

COLLECTING AND ANNOTATING DIGITAL PATHOLOGY IMAGES TO ASSESS COMPUTATIONAL PATHOLOGY

Brandon D. Gallas

Division of Imaging, Diagnostics, Software Reliability

Office of Science and Engineering Laboratories
Center for Devices and Radiological Health
U.S. Food and Drug Administration

From Mammograms to Microwaves

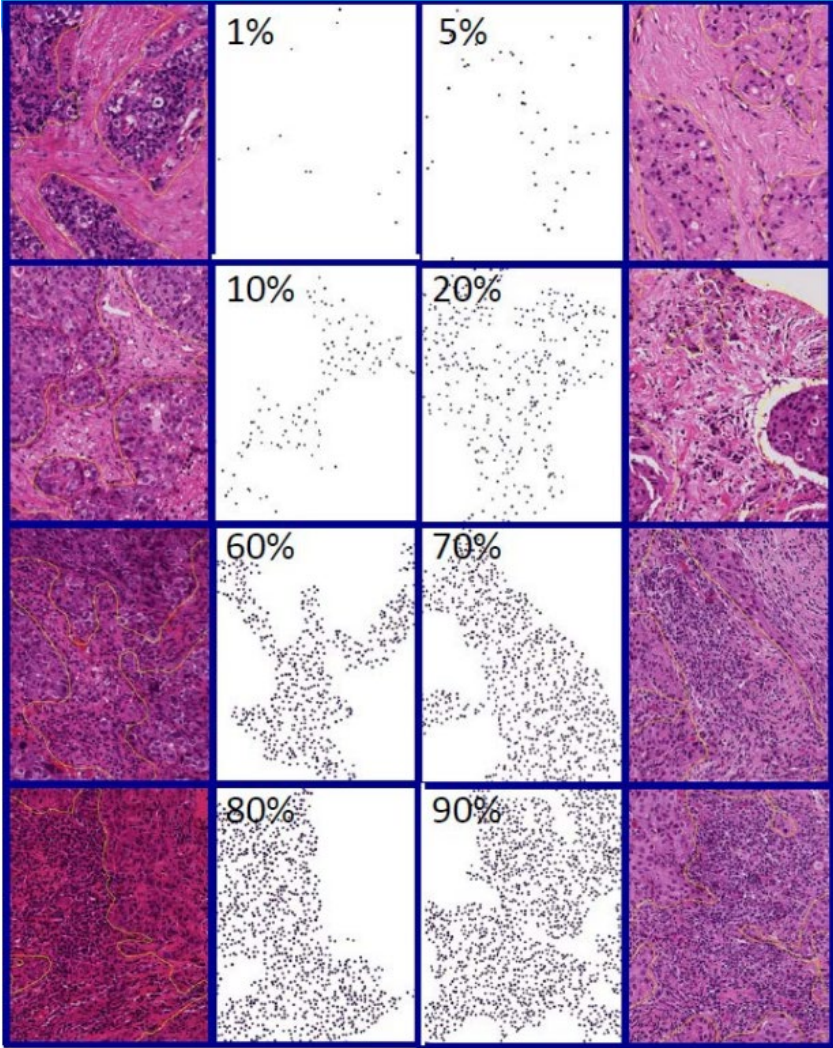
<https://www.fda.gov/about-fda/fda-organization/center-devices-and-radiological-health>



Outline

- HTT: High Throughput Truthing Project
- Training Materials
- Website
- Publications
- Related Activities

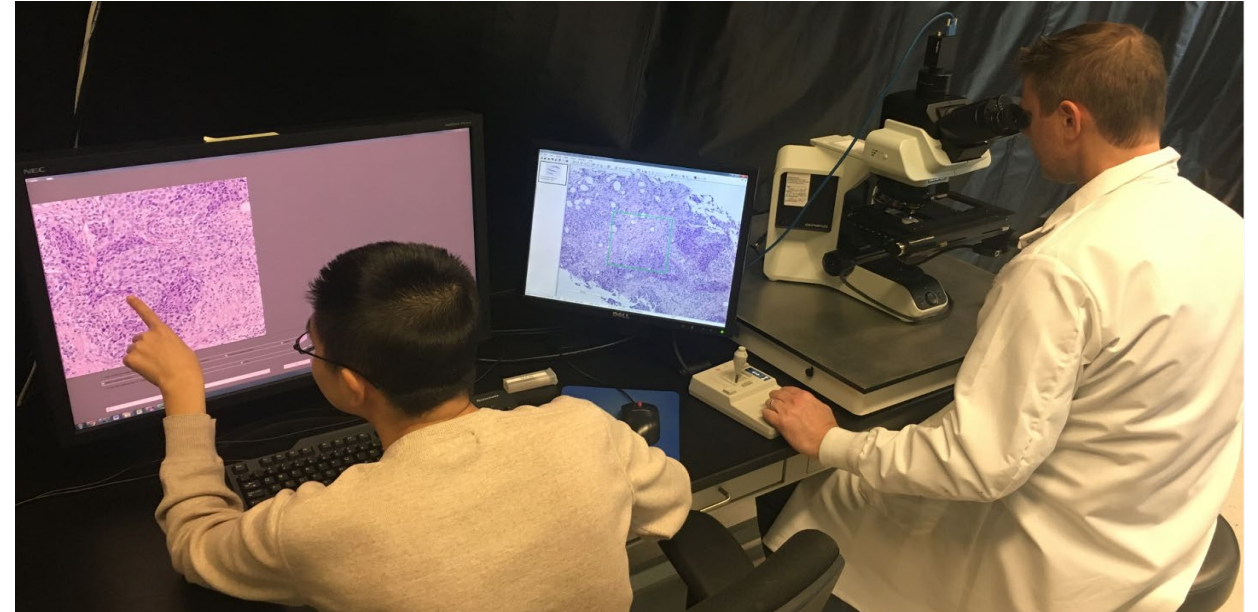
Quantitative Biomarker
TILs: Tumor Infiltrating Lymphocytes



High-Throughput Truthing (HTT) Project



- Clinical context:
 - Breast cancer
 - Quantitative 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



- Tools for AI-enabled Software Devices
 - Reference standard data set from pathologists
 - Data-collection methods and platforms
 - Methods to validate a quantitative algorithm

CME Course: Assessment of Stromal Tumor-Infiltrating Lymphocytes



Objectives

- Describe the **significance** of stromal tumor-infiltrating lymphocytes in triple negative breast cancer.
- Demonstrate knowledge of the **approach** to determining the density of stromal tumor-infiltrating lymphocytes.

