The Unique Regulatory, Legal and Practical Challenges of Artificial Intelligence/Machine Learning

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Medical Devices: FDA Regulation in the Era of Technology and Innovation Conference

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FDA ARTIFICIAL INTELLIGENCE / MACHINE LEARNING DISCUSSION PAPER

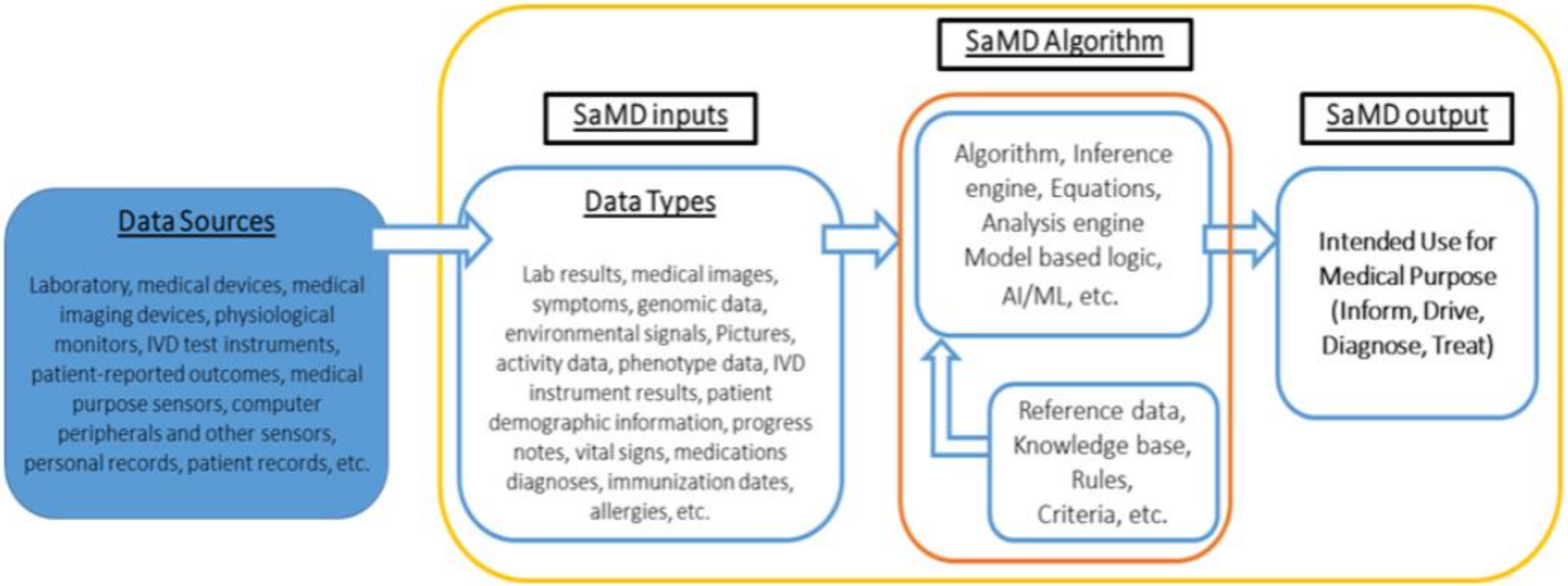
June 6, 2019

Agenda

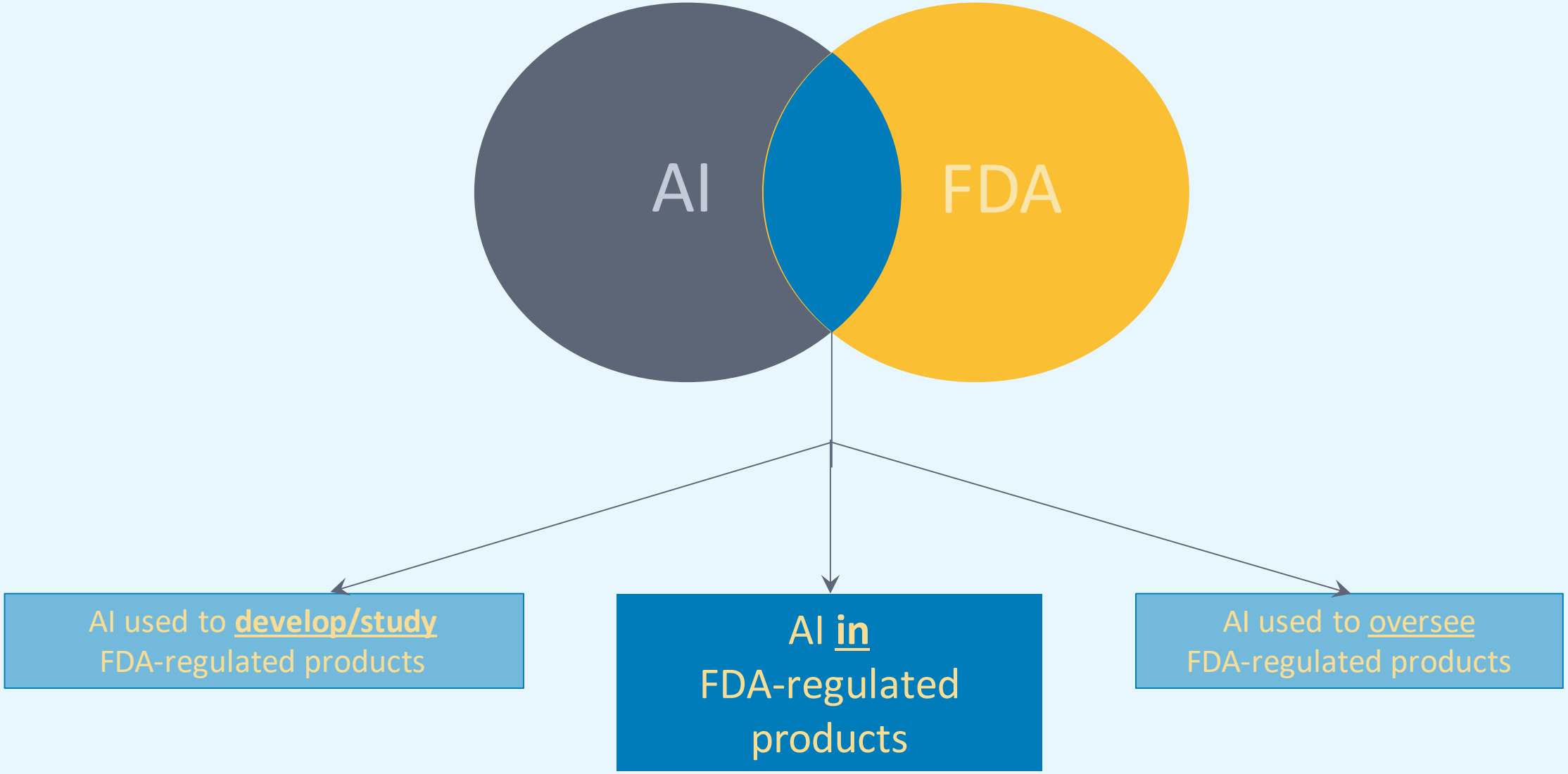
- Background & Introduction
- Proposed Framework for Pre-Specifying Modifications
- Examples & Questions

