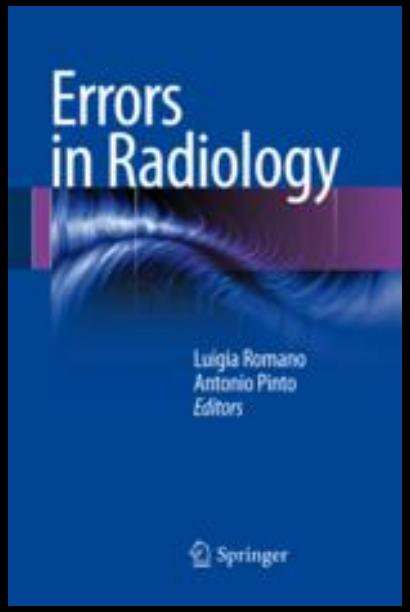
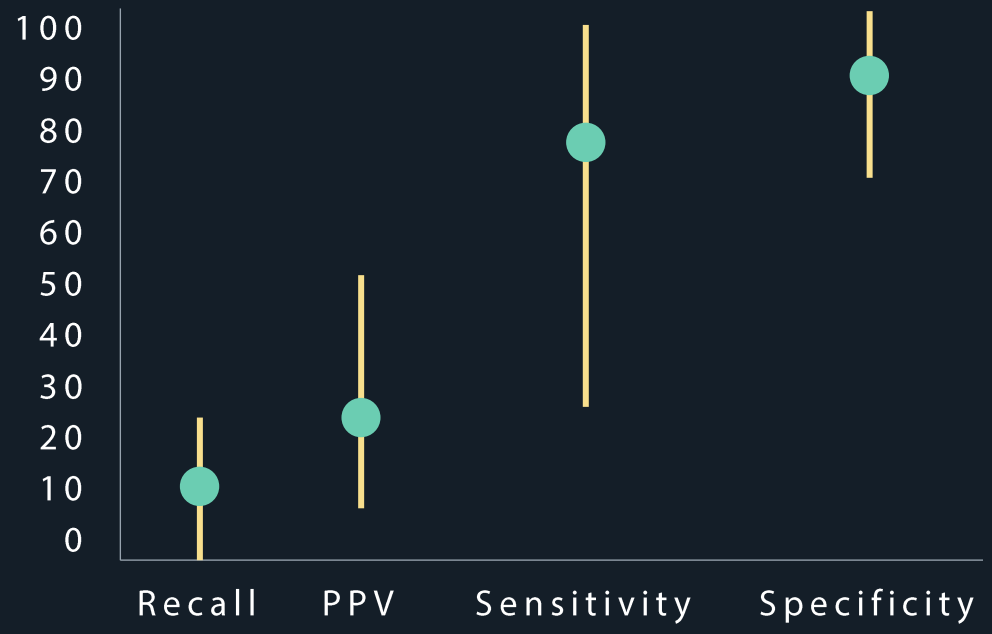
Our shared challenges and opportunities

