Regulatory Perspectives

Incorporating Integrated Diagnostics into Precision Oncology Care: A Workshop
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Overview

- Current FDA Review Framework
  - In Vitro Diagnostic (IVD) tests
  - Radiological devices
  - Artificial Intelligence (AI) based digital pathology/ radiological devices

Medical Devices Regulatory Pathway

Premarket Review

Postmarket

Device application submitted to FDA

Application processed according to risk classification

Safety and effectiveness

Device enters market

Ensure Safety and effectiveness: tracking systems, reporting of device malfunctions, reporting serious injuries

TPLC database: Adverse Events, and Recalls

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In vitro Diagnostics (IVD)

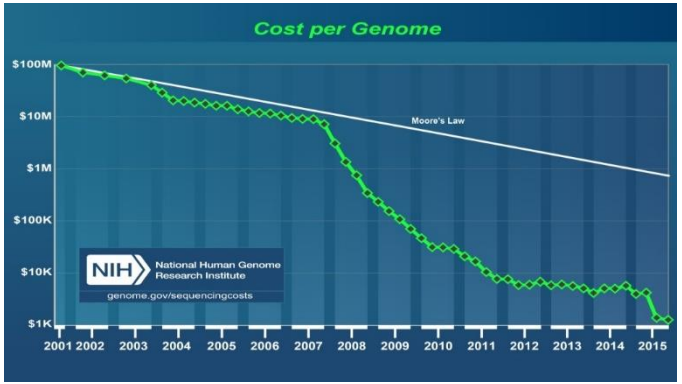
- In vitro diagnostic devices include "…those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae." *

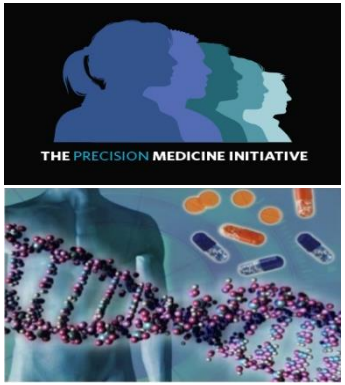
* 21 CFR § 809.3

Risk Based Classification of IVDs

Risk	Classification	Submission Type	Risk Mitigations	Examples
Low	Class 1 Exempt	None	General Controls	-Prealbumin -Extraction Kits
Low	Class 2 exempt	None	General Controls Special Controls	-Autosomal recessive carrier screening gene mutation detection
Moderate	**Class 2 ("Cleared tests")**	**510(k) (or 'De novo' for first of a kind moderate risk)**	**General Controls Special Controls**	-Gene expression for risk of breast cancer recurrence -**NGS based tumor profiling tests**
High	**Class 3 ("Approved tests")**	**PMA**	**Valid scientific evidence GMP inspection/ Postmarket**	-Colon cancer screening -**Companion diagnostics**

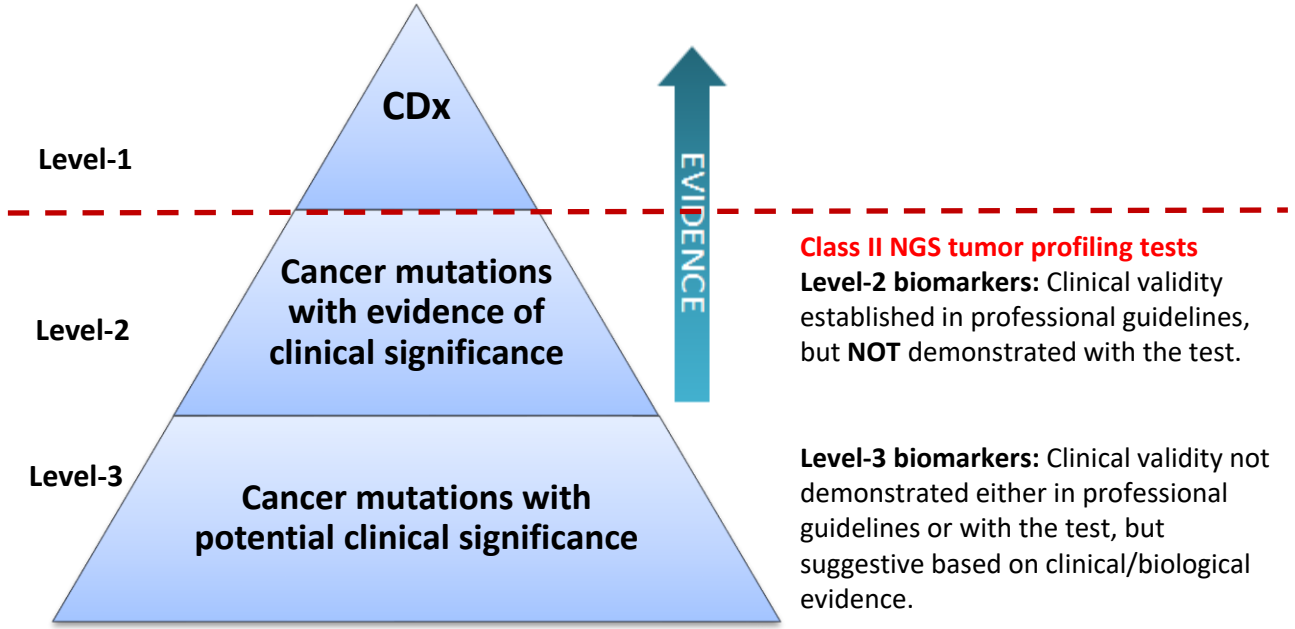
NGS Revolutionized Personalized Genomics & Medicine





