Regulatory Pathways and Science Related to Digital and 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

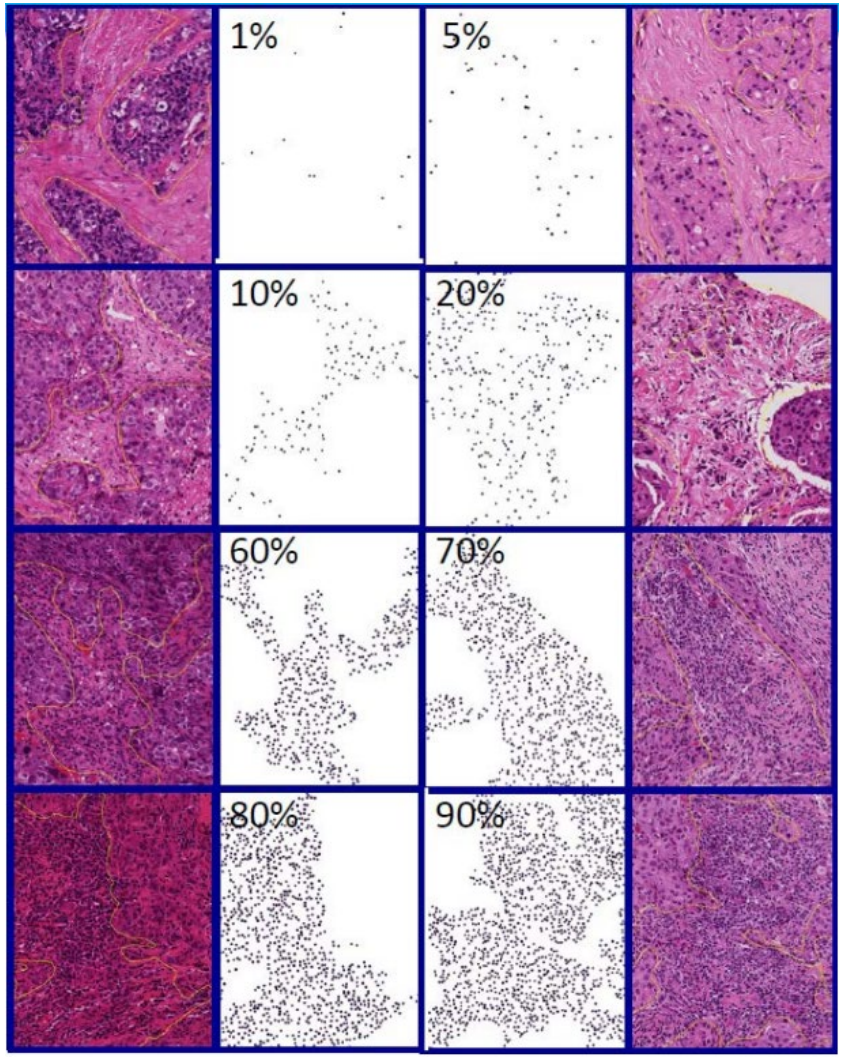
- Who I am and where I work
- HTT: High Throughput Truthing Project

  CLEARR-AI:

  Collection and Evaluation of Annotations for Reproducible Reporting of Artificial Intelligence

- Related Activities

Quantitative Biomarker
TILS: Tumor Infiltrating Lymphocytes



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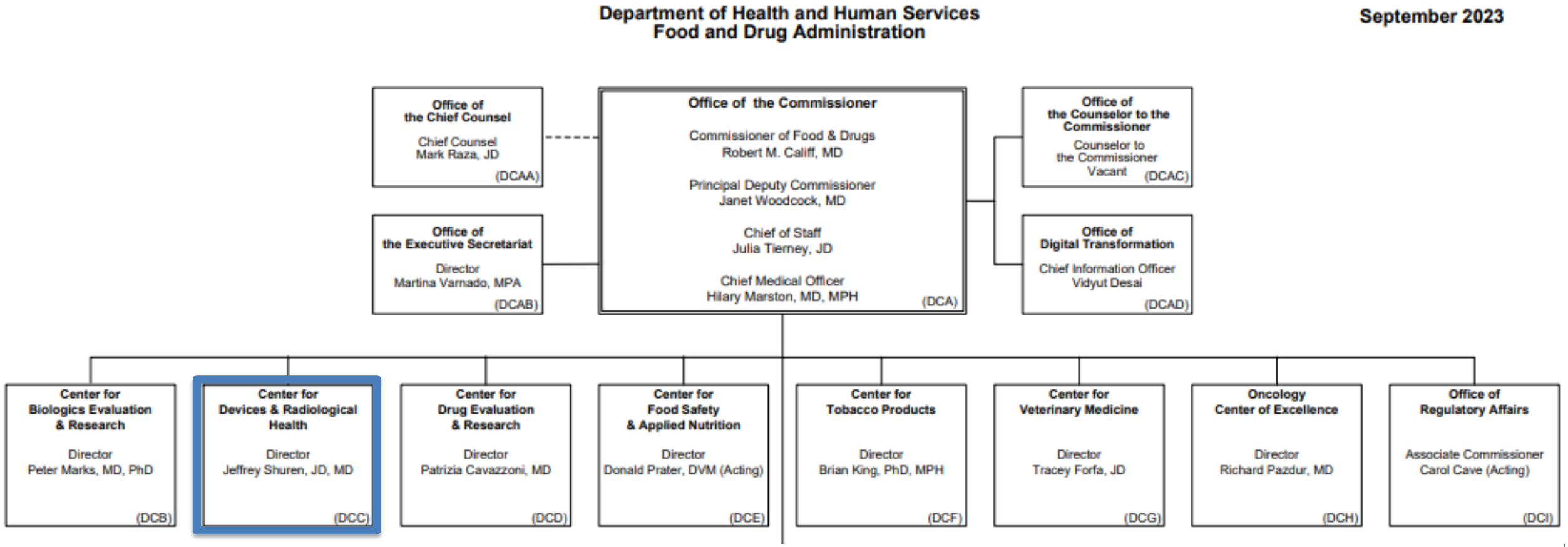
Acknowledgment

Research assistants supporting this work have been funded by appointments to the Research Participation Program at the Center for Devices and Radiological Health administered by the Oak Ridge Institute for Science and Education through an interagency agreement between the US Department of Energy and the US Food and Drug Administration.

FDA headquarter campus in Silver Spring, Maryland

Introduction to FDA/CDRH/OSEL/DIDSR



CDRH

- OSEL

- DIDSR

OSEL Accelerating patient access to innovative, safe, and effective medical devices through best-in-the-world regulatory science

Introduction to FDA/CDRH/OSEL/DIDSR

~1900
EMPLOYEES

18k
Medical Device Manufacturers

183k
Medical Devices
On the U.S. Market

22k/year
Premarket Submissions
including supplements and amendments

570k
Proprietary Brands

25k
Medical Device Facilities Worldwide

1.4MILLION/year
Reports on medical device adverse events and malfunctions

FDA's Office of Science and Engineering Laboratories (OSEL)

Introduction to FDA/CDRH/OSEL/DIDSR

Who We Are

CDRH is a team of over 1,900 dedicated, highly skilled, and internationally respected public health employees

Subject Matter Experts

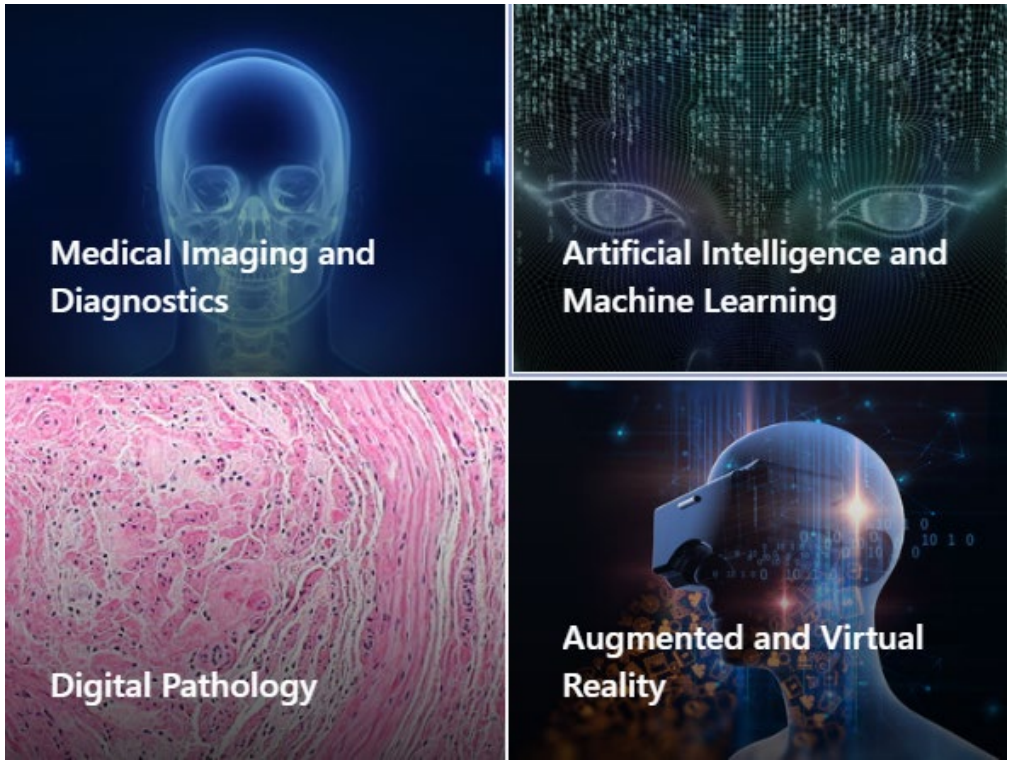
- Physicians
- Biologists
- Chemists
- Physicists
- Engineers
- Statisticians
- Epidemiologists
- Microbiologists
- Nurses
- Pharmacologists
- Veterinarians
- Toxicologists
- Specialists in Public Health Education and Communication

What We Do

- Provide subject matter expertise to the review of medical device submissions
- Conduct research and create tools to support the review of medical device submissions

Introduction to FDA/CDRH/OSEL/DIDSR

- The **Division of Imaging, Diagnostics and Software Reliability** (DIDSR) is the part of OSEL dedicated to imaging research.



~45

FEDERAL EMPLOYEES
~40 Fellows/Students

145/year

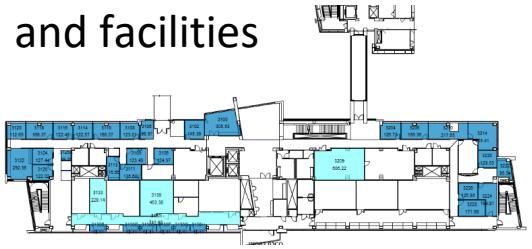
Peer reviewed articles, code and presentations

