Artificial Intelligence/Machine Learning (AI/ML)-Enabled Medical Devices: FDA Action Plan

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Chief Medical Officer for Digital Health, CDRH Digital Health Center of Excellence, US FDA
November 10, 2021

Digital Health Center of Excellence

Empowering digital health stakeholders to advance health care

AI/ML-Enabled Medical Devices

Artificial Intelligence (AI):
A branch of computer science, statistics, and engineering that uses algorithms or models to perform tasks and exhibit behaviors such as learning, making decisions and making predictions.

Machine Learning (ML):
A subset of AI that allows computer algorithms to learn through data, without being explicitly programmed, to perform a task.

AI/ML-Enabled Medical Device:
A medical device that uses machine learning to achieve its intended medical purpose.

Adapted from IMDRF Artificial Intelligence Medical Devices Key Terms & Definitions
Proposed document posted for public consultation Sept 2021 through Nov 29, 2021
http://www.imdrf.org/consultations/cons-aimd-mlmd-ktd.asp

Examples of AI/ML-Enabled Devices

FDA News Release

FDA Authorizes Marketing of First Cardiac Ultrasound Software That Uses Artificial Intelligence to Guide User

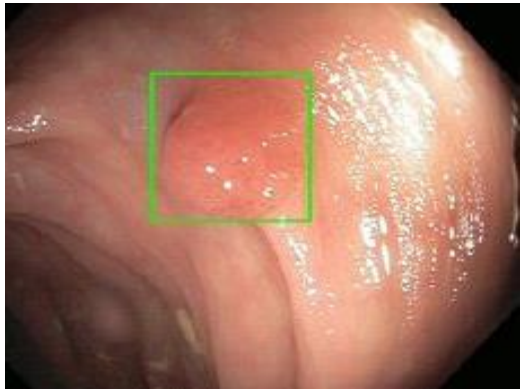
February 7, 2020

Caption Guidance

FDA News Release

FDA Authorizes Marketing of First Device that Uses Artificial Intelligence to Help Detect Potential Signs of Colon Cancer

