Regulatory Mechanisms and Tools for Software as a Medical Device

Focus on AI in Imaging

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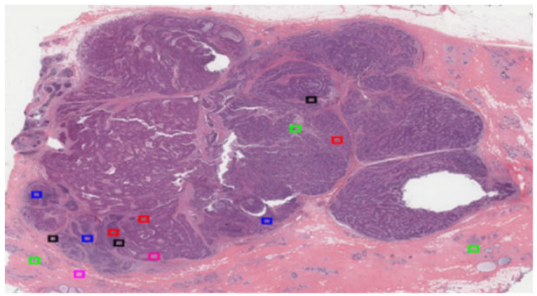
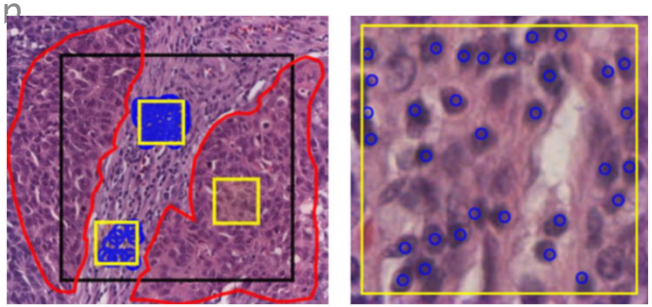
Office of Science and Engineering Laboratories

Center for Devices and Radiological Health

U.S. Food and Drug Administration



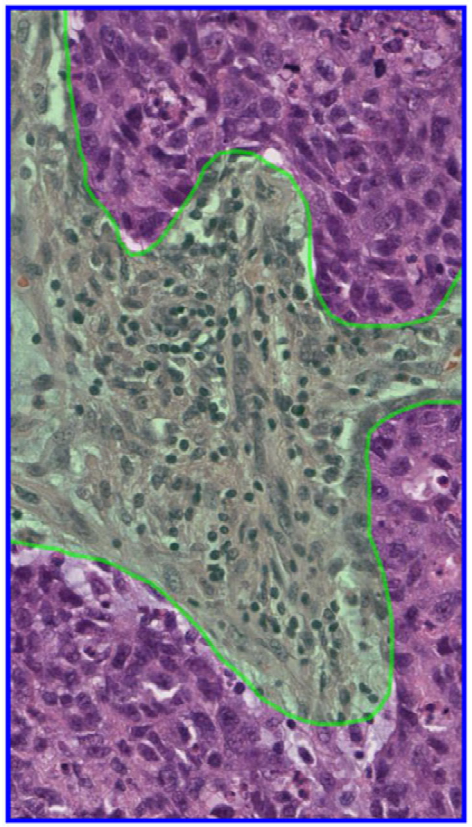
09 September 2021



Outline

- Overview of Software as a Medical Device (SaMD)
- Medical Device Development Tool Program (MDDT)
- Change Control Plans (CCP) … **Current thinking**
- High-throughput truthing project (HTT)

Software as a Medical Device (SaMD)



Segment Stroma and Tumor ->
score density of tumor-infiltrating lymphocytes
Amgad2020_NPJ-Breast-Cancer_v6p1

- Potential to fundamentally transform the delivery of health care:
  - E.g., Earlier disease detection, more accurate diagnosis, new insights into human physiology, personalized diagnostics and therapeutics
- Learn from curated datasets and real-world data
- Novel SaMD use cases appearing across all technologies

Overview of SaMD

- Bulk of regulatory experience is from radiology
  - CADe – computer aided detection
  - CADx – computer aided diagnosis
  - CADe + CADx – computer aided detection and diagnosis
  - CADt – computer aided triage
  - Quantitative Imaging
  - Image processing: de-noising, artifact reduction, image reconstruction, segmentation
- Wiki page of device advice
  - https://ncihub.org/groups/eedapstudies/wiki/DeviceAdviceAIMLImaging
  - Links to guidance documents
  - CAD examples: links to decision summaries (special controls)
  - Links to presentations in this space

