Tailoring a Regulatory Framework for Artificial Intelligence/ Machine Learning (AI/ML)-Enabled Medical Devices

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CDRH Digital Health Center of Excellence, US FDA

Disclaimer

Outline

- Digital Health and the CDRH DH Center of Excellence
- Artificial Intelligence/ Machine Learning (AI/ML)-Enabled Medical Devices
- FDA AI/ML Action Plan

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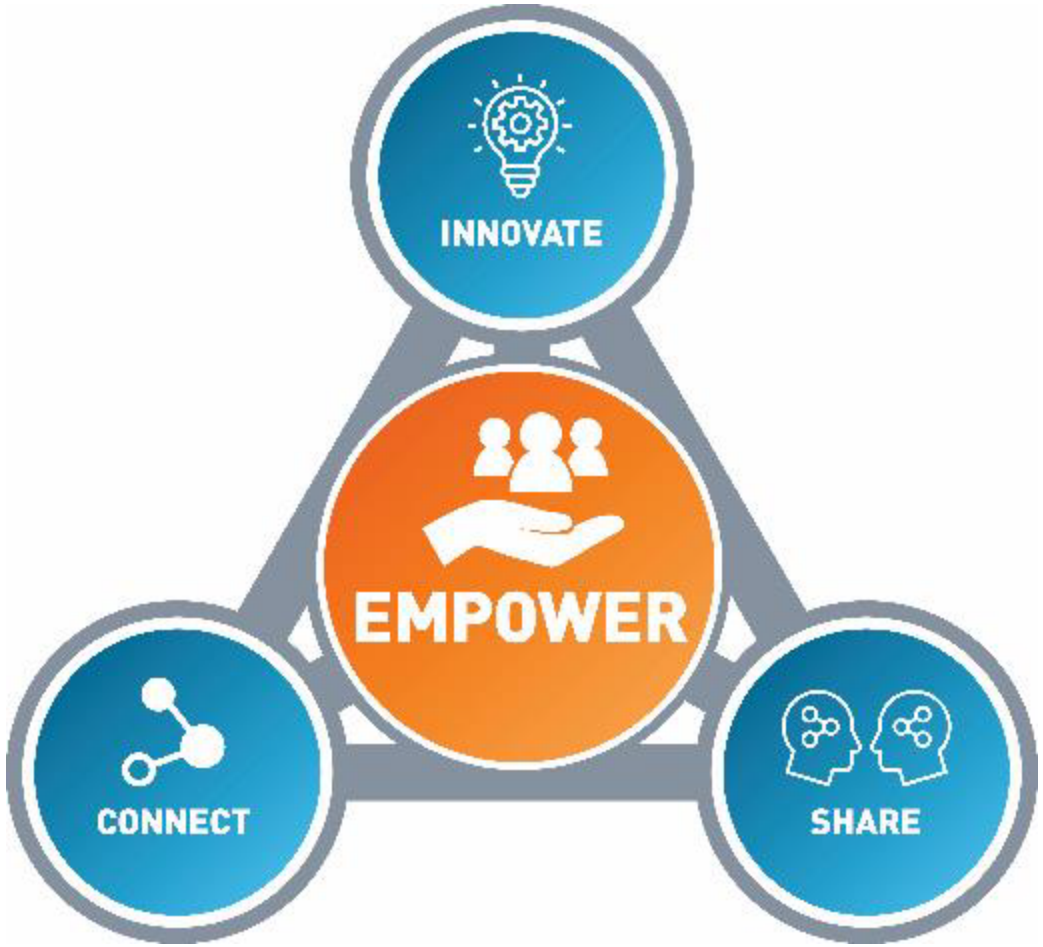
CDRH's Digital Health Center of Excellence

Empowering All to Advance Healthcare

Our goal: Empower stakeholders to advance public health by fostering responsible and high-quality digital health innovation.

- **Connect and build** partnerships to accelerate digital health advancements.
- **Share knowledge** to increase awareness and understanding, drive synergy, and advance best practices.
- **Innovate regulatory approaches** to provide efficient and least burdensome oversight while meeting the FDA standards for safe and effective products.



CDRH's Digital Health Center of Excellence

is advancing health care by fostering responsible and high-quality digital health innovation.

Digital Health Technologies play an increasingly significant role in health care.

Digital therapy device to reduce sleep disturbance for psychiatric conditions

Digital therapy device for Attention Deficit Hyperactivity Disorder

Electrocardiograph software for over-the-counter use

Self-fitting over-the-counter hearing aids

Virtual reality behavioral therapy device for pain relief

In 2022, CDRH's DHCoE focused on …

Fostering Innovation

Authorized more than **500 AI/ML-enabled medical devices**, and more are under development.

Omnibus provision allows for changes to a device consistent with an approved **Predetermined Change Control Plan** without supplemental action.