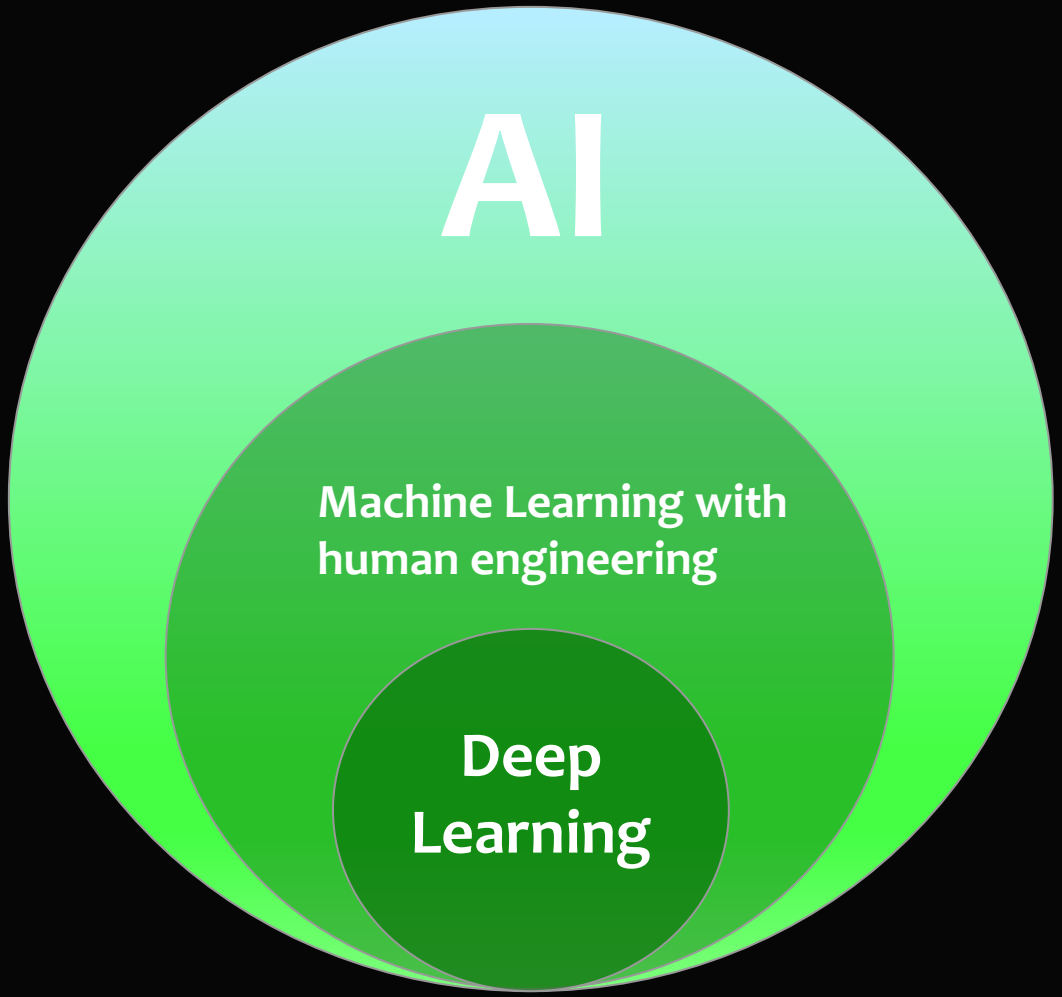
Access, Human Variation, Costs



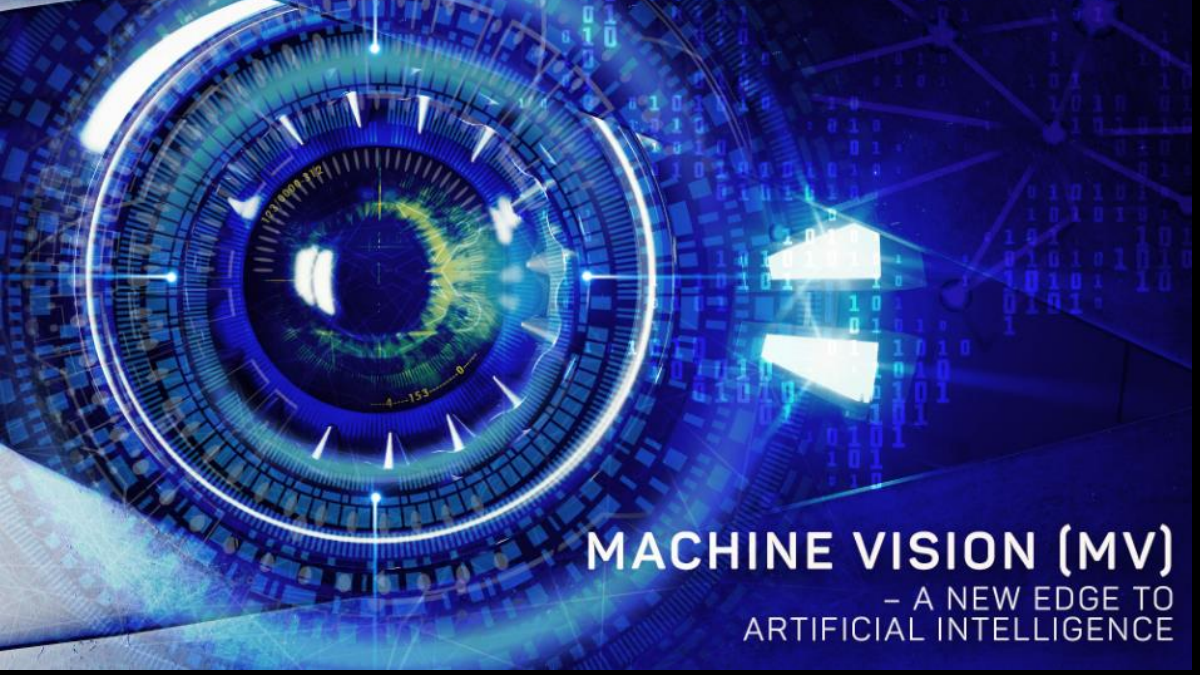
HUMAN VARIATION

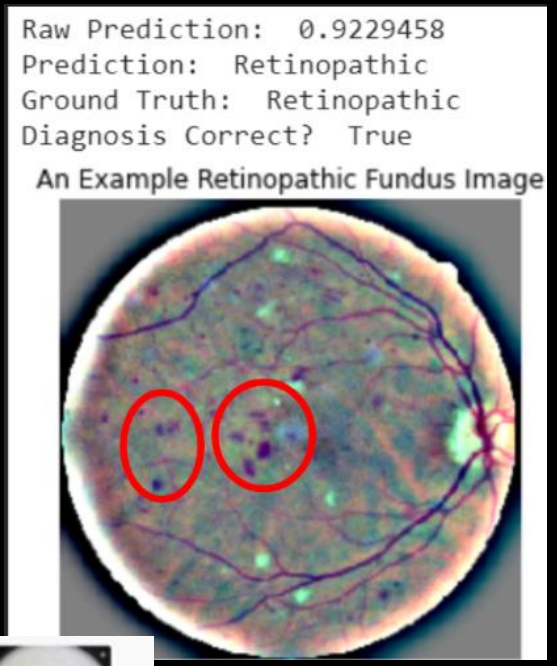


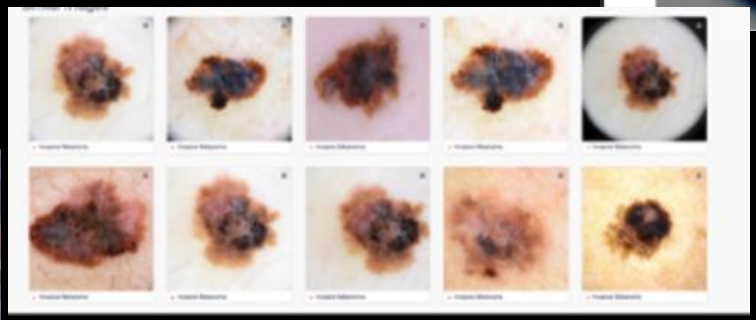
Source: Buist, Workshop Summary, 2015

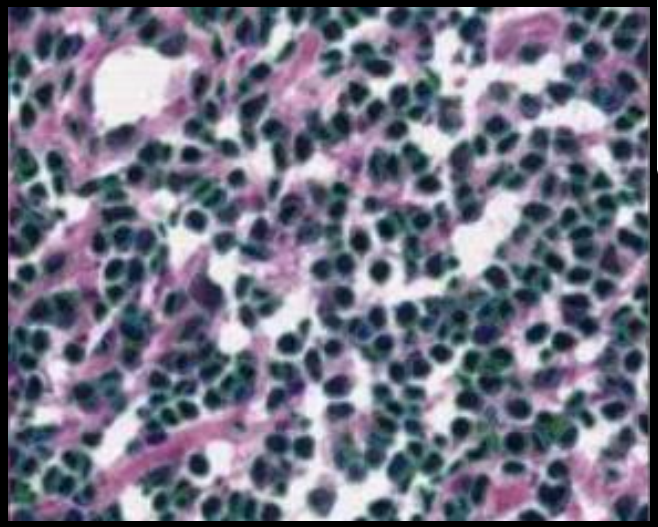


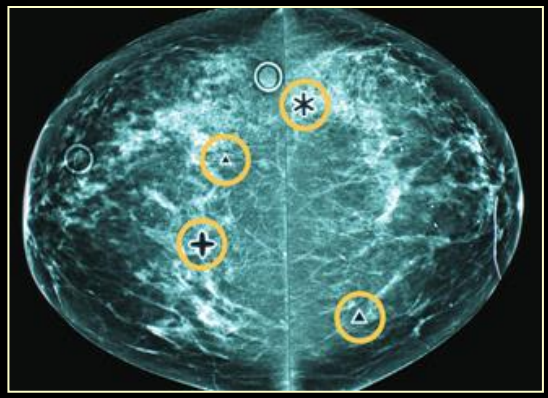
CAD


MACHINE VISION (MV)
– A NEW EDGE TO
ARTIFICIAL INTELLIGENCE


Raw Prediction: 0.9229458
Prediction: Retinopathic
Ground Truth: Retinopathic
Diagnosis Correct? True
An Example Retinopathic Fundus Image







IS THIS A

CAT or DOG?

CAT DOG

OUTPUT LAYER

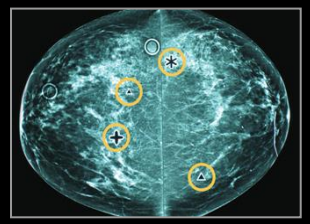
ACTIVATED NEURONS

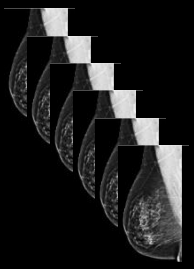
INPUT LAYER

DEEP *neural* NETWORK

FDA Approved SaMD AI Tools for screening mammography

- Assisting the radiologist in interpretation
  - Detection/Diagnosis
  - Density
- Triage
  - Separating high from low risk mammograms (current cancer)
    - “second” reader, diverse paradigms for image review





