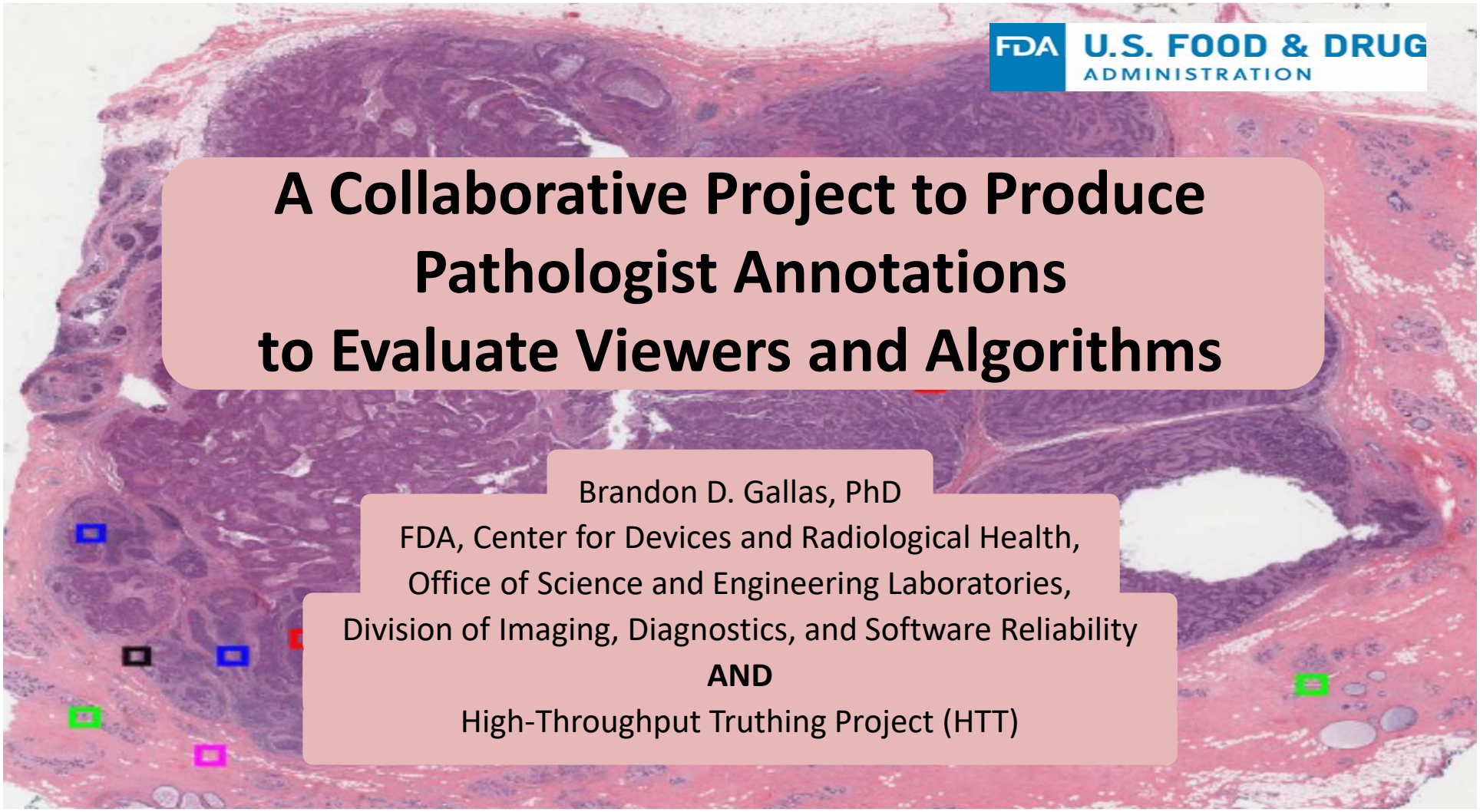


A Collaborative Project to Produce Pathologist Annotations to Evaluate Viewers and Algorithms

Brandon D. Gallas, PhD

FDA, Center for Devices and Radiological Health,
Office of Science and Engineering Laboratories,
Division of Imaging, Diagnostics, and Software Reliability

AND

High-Throughput Truthing Project (HTT)

Conflicts of Interest

- Brandon Gallas is a government employee and has no conflicts of interests to disclose
- Most current project collaborators have no conflicts of interest related to the project
  - Exceptions given on the next slide

HTT collaborators introduced later

- Project growing, future project collaborators expected to have all kinds of conflicts of interest
  - WSI scanners
  - Image viewers
  - Algorithms

Conflicts of Interest

- **Dr. Gilmore** received travel expenses from Sectra for a travel to Sweden to discuss projects.
- **Dr. Madabhushi** is an equity holder in Elucid Bioimaging and in Inspirata Inc.. He is also a scientific advisory consultant for Inspirata Inc. In addition he has served as a scientific advisory board member for Inspirata Inc, Astrazeneca and Merck. He also has sponsored research agreements with Philips and Inspirata Inc. His technology has been licensed to Elucid Bioimaging and Inspirata Inc. He is also involved in a NIH U24 grant with PathCore Inc, and 3 different R01 grants with Inspirata Inc.
- **Dr. Treanor** is on the advisory board of Leica/ Aperio. He receives no personal remuneration for these boards. DT has had a collaborative research project with FFEI in 2014-15, where technical staff were funded by them. DT is principle investigator on a research led deployment of digital pathology in collaboration with Leica in 2017. He received no personal remuneration for any of these research projects. DT is a co-inventor on a digital pathology patent was assigned to Roche-Ventana on behalf of his employer in 2015. He received no personal remuneration. DT provided consulting services to Roche in 2017. He received no personal remuneration.

Outline

- Project Origin Story
- Growing the project
- Alternative FDA programs
  - MDDT: Medical Device Development Tools
  - Mock submissions
- Project Details
- Staying up to date

What is Digital Pathology?