What is a SaMD?

"Software as a Medical Device" (SaMD) is defined as software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device.[5]



Potential Intersections of AI and FDA



Goals for a Tailored Regulatory Framework

Fostering Responsible Digital Health Innovation

- Enhance patients access to high quality digital medical products
- Enable manufacturers to rapidly improve software products with minor changes
- Maintain a reasonable assurance of safety and effectiveness
- Minimally burdensome

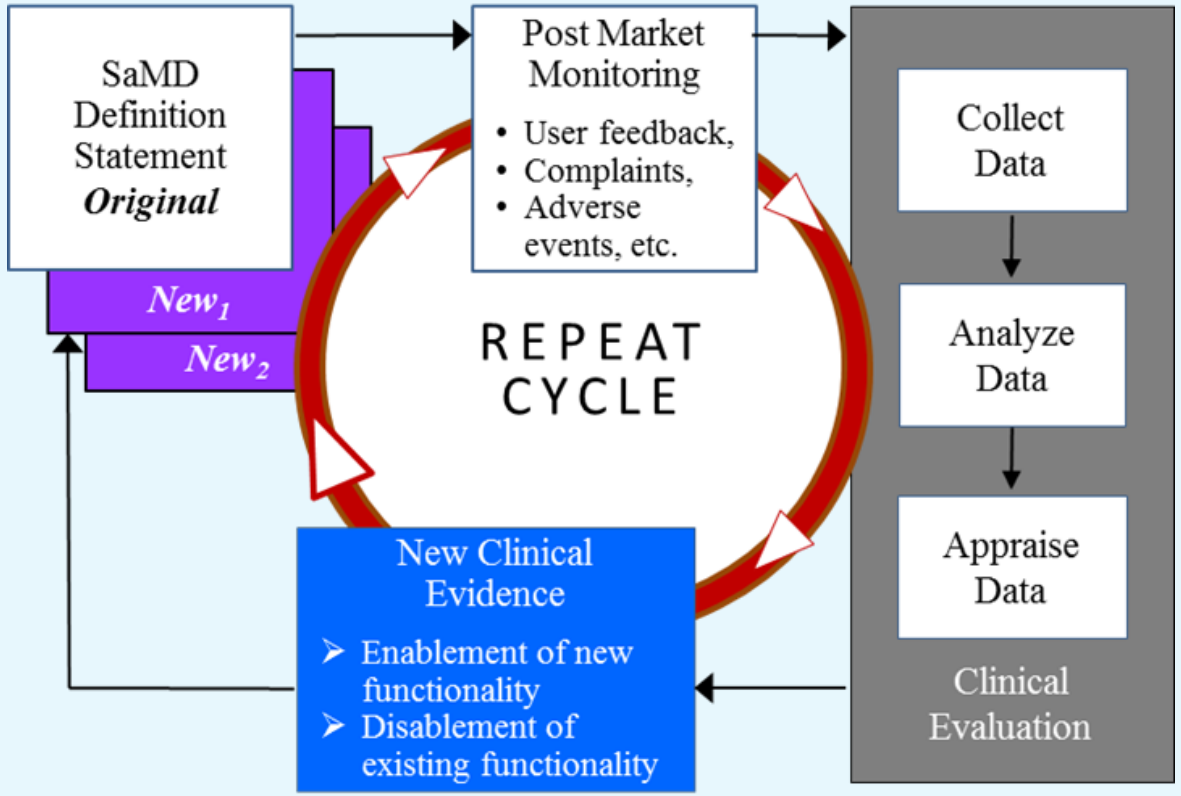
The Need for a Tailored Approach

While maintaining reasonable assurance of safety and effectiveness

Today's Device World (Hardware-based)	Digital Health Device World (Software-Based)
Product Development Timeline • Months to years + • Less frequent modifications	**Product Development Timeline** • Weeks to months (**incremental, iterative**) + • Frequent modifications
Postmarket Data • Limited availability and access to real world data (522, PAS, MDRs, MedSun)	**Postmarket Data** • Potential for **high availability** and access to rich real world data (benefits and risks)
FDA Premarket Program Volume: • Stable (~3,500 510(k) submissions / 2200 pre-submissions)	**FDA Premarket Program Volume:** • Potential for **exponential** increase in volume of submissions

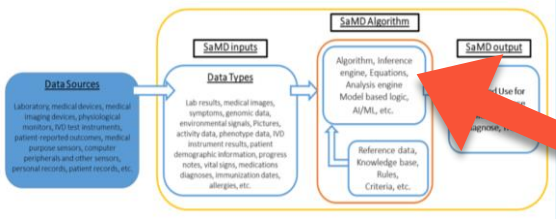
Pathway for Continuous Learning Leveraging Real World Performance Data

SaMD manufacturers are encouraged to leverage SaMD's technology capability to capture real world performance data to understand user interactions with the SaMD, and conduct ongoing monitoring of analytical and technical performance to support future intended uses.