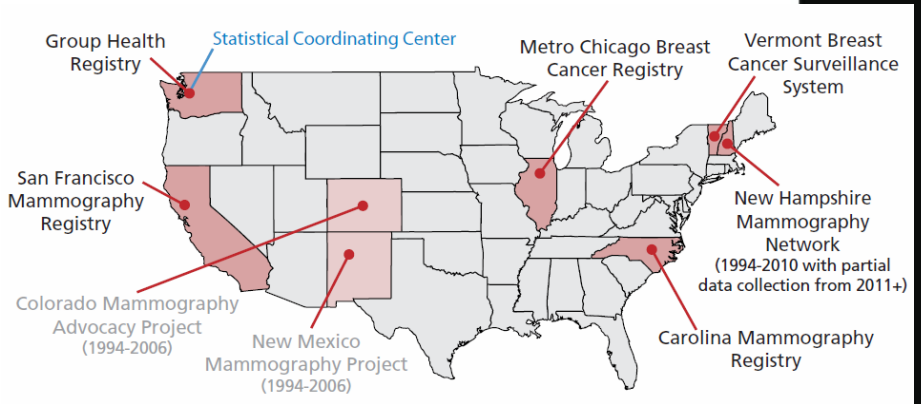
FDA Approved Lesion Detection and Diagnosis Applications for Screening Mammography

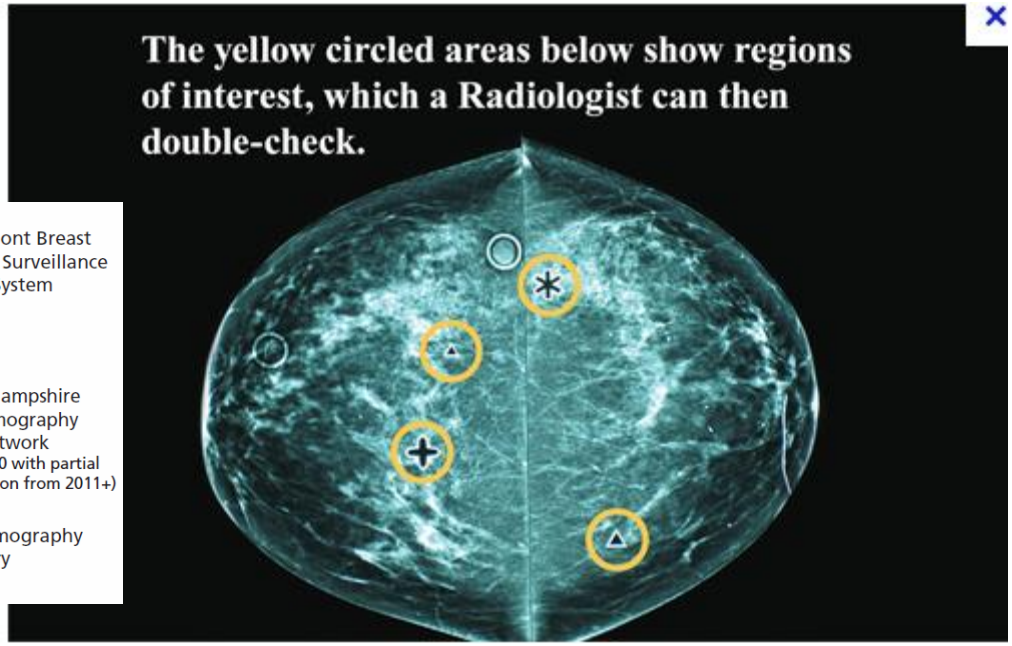
Tool (Company)	Number of Cases	Radiologists in Reader Study	Reported AUCs
MammoScreen 2.0 (Therapixel)	240 for DM 240 for DBT	14 for DM 20 for DBT	0.80 (radiologists aided) vs 0.77 (radiologists unaided) for DM 0.83 (radiologists aided) vs 0.79 (radiologists unaided) for DBT
Genius AI Detection (Hologic)	390	17	0.83 (radiologists aided) vs 0.79 (radiologists unaided)
ProFound AI Software V3.0 (iCAD)	260	24	0.85 (radiologists aided) vs 0.80 (radiologists unaided)
Transpara 1.7.0 (ScreenPoint Medical B.V.)	240 for DM 240 for DBT	14 for DM 18 for DBT	0.89 (radiologists aided) vs 0.87 (radiologists unaided) for DM 0.86 (radiologists aided) vs 0.83 (radiologists unaided) for DBT
Lunit INSIGHT MMG (Lunit)	240	12	0.81 (radiologists aided) vs 0.75 (radiologists unaided)

History of CAD

Breast Cancer Surveillance Consortium
BCSC
Working together to advance breast cancer research

- CAD applied to mammography approved by FDA in 1998
- With reimbursement, use rapidly increased across the U.S.
- Multiple study designs in early phases: retrospective, reader studies, prospective small single site, etc. with mixed results on impact of CAD on accuracy of mammographic interpretation





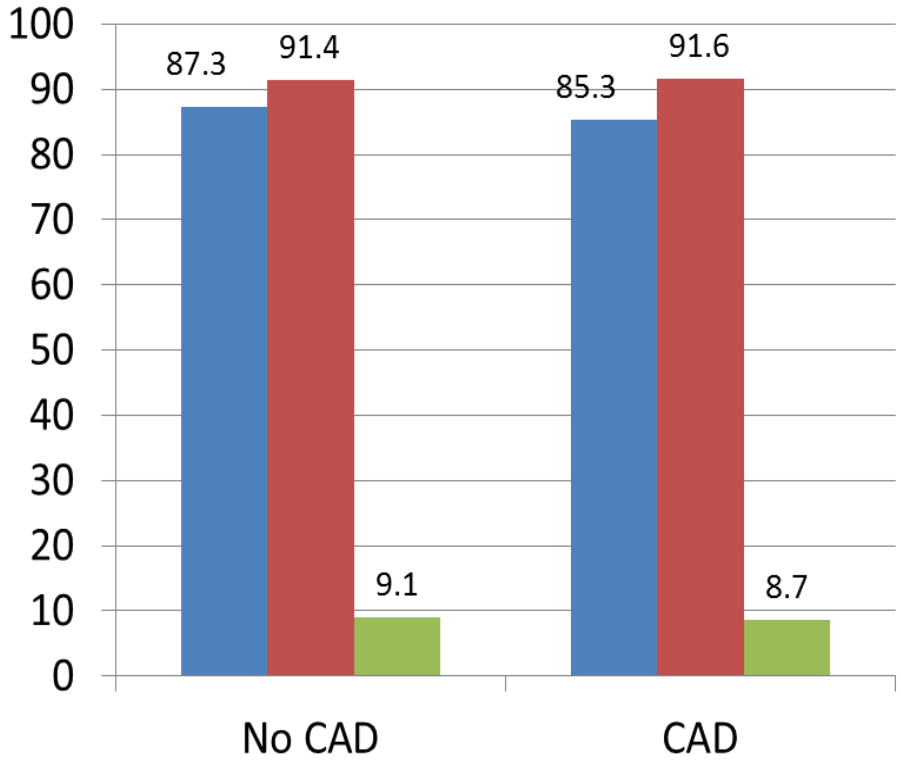
Original Investigation | LESS IS MORE

Diagnostic Accuracy of Digital Screening Mammography With and Without Computer-Aided Detection

Constance D. Lehman, MD, PhD; Robert D. Wellman, MS; Diana S. M. Buist, PhD; Karla Kerlikowske, MD; Anna N. A. Tosteson, ScD; Diana L. Miglioretti, PhD; for the Breast Cancer Surveillance Consortium

