8 Artificial Intelligence-based Software

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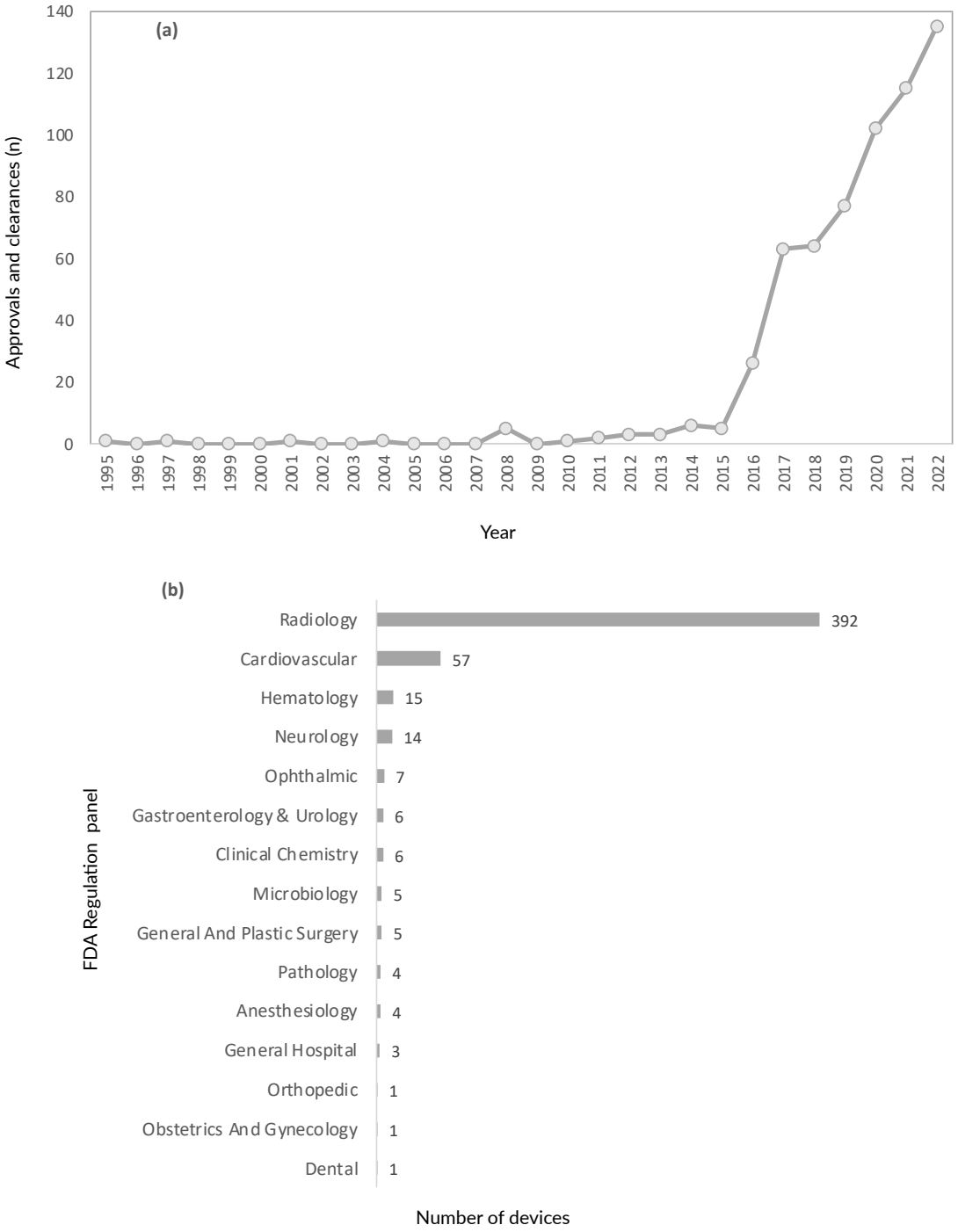
Introduction

Artificial intelligence (AI) has great potential to address clinical challenges in healthcare.[1] With the recent advancement in data science and information technology, software incorporating AI, and its subdivision machine learning (ML) technology, is becoming an integral part of an increasing number of medical devices. AI/ML technologies have revolutionized every aspect of our lives and are poised to reshape clinical practice by improving the experiences of physicians and patients.[2] The growth in AI research is evident from the number of peer-reviewed articles published between 1998 and 2018 which has grown by over 300 percent.[3] The exponential increase in AI research has led to a corresponding increase in the number of resulting patents. For example, the number of AI patents filed in 2021 has increased by more than 30 times compared to patents filed in previous years.[4,5] The increasing trend in AI research and resulting patents also correlates well with the increasing rate of marketing authorizations from the Food and Drug Administration (FDA) in the US.[6]

AI-based software in the context of medical devices includes standalone and embedded software – software as a medical device (SaMD) and software in a medical device (SiMD), respectively. The use of algorithms containing AI/ML in SaMD and SiMD has been proven to aid clinical users in image acquisition and processing, early disease detection and triage, accurate diagnosis, prognosis, and risk assessment. The first software incorporating AI/ML technologies was approved via a premarketing approval process (P970058) for mammography by the FDA in 1998. For the next 18 years, marketing authorizations trickled through the Agency with fewer than 30 SaMD reaching the US market. However, the pace of clearances and approvals has increased substantially since 2016.[7]

The FDA maintains a list of AI software that they have granted US marketing authorization on their website; as of June 2023, over 500 AI/ML algorithms are cleared or approved for clinical use.[6] As shown in **Figure 8-1**, the FDA has granted an increasing number of marketing authorizations every year, with the majority of applications being in radiology, followed by cardiology. With an increasing number of validated AI/ML models along with efforts from health authorities to streamline regulatory pathways to bring them to market, a growing number of manufacturers are developing AI/ML based software tools to support clinical decision-making in medical imaging. Despite the promise of AI/ML

Figure 8-1. Schematic Representation of (a) The Number of FDA Approvals and Clearances Per Year and (b) The Number of Device Authorizations by FDA Regulation Panel as of 31 December 2022



Source: Food and Drug Administration

as a tool in the clinical environment, widespread adoption in routine clinical practice faces some obstacles including trustworthiness, reliability, transparency, explainability, responsibility, privacy and security.[8]

This chapter provides an overview of AI/ML functionalities used for imaging and describes the evolution of FDA regulations related to AI/ML software in the radiological health space. Throughout this chapter the terms AI/ML software or technologies or systems or applications are used interchangeably. This chapter does not cover the standalone software used for auto-contouring in nuclear medicine and radiation therapy (NMRT) applications. For more information on NMRT software devices please refer to Chapter 6. This chapter also offers some key considerations for SaMD developers to ensure that their technology is safe and effective when deployed for clinical use. Finally, it provides an outlook on where the field is headed through the lens of the authors. A summary of the key terms, abbreviations and definitions used throughout this chapter is provided in **Table 8-1**.[9-22]

Historic Perspectives

The clinical use of software tools incorporating AI/ML is becoming more widespread within the radiological health space. The software tools have a range of applications, including assisting healthcare providers in:

- Image acquisition;
- Image reconstruction;
- Image processing (e.g., from computed tomography [CT], magnetic resonance [MR], ultrasound, positron emission tomography [PET], and single-photon emission computerized tomography scans);
- Image management and storage;
- Automation of radiology workflows via a radiology information system (RIS), and;
- Detection, segmentation, classification, and quantification of pathological findings.

Within radiology, computer-assisted devices (CAD) are becoming widely available in clinics to improve radiology workflow, with particular applications to the triage (CADt), detection (CADe) and diagnosis (CADx), or both (CADe/x) of different abnormalities in medical images.

Early research and development efforts to analyze medical images with CAD started in the 1960s.[23] More intense research investigation of CAD began in 1980s with the use of improved automation tools for conducting computer analysis on lesions seen on medical images.[24] The FDA approved the first CAD software in 1998 via the premarket approval (PMA) process to help radiologists identify and mark regions of interest (ROIs) on routine screening mammograms. Since then, numerous CAD devices have reached the US market, with the rate of marketing authorizations having increased substantially since 2016 (**Figure 8-2**).[25-33]

FDA-cleared or Approved AI Applications in Radiological Health

The FDA regulates software devices based on their risk to the patient (as previously described in Chapter 2, which provided an overview of regulatory pathways relevant to medical devices, and also in Chapter 7, which provided an overview of software regulation).