1. Additional clinical data is gathered.
2. The data may create and support new intended use(s).
3. The SaMD manufacturer will update the clinical evaluation and generate a new definition statement.
4. Then the cycle repeats.

Artificial Intelligence & Machine Learning



Artificial Intelligence (AI)

Programming computers to perform tasks to mimic human capabilities- such as understanding language, recognizing objects and sounds, learning, and problem solving – by using logic, decision trees, machine learning, or deep learning

Machine Learning (ML)

Subset of AI that gives "*Computers the ability to learn without being explicitly programmed*" -Arthur Samuel, 1959

Supervised Learning
(labeled data)

Unsupervised Learning

Deep Learning
Subset of ML: enable computer to teach itself by exposing it to vast amount of data

Reinforcement Learning

Open Questions

Evaluation of safety and effectiveness:

Open Questions:

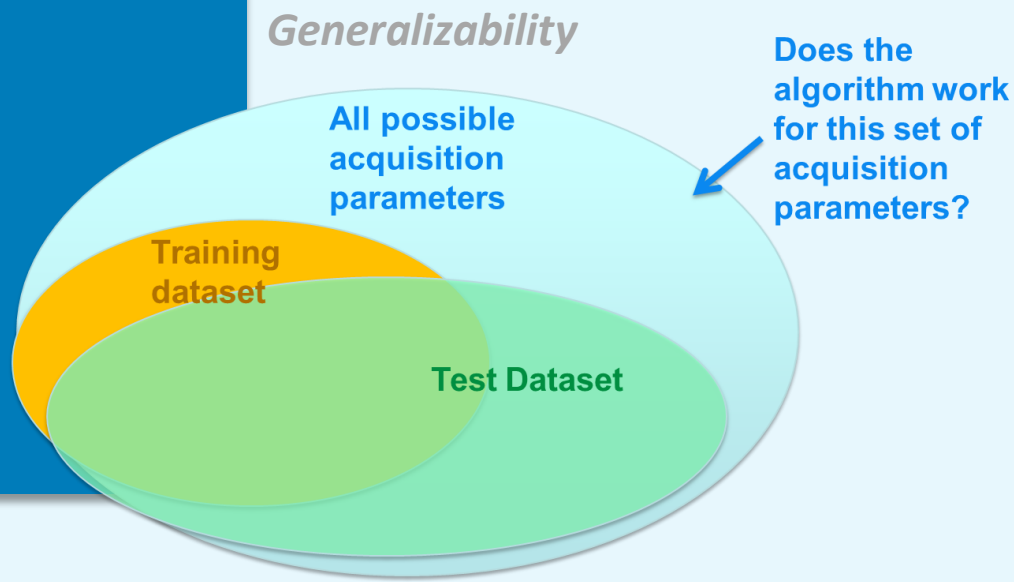
- Continuous learning while assuring safety and effectiveness?
- Availability for large and robust datasets with representable clinical variability
- Continuous algorithm updates
- Interpretability and explain-ability of the “basis of the recommendation”

Assurance for Safety and Effectiveness

IDx

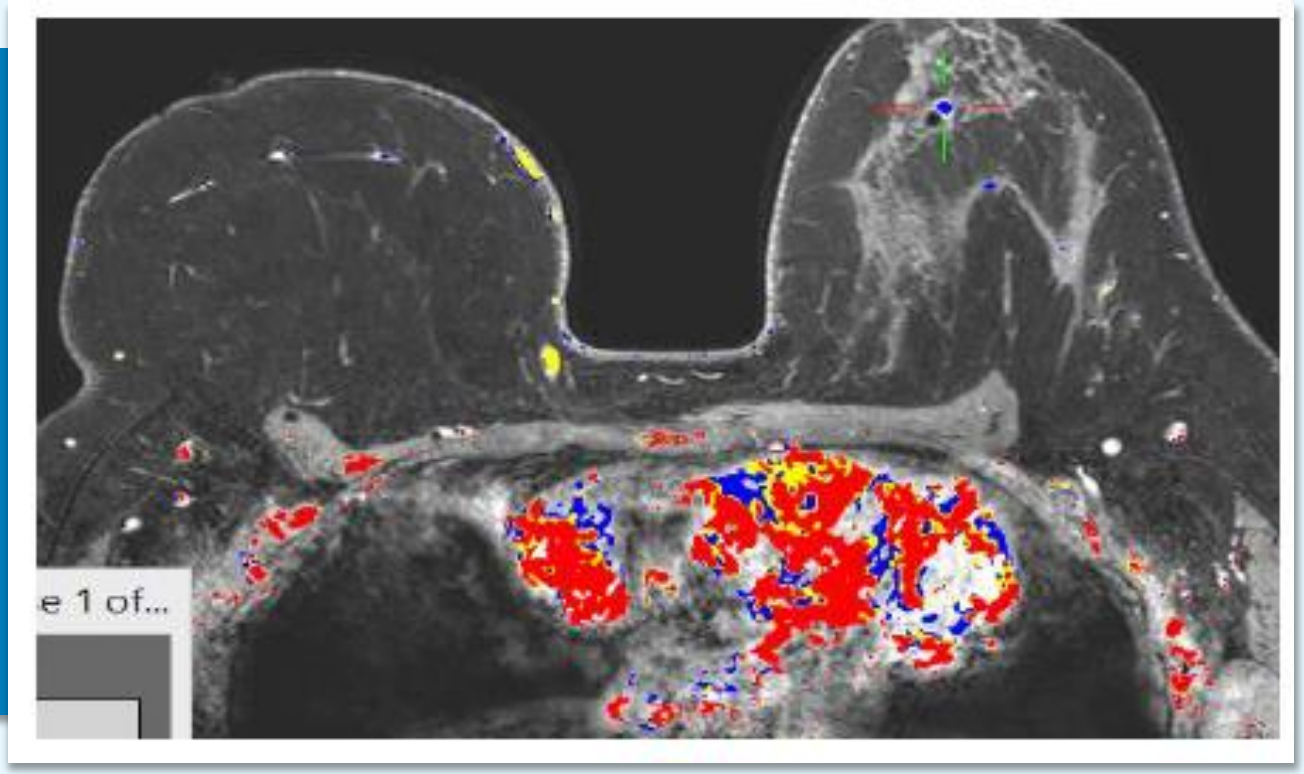
IDx-DR is intended for use by health care providers to automatically detect more than mild diabetic retinopathy (mtmDR) in adults diagnosed with diabetes who have not been previously diagnosed with diabetic retinopathy