Faculty

Victor Garcia, MD

Amy Ly, MD

Matthew Hanna, MD

Dieter Peeters, MD, PhD

Roberto Salgado, MD, PhD

Xiaoxian Li, MD, PhD

Kim Blenman, PhD, MS

Katherine Elfer, PhD, MPH

Bruce Werness, MD

Anna Ehinger, MD

Brandon Gallas, PhD

The screenshot shows the CE Portal interface for the course. At the top, it displays the FDA logo and 'U.S. FOOD & DRUG ADMINISTRATION'. To the right, it identifies the 'CE Consultation and Accreditation Team' and the 'Division of Learning and Organizational Development' at the 'Center for Drug Evaluation and Research'. A navigation bar includes links for Home, About Us, Calendar, Online Learning, Planning Tools, Policies, FAQ, and Contact Us. Below this, a user dashboard shows 'Dashboard', the user name 'Brandon Gallas', and a 'Sign Out' button. The main content area features the course title 'Assessment of Stromal Tumor-Infiltrating Lymphocytes'. Key details include: 'Starts On: Wed, 3/1/23: 12:00 AM EST', 'Ends On: Sun, 3/1/26: 12:00 AM EST', 'Type: Enduring Material', and 'Credits: 3'. A 'Description' paragraph states: 'Tumor-infiltrating lymphocytes have been established as a prognostic biomarker in early-stage triple negative breast cancer. The assessment of the density of stromal tumor-infiltrating lymphocytes at the time of diagnosis may improve the accuracy of prognosis determination and inform therapeutic decision-making.' To the right of the description is a progress table:

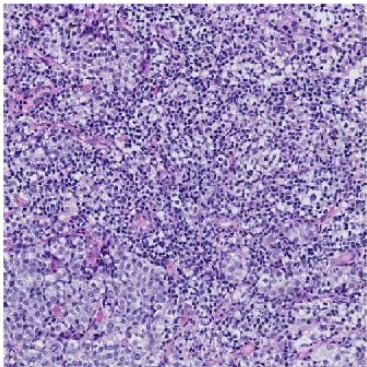
Step	Status
Educational Content <small>(Documents are shown beneath the session information)</small>	✓
Take Posttest <small>Attempts: 0/50 - Result: n/a</small>	◀
Evaluation	✗

<https://ceportal.fda.gov/>

192 participants



sTILs Reference Document and Pitfalls



caseID: HTT-TILS-001-04B.ndpi_x24343.2190_y11775.2190

Expert Panel Annotations

ROI Type	Percent Tumor-Associated Stroma	sTILs Density
Evaluable	30	90
Evaluable	60	95
Evaluable	50	92
Evaluable	50	75
Evaluable	60	90
Evaluable	60	90

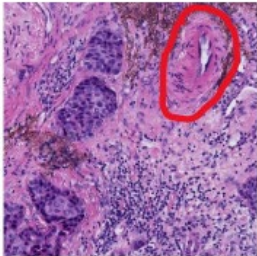
Mean Percent Tumor-Associated Stroma: 51.7
Mean sTILs Density: 88.7

Comments: A challenging case. The high density of lymphocytes results in difficulty determining whether the lymphocytes are located in stroma, or whether they infiltrate tumor cell nests. The presence of small blood vessels and small gaps between lymphocytes suggest the lymphocytes reside within stroma. Occasional tumor cells with small nuclei (possibly degenerating) may be confused for lymphocytes.

Pitfalls: In regions where the sTILs density is very high, the underlying stroma may be obscured. Non-lymphocytes with small nuclei may be confused for lymphocytes.

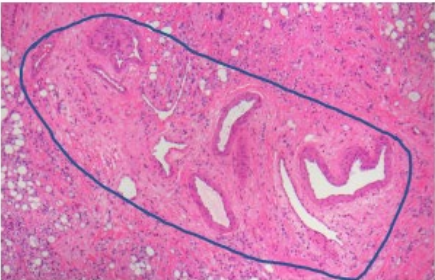
2

Thick-walled vessels are not considered stroma

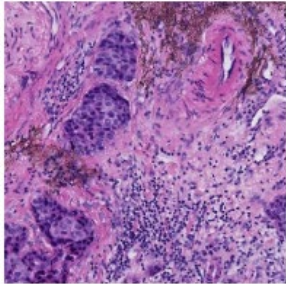


Area of tumoral stroma occupied by mononuclear inflammation x 100
Entire area of tumoral stroma

Thick-walled vessels are not considered stroma



How much tumor-associated stroma is present?

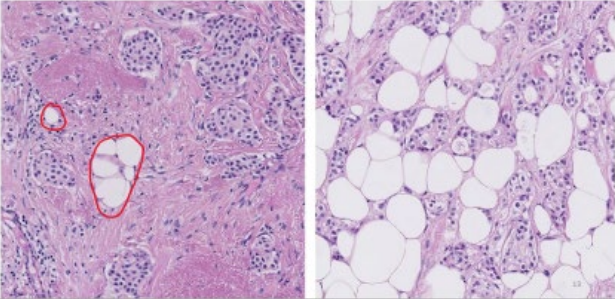


ROI Type	Percent Tumor-Associated Stroma	sTILs Density
Evaluable	75	30
Evaluable	35	60
Evaluable	86	15
Evaluable	75	30
Evaluable	70	25
Evaluable	70	20

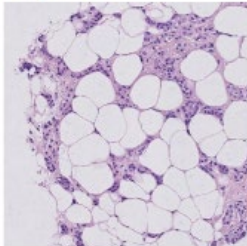
Mean Percent Tumor-Associated Stroma: 68.5
Mean sTILs Density: 30

Example Pitfalls

Adipose tissue is not considered stroma



How much tumor associated stroma is present?

