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"Nutrition Facts Labels" for Artificial Intelligence/Machine Learning-Based Medical Devices—The Urgent Need for Labeling Standards

*Sara Gerke**

Abstract

Artificial Intelligence ("AI"), particularly its subset Machine Learning ("ML"), is quickly entering medical practice. The U.S. Food and Drug Administration ("FDA") has already cleared or approved more than 520 AI/ML-based medical devices, and many more devices are in the research and development pipeline. AI/ML-based medical devices are not only used in clinics by health care providers but are also increasingly offered directly to consumers for use, such as apps and wearables. Despite their tremendous potential for improving health care, AI/ML-based medical devices also raise many regulatory issues. This Article focuses on one issue that has not received sustained attention in the legal or policy debate: labeling for AI/ML-based medical devices. Labeling is crucial to prevent harm to patients and consum-

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ers (e.g., by reducing the risk of bias) and ensure that users know how to properly use the device and assess its benefits, potential risks, and limitations. It can also support transparency to users and thus promote public trust in new digital health technologies.

This Article is the first to identify and thoroughly analyze the unique challenges of labeling for AI/ML-based medical devices and provide solutions to address them. It establishes that there are currently no standards of labeling for AI/ML-based medical devices. This is of particular concern as some of these devices are prone to biases, are opaque ("black boxes"), and have the ability to continuously learn. This Article argues that labeling standards for AI/ML-based medical devices are urgently needed, as the current labeling requirements for medical devices and the FDA's case-by-case approach for a few AI/ML-based medical devices are insufficient. In particular, it proposes what such standards could look like, including eleven key types of information that should be included on the label, ranging from indications for use and details on the data sets to model limitations, warnings and precautions, and privacy and security. In addition, this Article argues that "nutrition facts labels," known from food products, are a promising label design for AI/ML-based medical devices. Such labels should also be "dynamic" (rather than static) for adaptive algorithms that can continuously learn. Although this Article focuses on AI/ML-based medical devices, it also has implications for AI/ML-based products that are not subject to FDA regulation.

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Introduction

Alicia is a forty-six-year-old Black patient who sees her dermatologist for an annual skin exam. In earlier check-ups, the dermatologist inspected Alicia's skin with a dermatoscope, a device that enhances the doctor's view by visualizing the epidermis (the outer surface of the skin) and the layers beneath it, to diagnose cancerous and non-cancerous skin lesions.[1] This time, rather than using the dermatoscope, the dermatologist uses a new software program pow-

[1] For more information on annual skin exams and the dermatoscope, see *Annual Exams: Five Easy Steps to Prepare Yourself*, Skin Cancer Found. (2022), https://www.skincancer.org/early-detection/annual-exams [https://perma.cc/JM6B-2FBG]; Jenna Fletcher, *What Is a Dermatoscope, and What Does It See?*, MedicalNewsToday (Mar. 18, 2021), https://www.medicalnewstoday.com/articles/dermatoscope [https://perma.cc/Q6B6-6YF4].

ered by Artificial Intelligence ("AI")/Machine Learning ("ML") that has just received marketing authorization. The new AI/ML dermatology tool is based on artificial neural networks (so-called "deep learning," a subset of ML) to detect skin cancer in patients.[2]

The dermatologist takes several photos of Alicia's skin and moles from different angles and uploads them to a cloud server. A few seconds later, the AI/ML dermatology tool answers: "No skin cancer detected. Reassess in twelve months." Alicia is relieved that everything is alright and goes home satisfied. The AI/ML dermatology tool, however, missed that one of Alicia's moles shows the first signs of melanoma, a serious type of skin cancer that usually requires surgery and can be fatal if left untreated.[3]

How could this happen? Why did the new AI/ML dermatology tool miss this diagnosis? It turns out that the algorithm was primarily trained on images of people with white skin. Therefore, it is not surprising that the AI/ML tool is likely to provide incorrect answers for people with brown and black skin. Moreover, the tool uses deep learning and is thus a noninterpretable AI/ML—a so-called "black-box" model—which means that it was impossible for the dermatologist—and humans in general—to understand the basis for its decision.[4] In addition, the labeling of the AI/ML dermatology tool contains neither information about the training data set, such as race/ethnicity breakdown, nor warnings to dermatologists about the potential biases and risks related to the use of the tool.

This scenario is hypothetical, but it highlights a real-world issue. For example, Google has recently come under criticism for its AI-powered dermatology app because ninety percent of the training data set, consisting of a total of almost sixty-five thousand skin images, were images from people with light brown, darker white, or fair skin.[5] Google's AI-powered dermatology app is not yet available on the

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2 For more information on deep learning, see *infra* Section I.A.1.

3 *See Melanoma Overview: A Dangerous Skin Cancer*, SKIN CANCER FOUND. (Jan. 2022), https://www.skincancer.org/skin-cancer-information/melanoma [https://perma.cc/5L4P-29B2].

4 *See infra* Section I.A.2. (explaining black-box models).

5 *See* Yuan Lui et. al., *A Deep Learning System for Differential Diagnosis of Skin Diseases,* 26 NAT. MED. 900, 902 (2020); Todd Feathers, *Google's New Dermatology App Wasn't Designed for People with Darker Skin*, VICE (May 20, 2021, 9:40 AM), https://www.vice.com/en/article/m7evmy/googles-new-dermatology-app-wasn't-designed-for-people-with-darker-skin [https://perma.cc/67ZK-Q7H6]; Peggy Bui & Yuan Liu, *Using AI to Help Find Answers to Common Skin Conditions*, GOOGLE HEALTH (May 18, 2021), https://blog.google/technology/health/ai-dermatology-preview-io-2021 [https://perma.cc/A572-ERGQ] (describing Google's announcement of the plan to launch a pilot study of the new AI-powered dermatology app).

U.S. market,[6] but AI, especially its subset ML, is quickly entering medical practice. The U.S. Food and Drug Administration ("FDA") has already cleared or approved over 520 AI/ML-based products classified as medical devices ("AI/ML-based medical devices"),[7] and many more devices are in the research and development pipeline. The global health care AI market is forecasted to reach $51.3 billion by 2027, a compound annual growth rate of 41.4% from 2020.[8] AI/ML-based medical devices are not only used in clinics by health care providers but are also increasingly offered directly to consumers for use, such as apps and wearables.[9]

Despite their tremendous potential for improving health care, AI/ML-based medical devices also raise many regulatory issues.[10] This au-

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6 *See DermAssist*, Google Health, https://health.google/consumers/dermassist [https://perma.cc/5CTE-2ABS].

7 *Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices*, U.S. Food & Drug Admin. (Oct. 5, 2022), https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-aiml-enabled-medical-devices [https://perma.cc/8F5F-9G9S]. For other (non-FDA) literature, see, e.g., Stan Benjamens, Pranavsingh Dhunnoo & Bertalan Meskó, *The State of Artificial Intelligence-Based FDA-Approved Medical Devices and Algorithms: An Online Database*, 3 npj Digit. Med. no.118, 2020, at 1, 2 (counting sixty-four AI/ML-based medical devices); Urs J. Muehlematter, Paola Daniore & Kerstin N. Vokinger, *Approval of Artificial Intelligence and Machine Learning-Based Medical Devices in the USA and Europe (2015–20): A Comparative Analysis*, 3 Lancet Digit. Health e195 (2021) (counting 222 AI/ML-based medical devices); Casey Ross, *As the FDA Clears a Flood of AI Tools, Missing Data Raise Troubling Questions on Safety and Fairness*, STAT+ (Feb. 3, 2021), https://www.statnews.com/2021/02/03/fda-clearances-artificial-intelligence-data [https://perma.cc/8QMR-NS9W] (counting 161 medical AI tools). For two other online databases, see also *FDA-Approved A.I.-Based Algorithms*, Med. Futurist, https://medicalfuturist.com/fda-approved-ai-based-algorithms [https://perma.cc/2SPA-BGW6]; *AI Central*, Am. Coll. Radiology, Data Sci. Inst., https://models.acrdsi.org [https://perma.cc/K73Z-NFC5].

8 Rsch. & Mkts., Healthcare Artificial Intelligence Market (Dec. 2020), https://www.researchandmarkets.com/reports/4753853 [https://perma.cc/XL6J-X8PK].

9 The term "consumers" is understood here broadly and can include not only healthy individuals but also patients. For more information on direct-to-consumer uses, see *infra* Section I.B.2.