- High data quality for training
- Algorithm “correctness” (verification)
- Performance testing (validation)
- Generalizability (addressing bias)
- Interpretability



AI/ML-Based Medical Devices: Challenges

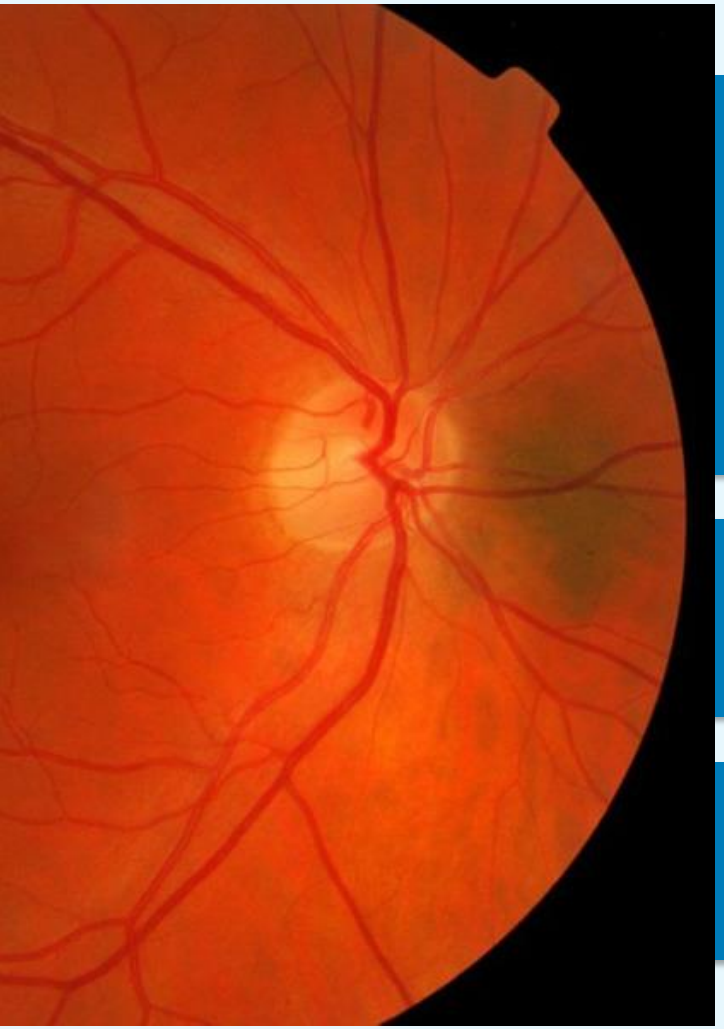
- Need for large, high-quality, well-curated data sets
- Explain-ability of these "black box" approaches
- Identifying and removing bias
- Providing oversight to an AI-based product that is changing



QuantX

AI/ML-Based Medical Devices

IDx-DR



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

Ability for AI/ML to learn from the wealth of real-world data and improve its performance

Already seen AI/ML lead to the development of novel medical devices

Examples of AI/ML-Based SaMD

FDA News Release

FDA permits marketing of clinical decision support software for alerting providers of a potential stroke in patients

February 13, 2018

Viz.Ai

FDA News Release

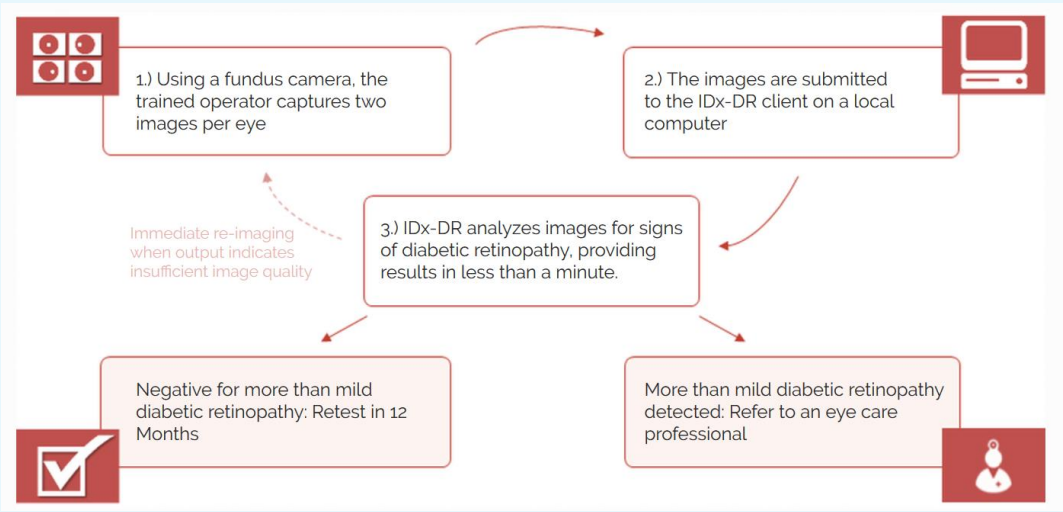
FDA permits marketing of artificial intelligence-based device to detect certain diabetes-related eye problems

April 11, 2018

IDx-DR

IDx-DR: AI-Based Medical Software for Diabetic Retinopathy

Designed and tested for use in a primary care setting



IDx-DR is intended for use by health care providers to automatically detect more than mild diabetic retinopathy (mtmDR) in adults diagnosed with diabetes who have not been previously diagnosed with diabetic retinopathy