550/year

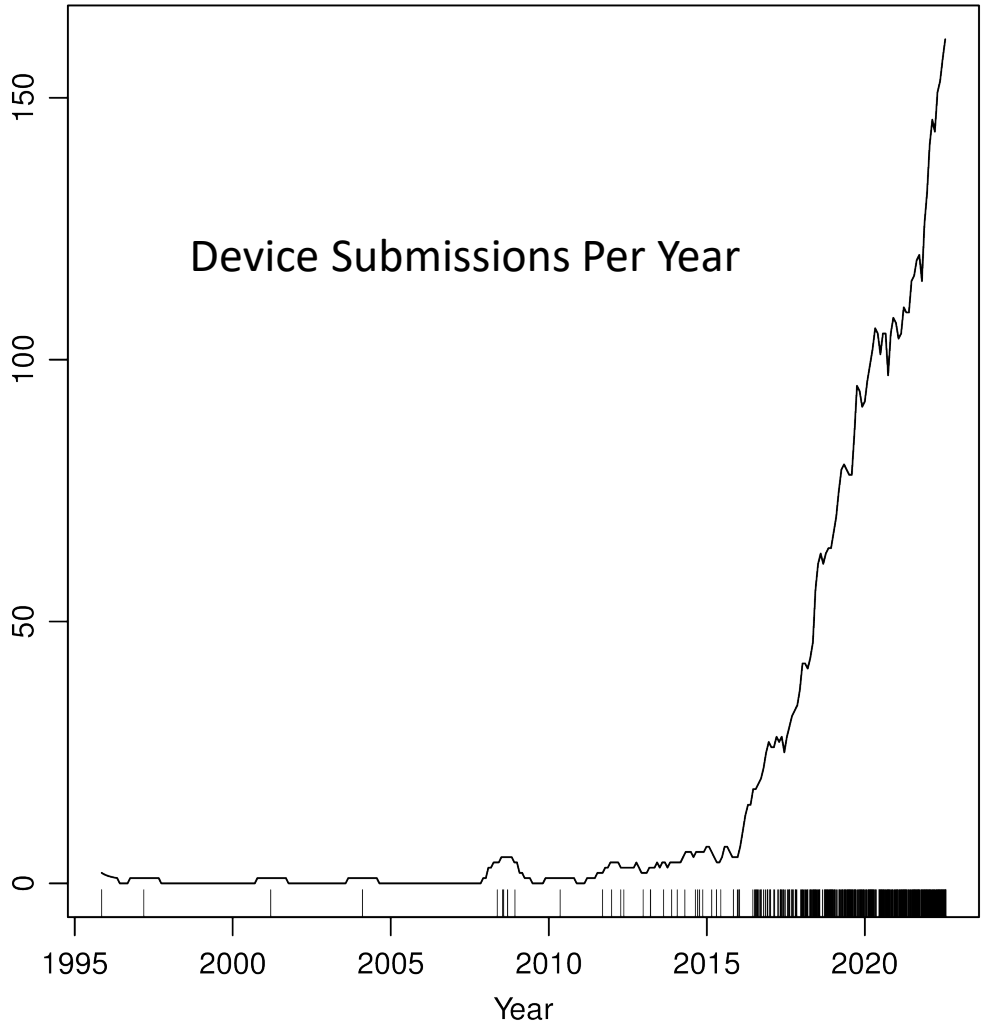
Premarket
Regulatory consults

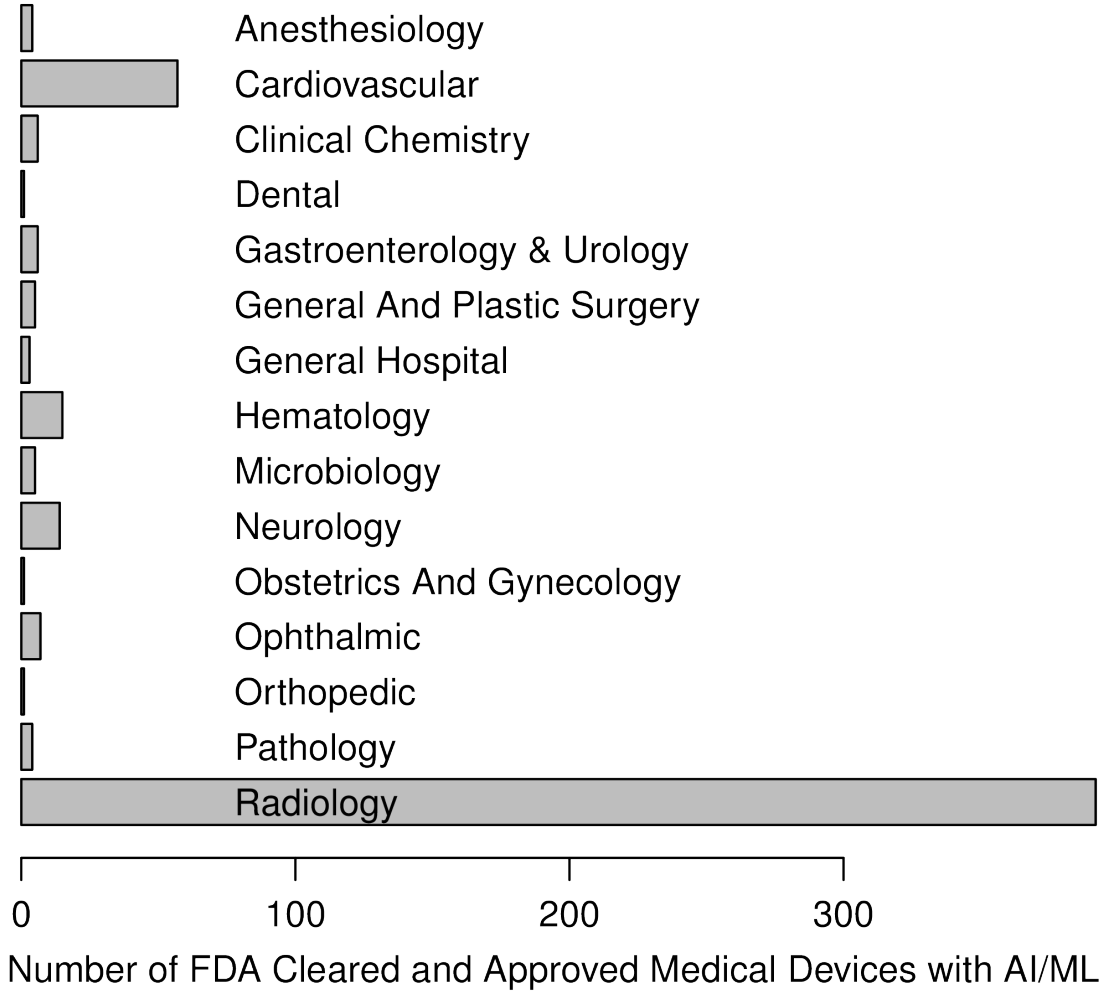
1400 m²

DIDSR Lab
and facilities



The Rise of AI/ML



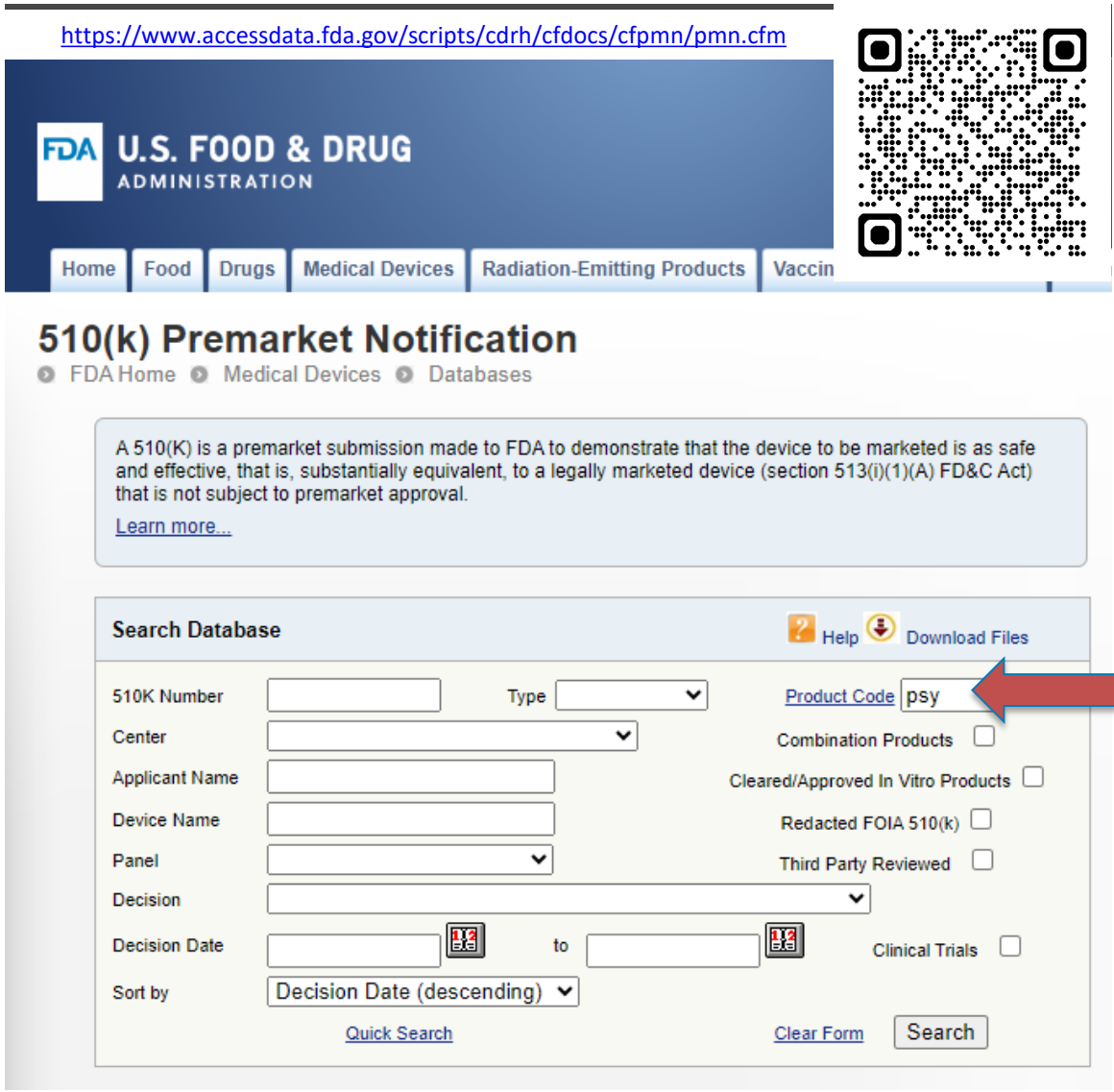


https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices

The Emergence of Digital and Computational Pathology

- Product Codes
  - **PSY**: Whole Slide Imaging System
  - **QKQ**: Digital Pathology Image Viewing And Management Software
  - **PZZ**: Digital Pathology Display
- 510(k) database
  - Search product codes, see devices

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm



The Emergence of Digital and Computational Pathology

- New cleared devices
  - Standalone displays
  - Standalone viewers
  - Standalone scanners

  … are creating interoperability

- Two most recent devices use images conformant to the DICOM standard
  - Scanner: Aperio GT 450 Dx
  - Viewer: Sectra Digital Pathology Module

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm

FDA U.S. FOOD & DRUG ADMINISTRATION

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Toba

510(k) Premarket Notification

FDA Home ⊙ Medical Devices ⊙ Databases

1 to 12 of 12 Results
ProductCode: *psy* **Decision Date To:** *05/01/2024*

Results per Page 25

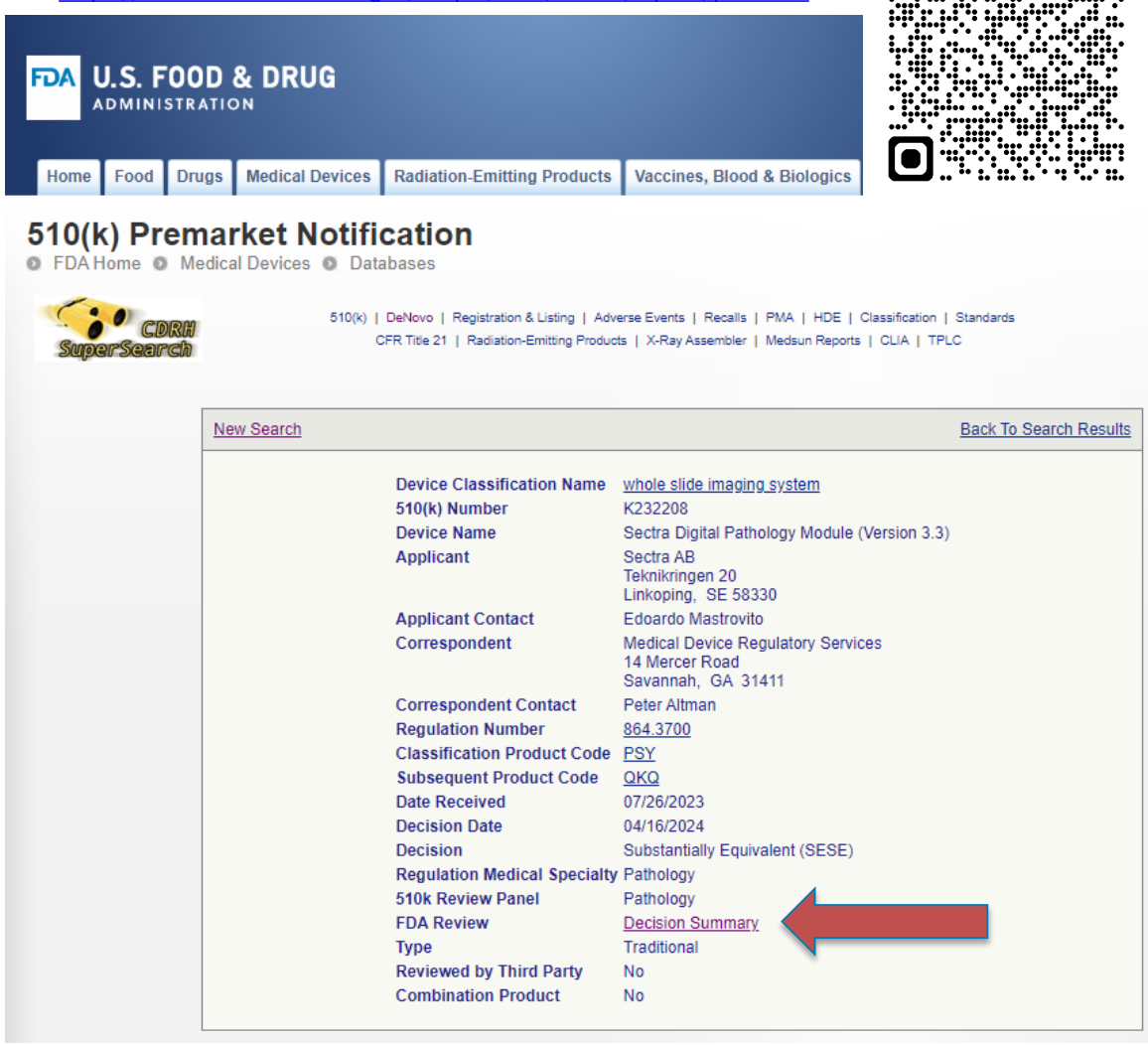
New Search | Export to Excel | Download Files | More About 510(k)

Device Name	Applicant	510(K) Number	Decision Date
Sectra Digital Pathology Module (Version 3.3)	Sectra AB	K232208	04/16/2024
Aperio Gt 450 Dx	Leica Biosystems Imaging, Inc.	K232202	04/16/2024
Concentriq Dx	Proscia, Inc.	K230839	02/08/2024
Nanozoomer S360md Slide Scanner System	Hamamatsu Photonics K.K.	K233027	12/22/2023
Nanozoomer S360md Slide Scanner System	Hamamatsu Photonics K.K.	K213883	09/27/2022
Dynamyx Digital Pathology Software	Inspirata, Inc.	K210811	03/01/2022
Philips Intellisite Pathology Solution	Philips Medical Systems Nederland B.V.	K203845	09/17/2021
Mdpc-8127	Barco NV	K203364	04/15/2021
Fullfocus	Paige.AI, Inc	K201005	07/15/2020
Philips Intellisite Pathology Solution	Philips Electronics Nederland B.V.	K192259	09/20/2019
Aperio At2 Dx System	Leica Biosystems Imaging, Inc.	K190332	05/20/2019
Philips Intellisite Pathology Solution	Philips Medical Systems Nederland B.V.	K172174	10/04/2017

