

# **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

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  - 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](http://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

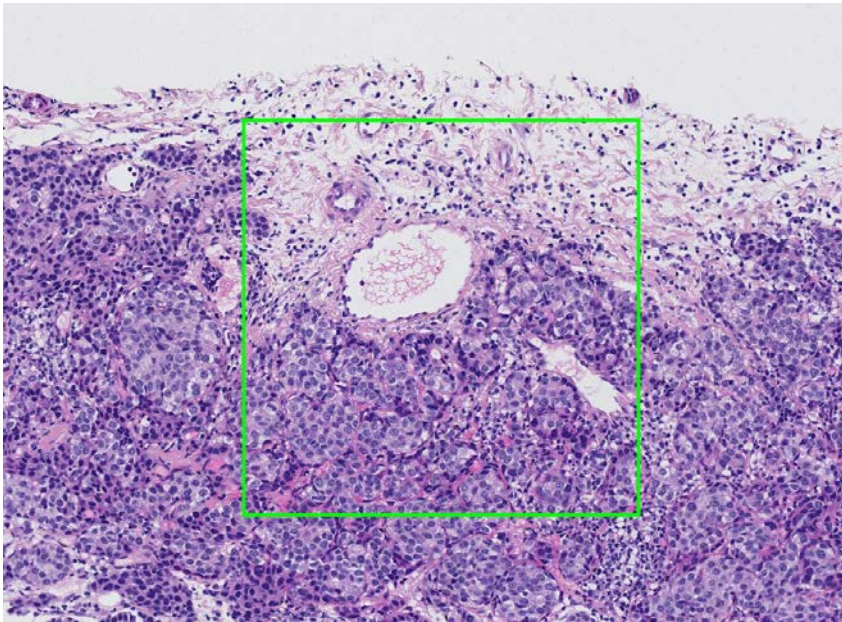
Task 3 – Record % TILs

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

# ROI: Region of Interest

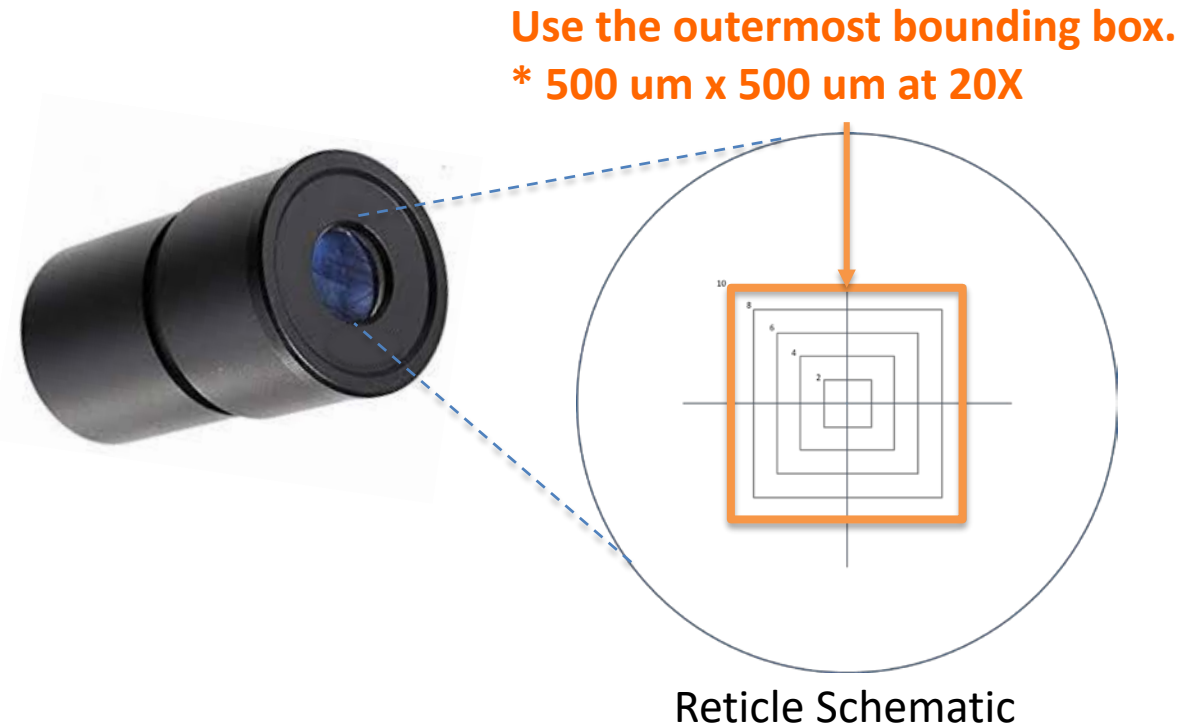
## Digital ROI:

- 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



# 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**

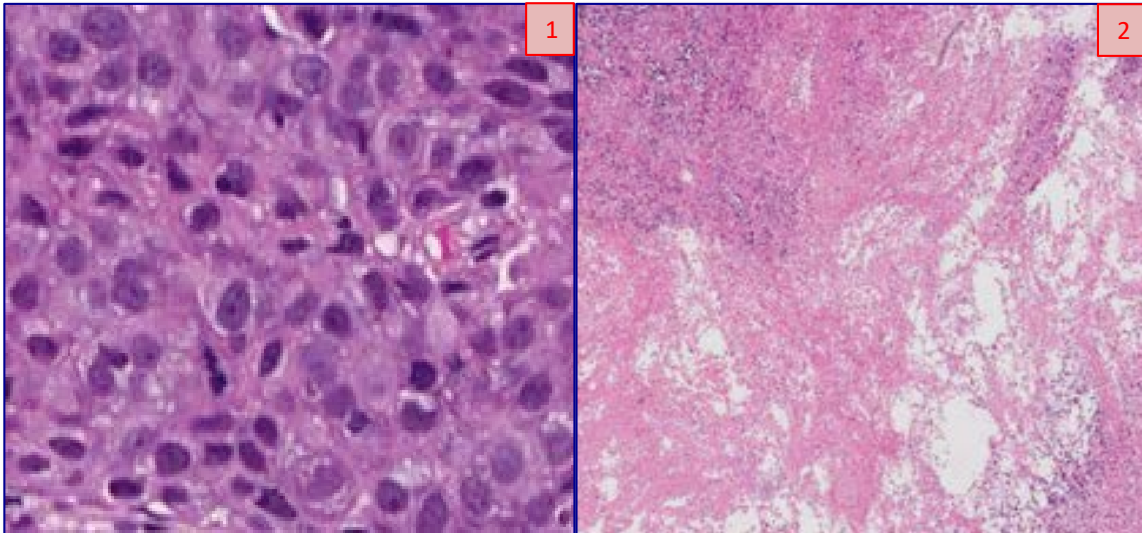
Necrosis, fibrosis, or other areas of granulocytic infiltrate

# Data Collection: Task 2

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

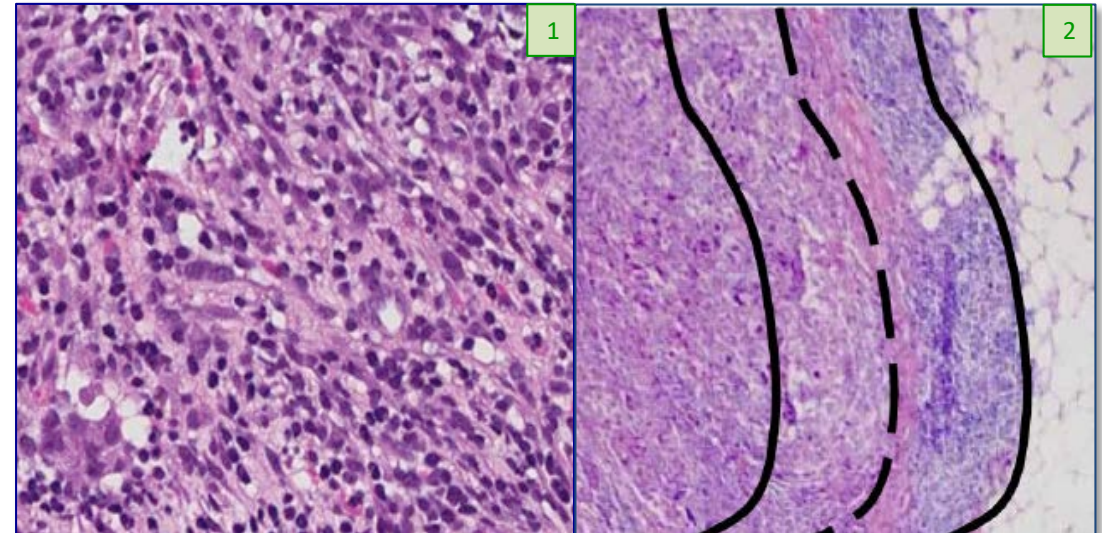
## NOT Eligible:

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

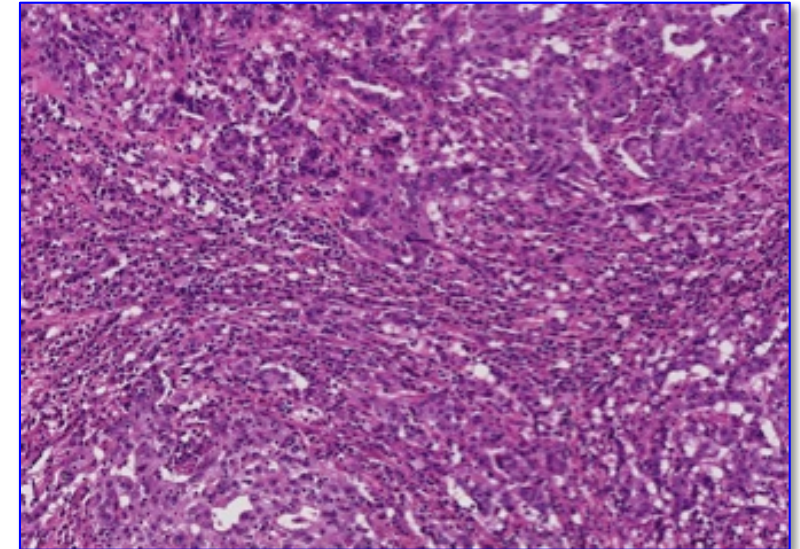
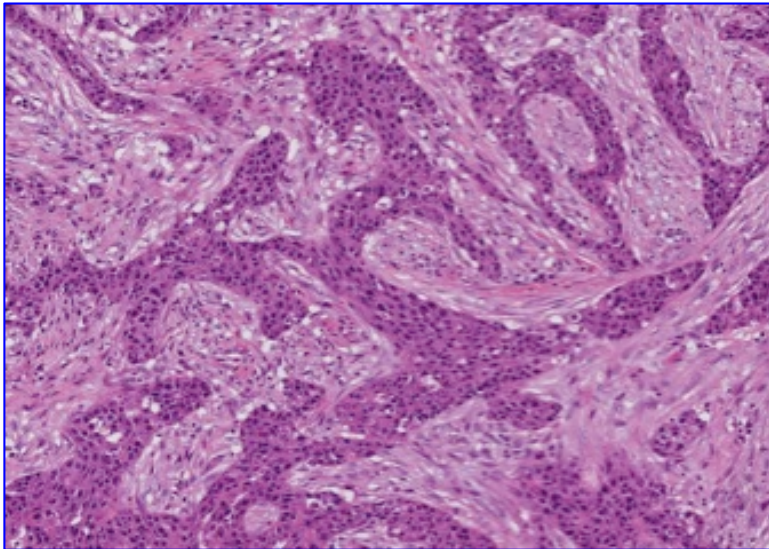
0-10% stromal TILs