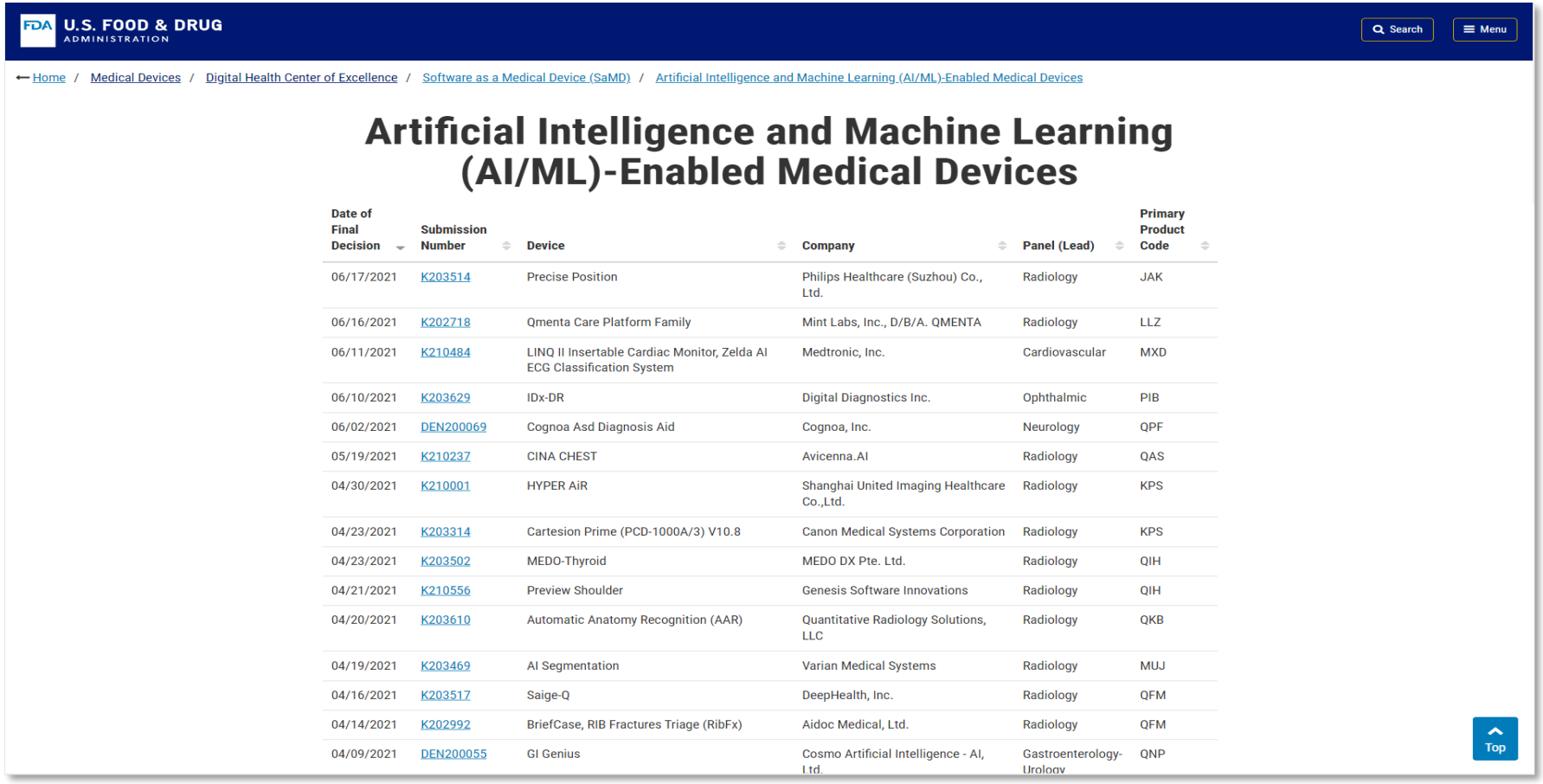
April 9, 2021



GI Genius

Caption Guidance™ (Caption Health, Brisbane AU). Figure from www.captionhealth.com
GI Genius™ (Medtronic Inc., Minneapolis, Minnesota, USA). Figure from Hassan C et al. Gut. 2019.

FDA Resources on AI/ML-Enabled Medical Devices



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Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices

Date of Final Decision	Submission Number	Device	Company	Panel (Lead)	Primary Product Code
06/17/2021	K203514	Precise Position	Philips Healthcare (Suzhou) Co., Ltd.	Radiology	JAK
06/16/2021	K202718	Qmenta Care Platform Family	Mint Labs, Inc., D/B/A. QMENTA	Radiology	LLZ
06/11/2021	K210484	LINQ II Insertable Cardiac Monitor, Zelda AI ECG Classification System	Medtronic, Inc.	Cardiovascular	MXD
06/10/2021	K203629	IDx-DR	Digital Diagnostics Inc.	Ophthalmic	PIB
06/02/2021	DEN200069	Cognoa Asd Diagnosis Aid	Cognoa, Inc.	Neurology	QPF
05/19/2021	K210237	CINA CHEST	Avicenna.AI	Radiology	QAS
04/30/2021	K210001	HYPER AiR	Shanghai United Imaging Healthcare Co.,Ltd.	Radiology	KPS
04/23/2021	K203314	Cartesion Prime (PCD-1000A/3) V10.8	Canon Medical Systems Corporation	Radiology	KPS
04/23/2021	K203502	MEDO-Thyroid	MEDO DX Pte. Ltd.	Radiology	QIH
04/21/2021	K210556	Preview Shoulder	Genesis Software Innovations	Radiology	QIH
04/20/2021	K203610	Automatic Anatomy Recognition (AAR)	Quantitative Radiology Solutions, LLC	Radiology	QKB
04/19/2021	K203469	AI Segmentation	Varian Medical Systems	Radiology	MUJ
04/16/2021	K203517	Saige-Q	DeepHealth, Inc.	Radiology	QFM
04/14/2021	K202992	BriefCase, RIB Fractures Triage (RibFx)	Aidoc Medical, Ltd.	Radiology	QFM
04/09/2021	DEN200055	GI Genius	Cosmo Artificial Intelligence - AI, Ltd.	Gastroenterology-Urology	QNP