- Clinical workflow
  - Image acquisition
  - Evaluation and Report:
    - Integration with patient record
  - Remote Consult, Archiving, and Retrieval
- Image Analysis

Whole Slide Imaging (WSI)
Enables AI

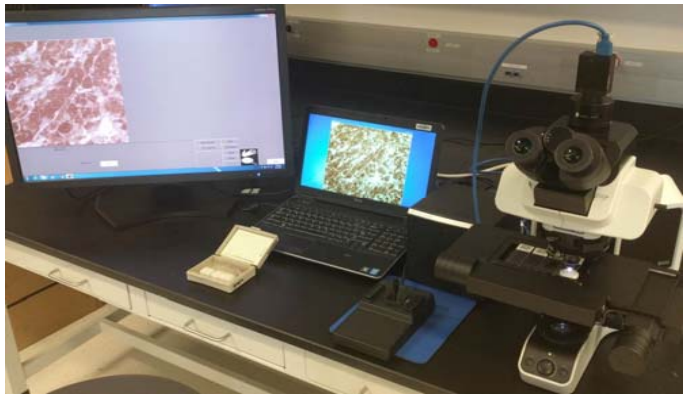
Glass slides in → Digital image out → AI

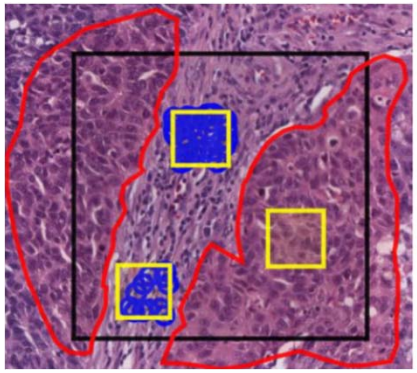
What is this project about?

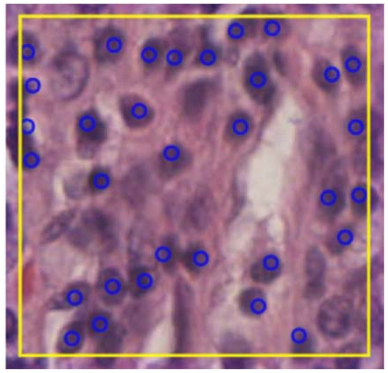
Origin Story

Internal funding proposal title

- High-throughput truthing of microscope slides to **evaluate artificial intelligence** algorithms
- analyzing digital scans of pathology slides:
- **data (slides + images + annotations)** as an FDA-qualified medical device development tool (MDDT).







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What is this project about?

Origin Story

Internal funding proposal title

- High-throughput truthing of microscope slides to **evaluate artificial intelligence** algorithms
- analyzing digital scans of pathology slides:
- **data (slides + images + annotations)** as an FDA-qualified medical device development tool (MDDT).

Clarifications

- Focus on truth by pathologists and the microscope
  - Crowdsource pathologists
- Key technology maps annotations and evaluations collected on the microscope to the digital scan
  - eeDAP: evaluation environment for digital and analog pathology
- New regulatory program

What is this project about?

Origin Story

MDDT

New program.

- ***Reduce burden to sponsors***
  - Skip the design of the clinical trial
  - Know performance evaluation methods FDA will accept
  - Replace 40-70 pages of a submission with,

  "We used the MDDT dataset and our algorithm performance was …"

- ***Reduce burden to FDA***
  - Qualify data and analysis methods once to support multiple sponsors

Building a pathway

Build consensus. Build tools. Disseminate.

What is this project about?

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MDDT

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Building a pathway

Build consensus. Build tools. Disseminate.

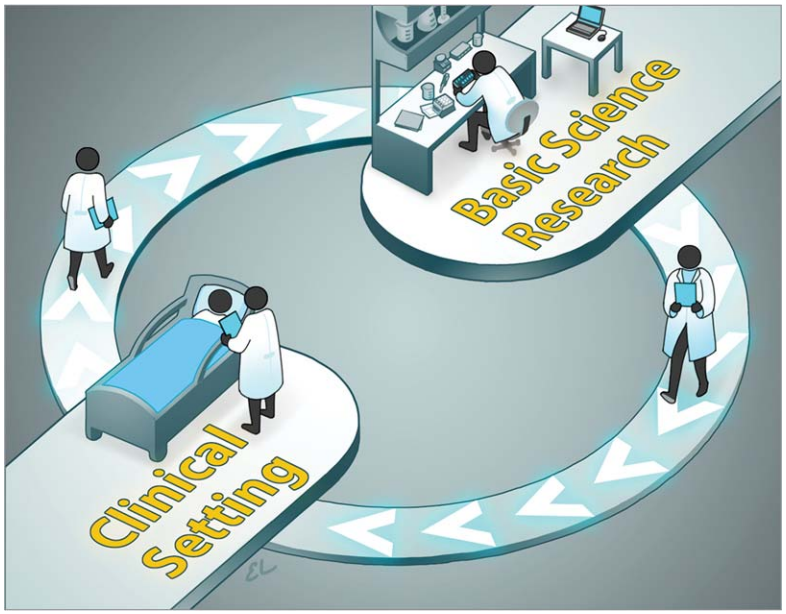
- High-throughput data-collection tools and protocols
- Standardize annotation formats for humans and algorithms
- Statistical methods and software for algorithm performance evaluation

Improve submissions.
Support and enable interoperability.

What is this project about?

Generalize beyond digital pathology

- Data
- Algorithms
  - Machine learning (ML)
  - Artificial Intelligence (AI)
- Why? *"To help encourage more developers to translate advances into clinically actionable tools to benefit patients"*
  - Scott Gottlieb, Commissioner FDA,
  - "Transforming FDA's Approach to Digital Health."



Tracy Hampton, PhD
JAMA. 2017;318(1):16-17. doi:10.1001/jama.2017.7276

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Utilize new and alternative mechanisms to interacting with FDA

- MDDTs
- Mock Submissions

Offer safe pre-competitive space to collaborate

- Identify challenging submission and review issues and offer novel solutions
- Address barriers with examples and method development
- Receive official agency feedback
- Increase transparency
- Reduce burden

- ***Share risk and cost. Reduce uncertainty.***

What are mock submissions?

Mock submissions

Representation of a premarket application

- PMA, 510(k), or IDE
- Hypothetical device with hypothetical characteristics and companion information

- ***Reduce uncertainty for sponsors***
  - ***Clarify pathway to market***

- ***FDA may join submission team (consultant) and creates regulatory review team***
  - ***Firewall between two groups***

Impact

Build consensus. Build tools. Disseminate.

- High-throughput data-collection tools and protocols
- Standardize annotation formats for humans and algorithms
- Statistical methods and software for algorithm performance evaluation

Improve submissions.
Support and enable interoperability.