tumor with intermediate/  
heterogeneous infiltrate

10-40% stromal TILs

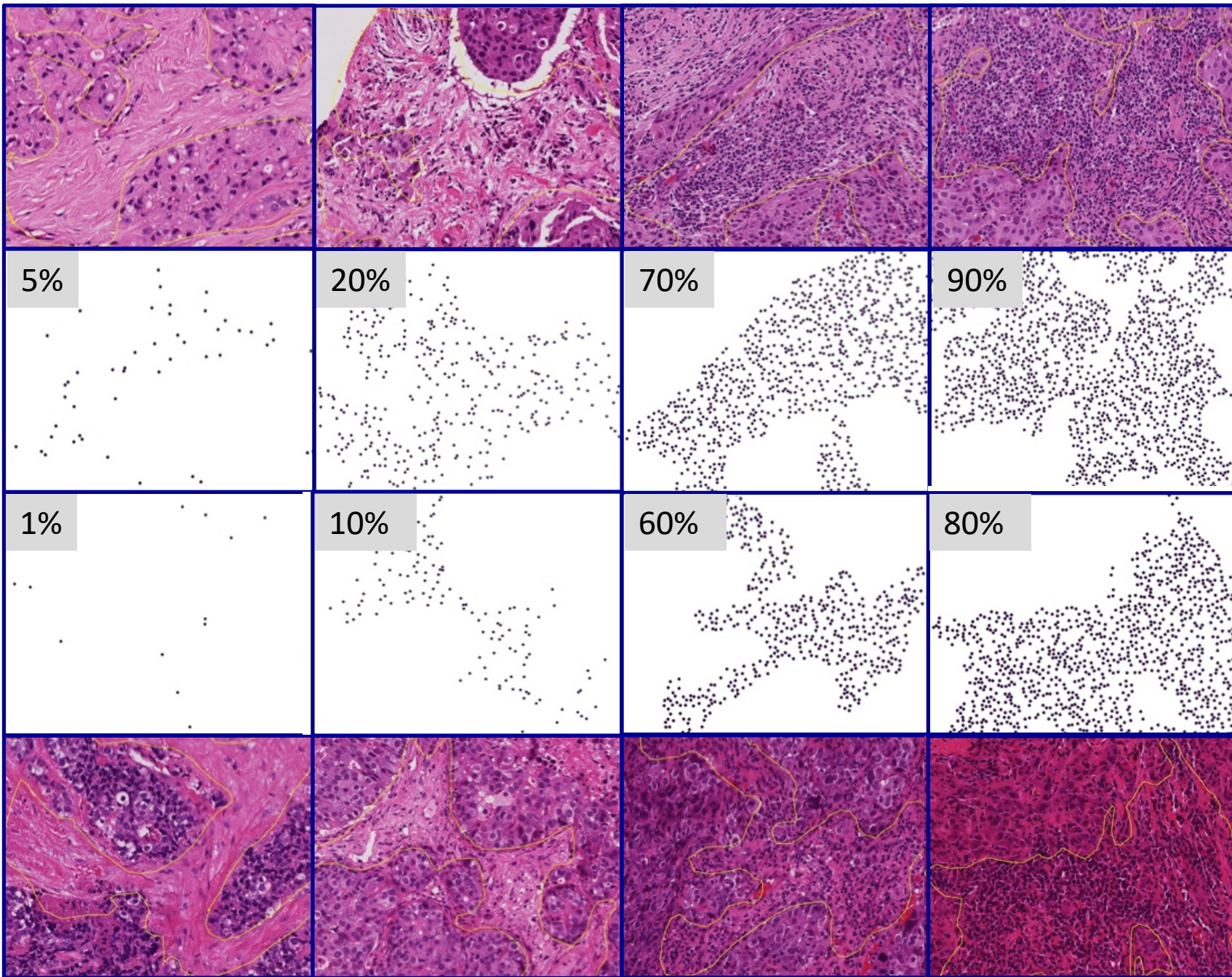
tumor with high  
immune infiltrate

40-90% stromal TILs





# Example VTAs

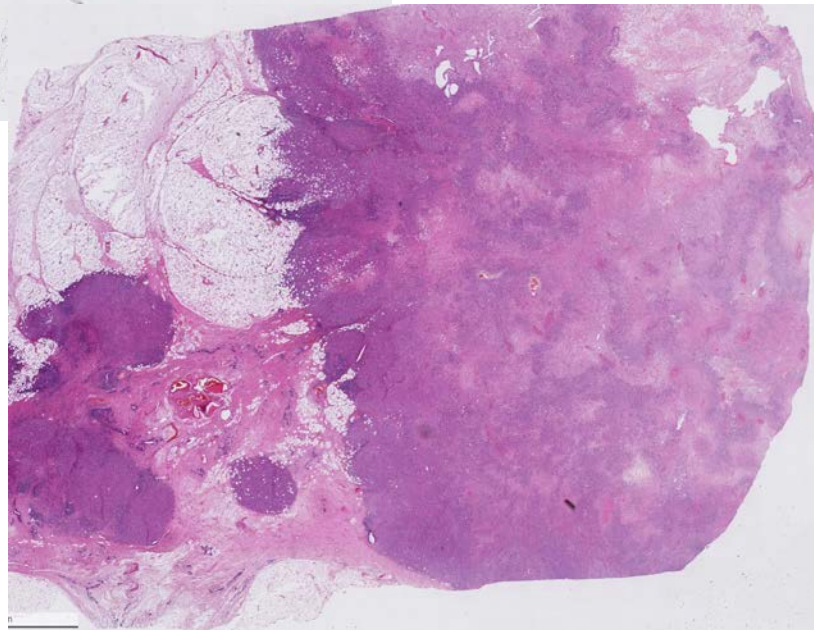




# Slides and Images for Evaluation



- 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

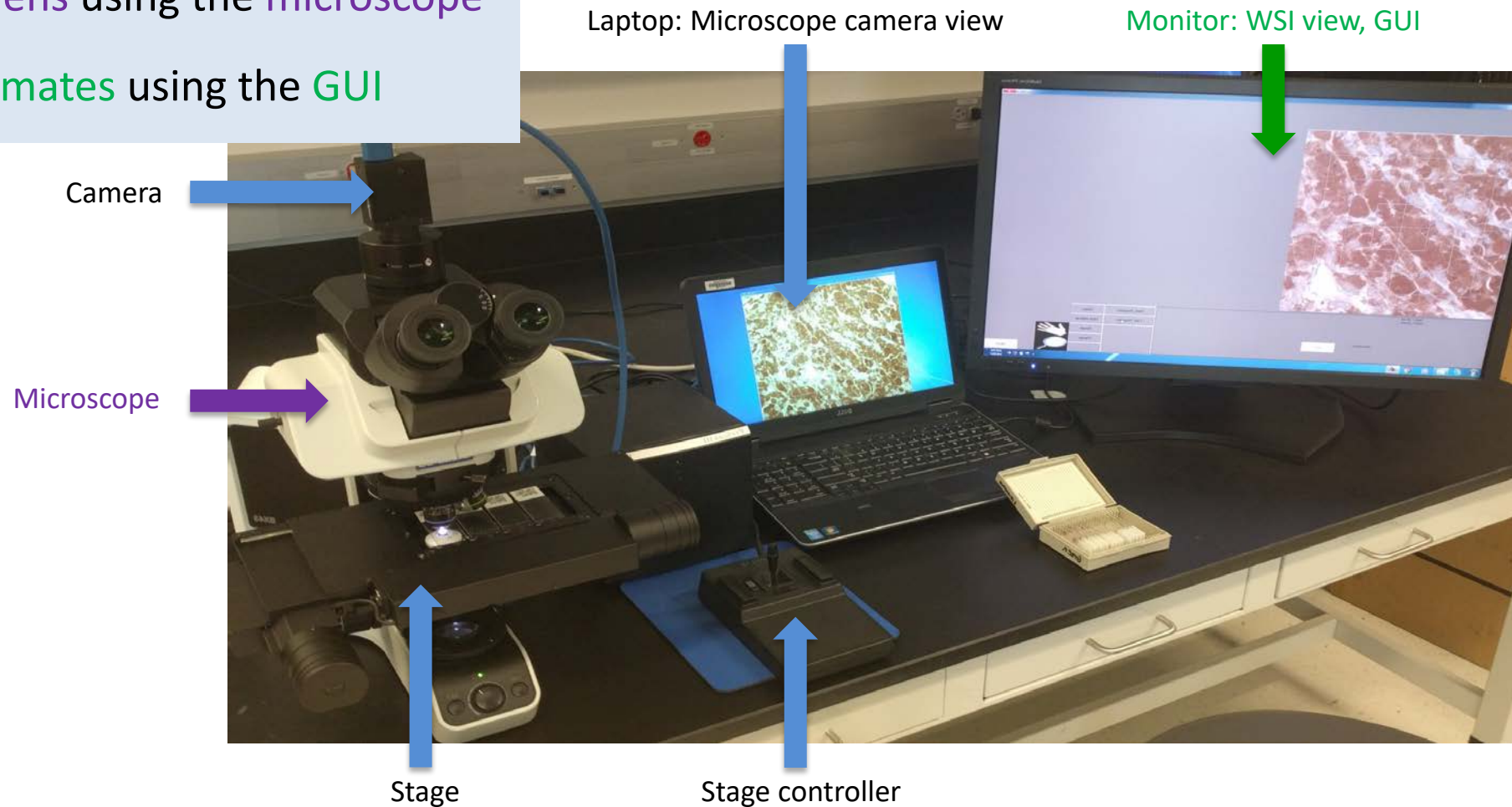


eeDAP

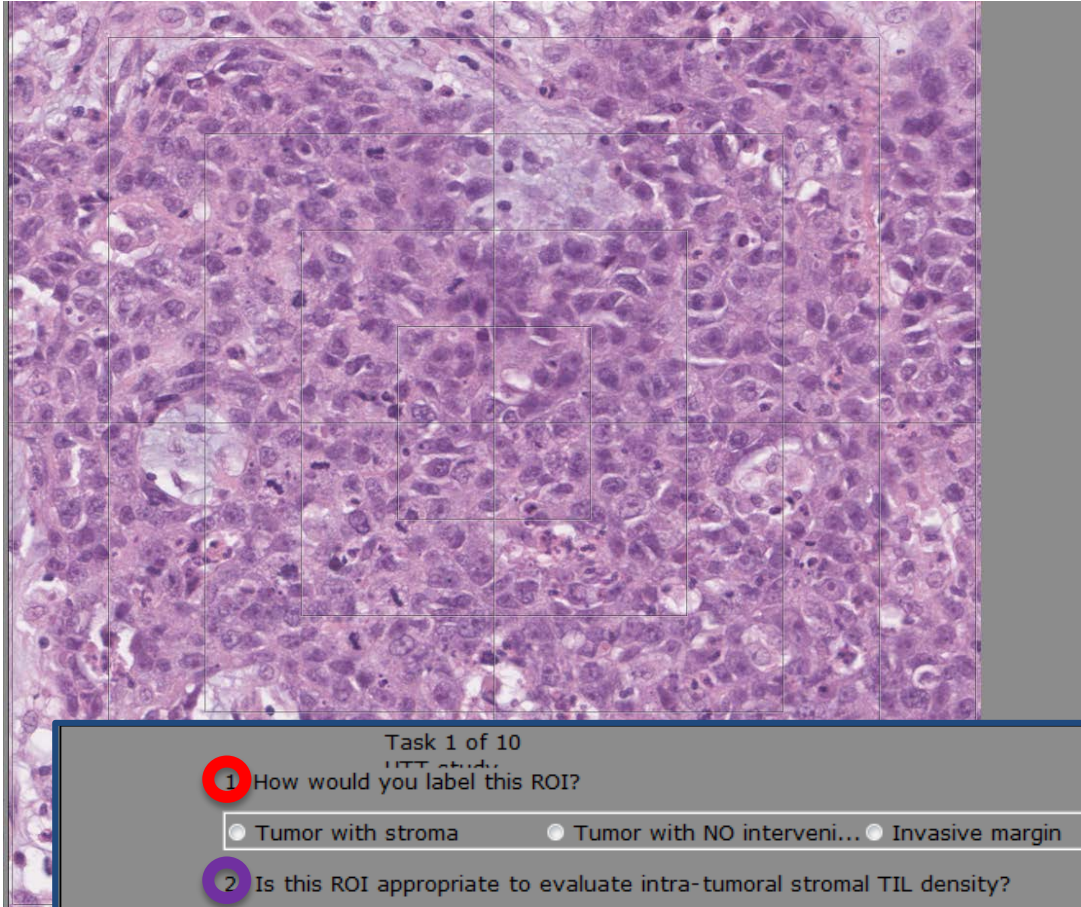
# Data Collection Systems

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

Switch to WSI thu...