Available regulatory pathways for AI/ML enabled medical devices include:

1. The PMA pathway – the most stringent review for high-risk devices);
2. The 510(k) premarket notification pathway- for moderate-risk devices; and
3. The De Novo premarket review (for novel low- and moderate-risk devices).

Based on publicly available data on FDA marketing authorizations, the FDA has cleared 96.4% of AI/ ML medical devices via the 510(k) pathway, granted Class II marketing authorization to 3.5% via the De Novo pathway, and approved the rest via the PMA process.[6]

While AI/ML algorithms play a role in the operation of many radiological health devices, the rest of this chapter will focus on AI/ ML image processing devices as well as CADe, CADx and CADt devices. **Figure 8-3** provides examples of CAD applications cleared in recent years within the radiology field.

Table 8-1. Terms, Abbreviations and Definitions Related to AI and ML Technologies

Term	Abbreviation	Definition
Artificial intelligence	AI	A branch of computer science, statistics, and engineering that uses algorithms or models to perform tasks and exhibit behaviors that mimics humans in making decisions and predictions. The FDA interprets AI as algorithms or mathematical models that can analyze and interpret data[9]
Computer-assisted triage	CADt	CADt is computerized image processing device intended to aid in prioritization and triage of time sensitive patient detection and diagnosis based on the analysis of medical images acquired from radiological signal acquisition systems[10]
Computer-assisted detection	CADe	These are computerized systems intended to identify, mark, highlight, or in any other manner, direct attention to portions of an image, or aspects of radiology device data, that may reveal specific abnormalities during interpretation of patient radiology images or patient radiology device data by the clinician[11]
Computer-assisted diagnosis	CADx	These are computerized systems intended to provide an assessment of disease or other conditions in terms of the likelihood of the presence or absence of disease, or are intended to specify disease type (i.e., specific diagnosis or differential diagnosis), severity, stage, or intervention recommended[12]
Computer-assisted detection and diagnosis	CADe/x	These are computerized systems intended to provide both CADe and CADx features[12]
Digital Imaging and Communications in Medicine	DICOM	It is an international standard that specifies the protocols used to facilitate the exchange of communication and management of medical image information and data[13]
Medical image management and processing system	MIMPS	A medical image management and processing system is a device that provides one or more capabilities relating to the review and digital processing of medical images for the purposes of interpretation by a trained practitioner of disease detection, diagnosis, or patient management[12]
Machine learning	ML	The subset of AI known as ML consists of algorithms that can learn from large data sets and make predictions without being explicitly programmed[14]
Intended use	–	The intended use describes the general purpose of the device or its function and encompasses the indications for use[15]
Indications for use	IFU	The IFU of a device is defined in 21 CFR §814.20(b)(3)(i) as "the disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended"[16]
Software as a medical device	SaMD	Software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device[17]
Software in a medical device	SiMD	Software embedded in hardware or that is an integral part of a medical device[18]
Supervised machine learning	–	Machine learning that makes use of labeled data during training. ML models are trained with training data that includes a known or determined output or target variable[19]
Unsupervised machine learning	–	Machine learning that makes use of unlabeled data during training[18]
Training data	–	A set of data used my manufacturers in procedures and machine learning training to build an ML model[20]

Table 8-1. Terms, Abbreviations and Definitions Related to AI and ML Technologies (cont.)

Term	Abbreviation	Definition
Tuning data	–	A set of data used by manufacturers to evaluate a small number of trained ML functions to explore different architecture or hyperparameters (parameters used to control the learning process)[19]
Testing data	–	The data used to characterize the performance of the ML model. An independent set of data that is never shown to the AI training algorithm during training and is used to estimate the actual ML model performance after training[20]
Verification	–	The confirmation that a system was built correctly and fulfils the specified requirements.[17] Validation is the confirmation, through objective evidence, that the requirements for a specific intended use have been fulfilled
Validation	–	The confirmation, through objective evidence, that the requirements for a specific intended use have been fulfilled[17]
Reference standard ('Gold standard' or 'ground truth')	–	An objectively determined benchmark that provides the expected result for comparison, assessment, training, etc.[21] In computer aided-detection applications, a reference standard indicates whether a disease, condition, abnormality, or all, are present, and if so, may include such attributes as its extent or location[22]
Ground truthing	–	The characterization of the reference standard for a patient (disease status) is known as the truthing process[20]
Locked algorithm	–	An algorithm that provides the same result each time the same input is applied to it and does not change
Continuous learning (adaptive)	–	Incremental training of an AI system that takes place on an ongoing basis during the operation[19]

Regulation of SaMDs Incorporating AI/ML

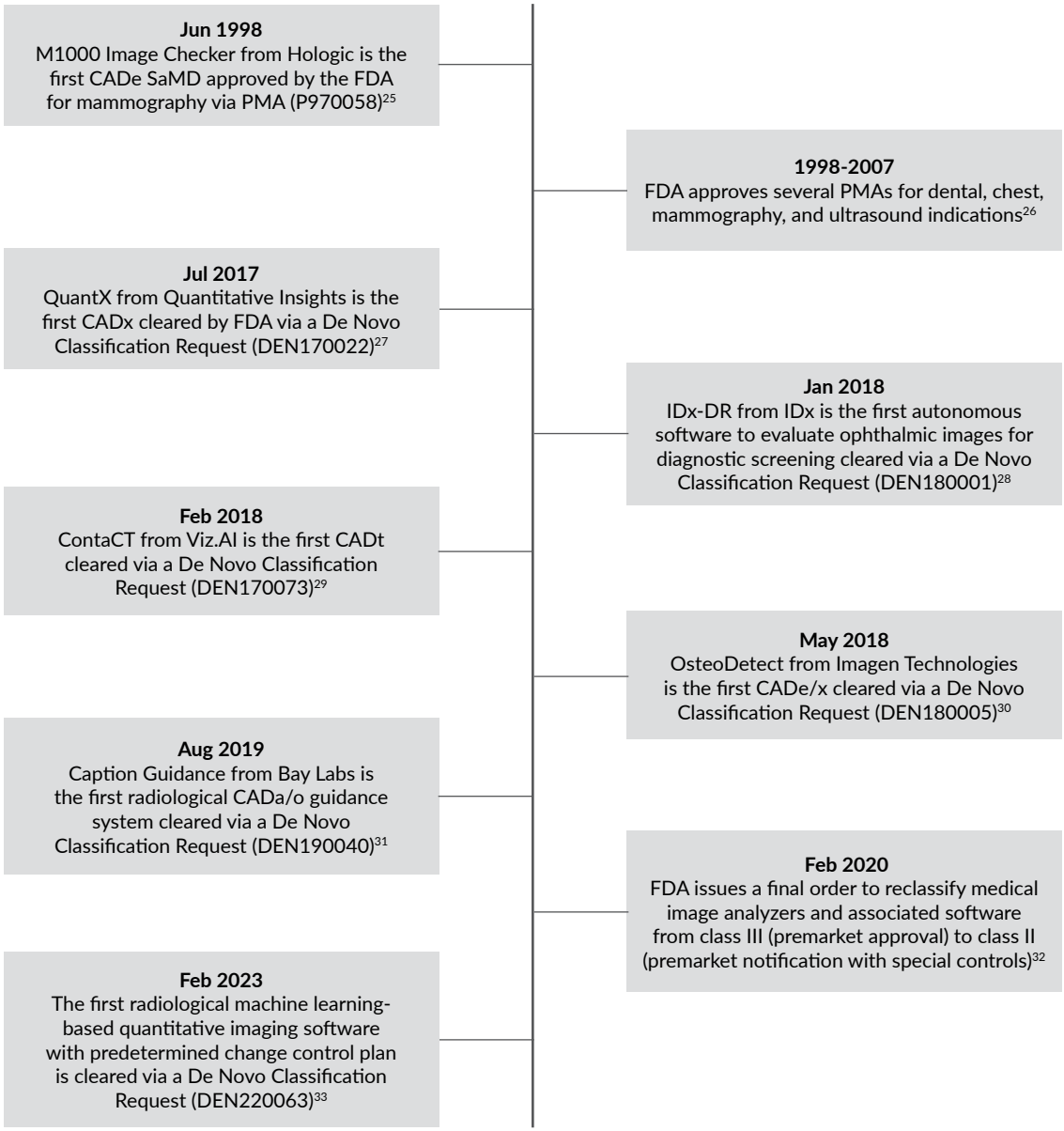
While the existing regulatory framework for traditional medical devices is still applicable to SaMD, the FDA is looking at innovative approaches to regulate SaMD. In recent years the Agency has issued guidance documents, white papers, and public workshops to clarify their current thinking on these technologies in order to promote public health and safety.