Mock submission history

- **Protein-based multiplex assays**
  - *2008-2010*
  - **IOTF MDx**: Interagency oncology task force, molecular diagnostics subcommittee
  - Origin: IOTF MDx workshop 2008
  - NCI was the sponsor/submitter
- **Virtual patient**
  - *2015-2017*
  - **MDIC**: Medical Device Innovation Consortium
  - Origin: MDIC computational modeling and simulation group
  - MDIC was the sponsor/submitter

- Essential to have FDA review division on board
  - Sees value in devoting resources to mock review
- Essential to have many stakeholders involved
  - Extensive interactions
- Sections submitted:
  - Intended Use
  - Device description
  - Analytical studies
  - Clinical trial protocol
  - Statistical evaluation plans

Protein-based multiplex assays

Mock submission 2008-2010

- Mock pre-submissions submitted to FDA for review:
  - Multiplex MRM mass spec platform
  - Multiplex affinity arrays
- "Lessons learned" intro paper
  - Served as examples of review comments to the proteomics community


Clinical Chemistry 56:2
000–000 (2010)

Special Report

Protein-Based Multiplex Assays:
Mock Presubmissions to the US Food and Drug Administration

Fred E. Regnier,[1] Steven J. Skates,[2] Mehdi Mesri,[3] Henry Rodriguez,[3] Živana Težak,[4] Marina V. Kondratovich,[4] Michail A. Alterman,[5] Joshua D. Levin,[4] Donna Roscoe,[4] Eugene Reilly,[4] James Callaghan,[4] Kellie Kelm,[4] David Brown,[6] Reena Philip,[4] Steven A. Carr,[7] Daniel C. Liebler,[8] Susan J. Fisher,[9] Paul Tempst,[10] Tara Hiltke,[3] Larry G. Kessler,[11] Christopher R. Kinsinger,[3] David F. Ransohoff,[12] Elizabeth Mansfield,[4] and N. Leigh Anderson[13]*

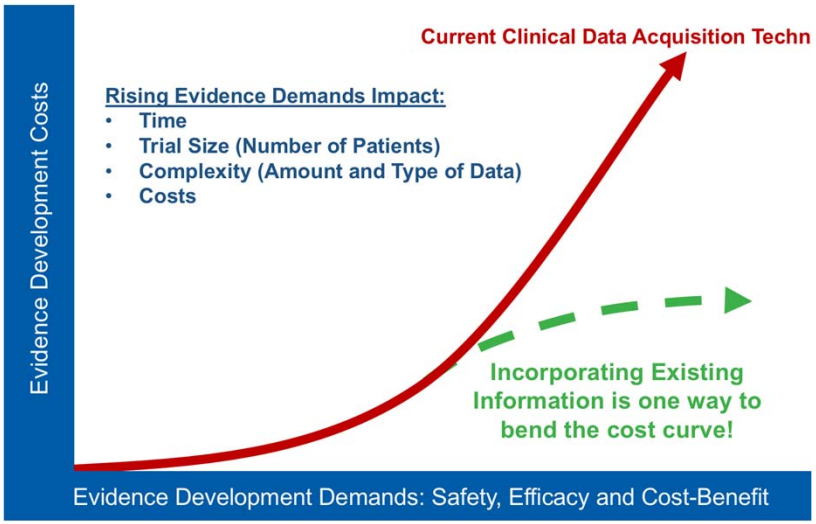
Regnier FE, et al. Protein-Based Multiplex Assays: Mock Pre-submissions to the US Food and Drug Administration. Clin Chem 56, 165-171, 2010.

- Supplementary Materials
  - Multiplex MRM mass spec & immunoaffinity array filings with FDA review memos
  - Courtesy of H. Rodriguez, NCI

Virtual Patient

Mock submission 2015-2017

- Proposed clinical trial for mock device
  - lead wire for implantable cardioverter defibrillator
- **Key enabling method**: *Bayesian framework to augment clinical trial data with virtual patients (VP) …*
  - *borrow evidence and statistical power*
- Website includes overview and
  - Working group description and opportunity
  - Virtual patient framework
  - Documents from the mock submission
  - Manuscripts, presentations, and *code*



https://mdic.org/project/virtual-patient-vp-model/

New technology. Pathways unclear.

New and alternative programs can blaze the path.

MDDTs and Mock submissions

Involve more stakeholders.

- Not just industry
- Pathologists, Academia, Health Providers
- Associations, Societies, Colleges (CAP, USCAP, ASCP)

- ***Involve experts.***
- ***Involve the community.***

Impact

Give pathologists a voice, ownership of evaluation, and confidence to use.

- What should algorithms do?
- How should algorithms be evaluated?

- ***Create an example for stakeholders to follow.***
- ***Improve public health.***

Deliverables under consideration

1. ***Data for algorithm evaluation***
   - MDDT submission
2. ***WSI viewer***
   - Mock submission
3. ***TILs in breast cancer algorithm***
   - Mock submission

- Having internal discussions to identify needs
- Workshops and white papers
- Demonstration projects
- Templates and tools
- Training of FDA staff

Big Tent Project

Academic/clinical collaborators

Opportunities related to

- Standards (e.g., DICOM)
- Image Quality (software tools)
- Clinical workflows, integrating the patient record
  (LIMS: laboratory information management systems)