Hide Reticle

Reset

Pause

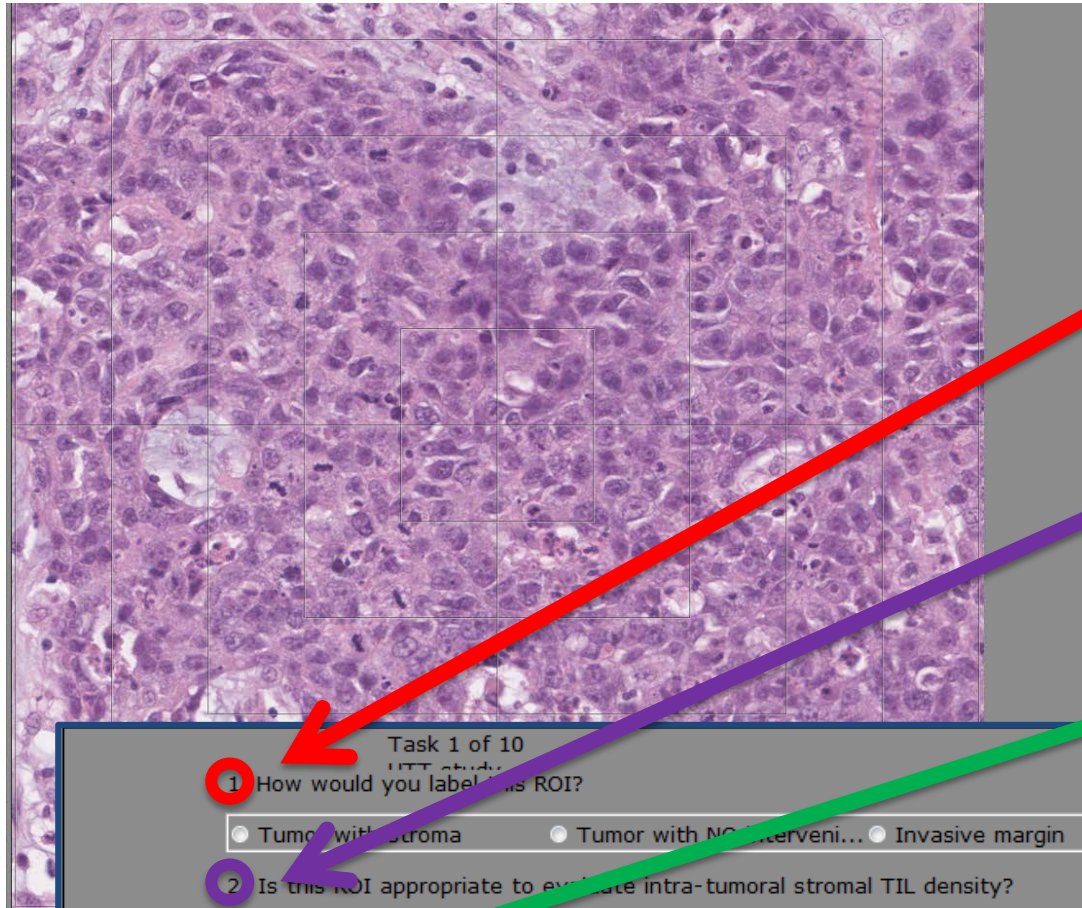
Resume

Next

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 intervening... ☐ 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 thumbnail

Hide Reticle

Reset

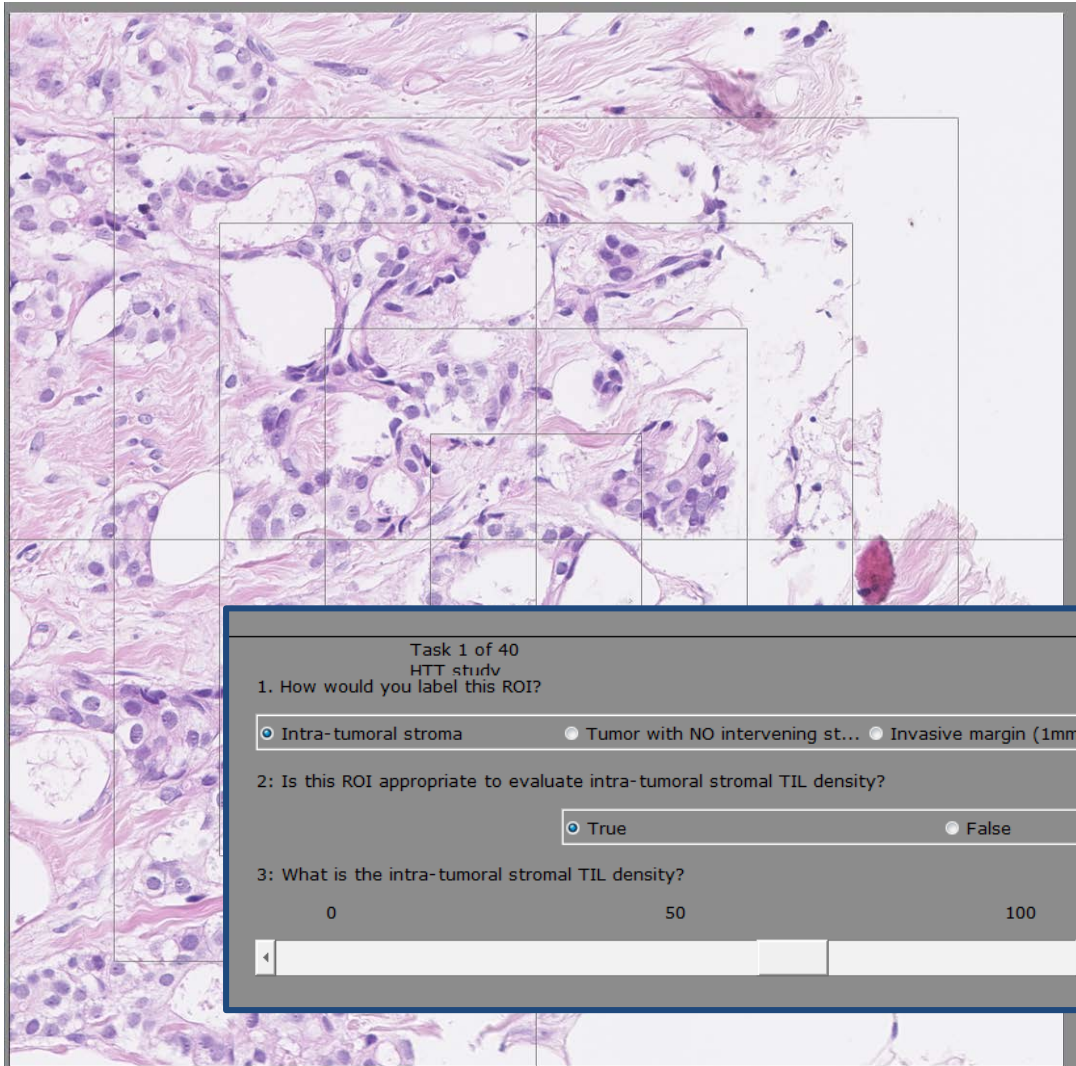
Pause

Resume

Next

Abort

# Data Collection Systems



Evaluate **Next** ROI

**Abort** the study

Task 1 of 40  
HTT study

1. How would you label this ROI?

☒ Intra-tumoral stroma
 ☐ Tumor with NO intervening stroma
 ☐ Invasive margin (1mm)
 ☐ Other