- NGS is the driving technology for precision medicine
- NGS-based assays have been widely adopted to clinical use

A Three-Tiered Approach for Reporting Biomarkers in NGS Onco Panel Tests



Class II NGS tumor profiling tests

Level-2 biomarkers: Clinical validity established in professional guidelines, but **NOT** demonstrated with the test.

Level-3 biomarkers: Clinical validity not demonstrated either in professional guidelines or with the test, but suggestive based on clinical/biological evidence.

*patients with solid malignant neoplasms to detect tumor gene alterations in a broad multi gene panel.

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Radiological Medical Device Regulation

FDA/CDRH	Other Regulatory Agencies	Accrediting Bodies

• Regulates **manufacturers** of the equipment & the **equipment** itself
  • Medical Device Amendments of 1976: Requires devices to be safe and effective
  • Radiation Control for Health and Safety Act of 1968
	• Regulate the **use of devices** through recommendations & requirements for:
	  • Federal Agencies – e.g., NRC, OSHA, EPA
	  • State Agencies – Agreement States
	  • Local Agencies – County, City
		• Measure the **quality** of healthcare organizations
		  • CMS – Medicare Improvements for Patients and Providers Act (MIPPA)
		  • American College of Radiology (ACR)
		  • The Joint Commission

Risk Based Classification of Radiological Devices

Device Class	Examples	Controls	Premarket Review Process
Class I (lowest risk)	Ultrasound gel Gloves	General	Most are exempt
Class II	MRI Catheter	General and Special	Premarket Notification [510(k)]
			De Novo
Class III (highest risk)	Radioactive microspheres Stents	General and Premarket Approval	Premarket Approval [PMA]

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Definitions

Artificial Intelligence (AI): *"A device or product that can imitate intelligent behavior or mimics human learning and reasoning. Artificial intelligence includes machine learning, neural networks, and natural language processing. Some terms used to describe artificial intelligence include: computer-aided detection/diagnosis, statistical learning, deep learning, or smart algorithms.*

Example AI: An imaging system that uses algorithms to provide diagnostic information for malignant melanoma or skin cancer in patients.