SaMD Regulatory Advice

Tell FDA your plans

- Pre-submission meeting

Start with a narrow scope

- Tie SaMD to one imaging system
- Limit the outputs and features

Expand indications over time

  - Other imaging systems & protocols
  - Algorithm updates/improvements

- Possibly less burdensome
  - FDA knows device and performance

Less burdensome methods

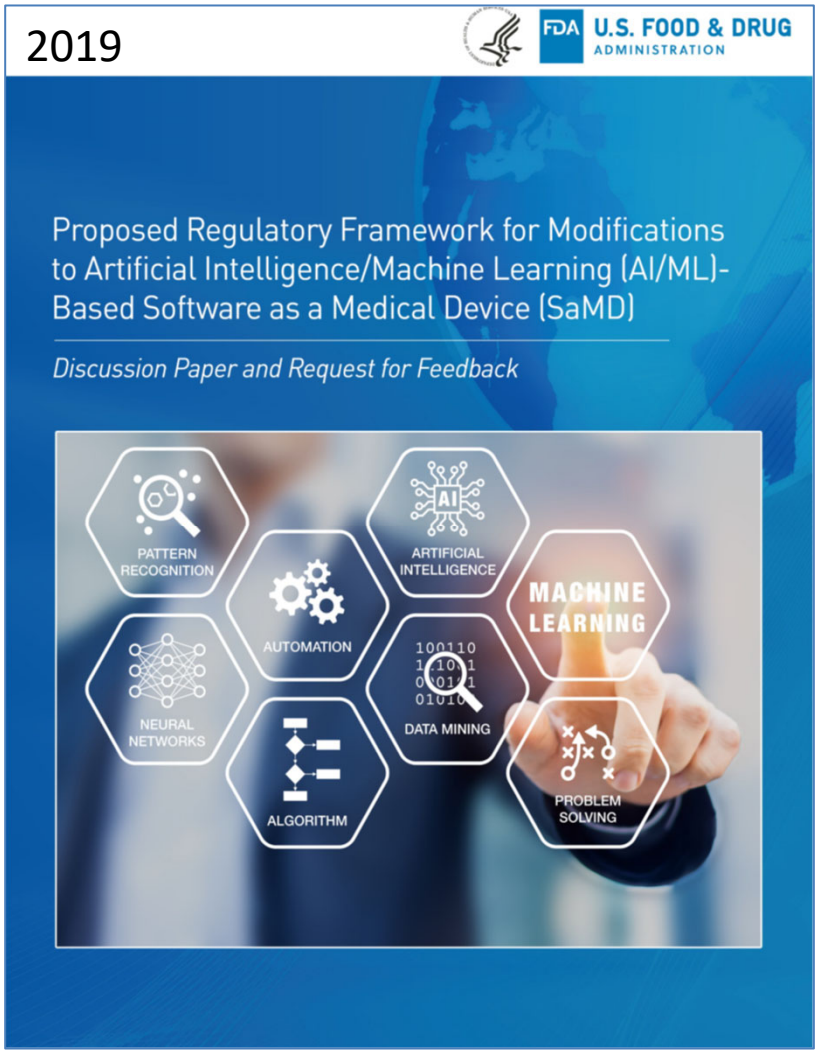
- Technical arguments
  - Phantoms, Simulation
- Reuse cases (rescan film, slides)
  - New reader study
- Studies with fewer cases or fewer readers
- Stand-alone performance only
- No statistical hypothesis test

SaMD Description

- Description
  - Indications for use
  - Clinical context, clinical workflow
  - Patient and clinician population
  - Imaging system and protocols
- Technological Characteristics
  - Algorithm design and function
  - Processing steps
  - Features
  - Models and classifiers
  - Training paradigm
- Imaging modality
  - Manufacturer and Model
  - Imaging parameters and techniques
- Databases: Training and Testing
  - Document data use
  - Sites, dates, collection protocols, patient characteristics
  - Training and testing sets must be Independent
- Reference standard
- Assessment
  - Depends on algorithm type: Aid vs. Automatic
  - Stand-alone performance study: No human in the loop
  - Clinical Performance: human in-the-loop

Change Control Plans
Current thinking

- Framework for algorithm updates
  - Without a new submission
  - **NOT REQUIRED**
- SaMD Pre-Specifications (SPS)
  - What will be changed
- Algorithm Change Protocol (ACP)
  - How the algorithm will change while remaining safe and effective



Software Pre-Specifications (SPS)
Current thinking

- The SPS should enumerate the list of **algorithm changes** that you **plan to make**
  - Be specific!

