fda.hhs.gov



Please send any **other** questions or comments to:

Roberto Salgado: roberto@salgado.be