Advancing Transparency and Equity

Patient Engagement Advisory Committee met to discuss **Augmented Reality/ Virtual Reality medical devices** and factors to consider when evaluating them.

Strengthening Cybersecurity

There was **a 17-fold increase** in device - related vulnerabilities from 2016 to 2020.

… And more is on the horizon.

Publish draft guidance on **Predetermined Change Control Plans** for **Artificial Intelligence / Machine Learning** –enabled devices.

Continued focus on how **DHTs can support decentralized trials and remote patient monitoring**, which will help underserved populations access health care.

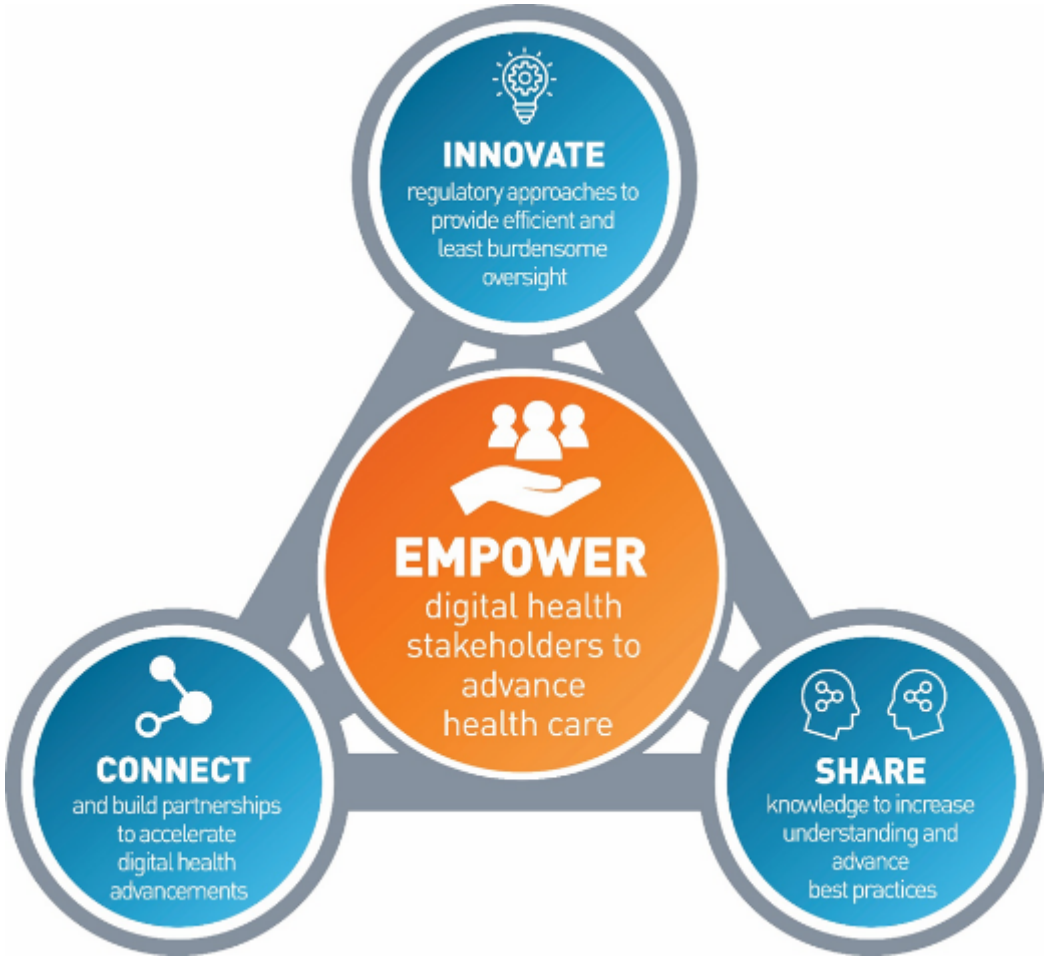
Engage with stakeholders, including patients, users, and industry to explore regulatory approaches to digital health technologies.

Continue to **develop software and digital health technical expertise**.

Continue to **participate in international harmonization efforts.**

CDRH Digital Health Center of Excellence

Empowering All to Advance Healthcare



- Software as a Medical Device (SaMD)
- Artificial Intelligence/ Machine Learning
- Wearables
- Software in a Medical Device (SiMD)
- Wireless connectivity
- Interoperability
- Medical Device Cybersecurity
- Virtual Reality/ Augmented Reality
- Real-world Evidence and Advanced Clinical Studies
- Advanced Manufacturing
- Patient-Generated Health Data