- Example changes
  - "Retrain on more data."
    - More sites – how many?
    - Rare/difficult cases – how will they be identified?
  - "Extend the SaMD use to new patient subgroup."
  - "Extend the SaMD use to new image acquisition devices."
    - Are there minimum specifications for the imaging devices?

Software Pre-Specifications (SPS)
Current thinking

- The SPS should enumerate the list of **algorithm changes** that you **plan to make**
  - Be specific!

- Changes that are not specific.
  - "Update detection and classification algorithms to improve performance."
  - "Update pre-processing and loss functions to improve performance."

- These changes provide no limit to the scope of changes.

Algorithm Change Protocol (ACP)
Current thinking

- Each change in the SPS should link to an ACP

- An ACP is a description of
  - Data management practices
  - Methods for changing and retraining the algorithm
  - Testing and acceptance criteria to assure safety and effectiveness
  - Dissemination and communication of updates to users

- An ACP ensures that the information that would otherwise be generated and submitted to the FDA will be generated

Algorithm Change Protocol (ACP)
Current thinking

- Be specific!
  - Specify data collection methods and sites
  - Specify truthing methods
  - Specify the size of datasets for training and testing
  - Identify statistical endpoints
    - Comparisons to previous data sets and algorithms
    - Absolute performance on new test data
  - Specify success criteria (give numbers)
  - Account for correlations and uncertainty
  - Compare and contrast with methods for original device

Medical Device Development Tools (MDDT)

Voluntary Program

Medical Device Development Tools (MDDT) Program

Voluntary Program

- Medical Device Development Tool (MDDT) is a method, material, or measurement used to assess the effectiveness, safety, or performance of a medical device

- Context Of Use (COU)
  - How MDDT should be used
  - Specific output/measure from the tool
  - Purpose in device evaluation and/or regulatory submission

- Qualification
  - The MDDT has been validated within the COU

MDDT Qualification Process

Voluntary Program

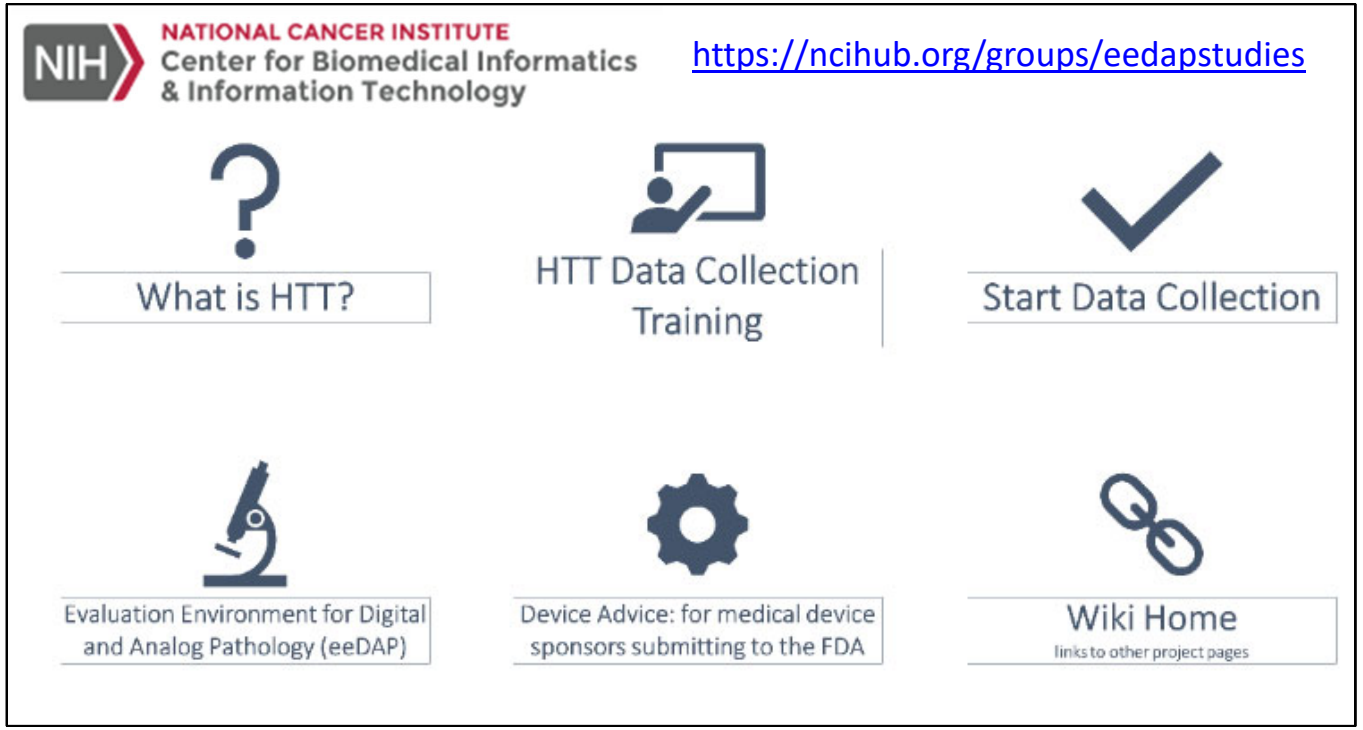
Inquiries for additional information: MDDT@fda.hhs.gov