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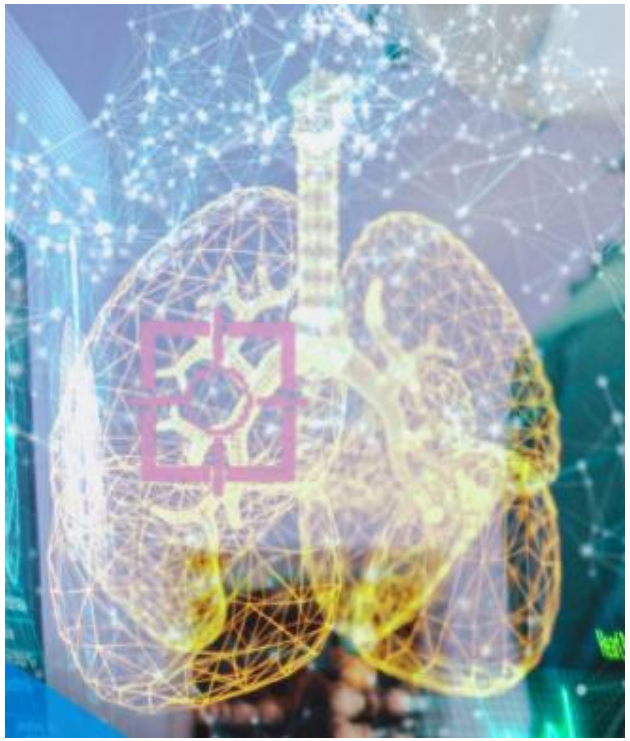
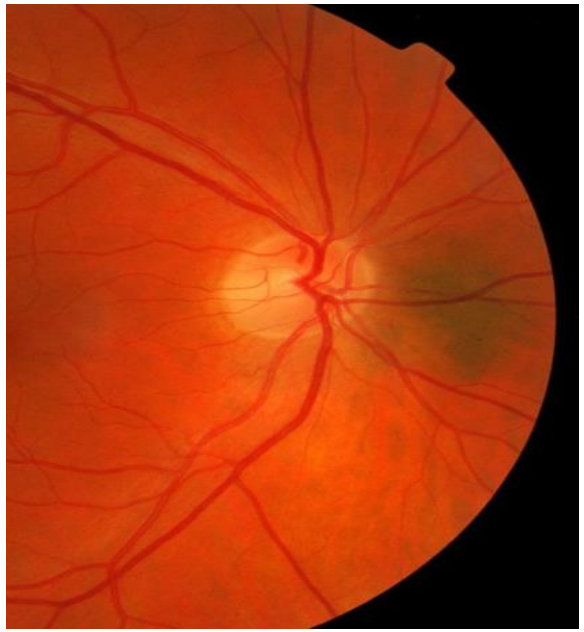
https://www.fda.gov/medical-devices/digital-health-center-excellence

AI/ML-Enabled Medical Devices: Opportunities



- Significant positive impact on health care
  - *Earlier disease detection*
  - *More accurate diagnosis*
  - *New insights into human physiology*
  - *Personalized diagnostics and therapeutics*
- Applications across all medical fields
- Ability to learn, adapt, and improve performance

AI/ML-Enabled Medical Devices: Challenges



- Fit-for-purpose data sets for development and testing, including diversity
- Identification and minimization of bias
- Opacity of some algorithms
- Providing oversight for an adaptive system
- Ensuring transparency to users