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

☒ True
 ☐ False

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

050100

Score

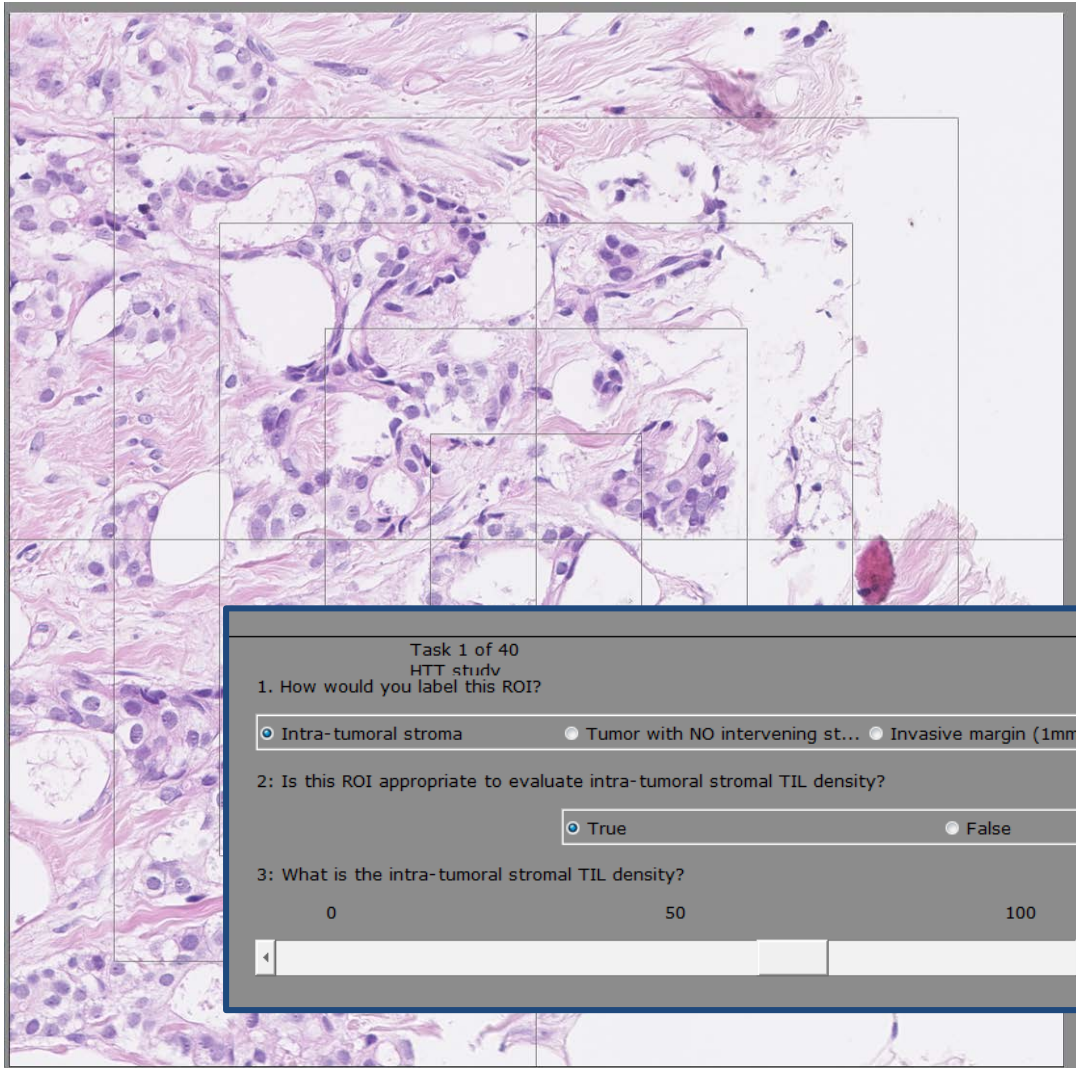
66

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

Task 1 of 40  
HTT study

1. How would you label this ROI?

☒ Intra-tumoral stroma    ☐ Tumor with NO intervening stroma    ☐ Invasive margin (1mm)    ☐ 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

66

Switch to WSI thumbnail

Best Register	Video
Fast Register	Hide Reticle
Refine Register	Reset
<b>Next</b>	Pause
	Resume
	<b>Abort</b>



# 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**

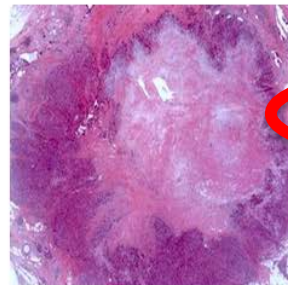


# Data Collection Systems

Sign in with your **Google** account

## HTT ROI ANNOTATION

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



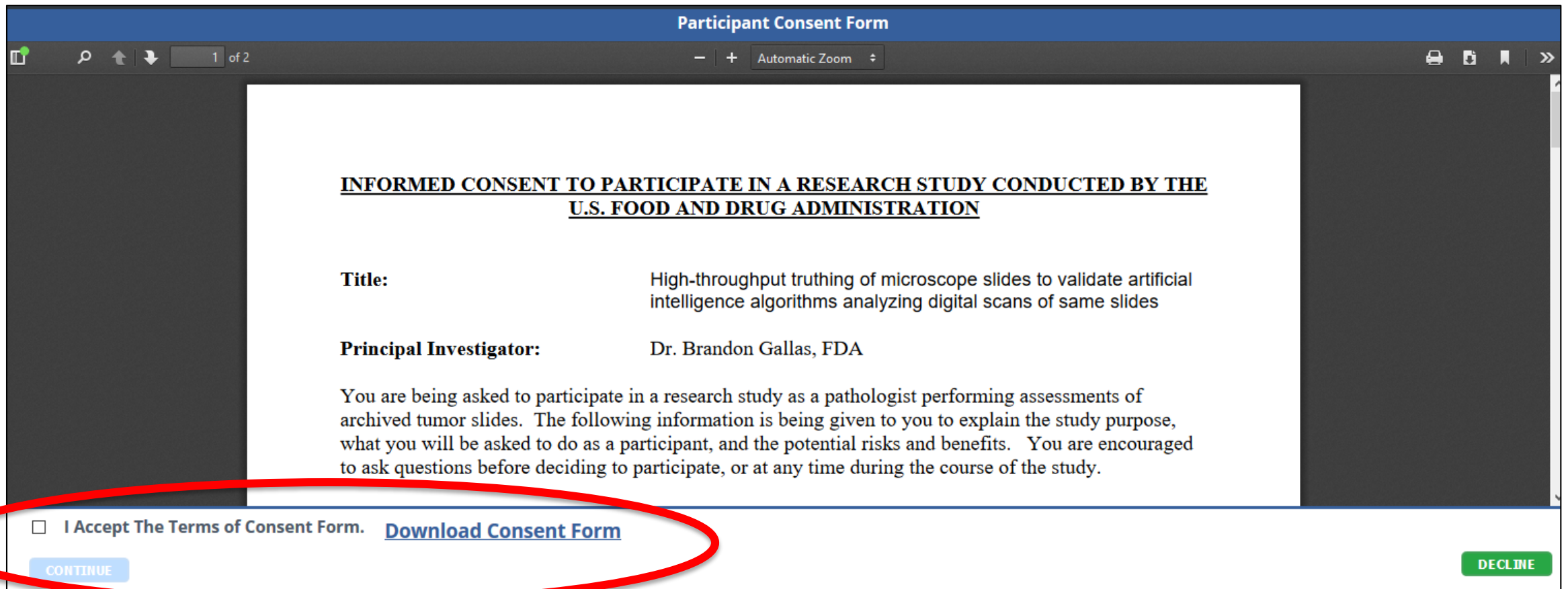
PLEASE SIGN IN WITH YOUR GOOGLE  
ACCOUNT



Sign in with Google

# Data Collection Systems

## 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

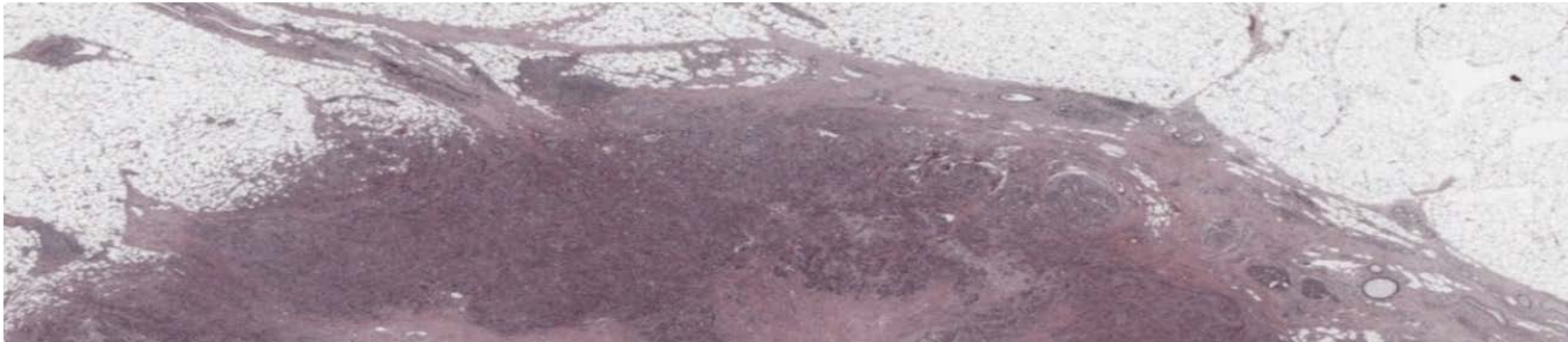
# Data Collection Systems



Digital Platforms:  
CaMicroscope

## HTT ROI ANNOTATION

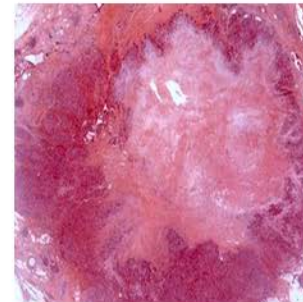
HTT ROI Annotation is a tool to view, label, and annotate biomedical images.



### 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.

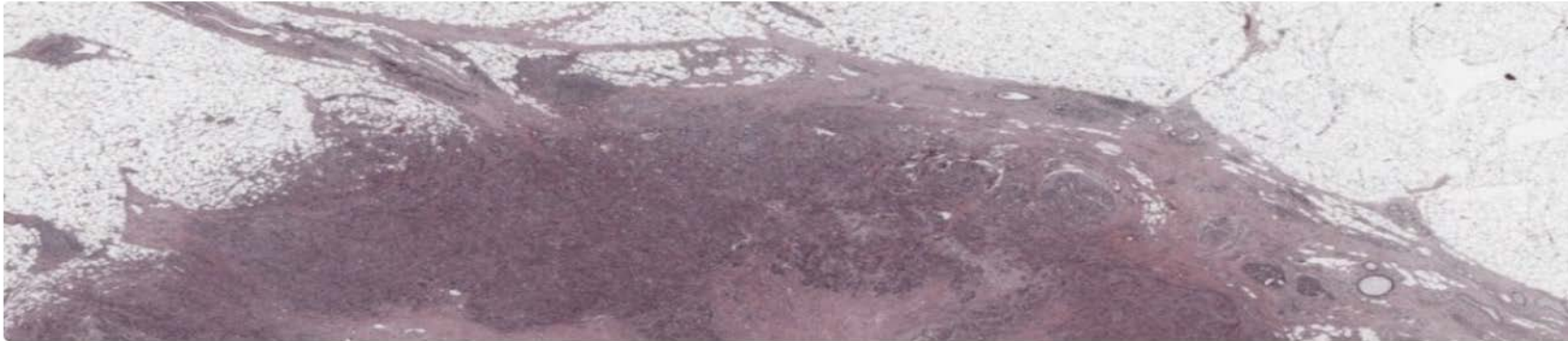
PICK & ANNOTATE

First take the **Participant Survey**

# Data Collection Systems

## HTT ROI ANNOTATION

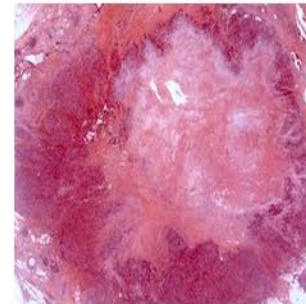
HTT ROI Annotation is a tool to view, label, and annotate biomedical images.