Proposal Phase	Qualification Phase
The goal of the proposal phase is to determine if the MDDT is suitable for qualification through the MDDT program. Those interested in seeking qualification should submit a complete ***Qualification Plan*** for collecting & gathering evidence for qualification of the tool, a description of the MDDT, and context of use. Qualification plan template: https://www.fda.gov/media/109056/download	The goal of the qualification phase is to determine whether, for a specific context of use, the tool is qualified based on the evidence and justifications provided. In this phase the data collected according to the Qualification Plan is submitted as the ***Full Qualification Package*** and is reviewed for qualification decision. Qualification Package Template (SEBQ) *Summary of Evidence and Basis of Qualification* https://www.fda.gov/media/106994/download

https://www.fda.gov/medical-devices/science-and-research-medical-devices/medical-device-development-tools-mddt

Data MDDT:
High-throughput truthing project (HTT)

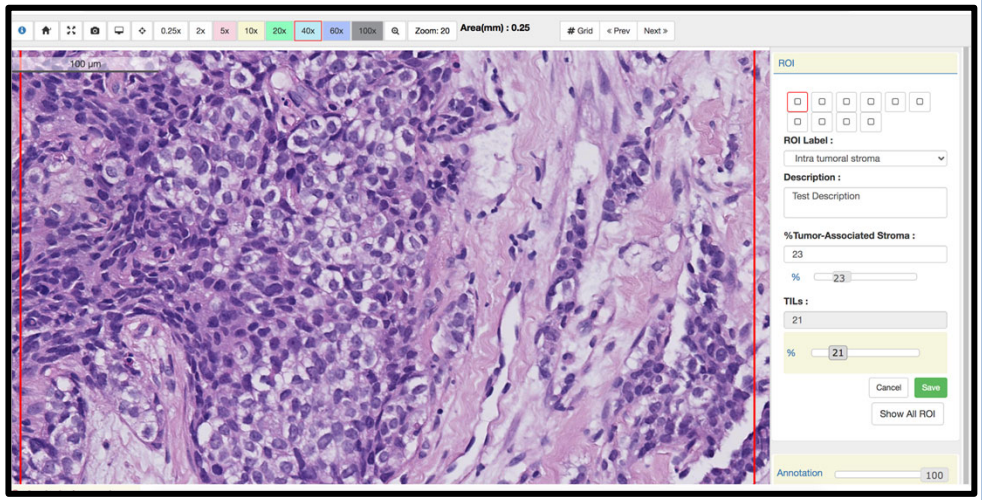
Research Project



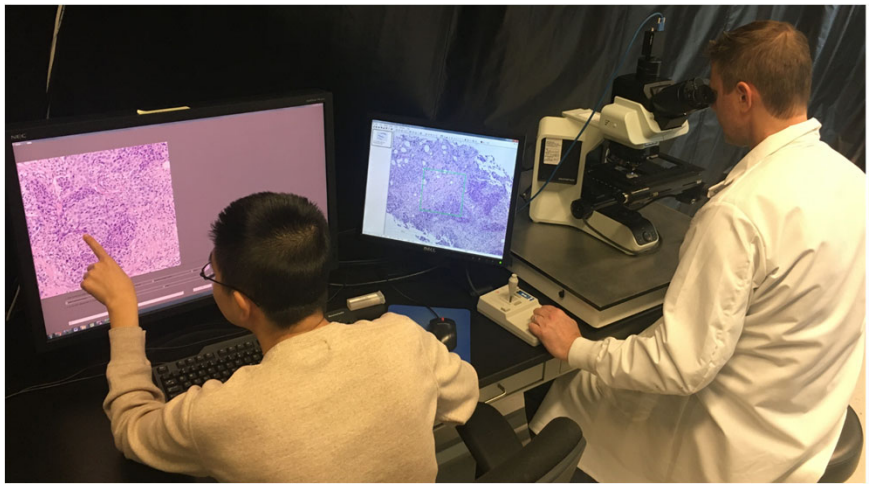
Data MDDT:
High-throughput truthing project (HTT)