The Emergence of Digital and Computational Pathology

- Decision Summary
  - IFU: Indications for Use
  - Describes the device
  - Intended population
  - Evidence supporting decision, including device performance

https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm



The Emergence of Digital and Computational Pathology

- 510(k) devices point to predicates
  - "Substantially equivalent"
  - Class II

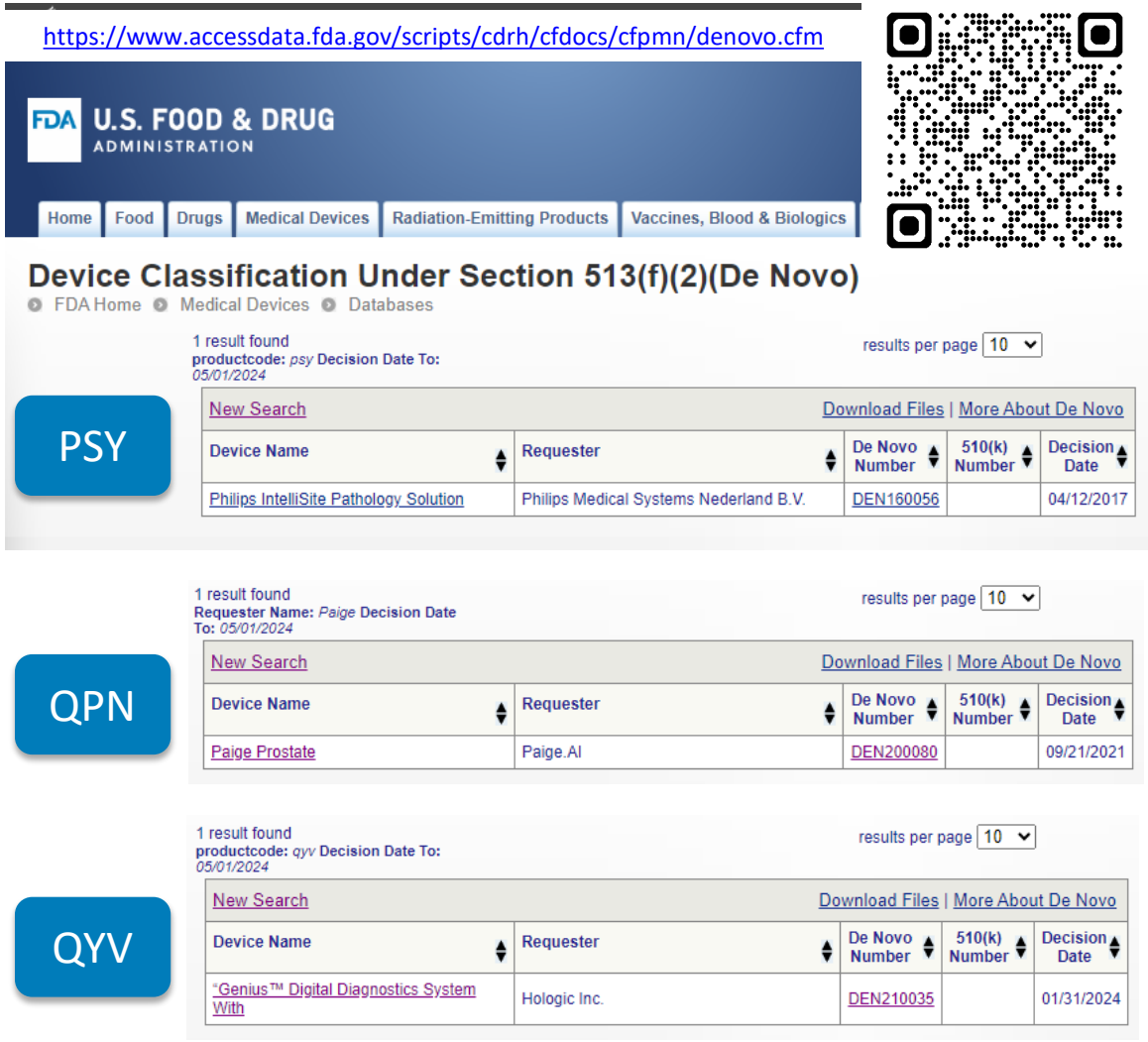
- De Novo devices are first-of-a-kind devices
  - Predicates for future devices
  - Define "special controls"

    = regulatory requirements for class II devices

  - **QPN**: Software Algorithm Device To Assist Users In Digital Pathology

  - **QYV**: Digital Cervical Cytology Slide Imaging System With Artificial Intelligence Algorithm

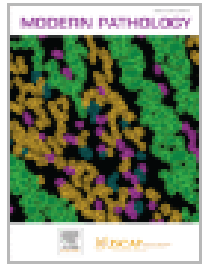
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/denovo.cfm



ELSEVIER

Modern Pathology

Volume 37, Issue 4, April 2024, 100439



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

Research Article

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

Katherine Elfer [a b], Emma Gardecki [a], Victor Garcia [a], Amy Ly [c], Evangelos Hytopoulos [d], Si Wen [a], Matthew G. Hanna [e], Dieter J.E. Peeters [f g], Joel Saltz [h], Anna Ehinger [i], Sarah N. Dudgeon [j], Xiaoxian Li [k], Kim R.M. Blenman [l m], Weijie Chen [a], Ursula Green [n], Ryan Birmingham [a n], Tony Pan [n], Jochen K. Lennerz [o], Roberto Salgado [p q], Brandon D. Gallas [a]

"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

- Datasets are plentiful, but reporting is inconsistent
- Reporting standards are being adapted for AI use in studies
- Inspired by Wahab et al.
- Checklist

equator network — Enhancing the QUAlity and Transparency Of health Research

THE JOURNAL OF PATHOLOGY Clinical Research Open Access — A Journal of The Pathological Society — Understanding Disease – Guiding Therapy

Original Article | Open Access

Semantic annotation for computational pathology: multidisciplinary experience and best practice recommendations

Noorul Wahab, Islam M Miligy, Katherine Dodd, Harvir Sahota, Michael Toss, Wenqi Lu, Mostafa Jahanifar, Mohsin Bilal, Simon Graham, Young Park, Giorgos Hadjigeorghiou, Abhir Bhalerao, Ayat G Lashen, Asmaa Y Ibrahim, Ayaka Katayama, Henry O Ebili, Matthew Parkin, Tom Sorell, Shan E Ahmed Raza, Emily Hero, Hesham Eldaly, Yee Wah Tsang, Kishore Gopalakrishnan, David Snead, Emad Rakha, Nasir Rajpoot, Fayyaz Minhas ... See fewer authors

First published: 10 January 2022 | https://doi.org/10.1002/cjp2.256 | Citations: 9

"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

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Study Component	Explanation
1. Objectives	Project objectives, dataset use case (training, testing models), degree of annotation, and patient population.
2. Data Dictionary	Training materials and reference documents(s) describing image features, anatomic/biological context, and details on annotations: • Types of annotation, constructs
3. Study Design	Specify the study design • Number of annotators, number of cases, number of annotators per case. • Randomization methods. Adjudication and consensus methods.
4. Annotation Methods	Determine how annotators will encounter the data and what tools will be used to access and view the images.
5. Image Curation	Specify annotator, patient, and image sampling methods for the entire study and individual sub-groups of a study.
6. Annotators	Define annotators: number of total annotators, number of annotators per case, qualifications (training and requirements), and how they were recruited.
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.

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7. Quality Review	

1. Define Objectives

High Throughput Truthing (HTT) Project

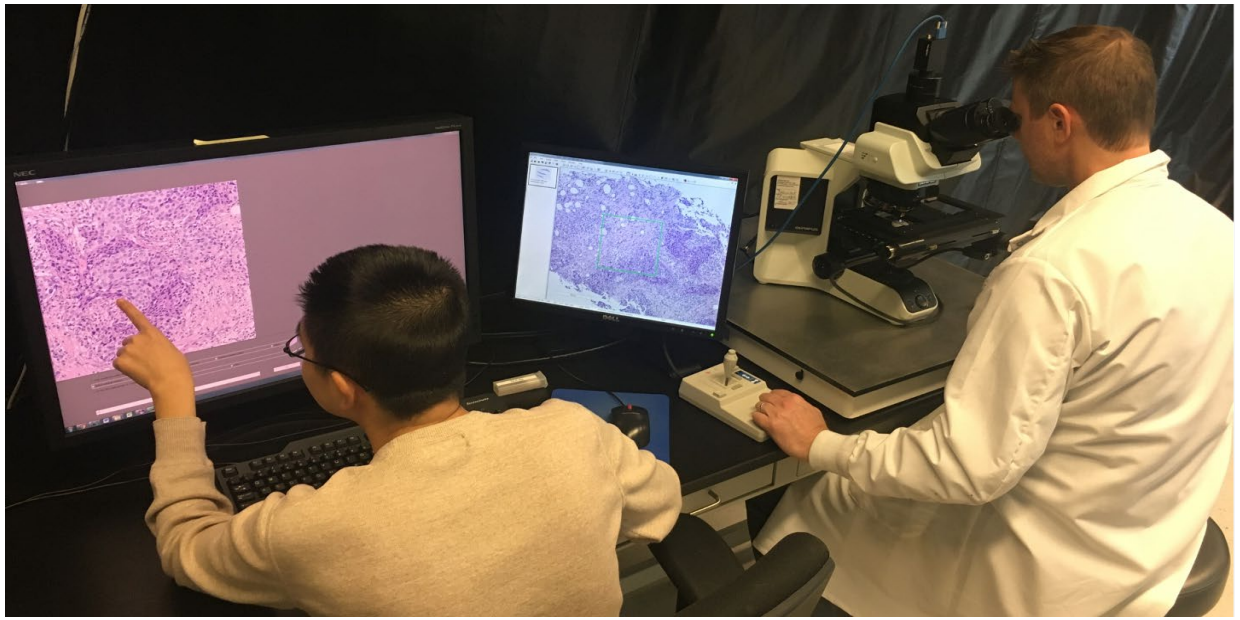
- **What**: a multi-stakeholder, multi-disciplinary project led by scientists at the FDA/CDRH/Division of Imaging, Diagnostics, and Software Reliability.

- **Goal**: Create a pathology dataset that is fit for a regulatory purpose which will serve as a proof-of-concept example for the AI & medical imaging communities.

CLEARR-AI For HTT

1. Define Objectives

- 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

1. Define Objectives

Patient Population

- Inclusion Criteria
  - Core biopsies of triple negative breast cancer (TNBC: ER/PR/HER2 negative)
  - Slides that have been stained with H&E within the last 7 years
- Exclusion Criteria
  - Tissue collected after administration of any therapy (e.g., neoadjuvant, chemotherapy, radiation therapy).

Metadata

Patient Features	Specimen Features	WSI Features
Age	Specimen Collection Site	Image resolution
Sex	Slide Preparation Site	Scanner make
Race	Slide Scanning Site	Scanner model
Ethnicity		Numerical aperture
Breast Cancer Stage		Objective magnification

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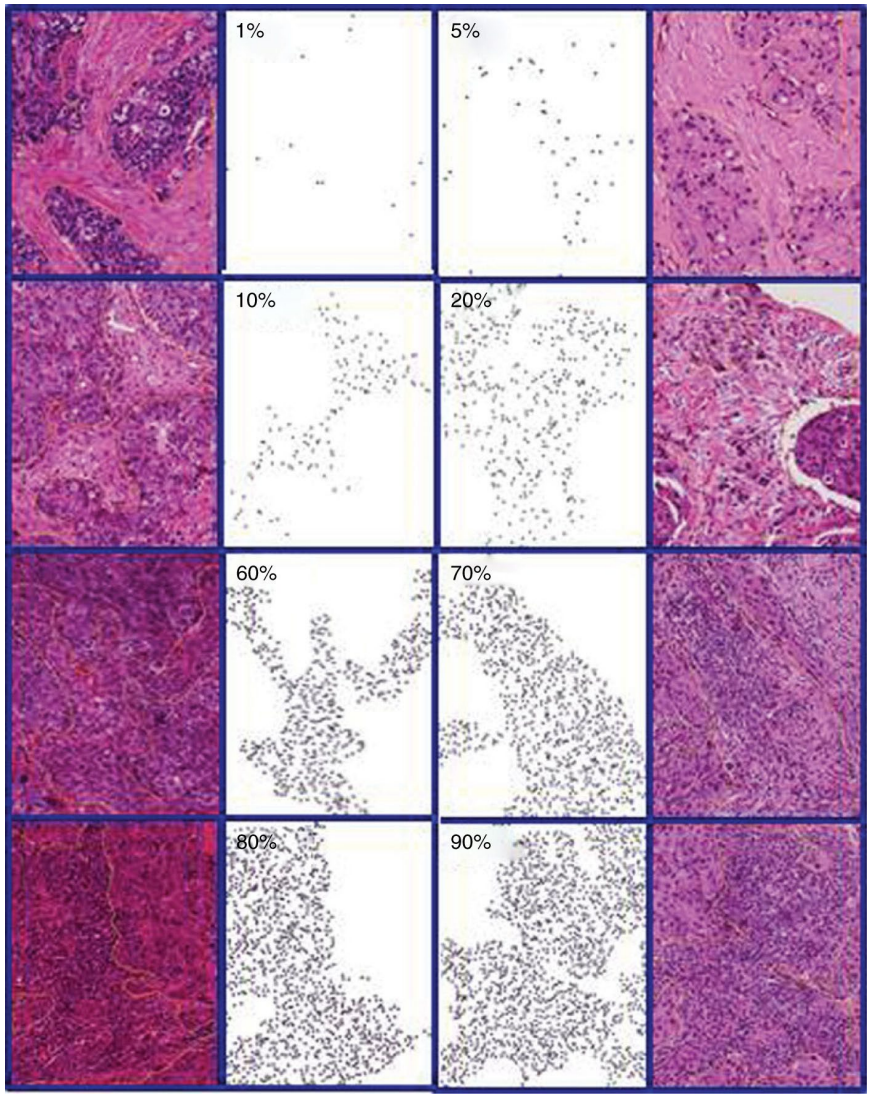
2. Data Dictionary

- **Percent Tumor Associated Stroma**

$$= \left(\frac{\text{Area of Tumor-Associated Stroma}}{\text{Area of Entire ROI}}\right) \times 100\%.$$

- **sTILs Density**

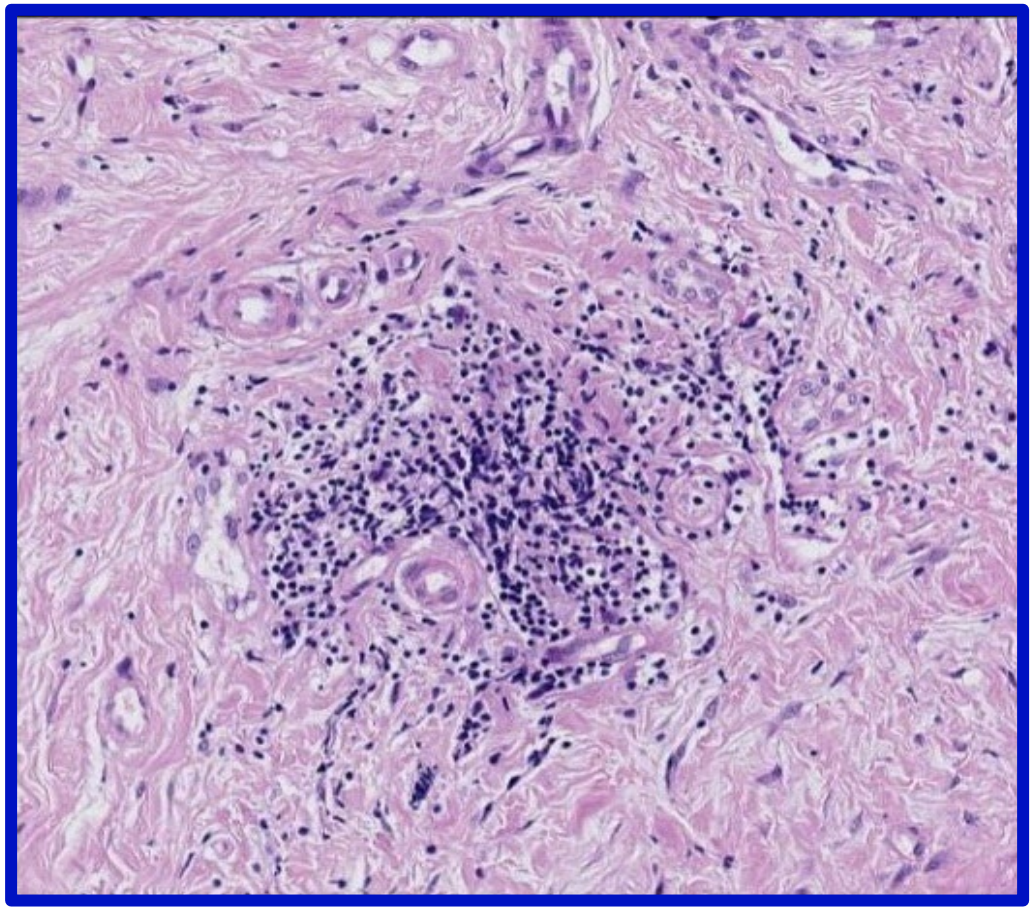
$$= \left(\frac{\text{Area of Tumor-Infiltrating Lymphocytes}}{\text{Area of Tumor-Associated Stroma}}\right) \times 100\%.$$