### 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



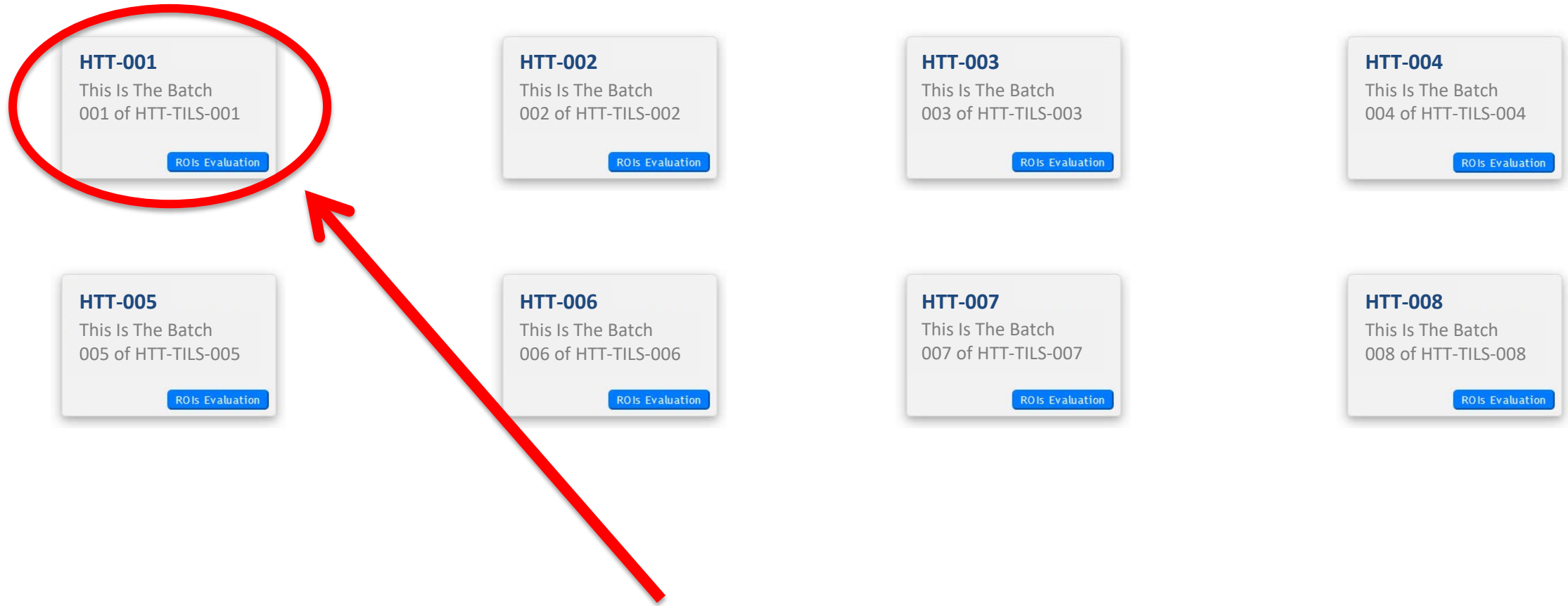
# Data Collection Systems



Digital Platforms:  
CaMicroscope

HOME

SIGN OUT



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

# Data Collection Systems

CaMicroscope Data Table

https://wolf.cci.emory.edu/camic/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 ✓
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

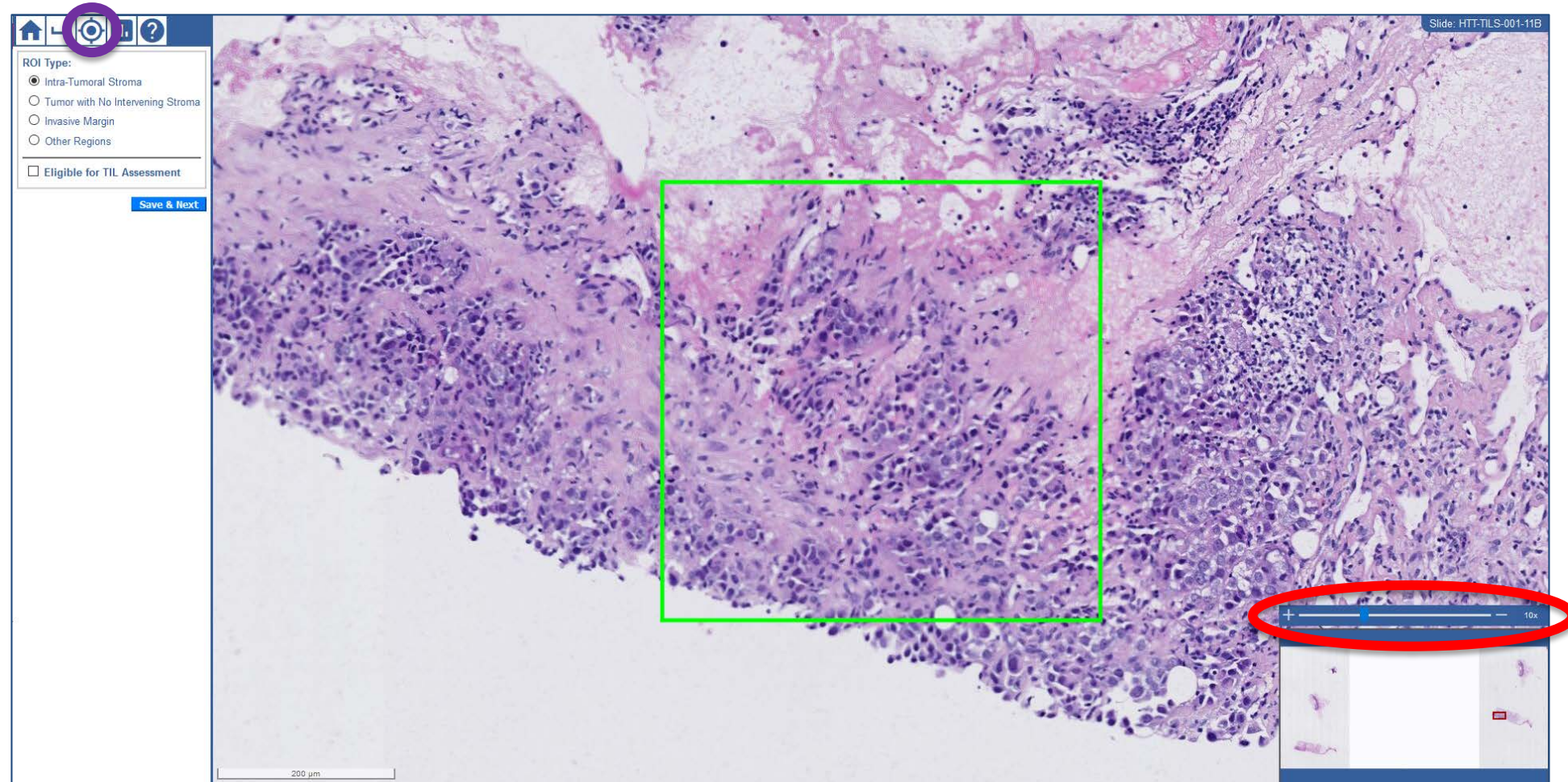
Please **complete all slides** in the batch