During the concept phase of developing AI/ML technologies, developers should first determine whether their software functions fall under the FDA's definition of a medical device. The FDA's Digital Health Policy Navigator (hereon referred to as Navigator) provides a convenient and efficient framework for developers to assess their software's functions.[34] This interactive seven-step process guides developers through the most relevant FDA medical device regulatory guidance documents and policies that may apply to their software product. After determination that the software function is in fact a medical device, developers should look into all applicable regulations for the subject device. Brief introductions to some examples of AI/ML software devices follow.

Medical Image Management and Processing Systems – 21 CFR §892.2050

Medical image management and processing systems (MIMPS) were previously known as picture archiving and communications system (PACS). PACS are ubiquitous in hospitals and these systems were intended to securely store, access and process medical images in healthcare facilities.[35] The 21st Century Cures Act amended the definition and identification description of a medical device in the Food Drug & Cosmetic Act to exclude certain functions.[36] In accordance with this change, the FDA amended 21 CFR §892.2050 on 19 April 2021, altering the title of the classification

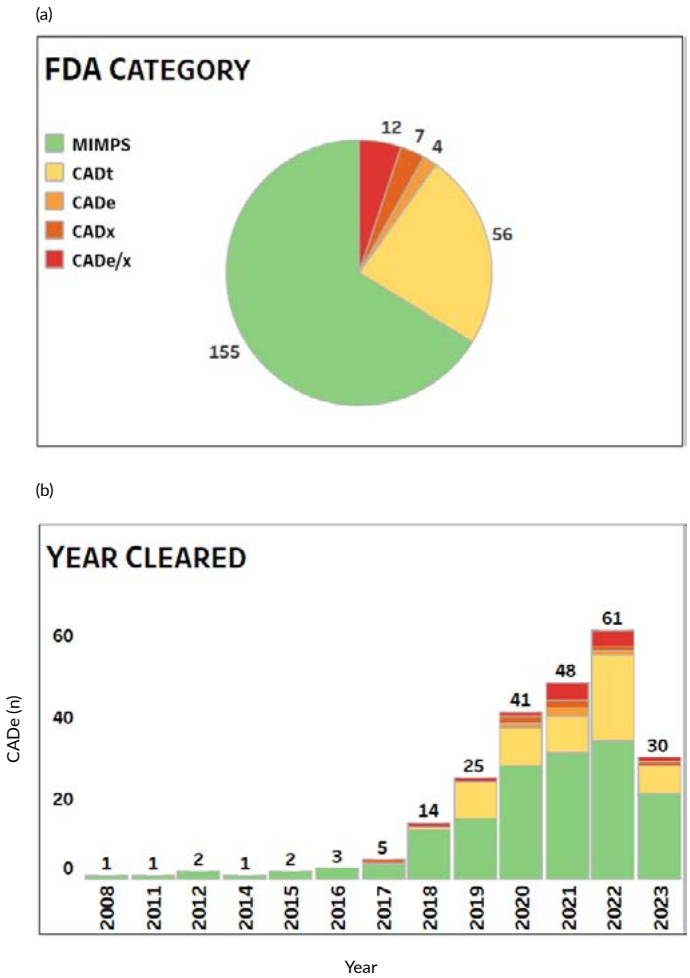
Figure 8-2. A Brief Chronology of Computer-Assisted Device Evolution



CADa/o, computer-assisted acquisition and/or optimization; **CADe**, computer-assisted detection; **CADx**, computer-assisted diagnosis; **FDA**, Food and Drug Administration; **PMA**, premarket approval; **SaMD**, Software as a medical device

Created by Gopal Abbineni and Hortense Allison

Figure 8-3. Schematic Representation of Number of Computer-Assisted Detection Clearances by (a) FDA Category and (b) by Year Cleared According to Data From the American College of Radiology's Data Science Institute – AI Central



CADe, computer-assisted detection; **CADe/x**, computer-assisted detection/diagnosis; **CADt**, computer-assisted triage; **CADx**, computer-assisted diagnosis; **MIMPS**, Medical image management and processing system

Source: ACR Data Science Institute AI Central

from Picture Archiving and Communications Systems to Medical Image Management and Processing Systems and excluded software functions for the storage and display of medical images from the definition. MIMPS currently only includes software components that provide advanced or complex image processing functions for image manipulation enhancement, or quantification that are intended for use in the interpretation and analysis of medical images. These devices are regulated as Class II medical devices via a 510(k) notification pathway.

AI/ ML devices classified as MIMPS should follow the the Digital Imaging and Communication in Medicine (DICOM) standard. The DICOM standard has evolved as the primary format for medical images in clinical use. In addition, the American Association of Physicists in Medicine (AAPM) Report 270 and the Report of Task Group (TG) 18 define

the necessary tests and performance criteria for display devices used in medical imaging to ensure consistent presentation of medical images.[37] Common performance test metrics MIMPS include spatial resolution, measurement accuracy, segmentation accuracy, reproducibility, signal to noise ratio (SNR), root mean square error (RMSE), Dice Similarity Coefficient (DSC), the Hausdorff distance, among others. It is the manufacturers responsibility to demonstrate the standalone performance tests meets or exceeds the preset acceptance criteria defined in the standard and task group report to ensure the safety and effectiveness of these devices.

One example of an image processing device includes AI-Rad Companion (Pulmonary) (K213713),[38] an image-processing software that provides quantitative and qualitative analysis from previously acquired CT DICOM images to support radiologists and physicians in the evaluation and assessment of disease of the lungs.

Medical Image Communication Systems, Medical Device Data System, and Medical Image Storage Device – 21 CFR §892.2020, §880.6310, and §892.2010

Medical imaging communication, data and image storage regulation is covered by 21 CFR §892.2020, §880.630, and §892.2010.

A sub-set of AI tools is intended to augment workflow solutions by reducing burden of basic repetitive tasks and increasing diagnostic precision when interpreting medical images. These are clinical decision software devices that may be considered Class I medical devices if the software functions are not performing advanced image processing functions.

Class I medical devices are products deemed to be low-risk, and as such are subject to the least amount of regulatory control including exemption from pre-market notification.

There are several AI/ML software solutions in this category that can be fully integrated into the image interpretation workflow, and which are intended to help clinical users handle their daily workload. Two examples include the multi-modality viewer (K182230)[39] and the Hologic SecureView DX-RT (K041555).[40]

CADe, CADx, and CADt Devices

Software incorporating AI/ML has applications in various types of clinical decision support. Here, the discussion is limited to CADe, CADx, and CADt applications, as overviewed in **Figure 8-4**.[41]

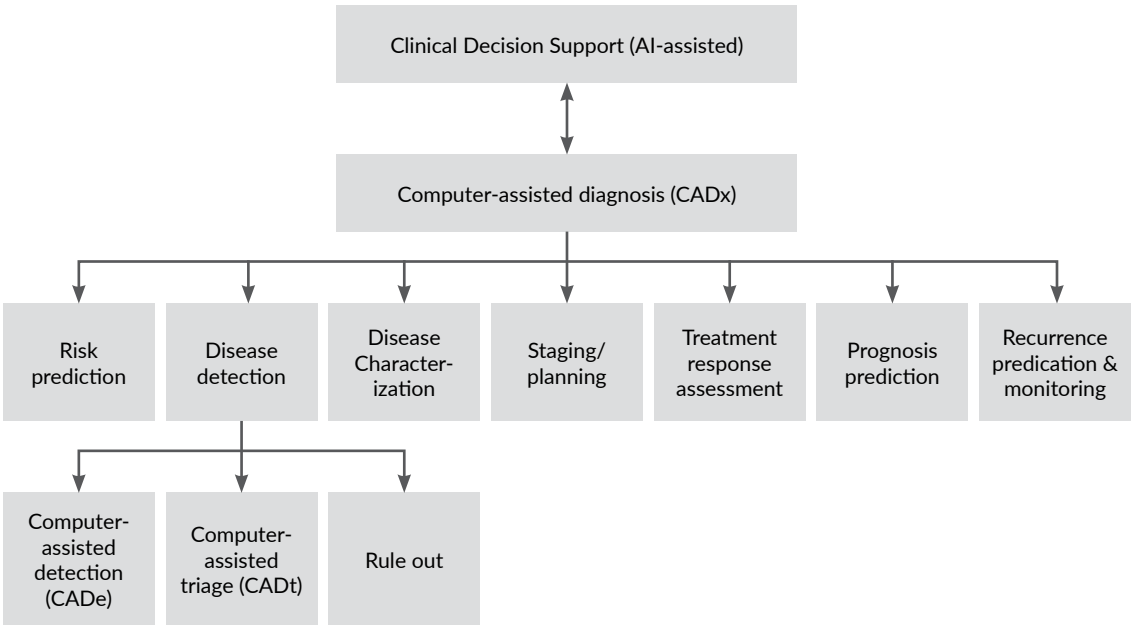
CADe (21 CFR §892.2070): Medical Image Analyzer