Clinical Evaluation & Evidence Gathering

Clinical Evaluation

① Valid Clinical Association

Generate evidence to demonstrate a valid clinical association between a SaMD output and a SaMD's targeted clinical condition

- **Use existing evidence** (e.g., literature searches, original clinical research, professional society guidelines), or
- **Generate new evidence** (e.g., secondary data analysis, perform clinical trials)

② Analytical Validation

+ +

Generate evidence to demonstrate that the SaMD correctly processes input data to generate accurate, reliable, and precise output data

- Generate evidence as part of **quality management system** or **good software engineering practices**

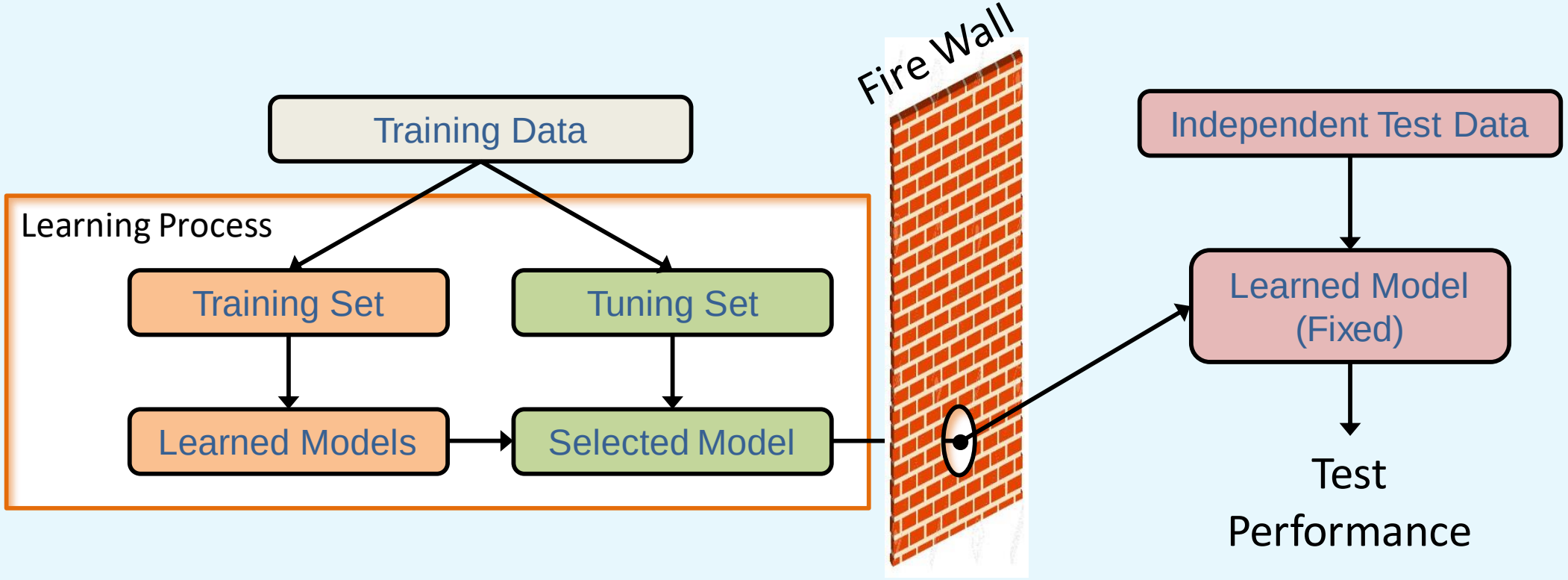
③ Clinical Validation

Generate evidence to demonstrate that the SaMD's accurate, reliable, and precise output data achieves its intended purpose in its target population in the context of clinical care

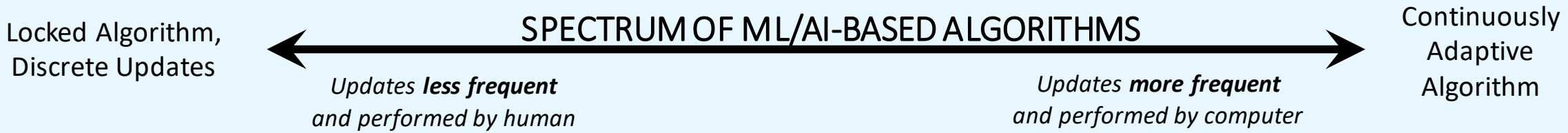
- Generate evidence that shows:
  - **The SaMD has been tested for its target population and for its intended use;**
  - **Users can achieve clinically meaningful outcomes through predictable and reliable use.**