# Data Collection Systems



Digital Platforms:  
CaMicroscope

Reset ROI view  
after scrolling  
and panning



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

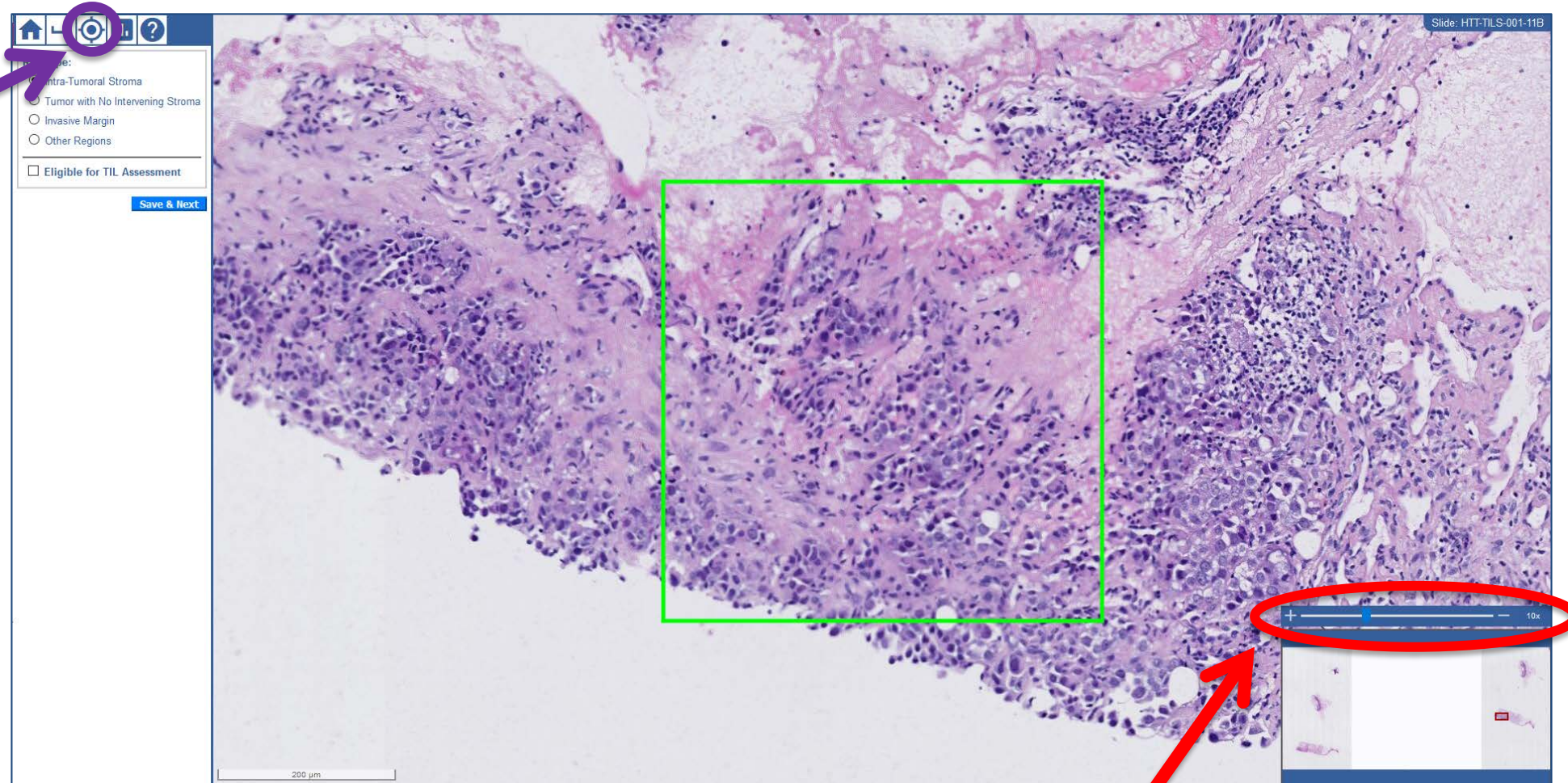


# Data Collection Systems



Digital Platforms:  
CaMicroscope

Reset ROI view  
after scrolling  
and panning



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



# Data Collection Systems



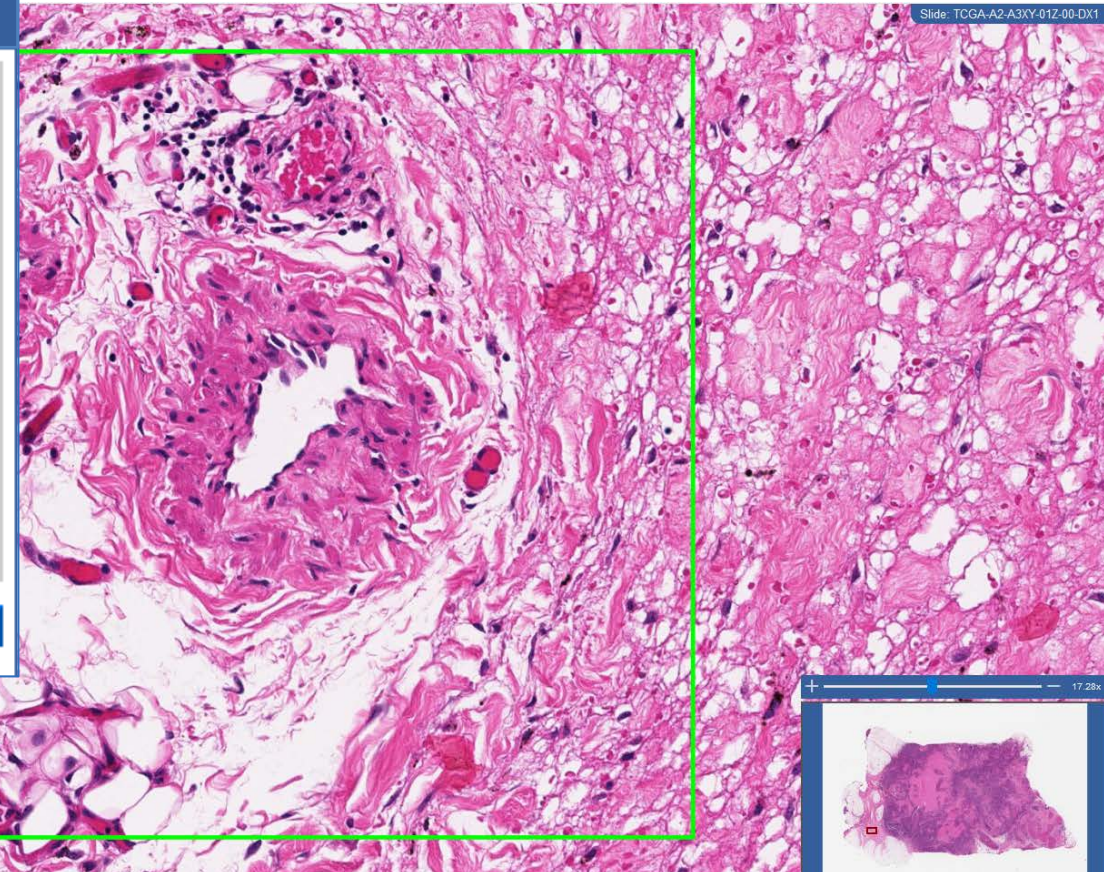
Digital Platforms:  
CaMicroscope

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 shows the CaMicroscope software interface. At the top is a navigation bar with icons for home, back, ROI selection, histogram, 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 radio buttons is a section with a checked checkbox labeled "Eligible for TIL Assessment" and a progress bar showing "0%". A red text prompt "Please Assess TIL Density" is displayed below the progress bar. At the bottom of the panel is a blue button labeled "Save & Next".





# Data Collection Systems



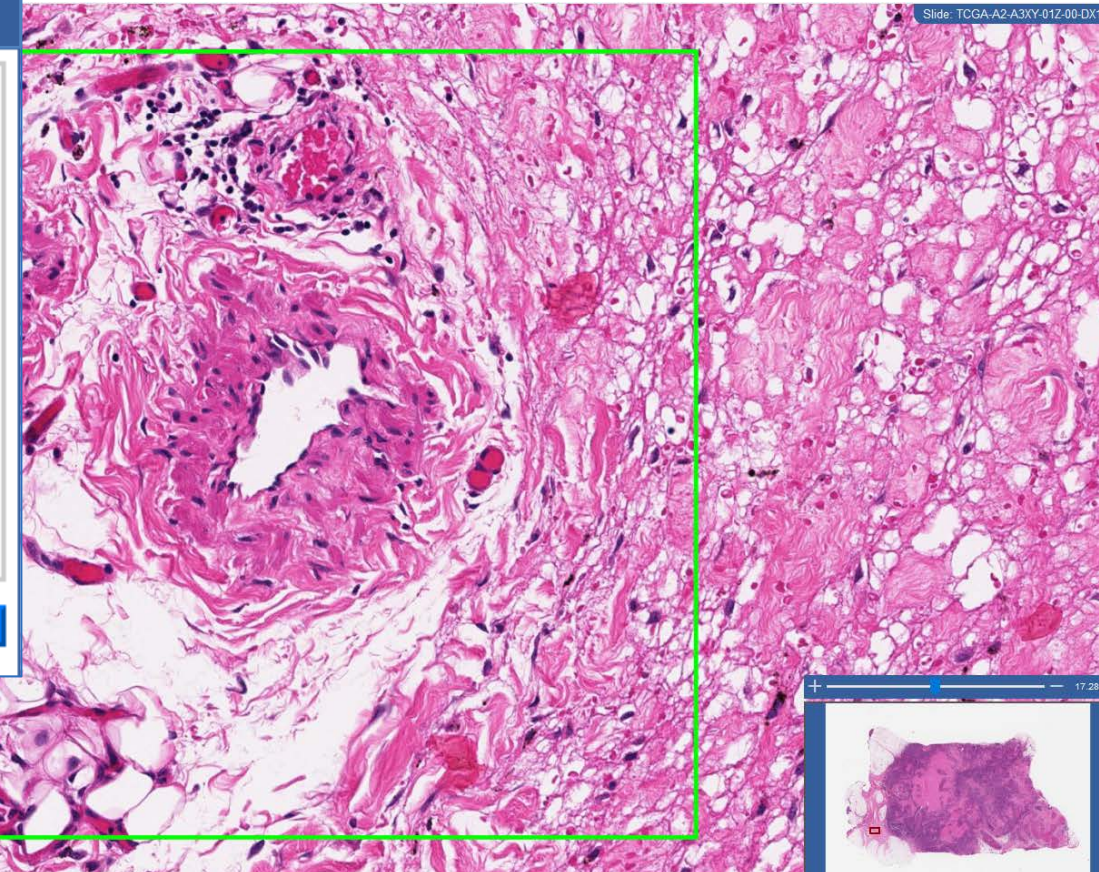
Digital Platforms:  
CaMicroscope

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 the CaMicroscope software interface. At the top is a navigation bar with icons for home, back, ROI selection, histogram, 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 radio buttons is a checkbox labeled 'Eligible for TIL Assessment' which is checked. To the right of the checkbox is a progress bar showing '0%'. Below the progress bar is the text 'Please Assess TIL Density' in red. At the bottom of the panel is a blue button labeled 'Save & Next'.

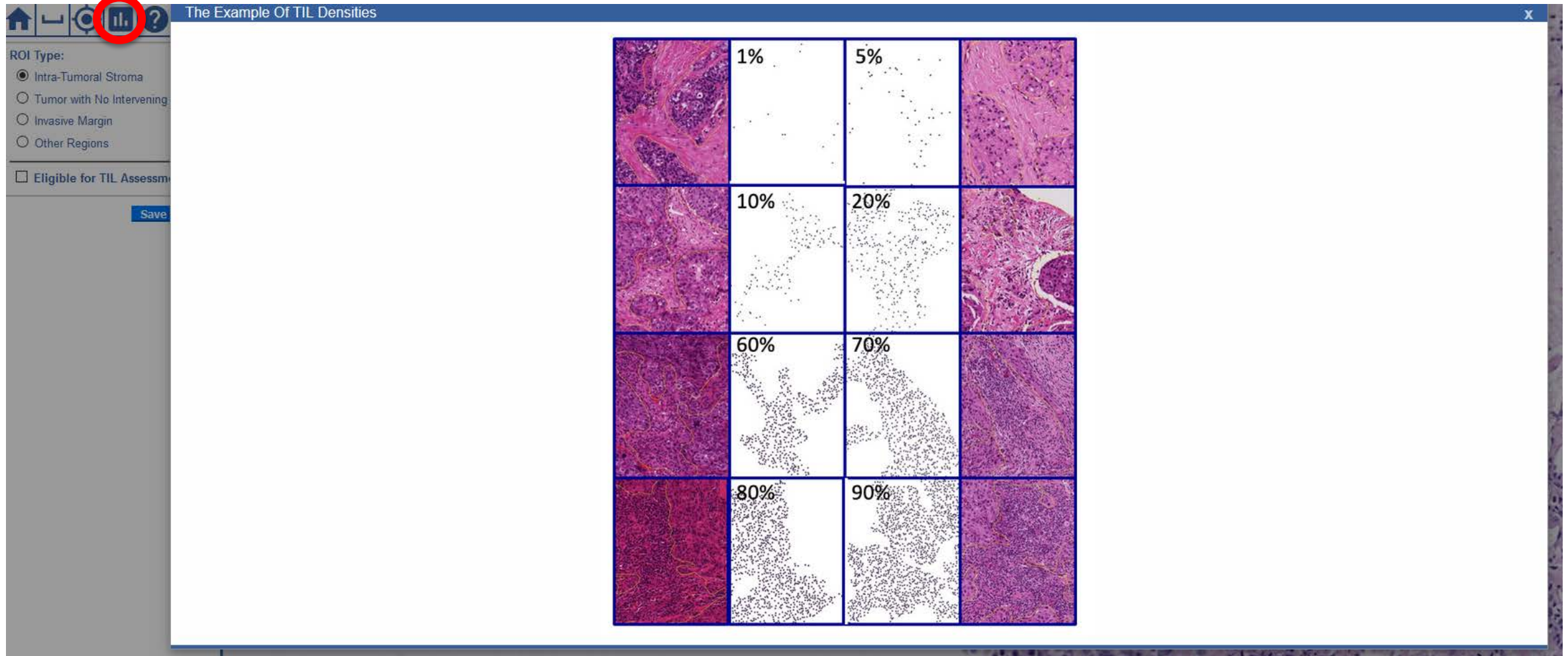


# Data Collection Systems



Digital Platforms:  
CaMicroscope

Use the **graph** button to review examples





# Data Collection Systems



Digital Platforms:  
CaMicroscope



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

The screenshot shows 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 a checkbox ☐ Eligible for TIL Assessment. Below these is a 'Save' button. The main window has a title bar 'Tutorial' and a toolbar with icons for home, back, forward, and a help icon (a question mark inside a circle). The help icon is circled in red. The main content area displays a tutorial slide titled 'Standardized evaluation of Tumor-Infiltrating Lymphocytes (TIL) in Breast Cancer for daily clinical and research practice or clinical trial setting'. Below the title, it says 'A tutorial prepared by the International Working Group for TIL in breast cancer – 2014 – adapted 2020' and lists the authors: Carsten Denkert, Roberto Salgado, and 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.