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

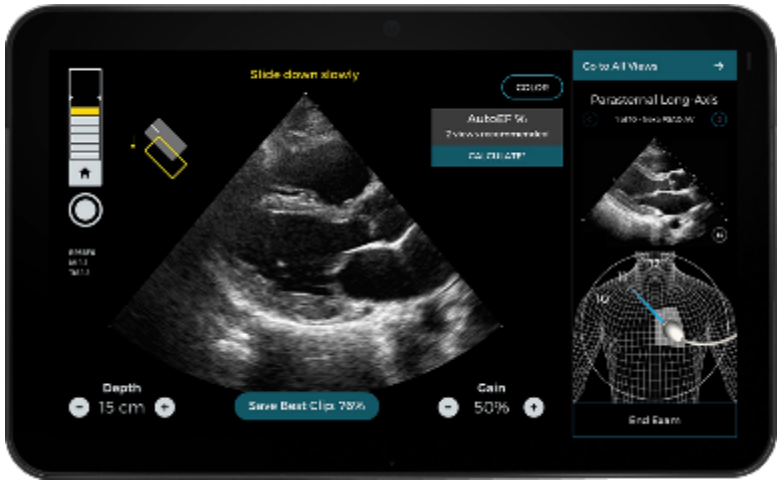
Artificial Intelligence (AI):
A branch of computer science, statistics, and engineering that uses algorithms or models to perform tasks and exhibit behaviors such as learning, making decisions and making predictions.

Machine Learning (ML):
A subset of AI that allows ML models to be developed by ML training algorithms through analysis of data, without models being explicitly programmed.

ML-Enabled Medical Device (MLMD):
A medical device that uses machine learning, in part or in whole, to achieve its intended medical purpose.

Adapted from IMDRF Artificial Intelligence Medical Devices Key Terms & Definitions
Final document posted May 9, 2022 at:
https://www.imdrf.org/documents/machine-learning-enabled-medical-devices-key-terms-and-definitions

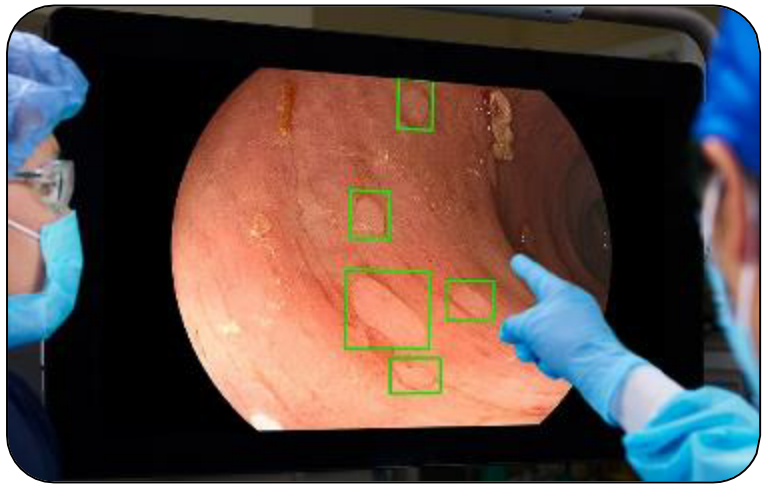
We are ensuring patient access to safe and effective AI/ML-Enabled Medical Devices



