

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**

Sarah Dudgeon

Brandon Gallas

Table of Contents

- Aim of this Tutorial
- Your HTT tasks
 - **VTA**: Visual TIL Assessment
 - **TIL**: Tumor-infiltrating lymphocyte
- Slides and Images for Evaluation
- Data Collection Systems:
 - Microscope
 - **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 – Indicate VTA Eligibility

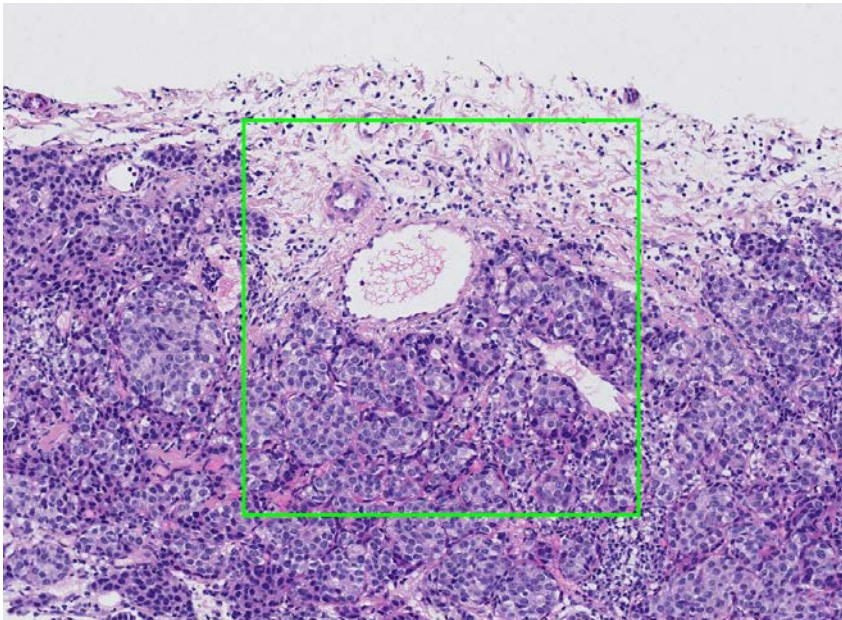
Task 3 – Record % TILs

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

ROI: Region of Interest

Digital ROI:

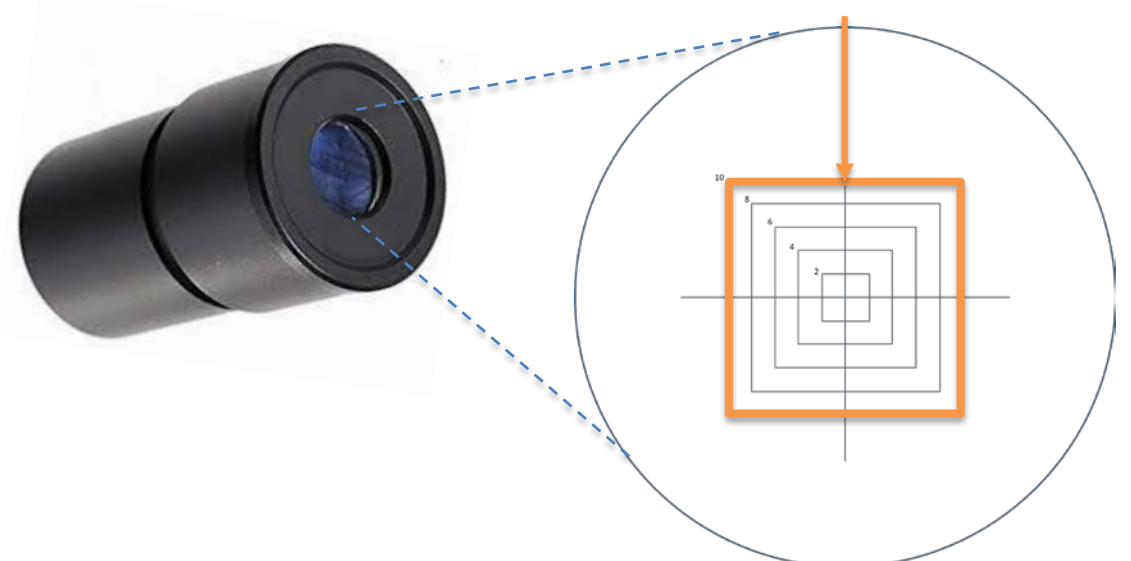
- The bounding box is digitally marked on the whole slide image (WSI)



Microscope ROI:

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

Use the outermost bounding box.
* 500 μm x 500 μm 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

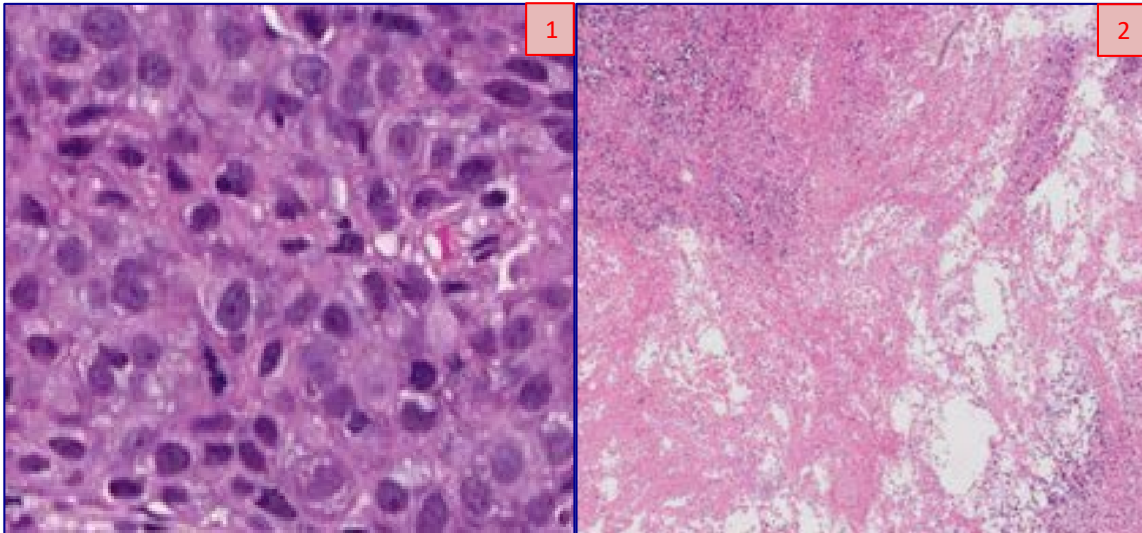
Necrosis, fibrosis, or other areas of granulocytic infiltrate

Data Collection: Task 2

- Within the same region of interest (ROI), assess eligibility for Visual TIL Assessment (VTA)

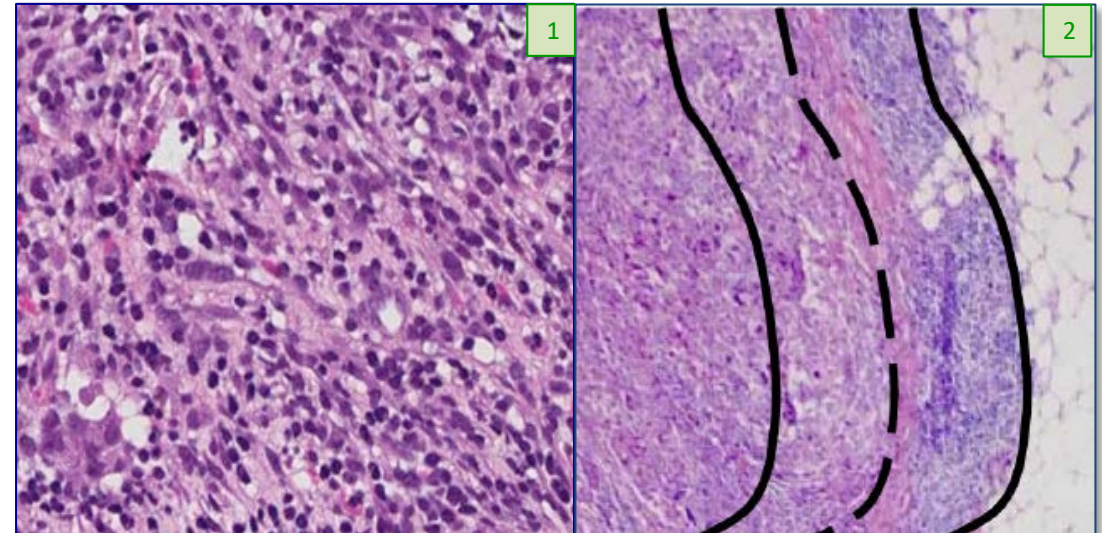
NOT Eligible:

1. Tumor with NO intervening stroma
2. Other regions



Eligible:

1. Intra-tumoral stroma
2. Invasive margin



Data Collection: **Task 3**

- 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

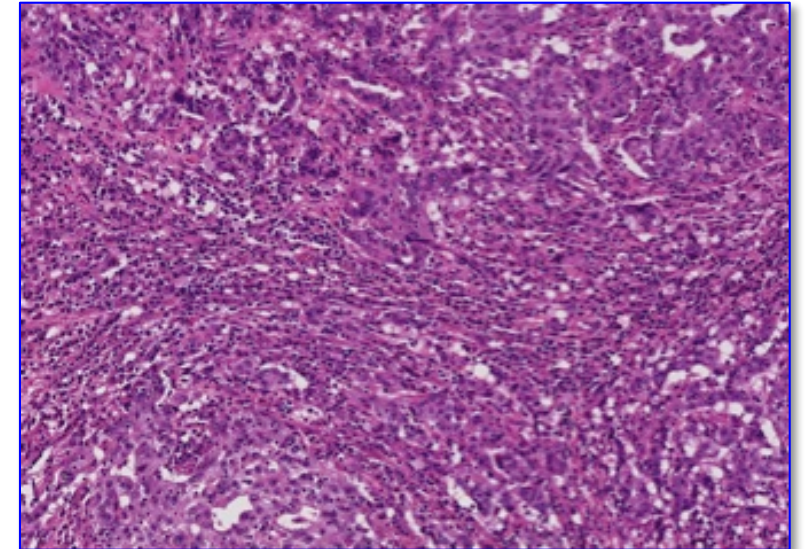
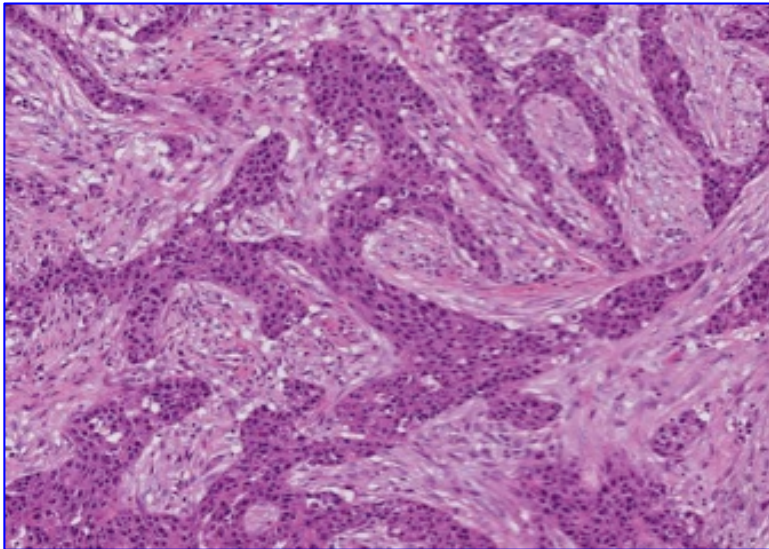
0-10% stromal TILs

tumor with intermediate/
heterogeneous infiltrate

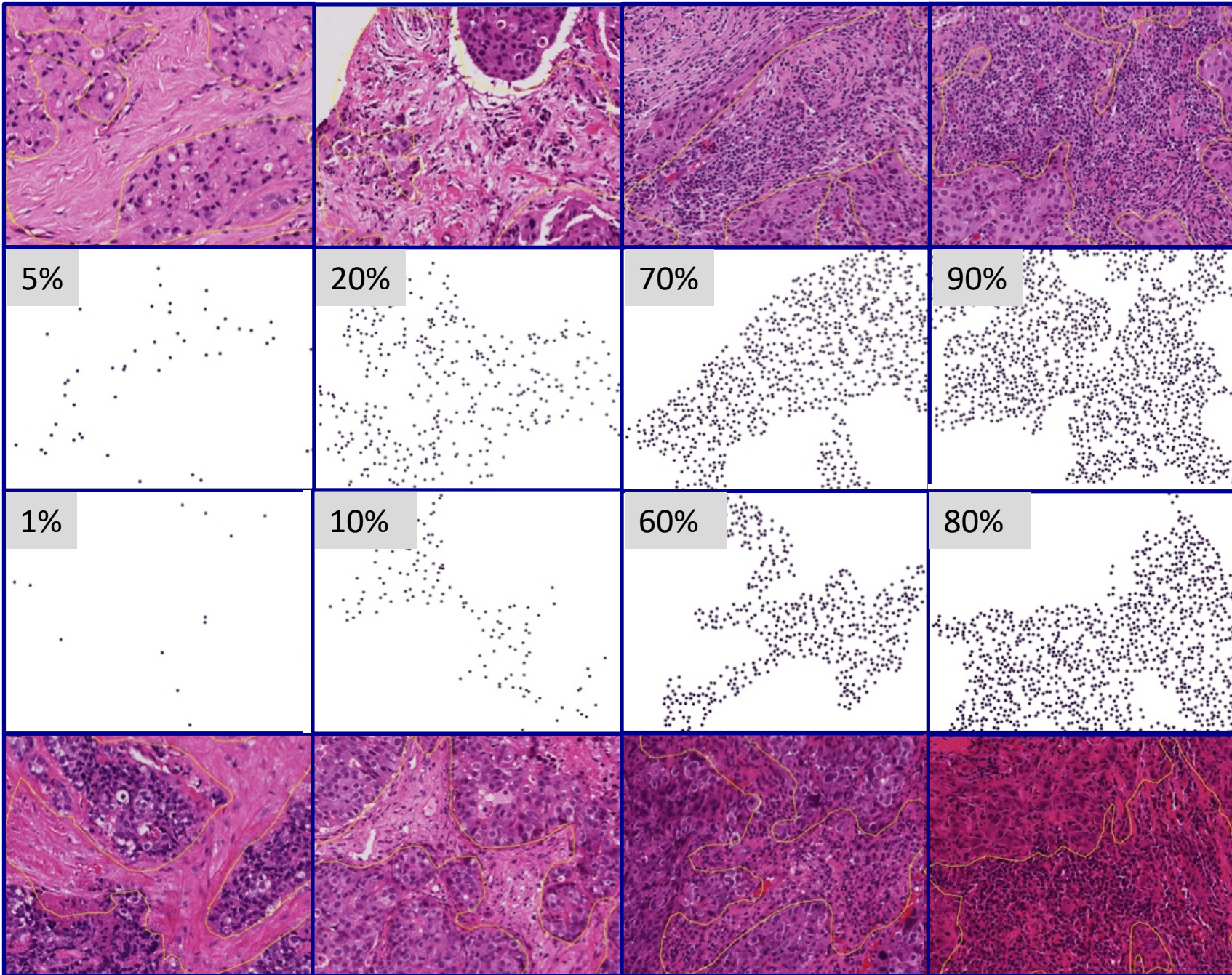
10-40% stromal TILs

tumor with high
immune infiltrate

40-90% stromal TILs



Example VTAs



Slides and Images for Evaluation

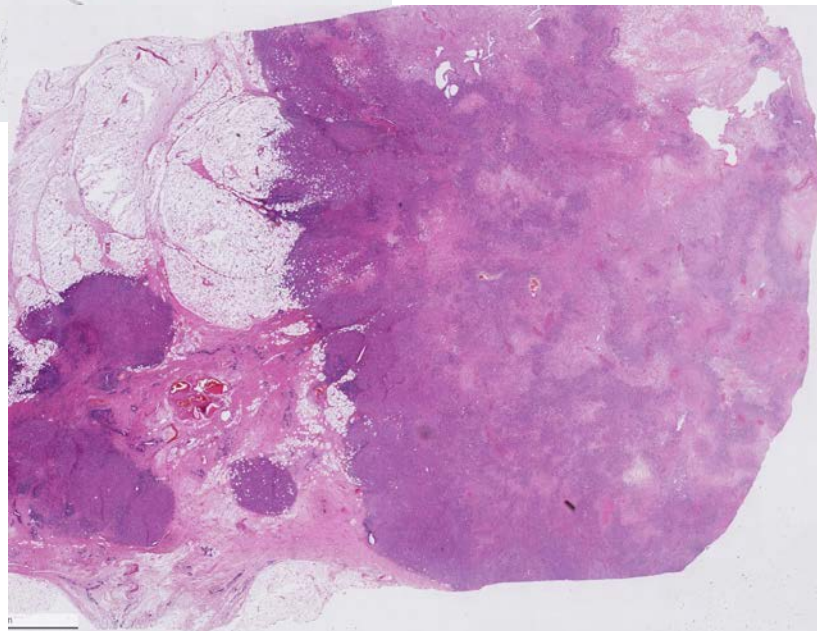


- Needle core biopsies of ductal breast carcinomas w/ H&E stain
- Each sample = unique patient.
- Hormone status and other IHC/orthogonal test outcomes unavailable.