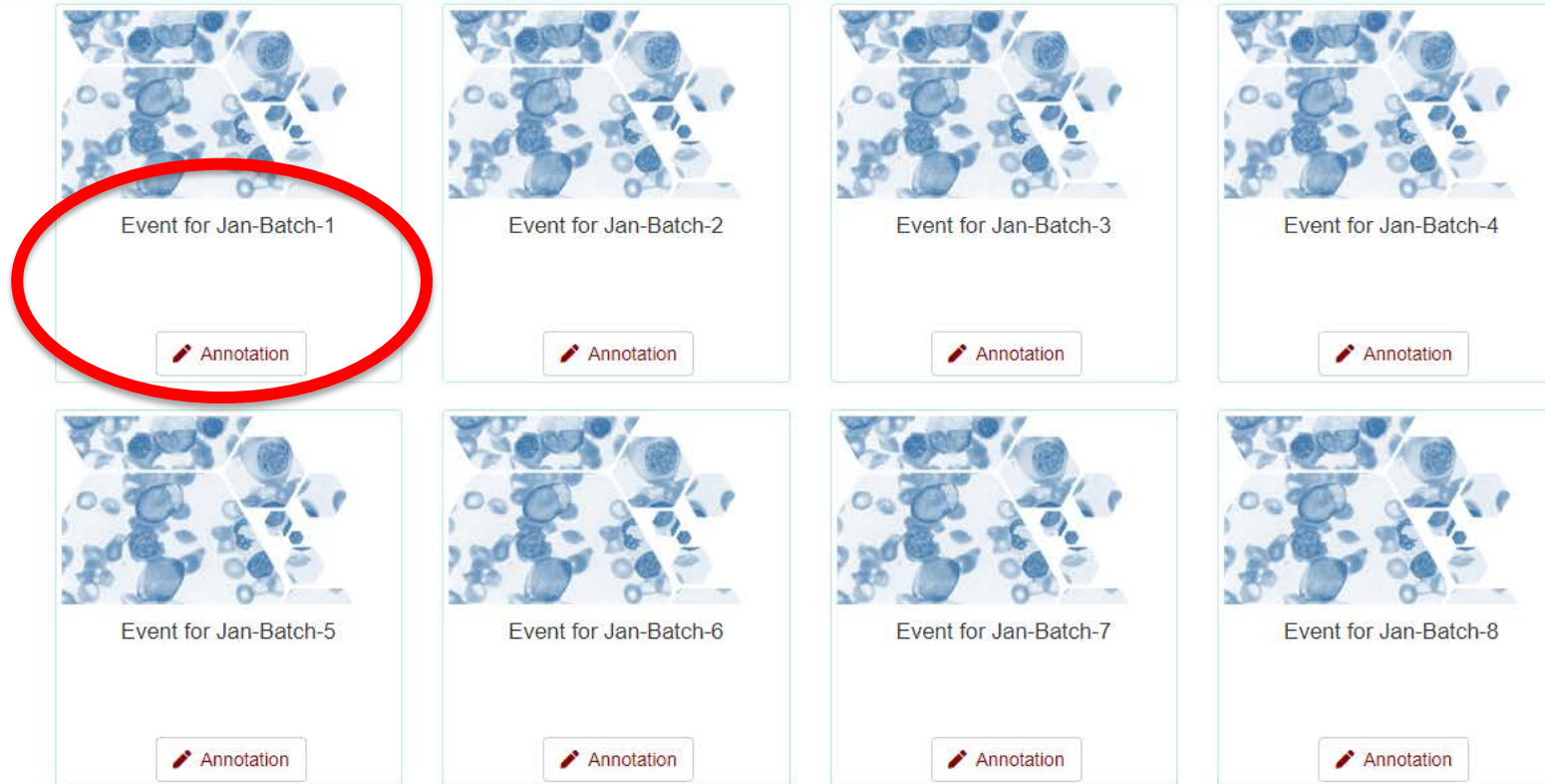
# Data Collection System



Digital Platforms:  
**PathPresenter**



# Data Collection Systems



Event for Jan-Batch-1

Annotation

Event for Jan-Batch-2

Annotation

Event for Jan-Batch-3

Annotation

Event for Jan-Batch-4

Annotation

Event for Jan-Batch-5

Annotation

Event for Jan-Batch-6

Annotation

Event for Jan-Batch-7

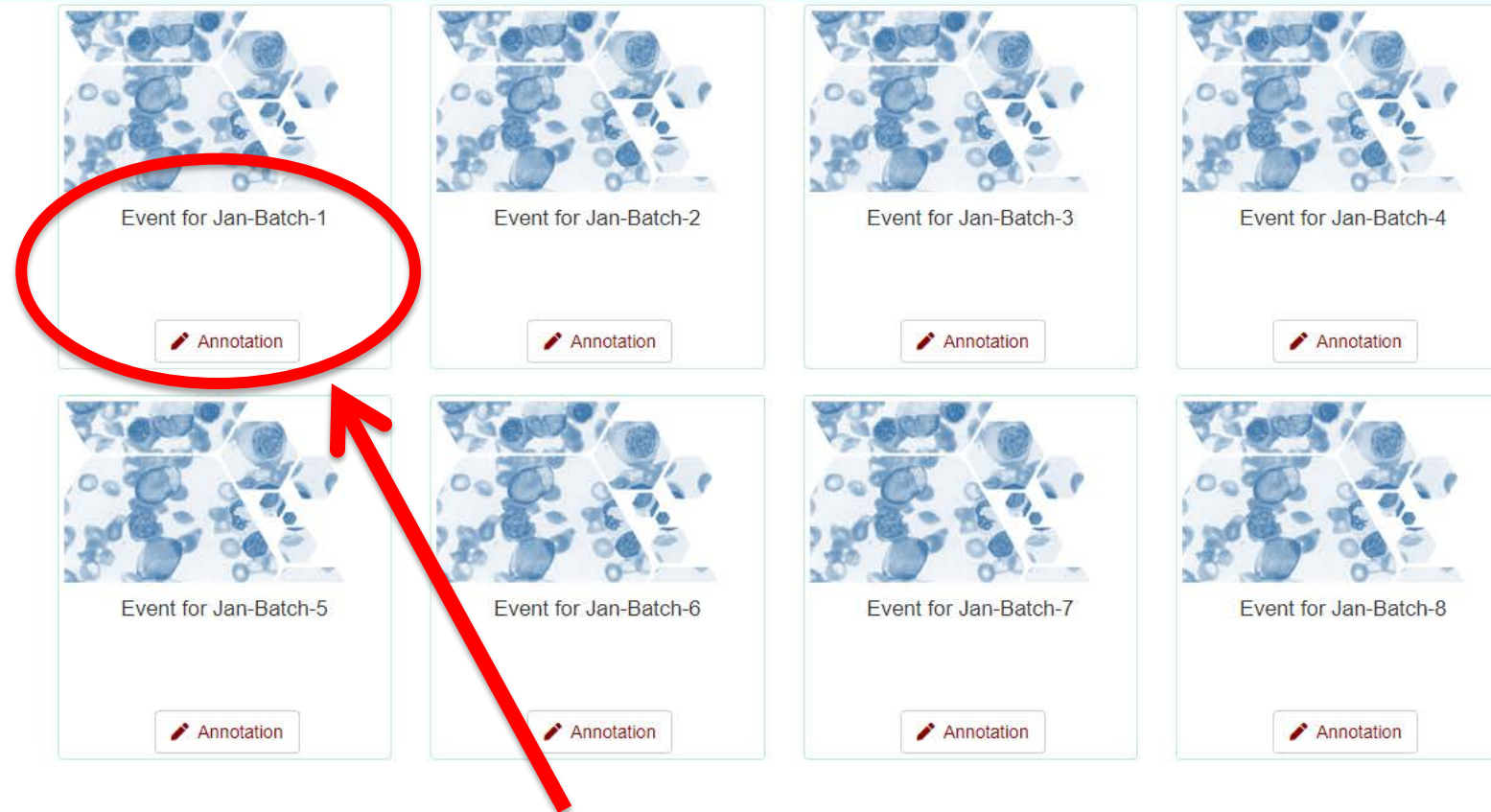
Annotation

Event for Jan-Batch-8

Annotation

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

# Data Collection Systems



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


# Data Collection Systems




Digital Platforms:  
PathPresenter

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	<a href="#">Analysis</a>
GM1578073114238.NDPI	HTT-TILS-001-04B.ndpi	10 [Pending : 10]	0	Pending	<a href="#">Analysis</a>
GM1578073114327.NDPI	HTT-TILS-001-07B.ndpi	10 [Pending : 10]	0	Pending	<a href="#">Analysis</a>
GM1578073114406.NDPI	HTT-TILS-001-08B.ndpi	10 [Pending : 10]	0	Pending	<a href="#">Analysis</a>
GM1578073114431.NDPI	HTT-TILS-001-09B.ndpi	10 [Pending : 10]	0	Pending	<a href="#">Analysis</a>
GM1578073114502.NDPI	HTT-TILS-001-11B.ndpi	10 [Pending : 10]	0	Pending	<a href="#">Analysis</a>
GM1578073114556.NDPI	HTT-TILS-001-12B.ndpi	10 [Pending : 10]	0	Pending	<a href="#">Analysis</a>
GM1578073114588.NDPI	HTT-TILS-001-13B.ndpi	10 [Pending : 10]	0	Pending	<a href="#">Analysis</a>

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**

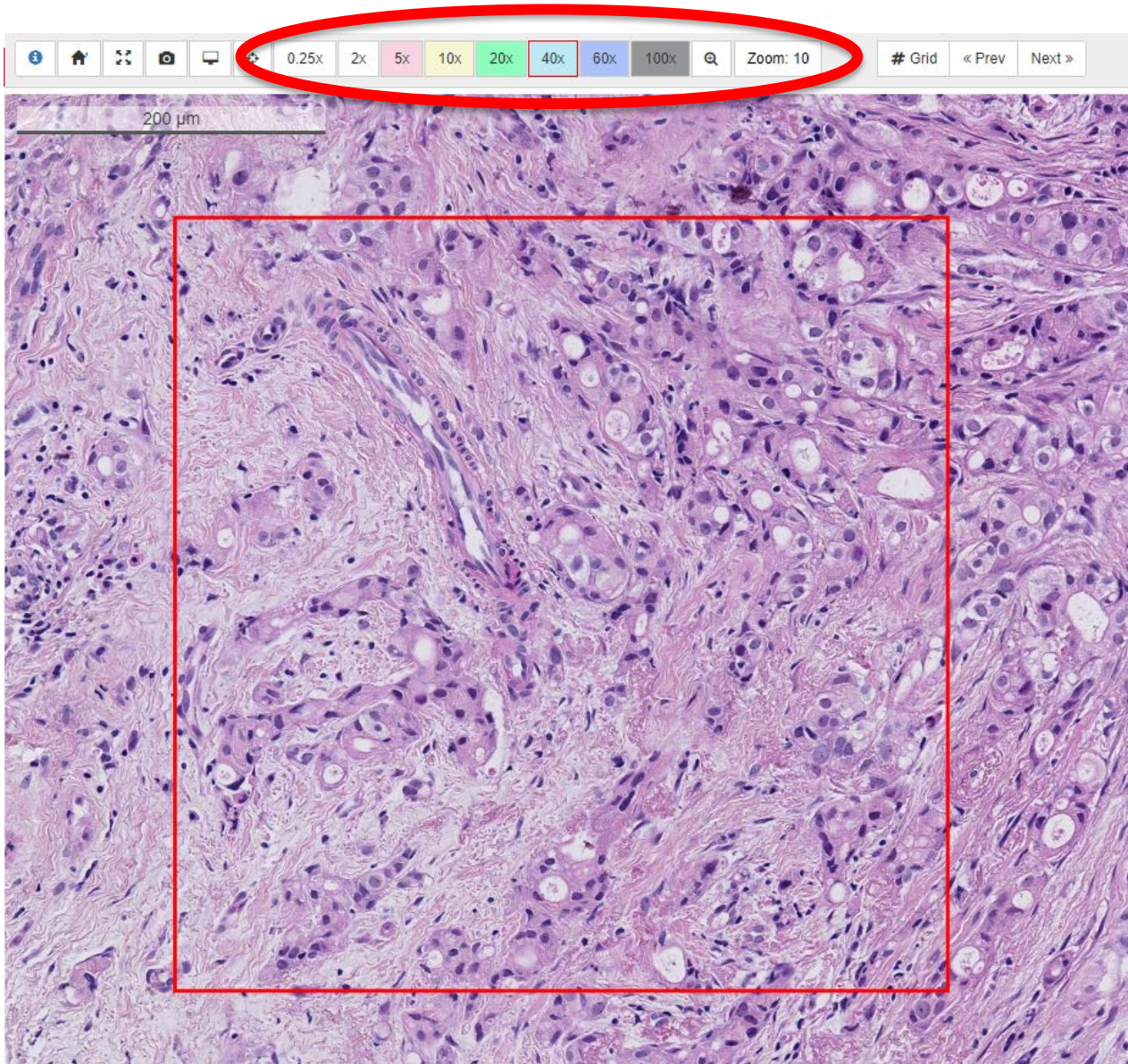
The screenshot displays the PathPresenter software interface. At the top, a toolbar contains various icons for navigation and zooming, with a zoom level of 40x selected. Below the toolbar, a large histology slide is shown with several rectangular regions of interest (ROIs) marked. A red square highlights one of these ROIs. To the right of the slide, a panel titled 'ROI' contains a grid of small square icons, a dropdown menu for 'ROI Label', a text input field for 'Description', a checkbox for 'Vta appropriate', and buttons for 'Cancel', 'Save', and 'Hide All ROI'. Below this panel, an 'Annotation' slider is set to 100. The 'Next' button in the top toolbar is circled in red, indicating the action to move to the next task.