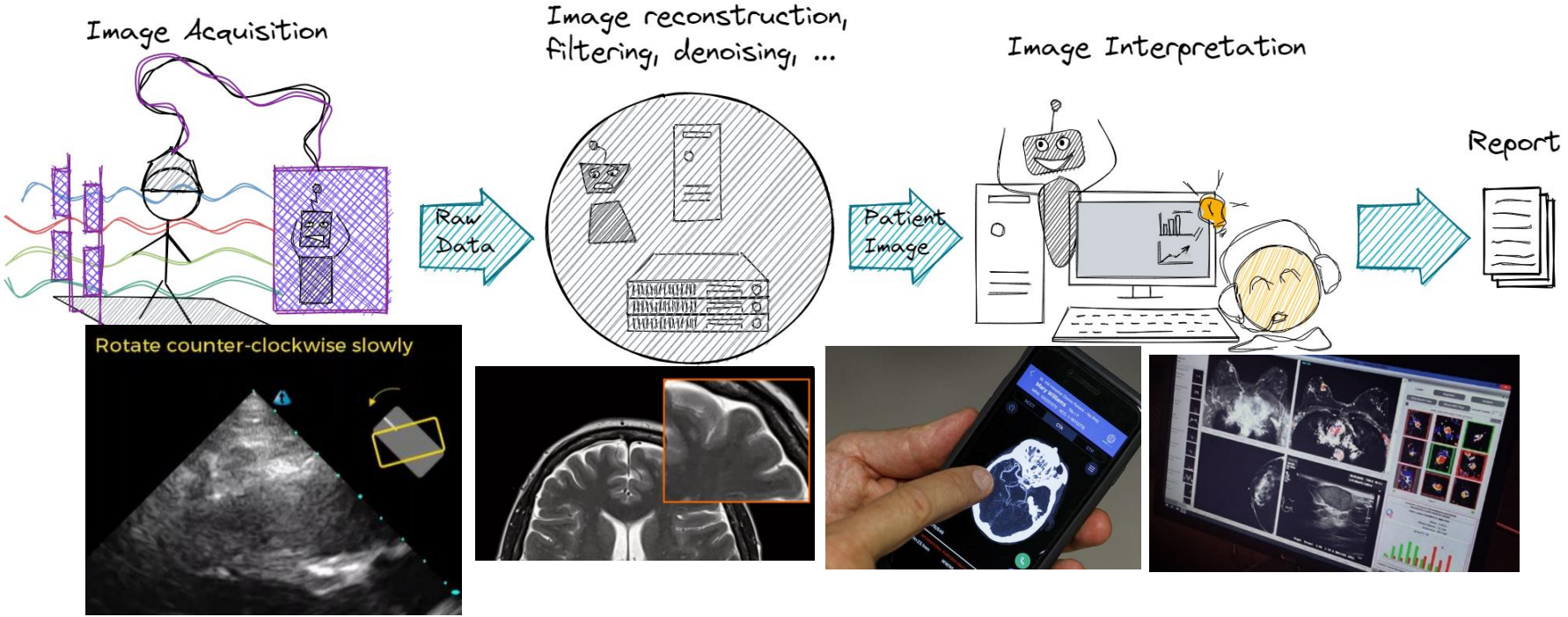
https://www.fda.gov/medical-devices/digital-health-center-excellence/digital-health-terms

AI in Digital Pathology

- Risk-based approach
- Type of AI algorithm: e.g., Locked
- Intended use (IU)
  - Concurrent review
  - In addition to standard of care review
  - Replaces standard of care
- Where does the AI device fit in the intended use workflow
- Currently, AI applications in digital pathology are mainly image-based, i.e., digital images of scanned glass slides. Therefore, differences in AI device performance based on differences in digital images should be assessed

AI in Radiological Devices

- Imaging software and artificial-intelligence/machine learning is used all along the medical imaging chain



Gossmann (2021) KDD 2021 Health Day and 2021 KDD Workshop on Applied Data Science for Healthcare

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AI/ML-Enabled Medical Devices-Recent Update FDA

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
04/02/2021	K202441	Eclipse II with Smart Noise Cancellation	Carestream Health, Inc.	Radiology	MQB
04/01/2021	DEN200038	Gili Pro Biosensor (Also Known as Gili Biosensor System)	Continuse Biometrics Ltd.	Cardiovascular	QOK
03/31/2021	K203258	syngo.CT Lung CAD (Version VD20)	Siemens Healthcare GmbH	Radiology	OEB

- Recently-released list by FDA
  - to be periodically updated
- Assembled by searching
  - FDA's publicly-facing information
  - Reviewing information in publicly available resources
  - Other publicly available materials published by manufacturers
  - ~ 70% related to Radiology

https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices

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Additional Resources

Guidance Documents

CADe: http://www.fda.gov/RegulatoryInformation/Guidances/ucm187249.htm

http://www.fda.gov/RegulatoryInformation/Guidances/ucm187277.htm

SaMD evaluation:
https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm524904.pdf

Draft guidance and discussion papers

Quantitative Imaging:
https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM636178.pdf

Modifications to AI/ML Software https://www.regulations.gov/document?D=FDA-2019-N-1185-0001

Regulations/reclassification orders

CADx: https://www.accessdata.fda.gov/cdrh_docs/pdf17/den170022.pdf
CADx+CADe: https://www.accessdata.fda.gov/cdrh_docs/pdf18/DEN180005.pdf
Triage: https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170073.pdf
Retinal diagnosis: https://www.accessdata.fda.gov/cdrh_docs/pdf18/DEN180001.pdf (outside of DRH)

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AI-based Medical Devices-Opportunities and Challenges

- Fundamentally transform the delivery of health care:

→*Earlier disease detection* → *more accurate diagnosis* → *new insights into human physiology* → *personalized diagnostics and therapeutics*

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

- Need for large, high-quality, well-curated data sets
- Explainability of "black box" approaches
- Identification and removal of bias
- Providing oversight for an evolving system
- Ensuring transparency to users

FDA-NIH Joint Leadership Council
Next Generation Sequencing (NGS) & Radiomics Working Group