A Collaborative Approach to AI/ML-Enabled Devices

Recent Milestones

Published AI/ML-SaMD Discussion Paper

First joined Collaborative Community related to AI/ML

WORKSHOP
Evolving Role of AI in Radiological Imaging

Public Workshop on AI/ML in Radiological Imaging

PEAC Mtg on Patient Trust in AI/ML Devices

2019

2020

Published AI/ML Medical Device Software Action Plan

Posted List of Currently Marketed AI/ML Devices

WORKSHOP
Transparency of AI/ML-Enabled Medical Devices

Public Workshop on Transparency of AI/ML Devices

Published GMLP Guiding Principles

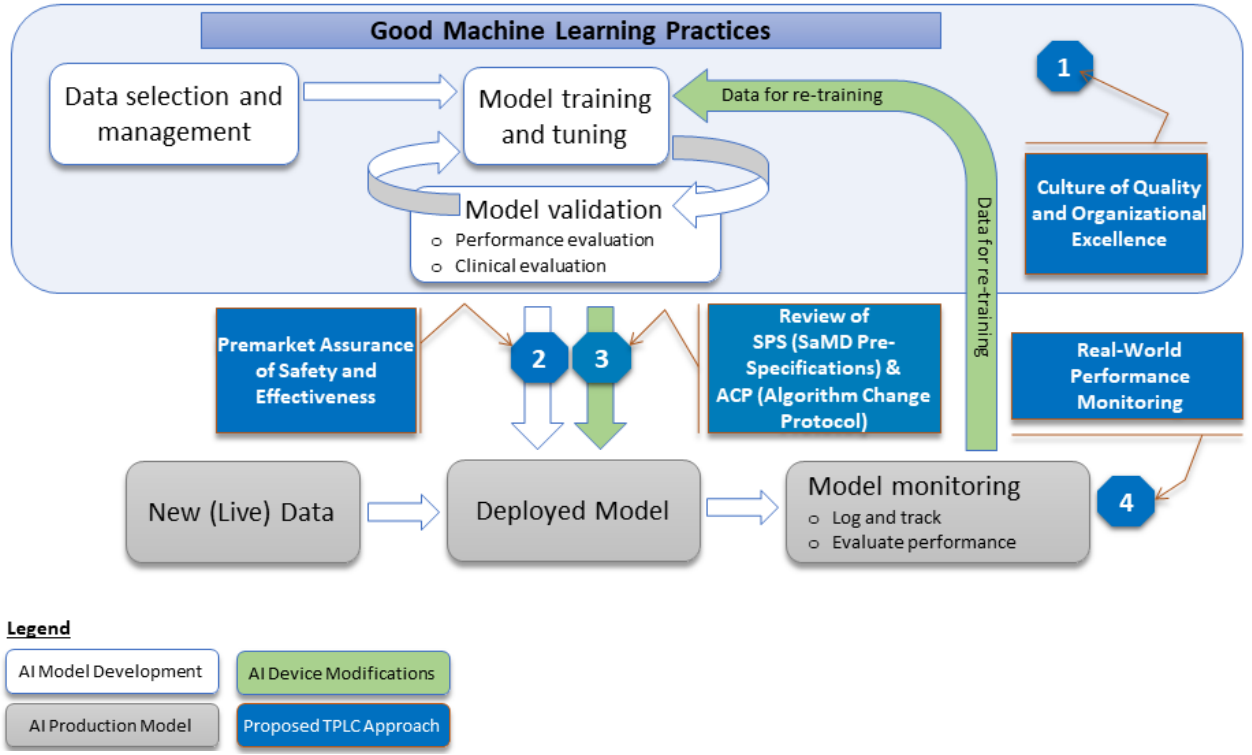
2021

Future Plans (2021+) AI/ML Medical Device Software Action Plan

- ❑ Update the proposed AI/ML framework
- ❑ Strengthen FDA's role in harmonizing GMLP
- ❑ Foster a patient-centered approach
- ❑ Support development of regulatory science methods
- ❑ Advance real-world performance pilots

Part 1: Regulatory Framework	Part 2: GMLP and Harmonization	Part 3: Pt-Centered Transparency	Part 4: Regulatory Science Methods	Part 5: RWP Considerations

Tailoring a Regulatory Framework for AI/ML-Enabled Devices



Overlay of FDA's TPLC approach on AI/ML workflow

Adapted from Proposed Regulatory Framework for Artificial Intelligence/Machine Learning (AI/ML)-Based SaMD

Tailoring a Regulatory Framework for AI/ML-Enabled Devices

Enhance patient access to high quality digital medical products

Maintain a reasonable assurance of safety and effectiveness

Enable manufacturers to rapidly improve software products with minor changes

Least burdensome

Internal FDA Use Only

Good Machine Learning Practice (GMLP)

GMLP

- **Accepted practices in AI/ML algorithm design, development, training, and testing that facilitate the quality development and assessment of AI/ML-enabled devices**
- **Based on concepts from quality systems, software reliability, machine learning, and data analysis**

- Standards Development:
  - IEEE AI Medical Device Working Group P2801
  - ISO/IEC SubCmte on AI 42 (ISO/ IEC JTC 1/SC 42)
  - AAMI/ BSI Initiative on AI in Medical Technology
- Collaborative Communities:
  - Xavier AI World Collaborative Community
  - Collaborative Community on Ophthalmic Imaging
  - Pathology Innovation Collaborative Community
- Other Collaborations:
  - IMDRF AI Medical Devices WG