Research Project

- **GOAL**
  - Collect pathologist annotations to serve as reference standard
  - Pursue MDDT qualification for slides, images, and annotations



- **Data as Tool**
  - Available to any algorithm developer to be used to validate their algorithm in a submission to the FDA



Data MDDT:
High-throughput truthing project (HTT)

Research Project

- **Reduce burden to sponsors**
  - Skip the design and execution 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 medical device submissions by multiple sponsors

Data MDDT:
High-throughput truthing project (HTT)

Research Project

- **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.

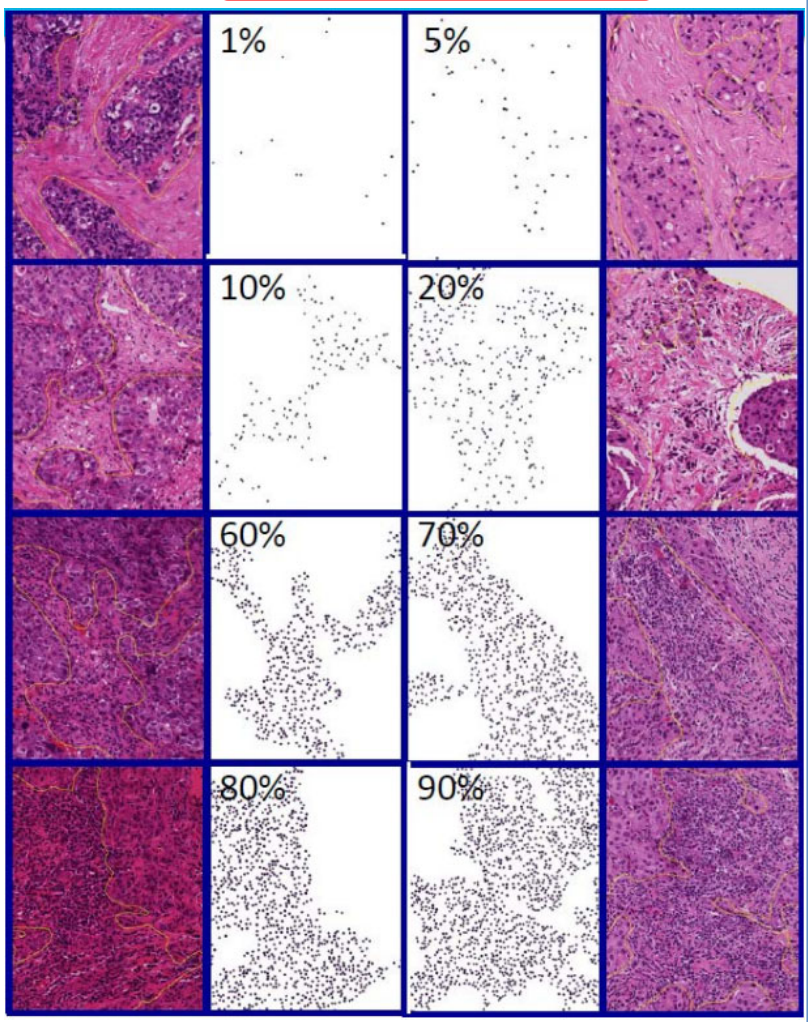
Data MDDT:
High-throughput truthing project (HTT)