- **Established:** November 2018 under Francis Collins and Rob Califf
- **Co-Chairs:** Jeff Shuren and Ned Sharpless
- **The problem:** Gaps in reference materials are impeding validation
- **Charge: explore joint needs for:**
  - Development of reference materials to support NGS test development and validation
  - Use of developing technologies such as artificial intelligence (AI)/machine learning (ML) to support NGS and radiomic/radiology data interpretation
  - Also identify opportunities to synergize and complement current NIH and FDA resources and activities in this space

Initial work and follow up

- The Working Group identified many key gaps in:
  - **Physical reference samples** (e.g., tumor/normal pairs)
  - **Datasets** (e.g., combined imaging, clinical, and genomic data)
  - **Tools** (e.g., data integration methodology)
  - **Infrastructure** (e.g., high-capacity platforms for storage and analysis)
  - **Methodology** (e.g., for curation and preprocessing of data for AI learning)
  - **Protection of and respect for patients and research participants**

Virtual Workshop on NGS and Radiomics:

Resource Requirements for Acceleration of Clinical Applications Including AI (Sept. 29-30, 2021)

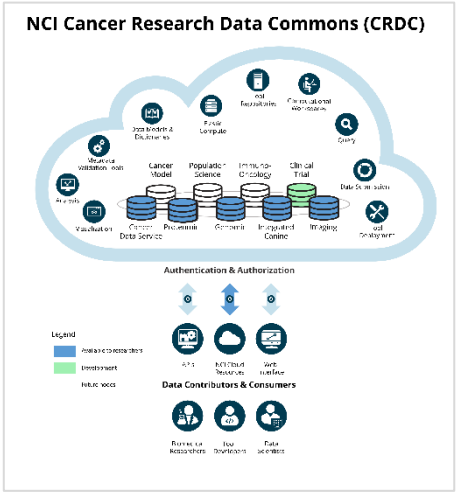
- **Highlights**
  - Discussions at the workshop were largely focused on processes and methodologies and emphasized the need, both in NGS and radiomics, for reference materials, especially highly annotated datasets for AI/ML applications.
  - Genomics
    - The need to scale and centralize expert knowledge of clinically relevant variants
    - Supplementing physical reference materials with the generation of in silico datasets, with a special emphasis on the importance of copy number variants and other structural rearrangements
  - Radiomics
    - The need for ML-ready annotated datasets that reflect real-world complexities, and standards to which these datasets should adhere
    - Directing resources towards existing best-practices operations to reach a broader audience with standardized expertise and technologies
- Workshop summary manuscript

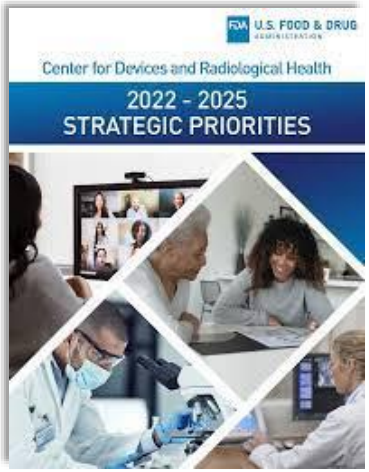
Workshop highlights and links to recordings:
https://dctd.cancer.gov/NewsEvents/20211122_NCI_Hosts_FDA_NIH_Workshop.htm

Ongoing related activities

- Medical Device Innovation Consortium (MDIC) Somatic Reference Sample (SRS) Initiative
- Digital Health Center of Excellence - AI/ML Software as a Medical Device Action Plan
- CDRH's 2022 – 2025 Strategic Priority to Advance Healthcare Equity
- NCI Cancer Research Data Commons Repositories

MDIC
MEDICAL DEVICE INNOVATION CONSORTIUM





precisionFDA

- A publicly available cloud-based portal
- A secure, collaborative, high-performance computing platform that builds a community of experts around the analysis of biological datasets in order to advance precision medicine
- A community of experts engaged in the analysis of diverse omics datasets with a focus on supporting FDA's mission and advancing regulatory science
- A framework, methodology, and platform for conducting crowdsourcing challenges advancing regulatory standards for bioinformatics, RWD, and AI through community-sourced science
- Example of Data Science applications at FDA: High-Throughput Truthing Project (HTT): creating a dataset of pathologist annotations for validating artificial intelligence and machine learning computational models (AI/ML models) that analyze digital scans of pathology slides
- Program Manager: Elaine Johanson https://precision.fda.gov/

Summary

- There is potential to integrate radiology, pathology and IVD such as NGS information
- Additional resource needed to prompt additional support and development

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