2/7/20

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

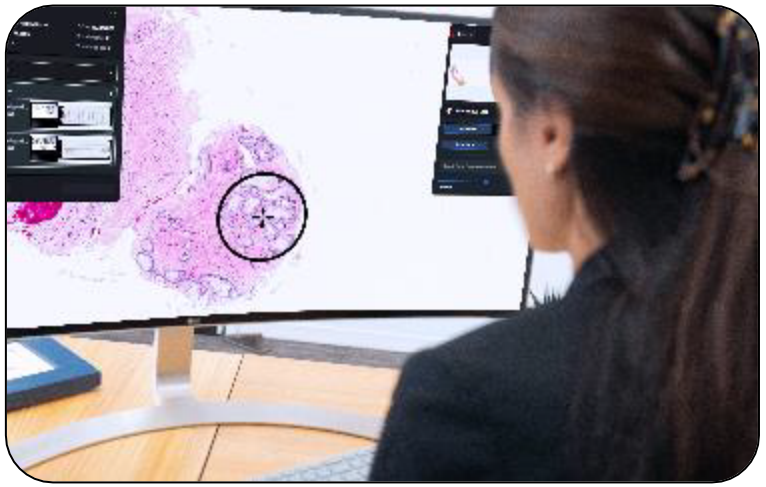
Caption Guidance™



4/9/21

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

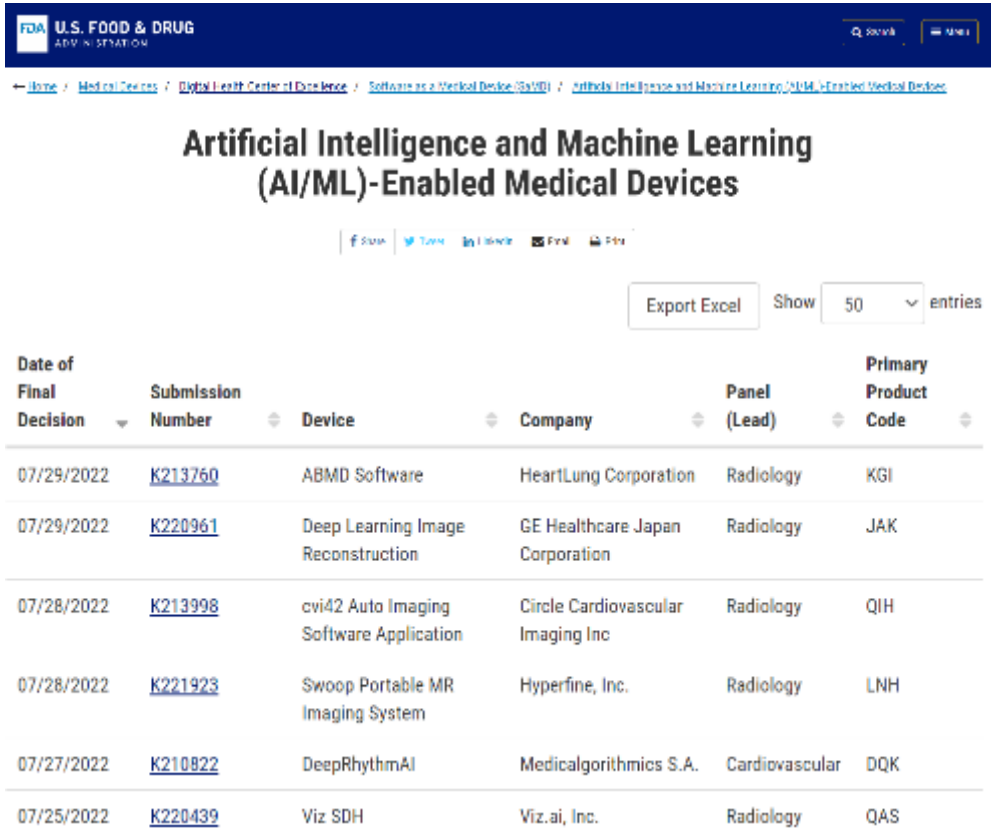
GI Genius™



9/21/21

FDA Authorizes Software that Can Help Identify Prostate Cancer, Paige Prostate

Resources on AI/ML-Enabled Medical Devices



U.S. FOOD & DRUG

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

Export Excel | Show 50 entries

Date of Final Decision	Submission Number	Device	Company	Panel (Lead)	Primary Product Code
07/29/2022	K213760	ABMD Software	HeartLung Corporation	Radiology	KGI
07/29/2022	K220961	Deep Learning Image Reconstruction	GE Healthcare Japan Corporation	Radiology	JAK
07/28/2022	K213998	cvi42 Auto Imaging Software Application	Circle Cardiovascular Imaging Inc	Radiology	QIH
07/28/2022	K221923	Swoop Portable MR Imaging System	Hyperfine, Inc.	Radiology	LNH
07/27/2022	K210822	DeepRhythmAI	Medicalgorithmics S.A.	Cardiovascular	DQK
07/25/2022	K220439	Viz SDH	Viz.ai, Inc.	Radiology	QAS

https://www.fda.gov/digitalhealth

Updated in October 2022

Currently Marketed AI/ML-Enabled Medical Devices

This list is meant to be:

1. A public resource on these devices and the FDA's work in this area
2. Show how AI/ML is being used across medical disciplines

A non-exhaustive list based on publicly available information

AI/ML-Enabled Medical Devices: Opportunities & Challenges

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**

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**

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- **FDA AI/ML Action Plan**

A Collaborative Approach to AI/ML-Enabled Devices

Recent Milestones

Published AI/ML-SaMD Discussion Paper

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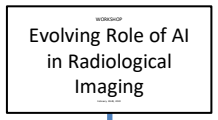
First joined Collaborative Community related to AI/ML



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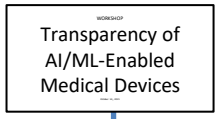

Public Workshop on Transparency of AI/ML Devices

Published GMLP Guiding Principles

2022

Contributed to IMDRF's Key Terms & Definitions

Updated List of Currently Marketed AI/ML Devices

Future Plans (2023+) 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

Stakeholder Feedback on AI/ML Approach

What we heard from stakeholders:

1. **Regulatory Framework**: Requested further development of proposed regulatory framework for AI/ML-based SaMD
2. **Good Machine Learning Practices (GMLP)**: Supported the idea of GMLP and the need for harmonization of its efforts
3. **Transparency**: Asked for further discussion with FDA on how these technologies interact with people, including transparency to users
4. **Regulatory Science**: Described need for improved methods related to algorithmic bias and robustness.
5. **Real-World Performance (RWP)**: Sought clarity on RWP monitoring for AI/ML software.