10 *See, e.g.*, W. Nicholson Price II, *Black-Box Medicine*, 28 Harv. J.L. & Tech. 419, 457–62 (2015); W. Nicholson Price II, *Regulating Black-Box Medicine*, 116 Mich. L. Rev. 421 (2017); Barbara Evans & Pilar Ossorio, *The Challenge of Regulating Clinical Decision Support Software After 21st Century Cures*, 44 Am. J.L. & Med. 237 (2018); Charlotte A. Tschider, *Regulating the Internet of Things: Discrimination, Privacy, and Cybersecurity in the Artificial Intelligence Age*, 96 Denv. L. Rev. 87 (2018); Boris Babic, Sara Gerke, Theodoros Evgeniou & I. Glenn Cohen, *Algorithms on Regulatory Lockdown in Medicine*, 366 Science 1202 (2019); W. Nicholson Price II, *Medical AI and Contextual Bias*, 33 Harv. J.L. & Tech. 65, 84–86, 100–15 (2019) [hereinafter Price, *Medical AI and Contextual Bias*]; Nicolas Terry, *Of Regulating Healthcare AI and Robots*, 21 Yale J.L. & Tech. 133 (2019); Nathan Cortez, *Digital Health and Regulatory Experimentation at the FDA*, 21 Yale J.L. & Tech. 4 (2019); Sara Gerke, Boris Babic, Theodoros Evgeniou & I. Glenn Cohen, *The Need for a System View to Regulate Artificial Intelligence/Machine Learning-Based Software as Medical Device*, 3 npj Digit. Med., no.53, 2020, at 1

thor has extensively written about the need for a new regulatory framework that ensures that AI/ML-based medical devices are reasonably safe and effective when brought to the U.S. market and will stay so throughout their life cycle and has made several suggestions as to what such a framework might entail.[11] This Article focuses on one issue that has not received sustained attention in the legal or policy debate[12] despite its importance: labeling for AI/ML-based medical devices. Labeling is crucial to prevent harm to patients and consumers (e.g., by reducing the risk of bias) and ensure that users know how to properly use the device and assess its benefits, potential risks, and limitations. It can also support transparency to users and thus promote public trust in new digital health technologies.

But what types of information should be included on the label of an AI/ML-based medical device? What are the limits of labeling? Or, in other words, when can disclosures on labels not be used as an excuse to introduce a poorly designed device into the market? This Article attempts to answer such questions and fill the existing literature gap. To the author's knowledge, it is the first to identify and thoroughly analyze the unique challenges of labeling for AI/ML-based medical devices while providing solutions to address them.

This Article establishes that the current labeling requirements in Title 21 of the Code of Federal Regulations ("C.F.R.") for medical devices are insufficient, and that there are currently no labeling standards for AI/ML-based medical devices.[13] As seen in our hypothetical example, this is of particular concern because AI/ML-based medical devices differ in many ways from traditional medical devices such as contact lenses. For instance, they are prone to biases, can be black-box models, and can continuously learn.[14] Many AI/ML-based medical devices available on the U.S. market do *not* provide users with important information, such as gender and race/ethnicity breakdowns of the data

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[hereinafter Gerke et al., *The Need for a System View*]; Timo Minssen, Sara Gerke, Mateo Aboy, Nicholson Price & Glenn Cohen, *Regulatory Responses to Medical Machine Learning*, J.L. & Biosci., Jan.–June 2020, at 1; Nicolas P. Terry, *Assessing the Thin Regulation of Consumer-Facing Health Technologies*, 48 J.L., Med. & Ethics 94 (2020); Sara Gerke, *Health AI for Good Rather Than Evil? The Need for a New Regulatory Framework for AI-Based Medical Devices*, 20 Yale J. Health, Pol'y, L. & Ethics 432 (2021) [hereinafter Gerke, *Health AI*].

11 *See*, in particular, Gerke, *Health AI*, *supra* note 10.

12 *See* Evans & Ossorio, *supra* note 10, at 248 (briefly mentioning the misuse of labeling in the context of clinical decision support software); Price, *Medical AI and Contextual Bias, supra* note 10, at 104–07 (briefly discussing the pros and cons of labeling for medical AI in relation to contextual bias).

13 *See infra* Section III.A.

14 *See infra* Section III.B.

sets used.[15] This is the case even for the majority of the few AI/ML-based medical devices for which the FDA required specific labeling requirements on a case-by-case basis, and thus patient health may be at risk from unnecessary treatment or biased care.[16]

Consequently, this Article argues that there is an urgent need for labeling standards for AI/ML-based medical devices, in particular, to avoid harm to patients and consumers and to create certainty for manufacturers. It also makes suggestions as to what such standards could look like. Although this Article focuses on AI/ML-based medical devices, it also has implications for AI/ML-based products that are not subject to FDA regulation.

This Article proceeds in four Parts. Part I explains what AI/ML is and how it is applied in health care. It first looks at key concepts of AI, including its definition and relevant subsets and types. It then discusses different applications of AI, ranging from clinical care to workflow optimization.

Part II analyzes when an AI/ML-based product is classified as a medical device under Section 201(h)(1) of the U.S. Federal Food, Drug, and Cosmetic Act ("FDCA").[17] It first investigates the principle of when an AI/ML-based product is considered a medical device and then explores relevant exceptions and the FDA's enforcement discretion. In particular, this Part argues that FDA's new final guidance on clinical decision support ("CDS") software ("CDS Guidance") to clarify the agency's regulatory approach to CDS software functions[18] falls short of expectations. Not only does the CDS Guidance seem to violate the 21st Century Cures Act,[19] but it also creates legal uncertainty for AI/ML manufacturers and safety concerns.

Part III focuses on the challenges of labeling for AI/ML-based medical devices. It first examines the relevant labeling requirements in Title 21 of the C.F.R. for medical devices and shows that none of them are specifically geared toward AI/ML-based medical devices. This is followed by an analysis of why AI/ML-based medical devices differ in many aspects from traditional medical devices. In particular, this Part argues that labeling standards for AI/ML-based medical de-

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15 *See* Ross, *supra* note 7. For more information on this issue, see *infra* Section III.C.

16 For more information on the FDA's case-by-case analysis, see *infra* Section III.C.

17 21 U.S.C. § 321(h)(1).

18 U.S. Food & Drug Admin., Clinical Decision Support Software: Guidance for Industry and Food and Drug Administration Staff 5 (2022), https://www.fda.gov/media/109618/download [https://perma.cc/5DDT-DQKF].

19 21st Century Cures Act, Pub. L. No. 114–255, § 3060, 130 Stat. 1033, 1130–33 (2016) (codified at 21 U.S.C. §§ 321(h)(1), 360j(o)).

vices are urgently needed, as the current labeling requirements for medical devices and the FDA's case-by-case approach for a few AI/ML-based medical devices are insufficient. AI/ML-based medical devices are not only increasingly deployed in clinical care but are also offered directly to consumers.[20] Without enough information on their benefits, potential risks, and limitations, AI/ML-based medical devices may harm patients and consumers. Lastly, Part III also discusses practical challenges and methods for implementing such new labeling standards.

Part IV proposes eleven key types of information that should be included on the label of any AI/ML-based medical device, namely: (1) Model Identifiers; (2) Model Type; (3) Model Characteristics; (4) Indications for Use; (5) Validation and Model Performance; (6) Details on the Data Sets; (7) Preparation Before Use and Application; (8) Model Limitations, Warnings, and Precautions; (9) Alternative Choices; (10) Privacy and Security; and (11) Additional Information. This list should not be considered exhaustive but should serve as a helpful starting point for the FDA to begin the overdue development of labeling standards for AI/ML-based medical devices. Moreover, this Part argues that "nutrition facts labels," known from food products, are a promising label design for AI/ML-based medical devices. Through their eye-catching design, they encourage users to read them. In addition, the proposed labels should also be "dynamic" (rather than static) for adaptive algorithms that can continuously learn.

I. What Is AI and How Is It Applied in Health Care?

To understand the challenges of labeling for AI/ML-based medical devices, one first needs to understand what AI is and how it is applied in health care. Part I clarifies relevant terms and applications.

A. Key Concepts

1. Definition of AI and Relevant Subsets

The term "Artificial Intelligence" ("AI") was coined for the first time in 1955[21] and has since been used with different meanings and in different contexts. Up to now, the term has not been universally de-

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20 *See infra* Section I.B.2.