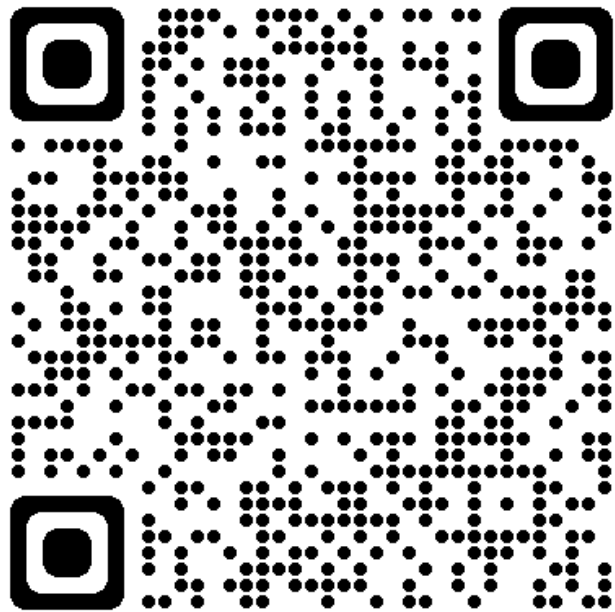


ROI Type	Percent Tumor-Associated Stroma	sTILs Density
Evaluable	10	0
Evaluable	5	1
Evaluable	14	4
Evaluable	20	0
Evaluable	40	0
Evaluable	50	2

Mean Percent Tumor-Associated Stroma: 23.2
Mean sTILs Density: 1.2

HTT project home

- <https://didsr.github.io/HTT.home/>



High Throughput Truthing Project

FDA DIDSr validation dataset creation for ML algorithm development.

Key Pages

- [What is the HTT project?](#)
- [Training Materials](#)
- [Pivotal Study](#)
- [Publications](#)
- [Commercial Products Disclaimer](#)
- [Regulatory Submission Information For Developers](#)

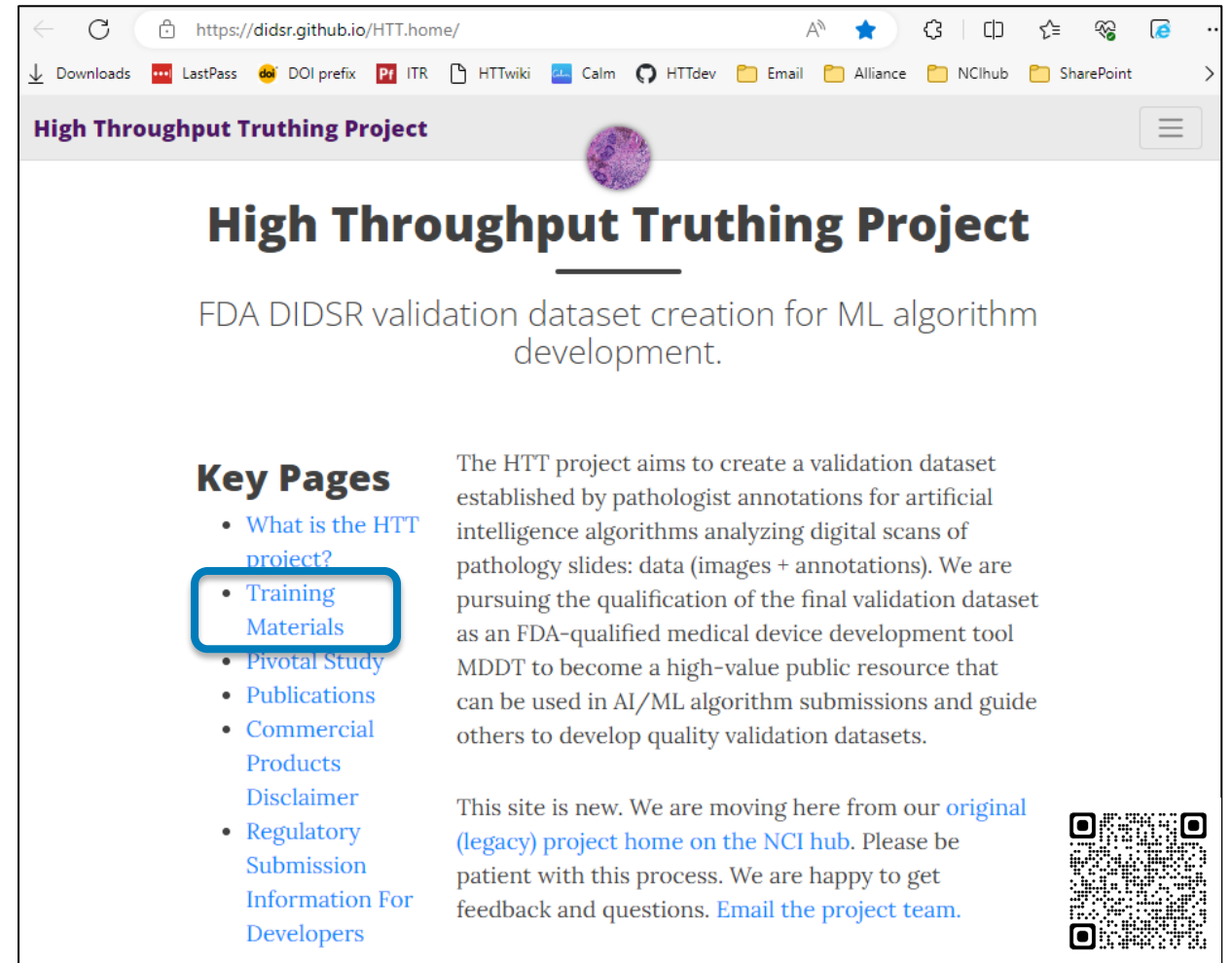
The HTT project aims to create a validation dataset established by pathologist annotations for artificial intelligence algorithms analyzing digital scans of pathology slides: data (images + annotations). We are pursuing the qualification of the final validation dataset as an FDA-qualified medical device development tool MDDT to become a high-value public resource that can be used in AI/ML algorithm submissions and guide others to develop quality validation datasets.

This site is new. We are moving here from our [original \(legacy\) project home on the NCI hub](#). Please be patient with this process. We are happy to get feedback and questions. [Email the project team](#).

<https://didsr.github.io/HTT.home/>

HTT project home: Training Materials

- CME Course Info and Mirror
- Interactive Training
 - Test with feedback
 - Proficiency test
 - Example test report
 - Reference document (feedback test content)



The screenshot shows a web browser displaying the 'High Throughput Truthing Project' website. The URL is <https://didsr.github.io/HTT.home/>. The page features a purple circular logo and the title 'High Throughput Truthing Project'. Below the title, it states 'FDA DIDSr validation dataset creation for ML algorithm development.' A 'Key Pages' section lists several links, with 'Training Materials' highlighted by a blue box. To the right, there is a paragraph describing the project's goal and a QR code in the bottom right corner.