2. Data Dictionary

- ROI type qualitative variable
  - "Evaluable for sTILs"
  - "Not Evaluable for sTILs"

- Pitfalls – challenges in sTILs assessment
  - Exclusions
  - Mimics
  - Challenging context



sTILs in Breast Cancer

2. Data Dictionary

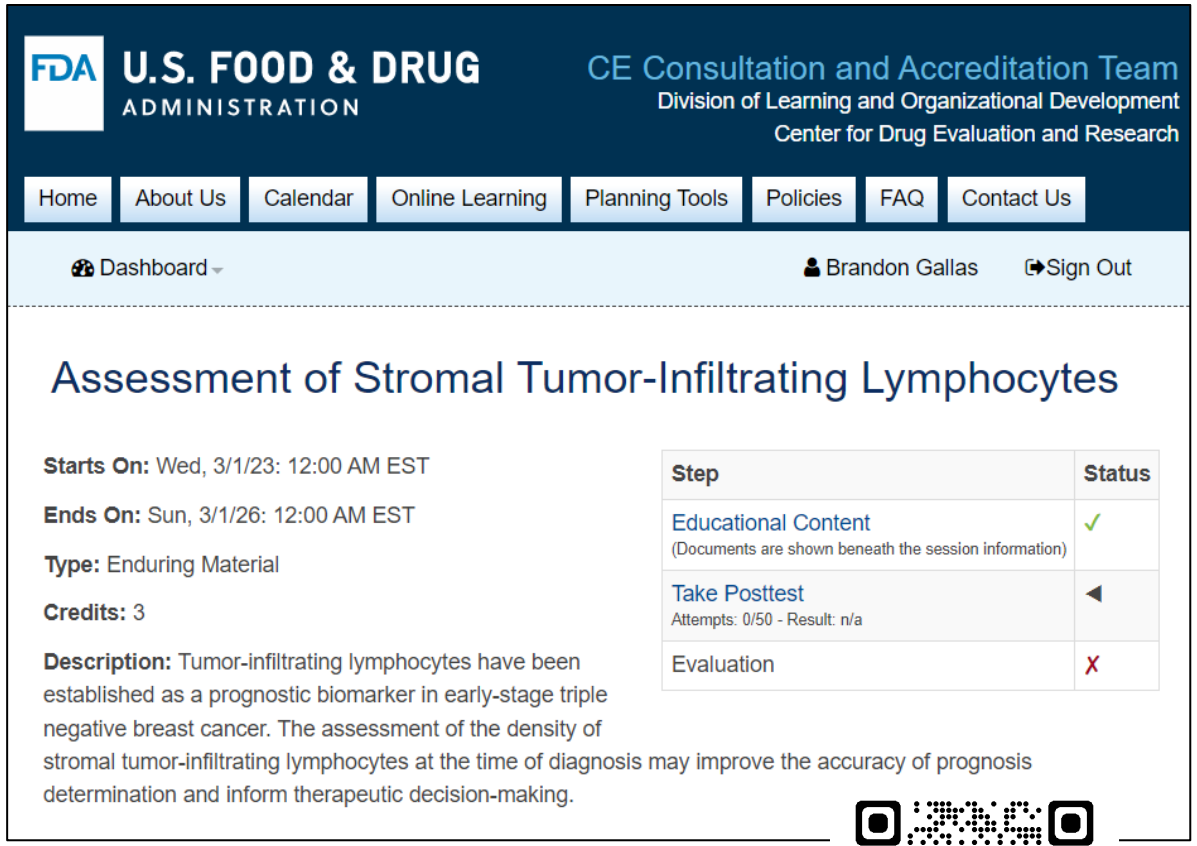
Objectives

- 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

CME Course

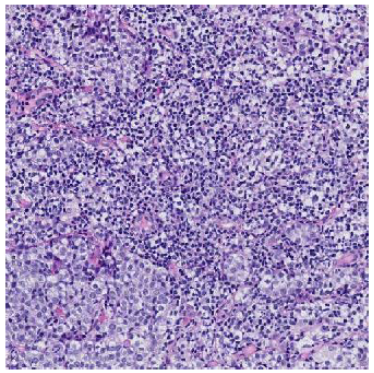


https://ceportal.fda.gov/

192 participants

2. Data Dictionary

Reference Document



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

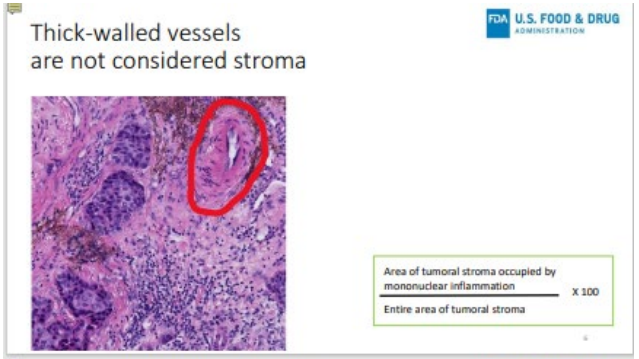
Mean Percent Tumor-Associated Stroma: 51.7

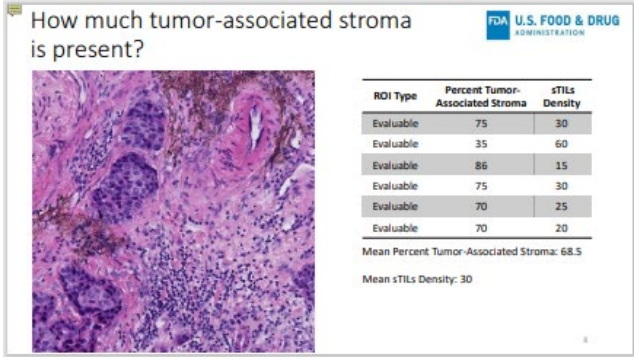
Mean sTILs Density: 88.7

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.

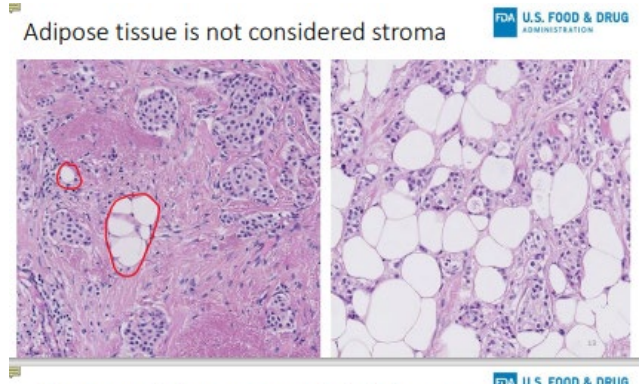
Pitfalls: In regions where the sTILs density is very high, the underlying stroma may be obscured. Non-lymphocytes with small nuclei may be confused for lymphocytes.

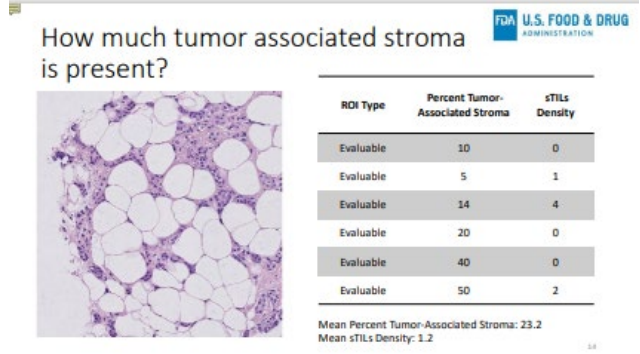
2





Example Pitfalls





CLEARR-AI For HTT

2. Data Dictionary

Interactive Training With Feedback

ROI Type:

- (●) Evaluable for sTILs
- ( ) Not Evaluable for sTILs

50%

% Tumor-Associated Stroma

5%

sTILs Density

Expert Panel Annotations:

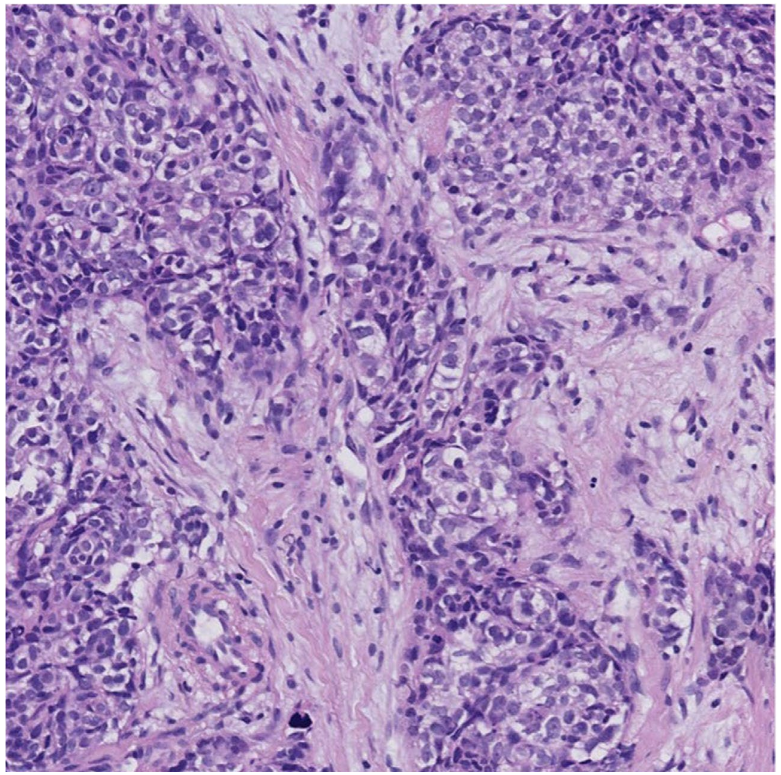
ROI Type	% Tumor-Associated Stroma	% sTIL Density
Evaluable	30	5
Evaluable	40	9
Evaluable	50	7
Evaluable	50	3
Evaluable	40	1
Evaluable	50	5

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.



2. Data Dictionary

cancers

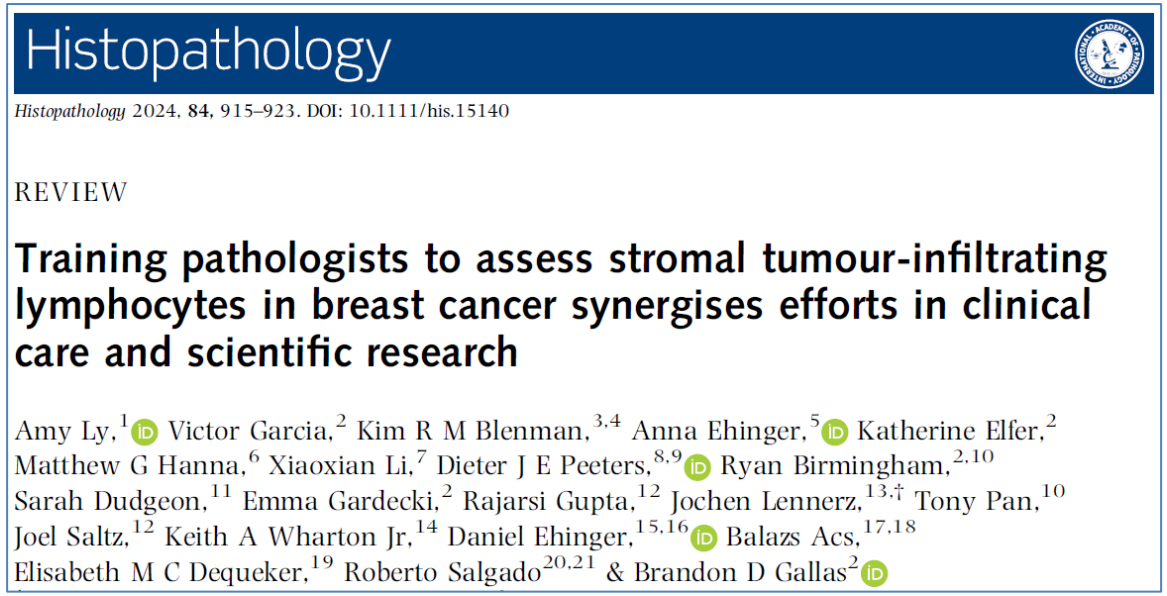
MDPI

Article

Development of Training Materials for Pathologists to Provide Machine Learning Validation Data of Tumor-Infiltrating Lymphocytes in Breast Cancer

Victor Garcia [1,*], Katherine Elfer [1,2], Dieter J. E. Peeters [3,4,5], Anna Ehinger [6], Bruce Werness [7,8], Amy Ly [9], Xiaoxian Li [10], Matthew G. Hanna [11], Kim R. M. Blenman [12,13], Roberto Salgado [14,15] and Brandon D. Gallas [1]

https://www.mdpi.com/2072-6694/14/10/2467



Histopathology

Histopathology 2024, **84**, 915–923. DOI: 10.1111/his.15140

REVIEW

Training pathologists to assess stromal tumour-infiltrating lymphocytes in breast cancer synergises efforts in clinical care and scientific research

Amy Ly,[1] Victor Garcia,[2] Kim R M Blenman,[3,4] Anna Ehinger,[5] Katherine Elfer,[2] Matthew G Hanna,[6] Xiaoxian Li,[7] Dieter J E Peeters,[8,9] Ryan Birmingham,[2,10] Sarah Dudgeon,[11] Emma Gardecki,[2] Rajarsi Gupta,[12] Jochen Lennerz,[13,†] Tony Pan,[10] Joel Saltz,[12] Keith A Wharton Jr,[14] Daniel Ehinger,[15,16] Balazs Acs,[17,18] Elisabeth M C Dequeker,[19] Roberto Salgado[20,21] & Brandon D Gallas[2]

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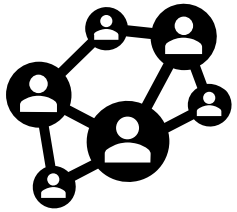
CLEARR-AI For HTT