21 *See* John McCarthy, M.L. Minsky, N. Rochester & C.E. Shannon, A Proposal for the Dartmouth Summer Research Project on Artificial Intelligence (1955), http://jmc.stanford.edu/articles/dartmouth/dartmouth.pdf [https://perma.cc/B2KU-LBZZ].

fined.[22] An often-cited definition is the one by John McCarthy, an American computer scientist renowned as the father of AI[23]: "It is the science and engineering of making intelligent machines, especially intelligent computer programs. It is related to the similar task of using computers to understand human intelligence, but AI does not have to confine itself to methods that are biologically observable."[24] Another definition that is frequently referred to is from the leading AI textbook *Artificial Intelligence: A Modern Approach* by Stuart Russell and Peter Norvig, in which the two computer scientists organized different definitions of AI into four categories: (1) Thinking Humanly, (2) Acting Humanly, (3) Thinking Rationally, and (4) Acting Rationally.[25]

Regardless of its definition, there seems to be a consensus that AI has several subsets. The most popular subset is machine learning (*see* Figure 1 below), which is "a set of methods that can automatically detect patterns in data, and then use the uncovered patterns to predict future data, or to perform other kinds of decision making under uncertainty."[26] Classical ML is categorized into supervised and unsupervised ML.[27] In supervised ML, the goal is to predict the desired output based on the input data.[28] The model is trained with input data and the desired output labels.[29] An example is pathology slides, some of which contain cancer cells and some of which do not.[30] The algorithm usually analyzes the patterns in the labeled input-output pairs and learns to predict the correct outputs for given inputs of new cases.[31] In unsupervised ML, algorithms are tasked with detecting patterns in unlabeled data.[32] For example, it can identify subclusters of

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22 Gerke, *Health AI*, *supra* note 10, at 440.

23 Martin Childs, *John McCarthy: Computer Scientist Known as the Father of AI*, Independent (Nov. 1, 2011, 1:00 PM), https://www.independent.co.uk/news/obituaries/john-mccarthy-computer-scientist-known-father-ai-6255307.html [https://perma.cc/VCP8-AAFU].

24 John McCarthy, *What Is Artificial Intelligence?* 2 (Nov. 12, 2007) (unpublished manuscript), http://www-formal.stanford.edu/jmc/whatisai.pdf [https://perma.cc/MD82-K38A].

25 Stuart Russell & Peter Norvig, Artificial Intelligence: A Modern Approach 1–5 (4th ed. 2020).

26 Kevin P. Murphy, Machine Learning: A Probabilistic Perspective 1 (2012).

27 *See* Kun-Hsing Yu, Andrew L. Beam & Isaac S. Kohane, *Artificial Intelligence in Healthcare*, 2 Nature Biomed. Eng'g 719, 720 (2018).

28 *Id.*

29 *Id.*

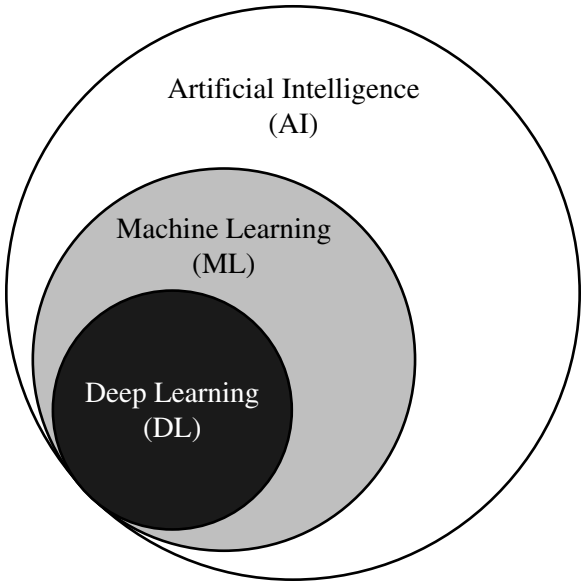
30 Am. Med. Ass'n, Report of the Council on Long Range Planning and Development 254 (2018), https://www.ama-assn.org/system/files/2018-11/a18-clrpd-reports.pdf [https://perma.cc/5MC2-QVSL].

31 Yu et al., *supra* note 27, at 719.

32 *Id.* at 720; Am. Med. Ass'n, *supra* note 30, at 254.

the original data or create low-dimensional data representations.[33] A subset of ML is *deep learning* (*see* Figure 1 below), which has driven the rapid advances of AI in recent years and uses artificial neural networks to detect patterns in data.[34]

FIGURE 1. AI AND RELEVANT SUBSETS



2. Types of AI

A distinction is also often made between *narrow or weak AI* and *general or strong AI*. Most AI-based products that currently surround us are narrow or weak AIs—AIs that perform specific tasks, such as playing Go, driving vehicles, or classifying skin cancer, just as well or occasionally better than humans.[35] In contrast, general or strong AI is a theoretical AI form that pertains to machines with an intelligence equal to humans, including self-aware consciousness.[36] Without a crystal ball, it is unclear what the future holds, but AI is expected to surpass human performance in complex tasks, such as performing surgeries.[37]

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33 Yu et al., *supra* note 27, at 720.

34 *Id.*; Gerke, *Health AI*, *supra* note 10, at 440.

35 *See* IBM Cloud Educ., *Artificial Intelligence (AI)*, IBM (June 3, 2020), https://www.ibm.com/cloud/learn/what-is-artificial-intelligence [https://perma.cc/7P9Q-KEQJ]; Ahmed Hosny, Chintan Parmar, John Quakenbush, Lawrence H. Schwartz & Hugo J.W.L. Aerts, *Artificial Intelligence in Radiology*, 18 NATURE REVS. CANCER 500, 502 (2018).

36 IBM Cloud Educ., *supra* note 35.

37 *See* Hosny et al., *supra* note 35, at 502.

Sometimes AI is also divided into three types based on its intelligence: *assisted, augmented, and autonomous*.[38] Assisted AI automates repetitive tasks, such as a universal robot that sorts blood samples.[39] This type of AI usually requires little or no human involvement.[40] In contrast, the term "augmented AI" emphasizes the idea that humans and machines work together collaboratively.[41] AI enhances the physician's intelligence instead of replacing it.[42] An example is CDS software, such as an AI that gives individualized treatment recommendations.[43] And then there is autonomous AI that makes decisions with little or no human involvement.[44] An example is IDx-DR, an autonomous AI-based medical device used in more than twenty primary care practices across the U.S. to detect "more than mild diabetic retinopathy" in diabetic adult patients.[45] The uniqueness of IDx-DR is that it makes a medical decision—namely, to "rescreen in 12 months" or "refer [the patient] to an eye care professional"—without human supervision, meaning the primary care physician does *not* need to review its decision.[46]

In recent times, a distinction has also been made between *interpretable AI/ML* and *explainable AI/ML*. Although there seems to be no universal definition or understanding of these terms, this Article interprets them as follows. Interpretable AI/ML refers to the use of "white-box" models, such as simple decision trees.[47] The use of inter-

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38 ANTHONY C. CHANG, INTELLIGENCE-BASED MEDICINE 12–13 (2020).

39 *Id.*; *Two UR5 Universal Robots Ensure Faster Delivery of Blood Sample Results*, UNIVERSAL ROBOTS, https://www.universal-robots.com/case-stories/gentofte-hospital [https://perma.cc/2CVA-8PRT].

40 CHANG, *supra* note 38, at 12–13.

41 *Id.* at 13.

42 AM. MED. ASS'N, *supra* note 30, at 254–55.

43 *See* CHANG, *supra* note 38, at 12. An example of clinical decision support software is Watson for Oncology, developed by IBM. For more information on Watson for Oncology, see, e.g., Gerke, *Health AI*, *supra* note 10, at 456–57.

44 CHANG, *supra* note 38, at 12.

45 *Id.* at 13; Jack Carfagno, *IDx-DR, the First FDA-Approved AI System, Is Growing Rapidly*, DOCWIRE NEWS (Nov. 12, 2019), https://www.docwirenews.com/docwire-pick/future-of-medicine-picks/idx-dr-the-first-fda-approved-ai-system-is-growing-rapidly [https://perma.cc/C66X-Y5L6]; *IDx-DR*, DIGIT. DIAGNOSTICS, https://dxs.ai/products/idx-dr/idx-dr-overview [https://perma.cc/3FBK-B3H8]; U.S. FOOD & DRUG ADMIN., DE NOVO NO. DEN180001, CLASSIFICATION REQUEST FOR IDX-DR 1 (2018), https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN180001.pdf [https://perma.cc/R4QY-RP93].

46 Press Release, U.S. Food & Drug Admin., FDA Permits Marketing of Artificial Intelligence-Based Device to Detect Certain Diabetes-Related Eye Problems (Apr. 11, 2018), https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-artificial-intelligence-based-device-detect-certain-diabetes-related-eye [https://perma.cc/4B7D-JHAE].