High Throughput Truthing Project


FDA DIDSr validation dataset creation for ML algorithm development.

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<https://didsr.github.io/HTT.home/>

HTT project home: Regulatory Submission Information



Links to information for Developers of Medical Imaging Algorithms

- Basic regulatory pathways
- Related guidance documents
- Decision summaries of related devices
- Presentations by FDA scientists

High Throughput Truthing Project

High Throughput Truthing Project


FDA DIDSr validation dataset creation for ML algorithm development.

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<https://didsr.github.io/HTT.home/>

HTT project home: Project Information



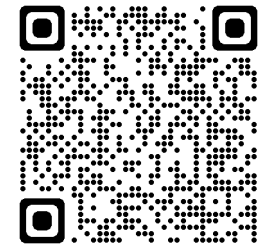
- Pivotal study entry point
 - Recruiting pathologists to be the reference standard
- Related publications

<https://didsr.github.io/HTT.home/>

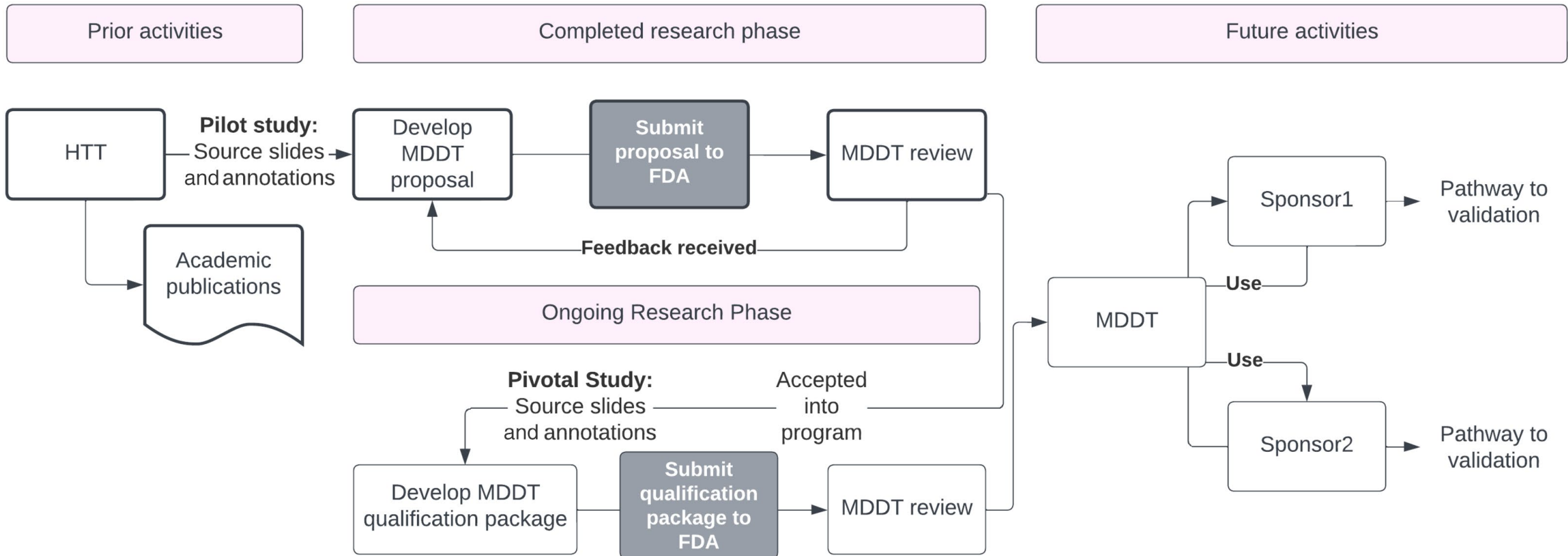
<https://didsr.github.io/HTT.home/>

“Initial interactions with the FDA on developing a validation dataset as a medical device development tool,”

S. Hart et al. (2023), *Journal of Pathology*, Vol. 261, p. 378-384

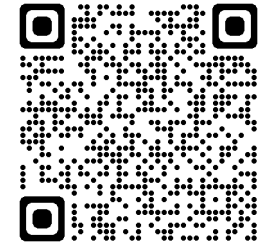


<https://doi.org/10.1002/path.6208>



“Training pathologists to assess stromal tumor infiltrating lymphocytes in breast cancer synergizes efforts in clinical care and scientific research”

A. Ly et al. (2023), *Histopathology*



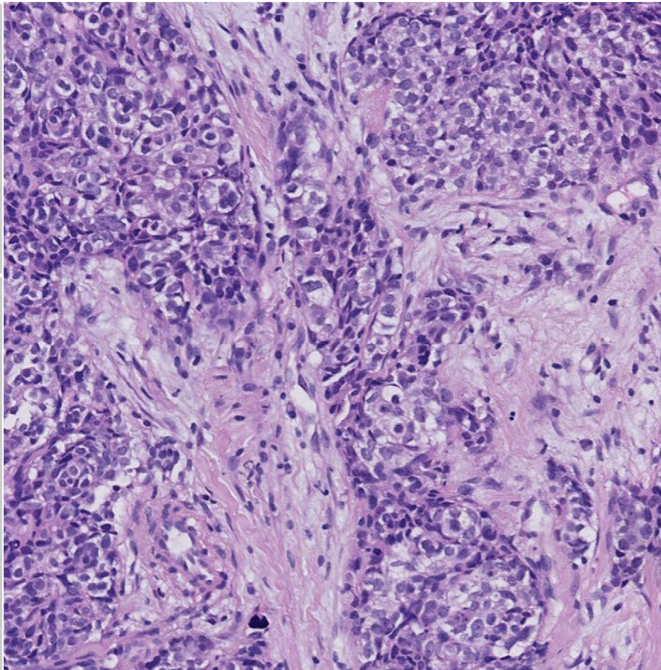
<https://doi.org/10.1111/his.15140>

ROI Type:

- Evaluable for sTILs
- Not Evaluable for sTILs

50%
% Tumor-Associated Stroma

5%
sTILs Density



Expert Panel Annotations:

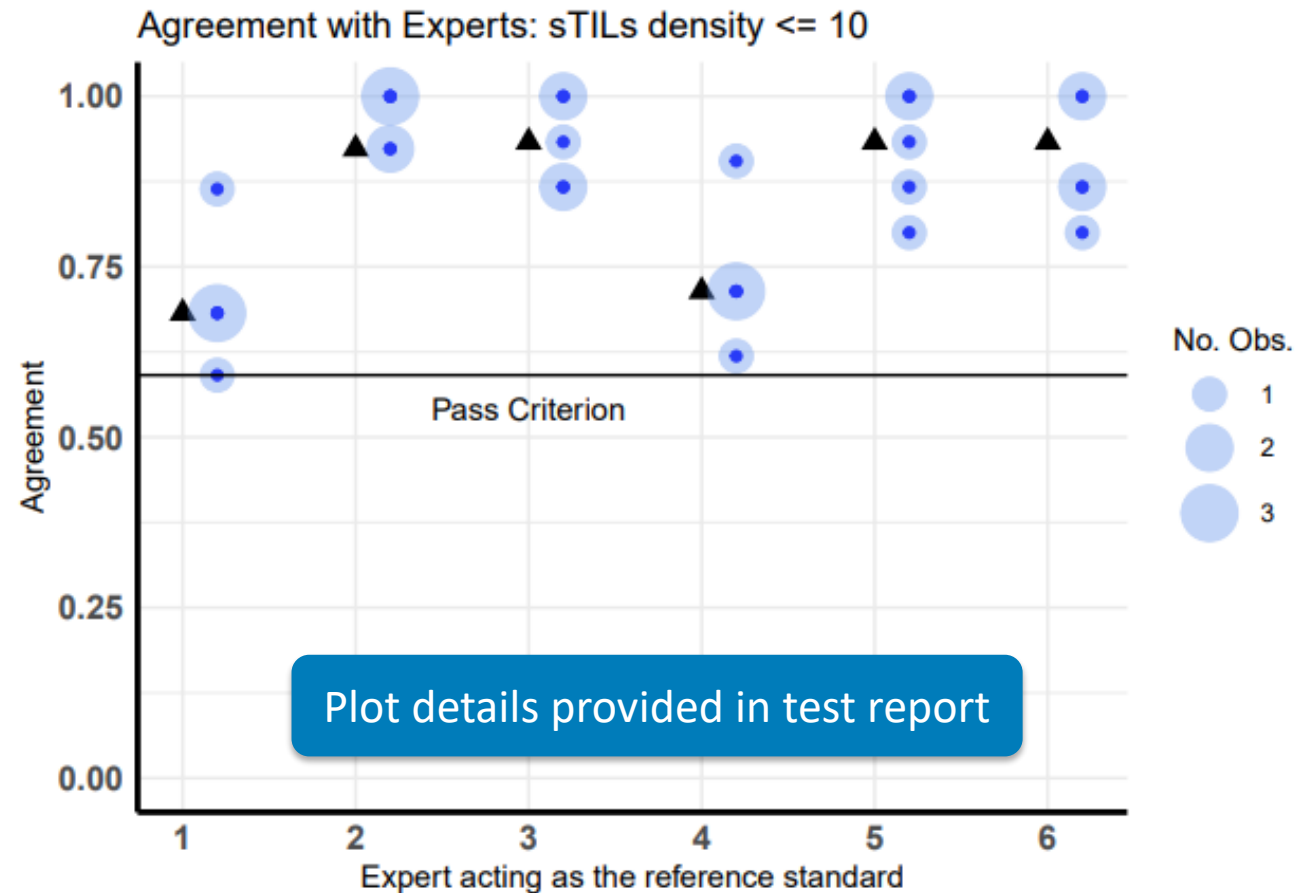
ROI Type	% Tumor-Associated Stroma	% sTIL Density
Evaluable	30	5
Evaluable	40	9
Evaluable	50	7
Evaluable	50	3
Evaluable	40	1
Evaluable	50	5

Mean Percent Stroma: 43.3
Mean sTILs Density: 5

Comments: It is difficult to distinguish between fibroblasts and sTILs in this case. The cells in the middle of the ROI are a bit wider than the other cells, so they probably are cancer cells that have artifact as a result of tissue processing. Though strong suspicion for a cancer cell, it could be a macrophage, which we see after treatment, and expect that an algorithm will have difficulty making this distinction on H&E stain.

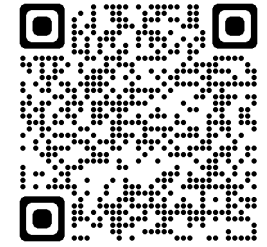
Pitfalls: Non-lymphocytes may be confused for lymphocytes if there is tissue fixation artifact. Axially sectioned fibroblasts may be mistaken for lymphocytes.

- Region of Interest
- Annotation Fields
- Expert Panel Annotations
- Comments
- Pitfalls