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Good Machine Learning Practice for Medical Device Development: Guiding Principles	
Multi-Disciplinary Expertise Is Leveraged Throughout the Total Product Life Cycle	Good Software Engineering and Security Practices Are Implemented
Clinical Study Participants and Data Sets Are Representative of the Intended Patient Population	Training Data Sets Are Independent of Test Sets
Selected Reference Datasets Are Based Upon Best Available Methods	Model Design Is Tailored to the Available Data and Reflects the Intended Use of the Device
Focus Is Placed on the Performance of the Human-AI Team	Testing Demonstrates Device Performance During Clinically Relevant Conditions
Users Are Provided Clear, Essential Information	Deployed Models Are Monitored for Performance and Re-training Risks are Managed

https://www.fda.gov/medical-devices/software-medical-device-samd/good-machine-learning-practice-medical-device-development-guiding-principles

Patient-Centered Approach Incorporating Transparency to Users

- AI/ML-enabled devices have unique considerations that necessitate a proactive patient-centered approach:
  - that takes into account issues including usability, equity, trust, and accountability
  - that promotes transparency to all users and to patients more broadly
- Patient Engagement Advisory Committee (PEAC) Meeting held Oct 2020
- Workshop on Transparency of AI/ML-Enabled devices held Oct 2021

Virtual Workshop on Transparency of AI/ML-Enabled Devices

- What are the needs of specific stakeholders?
- What is the appropriate information to communicate?
- What is the best way to communicate that information?
  - How can device labeling be improved?
  - How can other public-facing information be improved?
  - What else can be done to promote transparency?

Please submit your comments regarding the workshop to https://www.regulations.gov/, Docket No. FDA-2019-N-1185 by November 15, 2021.

Regulatory Science Methods Related to Algorithm Bias & Robustness

- Need for improved methodologies for the evaluation and development of machine learning algorithms
- Includes methods for the identification and minimization of bias, and on the robustness and resilience of these algorithms to withstand changing clinical inputs and conditions

Regulatory Science Methods Related to Algorithm Bias & Robustness

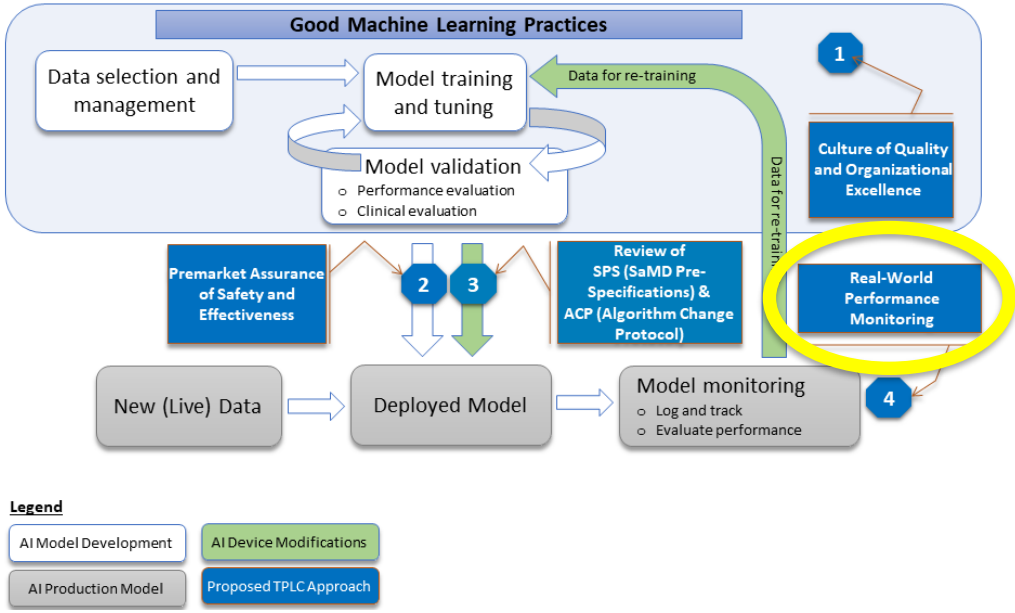
- Regulatory science research efforts to develop these methods to evaluate AI/ML-enabled medical software.
- Ongoing research being conducting in collaboration with Centers for Excellence in Regulatory Science and Innovation (CERSIs) at:
  - University of California San Francisco (UCSF)/ Stanford University;
  - Johns Hopkins University.
- These collaborations complement the ongoing research efforts and the AI/ML program charter at OSEL.