47 Gerke, *Health AI*, *supra* note 10, at 490; *see also* Boris Babic, Sara Gerke, Theodoros

pretable algorithms has the advantage that they are transparent and can be understood by humans with reasonable effort.[48] Many AI/ML-based medical devices that are available on the U.S. market or in development, however, use deep learning.[49] For example, RhythmAnalytics is cloud-based software that uses deep neural network architecture to detect over fifteen cardiac arrhythmia types.[50] In such cases, where accuracy is critical, the use of *black-box AI/ML models*—algorithms typically labeled as deep learning—may often be superior to the use of white-box models.[51] Black-box models, however, are frequently associated with a lack of trust and slow uptake in health care because the algorithms are very difficult, or even impossible, for human users to understand.[52] Thus, a new research field—namely explainable AI/ML—is emerging to address these criticisms and concerns.[53] Explainable AI/ML refers to a black-box AI/ML model that is used to make diagnoses or predictions and a second explanatory algorithm—itself a white-box model—which approximates the outputs of the black box and provides post-hoc explanations.[54]

Another important distinction is between *locked algorithms* and *adaptive algorithms*. The FDA defines a locked algorithm as "an algorithm that provides the same result each time the same input is applied to it and does not change with use."[55] Examples include "static look-up tables, decision trees, and complex classifiers."[56] Any AI/ML system that is fixed in advance can meet this definition.[57] As its name indicates, the term "adaptive algorithms" pertains to algorithms that

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Evgeniou & I. Glenn Cohen, *Beware Explanations From AI in Health Care*, 373 SCIENCE 284, 284 (2021); Boris Babic & Sara Gerke, *Explaining Medical AI Is Easier Said Than Done*, STAT (July 21, 2021), https://www.statnews.com/2021/07/21/explainable-medical-ai-easier-said-than-done [https://perma.cc/55Z4-YZ4J].

48 *See* sources cited *supra* note 47.

49 *See* Benjamens et al., *supra* note 7, at 3–4.

50 Biofourmis, *Biofourmis' RhythmAnalytics™ Platform Receives FDA Clearance for AI-Based Automated Interpretation of Cardiac Arrhythmias*, PR NEWSWIRE (Apr. 30, 2019, 5:00 PM), https://www.prnewswire.com/news-releases/biofourmis-rhythmanalytics-platform-receives-fda-clearance-for-ai-based-automated-interpretation-of-cardiac-arrhythmias-300841083.html [https://perma.cc/DDF3-QWZ5].

51 *See* Babic et al., *supra* note 47, at 284; Babic & Gerke, *supra* note 47.

52 *See* sources cited *supra* note 47.

53 *Id.*

54 *Id.*; Gerke, *Health AI*, *supra* note 10, at 490.

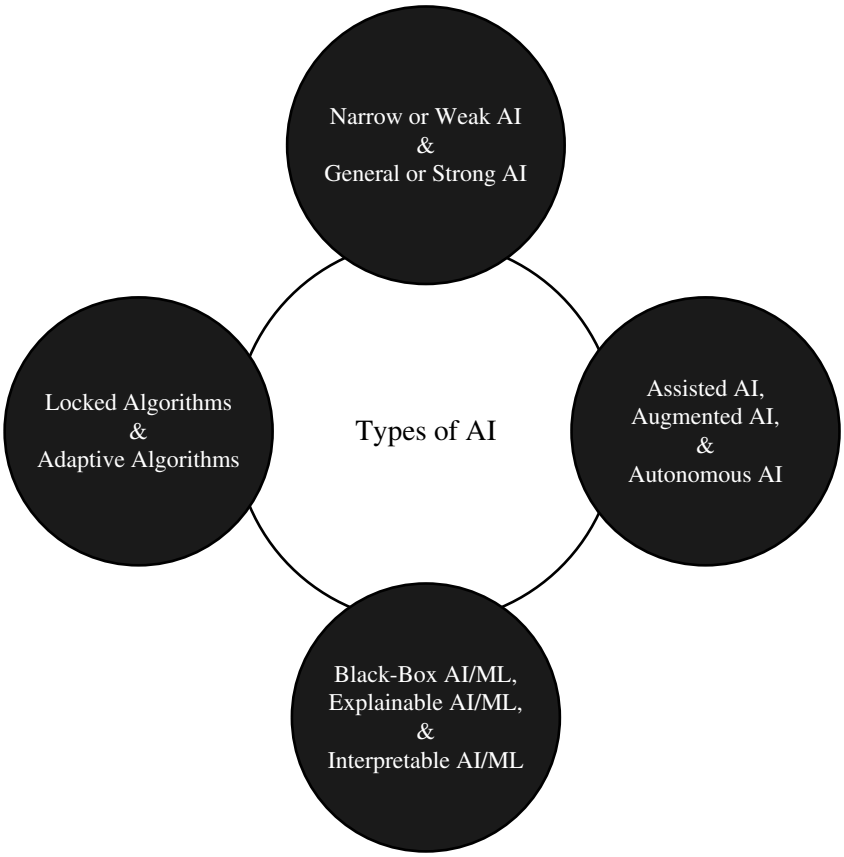
55 U.S. FOOD & DRUG ADMIN., PROPOSED REGULATORY FRAMEWORK FOR MODIFICATIONS TO ARTIFICIAL INTELLIGENCE/MACHINE LEARNING (AI/ML)-BASED SOFTWARE AS A MEDICAL DEVICE (SAMD) 3 n.7 (2019), https://www.fda.gov/media/122535/download [https://perma.cc/67VX-NJTF].

56 *Id.*

57 Babic et al., *supra* note 10, at 1203.

are adaptive. They have the ability to continuously learn from real-world experience and can change as they are applied to novel data.[58] The AI/ML-based medical devices that have received marketing authorization by the FDA thus far have typically included locked algorithms.[59] Figure 2 below depicts the different types of AI discussed in this Section.

FIGURE 2. TYPES OF AI



B. Different Applications and Different Users

AI can be applied in different contexts for different purposes and can be addressed to different users. In the health and research context, AI is expected to be increasingly used in four areas, as shown in Figure 3 and discussed below.

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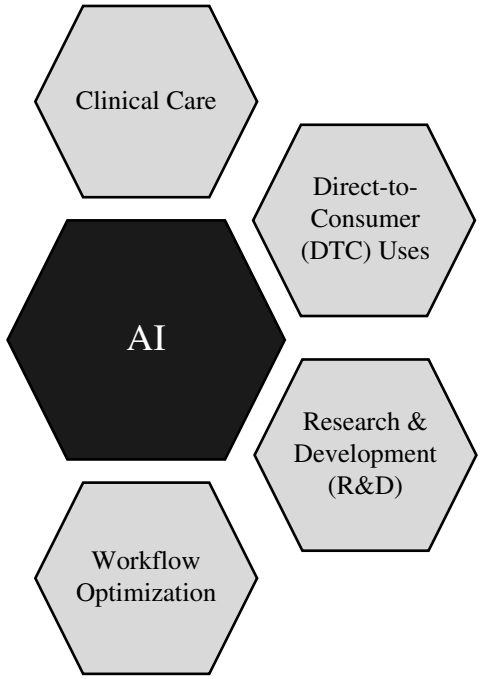
58 U.S. FOOD & DRUG ADMIN., *supra* note 55, at 3; Gerke et al., *The Need for a System View*, *supra* note 10, at 4.

59 U.S. FOOD & DRUG ADMIN., *supra* note 55, at 3.

FIGURE 3. KEY AREAS OF APPLICATIONS OF AI IN THE HEALTH AND RESEARCH CONTEXT



1. Clinical Care

AI is already applied in clinical care, especially in medical imaging and disease diagnostics.[60] For example, OsteoDetect is a software device used by clinicians to detect a common wrist fracture type, called distal radius fractures.[61] OsteoDetect uses deep learning to analyze adult wrist radiographs for this type of fracture.[62] Another example is Viz ICH, an AI/ML-based medical device that analyzes noncontrast computed tomography brain images.[63] If a suspected intracranial hemorrhage is identified, Viz ICH sends notifications to a

60 Gerke, *Health AI*, *supra* note 10, at 442.

61 Press Release, U.S. Food & Drug Admin., FDA Permits Marketing of Artificial Intelligence Algorithm for Aiding Providers in Detecting Wrist Fractures (May 24, 2018), https://www.fda.gov/news-events/press-announcements/fda-permits-marketing-artificial-intelligence-algorithm-aiding-providers-detecting-wrist-fractures [https://perma.cc/JP8Z-YZD6]; U.S. FOOD & DRUG ADMIN., DE NOVO NO. DEN180005, EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR OSTEODETECT 2 (2018), https://www.accessdata.fda.gov/cdrh_docs/reviews/DEN180005.pdf [https://perma.cc/4WWM-2VH2].

62 *See* U.S. FOOD & DRUG ADMIN., *supra* note 61, at 1–2.