Stakeholder Feedback on AI/ML Approach

What we heard, and what we're doing

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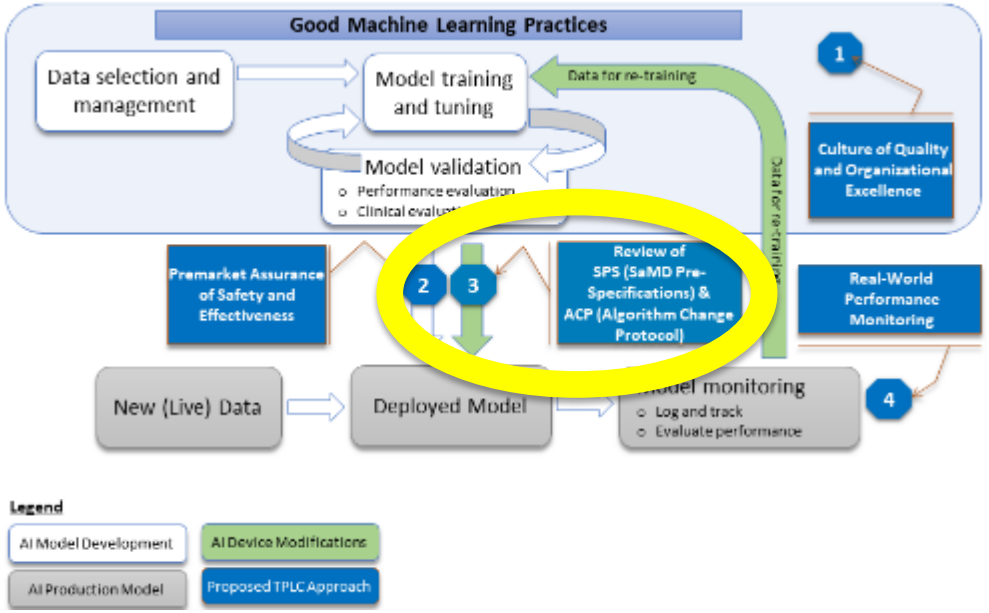
What we're doing -- The AI/ML Action Plan:

1. **Update the proposed AI/ML framework**, including through Guidance
2. **Strengthen FDA's role in harmonizing GMLP** through standards development & other initiatives
3. **Foster a patient-centered approach**, starting with a workshop on transparency to users
4. **Support development of regulatory science methods** related to algorithm bias and robustness
5. **Advance real-world performance pilots** in coordination with stakeholders and other programs

Tailoring a Regulatory Framework for AI/ML-Enabled SaMD

- A strength of AI/ML systems is their ability to learn from real world data and improve performance over time
- Change Control Plan includes:
  - **Software Pre-Specifications (SPS):** describes "what" aspects the manufacturer intends to change through learning,
  - **Algorithm Change Protocol (ACP):** explains "how" the algorithm will learn and change while remaining safe and effective
- Developing Draft Guidance on Change Control Plan



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

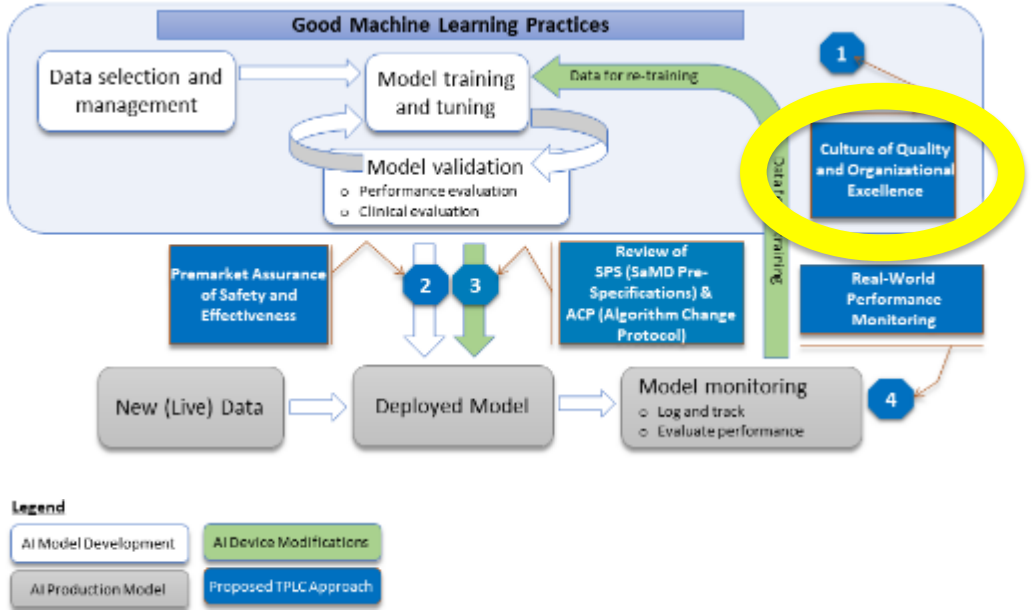
Maintain a reasonable assurance of safety and effectiveness