JAMA Intern Med. 2015;175(11):1828-1837. doi:10.1001/jamainternmed.2015.5231

Breast Cancer Surveillance Consortium
BCSC
Working together to advance breast cancer research

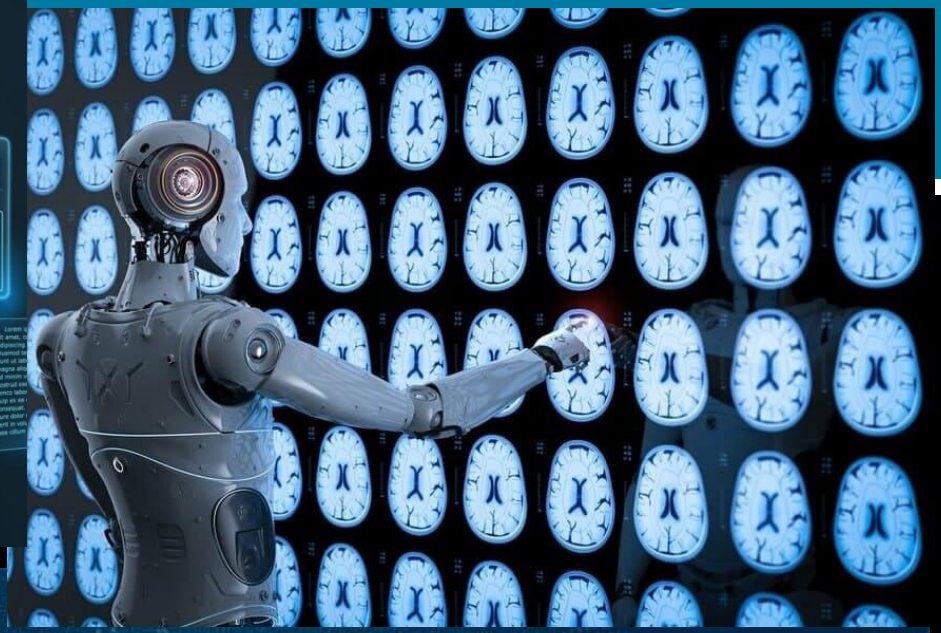


Study Strengths

- Current performance 2003-09
- Only digital mammo with CAD
- Learning curve addressed
- > 569k CAD exams

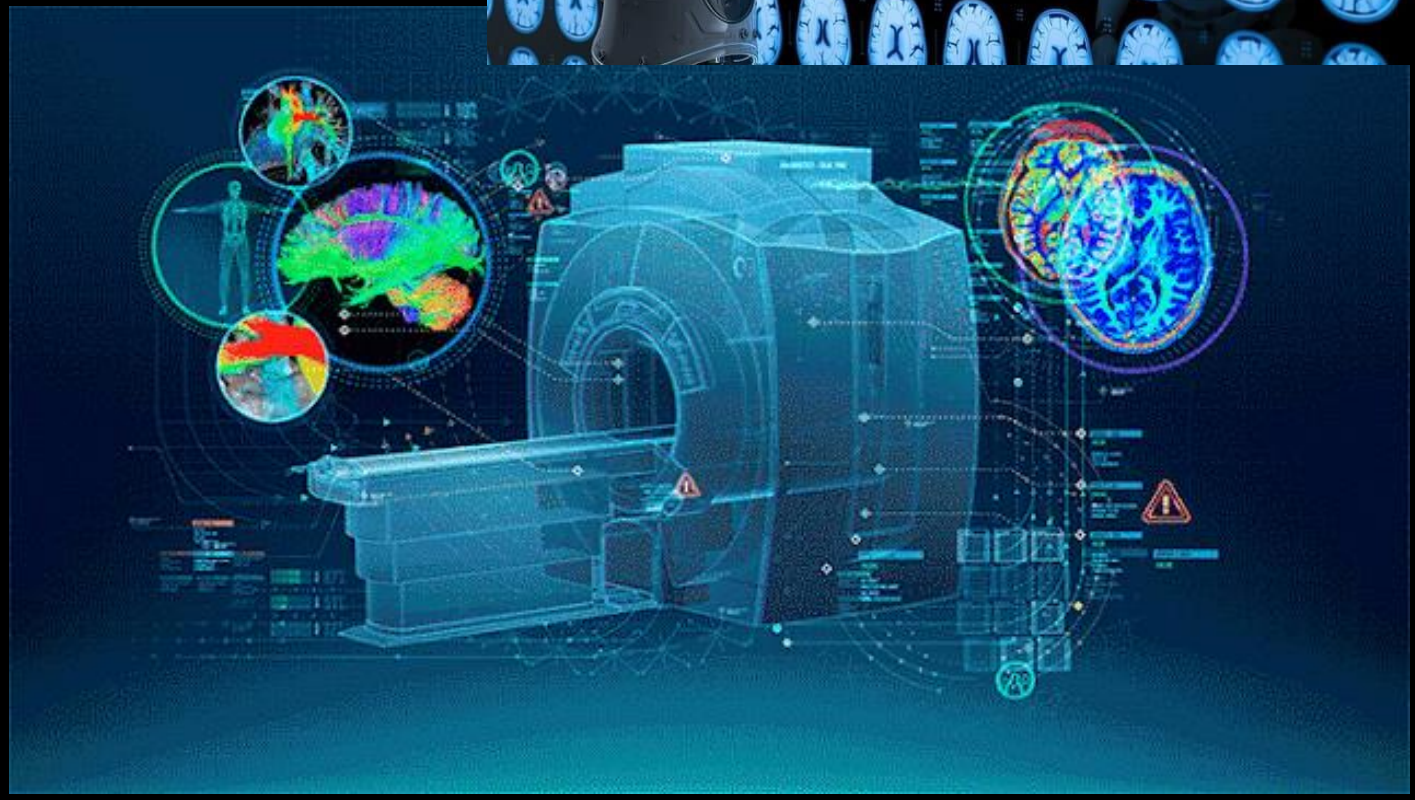
Challenges addressed by BCSC:
No improvement of digital mammography performance with CAD

Odds ratio for CAD vs. No CAD adjusted for site, age, race, time since prior mammogram and calendar year of exam using mixed effects model with random effect for exam reader and varying with CAD use found no significant difference in sensitivity, specificity or recall rate.