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 System

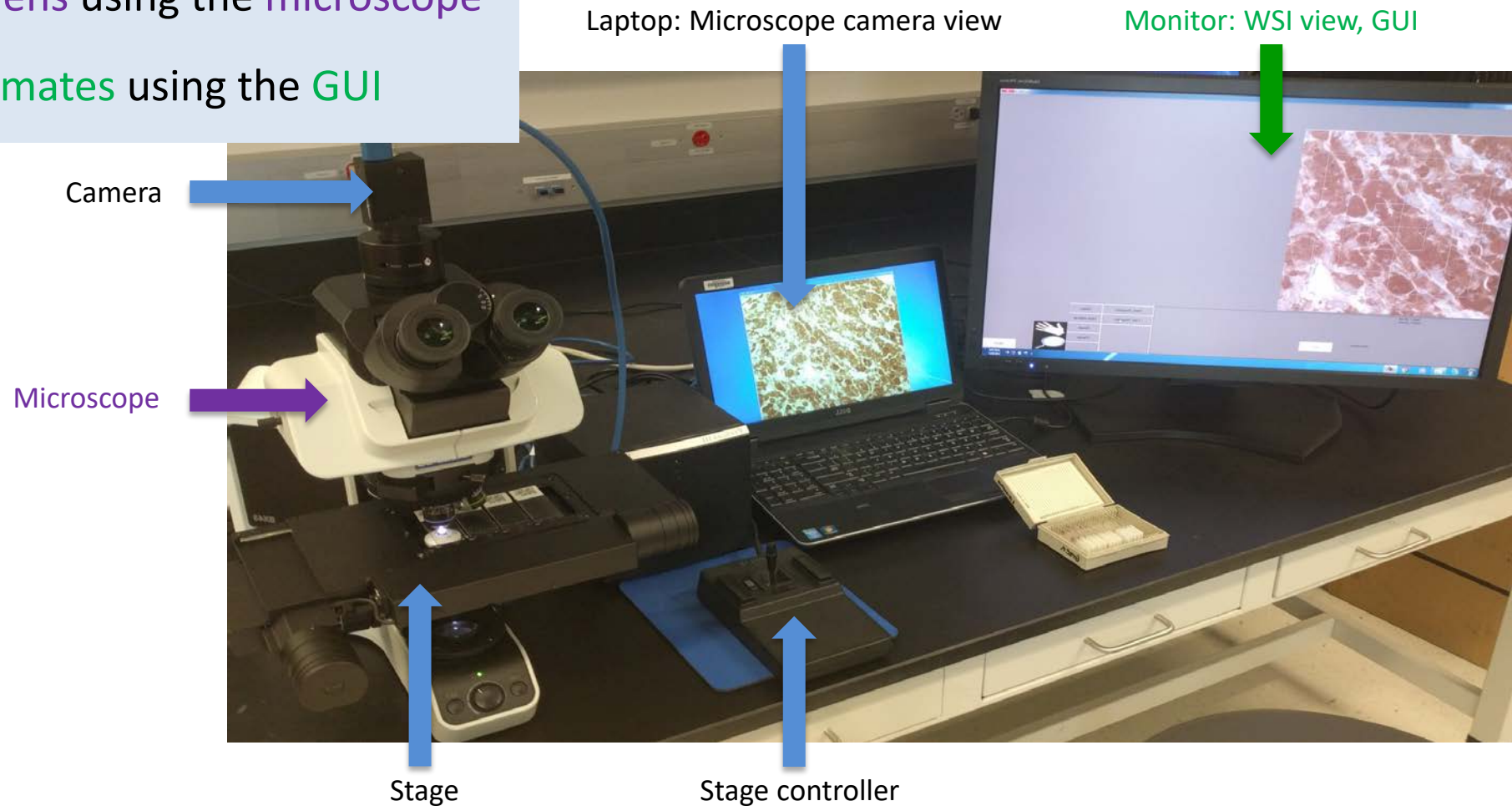


eeDAP

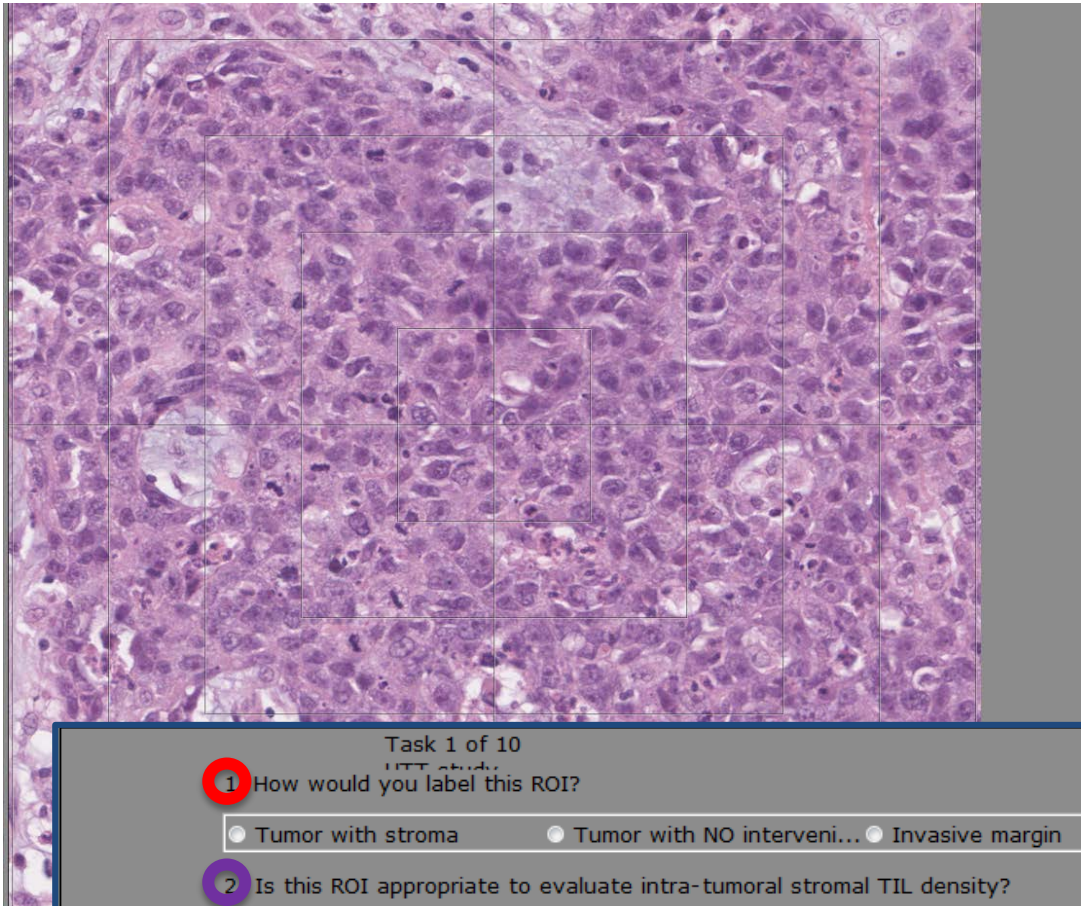
Data Collection Systems

eeDAP is comprised of hardware and software components.

Evaluate specimens using the microscope
record estimates using the GUI



Data Collection Systems



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

2. Verify that a **Visual TIL Assessment** can be conducted

3. Record **TIL Density (%)**

Task 1 of 10

1 How would you label this ROI?

Tumor with stroma Tumor with NO interveni... Invasive margin Other

2 Is this ROI appropriate to evaluate intra-tumoral stromal TIL density?

True False

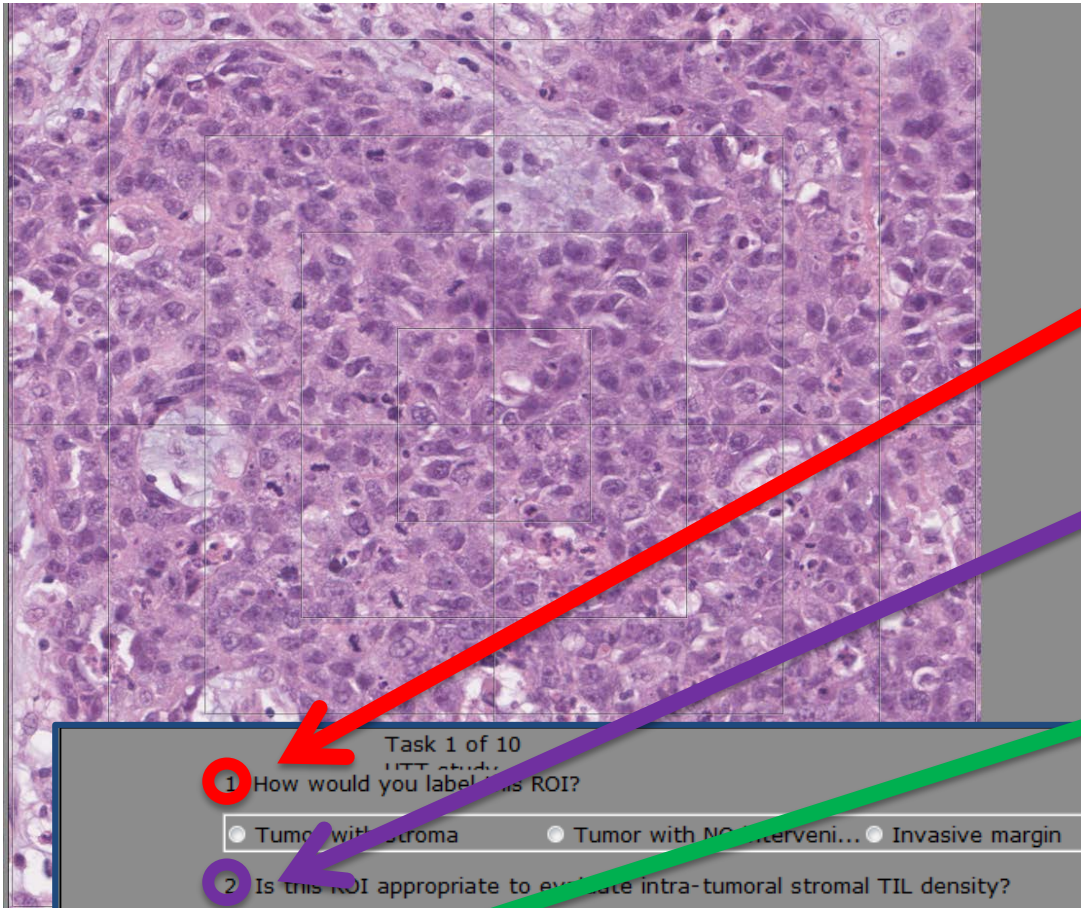
3 What is the intra-tumoral stromal TIL density?