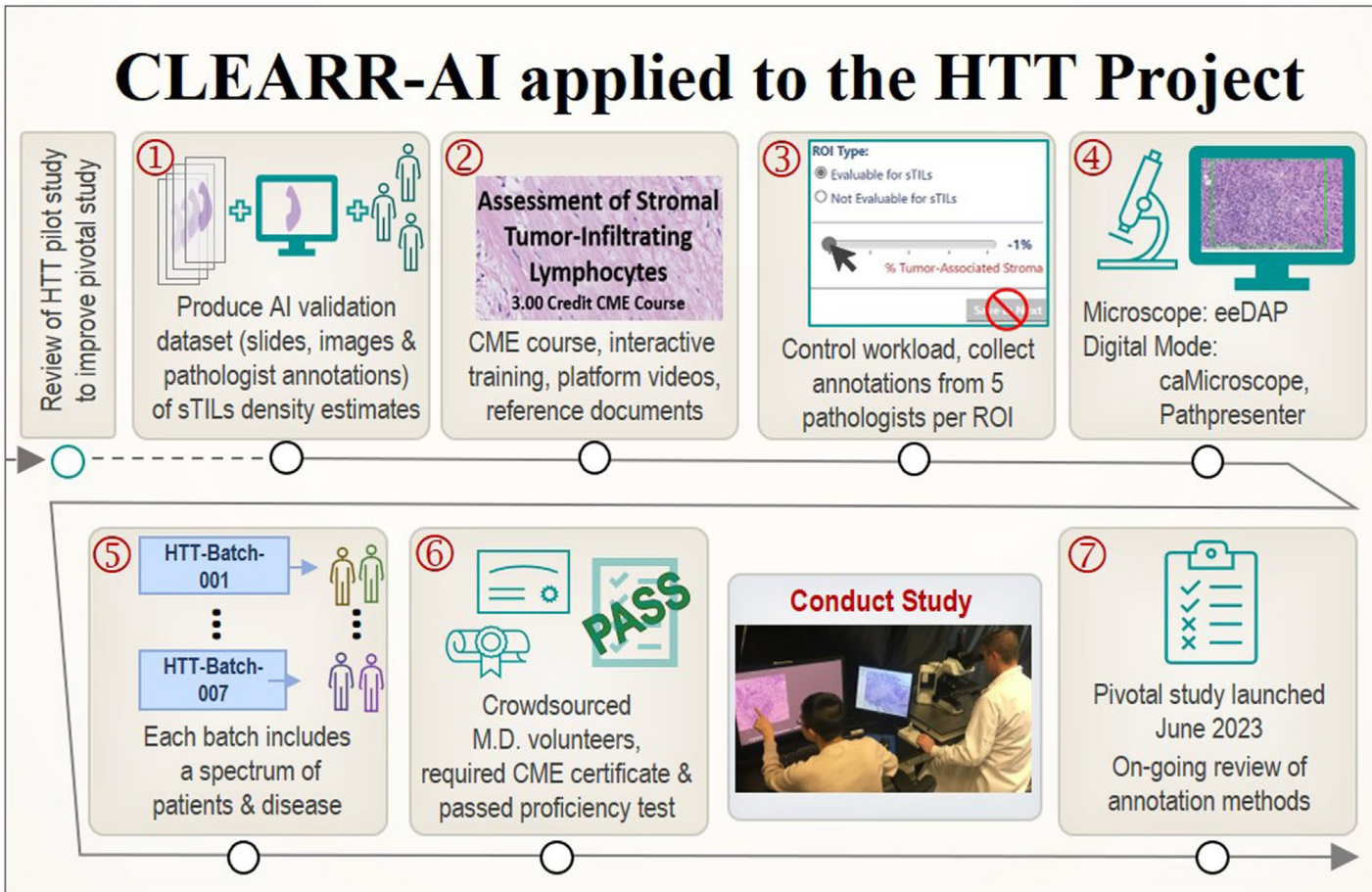
“Reproducible Reporting of the Collection and Evaluation of Annotations for Artificial Intelligence Models”

K. Elfer et al. (2024), *Modern Pathology*, Vol. 37, Issue 4, p. 100439



<https://doi.org/10.1016/j.modpat.2024.100439>

CLEAR-ARR-AI applied to the HTT Project



Study Component	Explanation	Origin
1. Objectives	Project objectives, dataset use case (training, testing models), degree of annotation (patient, image, ROI, or feature) and patient population.	Wahab <i>et al.</i> 1. Objectives and 2. Diagnostic/Prognostic Algorithm (modified) and 7. Degree of Annotation
2. Data Dictionary	Training materials and reference documents(s) describing image features, anatomic/biological context, and details on annotations: <ul style="list-style-type: none"> Types of annotation: nominal, ordinal, quantitative, or a mixture thereof; Constructs: arrows, outlines, slider bars, text boxes. 	Wahab <i>et al.</i> 3. Annotation Data Dictionary (modified), 5. Annotation Levels, and 6. Annotation Constructs
3. Study Design	Specify the study design <ul style="list-style-type: none"> Number of annotators, number of cases, number of annotators per case Methods to randomize cases or viewing conditions Time limits for annotation tasks Methods to assist or combine annotations (adjudication) 	Wahab <i>et al.</i> 9. Workload Distribution (modified)
4. Annotation Methods	Determine how annotators will encounter the data (digital platforms, in-person viewing, or mixed-methods), and what tools will be used to access and view the images.	Wahab <i>et al.</i> 4. Selection of Annotation Software, (modified)
5. Image Curation	Specify annotator, patient, and image sampling methods for the entire study and individual sub-groups of a study (e.g. case sampling methods including enrichment, and stratified sampling): <ul style="list-style-type: none"> Annotator: exhaustive in an allotted time-period, random subset, or stratified sampling of subgroups; Patient: demographic and clinical sub-groups, target features, and variability of features case sampling methods including enrichment, stratified sampling, and ROI selection; Image: quality and number of images in each subgroup. 	Wahab <i>et al.</i> 11. Quality Review (modified)
6. Annotators	Define annotators: number of total annotators, number of annotators per case, qualifications (training and requirements), and how they were recruited.	[New]
7. Quality Review	During and after the annotation study, identify, review and discuss adherence to the above components of the template, report the collected data, and report any deviations. Specify whether this was a single study or part of a larger study.	Wahab <i>et al.</i> 8. Phase of Annotation and 11. Quality Review (modified)

Status of HTT Pivotal Study



- **6/2023:** Training launched
(CME & Interactive Training)
- **6/2023:** Pivotal Study launched
- **8/2023:** New Website launched
- **52:** Pathologist Inquiries
- **5:** Active Pathologists
- **4:** Pathologists not passing proficiency
 - Training is a hurdle
- **155** cases
 - Still sourcing
- **113** cases curated
 - First pass ROI selection
- **40** cases batched for pivotal study
 - 5 pathologists per case: nearly complete
- **48** cases imminently batched



Related Activities

Pathology Innovation Collaborative Community



Plcc – “Pie See See”

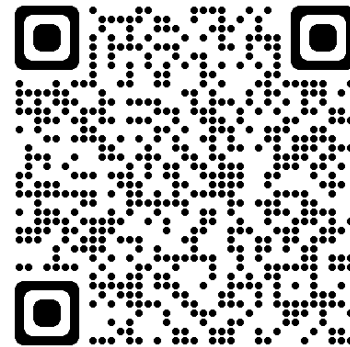
- FDA participates in Plcc
 - <https://pathologyinnovationcc.org/>

- Look for Joe!



Joe Lennerz ✓ · 1st
Chief Scientific Officer, BostonGene, Ma, USA

- Regulatory Landscape Survey



https://qualtricsxm9n4cl9pg.qualtrics.com/jfe/form/SV_4Sf41xG9Gm6XQM

The screenshot shows the website for the Pathology Innovation Collaborative Community (Plcc). At the top, it says "Plcc Alliance" with navigation links for Home, About, Working Groups, News & Events, Resources, Presentations, Projects, and Publications, and a "Join" button. The main heading is "Pathology Innovation Collaborative Community" followed by "Plcc". Below that, it reads "The Alliance for Digital Pathology" and "A collaborative community with FDA participation". It also mentions "& convened by Medical Device Innovation Consortium (MDIC)". At the bottom, there is a grid of logos for various partner organizations including FDA, MDIC, MGH, DPA, Friends of Cancer Research, Leica, ASIP, NIH, and many others. A large, colorful circular graphic is on the right side of the page, and a QR code is in the bottom right corner.