CADe systems use algorithms to recognize patterns on radiological images to detect abnormalities, such as a tumor or other lesion indicative of a disease condition. The majority of CAD devices introduced on to the US market between 1998 and 2016 were CADe systems.[23] These devices cover a wide range of clinical applications from highlighting suspicious areas of tissue on mammography or chest x-rays to improving the detection of lung nodules. Examples of CADe devices include Chest-CAD (K210666)[42] that analyzes chest radiographs using machine learning techniques to identify, categorize, and highlight suspicious ROIs and auto lung nodule detection (K201560)[43] which is used to identify and mark regions of suspected pulmonary nodules.

Several research studies suggest that CADe can improve a radiologist's ability to detect breast abnormalities on mammograms with increased confidence.[44] After the first CADe device became available on the US market in 1998, CADe adoption was initially slow but then began to increase dramatically in digital mammography, jumping from 5% in 2003 to 83% in 2012.[44]

When collating data to support FDA submissions of new CADe and CADx devices, clinical study design and the statistical methods used are important to consider. A successful submission should include both standalone performance testing , which is testing that demonstrates the device improves performance in the intended use population when used in accordance with the instructions for use (IFU) labeling, and a reader study. Manufacturers typically report details of the device's sensitivity and specificity, receiver operating characteristic (ROC) curves, and areas under the ROC curves (AUCs).[45] Setting an appropriate objective reference standard (ground truthing process) and

Figure 8-4. Overview of Computer-Assisted Diagnosis Applications



AI, Artificial intelligence

Source: Adapted from Hadjiiski L, et al.[41]

understanding the role of human readers (i.e., the physicians interpreting the images) and both inter- and intra-reader variability are vital during the reader study design. As reader variability poses challenges to the evaluation and comparison of imaging devices, health authorities often expect to see fully crossed multi-reader, multi-case (MRMC) reader studies.[12]

It is recommended that developers and manufacturers refer to the FDA guidance document Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data-Premarket Notification 510(k) Submissions, for more information.[12] Note that the majority of FDA-authorized CAD devices are intended to be decision support tools rather than primary diagnostic tools.[46]

CADx (21 CFR §892.2060): Radiological Computer-Assisted Diagnostic Software for Lesions Suspicious of Cancer

CADx systems are intended to aid in the characterization of lesions identified on acquired medical images, such as MR, mammography, radiography, or CT images. These software devices perform functions that may include automatically registering images, segmenting images, or analyzing user-selected ROI. In July 2017, the FDA granted a De Novo reclassification request for QuantX[27] as the first CADx intended to be used as a second reader for breast MRI (see Chapter 4).[23] The device presents an index indicating a QI score for the lesion site; the score is calculated via an AI algorithm from radiomic features. CADx software devices such as QuantX aid in providing diagnostic and patient management decisions to clinical users. Other examples of CADx include Brainomix 360 e-ASPECTS (K221564),[47] a software device intended to assist the physician in the assessment and characterization of brain tissue abnormalities using CT image data.

The performance study requirements for CADx are comparable to CADe requirements. The manufacturer should perform both stand-alone performance testing and a reader study.

It is recommended that manufacturers review the American Association of Physicists in Medicine TG Report 273[41] Clinical Performance Assessment: Considerations for Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data in Premarket Notification (510(k)) Submissions and Software as a Medical Device (SAMD): Clinical Evaluation.[18]

CADt (21 CFR §892.2080): Radiological CADt and Notification Software

Triage devices assist healthcare practitioners to quickly identify and prioritize patients based on the severity of their conditions. These devices allow patients to receive appropriate care in a timely manner. Some examples of cleared triage devices include BriefCase (K214043),[48] Annalise Enterprise CXR Triage Trauma (K222268)[49] and Syngo.CT Brain Hemorrhage (K203260).[50] Current evaluation methods for AI/ML-based triage devices mainly include standalone software testing (e.g., including measurement of sensitivity, specificity, AUC, and time-to-notification). It is very important that the manufacturer reiterate in their submission that triage devices are only for flagging and prioritizing patients and are not intended for disease detections and/or diagnosis.

Additional CAD Regulations

The discussion here has been limited to radiology image processing systems along with CADe, CADx, and CADt devices. **Table 8-2** gives examples of key performance metrics evaluated by the FDA during the clearance of recent CAD devices.[38,42,47-49] There are additional regulations pertaining to CAD that are outside the scope of this chapter that developers should be aware of, namely:

- The use of dual detection and diagnosis software (CADe/x) for lesions suspicious for cancer regulated under 21 CFR §892.2090
- Radiological Image Acquisition and/or Optimization Guided by Artificial Intelligence (CADa/o) regulated under 21 CFR §892.2100; and
- Radiological Machine Learning Based Quantitative Imaging Software with Change Control Plan regulated under 21 CFR §892.2050 and image reconstruction algorithms.

The line between quantitative imaging and CAD devices may occasionally have some ambiguity. They both provide advanced image analysis techniques for healthcare professionals. Quantitative imaging can go beyond the anatomy into the molecular level whereas CAD essentially relies mainly on the measurements from medical images For example, the FDA guidance Technical Performance Assessment of Quantitative Imaging in Radiological Device Premarket Submissions,[51] states that while the Agency would consider "a function that reports a percent stenosis value from the ratio of two vessel diameters… a quantitative imaging function," a device "linking the probability of a cardiac event to the percentage of vessel stenosis would be outside the scope of [the] guidance document," presumably because such a device falls outside the boundary of what FDA considers simple "quantitative imaging."

To ensure a smooth regulatory process, it is recommended that device manufacturers pay close attention to the importance of identifying the appropriate regulation for their device, with consultation to the FDA via the Q_submission process as necessary to determine whether the Agency considers the device in question a CAD. Per the special controls, the FDA has different expectations of performance data for CAD devices than for simpler measurement tools that do not provide detection or diagnosis information. In particular, CAD devices often require submission of a clinical performance assessment, whereas technical performance assessment may suffice for simple quantitative imaging or measurement devices that do not perform detection or diagnosis. Submitting without any clinical performance assessment, may result in regulatory delays or an immediate Not Substantially Equivalent" (NSE) determination.[52]

Table 8-2. Examples of Key Performance Metrics Evaluated by the FDA During the Clearance of recent Computer-Assisted Detection (CADe) Devices