63 Letter from Thalia T. Mills, Dir., Div. Radiological Health, Off. of In Vitro Diagnostics & Radiological Health, Off. of Prod. Eval. & Quality, Ctr. for Devices & Radiological Health, U.S. Food & Drug Admin., to Gregory Ramina, Dir. Regul. Affs., Viz.ai, Inc. (Mar. 23, 2021), https://www.accessdata.fda.gov/cdrh_docs/pdf21/K210209.pdf [https://perma.cc/PY2K-ZZGB].

neurosurgical or neurovascular specialist and recommends checking the images, which can be previewed via a mobile app.[64] BrainScope is another AI/ML-based medical device used by emergency physicians to assess patients with head injuries for brain concussions and brain bleeds.[65]

Most AI-based medical devices for clinical care are used by health professionals such as clinicians. Some AIs, however, are also intended for use by nonexperts. As seen, IDx-DR, for example, is an "autonomous" AI used by primary care physicians who are not eye specialists.[66] Another example is Caption Guidance: a cardiac ultrasound software device that can be used by nurses who are nonexperts in ultrasonography to capture cardiac ultrasound images.[67]

2. DTC Uses

An increasing number of AI-based products are directly addressed to consumers. According to one estimate, there are over four hundred thousand health care apps available in app stores, some of which use AI.[68] Examples include Apple's electrocardiogram

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For more information on Viz.ai's indications for use, see *Viz.ai Indications for Use*, VIZ.AI, https://www.viz.ai/indications-for-use [https://perma.cc/YCA5-QQDN].

64 *See* Letter from Thalia T. Mills to Gregory Ramina, *supra* note 63.

65 BRAINSCOPE, https://www.brainscope.com [https://perma.cc/N4XG-3V7L]. For the newest 510(k) clearance of BrainScope TBI (model: Ahead 500), see Letter from Jay Gupta, Assistant Dir., Div. Neurosurgical, Neurointerventional & Neurodiagnostic Devices, Off. Neurological & Physical Med. Devices, Off. Prod. Eval. & Quality, Ctr. Devices & Radiological Health, U.S. Food & Drug Admin., to Michael Singer, CEO, BrainScope Co., Inc. (Sept. 11, 2019), https://www.accessdata.fda.gov/cdrh_docs/pdf19/K190815.pdf [https://perma.cc/GAL8-FCR8].

66 *See supra* Section I.A.2.

67 Press Release, U.S. Food & Drug Admin., FDA Authorizes Marketing of First Cardiac Ultrasound Software That Uses Artificial Intelligence to Guide User (Feb. 7, 2020), https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-first-cardiac-ultrasound-software-uses-artificial-intelligence-guide-user [https://perma.cc/M3W3-HHMJ]; Letter from Robert Ochs, Ph.D., Deputy Dir. for Radiological Health, Off. of In Vitro Diagnostics & Radiological Health, Off. of Prod. Eval. & Quality, Ctr. for Devices & Radiological Health, U.S. Food & Drug Admin., to Sam Surette, RA/QA Manager, Caption Health, Inc. 1 (Feb. 7, 2020), https://www.accessdata.fda.gov/cdrh_docs/pdf19/DEN190040.pdf [https://perma.cc/GE84-2UZK].

68 Michael Georgiou, *Developing a Healthcare App in 2022: What Do Patients Really Want?*, IMAGINOVATION (Feb. 9, 2022), https://www.imaginovation.net/blog/developing-a-mobile-health-app-what-patients-really-want [https://perma.cc/B654-PN5T]; *see* Monomita Chakraborty, *10 Best AI Based Healthcare Apps You Can Try in 2021*, ANALYTICS INSIGHT (Apr. 13, 2021), https://www.analyticsinsight.net/10-best-ai-based-healthcare-apps-you-can-try-in-2021 [https://perma.cc/NJX4-XH7U]; Sara Gerke & Delaram Rezaeikhonakdar, *Privacy Aspects of Direct-to-Consumer Artificial Intelligence/Machine Learning Health Apps*, 6 INTEL.-BASED MED., no. 100061, 2022, at 1.

("ECG") app[69] and Apple's irregular rhythm notification feature[70]—two apps directly addressed to consumers aged twenty-two and older and designed to be used with the Apple Watch. The first app is intended to create, store, record, transfer, and display a single-channel ECG.[71] The second app notifies users of episodes of irregular rhythms suggestive of atrial fibrillation.[72]

In May 2021, Google also announced its AI-powered dermatology app that is designed to help users identify issues such as skin conditions, but it is not yet available on the U.S. market.[73] Moreover, AI-assisted symptom checkers are emerging. An example is Ada, which aims to help consumers find answers about the causes of their symptoms, ranging from bellyaches to headaches.[74] Consumers need to respond to questions about their symptoms, and then Ada will offer advice.[75] AI is also revolutionizing consumer-facing fitness trackers and other wearables, such as via self-learning motion sensors.[76]

3. R&D

AI shows great promise in research and development ("R&D"). Clinical trials of drugs and vaccines are costly (a median of $41,117 per patient), and they usually take several years.[77] In addition, the success rate of clinical trials is low—only about fourteen percent of all

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69 Letter from Angela C. Krueger, Deputy Dir., Eng'g & Sci. Rev., Off. of Device Eval., Ctr. for Devices & Radiological Health, U.S. Food & Drug Admin., to Donna-Bea Tillman, Senior Consultant, Biologics Consulting Grp., Inc. (Sept. 11, 2018), https://www.accessdata.fda.gov/cdrh_docs/pdf18/DEN180044.pdf [https://perma.cc/5D62-VU8H].

70 Letter from Angela C. Krueger, Deputy Dir., Eng'g & Sci. Rev., Off. of Device Eval., Ctr. for Devices & Radiological Health, U.S. Food & Drug Admin., to Donna-Bea Tillman, Senior Consultant, Biologics Consulting Grp., Inc. (Sept. 11, 2018), https://www.accessdata.fda.gov/cdrh_docs/pdf18/DEN180042.pdf [https://perma.cc/S2FM-Y3CP].

71 Letter from Angela C. Krueger to Donna-Bea Tillman, *supra* note 69, at 1; *see* Gerke, *Health AI*, *supra* note 10, at 444.

72 Letter from Angela C. Krueger to Donna-Bea Tillman, *supra* note 70, at 1; *see* Gerke, *Health AI*, *supra* note 10, at 444.

73 Bui & Liu, *supra* note 5; *DermAssist*, *supra* note 6. As mentioned in the introduction, this app has been criticized because of its non-representative training data set. *See, e.g.*, Feathers, *supra* note 5.

74 Ada Health, *Ada—Check Your Health*, Apple (2022), https://apps.apple.com/app/id1099986434?mt=8 [https://perma.cc/ND9H-2Q7W]; *see* Gerke, *Health AI*, *supra* note 10, at 445.

75 Ada Health, *supra* note 74.

76 *Sensors Get Clever: AI Revolutionizes Fitness Tracking*, Bosch, https://www.bosch-sensortec.com/news/ai-revolutionizes-fitness-tracking.html [https://perma.cc/22RC-CWZB].

77 Amit Pratap Singh Rathore, *Getting a Handle on Clinical Trial Costs*, Clinical Leader (Apr. 25, 2019), https://www.clinicalleader.com/doc/getting-a-handle-on-clinical-trial-costs-0001 [https://perma.cc/9Z7E-54VM].

clinical trials of drugs and vaccines are successful.[78] AI has the potential to contribute to the higher efficiency of clinical trials by improving patient recruitment and clinical trial design.[79] For example, AI-powered virtual assistants can help engage patients enrolled in clinical trials, which improves protocol adherence, expedites clinical trials, and reduces costs.[80]

Users of AI-based products designed to improve R&D can vary, ranging from researchers to study participants. For example, AI can also be deployed to accelerate the drug discovery process itself and cut costs. Relay Therapeutics developed an AI-based platform to enable a thorough understanding of protein motion and to help discover better medicines.[81] MediKanren is another AI-driven system that discovers therapies for rare diseases.[82] The system made headlines in August 2021 by pinpointing an unexpected drug, ketamine, as a potential treatment for ADNP syndrome, a neurodevelopmental genetic disorder.[83]

4. Workflow Optimization

AI-based products are increasingly being used in medicine to optimize workflows. They can be designed for different users, including physicians, hospital administration, and leadership. For example, Beth Israel Deaconess Medical Center has managed to open thirty percent of operating capacity with the help of an ML algorithm.[84] While each surgical patient initially received one hour in the operating room, the

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78 Alex Berezow, *Clinical Trial Success Rates by Phase and Therapeutic Area*, AM. COUNCIL SCI. & HEALTH (June 11, 2020), https://www.acsh.org/news/2020/06/11/clinical-trial-success-rates-phase-and-therapeutic-area-14845 [https://perma.cc/B5FF-QF6Z].

79 *See* Wullianallur Raghupathi & Viju Raghupathi, *Big Data Analytics in Healthcare: Promise and Potential*, 2 HEALTH INFO. SCI. & SYS. 3 (2014); Arun Bhatt, *Artificial Intelligence in Managing Clinical Trial Design and Conduct: Man and Machine Still on the Learning Curve?*, 12 PERSP. CLINICAL RSCH. 1, 1–2 (2021).