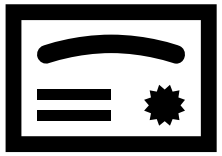
3. Study Design

Recruit Annotators



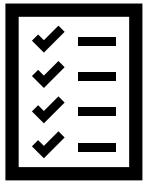
Crowdsource Pathologists

CME Course Completion



Annotators send in their CME certificate

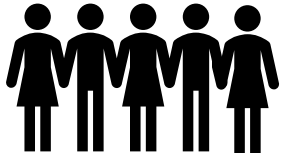
Pass Proficiency Test



Interactive training

- Test with feedback
- Proficiency test

Study Lead Assigns Batches



Study lead assigns 5 annotators per batch

- Work in progress: Statistical Analysis Plan
- Work in progress: Final size of dataset

1 Batch = 8 Slides = 80 ROIs

"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

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5. Image Curation	
6. Annotators	
7. Quality Review	

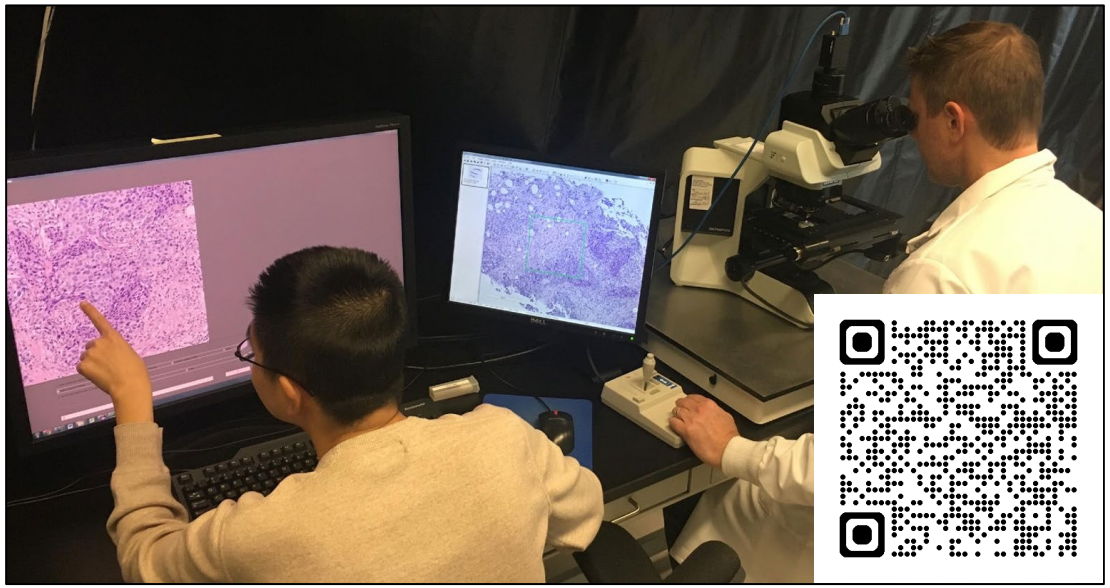
4. Annotation Methods

2 data collection platforms

Microscope: eeDAP

evaluation environment for Digital and Analogue Pathology

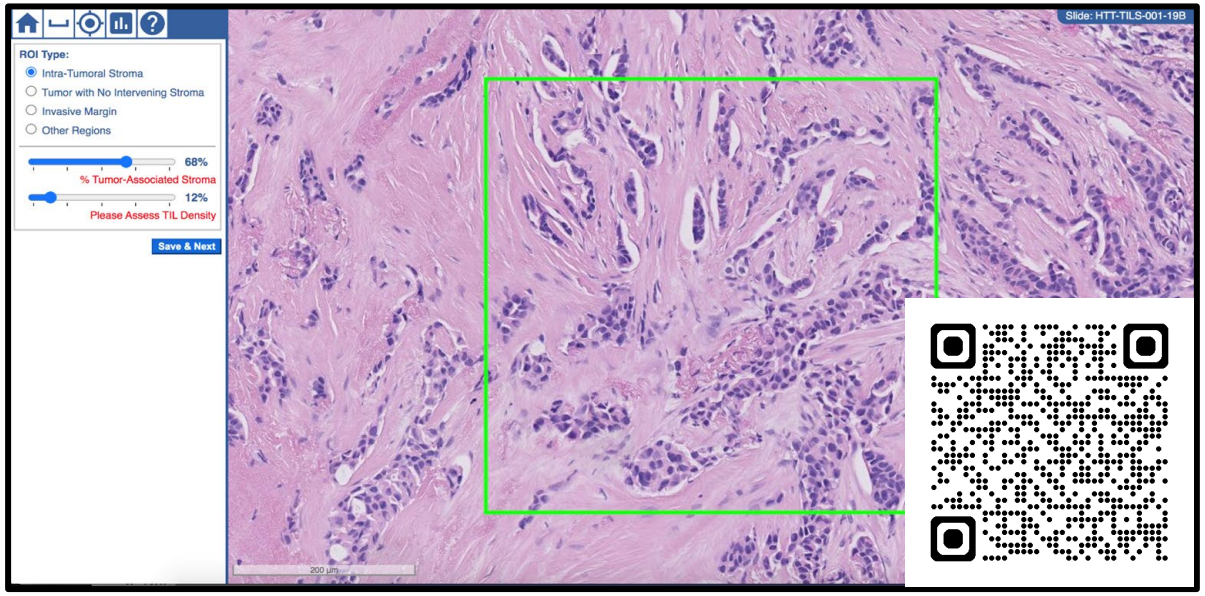
Open source: https://github.com/DIDSR/eeDAP



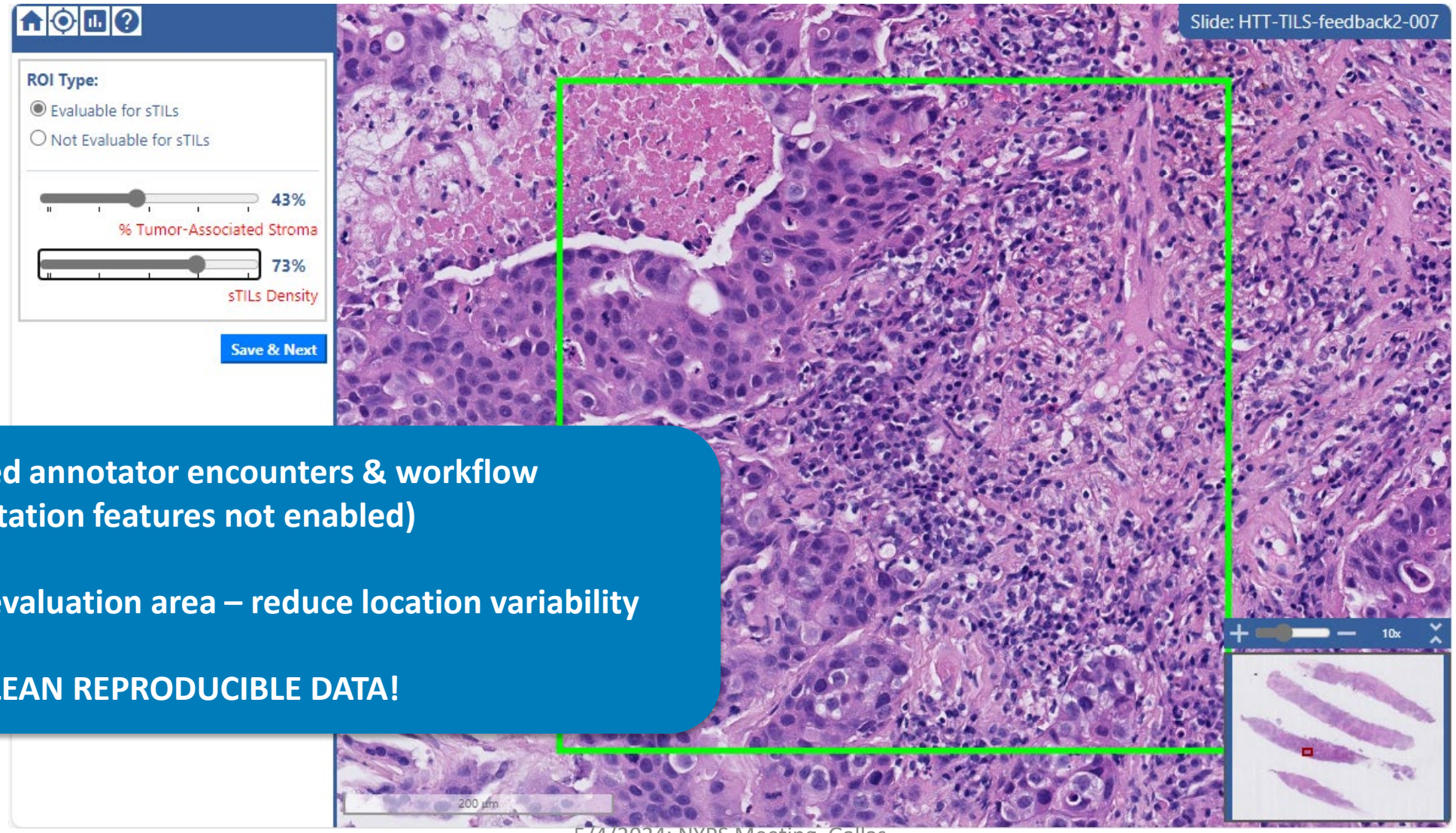
Digital: caMicroscope (caMic)

Open source: https://github.com/camicroscope

Look for specific "HTT" customizations of the software



4. Annotation Methods



Controlled annotator encounters & workflow (all annotation features not enabled)

Limited evaluation area – reduce location variability

WANT CLEAN REPRODUCIBLE DATA!

"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

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7. Quality Review	

5. Image Curation

Slide Sourcing Chart Review

Find patients that satisfy inclusion/exclusion.
Collect metadata. Prepare H&E slides.

↓

1 Patient : 1 Glass Slide
1 Whole Slide Image

Scan slides with an FDA cleared scanner.

↓

HTT Pathologists Select ROIs of Interest

Protocol provides instructions to
target diverse morphology and sTILs density.

↓

Batches of 8 Slides with 10 ROIs in Each Slide are Generated

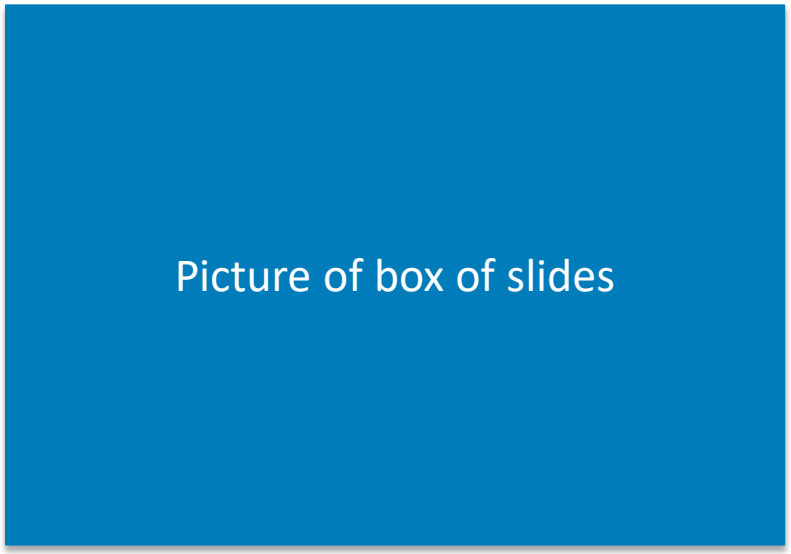
Algorithmic method to prioritize images
of underrepresented populations.

5. Image Curation

Slide Sourcing Chart Review

Find patients that satisfy inclusion/exclusion.
Collect metadata. Prepare slides.

- Emory School of Medicine
  - RCA approved
  - 90 slides contributed (on-going sourcing)
- Stony Brook Medicine
  - RCA approved
  - 64 slides contributed
- Yale School of Medicine
  - RCA approved
  - Slide sourcing to begin



5. Image Curation

1 Patient : 1 Glass Slide
1 Whole Slide Image

Scan slides with an FDA cleared scanner.

- Scanning site:
  - Department of Pathology at Ohio State University's Wexner Medical Center (OSU)

- Scanner Information
  - Make/Model: Aperio AT2 Dx
  - Resolution: 0.25 microns per pixel
  - Numerical aperture: 0.95 mm
  - Objective magnification: 40X equivalent

https://dmimedicalusa.com/product/aperio-at2-dx-system/

5. Image Curation

HTT Pathologists Select ROIs of Interest

Protocol provides instructions to target diverse morphology and sTILs density.

- Identify 10 ROIs per image
- First pass assessment of TILs and pitfalls
  - Used to prioritize images

Target diverse morphology and sTILs density

- Target high sTILs density
- Distribute ROIs across entire tissue.
- Numbers to select are guides.
  - Select 3 ROIs inside tumor with stroma
  - Select 2 ROIs at invasive margin if discernable with stroma
  - Select 2 ROIs inside tumor or at margin without stroma
  - Select 2 ROIs where there is no proximal tumor
  - Select 2 ROIs for each for the 16 pitfalls listed.

5. Image Curation

Batches of 8 Slides with 10 ROIs in Each Slide are Generated

Algorithmic method to prioritize images of underrepresented populations.