CERSI Johns Hopkins University

CERSI UCSF-Stanford

Real World Performance

- Collection and monitoring of real-world data will support a total product lifecycle (TPLC) approach to the oversight of AI/ML-enabled software
- By gathering data on real-world use and performance of software, manufacturers can:
  - Improve their understanding of how their products are being used
  - Identify opportunities for improvements, and
  - Respond proactively to safety or usability concerns



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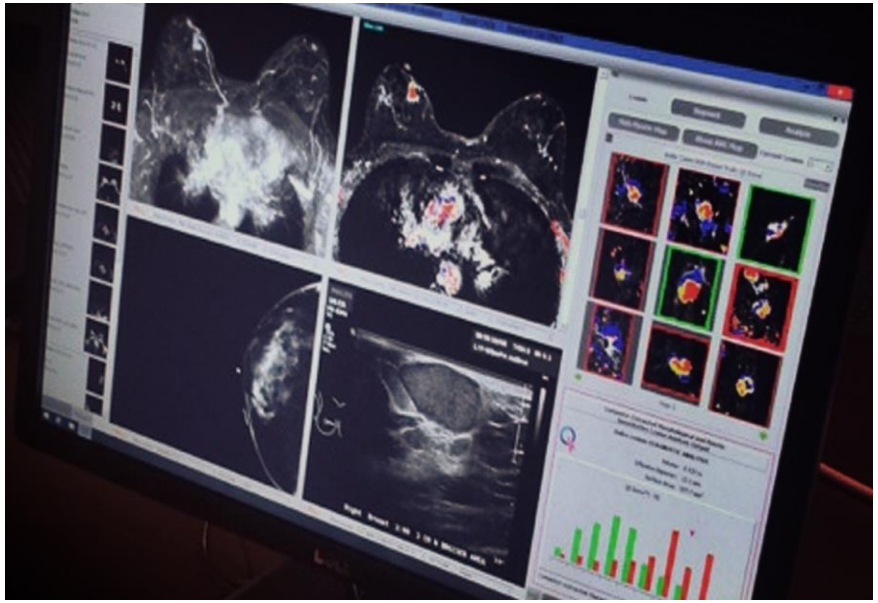
Real World Performance

Actions:

- Support the piloting of real-world performance monitoring by working with stakeholders on a voluntary basis
- Coordination with other ongoing FDA programs focused on the use of real-world data
- Develop a framework for seamless gathering, validation, and evaluation of relevant real-world performance metrics
- Continued stakeholder and public engagement



https://angel.co/quantitative-insights

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Further Questions or Feedback:

www.fda.gov/digitalhealth

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Adaptive's T-Detect COVID Test: An AI/ML Based Classifier in a Medical Device

Sally Howard, J.D.

Vice President, Regulatory, Quality & External Affairs
Adaptive Biotechnologies

FDLI, November 10, 2021

FDLI

Approach for Identifying Public, Diagnostic T-Cell Receptors Specific to SARS-CoV-2[1-3]

Sequence TCR Repertoires

SARS-CoV-2–positive cases confirmed by PCR

n=2481

SARS-CoV-2–negative controls

n=7990

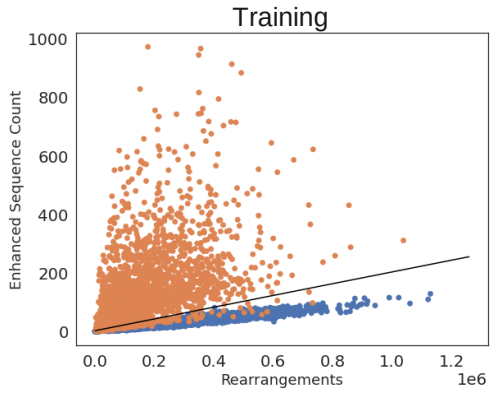
Identify TCR Sequences Associated With SARS-CoV-2 (Enhanced Sequences):