Performance Testing of AI/ML-Based SaMD

Performance testing using an independent data set



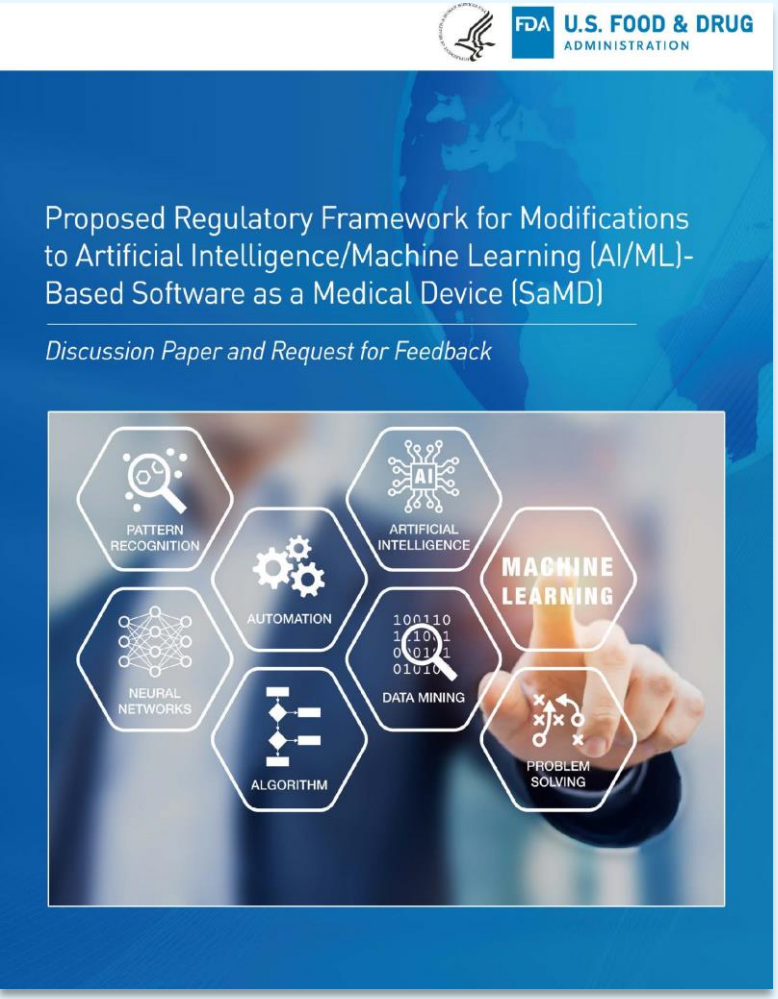
Spectrum of ML/AI-Based Algorithms



Discussion Paper

A **TPLC** approach
for modifications to Ai/ML
Software as a Medical Device (SaMD)

AI/ML Discussion Paper

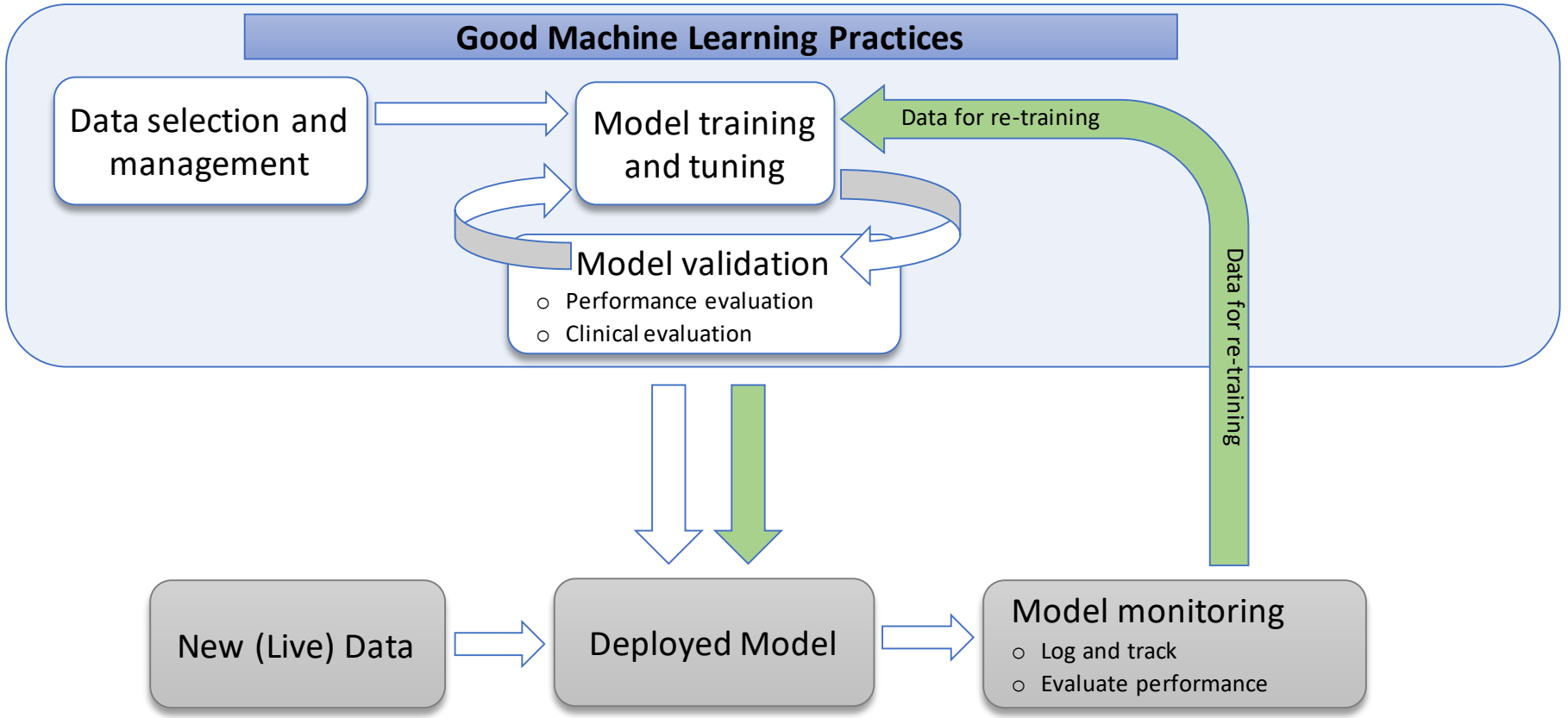


"Today, we're announcing steps to consider a new regulatory framework specifically tailored to promote the development of safe and effective medical devices that use advanced artificial intelligence algorithms."