0 50 100 Score

50

Next Hide Reticle Reset Pause Resume Abort

Data Collection Systems



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

2. Verify that a **Visual TIL Assessment** can be conducted

3. Record **TIL Density (%)**

Task 1 of 10
TIL Study

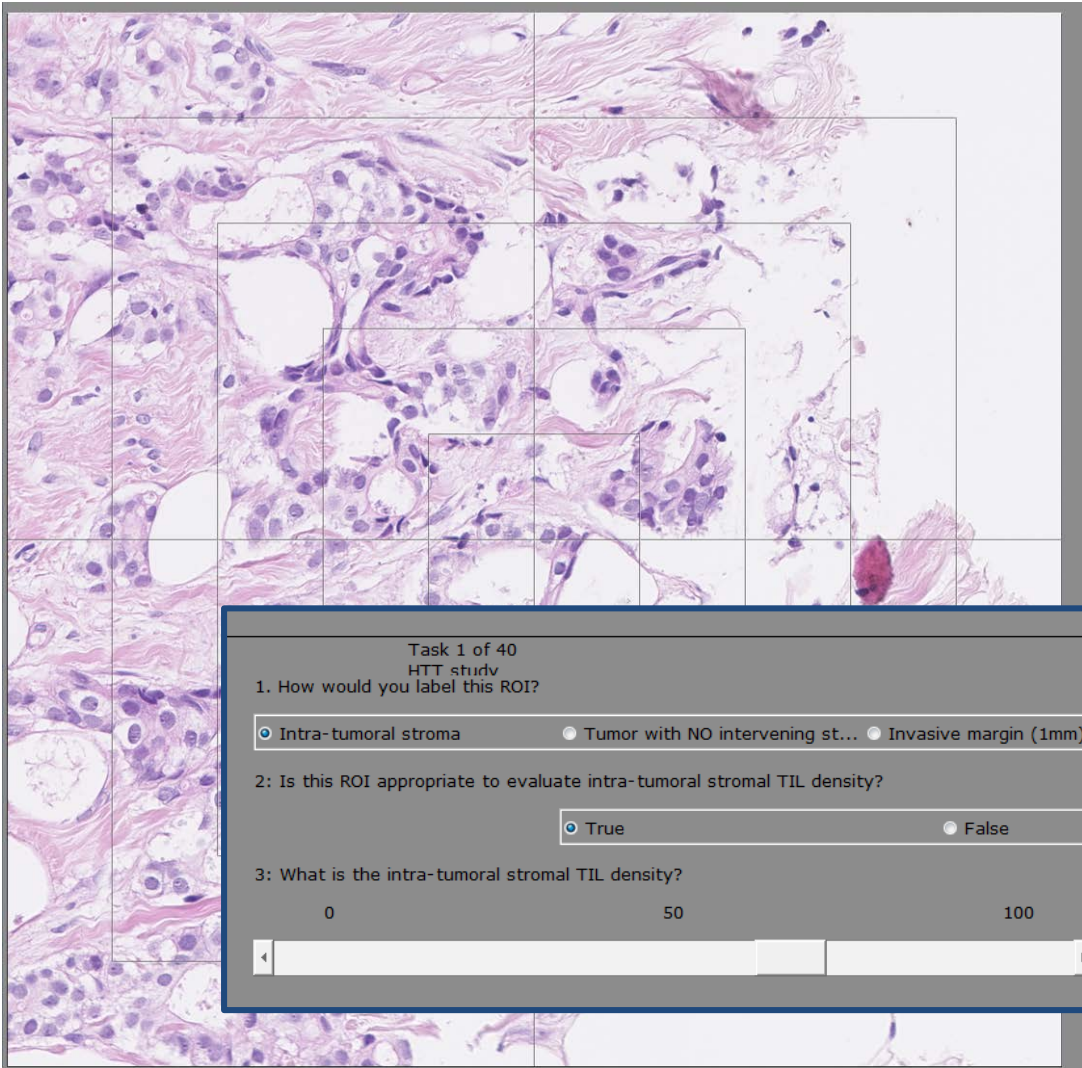
1 How would you label this ROI?
 Tumor with stroma Tumor with no interven... Invasive margin Other