Research Project

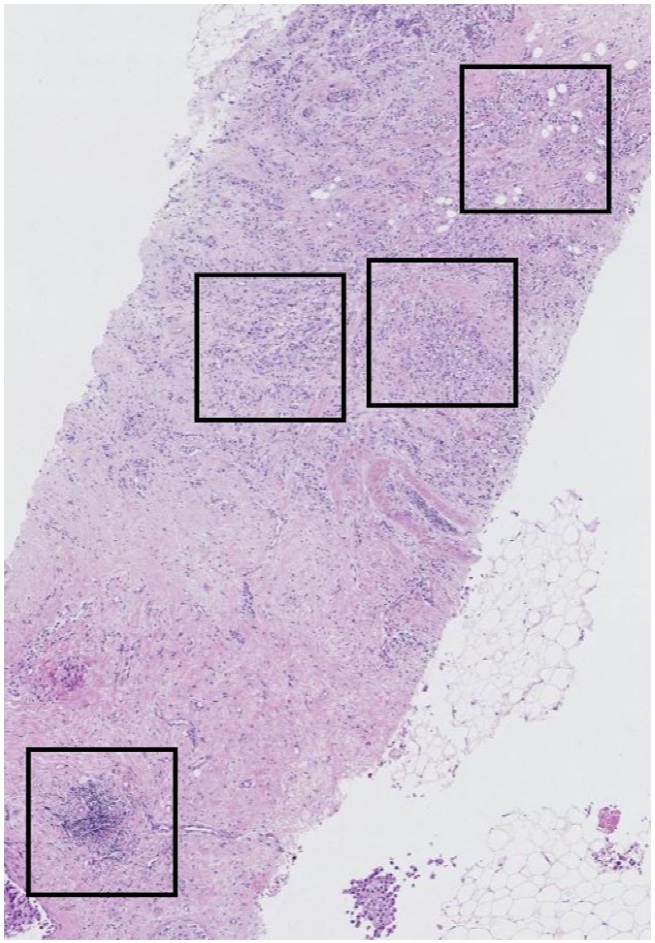
- Clinical application:
  - Stromal Tumor Infiltrating Lymphocytes (sTILs) in breast cancer
  - Biomarker

- Clinical relevance of sTILs:
  - Prognostic for survival
  - Expected to inform patient management
  - Expected to reduce use of toxic chemotherapies

- Software as a medical device (SaMD)
  - Reduce burden on pathologist
  - Reproducible
  - Quantitative



Data MDDT:
High-throughput truthing project (HTT)



Pilot Study Materials

- **64** Hematoxylin & Eosin Slides
  - "40X" Imaging (0.23 um/pixel)
- **10** ROIs per Slide (pre-selected by protocol)
  - ROI: region of interest
  - 500 um x 500 um squares
- **640** ROIs Total
  - 8 batches of 8 slides

Data MDDT:
High-throughput truthing project (HTT)

- R Data Package is live!
- https://github.com/DIDSR/HTT
  - User manual on GitHub release page and via R `help` command
- Annotation data: `pilotHTT`