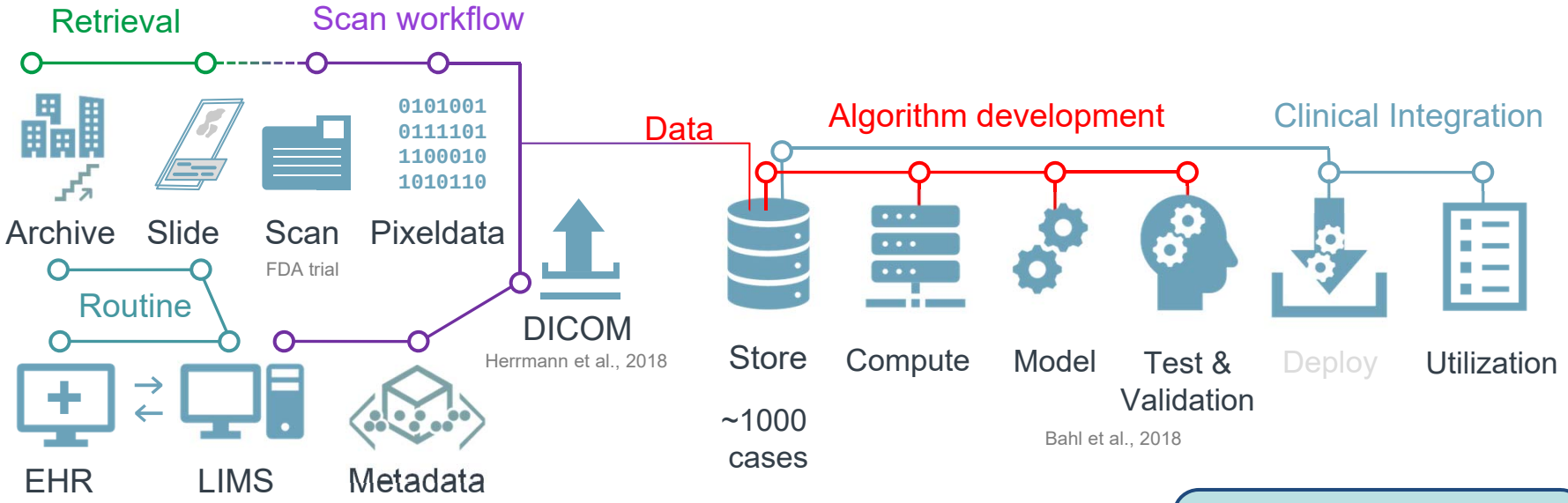
Industry

What are the opportunities?

- What are the challenging submission and review issues?
- Where is guidance needed?
- What novel methods can,
  - Overcome barriers to innovation?
  - Reduce regulatory burden?

What is the key limiting factor for widespread adoption of AI?

Courtesy of Dr. Lennerz (unpublished)



"The key issue is recognizing the importance of a reliable front-end workflow. The 'Garbage in garbage out' concept fully applies – and the multi-chain process relies heavily on many non-interoperable components. Unfortunately, this is currently largely overlooked."
Joe Lennerz, World Medical Innovation Forum 2019

A whole lot of non-simple.
Brandon Gallas email to Joe Lennerz, 2019

IDG

PARTNERS HEALTHCARE | FOUNDED BY BRIGHAM AND WOMEN'S HOSPITAL AND MASSACHUSETTS GENERAL HOSPITAL

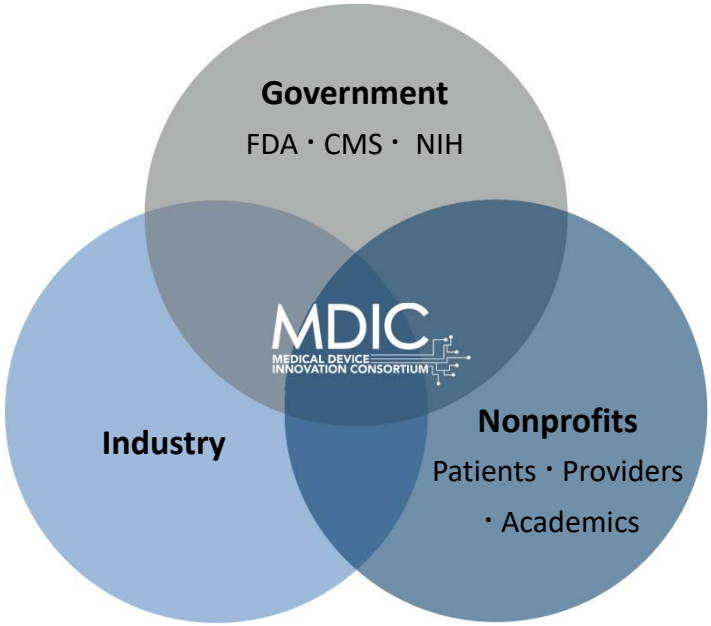
Imaging and diagnostics are part of drug development

- Pharma wants algorithms for high-throughput drug development and trials
- Need more CDRH-CDER projects bringing device expertise to drugs

IDG

PARTNERS HEALTHCARE | FOUNDED BY BRIGHAM AND WOMEN'S HOSPITAL AND MASSACHUSETTS GENERAL HOSPITAL

WHAT IS MDIC?



www.mdic.org

Medical Device Innovation Consortium (MDIC) is a public-private partnership & membership organization created with the sole objective of advancing regulatory science of medical devices for patient benefit.

MDIC IS ALIGNED WITH FDA/CDRH PRIORITIES

MDIC collaborates with CDRH by developing tools, guidelines, and methods to help assess the safety, efficacy, quality, and performance of FDA-regulated products.

ACCELERATING PATIENT ACCESS TO INNOVATIVE MEDICAL TECHNOLOGIES

FDA

ALIGN RESOURCES

WORKING COOPERATIVELY to re-engineer pre-competitive technology innovation

ACCELERATE PROGRESS

REDUCING TIME and resources needed for new technology development, assessment, and review

ACHIEVE RESULTS

HELPING PATIENTS gain access to new medical technologies sooner

MDIC MEDICAL DEVICE INNOVATION CONSORTIUM

Members help MDIC create methods, tools, and resources used in managing the total product life cycle (TPLC) of a medical device to improve patient access to high-quality, safer, and effective medical technology.