2 Is this ROI appropriate to evaluate intra-tumoral stromal TIL density?
 True False

3 What is the intra-tumoral stromal TIL density?
0 50 100 Score 50

Switch to WSI thu...
Hide Reticle
Reset
Pause
Resume
Next
Abort

Data Collection Systems

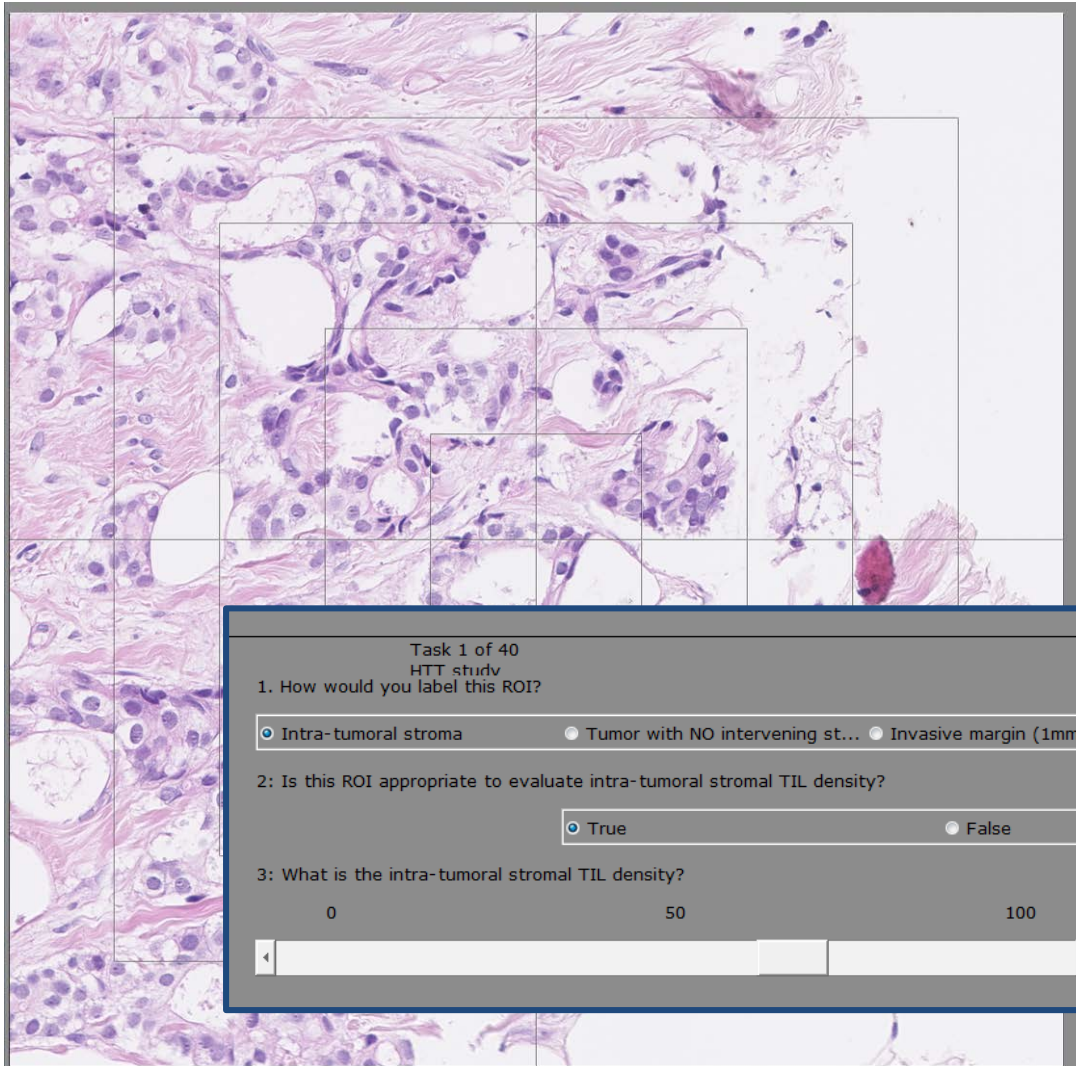


Evaluate **Next** ROI

Abort the study

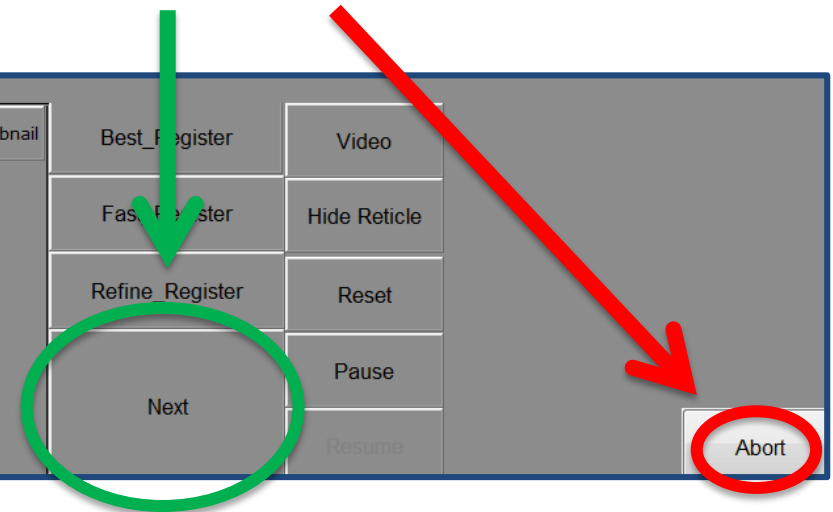
Switch to WSI thumbnail	Best_Register	Video
	Fast_Register	Hide Reticle
	Refine_Register	Reset
	Next	Pause
		Resume
		Abort

Data Collection Systems



Evaluate **Next** ROI

Abort the study



The control panel features a grid of buttons: Best_Register, Video, Fast_Register, Hide Reticle, Refine_Register, Reset, Next, Pause, and Abort. A green arrow points to the 'Next' button, which is also circled in green. A red arrow points to the 'Abort' button, which is circled in red.

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 System



Digital Platforms:
CaMicroscope

Data Collection Systems

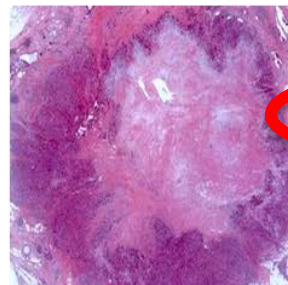


Digital Platforms:
CaMicroscope

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

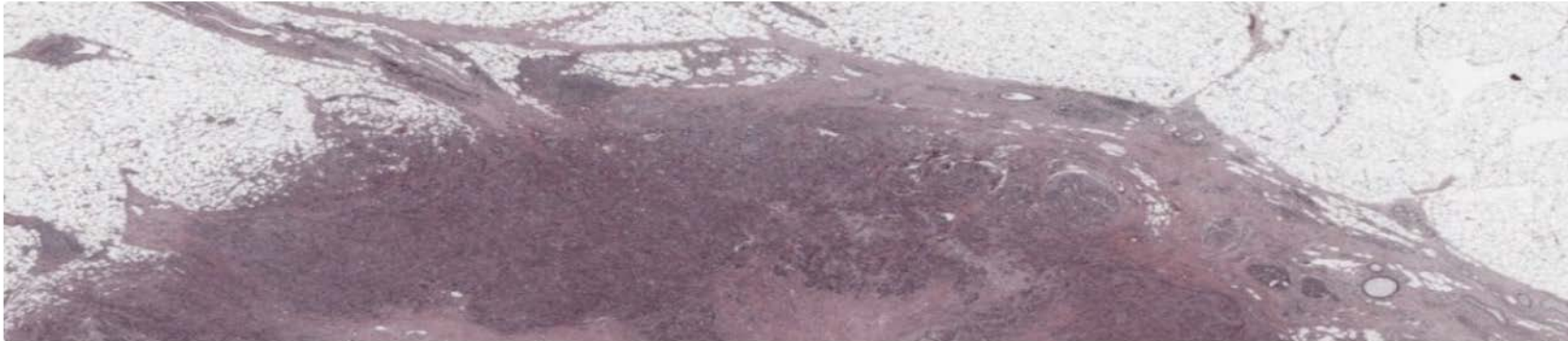
Data Collection Systems



Digital Platforms:
CaMicroscope

HTT ROI ANNOTATION

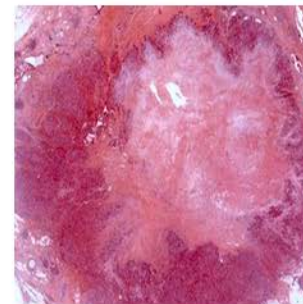
HTT ROI Annotation is a tool to view, label, and annotate biomedical images.



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

First take the **Participant Survey**

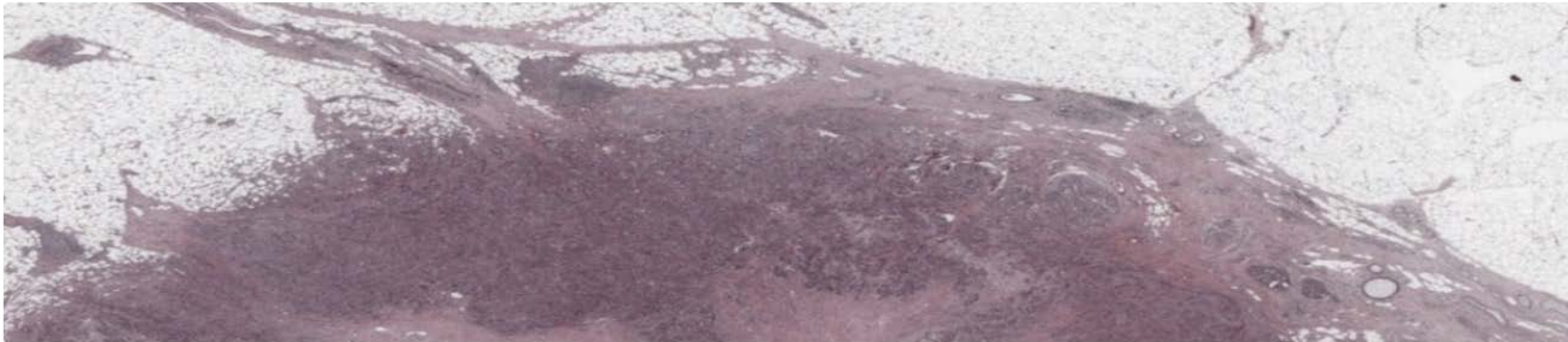
Data Collection Systems



Digital Platforms:
CaMicroscope

HTT ROI ANNOTATION

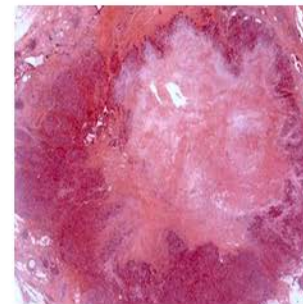
HTT ROI Annotation is a tool to view, label, and annotate biomedical images.