Enable manufacturers to rapidly improve software products with minor changes

Least burdensome

Good Machine Learning Practice (GMLP)

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



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Good Machine Learning Practice (GMLP)

Examples of Collaborative Efforts

- Standards Development:
  - IEEE AI Medical Device Working Group
  - ISO/IEC SubCommittee on AI 42 (ISO/ IEC JTC 1/SC 42)
  - AAMI/BSI Initiative on AI in Medical Technology
  - CTA R13 Artificial Intelligence in Healthcare
- Collaborative Communities:
  - Collaborative Community on Ophthalmic Imaging
  - Pathology Innovation Collaborative Community
  - Digital Health Measurement Collaborative Community
  - AFDO/RAPS Healthcare Products Collaborative*
- Other Collaborations:
  - IMDRF AI Medical Devices WG

CCOI

Collaborative Community on Ophthalmic Imaging

Pathology Innovation Collaborative Community

Pathology Innovation Collaborative Community

DATAcc

Digital Health Measurement Collaborative Community

Digital Health Measurement Collaborative Community

AFDO RAPS

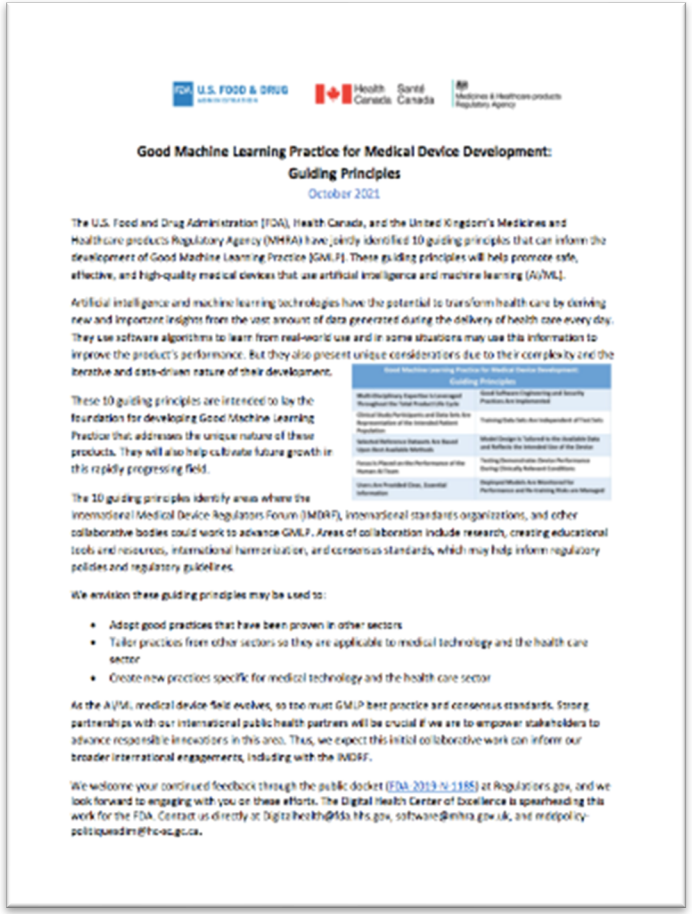
HEALTHCARE PRODUCTS COLLABORATIVE

Healthcare Products Collaborative Community

*Recently transitioned from Xavier AI World Consortium Collaborative Community to the Association of Food and Drug Officials/Regulatory Affairs Professionals Society (AFDO/RAPS)

Good Machine Learning Practice (GMLP) Guiding Principles

- Ten guiding principles issued by US FDA, MHRA (UK) and Health Canada
- Intended to help inform the development of GMLP and encourage broad stakeholder engagement
- Promote global harmonization in efforts for the identification of best practices and the creation of standards



Good Machine Learning Practice for Medical Device Development: Guiding Principles

October 2021

The U.S. Food and Drug Administration (FDA), Health Canada, and the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) have jointly identified 10 guiding principles that can inform the development of Good Machine Learning Practice (GMLP). These guiding principles will help promote safe, effective, and high-quality medical devices that use artificial intelligence and machine learning (AI/ML).

Artificial intelligence and machine learning technologies have the potential to transform health care by deriving new and important insights from the vast amount of data generated during the delivery of health care every day. They use software algorithms to learn from real-world use and in some situations may use this information to improve the product's performance. But they also present unique considerations due to their complexity and the iterative and data-driven nature of their development.

These 10 guiding principles are intended to lay the foundation for developing Good Machine Learning Practice that addresses the unique nature of these products. They will also help cultivate future growth in this rapidly progressing field.

The 10 guiding principles identify areas where the International Medical Device Regulators Forum (IMDRF), international standards organizations, and other collaborative bodies could work to advance GMLP. Areas of collaboration include research, creating educational tools and resources, international harmonization, and consensus standards, which may help inform regulatory policies and regulatory guidelines.