- Prioritize underrepresented populations with sort method
- Distribute cases into batches

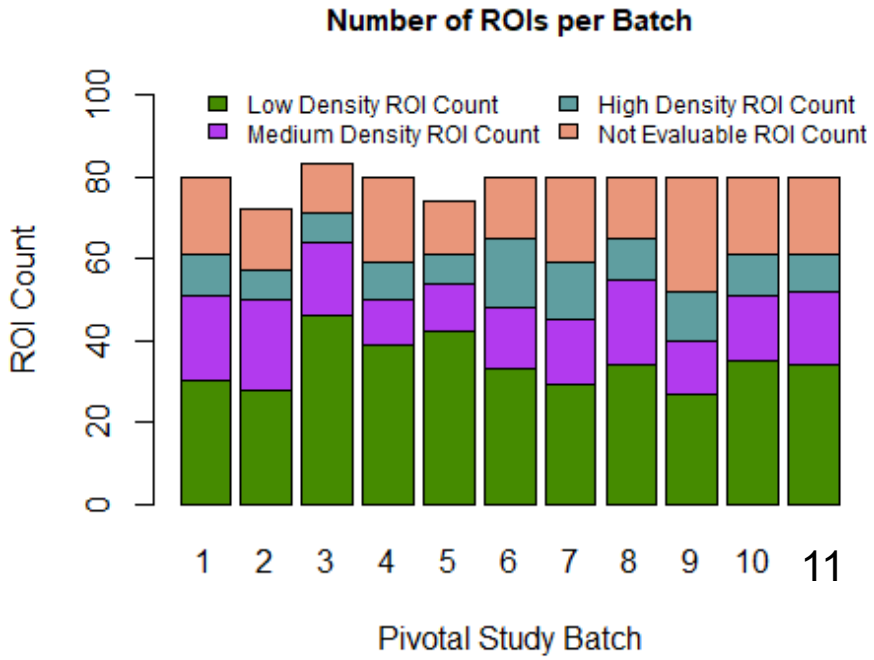
Sort Order

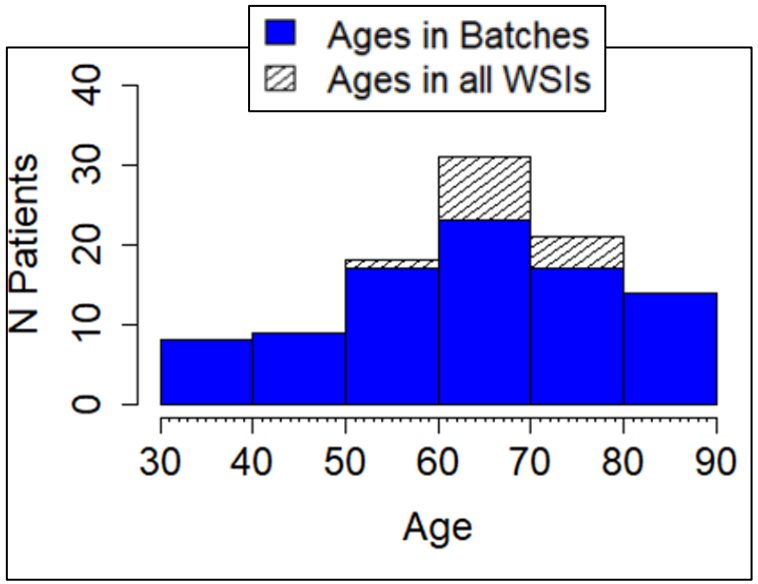
Points	Normalized Density Count Score	Race and Ethnicity Score	BCS, Age, Sex Score	Pitfall Score
2	$\frac{\text{High density count ROIs}}{\text{Total \# ROIs in WSIs}}$	Race ≠ White Ethnicity = Hispanic	BCS = III, IV Age ≤ 40 41 ≤ Age ≤ 50 81 ≤ Age ≤ 90 Sex ≠ F	- Rare pitfalls (≤2 cases) - Carcinoma In Situ, Ischemia - Sparse Distribution, Fibers - Over/Under Staining
1	$\frac{\text{Medium density count ROIs}}{\text{Total \# ROIs in WSIs}}$		BCS = I, II 51 ≤ Age ≤ 60 71 ≤ Age ≤ 80	- Semi-rare pitfalls (3-10 cases) - Benign Glands - Necrosis/Fibrin - Eosinophilia - Perinuclear Clearing - Crush Artifact
0	$\frac{\text{Low density count ROIs}}{\text{Total \# ROIs in WSIs}}$	Race = White Ethnicity = Not Hispanic	BCS = NA 61 ≤ Age ≤ 70 Sex = F	- Common pitfalls (>10 cases) - Adipocytes - Nerves/Vessels - Pyknotic Nuclei, Fibroblasts

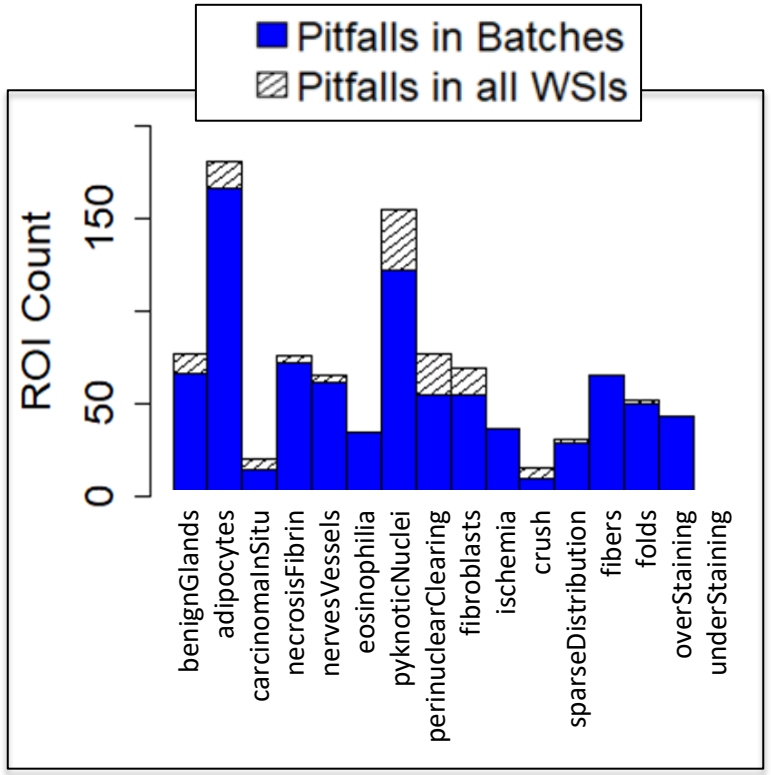
5. Image Curation

Batches of 8 Slides with 10 ROIs in Each Slide are Generated

Algorithmic method to prioritize images of underrepresented populations.







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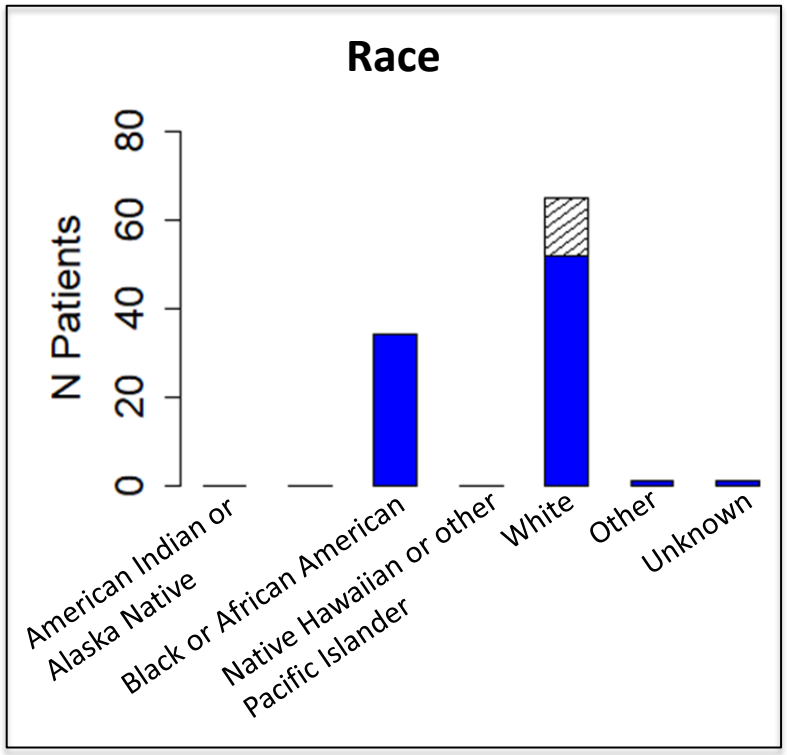
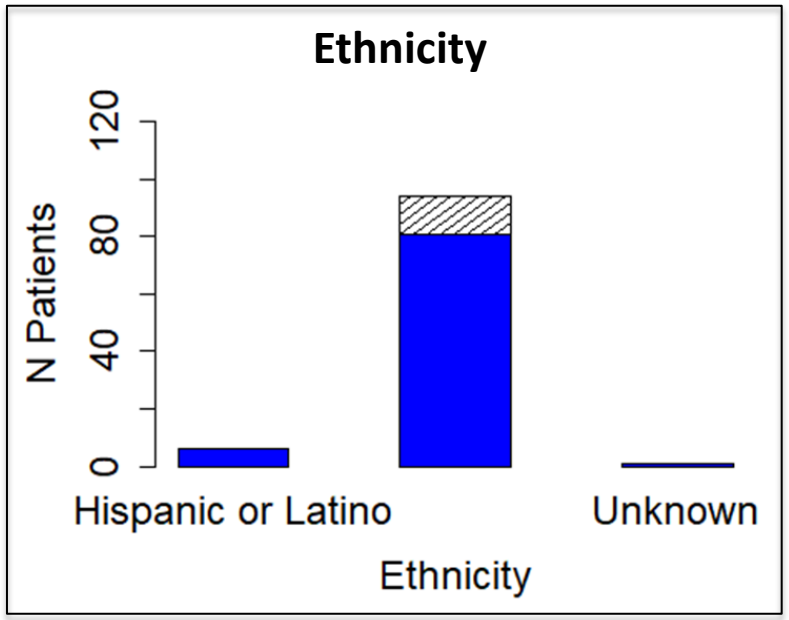
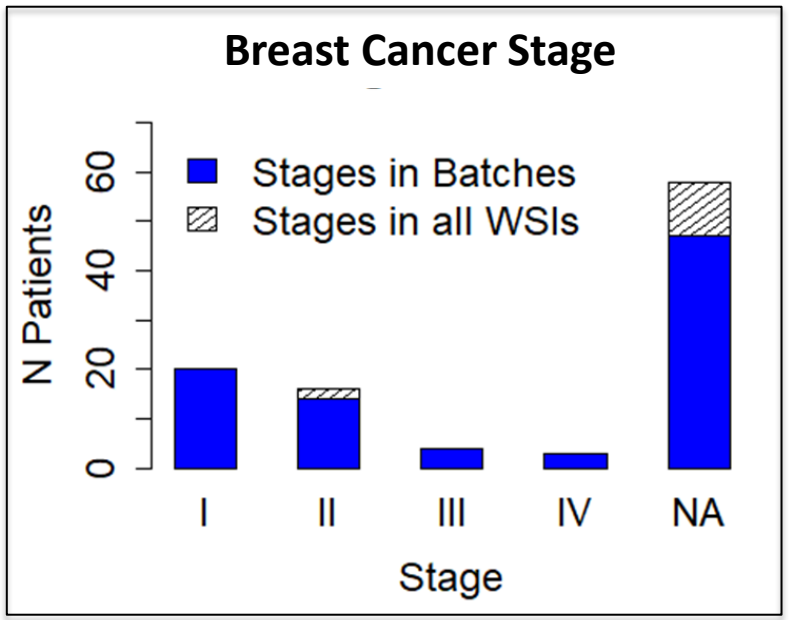
Algorithmic method to prioritize images of underrepresented populations.







Diversity in Race and Ethnicity is not great.
Breast cancer stage is unknown in approximately half the cases

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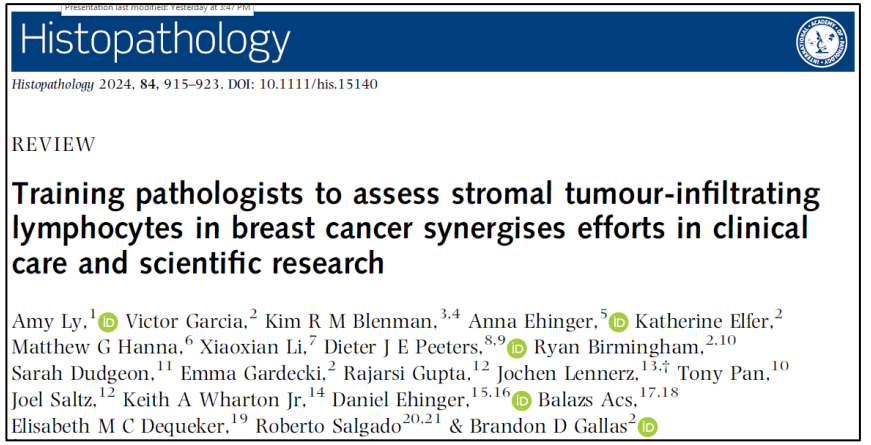
7. Quality Review	

6. Annotator Information

- **WHO**
  - Listservs, Social Media, Flyers, Hosting Platforms, Word-of-Mouth
  - Board Certified (or international equivalent) pathologists
  - Completed sTILs Assessment CME Course
  - Passed proficiency test

- Pathologist-specific performance reports
  - Describe agreement endpoints
  - Describe pass criteria
  - Feedback test includes reader and expert scores for every case



Histopathology

Histopathology 2024, **84**, 915–923. DOI: 10.1111/his.15140

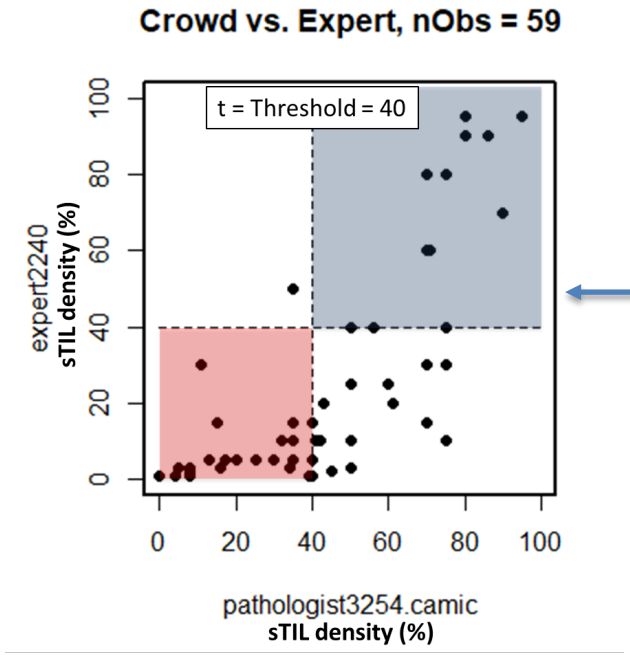
REVIEW

Training pathologists to assess stromal tumour-infiltrating lymphocytes in breast cancer synergises efforts in clinical care and scientific research