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

Start the study: **Pick & Annotate**

Data Collection Systems



Digital Platforms:
CaMicroscope

HOME

SIGN OUT

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

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

Data Collection Systems



Digital Platforms:
CaMicroscope

HOME

SIGN OUT

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

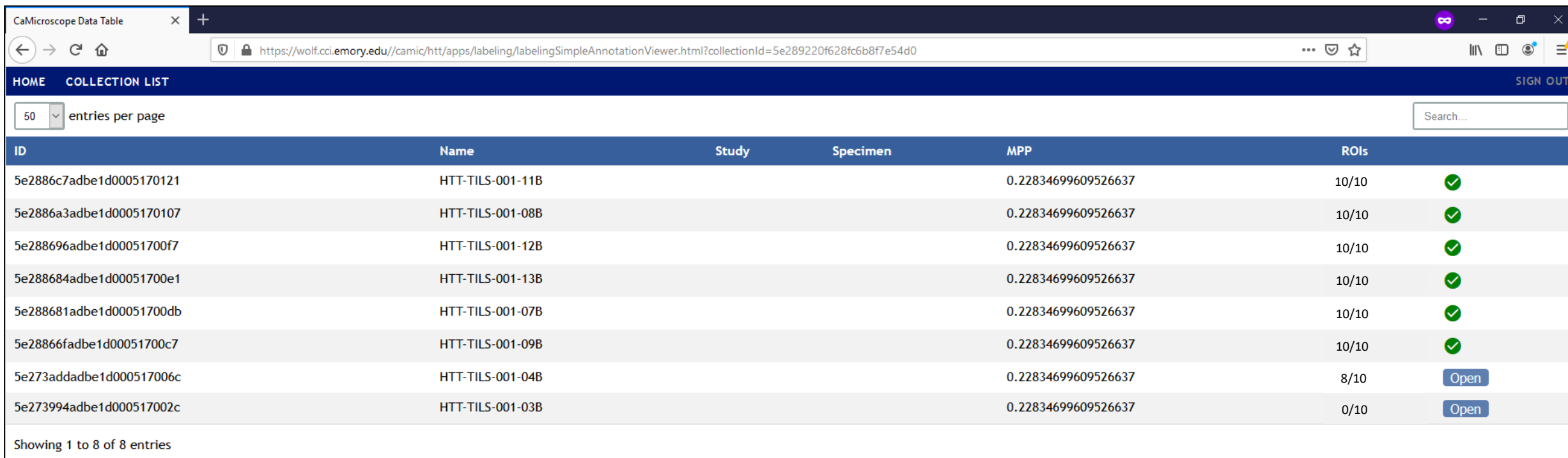
HTT-006
This Is The Batch
006 of HTT-TILS-006
ROIs Evaluation

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

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

Data Collection Systems



The screenshot shows a web browser window with the URL <https://wolf.cci.emory.edu/camic/htt/apps/labeling/labelingSimpleAnnotationViewer.html?collectionId=5e289220f628fc6b8f7e54d0>. The page title is "CaMicroscope Data Table". The interface includes a navigation bar with "HOME" and "COLLECTION LIST" tabs, and a "SIGN OUT" link. Below the navigation bar, there is a dropdown menu set to "50 entries per page" and a search box. The main content is a table with the following columns: ID, Name, Study, Specimen, MPP, ROIs, and a status column. The table contains 8 entries, all with a "Study" of "HTT-TILS-001" and an "MPP" of "0.22834699609526637". The "ROIs" column shows the number of ROIs out of 10 for each entry. The status column contains green checkmarks for the first six entries and "Open" buttons for the last two.

ID	Name	Study	Specimen	MPP	ROIs	
5e2886c7adbe1d0005170121	HTT-TILS-001-11B			0.22834699609526637	10/10	✓
5e2886a3adbe1d0005170107	HTT-TILS-001-08B			0.22834699609526637	10/10	✓
5e288696adbe1d00051700f7	HTT-TILS-001-12B			0.22834699609526637	10/10	✓
5e288684adbe1d00051700e1	HTT-TILS-001-13B			0.22834699609526637	10/10	✓
5e288681adbe1d00051700db	HTT-TILS-001-07B			0.22834699609526637	10/10	✓
5e28866fadbe1d00051700c7	HTT-TILS-001-09B			0.22834699609526637	10/10	✓
5e273addadbe1d000517006c	HTT-TILS-001-04B			0.22834699609526637	8/10	Open
5e273994adbe1d000517002c	HTT-TILS-001-03B			0.22834699609526637	0/10	Open

Showing 1 to 8 of 8 entries

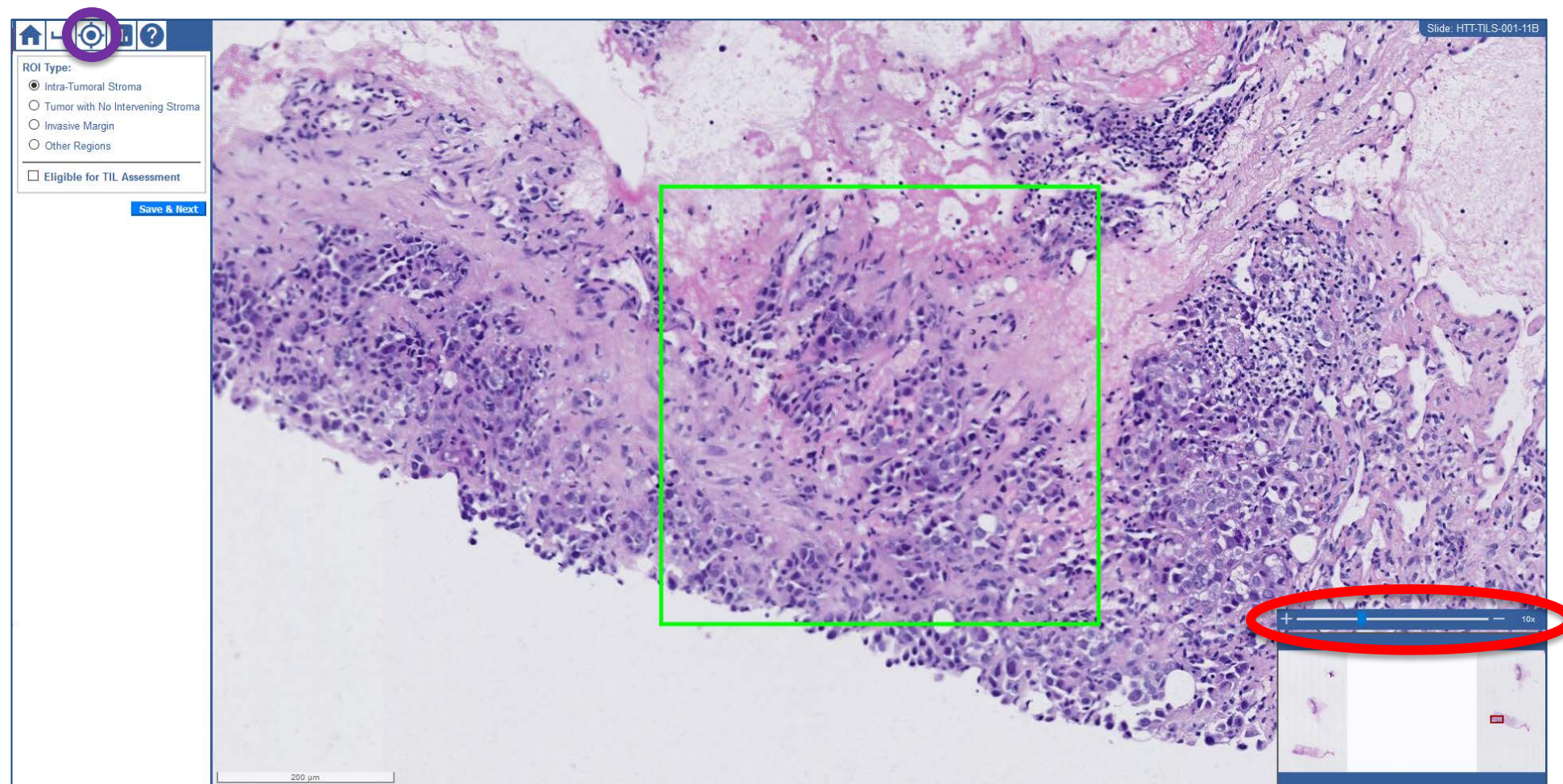
Please **complete all slides** in the batch