We envision these guiding principles may be used to:

- Adopt good practices that have been proven in other sectors
- Tailor practices from other sectors so they are applicable to medical technology and the health care sector
- Create new practices specific for medical technology and the health care sector

As the AI/ML medical device field evolves, so too must GMLP best practice and consensus standards. Strong partnerships with our international public health partners will be crucial if we are to empower stakeholders to advance responsible innovations in this area. Thus, we expect this initial collaborative work can inform our broader international engagements, including with the IMDRF.

We welcome your continued feedback through the public docket (FDA-2019-N-1185) at Regulations.gov, and we look forward to engaging with you on these efforts. The Digital Health Center of Excellence is spearheading this work for the FDA. Contact us directly at DigitalHealth@fda.hhs.gov, software@mhra.gov.uk, and medicalpolicyconsultation@hc-sc.gc.ca.

FDA U.S. FOOD & DRUG ADMINISTRATION

Health Canada Santé Canada

Medicines & Healthcare products Regulatory Agency

October 2021

Good Machine Learning Practice for Medical Device Development: Guiding Principles	
Multi-Disciplinary Expertise are 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 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 AIML-enabled devices held Oct 2021

Topics of AI/ML Transparency Workshop Discussion

What does AI/ML Transparency mean?

- Safe and effective
  - Clear intended use
  - Works as described
- Health equity
  - Fair to all people
  - Bias management
- Real world performance
  - Assurance of improved health outcomes

How to promote AI/ML Transparency?

- User facing information/ labeling
  - Accessible language/terminology
  - Clear functionality and limitations
- Public education on AI/ML
- Dataset requirements
- Pre-market guidance
- Post-market monitoring

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 the Office of Science & Engineering Laboratories (OSEL).

CERSI Johns Hopkins University

CERSI UCSF-Stanford

Major Regulatory Science Gaps and Challenges Driving the OSEL AI/ML Program

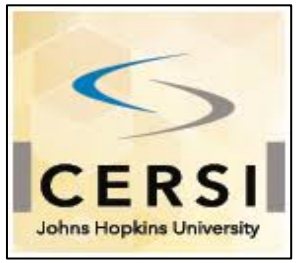
- Need for methods to enhance AI/ML algorithm training for clinical datasets that are typically much smaller than non-clinical datasets
- Need for clear definition or understanding of artifacts, limitations, and failure modes for fast-growing applications of Deep-Learning (DL) algorithms in the denoising and reconstruction of medical images
- Need for assessment techniques to evaluate the trustworthiness of adaptive and autonomous AI/ML devices (for example, continuously learning algorithms)
- Need for systematic approaches to address the robustness of various AI/ML input factors, such as data acquisition factors, patient demographics, and disease factors, to patient outcomes in a regulatory submission
- Need for a clear reference standard for assessing accuracy of AI/ML-based Quantitative Imaging (QI) and radiomics tools

OSEL Research Related to Algorithm Bias & Robustness

- Data
  - Data augmentation
    - Weakly-labeled data
    - Synthetic data
  - Bias
    - Distribution shift
    - Sex-bias
- Evaluation
  - Metrics
    - Multi-class decision support systems
    - Performance metric selection tool
  - Continual learning systems
    - New evaluation framework

CERSI Research Related to Algorithm Bias & Robustness

- Safe Algorithmic Change Protocols for Modifications to AI/ML-Based Software as a Medical Device

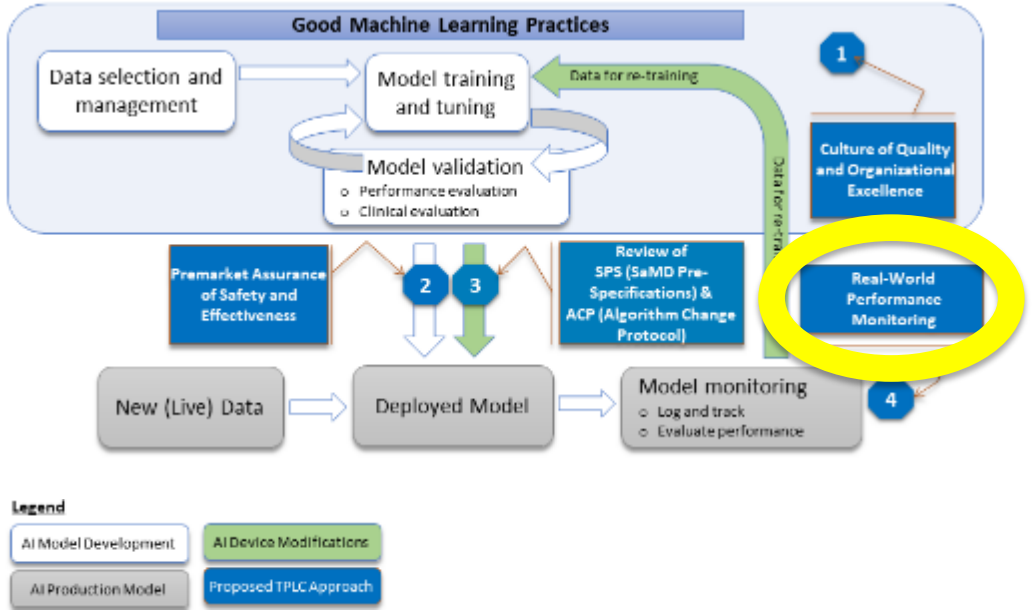


- Assessing the Robustness of Clinical Machine Learning Models to Changes in Context of Use