80 *See, e.g.*, *Patient Engagement with Co-PRO®*, PATCHAI, https://www.patchai.io [https://perma.cc/6XNN-9FND].

81 *Dynamo Platform*, RELAY THERAPEUTICS, https://relaytx.com/dynamo-platform [https://perma.cc/4H84-DEMB].

82 Katie Palmer, *With a Nudge from AI, Ketamine Emerges as a Potential Rare Disease Treatment*, STAT (Aug. 5, 2021), https://www.statnews.com/2021/08/05/artificial-intelligence-rare-disease-andp-medikanren [https://perma.cc/ZQY7-7DJ5].

83 *See id.*

84 Jonah Comstock, *Beth Israel's Halamka on How Machine Learning Can Add Value for Hospitals Today*, MOBIHEALTHNEWS (Feb. 13, 2019, 4:38 PM), https://www.mobihealthnews.com/content/beth-israels-halamka-how-machine-learning-can-add-value-hospitals-today [https://perma.cc/D6MU-HQ5U].

now-used ML algorithm predicts how much time each patient actually needs and schedules surgery times more efficiently.[85]

Voice-enabled virtual assistants can also help enable physicians to have more face time with their patients and spend less time on their computer for clinical documentation.[86] For example, the California-based company Suki developed an AI assistant called "Suki Assistant," reducing about seventy-six percent of clinical documentation time.[87] Physicians speak their notes to Suki Assistant, which listens and documents.[88] Suki Assistant also learns the user's preferences by tagging the data for ML.[89]

The following focuses mainly on AI/ML-based medical devices that belong to the first two application areas, namely clinical care and DTC uses. The reason for this is that AI/ML-based medical devices belonging to such areas especially can endanger patient safety.

II. When Is an AI/ML-Based Product a Medical Device?

Part II analyzes when an AI/ML-based product is considered a medical device under the FDCA. This information is essential to understand the issue of labeling for AI/ML-based medical devices. This Part first examines the principle of when an AI/ML-based product is classified as a medical device, and then explores relevant exceptions and the FDA's enforcement discretion.

In particular, Part II argues that the FDA's new final CDS guidance of September 28, 2022,[90] falls short of expectations. It creates legal uncertainty for AI/ML manufacturers, safety concerns, and seems to violate the 21st Century Cures Act.[91] Especially the FDA's new interpretation of criterion (4) of the CDS software exception in FDCA Section 520(o)(1)(E)[92] no longer excludes a priori certain types of AI/ML. Thus, even CDS using black-box AI/ML can meet this medical device exception and fall outside FDA regulation. The agency's current focus concerning criterion (4) appears to be primarily

85 *Id.*

86 Forbes Insights, *The Future of Voice AI in Patient Care*, Forbes (Feb. 11, 2019, 1:03 PM), https://www.forbes.com/sites/insights-intelai/2019/02/11/the-future-of-voice-ai-in-patient-care/#726bcb6f309c [https://perma.cc/2BX3-6YNX].

87 *Suki Assistant: How It Works*, Suki, https://www.suki.ai/how-suki-works [https://perma.cc/QBX3-6HF4].

88 *Id.*

89 *Id.*

90 U.S. Food & Drug Admin., *supra* note 18.

91 21st Century Cures Act, Pub. L. No. 114–255, § 3060, 130 Stat. 1033, 1130–33 (2016) (codified at 21 U.S.C. §§ 321(h)(1), 360j(o)).

92 *Id.* § 360j(o)(1)(E)(iii).

on improved labeling to circumvent regulation rather than safety and effectiveness. This Part argues that labeling is a crucial piece of the puzzle for successfully implementing AI/ML in health care but not to the detriment of patients' health. It must be coupled with a robust regulatory framework for CDS software functions and should not be used as a loophole to escape regulatory oversight. The current burden of assessing the safety and effectiveness of CDS that do *not* fulfill the medical device definition in FDCA Section 201(h)(1) ("Non-Device CDS")—which may even be an artificial deep neural network, according to the FDA's newest interpretation—is borne primarily by health care professionals who use the Non-Device CDS in question. In general, the FDA's final CDS Guidance creates confusion among stakeholders, and there is no clear, consistent line as to when a CDS software function is or is not considered a medical device. To be fair, the FDA is trying to fix a mistake that Congress made in the first place when enacting the CDS software exception as part of the 21st Century Cures Act. Now is the time for Congress to act and amend the FDCA by deleting FDCA Section 520(o)(1)(E).

A. Principle

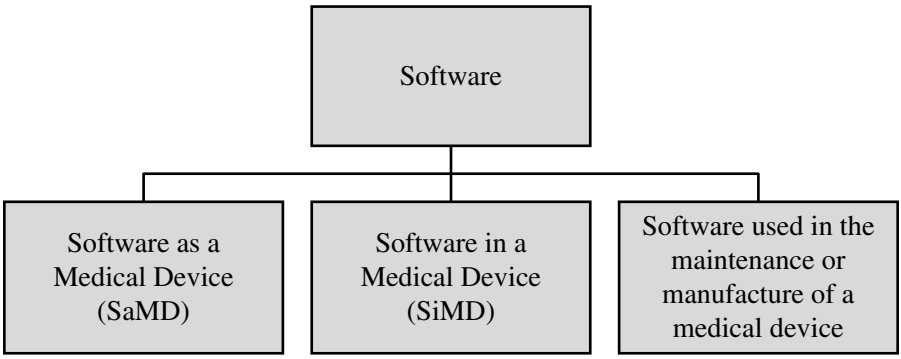
If an AI/ML-based product is classified as a medical device, the FDA can regulate it. FDCA Section 201(h)(1) defines the term "medical device" as follows:

> 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 520(o).*[93]

[93] FDCA § 201(h)(1), 21 U.S.C. § 321(h)(1) (emphasis added).

In general, the term "medical device" also includes software functions (i.e., device software functions). This results from an *a contrario* reading of the second sentence of FDCA Section 201(h)(1).[94] Software can be divided into three types,[95] as shown in Figure 4 below.

FIGURE 4. SOFTWARE TYPES



In particular, the first two types, SaMD and SiMD, are relevant in the context of AI/ML-based medical devices. The International Medical Device Regulators Forum ("IMDRF") is a forum of voluntary medical device regulators from across the world, such as the U.S., Canada, European Union, China, Japan, and Singapore, that drives international medical device regulatory harmonization forward.[96] In 2013, one of the IMDRF Working Groups published a document with key definitions on the topic of SaMD.[97] This document defines SaMD as "software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device."[98] The FDA endorses this definition and has made clear that the agency understands the term "medical purposes" to mean "those purposes that are intended to treat, diagnose, cure, mitigate, or prevent disease or other conditions."[99] In other words, SaMD is

94 *See id.*

95 *Software as a Medical Device (SaMD)*, U.S. FOOD & DRUG ADMIN. (Dec. 4, 2018), https://www.fda.gov/medical-devices/digital-health/software-medical-device-samd [https://perma.cc/73P7-CEWY].

96 INT'L MED. DEVICE REGULS. F., http://www.imdrf.org [https://perma.cc/48TQ-DSJ7]; Gerke, *Health AI*, *supra* note 10, at 446.

97 IMDRF SaMD Working Grp., *Software as a Medical Device (SaMD): Key Definitions*, IMDRF Doc. IMDRF/SaMD WG/N10FINAL:2013 (Dec. 9, 2013), http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-131209-samd-key-definitions-140901.pdf [https://perma.cc/Z2VV-B3F5].

98 *Id.* at 6.

99 U.S. FOOD & DRUG ADMIN., *supra* note 55, at 2; Gerke, *Health AI*, *supra* note 10, at 446–47.

"standalone software";[100] the software is itself the medical device.[101] SaMD is operated with familiar, everyday technology such as laptops, smartphones, and smartwatches.[102] Examples of SaMD include Apple's ECG app and irregular rhythm notification feature app, Viz ICH (analysis of noncontrast computed tomography brain images), and RhythmAnalytics (detection of over fifteen cardiac arrhythmia types).[103]

The FDA defines "SiMD" as "software that is integral to a medical device."[104] It thus has software and hardware components.[105] The software needs to help the function of the medical device in some way, such as controlling or powering the device or processing its information.[106] An example is software that helps run an insulin pump.[107] But the majority of AI/ML-based medical devices that are currently being developed or available on the U.S. market are SaMD.[108]

B. Exceptions, FDCA Section 520(o)

Some software functions, however, are not considered to be medical devices (non-device software functions). The 21st Century Cures Act introduced exceptions in FDCA Section 520(o) and added clarifying language to FDCA Section 201(h)(1).[109] FDCA Section 520(o)[110] lists *five categories* of software functions, as illustrated in Figure 5 below.