Dr. Scott Gottlieb, FDA Commissioner

April 2, 2019

Typical AI/ML Model Lifecycle



Legend

- AI Model Development
- AI Production Model
- AI Device Modifications

Locked Algorithm, Discrete Updates

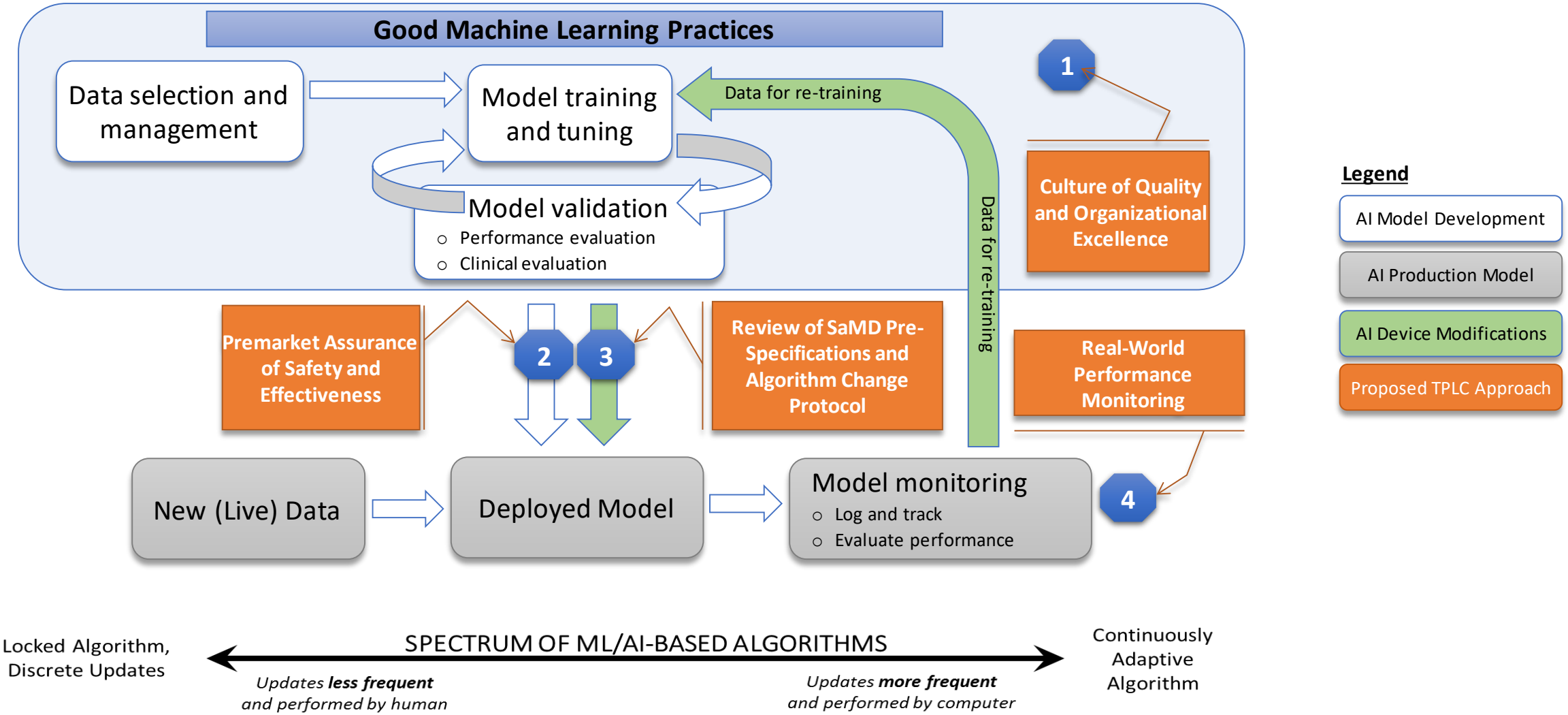
SPECTRUM OF ML/AI-BASED ALGORITHMS

*Updates **less frequent** and performed by human*

*Updates **more frequent** and performed by computer*

Continuously Adaptive Algorithm

FDA's Proposed TPLC Approach Overlaid on AI/ML Workflow



SPS & ACP: A Pre-Determined Change Control Plan

SaMD Pre-Specifications (SPS):

- Delineates the proposed types of modifications to the SaMD (i.e., what types of changes the sponsor plans to achieve)
- Draws a virtual "region of potential changes" around the initial specifications and labeling of the original device

Algorithm Change Protocol (ACP):

- Describes the methods for performing and validating the changes pre-specified in SPS (i.e. how the sponsor intends to achieve the changes)
- Typically specific to the device and type of change
- Expected to contain a step-by-step delineation of the procedures to be followed

Good ML Practices (GMLP):

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

Algorithm Change Protocol (ACP)

Data Management	➢ For new training & test data: • Collection protocols • Quality assurance • Reference standard determination ➢ Auditing and sequestration of training and test sets
Re-training	➢ Re-training objectives ➢ Changes related to: • ML methods, including architecture and parameters • Data pre-processing ➢ Criteria to initiate performance evaluation
Performance Evaluation	➢ Assessment metrics ➢ Statistical analysis plans ➢ Frequency and triggers for evaluation ➢ Performance targets ➢ Methods for testing with “clinicians in the loop” when necessary
Update Procedures	➢ Software verification and validation ➢ When and how updates will be implemented ➢ Plans for global and local updates ➢ Communication and transparency to users

Q&A

Further Questions or Feedback

www.fda.gov/digitalhealth

DigitalHealth@fda.hhs.gov

FDA is seeking input on the concepts explored in the AI/ML Discussion Paper.

Please submit comments by June 3, 2019.

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Good Machine Learning Practices fit into your QMS