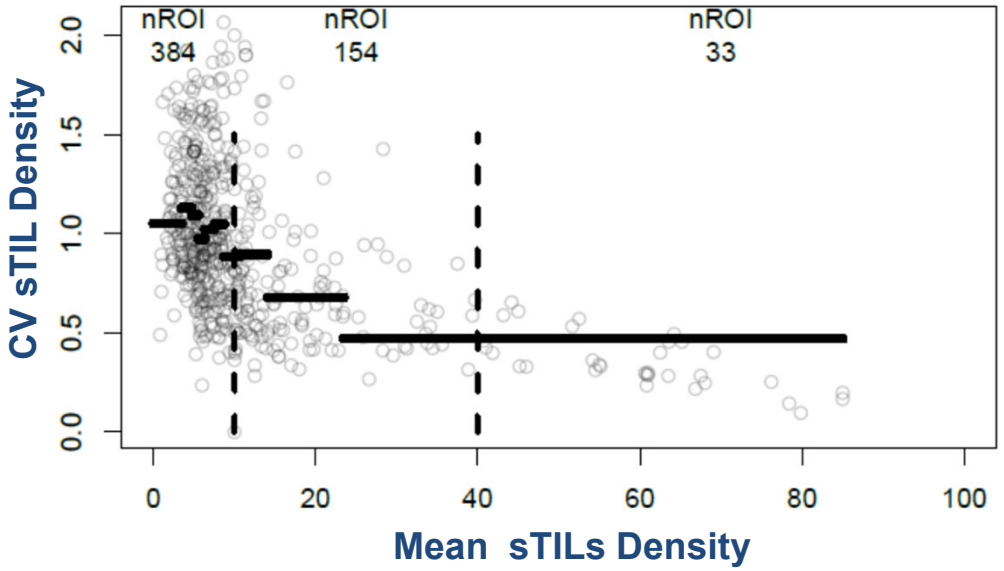
```
> str(HTT::pilotHTT)
'data.frame':   7292 obs. of  18 variables:
 $ batch              : Factor w/ 8 levels "FDA-HTT-batch001",..
 $ WSI                : Factor w/ 64 levels "HTT-TILS-001-03B.n
 $ caseID             : Factor w/ 140 levels "HTT-TILS-001-03B
 $ readerID           : Factor w/ 27 levels "pathologist2899",..
 $ modalityID         : Factor w/ 3 levels "camic","pathp",..:
 $ score              : num  NA 5 10 NA 5 5 1 5 NA NA ...
 $ experience         : num  100 100 100 100 100 100 100 100 10
 $ experienceResident: num  100 100 100 100 100 100 100 100 10
 $ labelROI           : Factor w/ 4 levels "Intra-Tumoral Stro
 $ VTA                : logi  FALSE TRUE TRUE FALSE TRUE TRUE ..
 $ percentStroma      : num  NA NA NA NA NA NA NA NA NA NA ...
 $ densityTILs        : num  NA 5 10 NA 5 5 1 5 NA NA ...
 $ createDate         : POSIXct, format: "2020-02-18 21:48:38"
 $ viewerWidth        : num  NA NA NA NA NA NA NA NA NA NA ...
 $ viewerHeight       : num  NA NA NA NA NA NA NA NA NA NA ...
 $ viewerMag          : num  NA NA NA NA NA NA NA NA NA NA ...
 $ task               : Factor w/ 3 levels "doVTA_caMicro_v1.0
 $ inputFileName      : chr  NA NA NA NA ...
```

caseID	readerID	modalityID	labelROI	percentStroma	densityTILs
HTT-TILS-001-11B.ndpi_x124700.2190_y17272.2190	unknown5139	camic	Other Regions	*NA*	*NA*
HTT-TILS-001-11B.ndpi_x112500.2190_y34683.2190	unknown5139	camic	Intra-Tumoral Stroma	*NA*	5
HTT-TILS-001-11B.ndpi_x124179.2190_y13060.2190	unknown5139	camic	Intra-Tumoral Stroma	*NA*	10
HTT-TILS-001-11B.ndpi_x127215.2190_y12508.2190	unknown5139	camic	Other Regions	*NA*	*NA*

Data MDDT:
High-throughput truthing project (HTT)

- Each circle is one ROI
- Mean and CV are averages over all readers
- Horizontal lines:
  - Average CV in 10% bins of the data (57 ROIs)
- Vertical dashed lines:
  - "Clinical" bins
  - low (≤ 10%)
  - medium (>10% & ≤ 40%)
  - high (>40%)

CV: Coefficient of Variation = STD/Mean
(n=571, caMic)



Data MDDT:
High-throughput truthing project (HTT)

Next Steps

- Update Pathologist Training
  - Immediate
    - Emphasize the calibration cheat sheet
  - For pivotal study
    - Test with feedback
    - Proficiency test
- Continue with pilot study
  - Collect more PathPresenter data
  - Collect microscope-mode data
  - Road trip!
  - Looking for sites and pathologists to help with data collection
- Finalize pivotal study statistical analysis plan
  - Determine study size and power
  - Simulation methods
- Get feedback from the community (including MDDT)
- Source and curate pivotal study slides
  - Looking for one or two more sites
- Plan and execute data-collection

Summary

- Overview of SaMD
  - Appearing in all technologies
  - History from radiology
  - Terminology, framework, and advice
- Change Control Plans (CCP) … **Current thinking**
  - Not required
  - Summarized software pre-specifications (SPS)
  - Summarized algorithm change protocol (ACP)
  - Outlined a few prototypical examples
- Medical Device Development Tool Program (MDDT)
  - Voluntary program
  - Introduced “context of use”
  - Proposal phase … Qualification phase
- High-throughput truthing project (HTT)
  - Research project
  - Data as a tool
  - Clinical application: TILs
  - Pilot Study … Pilot Data on GitHub
  - Next steps