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- Check time

https://www.schoolhouse.com/collections/clocks

HTT project essentials

- ***eeDAP***: evaluation environment for digital and analog pathology

- Deliverables' essentials
  - 5 minutes

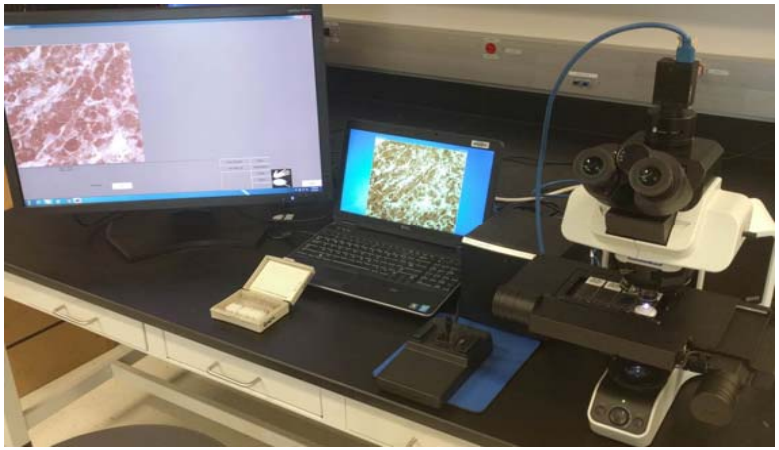
- Staying up to date
  - 5 minutes

https://www.schoolhouse.com/collections/clocks

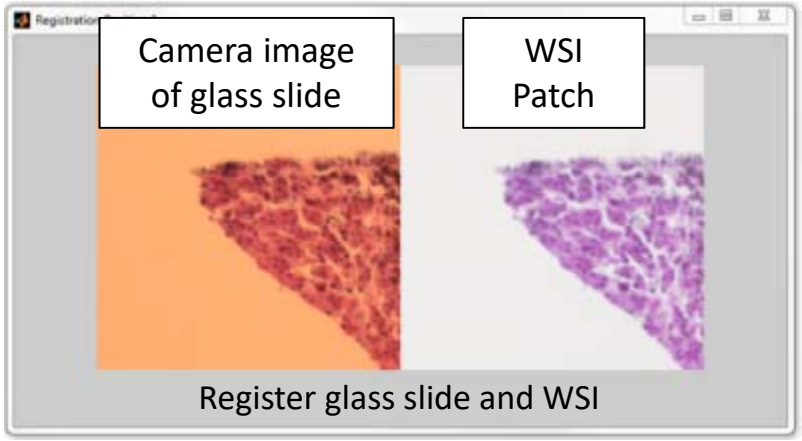
Microscope mode, eeDAP:

Evaluation Environment for Digital and Analog Pathology

- Microscope with mounted camera, motorized stage (+ joystick), and reticle in eyepiece
- Laptop and large format monitor



https://github.com/DIDSR/eeDAP



Allow pathologists to create annotations using microscope … **scanner agnostic annotations**.

Then map annotations to WSI's from any scanner … even future scanners

Deliverable 1: FDA qualified MDDT dataset for algorithm evaluation

- Collect slide annotation data at pathology conferences and other high-volume settings
- Use microscope and system that records evaluation locations (eeDAP)
- Microscope-based annotations are **scanner agnostic**
  - Annotations can be mapped to digital scans of the slides from any scanner

Data Collection: ASCP 2018
- Stromal TILs Density & TILs marking
- eeDAP and digital modes
- 26 pathologists 13 collection hours total

Deliverable 1: FDA qualified MDDT dataset for algorithm evaluation

- Also collect annotations from WSI's (digital mode)
  - Understand evaluation differences and pathologist variability
  - Support viewer and algorithm deliverables
- 5 to 15 pathologists per slide or ROI
- MDDT will include
  - Slides, annotations, algorithm evaluation plan
- MDDT will be available to developers to use in FDA submissions

Data Collection: ASCP 2018
- Stromal TILs Density & TILs marking
- eeDAP and digital modes
- 26 pathologists 13 collection hours total

Deliverables 2 & 3: Mock Submissions

Mock submission:
WSI viewer

- The WSI viewer is an enabling technology that has been developed by many groups.
- Goal: Demonstrate regulatory pathway to allow innovation enabled by different viewers.
- Use MDDT data (deliverable 1). Share process publicly. Community follows the example.

Mock submission:
TILs in breast cancer algorithm

- Create an algorithm use case (= FDA Indications for Use).
- Evaluate algorithm with MDDT data (deliverable 1).
- Share process publicly. Community follows the example.

Workgroup Leadership

Slides

Anant Madabhushi

- F. Alex Nason Professor II of Biomedical Engineering, Case Western Reserve University and Research Health Scientist, Louis Stokes Cleveland Veterans Health Administration Medical Center, Cleveland, OH, US

Hannah Gilmore

- Division of Anatomic Pathology, University Hospitals Cleveland Medical Center, Case Western Reserve University

Conference Logistics

Jithesh Veetil

- Data Science & Technology Div., Medical Device Innovation Consortium, VA, US

MDDT Development

Sarah Dudgeon

- FDA, CDRH, Office of Science and Engineering Laboratories, Division of Imaging, Diagnostics, and Software Reliability, Silver Spring, MD, US

Raj Gupta

- Renaissance School of Medicine and Dept. of Biomedical Informatics, Stony Brook Medicine, Stony Brook, NY, US

Infrastructure and Viewer

Ashish Sharma

- Dept. of Biomedical Informatics, Emory University School of Medicine, Atlanta, GA, US

Joel Saltz

- Dept. of Biomedical Informatics and Dept. of Pathology Stony Brook Medicine, Stony Brook, NY, US

Workgroup Leadership

Human Annotations

Darren Treanor

- NPIC: Northern Pathology Imaging Co-operative, Leeds Teaching Hospitals, NHS Trust, Leeds, UK

Bethany Williams

- Leeds Teaching Hospitals, NHS Trust, Leeds, UK

Algorithm Annotations

Lee Cooper

- Dept. of Biomedical Informatics, Emory University School of Medicine, Atlanta, GA, US

Mohamed Amgad

- Dept. of Biomedical Informatics, Emory University School of Medicine, Atlanta, GA, US

Algorithm

Roberto Salgado

- Department of Pathology, GZA-ZNA, Antwerp, Belgium; Division of Research, Peter Mac Callum Cancer Centre, Melbourne, Australia

Jeroen van der Laak

- Radboud University, The Netherlands

Stats

Weijie Chen

- FDA, CDRH, Office of Science and Engineering Laboratories, Division of Imaging, Diagnostics, and Software Reliability, Silver Spring, MD, US

Pathologist Recruitment, and Training

Opportunity!