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100 U.S. Food & Drug Admin., *supra* note 95; Gerke, *Health AI*, *supra* note 10, at 446.

101 *See* sources cited *supra* note 100; Codrin Arsene, *SaMD vs SiMD: What's the Difference?*, HealthTechZone.com (June 29, 2020), https://www.healthtechzone.com/topics/healthcare/articles/2020/06/29/445836-samd-vs-simd-whats-difference.htm [https://perma.cc/9NNB-6V7G].

102 Arsene, *supra* note 101.

103 For more information on these medical devices, see *supra* Section I.A.2., I.B.1.–.2.

104 U.S. Food & Drug Admin., *supra* note 95.

105 David Ritscher, *The New FDA?*, Cambridge Consultants (Feb. 4, 2018), https://www.cambridgeconsultants.com/insights/opinion/new-fda [https://perma.cc/R64K-GLKV].

106 Arsene, *supra* note 101.

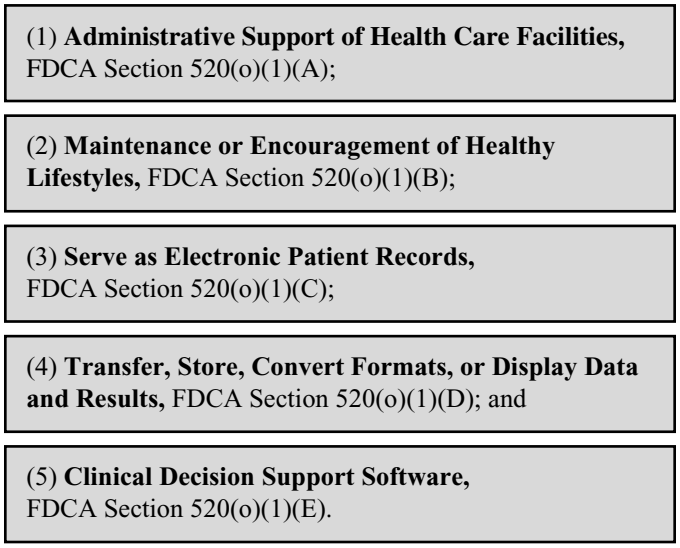
107 *Id.*

108 *See, e.g.*, Simeng Zhu, Marissa Gilbert, Indrin Chetty & Farzan Siddiqui, *The 2021 Landscape of FDA-Approved Artificial Intelligence/Machine Learning-Enabled Medical Devices: An Analysis of the Characteristics and Intended Use*, 165 Int'l J. Med. Informatics, no. 104828, 2022, at 1, 2.

109 21st Century Cures Act, Pub. L. No. 114–255, § 3060, 130 Stat. 1033, 1130–33 (2016) (codified at 21 U.S.C. §§ 321(h)(1), 360j(o)).

110 FDCA § 520(o), 21 U.S.C. § 360j(o).

FIGURE 5. CATEGORIES OF NON-DEVICE SOFTWARE FUNCTIONS



If the specific requirements of one of these five categories are fulfilled, the software function in question is *not* classified as a medical device and thus is *not* subject to FDA regulation.[111] In the context of AI/ML-based medical devices for clinical care or DTC uses,[112] the second and fifth categories are especially pertinent.

1. Maintenance or Encouragement of Healthy Lifestyles, FDCA Section 520(o)(1)(B)

The second category laid down in FDCA Section 520(o)(1)(B) applies to a software function that is intended "*for maintaining or encouraging a healthy lifestyle* and *is unrelated to* the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition."[113] The FDA has published two nonbinding guidance documents that are relevant to this category and express the agency's current thinking:

(1) *Changes to Existing Medical Software Policies Resulting from Section 3060 of the 21st Century Cures Act* ("Cures Act Guidance")[114] and

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111 *See* FDCA § 201(h)(1), 21 U.S.C. § 321(h)(1).

112 For more information on AI/ML-based products for clinical care or DTC uses, see *supra* Section I.B.1.-2.

113 FDCA § 520(o)(1)(B), 21 U.S.C. § 360j(o)(1)(B) (emphasis added).

114 U.S. FOOD & DRUG ADMIN., CHANGES TO EXISTING MEDICAL SOFTWARE POLICIES RESULTING FROM SECTION 3060 OF THE 21ST CENTURY CURES ACT—GUIDANCE FOR INDUSTRY AND FOOD AND DRUG ADMINISTRATION STAFF (2019), https://www.fda.gov/media/109622/download [https://perma.cc/LZY5-LBL9].

(2) *General Wellness: Policy for Low Risk Devices* ("General Wellness Guidance").[115]

The Cures Act Guidance clarifies that software functions fall under the medical device exception in FDCA Section 520(o)(1)(B) if they are products that belong to the first category of general wellness intended uses, as described in the General Wellness Guidance.[116] This is the case where software functions have "an intended use that relates to maintaining or encouraging a general state of health or a healthy activity," such as "self-esteem," "physical fitness," or "stress management."[117] This category of general wellness intended uses exclusively involves claims that do *not* refer to diseases or conditions.[118]

The intended use—i.e., "the objective intent of the persons legally responsible for the labeling of" devices, usually of the manufacturers[119]—is decisive when assessing whether a software function falls under the medical device exception in FDCA Section 520(o)(1)(B). For example, the objective intent may be demonstrated by labeling claims, advertisement, and other written or oral statements by these persons or their representatives.[120]

Many DTC AI/ML apps fall under FDCA Section 520(o)(1)(B) and thus are *not* considered to be medical devices and are *not* reviewed by the FDA. An example is a DTC AI/ML app that helps users manage weight, as its claims are "unrelated to the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition."[121] In fact, only a few DTC AI/ML apps are classified as medical devices ("DTC medical AI/ML apps"), such as Apple's ECG app and Apple's irregular rhythm notification feature app.[122]

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115 U.S. Food & Drug Admin., General Wellness: Policy for Low Risk Devices—Guidance for Industry and Food and Drug Administration Staff (2019), https://www.fda.gov/media/90652/download [https://perma.cc/YF4L-S95Q].

116 U.S. Food & Drug Admin., *supra* note 114, at 4–5.

117 *Id.* at 5; U.S. Food & Drug Admin., *supra* note 115, at 3.

118 U.S. Food & Drug Admin., *supra* note 115, at 3. This is in contrast to the second category of general wellness intended uses that are considered medical devices. *See* Gerke, *Health AI*, *supra* note 10, at 450.

119 21 C.F.R. § 801.4.

120 *Id.*; Gerke, *Health AI*, *supra* note 10, at 450.

121 U.S. Food & Drug Admin., *supra* note 114, at 5.

122 *See* Boris Babic, Sara Gerke, Theodoros Evgeniou & I. Glenn Cohen, *Direct-to-Consumer Medical Machine Learning and Artificial Intelligence Applications*, 3 Nature Mach. Intel. 283, 284 (2021). For more information on these apps, see *supra* Section I.B.2.

2. *Clinical Decision Support Software, FDCA Section 520(o)(1)(E)*

The fifth category of software functions laid down in FDCA Section 520(o)(1)(E) that are not classified as medical devices applies to software functions that are intended to support particular clinical decisions. On September 28, 2022, the FDA issued the long-awaited, final CDS Guidance to clarify the agency's regulatory approach to CDS software functions.[123] In its CDS Guidance, the FDA delineates *four criteria* that need to be fulfilled for a software function to fall under the medical device exception in FDCA Section 520(o)(1)(E):[124]

- Criterion (1): The software function is *not* "intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system . . . ";[125]
- Criterion (2): The software function is intended for the purpose of "displaying, analyzing, or printing medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines) . . . ";[126]
- Criterion (3): The software function is intended for the purpose of "supporting or providing *recommendations to a health care professional* about prevention, diagnosis, or treatment of a disease or condition . . . ";[127]
- Criterion (4): The software function is intended for the purpose of "*enabling such health care professional to independently review the basis for such recommendations* that such software presents so that it is not the intent that such health care professional rely primarily on any of

123 U.S. Food & Drug Admin., *supra* note 18, at 5; *see also Your Clinical Decision Support Software: Is It a Medical Device?*, U.S. Food & Drug Admin. (Sept. 27, 2022), https://www.fda.gov/medical-devices/software-medical-device-samd/your-clinical-decision-support-software-it-medical-device [https://perma.cc/P899-53R6] (providing an overview of the new CDS Guidance). There are many definitions of the term "CDS." For example, the Office of the National Coordinator for Health Information Technology ("ONC") defines "CDS" as a tool that "provides clinicians, staff, patients or other individuals with knowledge and person-specific information, intelligently filtered or presented at appropriate times, to enhance health and health care." *Clinical Decision Support*, Off. Nat'l Coordinator for Heath Info. Tech. (Apr. 10, 2018), https://www.healthit.gov/topic/safety/clinical-decision-support [https://perma.cc/5XDJ-HHLQ].