Acknowledge Collaborators

- **Katherine Elfer, PhD, MPH**
  - FDA/CDRH/OSEL/DIDSR
- **Mohamed Amgad, MD**
  - Department of Pathology, Northwestern University
- **Weijie Chen, PhD**
  - FDA/CDRH/OSEL/DIDSR
- **Sarah Dudgeon, MPH**
  - CORE Center for Computational Health Yale-New Haven Hospital
- **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
- **Richard Huang, MD**
  - Massachusetts General Hospital/Harvard Medical School
- **Evangelos Hytopoulos, PhD**
  - iRhythm Technologies Inc
- **Denis Larsimont, MD**
  - Department of Pathology, Institut Jules Bordet
- **Xiaoxian Li, MD/PhD**
  - Emory University School of Medicine
- **Anant Madabhushi, PhD**
  - Case Western Reserve University
- **Hetal Marble, PhD**
  - Massachusetts General Hospital/Harvard Medical School
- **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**
  - Northwell health and Zucker School of Medicine
- **Evan Szu, PhD**
  - Arrive Bio
- **Darick Tong, MS**
  - Arrive Bio
- **Si Wen, PhD**
  - FDA/CDRH/OSEL/DIDSR
- **Bruce Werness, MD**
  - Arrive Bio

Acknowledge Collaborators

TILS BREAST CANCER
INTERNATIONAL IMMUNO-ONCOLOGY WORKING GROUP

International Agency for Research on Cancer
World Health Organization

IC3R International Collaboration for Cancer Classification and Research

Thank You

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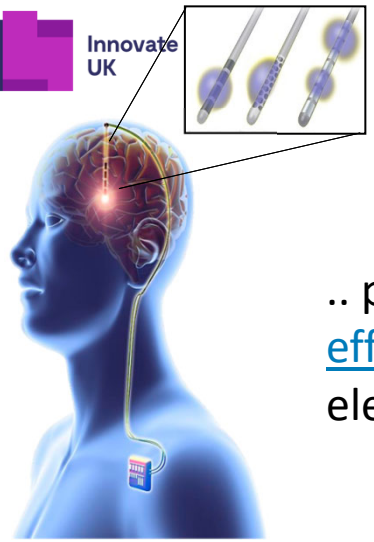
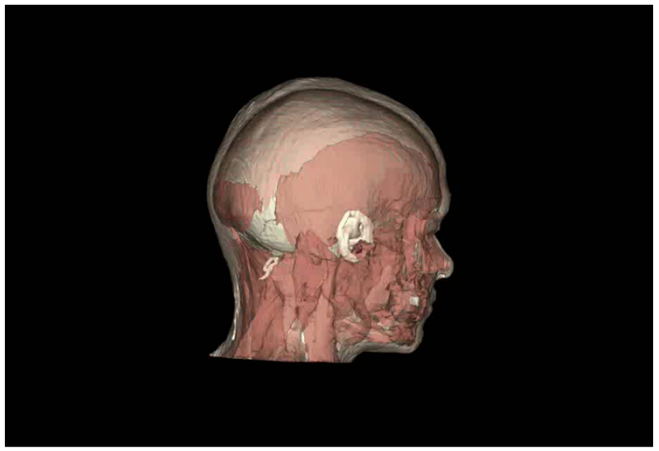
Innovate UK



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

1900
EMPLOYEES

18k
Medical Device Manufacturers

183k
Medical Devices
On the U.S. Market

22k/year
Premarket Submissions
includes supplements and amendments

570k
Proprietary Brands

25k
Medical Device Facilities Worldwide

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

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

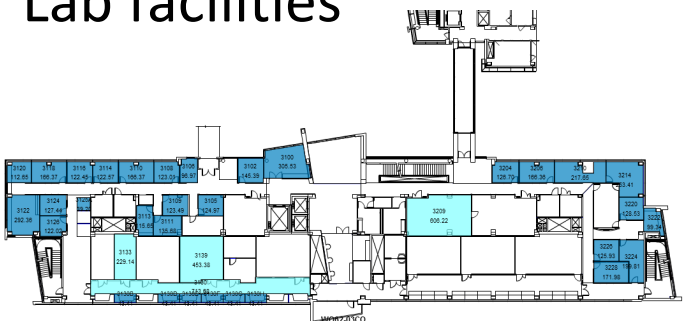
400/year
Peer reviewed presentations, articles, and other public disclosures

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

~15,000 ft²
DIDSR Lab and facilities