Data Collection Systems



Digital Platforms:
CaMicroscope

Reset ROI view
after scrolling
and panning



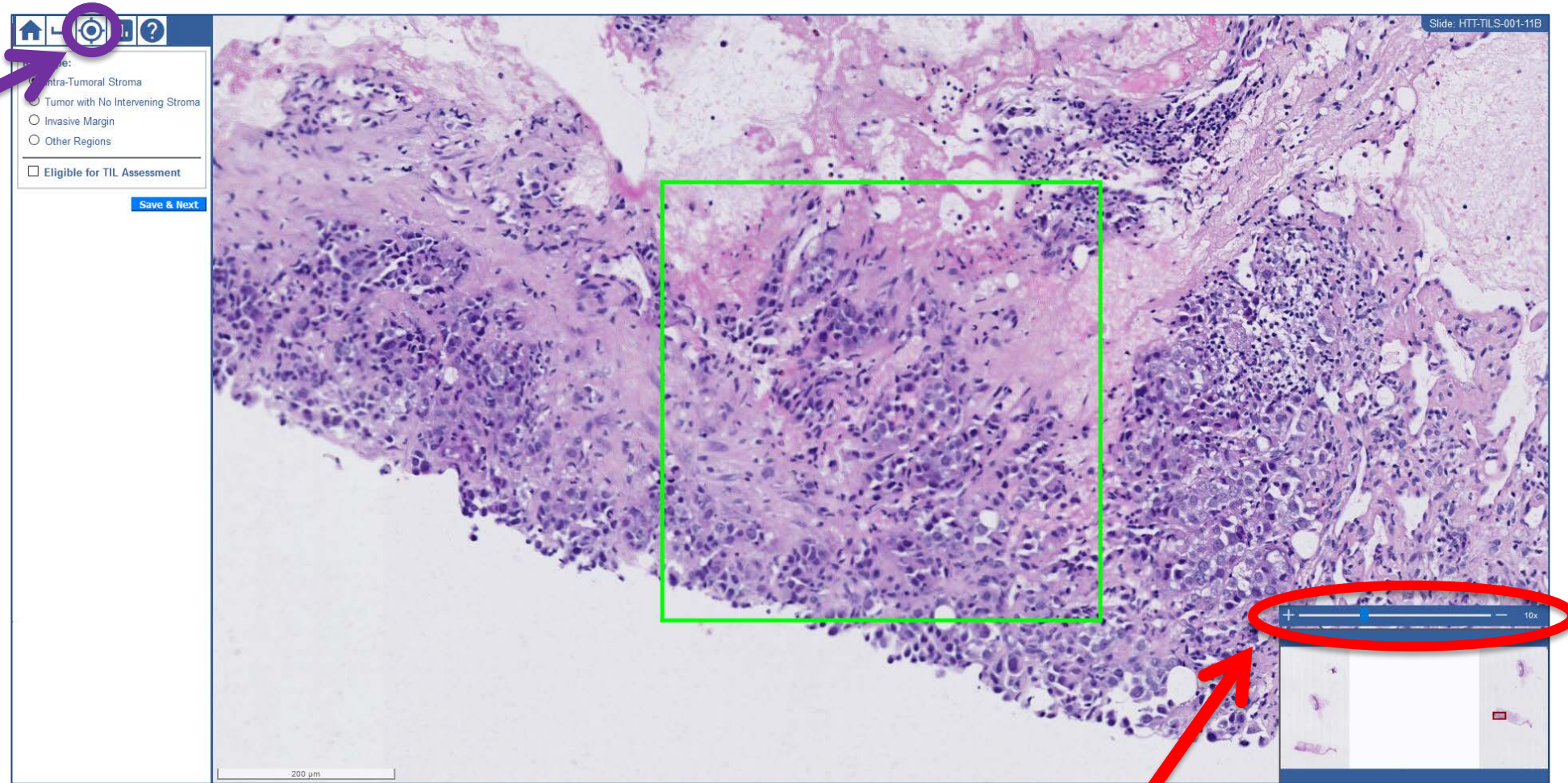
Zoom & pan by using your mouse or the **sliding bar**

Data Collection Systems



Digital Platforms:
CaMicroscope

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 displays the CaMicroscope software interface. On the left, a navigation bar contains icons for home, back, ROI selection, list, and help. Below this is a panel titled "ROI Type:" with four radio button options: "Intra-Tumoral Stroma" (selected), "Tumor with No Intervening Stroma", "Invasive Margin", and "Other Regions". Below the options is a section for "Eligible for TIL Assessment" with a checkmark icon and a progress bar showing 0%. A red text prompt reads "Please Assess TIL Density". A blue "Save & Next" button is at the bottom of the panel. The main area shows a histology slide with a green rectangular ROI box. A small thumbnail of the slide is visible in the bottom right corner. The slide ID "Slide: TCGA-A2-A3YX-01Z-00-DX1" is visible in the top right corner of the slide area.

Data Collection Systems

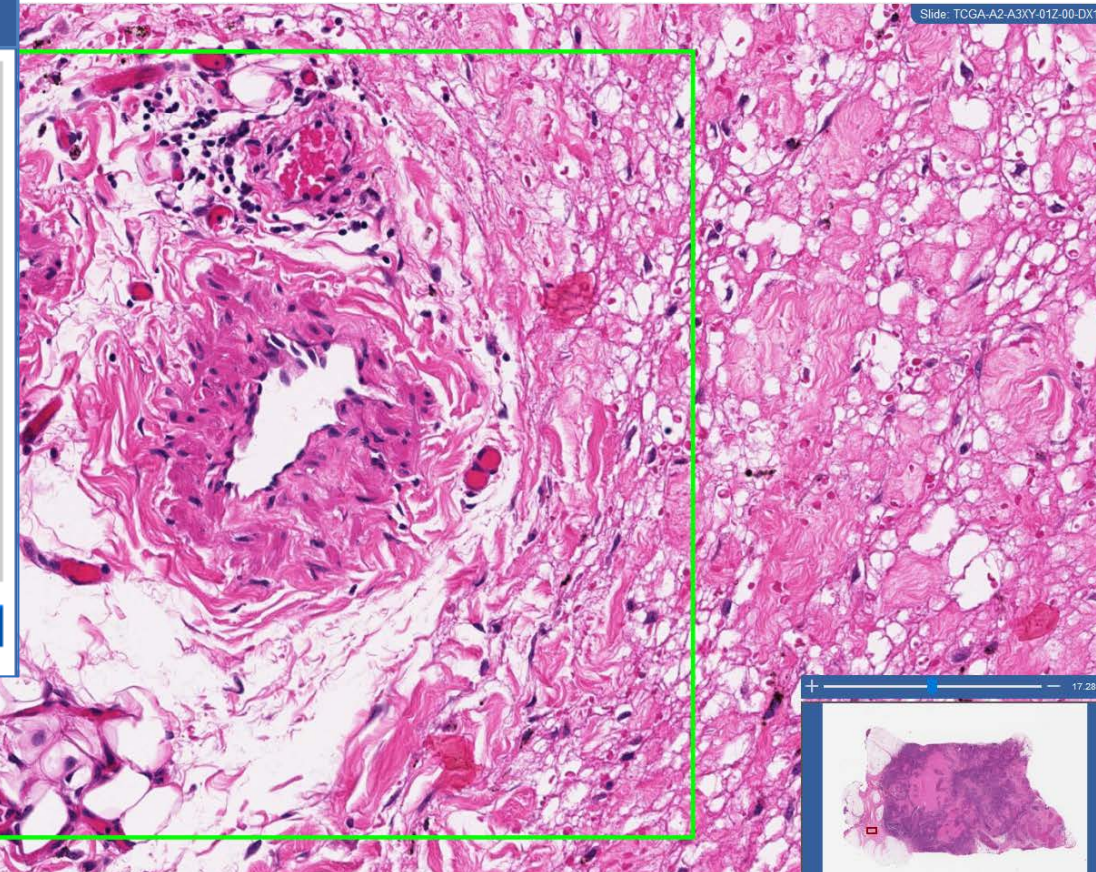


1. Select an ROI label from the list of options →

2. Verify that a Visual TIL Assessment can be conducted →

3. Record TIL Density (%) →

The screenshot shows the software interface with a navigation bar at the top containing icons for home, back, ROI selection, list, and help. Below the navigation bar is a form titled "ROI Type:" with four radio button options: "Intra-Tumoral Stroma" (selected), "Tumor with No Intervening Stroma", "Invasive Margin", and "Other Regions". Below the options is a section for "Eligible for TIL Assessment" with a checked checkbox and a progress bar showing 0%. A red text prompt says "Please Assess TIL Density" and a blue "Save & Next" button is at the bottom.



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 a 'ROI Type' section with radio buttons for 'Intra-Tumoral Stroma' (selected), 'Tumor with No Intervening', 'Invasive Margin', and 'Other Regions'. Below this is a checkbox for 'Eligible for TIL Assessment' and a 'Save' button. The main window, titled 'The Example Of TIL Densities', shows a 4x2 grid of images. Each image consists of a histology section on the left and a corresponding TIL density map on the right. The density maps are labeled with percentages: 1%, 5%, 10%, 20%, 60%, 70%, 80%, and 90%. A red arrow points to the 'graph' button in the top toolbar.