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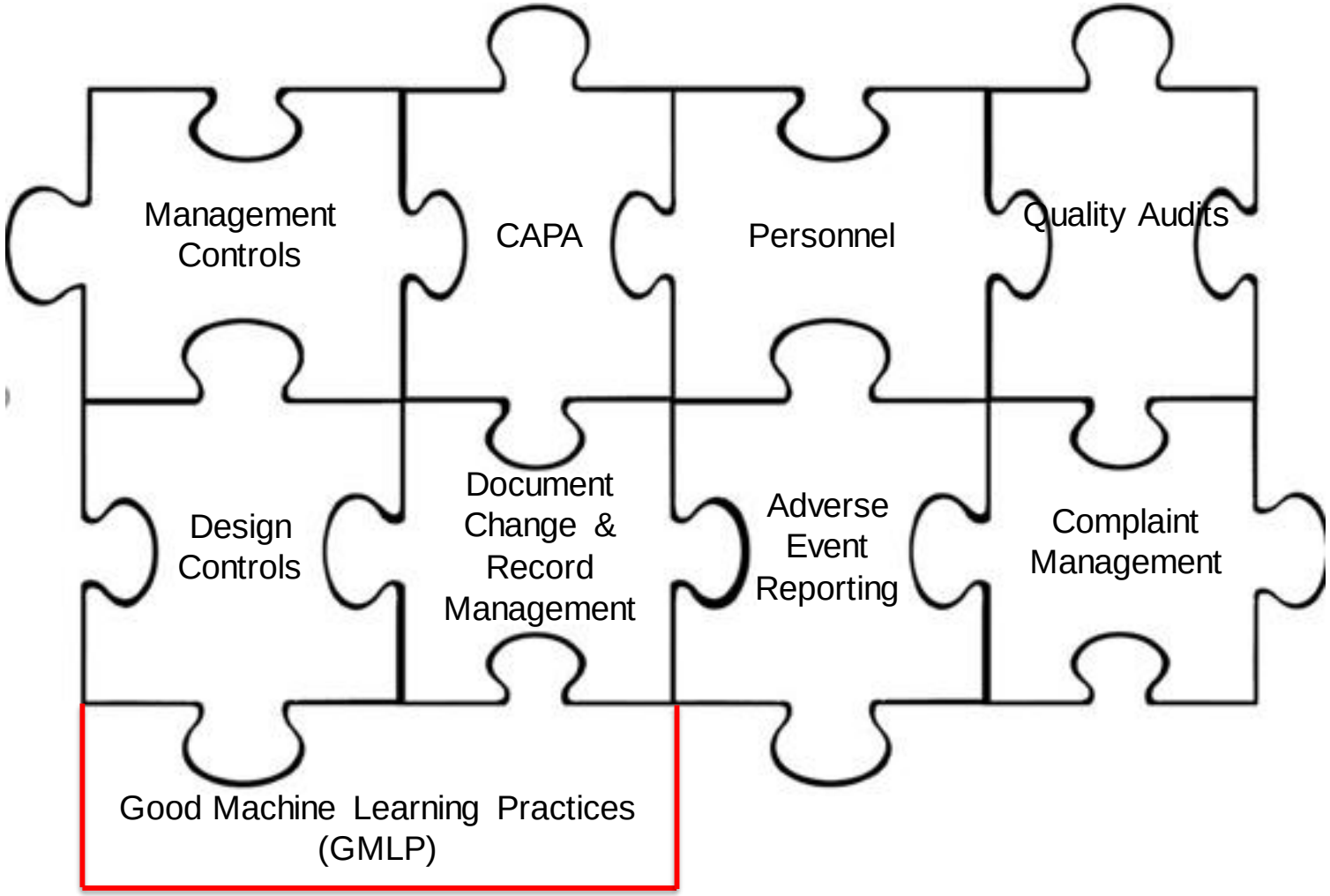
Quality Systems and Good Machine Learning Practices



GMLP fits into QMS

Design Controls

- Design Inputs & Outputs
- Verification & Validation

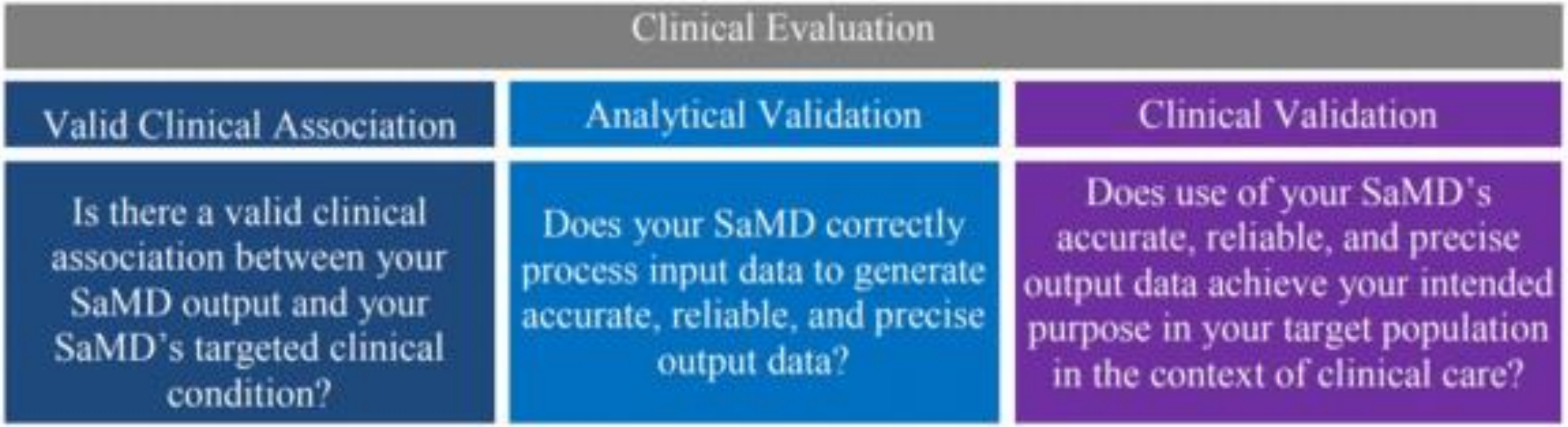
Document Change & Record Management

- Change Control
- Record Creation & Retention

Design Controls

- According to 21CFR 820.30
  - Need clear design inputs and outputs to ensure intended use is identified and outlined in clear objectives.
  - Verification and validation activities validate inputs and outputs. Specific requirements for software validation are a part of 820.30 (g)
- AI/ML-based SaMD rely heavily on data
  - V&V plans need to ensure data acquired correctly
  - Clinical Evaluation plays large role

Design Controls & Clinical Evaluation



Document Change & Record Management

- Change control maintains oversight over what changes are being made for all aspects of the device throughout it's lifecycle.
- Record creation and retention keeps track of all changes being made and all documents and records generated.
  - Test protocols
  - Test results
  - Data collected
  - Etc.

Algorithm change protocol and SaMD Pre-specifications

- If the proposed algorithm change fits into the ACP and SPS submitted- Simply document and approve the change via the change control program of your QMS.
- If not, refer guidance ‘Deciding When to Submit a 510(k) for a Software Change to an Existing Device’

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