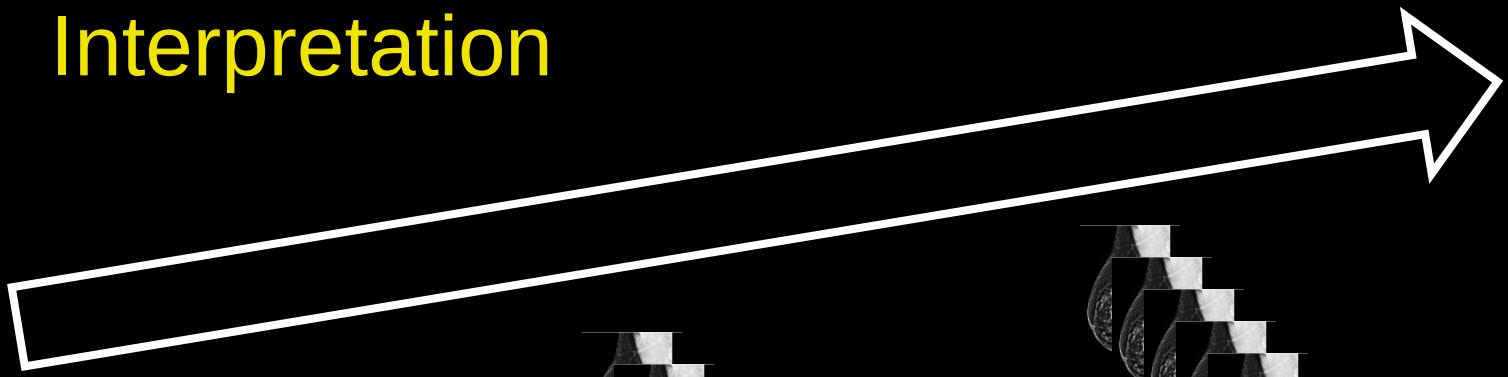


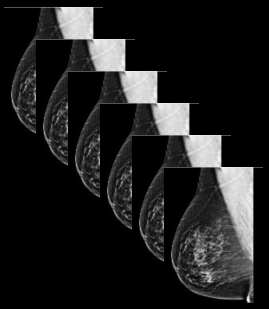
Human-Computer Interactions are complex

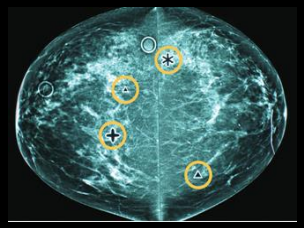
Simulations are not the same as actual "real world" performance

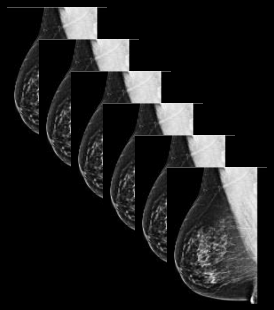


Computer Assistance vs Autonomous Interpretation

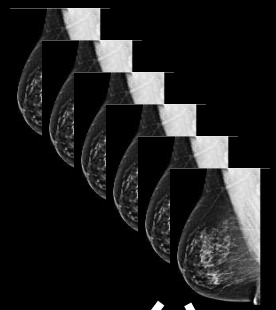


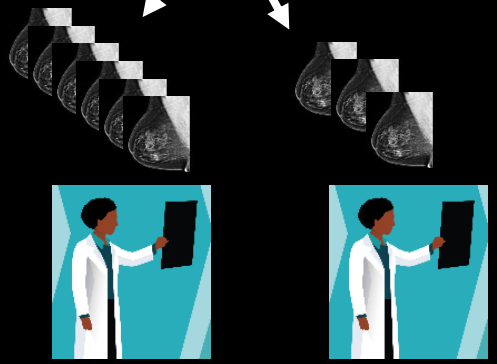




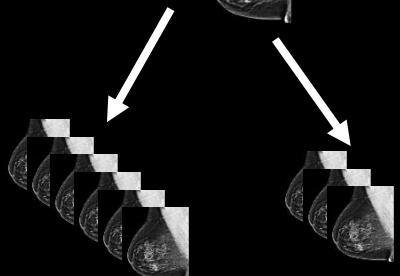


Traditional CAD





AI Triage



Fully Autonomous Interpretation of All Exams for Specific Case Use

Fully Autonomous Interpretation of Subset of Exams

SheppardMullin

Judges and Lawyers Breast Cancer Alert (JALBCA)

Ellen P. Hermanson Memorial Symposium – March 22, 2023

Scott S. Liebman

Partner, FDA Regulatory & Compliance

Device Classification – Overview

FDA classifies devices according to risk and intended use.

- Class I vs Class II vs Class III
- Classification Regulation
- 513(g) Request for Information

Identify the claims being made (Is it a "device"?) → Identify device functions (What does the device do?) → Look for appropriate classification regulation (How does FDA classify the device?)

Device Classification Panels

Medical Specialty		Regulation Citation (21CFR)
73	Anesthesiology	Part 868
74	Cardiovascular	Part 870
75	Chemistry	Part 862
76	Dental	Part 872
77	Ear, Nose, and Throat	Part 874
78	Gastroenterology and Urology	Part 876
79	General and Plastic Surgery	Part 878
80	General Hospital	Part 880
81	Hematology	Part 864
82	Immunology	Part 866
83	Microbiology	Part 866
84	Neurology	Part 882
85	Obstetrical and Gynecological	Part 884
86	Ophthalmic	Part 886
87	Orthopedic	Part 888
88	Pathology	Part 864
89	Physical Medicine	Part 890
90	Radiology	Part 892
91	Toxicology	Part 862

Device Classification – Class I Devices

- Class I Devices
  - General controls

Title 21: Food and Drugs
PART 872—DENTAL DEVICES
Subpart G—Miscellaneous Devices

---

§872.6390 Dental floss.

(a) *Identification.* Dental floss is a string-like device made of cotton or other fibers intended to remove plaque and food particles from between the teeth to reduce tooth decay. The fibers of the device may be coated with wax for easier use.

(b) *Classification.* Class I (general controls). The device is exempt from the premarket notification procedures in subpart E of part 807 of this chapter subject to §872.9.

[52 FR 30097, Aug. 12, 1987, as amended at 61 FR 1121, Jan. 16, 1996; 65 FR 2315, Jan. 14, 2000]

Device Classification – Class II Devices

- Class II Devices
  - General controls
  - Special controls
  - 510(k) Premarket Notification

Title 21: Food and Drugs
PART 872—DENTAL DEVICES
Subpart D—Prosthetic Devices

---

§872.3570 OTC denture repair kit.

(a) *Identification.* An OTC denture repair kit is a device consisting of a material, such as a resin monomer system of powder and liquid glues, that is intended to be applied permanently to a denture to mend cracks or breaks. The device may be available for purchase over-the counter.

(b) *Classification.* Class II. The special controls for this device are FDA's:

(1) "Use of International Standard ISO 10993 'Biological Evaluation of Medical Devices—Part I: Evaluation and Testing,'" and

(2) "OTC Denture Reliners, Repair Kits, and Partially Fabricated Denture Kits."

[52 FR 30097, Aug. 12, 1987, as amended at 65 FR 17144, Mar. 31, 2000]

Device Classification – Class III Devices

- Class III Devices
  - General Controls
  - Premarket Approval

Title 21: Food and Drugs
PART 872—DENTAL DEVICES
Subpart D—Prosthetic Devices

---

§872.3960 Mandibular condyle prosthesis.

(a) *Identification.* A mandibular condyle prosthesis is a device that is intended to be implanted in the human jaw to replace the mandibular condyle and to articulate within a glenoid fossa.

(b) *Classification.* Class III.

(c) *Date PMA or notice of completion of a PDP is required.* A PMA or a notice of completion of a PDP is required to be filed with the Food and Drug Administration on or before March 30, 1999, for any mandibular condyle prosthesis that was in commercial distribution before May 28, 1976, or that has, on or before March 30, 1999, been found to be substantially equivalent to a mandibular condyle prosthesis that was in commercial distribution before May 28, 1976. Any other mandibular condyle prosthesis shall have an approved PMA or a declared completed PDP in effect before being placed in commercial distribution.