Amy Ly,[1] Victor Garcia,[2] Kim R M Blenman,[3,4] Anna Ehinger,[5] Katherine Elfer,[2] Matthew G Hanna,[6] Xiaoxian Li,[7] Dieter J E Peeters,[8,9] Ryan Birmingham,[2,10] Sarah Dudgeon,[11] Emma Gardecki,[2] Rajarsi Gupta,[12] Jochen Lennerz,[13,†] Tony Pan,[10] Joel Saltz,[12] Keith A Wharton Jr,[14] Daniel Ehinger,[15,16] Balazs Acs,[17,18] Elisabeth M C Dequeker,[19] Roberto Salgado[20,21] & Brandon D Gallas[2]

https://onlinelibrary.wiley.com/doi/10.1111/his.15140

6. Annotator Information



Crowd Reader vs. Expert 1 Agreement

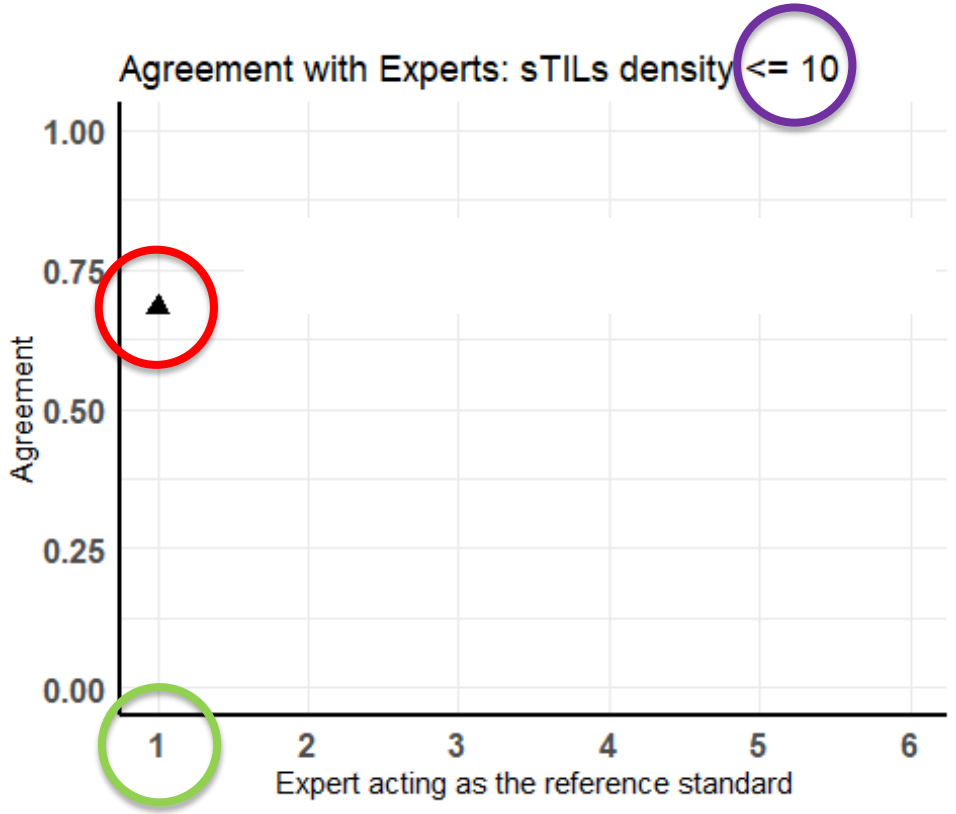
- Apply threshold
- Create 3x3 table
- Determine rates of agreement
  - GT threshold
  - LE threshold
  - Not Evaluable

Threshold = 10	reader. NotEvaluable	reader. LE	reader. GT	Fraction Agree	Rate Agree
expert. GT	0	3	11	11/14	0.786
expert. LE	3	15	4	15/22	0.682
expert. NotEvaluable	0	0	0	0	NA

6. Annotator Information

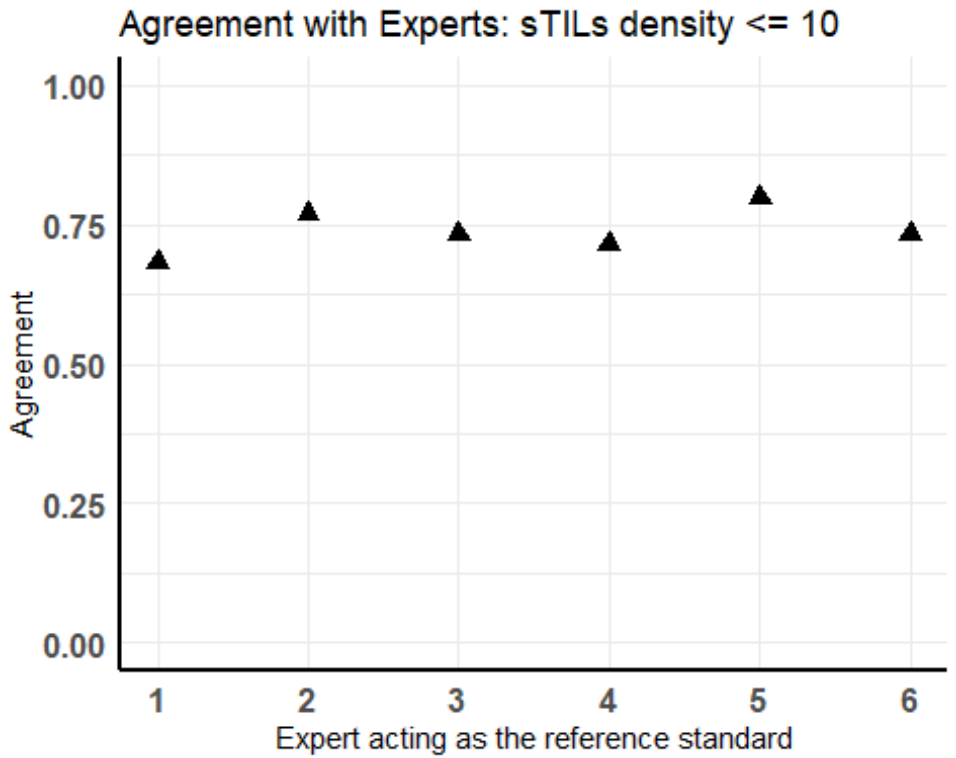
Crowd Reader vs. Expert 1 Agreement

Threshold = 10	reader. NotEvaluable	reader. LE	reader. GT	Fraction Agree	Rate Agree
expert. GT	0	2	11	11/13	0.846
expert. LE	3	15	4	15/22	0.682
expert. NotEvaluable	0	0	0	0	NA



6. Annotator Information

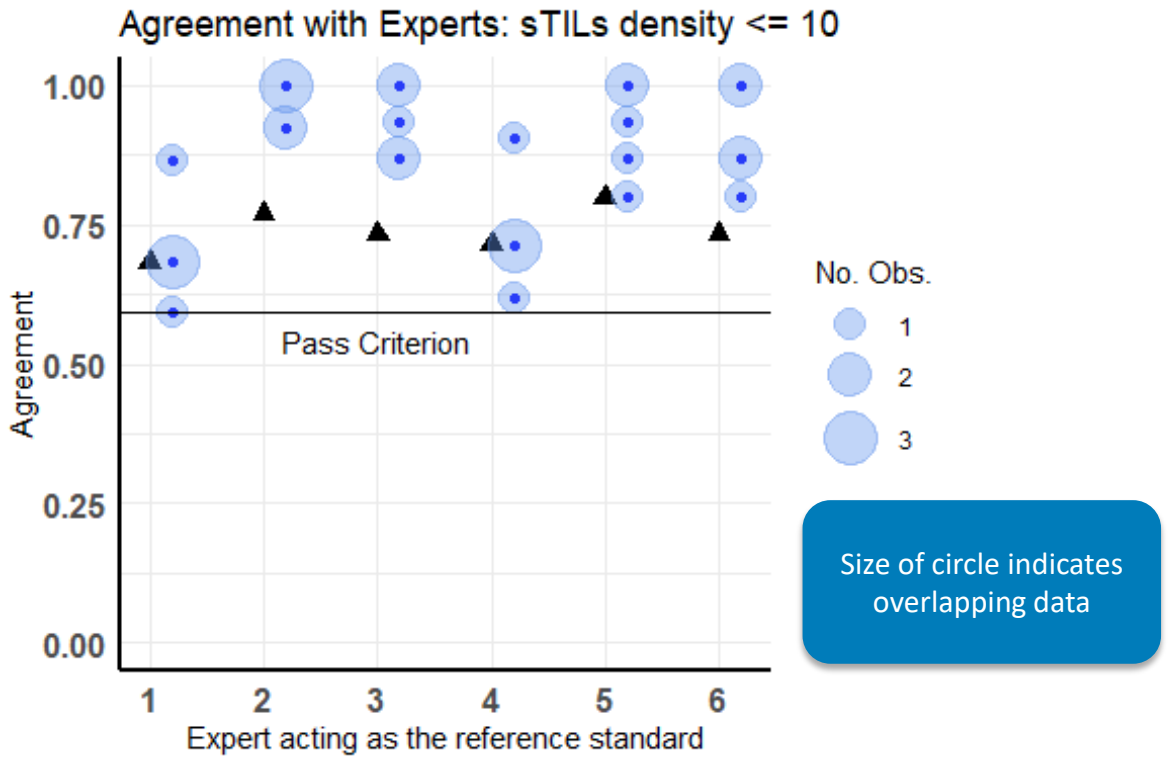
- Black Triangles
  - Reader vs. Experts Agreement
  - 6 experts



6. Annotator Information

- Black Triangles
  - Reader vs. Experts Agreement
- Blue Circles:
  - Experts vs. Experts Agreement

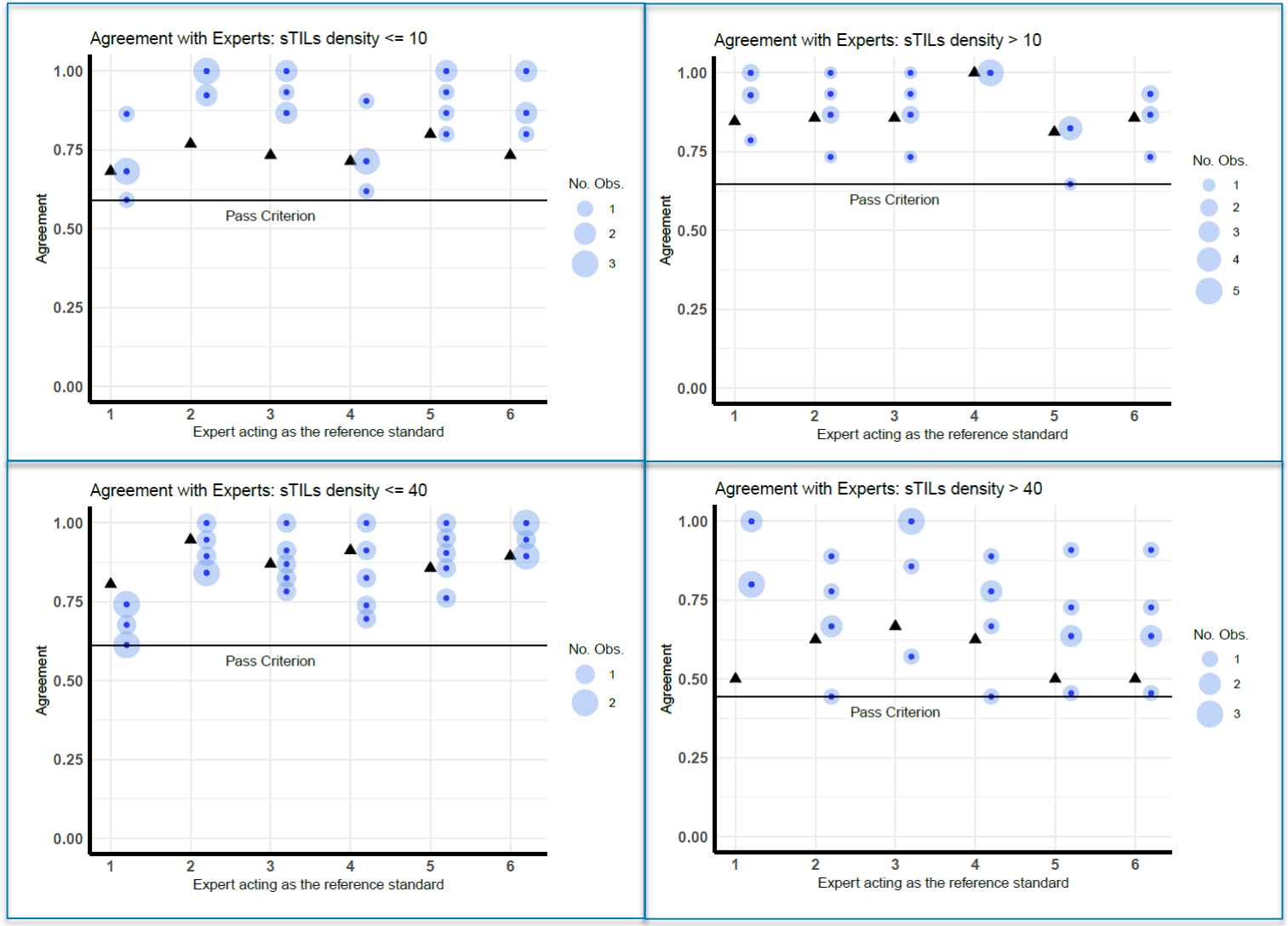
Pass Criterion = lowest expert-expert agreement



6. Annotator Information

- Black Triangles
  - Reader vs. Experts Agreement
- Blue Circles:
  - Experts vs. Experts Agreement

- Four criteria
  - sTILs density ≤ 10
  - sTILs density > 10
  - sTILs density ≤ 40
  - sTILs density > 40



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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.