Possible Data Collection Events

- **FDA**
  - 17 July, Silver Spring, MD
  - Stress test
- **ECP**
  - 7-11 September, Nice, France
- **ASCP**
  - 11-13 September, Phoenix, AZ
- **CAP**
  - 21-25 September, Orlando, FL
- Complimentary web-based studies

Default Plan

- Four workstations
  - 2 eeDAP microscopes + 2 digital mode
- Semi-private space on exhibit floor or a small conference room
- Need advertising for recruiting ahead of and during conference
- Opportunity to organize a session of speakers about the different project elements

MDDT *Context for Use*

Context of use depends on:

- Product area
- Specific output or measure from the MDDT
- Role of the MDDT
- Medical device development phase

Context of use for HTT data

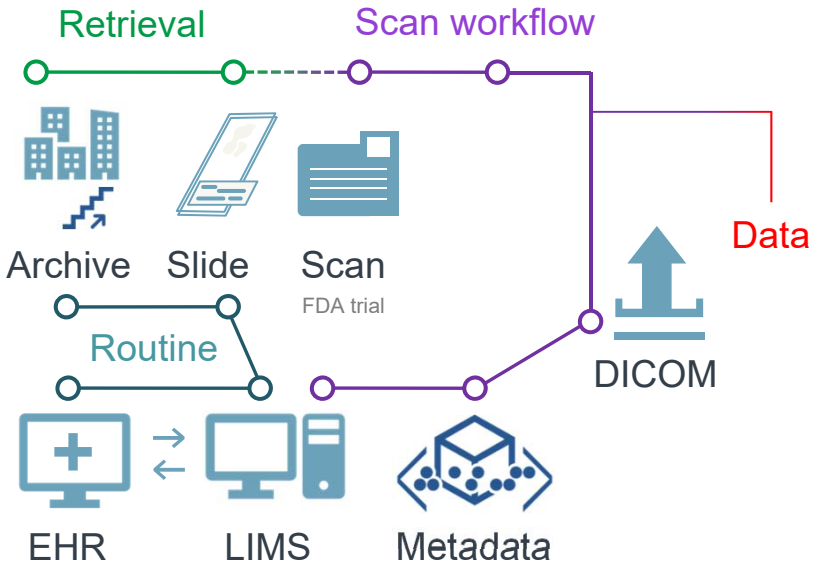
- Algorithms analyzing TILs in breast cancer
- Annotations can be used to evaluate algorithm
  - Stand-alone performance
  - Clinical performance
- Pivotal clinical trial

Protocol for HTT data

- **Identify, clarify and organize dataset requirements**.

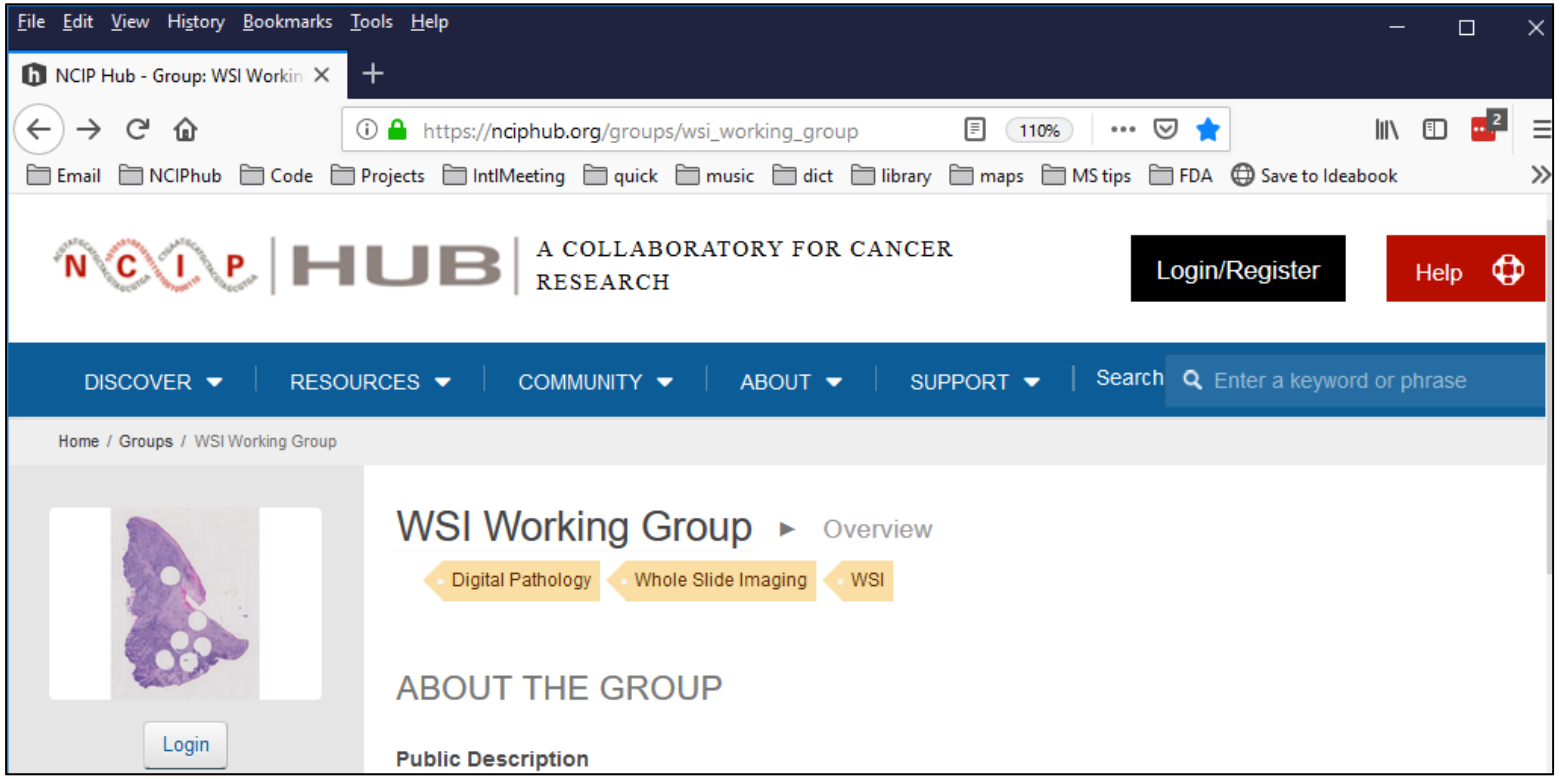
What needs to be specified:

- The inputs to the algorithm.
- Number of sections/slides required.
- The evaluation area: entire WSI or pathologist identified regions of interest (ROIs)?
- Patient inclusion and exclusion criteria: organ, disease.
- Procedures or referrals that yield the appropriate specimen.
- Imaging specifications: magnification, stain.
- Other diagnostic results that are required.
- The outputs from the algorithm.