[59 FR 65478, Dec. 20, 1994, as amended at 63 FR 71746, Dec. 30, 1998; 78 FR 79310, Dec. 30, 2013]

Premarket Pathways

Premarket approval (PMA)

PMA is the FDA process of scientific and regulatory review to evaluate the safety and effectiveness of Class III medical devices.

Cleared 510(k) premarket notification

A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is as safe and effective.

De novo review

De Novo classification is a risk-based classification process.

Exempt from premarket notification

A device may be exempt if FDA determines that a 510(k) is not required to provide reasonable assurance of safety and effectiveness.

Pre-1976, grandfathered device

Also known as a "preamendments device" that has been "grandfathered" in due to its existence on the market before May 28, 1976.

Device Approval Pathways: Premarket Approval

- Premarket Approval (PMA)

  - A PMA is required prior to marketing any Class III device.

  - FDA assesses a PMA to determine whether the information provided by the sponsor provides a *"reasonable assurance of safety and effectiveness".*

  - Applicant must provide *"valid scientific evidence"* of safety and effectiveness.

Device Approval Pathways: Premarket Approval

- PMA Supplements

PMA Supplement Type	Description
Prior approval (180 days)	• For significant changes that affect the safety and effectiveness of the device • In-depth review and approval by FDA required before implementation of the change
30-Day Notice	• Used for modifications to manufacturing procedures that affect the safety and effectiveness of the device • Change may be made 30 days after FDA receives the notice, unless FDA informs the PMA holder that the notice is not adequate
Changes Being Effected	• Can implement after FDA acknowledges receipt that submission qualifies for “CBE” supplement
Annual Report	• Certain changes not reported in PMA supplement

Device Approval Pathways: Premarket Notification

- 510(k) Clearance

  - A 510(k) notification does not lead to the "approval" of a device.

  - A manufacturer must wait for FDA to issue an order that the device is *"substantially equivalent"* to a predicate device.

  - Certain modifications to previously cleared devices require a new 510(k).

Premarket Notification: 510(k) Clearance

- 510(k) Clearance

  - Must establish that the device has the same intended use as a legally marketed predicate device and

    - Has the same technological characteristics as the predicate device, or

    - Has different technological characteristics and the information submitted demonstrates that the device is as safe and effective as a legally marketed device, and does not raise different questions of safety and effectiveness than the predicate device

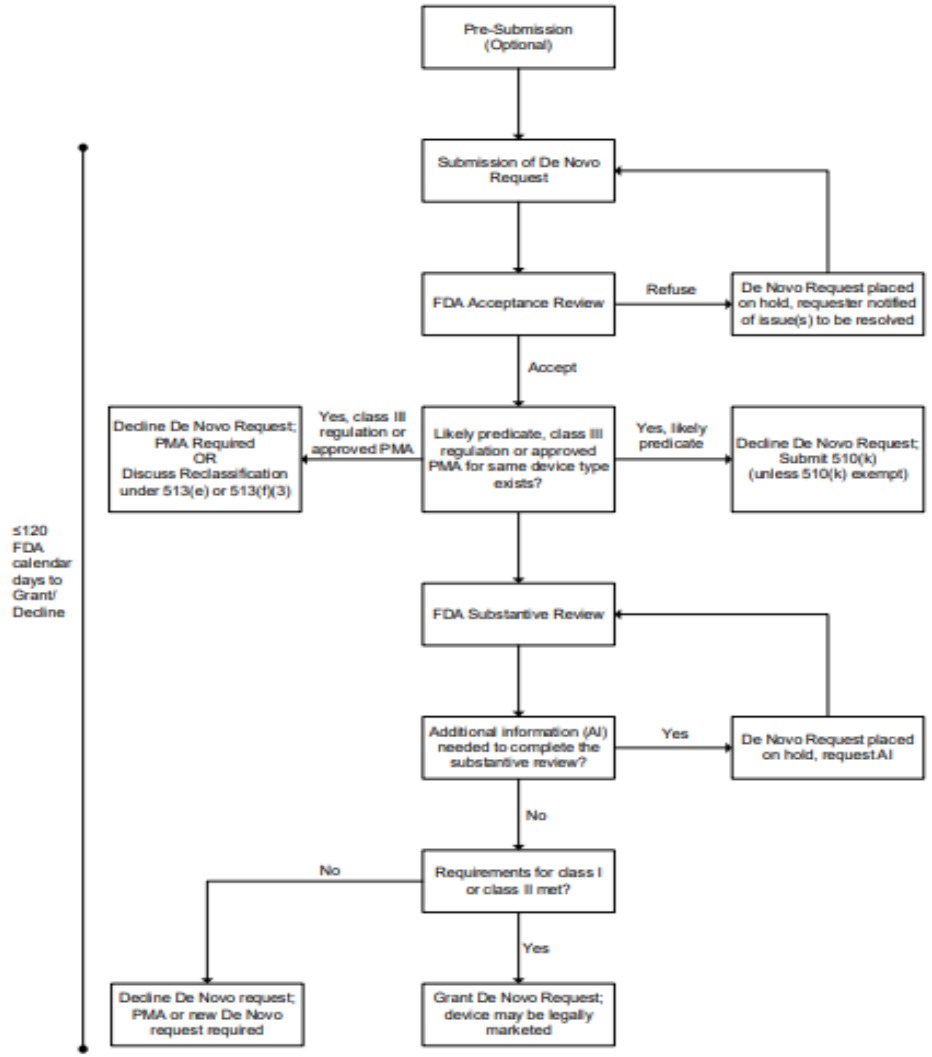
Premarket Pathways: De Novo Review

- De Novo Review

  - Devices not otherwise classified by §513(a)(1) of the FD&C Act.

  - Two pathways

    1. submission of a 510(k) notice; or
    2. direct de novo application pathway.



Judges and Lawyers ~~Breast Cancer Alert~~

Ellen P. Hermanson Memorial Symposium – March 22, 2023

Nancy K. Stade
Partner, FDA Group

What is a Device?

FDC Act § 201(h)(1):

(h)(1) The term "device" … means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is-

(A) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,

(B) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(C) intended to affect the structure or any function of the body of man or other animals, and