TGGAGCTAATCGAGCTTAG
ACGCGCGATTAGCATTAGT
AGCCTCGGAGCGCGGATA
TTATGAAGCGCGATTAGCA

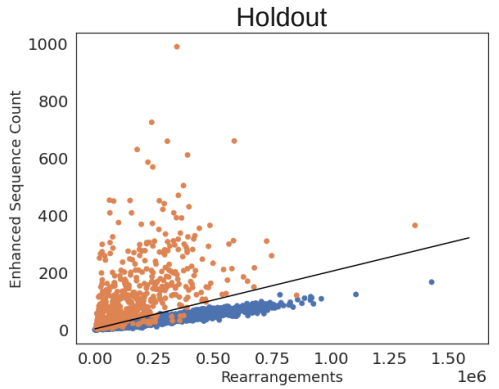
Presence in cases: **15.6%**
Presence in controls: 0.2%

8631
Enhanced sequences were identified

Create a Classifier to Assess Past SARS-CoV-2 Infection



Training	
Cases, n	Controls, n
2009	3909



Holdout	
Cases, n	Controls, n
472	4081

Plotting the frequency and quantity of enhanced sequences allows calculation of a regression line that acts as a threshold to identify SARS-CoV-2–positive samples with 99.8% specificity

PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TCR, T-cell receptor.

1. Dalai SC et al. medRxiv. 2021. https://doi.org/10.1101/2021.01.06.21249345. Published January 8, 2021. 2. Snyder TM et al. medRxiv. 2020. https://doi.org/10.1101/2020.07.31.20165647. Published September 17, 2020. 3. Data on File. Adaptive Biotechnologies. 2021.

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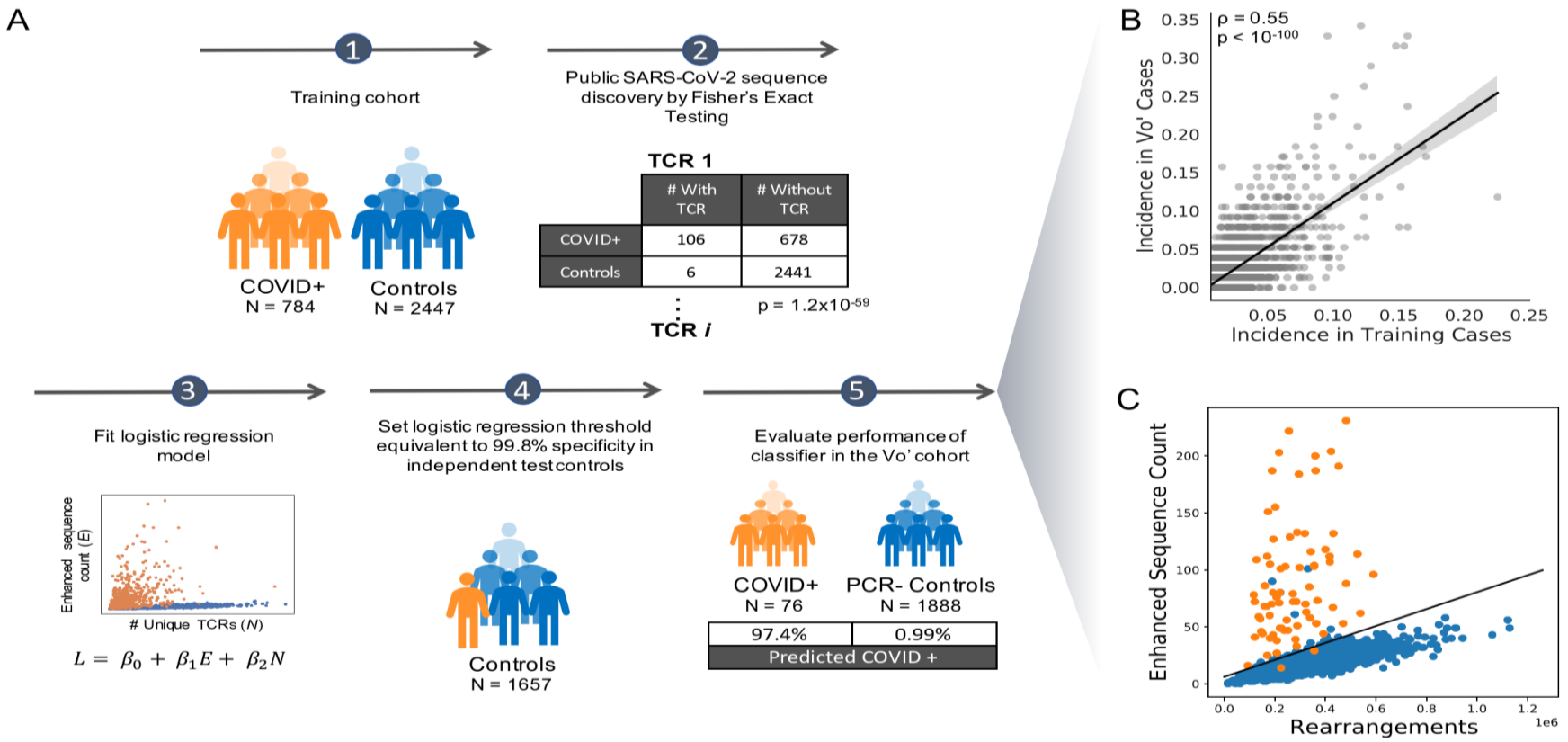
T-Detect COVID: Development and Validation Efforts