Related Activity: FNIH BC-CSC:

Foundation for NIH Biomarkers Consortium Cancer Steering Committee

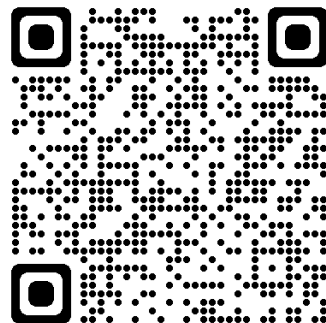


- Plcc coordinating project pitch to FNIH
 - New Plcc members welcome to the effort
- Presented vision to create a pipeline of real-world data for validating AI models
 - FNIH meeting 11/2023
 - Summary: <https://fnih.org/our-programs/biomarkers-consortium-csc-scientific-symposium/>
- Currently producing a skeleton proposal for 1-1 discussions with FNIH members

Call for Feedback!

ARPA-H FDA/CDRH Medical Imaging Data Marketplace

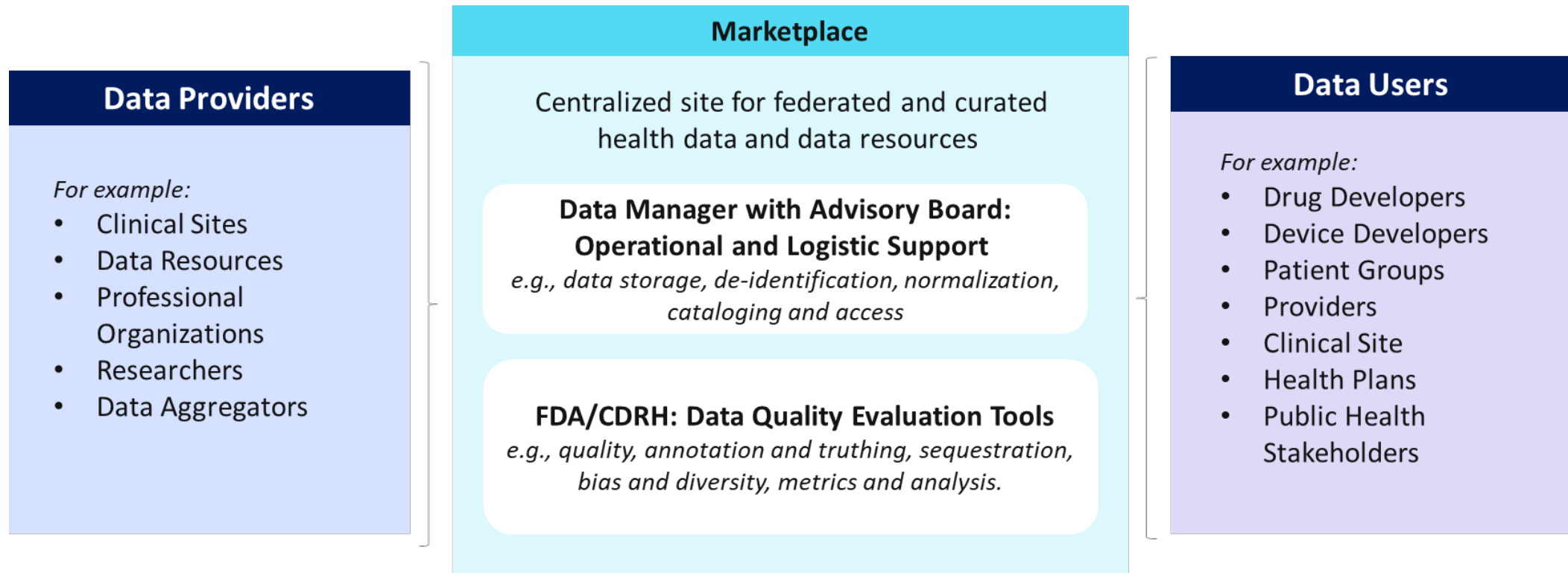
- *A self-sustaining, federated, national marketplace to catalyze transformative medical and health AI innovations*
- Network survey to provide feedback
 - <https://investorcatalysthub.org/medical-imaging/>
- Email for more Information:
 - midm@arpa-h.gov



Call for Feedback!

ARPA-H FDA/CDRH Medical Imaging Data Marketplace

- *A self-sustaining, federated, national marketplace to catalyze transformative medical and health AI innovations*



Summary

- @Pathologists
 - CME and interactive training for the assessment of TILs in breast cancer
 - **Recruiting pathologists** to be the reference standard to validate AI

- @AI-Developers
 - Regulatory information for developers of medical imaging algorithms
 - Materials and lessons learned for creating a validation dataset
 - Approaches to evaluating pathologists against experts
 - Feedback from FDA reviewers

- @All
 - Find out more at: <https://didsr.github.io/HTT.home/>
 - Related digital and computational collaborations

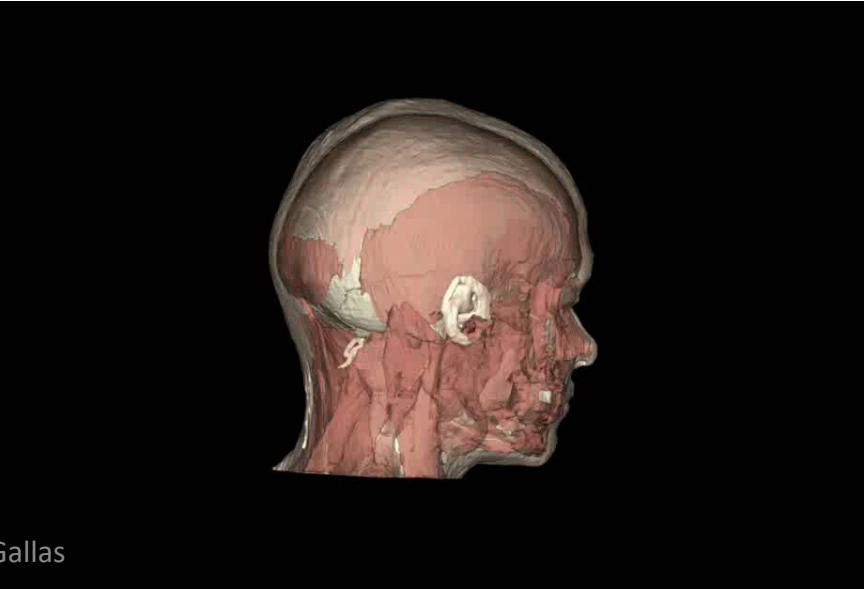
Title and content (black background)