Device Name	Premarket Clearance # (Class II)	Summarized Indications	Imaging Modality	Test Cases (n)	Standalone Performance Metrics
BriefCase[48]	K214043	Triage device intended for flagging and communication of suspect positive pneumothorax findings	CXR	619 (139 positive; 480 negative)	**Sensitivity:** 94.2% (95% CI: 89.9%, 97.8%) **Specificity:** 90.8% (95% CI: 88.1%, 93.1%) **Area under the curve (AUC):** 0.969 (95% CI: 0.954, 0.985) **Time to Notification:** 13.1 seconds
Annalise Enterprise CXR Triage Trauma[49]	K222268	Software workflow tool designed to aid the clinical assessment of adult chest x-ray cases with features suggestive of vertebral compression fracture in the medical care	CXR	589 (272 positive; 317 negative)	**Sensitivity:** 89.3% (95% CI : 85.7%, 93.0%)[a] **Specificity:** 89.0% (95% CI : 85.8%, 92.1%)[a] **AUC:** AUC: 0.954 (95% CI: 0.939-0.968) **Time to Notification:** 30 seconds
Chest-CAD[42]	K210666	CADe software that analyzes chest radiographs to identify, categorize and highlight suspicious regions of interest	CXR	20,000	**Sensitivity:** 90.8% (95% CI: 90.5%, 91.1%) **Specificity:** 88.7% (95% CI: 88.5%, 88.9%) **AUC of receiver operating characteristic:** 0.976% (0.975-0.976, 95% CI) **Other:** Clinical reader study: multiple-reader, multiple-case (MRMC) cross-over study. The study evaluated the performance of 24 clinical readers evaluating 238 cases to determine whether the accuracy of readers aided by Chest-CAD ("Aided") was superior to the accuracy of readers when unaided by Chest-CAD ("Unaided") by the case-level, across-category aggregate
Brainomix 360 e-ASPECTS[47]	K221564	A computer-assisted diagnosis (CADx) software device used to assist the clinician in the assessment and characterization of brain tissue abnormalities using CT image data	CT	256 non-contrast CT scans	**Sensitivity:** 68.0% (95% CI: 57.0%, 72.0%) **Specificity**: 97% (95% CI: 86.0%, 98.0%) **AUC**: 83.0% (95% CI: 81.0%, 85.0%I) **Digital phantom testing:** **Other**: Clinical reader study: MRMC cross-over study. The study evaluated the performance of 10 clinical readers evaluating 54 retrospective scans with and without the aid of Brainomix 360 e-ASPECTS
AI-Rad Companion[38]	K213713	Image-processing software that provides quantitative and qualitative analysis from previously acquired CT DICOM images. Supports radiologists and physicians from emergency medicine, specialty care, urgent care, and general practice in the evaluation and assessment of disease of the lungs	CT	200	**Sensitivity:** 94.3% **Average positive predictive value**: 99.1%

AUC, area under the receiver operative characteristic curve; **CAD**, computer-assisted device; **CADx**, computer-assisted diagnosis device; **CADe**, computer-assisted detection device, CT, computed tomography; **CXR**, chest x-ray; **DICOM**, Digital Imaging and Communications in Medicine; **MRMC**, multiple-reader, multiple-case

[a]Vertebral compression fraction at operating point 0.3849.

21 CFR §870: Cardiovascular Devices

After general radiology, the second highest number of AI/ML SaMD applications that the FDA has granted marketing authorization for are used in cardiology.[53] A number of cardiological applications use AI and have significant overlap with medical imaging.[54] **Table 8-3** provides a few examples of FDA-cleared AI/ML clinical applications for cardiology use that are related to medical imaging; the majority are programmable diagnostic devices that can compute various physiologic, or blood flow parameters based on medical images.[55-57]

21 CFR §892.1750: CT X-ray system – Image Reconstruction Algorithms

In addition to standalone SaMD incorporating AI/ML, these technologies are also frequently integrated within the medical device itself (i.e., SiMD). Examples of the latter exist throughout the radiological health space and one example is the use of AI/ML for medical image reconstruction. Deep learning-based reconstruction algorithms have recently begun to be used in CT, MR, and nuclear medicine devices; examples include GE Healthcare's Deep Learning Image Reconstruction (DLIR) (K183202)[58] for CT and Precision DL for PET/CT, Canon Medical's Precise IQ Engine (PIQE) for CT (K182901),[59] and Siemens Deep Resolve for MR (K220939);[60] see Chapters 3, 4, and 6 for more on these systems). When used in image reconstruction, deep learning-based algorithms have the potential to maintain quantitative integrity while providing denoising capabilities.[61]

Image reconstruction software is part of embedded hardware and therefore falls within the scope of the existing regulations for imaging hardware; for example, CT and MR reconstruction are regulated under the 21 CFR §892.1750 and 21 CFR §892.1000 regulations respectively. Image reconstruction is a mathematical process that generates images from noisy sample measurements. For example: Philips Iterative Reconstruction Technique Software Application (K113483)[62] is cleared to reconstruct raw data from CT scanners to produce images containing less or equal noise when compared to images produced by standard filtered back projection reconstruction. DLIR (K183202)[58] was the first FDA-cleared technology to use deep neural network-based CT reconstruction, followed 2 months later by Canon Medical's Advanced intelligent Clear-IQ Engine (AiCE) (K183046).[63] According to the 510(k) summary for K183202, the latter's FDA clearance was based on a combination of bench data and a retrospective study of 60 cases, with images evaluated by nine radiologists using a Likert-scale study. Efficient validation methods for AI/ML based reconstruction algorithms remain a subject of ongoing research.[61]

21 CFR §886.1100: Retinal Diagnostic Software Device

While ophthalmology is not directly connected to radiological health, developments in

Table 8-3. Examples of FDA-Cleared AI/ML Devices for Cardiology

Device Name	Regulation	Clearance Number	Company	Short Description
DeepVessel FFR[55]	21 CFR §870.1415 (Product code: PJA)	K213657	KeyaMed NA Inc.	Coronary physiological simulation software intended for evaluation and assessment of coronary arteries
HeartFlow Analysis[56]	21 CFR §870.1415 (Product code: PJA)	K203329	HeartFlow, Inc.	Semi-automated tool for extraction of anatomic data for coronary physiologic simulation to aid in diagnosis of coronary artery disease
Feops HEARTguide[57]	21 CFR §870.1405 (Product code: QQI)	K214066	Feops NV	Software that performs computer simulation to predict implant frame deformation to support the evaluation for left atrial appendage occlusion device size and placement

ophthalmic AI devices are likely to have potential future implications for the regulation of radiological health. This is due to the first FDA marketing authorizations of autonomous AI/ML devices being granted within the specialty.

Ophthalmology is an image-based and data-rich specialty with a trend toward the increasing use of AI/ML algorithms.[64] To date only a few SaMD AI/ML devices are FDA-cleared for use in ophthalmology, for diagnostic screening purposes. These can help identify retinal diseases or conditions early enough (e.g., mild diabetic retinopathy) to enable treatment to prevent vision loss.[65]

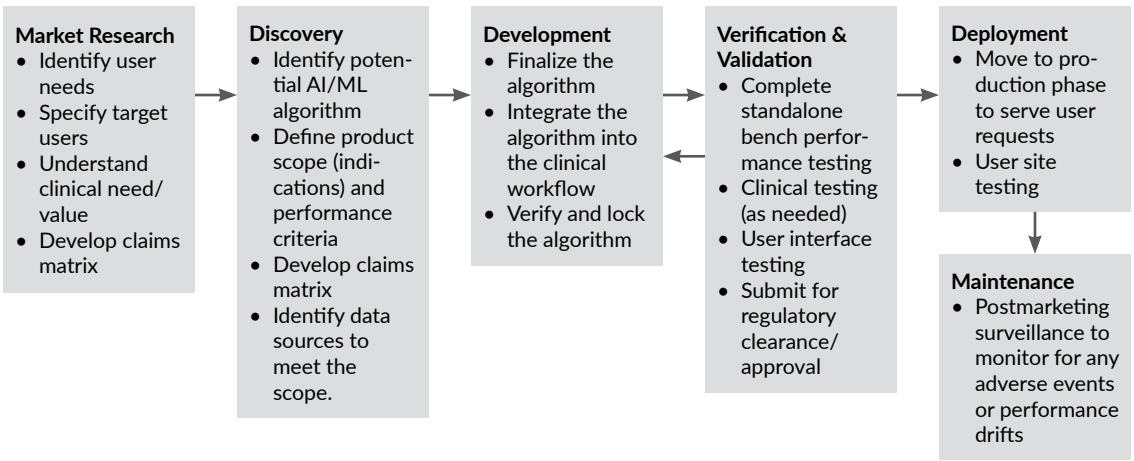
The first SaMD, IDx-DR (Idx, LLC, Coralville IA) received FDA marketing authorization via the De Novo pathway (DEN180001).[28] Special controls established by 21 CFR §886.1100 included a requirement for clinical performance data evaluating sensitivity, specificity, negative predictive value, and positive predictive value, in addition to software verification and validation tests and usability testing information.[66]

Key Design Considerations for Successful Development of AI/ML SaMDs

When developing AI/ML medical devices, developers should always consider the Total Product Life Cycle (TPLC) aspects of the product (i.e., from initial design to post-marketing monitoring). The first aspect is understanding the steps involved in the development of an AI/ML product (**Figure 8-5**). In 2021, the FDA, Health Canada, and the UK's Medicines and Healthcare products Regulatory Agency (MHRA) jointly identified 10 guiding principles that could inform the development of good machine learning practice.[67] The key principles are a useful resource for developers and are outlined in **Table 8-4**.[68]

The development of SaMD requires enlisting multiple internal and external stakeholders to ensure robust development. Developers should have a systematic process for engaging key stakeholders, including physicians and other end users, to participate in device design and continuously test and validate assumptions and ideas during device development. **Table 8-5** contains some key considerations for successful development of a SaMD.