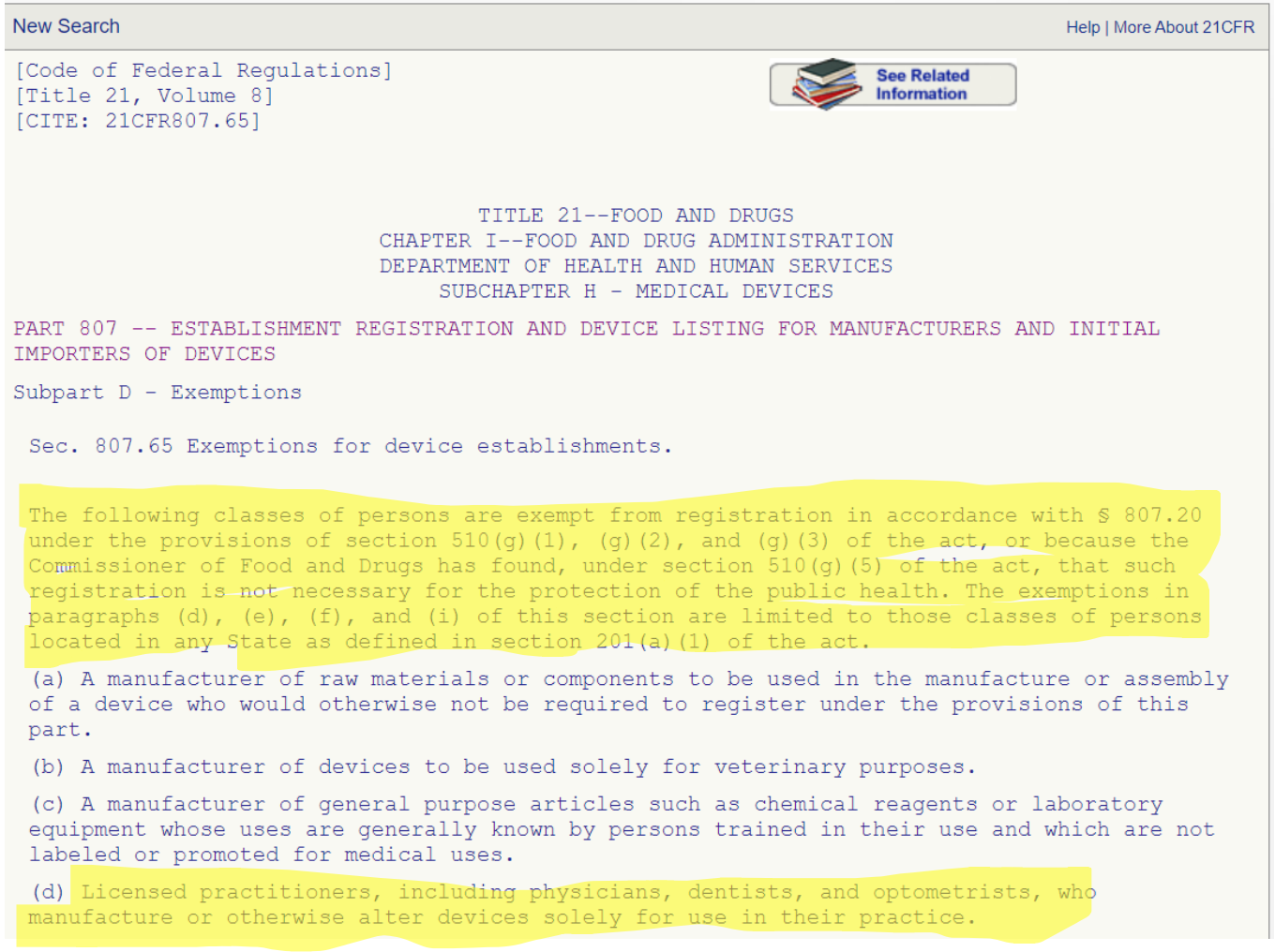
which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term "device" does not include software functions excluded pursuant to section 360j(o) of this title.

Does the FDA regulate the practice of medicine?

FDC Act §396. Practice of medicine

Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship. This section shall not limit any existing authority of the Secretary to establish and enforce restrictions on the sale or distribution, or in the labeling, of a device that are part of a determination of substantial equivalence, established as a condition of approval, or promulgated through regulations. Further, this section shall not change any existing prohibition on the promotion of unapproved uses of legally marketed devices.

Can doctors develop AI for use in their own practice?



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[Code of Federal Regulations]
[Title 21, Volume 8]
[CITE: 21CFR807.65]

See Related Information

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H - MEDICAL DEVICES

PART 807 -- ESTABLISHMENT REGISTRATION AND DEVICE LISTING FOR MANUFACTURERS AND INITIAL IMPORTERS OF DEVICES

Subpart D - Exemptions

Sec. 807.65 Exemptions for device establishments.

The following classes of persons are exempt from registration in accordance with § 807.20 under the provisions of section 510(g)(1), (g)(2), and (g)(3) of the act, or because the Commissioner of Food and Drugs has found, under section 510(g)(5) of the act, that such registration is not necessary for the protection of the public health. The exemptions in paragraphs (d), (e), (f), and (i) of this section are limited to those classes of persons located in any State as defined in section 201(a)(1) of the act.

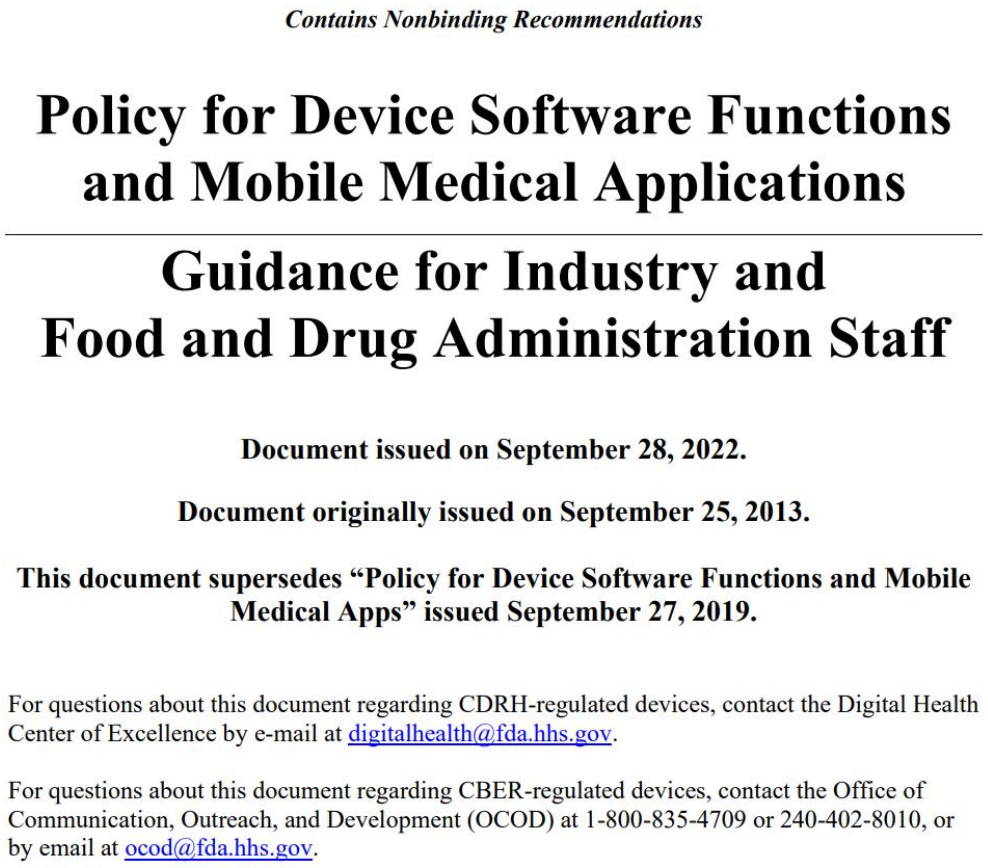
(a) A manufacturer of raw materials or components to be used in the manufacture or assembly of a device who would otherwise not be required to register under the provisions of this part.