- Train model on large case/control cohorts, identify unique TCR signals to make model, test in other studies
- Application in Vo', Italy cohort (~2500 subjects) demonstrates 97.4% sensitivity and 99% specificity



Gittelman, et al. medRxiv 2021

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Overview of Clinical Cohorts[1,2]

Cohort	Location	Phase of Illness	Samples, n	Participants, n	Age, Median (Range)	Male, %
COVID-19–BWNW	Bloodworks Northwest Seattle, WA	Convalescent	50	50	53 (20–79)	46
COVID-19–DLS	Discovery Life Sciences (multiple sites) Huntsville, AL	Acute or convalescent	433	350	68 (23–89)	53
COVID-19–ISB	Institute for Systems Biology Seattle, WA	Active	444	184	55 (18–89)	46
COVID-19–NIH/NIAID	Brescia and Monza (Italy) NIAID for DNA extraction	Active	629	353	63 (24–89)	42
COVID-19–H12O	Hospital Universitario 12 de Octubre Madrid, Spain	Active or convalescent	1142	1080	61 (6–89)	56
COVID-19–IRST	Instituto Scientifico Romagnolo per lo Studio e la Cura del Tumori (IIRST)/AUSL Romagna, Italy	Active	64	64	77 (20–89)	52
COVID-19–ImmuneRACE	24 geographic areas in the US Adaptive Biotechnologies Seattle, WA	Exposure to SARS-CoV-2, active infection, or recovered from COVID-19	163	163	43 (18–79)	29
COVID-19-UW-Livingston	University of Washington, US	Active or convalescent	129	38	65 (21-89)	NA
COVID-19-Koelle	University of Washington, US	Convalescent	387	320	50 (19-89)	46
COVID-19-Sergas	Servizo Galego de Saude, Spain	Active or convalescent	100	100	52 (0-89)	52
COVID-19-Padova	University of Padua, Vo' Italy	Convalescent	97	97	NA	52

1. Snyder TM et al. *medRxiv*. 2020. https://doi.org/10.1101/2020.07.31.20165647. Published September 17, 2020. 2. Data on File. Adaptive Biotechnologies. 2021.

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T-Detect COVID March 5, 2021, EUA Intended Use and Performance

- The T-Detect COVID Test is intended for use as an aid in identifying individuals with an adaptive T-cell immune response to SARS-CoV-2, indicating recent or prior infection with SARS-CoV-2.
- A machine learning algorithm developed specifically for use as part of your product is employed to identify patients with an immune response to SARS-CoV-2 based on the observed rearranged TCR β sequences identified by your product.
- PERFORMANCE:
  - **PPA/Sensitivity:**
    - >15 days Post Symptom Onset: 92.11%
    - >15 days Post PCR: 97.1%
  - **NPA/Specificity:** 100% in retrospective cohort, 98.7% in prospective, symptomatic, COVID Neg. cohort.

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Potential Modifications

- Performance: no change to intended use or input:
  - Improved sensitivity/specificity
  - Better delineate performance in different time frames
- Modifications related to inputs, with no change to intended use:
  - Vaccine Aware model used new input (vaccinated people) to distinguish positives resulting from vaccine vs. natural infection
- Modification related to intended use:
  - T-cell response for infection OR vaccine
  - Semi-Quantitative or Quantitative assay
  - Quantitative with correlate of protection claim

We don’t know at time of submission which modification should be pursued

What data is available for use

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