Figure 8-5. Schematic Representation of Various Development Stages in SaMD



AI, Artificial intelligence; **ML**, machine learning; **SaMD**, software as a medical device

Created by Gopal Abbineni and Hortense Allison

Table 8-4. Good Machine Learning Practice for Medical Device Development: Guiding Principles

Multi-disciplinary expertise is leveraged throughout the TPLC	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-artificial intelligence 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

TPLC, Total Product Life Cycle

Design and Development

Similarly, when designing a software product, companies should consider a systematic and methodical approach. Models, methods, architecture, and design-modelling techniques should be used that are appropriate for product development based on the intended use and the patient population to which the device is being applied.[67] Successful AI/ML medical device development includes establishing a process governing data curation, data quality control, data annotation, algorithm training, validation, and final product deployment.

The first step in development of AI/ML based SaMD is the data curation process that involves defining the scope or use case of the project, identifying the data requirements establishing a baseline, and data collection methods. Curated data must be properly labelled and organized. Structured and unstructured data should be organized in a manner that allows for traceability to the data collected. When organizing and labeling, the data developers should work closely with physicians and other clinical end users to ensure that the data annotation reflects clinical knowledge. A critical step in the initial phase of model development is ensuring that the quality and quantity of data are sufficiently high to train the algorithm successfully. This is the most time-consuming step in AI/ ML development and should follow a governance process. The curated data should be separated into independent training and testing datasets.

Training, tuning, and testing data

Training, tuning, and independent testing of data are crucial steps in any AI software development lifecycle. Each step has a specific purpose and requires collaboration of interdisciplinary teams to work closely with different methods and available scientific tools. Images from a single medical center may be insufficient to train a model for a given task or may be biased because of the sampled population. Multicenter datasets help to address this issue but could also introduce other challenges related to standardization.

Training is the process of feeding the algorithm with data so it can learn specific patterns and behavior. The accuracy and performance of the algorithm depends primarily on the quality and quantity of data used in the training (put colloquially, garbage in, garbage out). To demonstrate the generalizability of an algorithm a diverse representation of real-world scenarios should be considered so that the algorithm can learn and perform better.

Tuning or fine tuning is the process of optimizing a model to improve its accuracy and reliability. This step includes adjusting the parameters, such as hidden layers, within a neural network. Note that the performance of a deep learning model on training data does not predict its ability to generalize to cases it has never seen before.

Training is a highly iterative process requiring repeated experiments to identify optimal settings for the device. Training is the process of evaluating the performance of the algorithm. Training should always be performed

Table 8-5. Key Considerations for Successful CAD Regulatory Documentation

1.	Understand the real clinical need from the healthcare professionals' and/or patients' perspectives
2.	Define the intended use, indications for use, and the target patient population
3.	Develop good data collection strategies (ensure data include positive, negative, and borderline cases, and demographics, etc.)
4.	When possible, data can be enriched to assess generalizability (e.g., in the case of a rare disease)
5.	Ensure there are appropriate quality checks for input data
6.	Ensure the objective reference standard is robust with clinical justification (for retrospective studies consider collecting as much data as possible including biopsy, pathology reports, clinical reports, and long-term follow-up)
7.	If subjective reference standard is considered, ensure at least three expert clinicians with appropriate training and experience
8.	Model development (use appropriate machine learning strategies)
9.	Performance assessment should include both standalone performance and clinical validation (if applicable)
10.	Ensure the validation datasets are independent of training datasets
11.	Ensure the statistical analysis plan is robust
12.	Ensure the bench performance testing includes appropriate evaluation or scoring methods which are clinically justifiable
13.	Get alignment with health authorities on the clinical validation study (where applicable) • Ensure the design includes multiple-reader, multiple-case design • Access the appropriateness of the study design (e.g., retrospective/prospective) • Ensure the clinical endpoints adequately cover the proposed indications • Ensure the established ground truth and the truthers involved are acceptable • Ensure the design includes robust statistical comparison between reference, aided and un-aided clinical reads. • Where possible include a clinical quality control process (confirming the artificial intelligence/machine learning functionality)
14.	Ensure the labeling follows all the regulatory requirements

using independent datasets that are new to the algorithm.

Verification and Validation

Verification and validation testing requirements for AI/ML clinical applications depend on the IFU statement and the clinical performance claims. For example, a device that acts as a second reader to assist physicians by identifying a specific image may need a different validation study to that of a mammography screening device that can be read without any further review by a radiologist.[69] Manufacturers should carefully plan their validation studies to support their desired indications and clinical claims. The FDA reviews and clears devices based on the specific indications. Special considerations are needed if the subject device is indicated for pediatric population. Hence, it is recommended to highlight the availability of performance data from pediatric patients if applicable in the regulatory submission.[70]

Standalone Performance Assessment

A standalone performance assessment can help demonstrate that an algorithm performs as intended. The performance study is usually based on an independent dataset representative of the target clinical population for which the device is indicated. It is recommended that the manufacturers use the FDA 510(k), De Novo, and PMA databases to review publicly available information for recent device marketing authorizations to

obtain a general idea of what current practices are for appropriate standalone performance metrics.

Widely accepted performance assessment methodologies include ROC and free-response ROC (FROC) curves, sensitivity, specificity, positive predictive value (precision), negative predictive value and area under the ROC curve. Manufacturers also use performance metrics including the Dice coefficient, the Hausdorff distance for image segmentation features, and mean square errors. The inclusion of 95% confidence intervals is critical when reporting results, as the margin of error reports the uncertainty or variability in the results.[41] For example, time-sensitive triage devices that fall under the FDA product codes QFM (Radiological Computer-Assisted Prioritization Software for Lesions) and QAS (Radiological Computer-Assisted Triage and Notification Software) have established high sensitivity and specificity with >95% AUC.

Clinical Reader Performance Assessment

In general, reader studies are used to assess the clinical performance of detection and diagnostic devices. A reader study (either retrospective or prospective) directly compares the performance of a reader with and without the assistance of the device. A well-designed reader study with an appropriate statistical analysis plan is essential to show direct assessment of diagnostic performance in clinical practice. Having a good reference standard or ground truth, a number of experts providing the ground truth, and the appropriate selection of readers are important things to consider in reader studies as each of these factors impact the reported performance studies.

It is also important to select appropriate board-certified readers with experience in the disease area to conduct the study. In general, US-board certified readers should be used as this then avoids the burden of having to demonstrative to the FDA that international readers' training is equivalent to that of their US counterparts, and that clinical practice in their countries is similar to that of the US. In addition, close attention needs to be paid to the potential source of bias and variability among the readers. Factors such as study population, data acquisition, characteristics of the AI/ML applications, and human-AI interactions need to carefully be evaluated to avoid bias and ensure the reproducibility of the results. Lesion detection and segmentation, for example, require metrics that describe how well a predicted area matches the reference area, which is typically delineated by a radiologist. It is recommended that developers consult with the FDA via the pre-submission process prior to executing the clinical reader study. Although this does not appear to be a regulatory requirement or stated explicitly in a guidance, manufacturers should be aware that FDA often requests that at least 50% of data used to test a device come from a US-based dataset.

It is vital to ensure appropriate risk-based models are considered in the software life cycle development as per IEC 62304[71] and well-defined training and validation studies are planned to demonstrate the generalizability as per AAPM TG Report 273.[41]

Ground Truthing

Establishing a robust reference standard is one of the key steps in developing successful CAD applications. There are two types of reference standards, one is subjective, and the other is objective. Reference standards based on physicians' opinion are considered subjective and are considered reliable only if they are based on consensus of multiple experts. Based on the authors' experience, it is recommended that developers include at least three or more experts to establish a subjective reference standard. In addition, it is always preferable to include an objective reference standard. This should consider pathology results, clinical diagnosis and outcomes, and the results of longitudinal studies.