# Data Collection Systems



Digital Platforms:  
**PathPresenter**

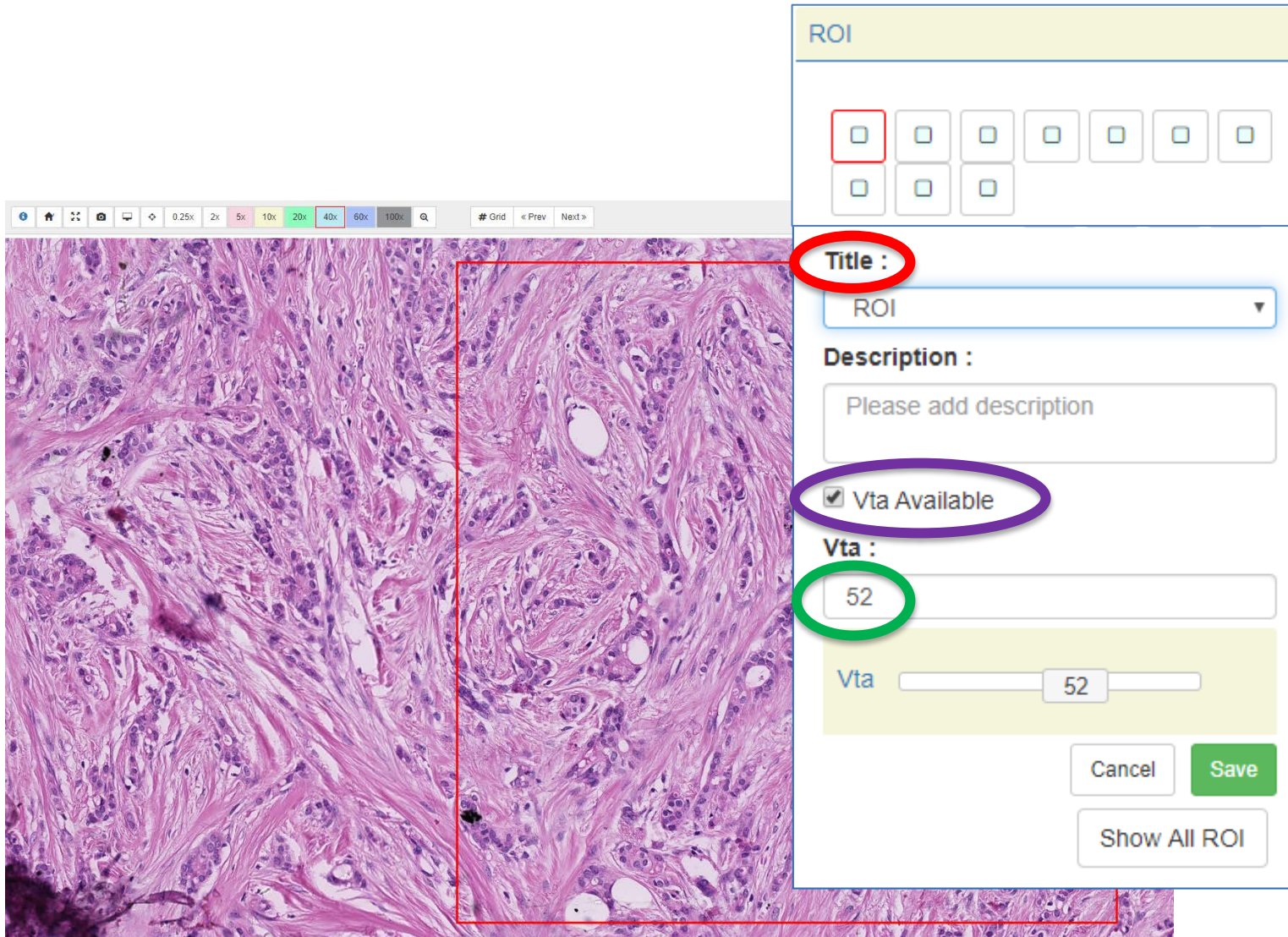


Zoom & pan by using your  
mouse or the  
**magnification buttons**



\*\*New image soon

# Data Collection Systems



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 is overlaid. The form has a yellow header labeled 'ROI'. Below the header, there is a grid of nine small square icons; the first icon in the top-left corner is highlighted with a red border. The form contains the following fields and controls:

- Title :** A dropdown menu with 'ROI' selected.
- Description :** A text input field with the placeholder text 'Please add description'.
- ☒ **Vta Available** (This checkbox is circled in purple).
- Vta :** A text input field containing the value '52' (This field is circled in green).
- A slider control labeled 'Vta' with a value of '52' (This slider is highlighted with a yellow background).
- Buttons:** 'Cancel', 'Save', and 'Show All ROI'.

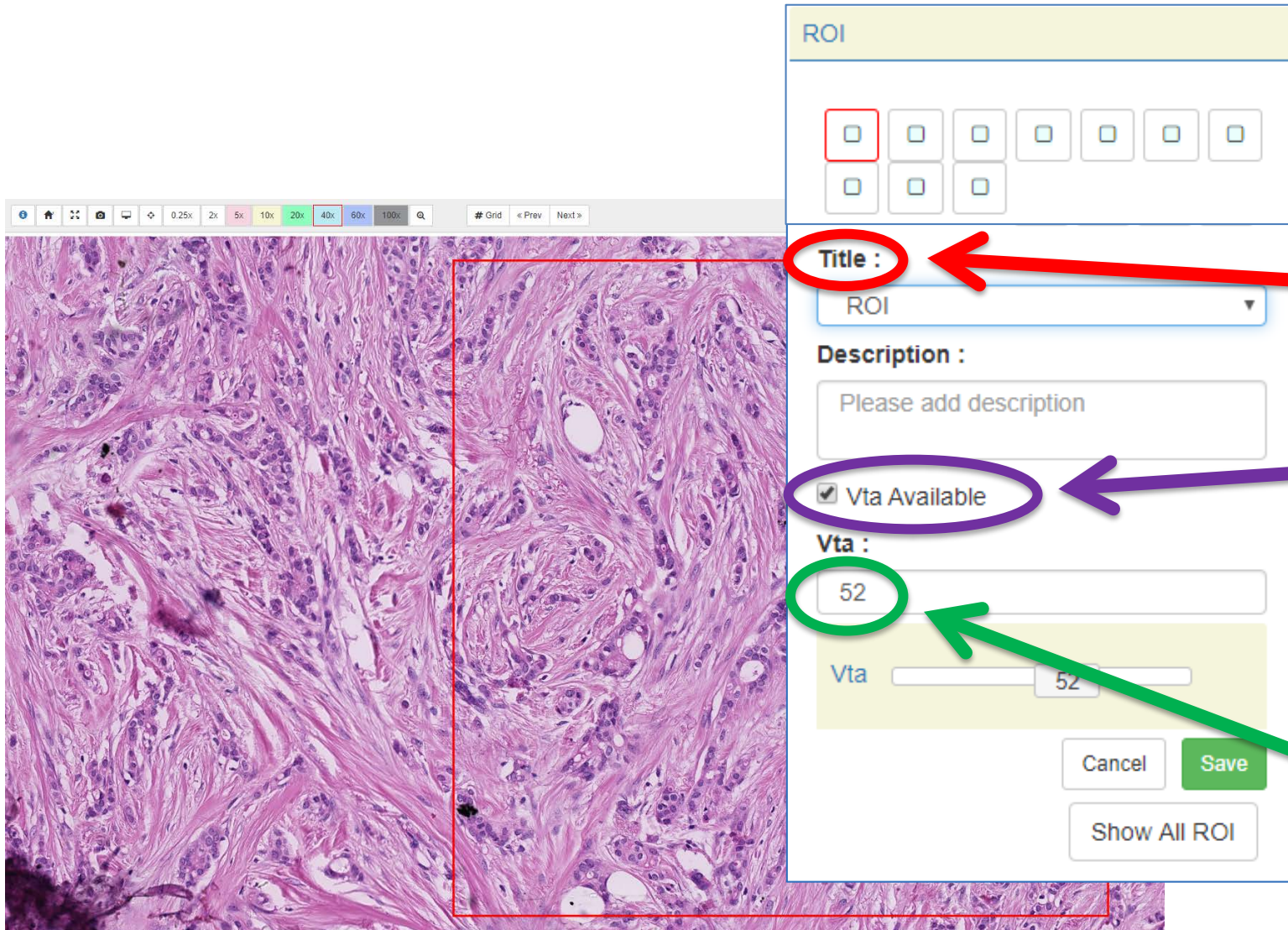
1. Select an **ROI label** from the list of options

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

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

\*\*New image soon

# Data Collection Systems



The screenshot shows a histology image on the left with a red rectangular ROI (Region of Interest) box. On the right is a data collection form titled 'ROI'. The form has a grid of 10 small square icons at the top, with the first one highlighted in red. Below this is a 'Title :' field with a dropdown menu currently showing 'ROI'. Underneath is a 'Description :' field with the placeholder text 'Please add description'. Then there is a checkbox labeled 'Vta Available' which is checked. Below that is a 'Vta :' field with the number '52' entered. At the bottom of the form are three buttons: 'Cancel', 'Save', and 'Show All ROI'. A red arrow points from the first icon in the grid to the 'Title :' field. A purple arrow points from the 'Vta Available' checkbox to the text 'Verify that a Visual TIL Assessment can be conducted'. A green arrow points from the '52' in the 'Vta :' field to the text 'Record TIL Density (%) (Keyboard or Slider)'.

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](mailto:brandon.gallas@fda.hhs.gov)

Sarah Dudgeon: [sarah.dudgeon@fda.hhs.gov](mailto:sarah.dudgeon@fda.hhs.gov)



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

Roberto Salgado: [roberto@salgado.be](mailto:roberto@salgado.be)

# MISSING: PathPresenter (to do)

- Show informed consent
- Location of tutorial(s)