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

Data Collection Systems



Digital Platforms:
CaMicroscope



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

ROI Type:

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

Eligible for TIL Assessment

Save

Tutorial

1 of 15

Automatic Zoom

**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 System



Digital Platforms:
PathPresenter

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

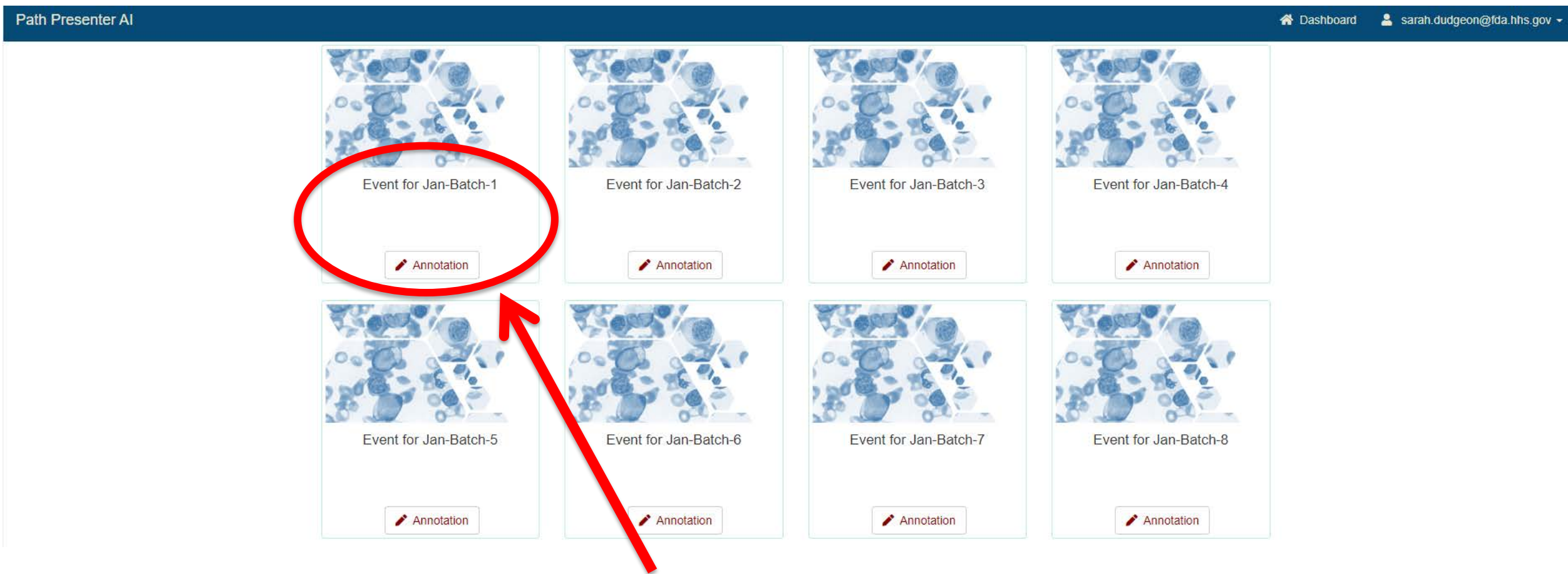
Event for Jan-Batch-7

Event for Jan-Batch-8

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

Data Collection Systems

Path Presenter AI Dashboard sarah.dudgeon@fda.hhs.gov



The screenshot displays a grid of eight event cards, each featuring a microscopic image of cells. The cards are labeled 'Event for Jan-Batch-1' through 'Event for Jan-Batch-8'. Each card includes an 'Annotation' button with a red pencil icon. The first card, 'Event for Jan-Batch-1', is highlighted with a red circle, and a red arrow points to it from the bottom center of the grid.

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

Data Collection Systems



Path Presenter AI Dashboard sarah.dudgeon@fda.hhs.gov

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

My Annotations : 0

Visualization

Show 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 Next

← Back to DataSets ← Back to Analysis Projects

Please **complete all slides** in the batch

Data Collection Systems



Digital Platforms:
PathPresenter

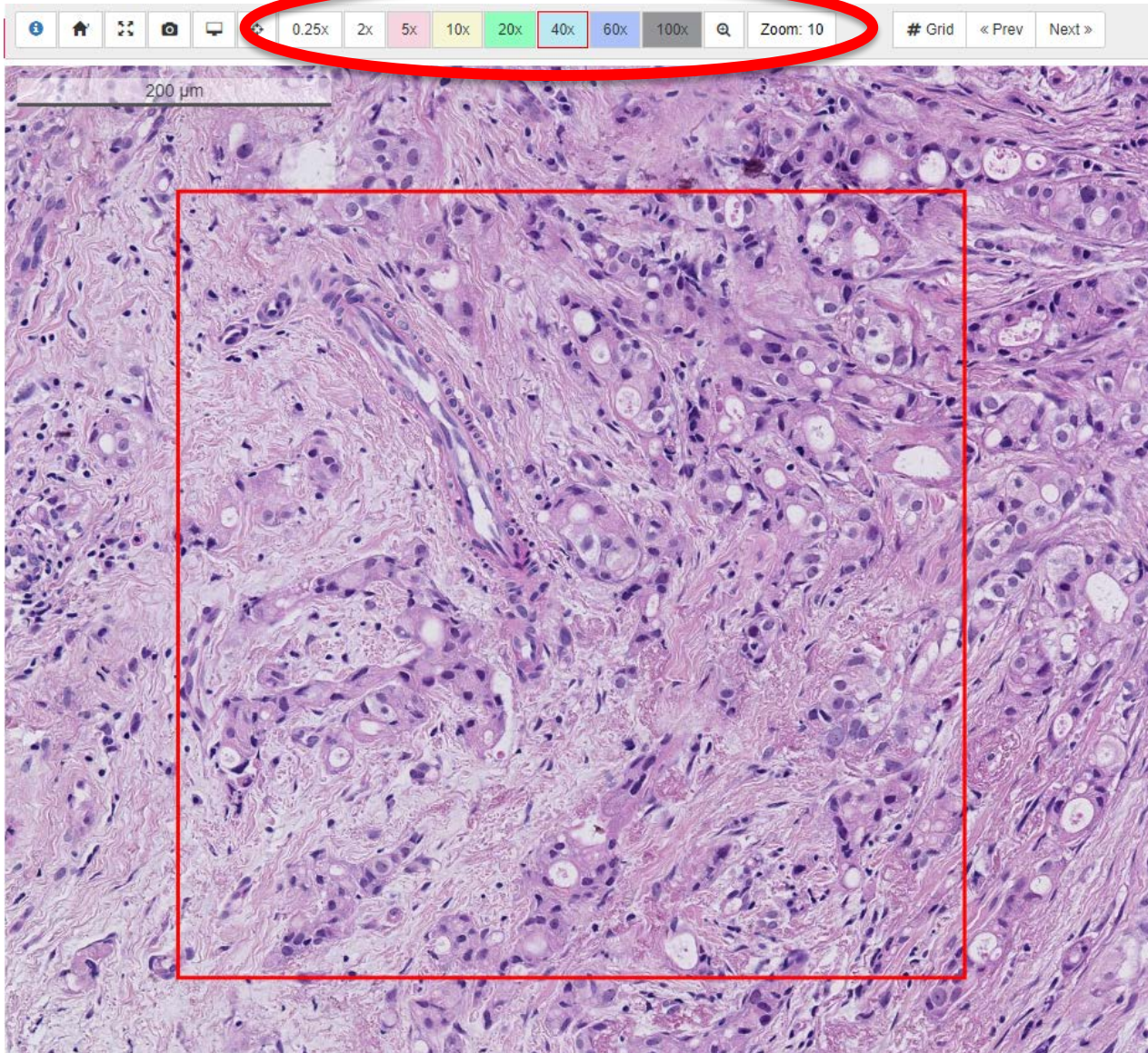
Move through your tasks using **Next & Previous**

The screenshot displays the PathPresenter software interface. At the top, a toolbar includes navigation icons and zoom settings (0.25x, 2x, 5x, 10x, 20x, 40x, 60x, 100x). The '40x' zoom level is highlighted in red. To the right of the zoom settings, 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 with a red border. On the right side, a control panel for the ROI is visible, featuring a grid of ROIs, a dropdown for 'ROI Label', a text input for 'Description', a checkbox for 'Vta appropriate', and buttons for 'Cancel', 'Save', and 'Hide All ROI'. Below the ROI panel, an 'Annotation' slider is set to 100.

Data Collection Systems



Digital Platforms:
PathPresenter



Zoom & pan by using your
mouse or the
magnification buttons

**New image soon

Data Collection Systems



Digital Platforms:
PathPresenter

The screenshot displays the PathPresenter software interface. On the left, a histology image is shown with a red rectangular ROI (Region of Interest) box. On the right, an annotation panel titled "ROI" is visible. The panel contains a grid of seven small square icons, with the top-left icon highlighted in red. Below the grid, the "Title" field is set to "ROI" and is circled in red. The "Description" field contains the placeholder text "Please add description". The "Vta Available" checkbox is checked and circled in purple. The "Vta" field contains the value "52" and is circled in green. Below the "Vta" field is a slider control with the value "52" displayed. At the bottom of the panel are "Cancel", "Save", and "Show All ROI" buttons. The top of the interface shows a toolbar with various navigation and zooming options.

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

2. Verify that a **Visual TIL Assessment** can be conducted

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

**New image soon

Data Collection Systems



Digital Platforms:
PathPresenter

The screenshot displays the PathPresenter interface. On the left, a histology image is shown with a red rectangular ROI (Region of Interest) box. On the right, a data collection form titled 'ROI' is visible. The form includes a grid of colored squares for selecting an ROI label, a 'Title' field with a dropdown menu, a 'Description' field, a 'Vta Available' checkbox, a 'Vta' input field, and a slider control for 'Vta'. The 'Title' field is set to 'ROI', the 'Vta Available' checkbox is checked, and the 'Vta' input field contains the value '52'. The slider control also shows '52'. At the bottom of the form are 'Cancel', 'Save', and 'Show All ROI' buttons.

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

2. Verify that a **Visual TIL Assessment** can be conducted

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

MISSING: PathPresenter (to do)

- Show informed consent
- Location of tutorial(s)