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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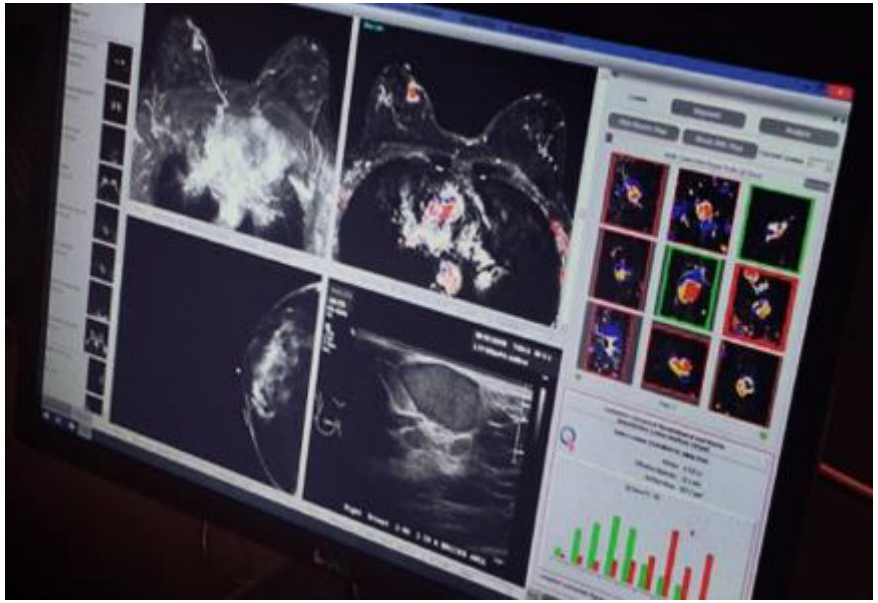
Real World Performance

- What type of reference data are appropriate to utilize in measuring the performance of AI/ML software devices in the field?
- How much of the oversight should be performed by each stakeholder?
- How much data should be provided to the Agency, and how often?
- How can the algorithms, models, and claims be validated and tested?
- How can feedback from end-users be incorporated into the training and evaluation of AI/ML-enabled software?

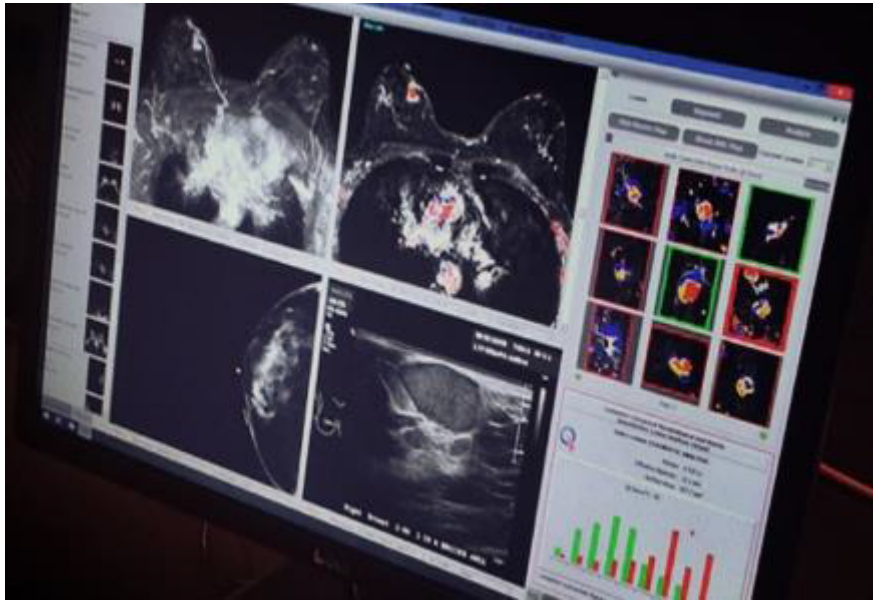


https://angel.co/quantitative-insights

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



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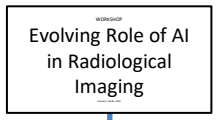

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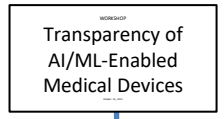

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Further Questions or Feedback:

www.fda.gov/digitalhealth

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