(b) A manufacturer of devices to be used solely for veterinary purposes.

(c) A manufacturer of general purpose articles such as chemical reagents or laboratory equipment whose uses are generally known by persons trained in their use and which are not labeled or promoted for medical uses.

(d) Licensed practitioners, including physicians, dentists, and optometrists, who manufacture or otherwise alter devices solely for use in their practice.

Can doctors develop AI for use in their own practices?



Contains Nonbinding Recommendations

Policy for Device Software Functions and Mobile Medical Applications

Guidance for Industry and Food and Drug Administration Staff

Document issued on September 28, 2022.

Document originally issued on September 25, 2013.

This document supersedes "Policy for Device Software Functions and Mobile Medical Apps" issued September 27, 2019.

For questions about this document regarding CDRH-regulated devices, contact the Digital Health Center of Excellence by e-mail at digitalhealth@fda.hhs.gov.

For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010, or by email at ocod@fda.hhs.gov.

Exemptions:
Licensed practitioners, including physicians, dentists, and optometrists, who manufacture a mobile medical app or alter a mobile medical app solely for use in their professional practice and do not label or promote their mobile medical apps to be generally used by other licensed practitioners or other individuals.29,30 For example, if Dr. XYZ, a licensed practitioner, creates a mobile medical app called the "XYZ-recorder" that enables attaching an ECG electrode to a smartphone, and provides the "XYZ-recorder" to his/her patient to use it to record the patient's electrocardiographic readings for 24 hours, Dr. XYZ is not considered a mobile medical app manufacturer. If Dr. XYZ is in a group practice (including a telehealth network) and permits other physicians in the practice to provide the XYZ-recorder to their patients, Dr. XYZ is not considered a mobile medical apps manufacturer. However, if Dr. XYZ, the licensed practitioner, distributes the "XYZ-recorder" and, through labeling or promotion intends to make it generally available to or to be generally used by other physicians (or other specially qualified persons), Dr. XYZ would be considered a mobile medical app manufacturer.

How have FDA's authorities adapted to software?

Excluding low risk software through legislation…

Public Law 114–255
114th Congress

An Act

To accelerate the discovery, development, and delivery of 21st century cures, and for other purposes.

Dec. 13, 2016
[H.R. 34]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

21st Century Cures Act.
42 USC 201 note.

SECTION 1. SHORT TITLE; TABLE OF CONTENTS.

(a) SHORT TITLE.—This Act may be cited as the "21st Century Cures Act".

(b) TABLE OF CONTENTS.—The table of contents for this Act

Excludes certain software from regulation as a device:

- Software used for administrative support in healthcare facilities;
- Software used for general health and wellness;
- Electronic health records
- Software used only to transfer, store, convertor display data or results (aka Medical Device Data Systems)

and policy development:

List of FDA Guidance Documents with Digital Health Content

* Highlighted documents exclude certain software from regulation

Search:

Show 100 entries

Issue Date	Guidance	Guidance Status
09/28/2022	Clinical Decision Support Software	Final
09/28/2022	Policy for Device Software Functions and Mobile Medical Applications	Final
09/28/2022	Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communications Devices	Final
04/08/2022	Cybersecurity in Medical Devices: Quality System Considerations and Content of Premarket Submissions	Draft
12/23/2021	Digital Health Technologies for Remote Data Acquisition in Clinical Investigations	Draft
11/04/2021	Content of Premarket Submissions for Device Software Functions	Draft
11/04/2020	Multiple Function Device Products: Policy and Considerations	Final
09/27/2019	Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act	Final
09/27/2019	General Wellness: Policy for Low Risk Devices	Final
09/27/2019	Off-The-Shelf Software Use in Medical Devices	Final
12/20/2017	Medical Device Accessories - Describing Accessories and Classification Pathways	Final
12/08/2017	Software as a Medical Device (SAMD): Clinical Evaluation	Final
10/25/2017	Deciding When to Submit a 510(k) for a Software Change to an Existing Device	Final
09/06/2017	Design Considerations and Pre-market Submission Recommendations for Interoperable Medical Devices	Final
12/28/2016	Postmarket Management of Cybersecurity in Medical Devices	Final
02/03/2016	Applying Human Factors and Usability Engineering to Medical Devices	Final
09/02/2014	Content of Premarket Submissions for Management of Cybersecurity in Medical Devices	Final
08/14/2013	Radio Frequency Wireless Technology in Medical Devices	Final
07/03/2012	Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Notification [510(k)] Submissions	Final
07/03/2012	Clinical Performance Assessment: Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data - Premarket Approval (PMA) and Premarket Notification [510(k)] Submissions	Final
03/18/2010	Guidance: Acceptable Media for Electronic Product User Manuals	Final
05/11/2005	Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices	Final
02/09/2005	Information for Healthcare Organizations about FDA's "Guidance for Industry: Cybersecurity for Networked Medical Devices Containing Off-The-Shelf (OTS) Software"	Final

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How have FDA's authorities adapted to software?

Re-thinking authorities and practices to handle sophisticated software (AI/Machine Learning) and other Software as a Medical Device.

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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
07/22/2022	K220624	AI4CMR v1.0	AI4MedImaging Medical Solutions S.A.	Radiology	LLZ
07/22/2022	K220882	Vivid E80, Vivid E90, Vivid E95	GE Medical Systems Ultrasound and	Radiology	IYN
07/22/2022	K220940	EchoPAC Software Only, EchoPAC Plug-in	GE Medical Systems Ultrasound and Primary Care Diagnostics,	Radiology	QIH
07/20/2022	K220956	Libby Echo:Prio	Dyad Medical, Inc	Radiology	QIH

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Judges and Lawyers Breast Cancer Alert

26 Annual Ellen P. Hermanson Memorial Symposium

Can Artificial Intelligence Detect Breast Cancer Better Than Your Doctor?

Betsy D. Baydala, Esq.
Partner, Kaufman Borgeest & Ryan, LLP

March 22, 2023

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AI Privacy & Security Concerns

- **HIPAA privacy and security in data exchange**
  - Transparent data collection (patient consent), Big Data
- **Ethical and social implications**
  - Implementation standards and obligations
- **Properly validated algorithm**
  - Sample size and data input
- **Cyber Security**
  - Corrupting data systems, malware, hacks, nefarious actors

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Medical Malpractice: Delay/Failure to Diagnose

- **~30% of all medical malpractice lawsuits**
- **~12 million significant misdiagnoses a year**
- **~ 1/3rd of medical operations are unnecessary**

- **~30% of radiologists have experienced a malpractice claim**
- **800 million annual scans**
  - 2% false positive
  - >25% false negative

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Promise of Radiology AI: Aid in Correct Diagnosis

- **Machine-assisted diagnosis**
  - Collective intelligence of doctors + machine learning to improve diagnostic accuracy
- **Serve as a second opinion**
  - Improve likelihood of arriving at correct diagnosis
- **Upgrade diagnosis**
  - From an art → digital data-driven science

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AI as a Medical Standard of Care?

- **Accuracy in diagnosis and treatment**
  - Essential part of diagnostic care
  - Hone ability to predict response to treatment
  - More mainstream in clinical care
- **A new medical malpractice liability trap?**

"Teaching a machine to read is harder than anyone thought."

-Lynda Chin, M.D.

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