Public

Info and Updates



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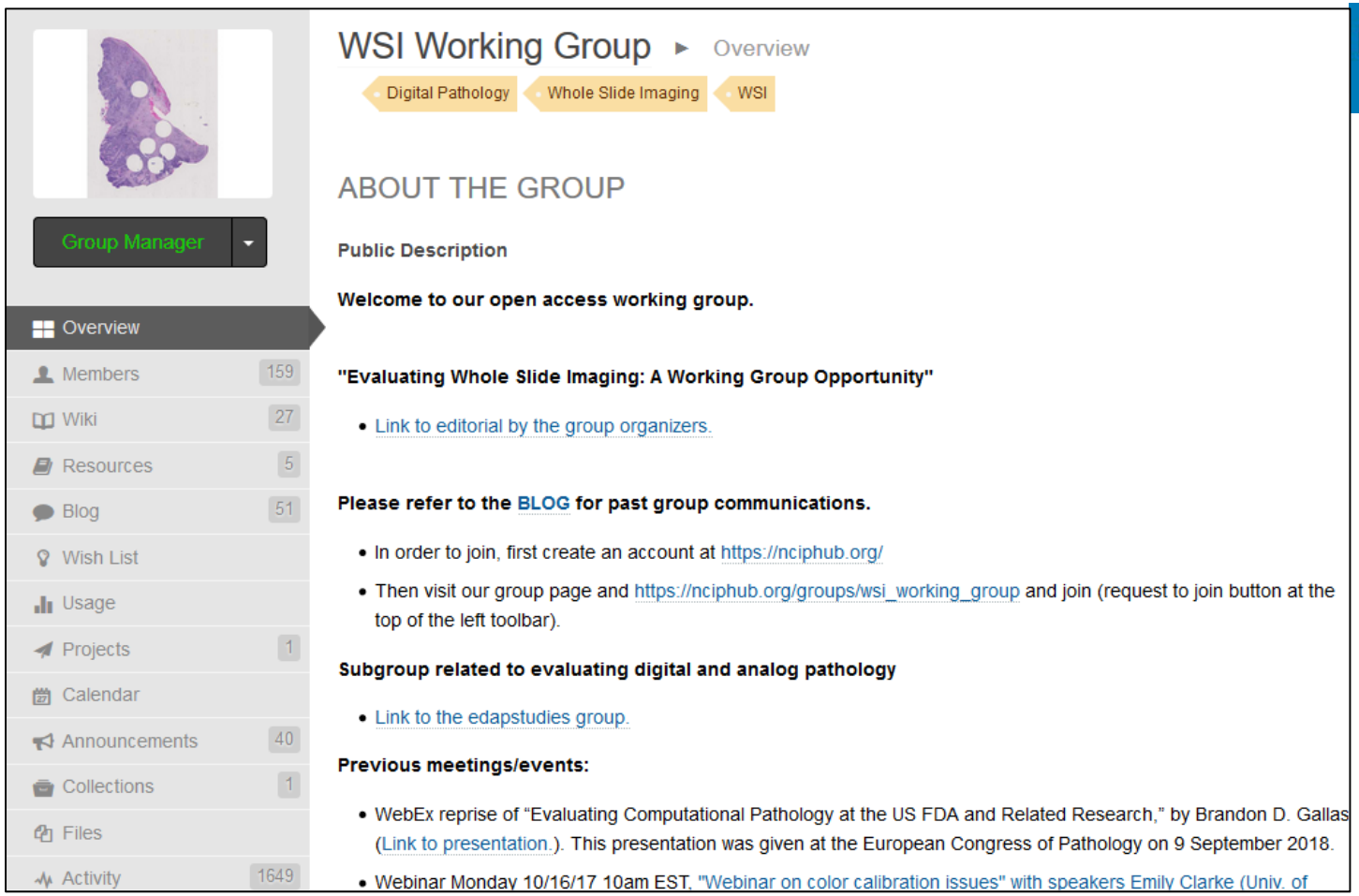
Public