CDRH Mission

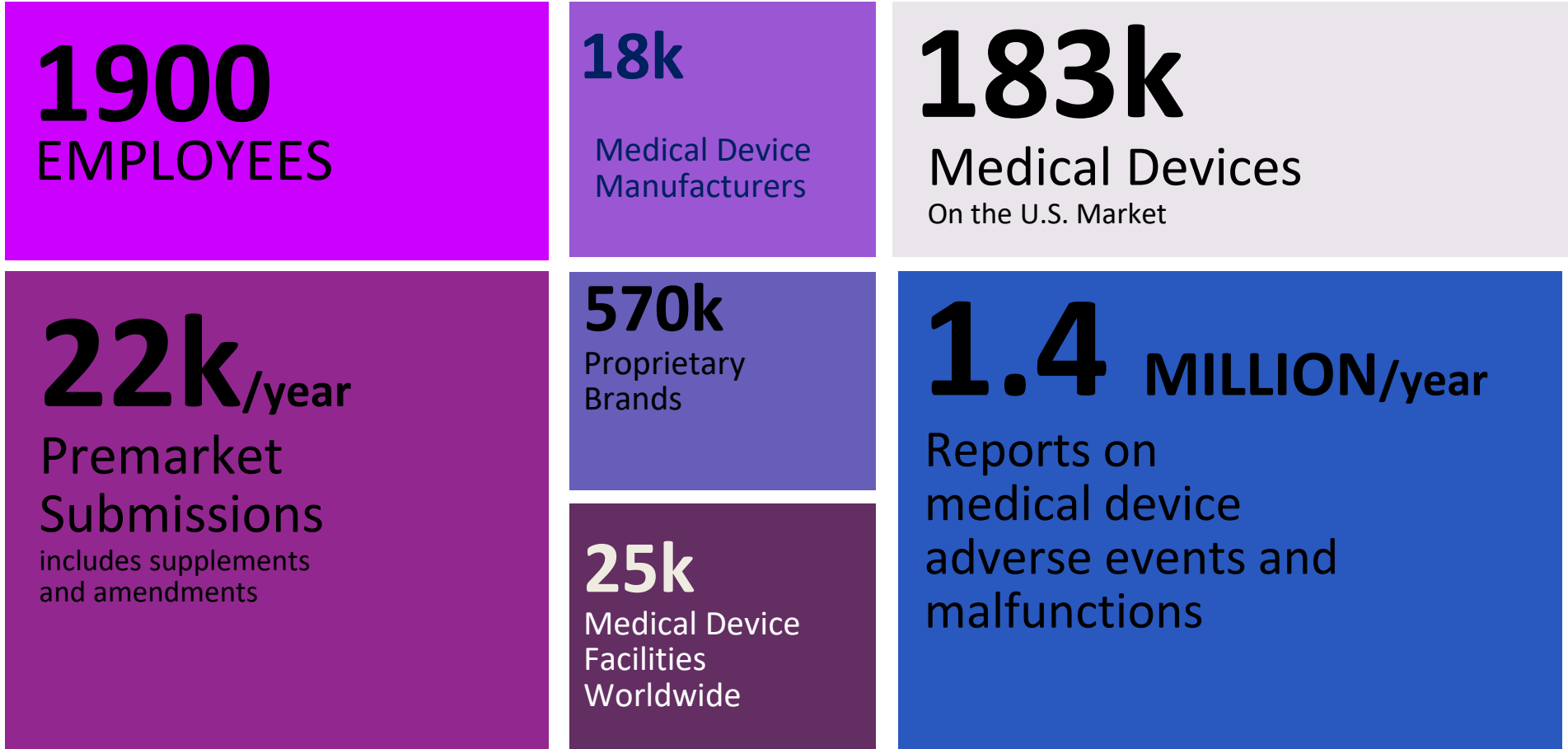


.. protect and promote the health of the public by ensuring the safety and effectiveness of **medical devices** and the safety of radiation-emitting electronic products...

We facilitate medical device innovation by advancing regulatory science, providing industry with predictable, consistent, transparent, and efficient regulatory pathways, and assuring consumer confidence in devices marketed in the U.S.



CDRH in Perspective



Office of Science and Engineering Laboratories (OSEL)

- Conduct laboratory-based regulatory research to facilitate development and innovation of safe and effective medical devices and radiation emitting products
- Provide scientific and engineering expertise, data, and analyses to support regulatory processes
- Collaborate with colleagues in academia, industry, government, and standards development organizations to develop, translate, and disseminate science and engineering-based information regarding regulated products
- <https://www.fda.gov/about-fda/cdrh-offices/office-science-and-engineering-laboratories>

OSEL in Perspective

183
FEDERAL EMPLOYEES
Up to 180 visiting scientists

140 Projects
In 27 Laboratories
and Program
Areas

400/year
Peer reviewed presentations,
articles, and other public disclosures

2,500k/year
Premarket
Regulatory consults

75
Standards and
conformity
assessment
committees

70%
Staff with post
graduate degree

55,000 ft²
Lab facilities

Division of Imaging, Diagnostics and Software Reliability (DIDSR)



- Develop least burdensome approaches for regulatory evaluation of imaging and big-data devices
 - Efficient clinical trials accounting for reader variability, simulation tools, in silico phantoms and imaging trials, addressing issues related to imperfect / missing reference standards, and limited data for training/testing of machine classifiers
- Develop measures of technical effectiveness of imaging and big-data technologies
 - Phantoms, laboratory measurements, computational models

DIDSR in Perspective

35
FEDERAL EMPLOYEES
14 Fellows/Students
3 Open Staff Positions

145/year
Peer reviewed articles, code and presentations

- 4** Program Areas
- AI/ML
 - Medical Imaging and Diagnostics
 - Digital Pathology
 - Mixed Reality (AR/VR/XR)

550/year
Premarket
Regulatory consults