There are, or course, other processes employed for setting the reference standard. For example, with reconstructive algorithms, one method used is establishing the ground truth based on CT images reconstructed by filtered back projection – a high radiation dose version of the same data. Filtered back projection is a mathematically accurate reconstruction algorithm developed under the best data acquisition and reconstruction conditions. The ground truth images could be based on images collected from both phantoms in the

laboratory and patients in a clinical setting and span a variety of acquisition protocols.

Deployment

The story of product development does not end at obtaining FDA marketing authorization; in fact, in many ways, FDA market clearance is the beginning. The FDA expects that AI/ML models follow a TPLC process. Once an AI/ ML model is trained, validated, and obtains FDA marketing authorization, it needs to be deployed and integrated into a healthcare provider's existing information technology infrastructure. It is important to ensure that the AI/ML clinical applications are compatible with customers' existing software systems and does not negatively impact the clinical workflow.

The deployment step involves careful planning, implementation and monitoring by both developers and clinical users to ensure the algorithm's accuracy, reliability, and safety. Between regulatory marketing authorization and deployment at the final clinical sites, best practice is to perform additional testing at designated clinical sites (beta sites). This additional testing, though potentially burdensome to manufacturers as well as to the clinical facility's information technology team, is important to ensure that the software performs seamlessly and as intended.

Monitoring

It is common to observe performance drifts over time in real-world use. Therefore, it is necessary to have a robust post-market monitoring systems in place to detect any errors or bias that may arise during the use of the algorithms. By implementing a robust and effective monitoring system, manufacturers can ensure that AI/ML devices continue to consistently deliver high-quality care without compromising the patient's safety.

Key Ethical Considerations for AI software

All involved stakeholders should understand the ethical considerations in SaMD development. General guidance on key ethical considerations derived from the literature is overviewed below.

Data Governance

There are different types of data including clinical data, business operational and analytic data, raw image data, augmented data, and synthetic data.[72] The collection, analysis and use of patient data forms the basis for AI/ML medical product development. The successful AI system will primarily depend on thousands of high-quality data for training the algorithm and independently validating the locked models. Limited access, either due to cost or availability, to data is one of the most challenging aspects in SaMD development, resulting in training data with systemic biases because of under-representation of a gender, age, race, sexual orientation, or disease characteristic. These biases will impact or limit the use of the resulting algorithm. Lack of proper data governance controls will result in data inconsistencies and anomalies resulting in regulatory compliance issues.

Black Box

One of the challenges in the adoption of AI/ ML in healthcare are black-box algorithms which do not explain or justify the results. It is important to be able to explain how the output from an AI algorithm is related to clinical practice and scientific literature.[73] Regardless of the complexity of the software and whether or not it is proprietary, the software developer should describe the underlying data used to develop the algorithm and should include plain language descriptions of the logic or rationale used by an algorithm to render a recommendation. The FDA's guidance on clinical decision support software[74] points out that the requirement for transparency into algorithm decision making and ensuring that this information is available to users so that they can "independently review the basis" for the software's recommendations. Healthcare providers may more critically evaluate recommendations from AI tools and therefore make better decisions if they better understand how such technologies work.

AI/ML devices developed based on discrete data from larger hospitals, scanner models, type of imaging modality, or certain patient demographics, may not perform as well in a different environment. The radiologist may not be aware

of the limitations of the AI/ML technology's intended use and therefore improperly interprets the output of the AI/ML results. It is recommended that the radiologist understands the capabilities and limitations of the systems. In addition to the operator manual, manufacturers should consider a tool, which allows the radiologist, for example, to better understand how well the AI/ML model might work for the intended use cases. In the Association for Computing Machinery's Proceedings of the Conference on Fairness, Accountability and Transparency, published in 2019,[75] a 'Model Card' was introduced. This captures information that could be useful to radiologists and supplements the AI/ML device's cleared label.

Clinical Practice

Trustworthiness, transparency, and accountability are some important ethical factors to consider in clinical practice.

Once validated algorithms are on the commercial market, they can be used on millions of patients. Therefore, the degree to which the clinical end user has insights into the requirements and limitations of the device for specific diseases or conditions is important to ensure that the algorithms are transparent and trustworthy. Also, if the algorithms are not transparent, the users will not be able to justify their actions. Likewise, if the physicians cannot trust the algorithms, they are more reluctant to use it in their practices resulting in diminished use in hospitals. In addition, lack of accountability raises concerns about the possible safety consequences of using unverified or unvalidated algorithms in clinical settings.

Therefore, it is essential to have a framework and process in place at hospitals to identify a person responsible for its use.[76] Another aspect is monitoring the AI performance over time or monitoring for variance amongst users. AI systems can change in performance over time due to data drifts such as changes in image acquisition device, disease prevalence, virus mutation etc. Developers and manufacturers should consider tools for monitoring their AI/ML system's performance, and for communicating any degradation in its performance back to them for modification.

Data Privacy and Security

To achieve the full potential of AI/ML in healthcare the following are important factors to consider:[77]

a) Informed consent to use data,
b) Safety and transparency,
c) Algorithms fairness and biases, and
d) Data privacy.

Patient data collection and sharing have consistently raised concern from various groups about maintaining an individual's privacy and/or dignity when sensitive health information is shared with others. Likewise, patient data collection and use in AI/ML algorithms raises concerns from regulators, payors, healthcare providers and administrators, and patients about potential data breaches.

There is an absolute need for protecting patient data from cyber attacks.[78] Therefore, it is important that the involved stakeholders consider the right of the patients to take their own choices. This can be easily achieved by an informed consent form. To ensure patient privacy and confidentiality during data collection, handling, storage and evaluation, the developers must follow the applicable federal guidelines.

Increasingly, regulatory bodies are implementing more stringent requirements for cybersecurity. The Omnibus Act was passed into law by Congress in December 2022.[79] The Act gives the FDA statutory authority over cybersecurity in medical devices rather than the traditional implicit authority via regulation of quality systems and as part of the risk management process that we have seen in the past. The Act also gives the FDA direct oversight of cybersecurity of medical devices including AI devices. In March 2023, the FDA issued an updated policy to ensure manufacturers have processes in place to address vulnerabilities, provide regular updates and patches, ensure inclusion of coordinated vulnerability disclosure, and include Software Bill of Materials in their regulatory submissions.[80]

Recent Developments and Future Perspectives

FDA guiding principles for Good Machine Learning Practice

As AI/ML is becoming increasingly popular in medical device software development, it is important to have a framework of key considerations or guiding principles to help manufacturers produce safe, effective, and high-quality SaMDs.

As previously discussed in the Key Design Considerations for Successful AI/ML SaMD Development section of this chapter, such a framework has been proposed and is outlined in **Table 8-4**.[68]

The 10 guiding principles proposed cover the development and deployment of SaMD AI/ML models into the clinical workflow while considering the potential risks and benefits to patients. Pointers are given to manufactures regarding data collection, management, and quality assurance practices. The importance of considering the best available methods while selecting a reference standard are reiterated, as well as the need to focus on the AI/ML model's impact on both the global and local performance. The good machine learning practice pointers also suggest that manufacturers consider performance degradation over time and encourage companies to obtain feedback from real-world performance.

Development of the FDA Digital Health Center of Excellence and Ongoing FDA Activities

The FDA has recognized the vital role that AI/ML can play in software-based medical devices and has developed strategies for a regulatory framework to advance the development of digital health products.[81] **Table 8-6** provides a summary of key FDA activities in the digital health space from 2013 onwards, including the inception of the Digital Health Center of Excellence (DHCoE) in 2020.[6,17-20,32,36,68,74,81-95]

In December 2013, the International Medical Device Regulatory Forum (IMDRF) formed the Software as a Medical Device Working Group to develop guidance for manufacturers to support innovation and timely access to safe and effective SaMD globally.[17-19] The working group developed guidance around the definitions to use, framework for risk categorization, quality management system, and clinical evaluation of AI/ML technologies.

The Association for the Advancement of Medical Instrumentation (AAMI) has published a consensus report for identifying, evaluating, and managing the risk of healthcare technology that incorporates AI or ML.[92] This report responds to an urgent, immediate need to understand how to apply risk management principles to SaMD development and its life cycle.[92]

The Future – Adaptive Learning, Global Harmonization

The full potential of AI/ML SaMD technologies has yet to be uncovered as the use of AI continues to grow in medical devices. The recent White House AI Bill of Rights[91] suggests that in the coming years, health authorities will focus on the development of safe and effective systems; algorithmic discrimination protections; data privacy; notice and explanation; and human alternatives, consideration, and fallback.[90] Moreover, the release of recent FDA guidance documents on clinical decision support software,[76] recommendations on predetermined change control plans,[81] software device functions,[94] and the creation of the NIST Public Working Group on Generative AI by White House[95] suggest a significant federal investment in AI/ML SaMD regulation and governance.