Status of HTT Pivotal Study

- **6/2023**: Training launched
  (CME & Interactive Training)
  - 223 participants have taken the CME course
- **6/2023**: Pivotal Study launched
- **8/2023**: New Website launched

- **52**: Pathologist Inquiries
- **6**: Pathologists passed training and have provided pivotal study annotations
- Time for training and annotating is a hurdle
  - Everyone is very busy
- **156** cases
  - Still sourcing
- **111** cases curated
  - First pass ROI selection
- **88** cases batched for pivotal study
- **2500** ROIs annotated

Journal of Pathology
J Pathol 2023
Published online 4 October 2023 in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/path.6208

INVITED PERSPECTIVE

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

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

Steven Hart[1], Victor Garcia[2], Sarah N Dudgeon[3], Matthew G Hanna[4], Xiaoxian Li[5], Kim RM Blenman[6,7], Katherine Elfer[2], Amy Ly[8], Roberto Salgado[9,10], Joel Saltz[11], Rajarsi Gupta[11], Evangelos Hytopoulos[12], Denis Larsimont[13], Jochen Lennerz[14] and Brandon D Gallas[2*]

Regulatory Science Tools

Medical Device Development Tools

- Voluntary program for any stakeholder – high bar
- HTT dataset may reduce burden to sponsors
  - *"We used the MDDT dataset and our algorithm performance was …"*
- HTT dataset may reduce burden to FDA
  - Qualify data and analysis methods once to support multiple sponsors

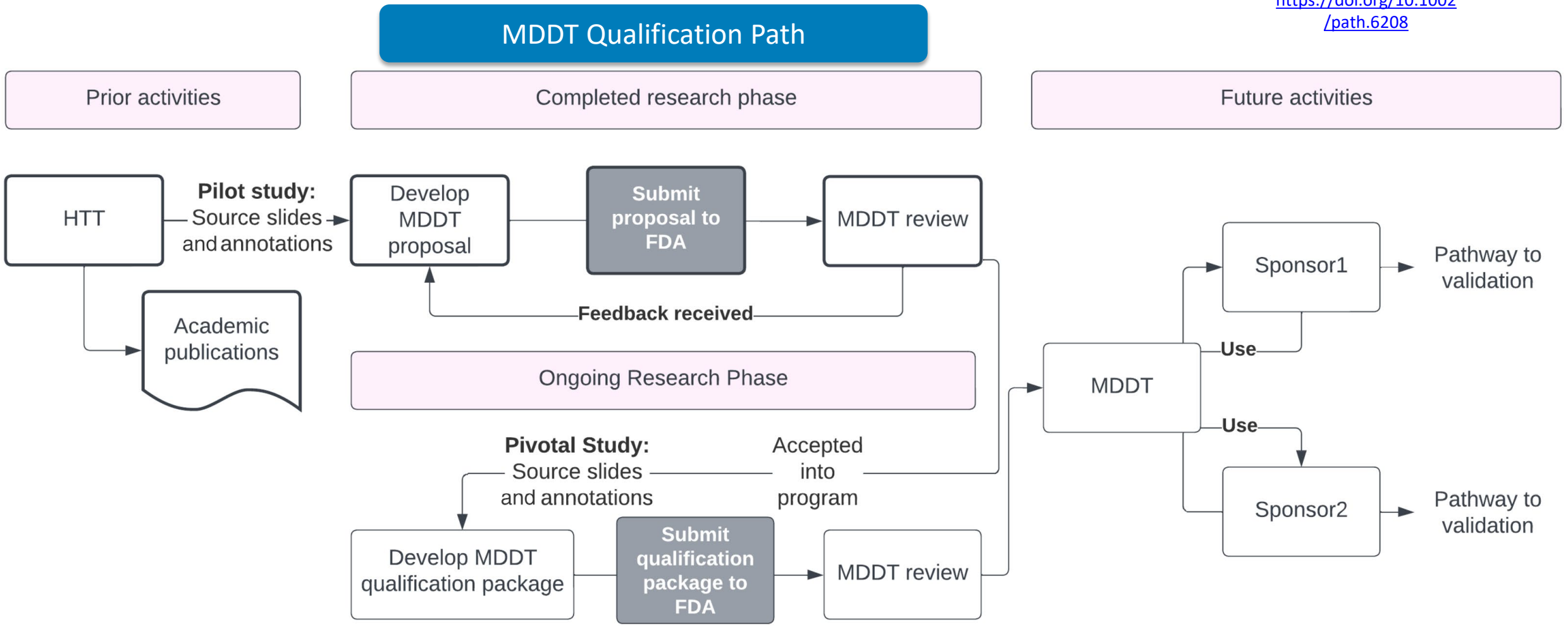
Regulatory Science Tool Catalog

- Created by CDRH scientist to address gaps and needs

"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



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

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

- Feedback from MDDT Reviewers
  - Identifies deficiencies in the submission

- Q: To power our study, what are the FDA's recommendations on the number of sites, slides per site, and readers per slide?
  - The samples (cases and pathologists) should be representative of the intended populations.
  - The number of pathologists and cases should target certain precision of the truthing.

- Q: Should we expand the collected slides to include non-TNBC cases,which could facilitate data collection?
  - The Agency recommends that TNBC cases be used.

- Include a detailed description of devices used that are not FDA qualified or cleared to collect pathologist annotations.

Related Activities

Pathology Innovation Collaborative Community

PIcc – "Pie See See"

- FDA participates in PIcc
  - https://pathologyinnovationcc.org/

- Look for Joe!

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

- Regulatory Landscape Survey

https://qualtricsxmq9n4cl9pg.qualtrics.com/jfe/form/SV_4Sf41xG9Gm6XQMu

Related Activity: FNIH BC-CSC:

Foundation for NIH Biomarkers Consortium Cancer Steering Committee

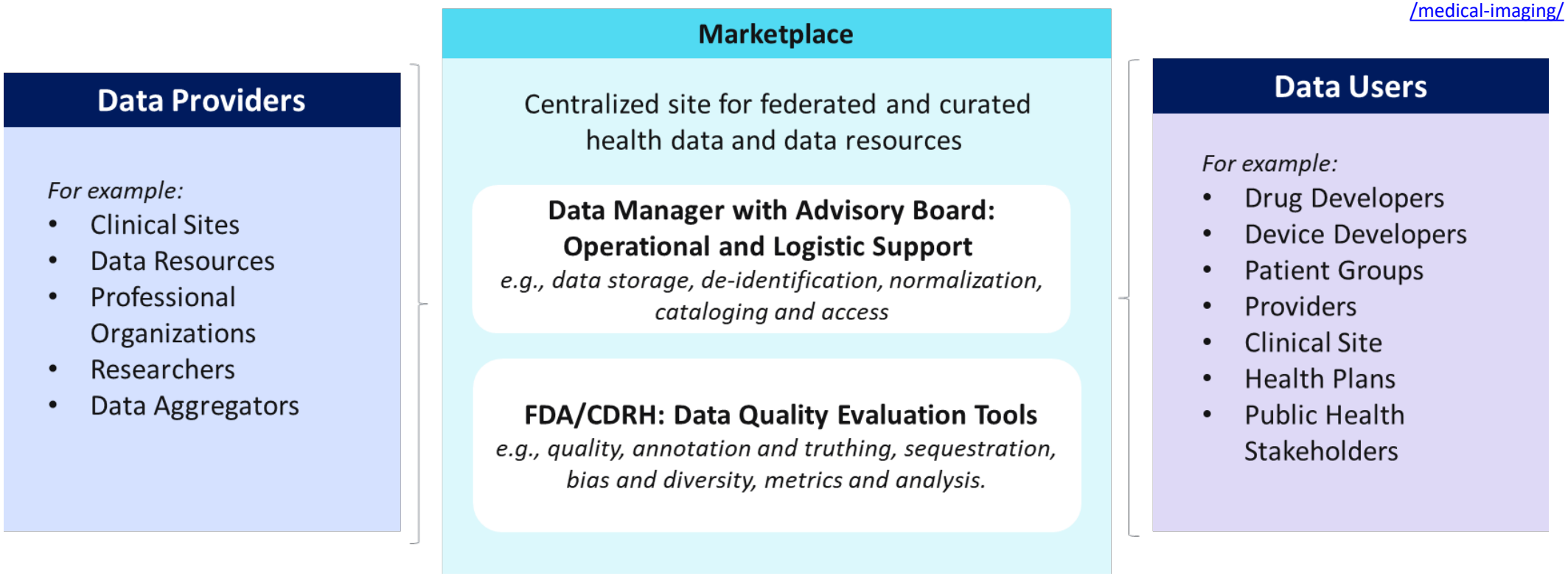
- PIcc coordinating project pitch to FNIH
  - New PIcc members welcome to the effort
- Presented vision to create a pipeline of real-world data for validating AI models
  - FNIH meeting 11/2023
  - Summary: https://fnih.org/our-programs/biomarkers-consortium-csc-scientific-symposium/
- Currently producing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

ARPA-H FDA/CDRH Medical Imaging Data Marketplace

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

- Feedback and Information
  - midm@arpa-h.gov

https://investorcatalysthub.org/medical-imaging/



Summary

- Digital and computational pathology regulatory landscape
  - Databases and decision summaries
  - Useful for device users and device developers
  - Interoperability growing with new standalone submissions
- HTT project overview
  - CLEARR-AI provides reporting structure
  - Demonstration project: Deep Dive
  - Prevalence of TNBC patients is low, difficult to source
  - Pathologist qualifications to be reference standard
    - TILs is a new and challenging biomarker
    - Training is critical
  - Feedback from FDA reviewers
- HTT Deliverables
  - Protocols and methods:
    slide sourcing, chart review,
    ROI selection and ROI prioritization
    - Paper submitted
  - Proficiency test performance assessment and criteria
    - Examples available and more to come
  - Data-collection tools
    - Controlled methods
    - Open source

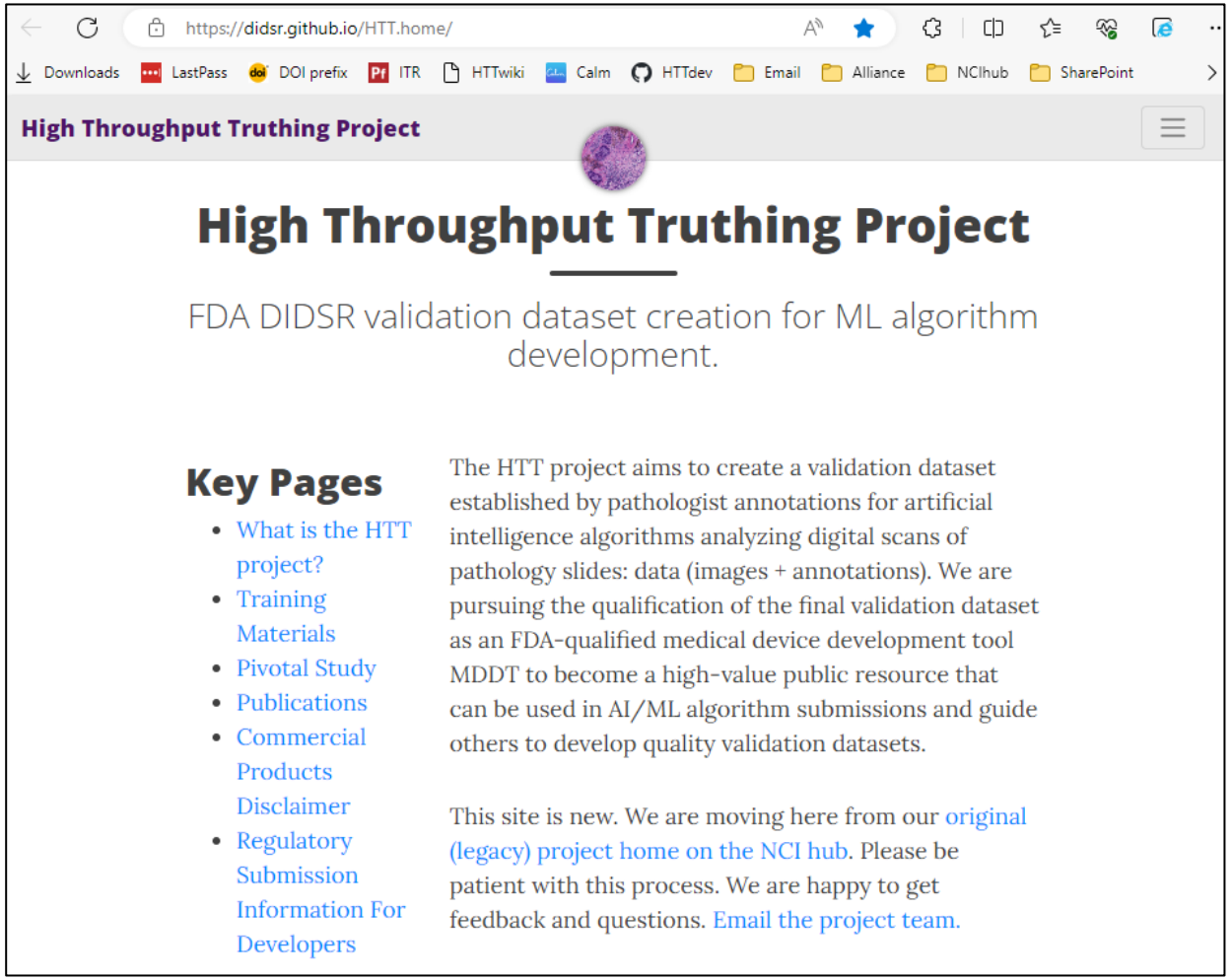
Parting Message

@Pathologists

- CME and interactive training available
- **Recruiting pathologists:** digital mode
- **Recruiting pathologists:** microscope mode
  - Yale University, School of Medicine
  - Dr. Kim Blenman
  - Paid gig ($)

Brandon.gallas@fda.hhs.gov

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



Collaborators – Current and Past

Pathologists, Academics, Industry, International

Volunteers

- **Mohamed Amgad, MD, PhD**
  - Northwestern University - The Feinberg School of Medicine
- **Kim Blenman, PhD**
  - Yale School of Medicine and Cancer Center, Yale School of Engineering and Applied Science
- **Weijie Chen, PhD**
  - FDA/CDRH/OSEL/DIDSR
- **Sarah Dudgeon, MPH**
  - CORE Center for Computational Health Yale-New Haven Hospital
- **Kate Elfer, MPH**
  - FDA/CDRH/OSEL/DIDSR
- **Anna Ehinger**
  - Lund University
- **Emma Gardecki, BS**
  - FDA/CDRH/OSEL/DIDSR
- **Victor Garcia, MD**
  - FDA/CDRH/OSEL/DIDSR
- **Rajarsi Gupta, MD/PhD**
  - Stony Brook Medicine Dept of Biomedical Informatics
- **Matthew Hanna, MD**
  - Memorial Sloan Kettering Cancer Center
- **Steven Hart, PhD**
  - Department of Health Sciences Research, Mayo Clinic
- **Evangelos Hytopoulos, PhD**
  - iRhythm Technologies Inc
- **Denis Larsimont, MD**
  - Department of Pathology, Institut Jules Bordet
- **Xiaoxian Li, MD/PhD**
  - Emory University School of Medicine
- **Amy Ly, MD**
  - Massachusetts General Hospital
- **Anant Madabhushi, PhD**
  - Case Western Reserve University
- **Hetal Marble, PhD**
  - Immuto Scientific
- **Dieter Pieters**
  - Sint-Maarten Hospital; University of Antwerp; CellCarta
- **Roberto Salgado, PhD**
  - Division of Research, Peter Mac Callum Cancer Centre, Melbourne, Australia; Department of Pathology, GZA-ZNA Hospitals
- **Joel Saltz, MD/PhD**
  - Stony Brook Medicine Dept of Biomedical Informatics
- **Manasi Sheth, PhD**
  - FDA/CDRH/OPQE/Division of Biostatistics
- **Rajendra Singh, MD**
  - PathPresenter Corporation
- **Evan Szu, PhD**
  - Arrive Bio
- **Darick Tong, MS**
  - Arrive Bio
- **Si Wen, PhD**
  - FDA/CDRH/OSEL/DIDSR
- **Bruce Werness, MD**
  - Arrive Bio