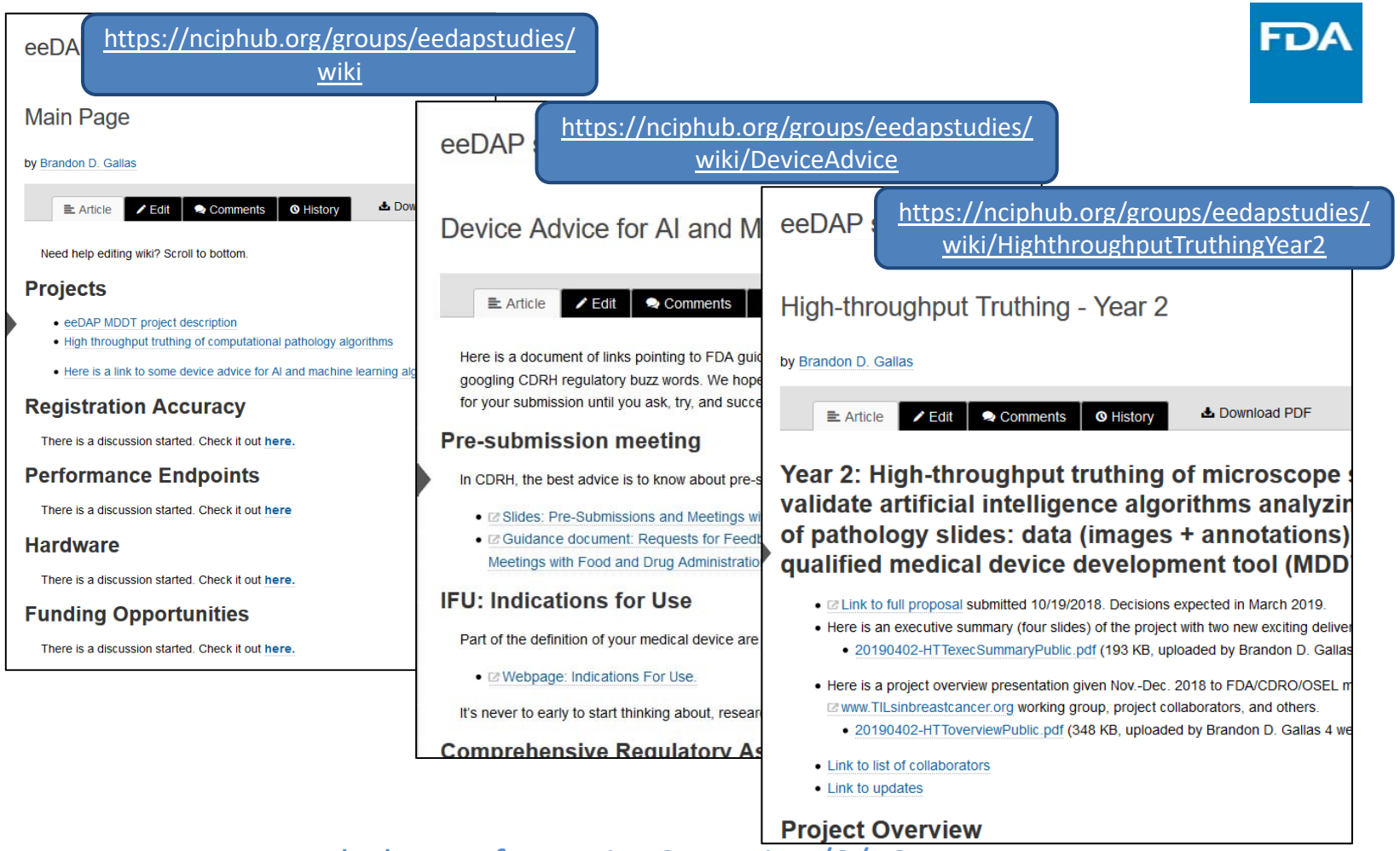

WSI Working Group ► Overview
Digital Pathology
Whole Slide Imaging
WSI
FDA
Group Manager
Overview
Members 159
Wiki 27
Resources 5
Blog 51
Wish List
Usage
Projects 1
Calendar
Announcements 40
Collections 1
Files
Activity 1649
ABOUT THE GROUP
Public Description
Welcome to our open access working group.
"Evaluating Whole Slide Imaging: A Working Group Opportunity"
Link to editorial by the group organizers.
Please refer to the BLOG for past group communications.
In order to join, first create an account at https://nciphub.org/
Then visit our group page and https://nciphub.org/groups/wsi_working_group and join (request to join button at the top of the left toolbar).
Subgroup related to evaluating digital and analog pathology
Link to the edapstudies group.
Previous meetings/events:
WebEx reprise of "Evaluating Computational Pathology at the US FDA and Related Research," by Brandon D. Gallas (Link to presentation.). This presentation was given at the European Congress of Pathology on 9 September 2018.
Webinar Monday 10/16/17 10am EST, "Webinar on color calibration issues" with speakers Emily Clarke (Univ. of

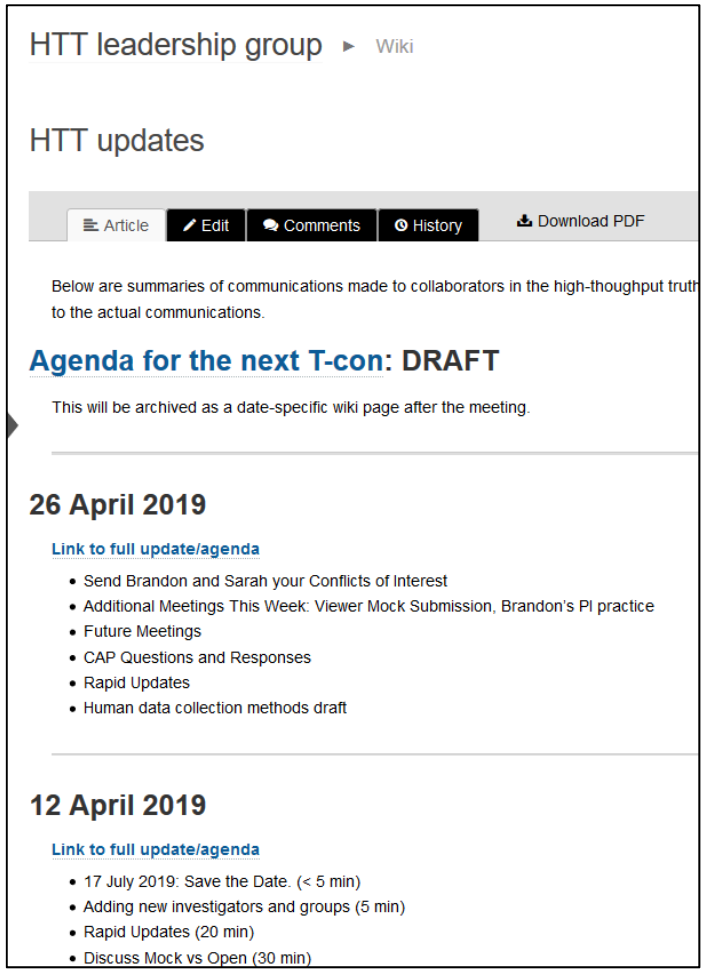
Public

https://nciphub.org/groups/eedapstudies/wiki

https://nciphub.org/groups/eedapstudies/wiki/DeviceAdvice

https://nciphub.org/groups/eedapstudies/wiki/HighthroughputTruthingYear2





HTT leadership group ▸ Wiki

HTT updates

Article | Edit | Comments | History | Download PDF

Below are summaries of communications made to collaborators in the high-thoughput truth to the actual communications.

Agenda for the next T-con: DRAFT

This will be archived as a date-specific wiki page after the meeting.

26 April 2019

Link to full update/agenda

- Send Brandon and Sarah your Conflicts of Interest
- Additional Meetings This Week: Viewer Mock Submission, Brandon's PI practice
- Future Meetings
- CAP Questions and Responses
- Rapid Updates
- Human data collection methods draft

12 April 2019

Link to full update/agenda

- 17 July 2019: Save the Date. (< 5 min)
- Adding new investigators and groups (5 min)
- Rapid Updates (20 min)
- Discuss Mock vs Open (30 min)

FDA

- Leadership meetings every other week
- Establishing weekly satellite meetings

Summary

- **"HTT" → "HTT+"**
  - HTT data project growing into MDIC project
  - Collaboration between FDA and stakeholders
  - Standards? Image Quality? Clinical workflows? Others?
- HTT project overview
  - More details on deliverables
- Info and updates

Project needs: Looking for collaborators

All project workgroups would benefit from more support, especially

- Slides (and expertise with IRBs and RCAs)
- Submission Development
- Statistics … ***Literature Review***
- Conference Logistics
- Pathologist Recruitment, Management, and Training

- Brandon.Gallas@fda.hhs.gov