To date, the majority of AI/ML algorithms that have received FDA marketing authorization are locked algorithms. As more developers and manufacturers attempt to optimize algorithm performance over time by continuously training models on real world data, the FDA appears to be focusing on streamlining reviews related to regulating adaptive algorithms. The direction towards adaptive algorithms is clear from the recent De Novo marketing authorization DEN220063 of the Caption Interpretation Automated Ejection Fraction software (Caption Health, Inc., San Mateo, CA)[33] and the creation of the associated new regulation (21 CFR §892.2055) for Radiological Machine Learning Based Quantitative Imaging Software with Change

Table 8-6. Summary of Key Digital Health Activities

Year	Guidance/Workshops/Other Developmental Activities
2013	i. The IMDRF formed the SaMD Working Group 14 to develop guidance for manufacturers to support innovation and timely access to safe and effective SaMD globally. The working group developed guidance around the definitions, framework for risk categorization, quality management system, and clinical evaluation [17-19]
2016	i. The FDA released draft guidance on the clinical evaluation of SaMD to help emphasize the essential clinical considerations[18] ii. Section 3060(a) of the 21st Century Cures Act was amended to exclude certain software functions (e.g., administrative functions, healthy lifestyle, and electronic patient records) from the definition of 'medical device'[36]
2017	i. The FDA announced a voluntary software precertification pilot program to evaluate the quality standards for software design, validation and maintenance of software products.[82,83] ii. The FDA published a 'Digital Health Innovation Action Plan' to protect and promote the public health[84]
2019	i. The FDA released a discussion paper that described the FDA's foundation for a TPLC approach to premarket review of AI/ML-driven software modifications[20] ii. The FDA announced a partnership with the National Evaluation System for Health Technology Coordinating Center Collaborative Community and the Ophthalmic Imaging Collaborative Community to develop solutions to medical device innovation challenges.[85] iii. The FDA provided a 'Regulatory Framework for Conducting the Pilot Program within Agencies' Authorities'[86]
2020	i. The Digital Health Center of Excellence was established within the FDA to advance digital health by facilitating cross-collaborations to promote safe and effective digital products[81] ii. The FDA down-classified a subset of medical image analyzers from Class III to Class II; particularly, CADe devices applied to mammography breast cancer, ultrasound breast lesions, radiograph lung nodules, and radiograph dental caries detection from Class III to Class II[32] iii. The FDA organized a public workshop to discuss emerging applications of AI in radiological imaging[87] iv. The FDA organized a Patient Engagement Advisory Committee to ensure transparency in AI and ML medical device software[88]
2021	i. The FDA published their AI/ML-Based SaMD Action Plan in response to stakeholder feedback summarizing the Regulatory Framework and feedback on 'Predetermined Change Control Plan; Good Machine Learning Practice; Patient-Centered Approach Incorporating Transparency to Users; and Real-World Performance'[84,85,88] ii. The Department of Health and Human Services published the Trustworthy AI playbook[89] iii. The FDA announced a virtual public workshop on transparency of AI/ML-enabled medical devices to patients, caregivers, and providers[87] iv. The FDA and other health authorities released 10 guiding principles for good machine learning practice for medical device development[68]
2022	i. The FDA released a draft cybersecurity guidance to ensure the need for robust cybersecurity controls in medical devices[90] ii. The FDA released a CDS software guidance to clarify the types of CDS software functions that are excluded from the definition of device[74] iii. The FDA released a report of the completed software precertification (Pre-Cert) pilot program. The summary of this report suggested that the approach described in the 'working model' is not practical to implement under the FDA's current statutory and regulatory authorities[82] iv. The White House released a blueprint for an AI Bill of Rights. The Bill discusses the principles for design, use and deployment of automated systems[91] v. The FDA released a list of AI/ML-enabled medical devices currently being marketed in the United States[6] vi. The Association for the Advancement of Medical Instrumentation (AAMI) published a consensus report for identifying, evaluating, and managing risk for healthcare technology that incorporates AI or ML[92]
2023	i. NIST released their AI Risk Management Framework[93] ii. The FDA issued a draft guidance on recommendations for a Predetermined Change Control Plan for AI software devices. This guidance suggests an openness in Agency's thinking to allow manufacturers developing AI/ML algorithms to retrain their models from data in real time[20] iii. The FDA released an updated software guidance on the information necessary to include in premarket submissions for the FDA's evaluation of the safety and effectiveness of device software functions[94] iv. The Biden-Harris Administration announced the creation of the NIST Public Working Group on Generative AI, which will build on the NIST AI Risk Management Framework to address AI technologies that can generate content, including images[95]

AI, artificial intelligence; **CADe**, computer-assisted detection; **CDS**, clinical decision support; **FDA,** Food and Drug Administration; **IMDRF**, International Medical Device Regulatory Forum; **ML**, machine learning; **NIST**, National Institute of Standards and Technology; **SaMD**, software as a medical device; **TPLC**, Total Product Life Cycle

Control Plan.[33] This development suggests that the future is headed towards adaptive algorithms, and the Agency seems to be open and encouraging companies to develop adaptive algorithms.

As the federal government continues to receive input on the trustworthiness of AI the industry should expect to see more guiding principles and recommendations. NIST continues to lead efforts in developing AI/ML standards and best practices for measuring and assessing of AI/ML technologies. Towards this goal, NIST launched the Trustworthy and Responsible AI Resource Center which is intended to facilitate implementation and international alignment with risk management framework.[93] The Organization for Economic Co-operation and Development (OECD) has also provided a set of internationally agreed principles and recommendations that can promote an AI/ML-powered crisis response that is trustworthy and respects human-centered and democratic values.[96] Hence, in coming years we expect to see various health authorities across the globe coming together to develop frameworks and recommendations towards global harmonization.

As the use of AI products increases, protecting an individual's information and privacy becomes important. Hence, in the coming years it is expected that there will be an increased vigilance on the privacy and cybersecurity issues mentioned in this chapter.

Summary and Conclusion

SaMD and SiMD incorporating AI/ML technologies have the potential to revolutionize clinical practice in the radiological health space.[1] The applications of AI/ML are diverse, and they have the potential to impact not only every step of the diagnostic imaging chain – from protocol creation to image generation and image analysis, to the analysis of electronic health records – but also the therapeutic space in radiation oncology where the treatment planning process can be streamlined.

This chapter has focused on an area of rapid evolution: regulatory considerations for CAD devices. CAD devices are helping physicians manage workflow, detect disease early and accurately, and assess risk to improve patient outcomes and medical care.

Major developments in the FDA regulation of CAD in the last few years have included the down-classification of some CAD devices from Class III to Class II,[36] the creation of a mechanism for FDA review of predetermined change control plans for AI/ML enabled device software functions,[97] the De Novo reclassification and creation of regulations[19] for different types of CAD devices that can now serve as predicates for 510(k)'s, and FDA marketing authorization of a wide range of CAD devices via the De Novo pathway.[31]

While regulation helps ensure safety, innovative technologies can also challenge regulatory frameworks. For example, adaptive AI/ML technologies with the potential to optimize their performance in real-time have found applications in the financial sector, marketing and e-commerce industries, but do not necessarily fit well into the current frameworks of medical device regulation. The regulation of these tools in healthcare will require new approaches allowing the devices to continually improve while providing effective safeguards.

With the increasing availability of patient data and advancement in machine learning algorithms, an increasing range of AI/ML-based software tools will become available for clinical use; however, multiple challenges such as algorithm generalizability,[45] data privacy,[80] and cybersecurity[90] will need to be addressed in order to ensure widespread clinical adoption of these tools.

AI/ML algorithms are expected to continuously improve over time, and regulation will need to adapt alongside. Moreover, as the use of AI/ML technologies in medical devices continues to advance, all involved stakeholders including manufacturers, developers, regulators, users, patients, and payors across the globe should work closely together to develop safe and effective methods to improve patient outcomes in healthcare.

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