124 U.S. Food & Drug Admin., *supra* note 18, at 6.

125 FDCA § 520(o)(1)(E), 21 U.S.C. § 360j(o)(1)(E).

126 FDCA § 520(o)(1)(E)(i), 21 U.S.C. § 360j(o)(1)(E)(i).

127 FDCA § 520(o)(1)(E)(ii), 21 U.S.C. § 360j(o)(1)(E)(ii) (emphasis added).

> such recommendations to make a clinical diagnosis or treatment decision regarding an individual patient."[128]

If all four of the above criteria are fulfilled, the software function is a "Non-Device CDS," a CDS that is *not* a medical device under the FDCA and thus is *not* subject to FDA regulation.[129]

Criterion (1) requires a software function that is *not* "intended to acquire, process, or analyze a medical image or a signal from an in vitro diagnostic device or a pattern or signal from a signal acquisition system . . . ."[130] The FDA clarifies in its new CDS Guidance that the types of data inputs described in criterion (1) (i.e., medical images, signals from in vitro diagnostic devices, or patterns or signals from signal acquisition systems) are used in medical devices.[131] For example, criterion (1) is *not* met when a software function uses image sets, such as magnetic resonance of a patient, to develop a personal treatment plan for review by a health care professional for patients undergoing external beam radiation therapy.[132] Because such a software function is intended to analyze medical images, it is an example of a device software function subject to the FDA's regulatory oversight.[133]

In contrast to criterion (1), criterion (2) describes the types of data inputs ("medical information about a patient or other medical information (such as peer-reviewed clinical studies and clinical practice guidelines)")[134] utilized in Non-Device CDS.[135] In its final CDS Guidance, the FDA interprets the term "medical information about a patient" as

> the type of information that normally is, and generally can be, communicated between HCPs [health care professionals] in a clinical conversation or between HCPs and patients in the context of a clinical decision, meaning that the relevance of the information to the clinical decision being made is well understood and accepted.[136]

The FDA interprets the term "other medical information" as "information such as peer-reviewed clinical studies, clinical practice guidelines, and information that is similarly independently verified

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128 FDCA § 520(o)(1)(E)(iii), 21 U.S.C. § 360j(o)(1)(E)(iii) (emphasis added).

129 U.S. Food & Drug Admin., *supra* note 18, at 4, 7.

130 FDCA § 520(o)(1)(E), 21 U.S.C. § 360j(o)(1)(E).

131 U.S. Food & Drug Admin., *supra* note 18, at 7.

132 *Id.* at 21.

133 *Id.* at 20–21.

134 FDCA § 520(o)(1)(E)(i), 21 U.S.C. § 360j(o)(1)(E)(i).

135 U.S. Food & Drug Admin., *supra* note 18, at 7, 9.

136 *Id.* at 9.

and validated as accurate, reliable, not omitting material information, and supported by evidence."[137]

According to the FDA's current thinking, the above example of the software function that uses a patient's medical images to develop a personal treatment plan for review by a health care professional for patients undergoing external beam radiation therapy also does not fulfill criterion (2) because such a software function is not intended for the purpose of "display[ing], analyz[ing], or print[ing] medical information."[138]

Criterion (3) requires a software function that is intended for the purpose of "supporting or providing *recommendations to a health care professional* about prevention, diagnosis, or treatment of a disease or condition."[139] In contrast to the previous draft guidance on CDS software of September 27, 2019 ("CDS Draft Guidance"),[140] the new final CDS Guidance defines the term "health care professional" (albeit in a footnote) as

> an individual who is licensed, registered, or certified by a State, territory, or other governing body, to administer health care, including but not limited to, nurse practitioner, registered nurse, licensed practical nurse, clinical social worker, dentist, occupational therapist, pharmacist, physical therapist, physician, physician assistant, psychologist, respiratory therapist, speech-language pathologist, technologist, or any other practitioner or allied health professional.[141]

According to the FDA, patients and caregivers do not fall within this definition.[142] Thus, software functions that are intended for the purpose of supporting or providing recommendations to patients and caregivers are medical devices under the FDCA.[143]

The FDA also clarifies in its CDS Guidance that criterion (3) is *not* satisfied in cases where software functions provide specific preventive, diagnostic, or treatment directives or outputs and in time-critical decision making.[144] The FDA states:

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137 *Id.*

138 *Id.* at 21; FDCA § 520(o)(1)(E)(i), 21 U.S.C. § 360j(o)(1)(E)(i).

139 FDCA § 520(o)(1)(E)(ii), 21 U.S.C. § 360j(o)(1)(E)(ii) (emphasis added).

140 U.S. Food & Drug Admin., Clinical Decision Support Software: Draft Guidance for Industry and Food and Drug Administration Staff (2019), https://www.regulations.gov/document/FDA-2017-D-6569-0041 [https://perma.cc/Y42F-8RG3].

141 U.S. Food & Drug Admin., *supra* note 18, at 4 n.1.

142 *Id.* at 13.

143 *Id.*

144 *Id.* at 10.

> Two aspects of software functionality may affect whether a software function is being used to support or provide recommendations to an HCP [health care professional]: (1) the level of software automation, and (2) the time-critical nature of the HCP's decision making. FDA considers both these aspects when determining whether a software function is being used to enhance, inform and/or influence an HCP's decision-making (satisfying Criterion 3) or rather, to substitute, replace, or direct the HCP's judgment (failing Criterion 3).[145]

The FDA's interpretation of criterion (3) ("support[ing] or provid[ing] recommendations") is informed by the understanding of automation bias—i.e., "the propensity of humans to over-rely on a suggestion from an automated system."[146] The agency explains in its CDS Guidance that automation bias is more probable to occur if a software function provides users with a specific output or solution instead of a list of options or comprehensive information for them to consider.[147] The risk of automation bias also increases in time-critical decision making because users do not have enough time to consider other information properly.[148]

For example, based on the FDA's interpretation of criterion (3), a software function that uses a patient's medical images to develop a personal treatment plan for review by a health care professional for patients undergoing external beam radiation therapy meets neither criterion (1) nor (2) (as explained above) nor criterion (3).[149] Criterion (3) is not met because the software function generates the treatment plan that is intended to offer a specific treatment directive.[150] Similarly, a software function that detects patients with a likely diagnosis of opioid addiction also fails criterion (3) since it provides a specific treatment or diagnostic directive or output.[151] Criterion (3) is also not satisfied when a software function provides time-critical alerts to prompt clinical intervention, such as for sepsis, or when a software function identifies a risk score or probability for a specific condition or disease.[152] In contrast, a software function fulfills criteria (1) to (3) when it provides a health care professional with a list of treatment

145 *Id.* at 11.

146 *Id*. at 10–11.

147 *Id*. at 11.

148 *Id*.

149 *Id.* at 21.

150 *Id*.

151 *Id*.

152 *Id*. at 12, 13, 22.

order options based on clinical guidelines for the treatment of patients presenting with pneumonia symptoms.[153]

In the context of AI/ML-based products, the interpretation of criterion (4) ("enabling such health care professional to independently review the basis for such recommendations")[154] is especially relevant.

In order to fulfill criterion (4), the FDA recommends in its new CDS Guidance that:

> a) The software or labeling include the *purpose or intended use* of the product, including the *intended HCP [health care professional] user* and *intended patient population*. FDA does *not* consider software functions intended *for a critical, time-sensitive task or decision* to meet Criterion 4, because an HCP is unlikely to have sufficient time to independently review the basis of the recommendations . . . .
> b) The software or labeling identify the required *input medical information*, with plain language instructions on how the inputs should be obtained, their relevance, and data quality requirements.
> c) The software or labeling provide a plain language description of the *underlying algorithm development and validation that forms the basis for the CDS implementation*, including:
> i. A *summary of the logic or methods relied upon to provide the recommendations* (e.g., meta-analysis of clinical studies, expert panel, statistical modeling, AI/ML techniques);
> ii. A *description of the data relied upon so that an HCP can assess whether the data is representative of their patient population* (e.g., relevant sub-groups, disease conditions, collection sites, sex, gender, ethnicity) and *assess if best practices were followed* (e.g., independent development and validation datasets); and
> iii. A *description of the results from clinical studies conducted to validate the algorithm/recommendations* so that an *HCP can assess the potential performance and limitations when applied to their patients* (e.g., subpopulations with untested or highly variable algorithm performance).
> d) The *software output provides the HCP user with relevant patient-specific information and other knowns/unknowns*

153 *Id.* at 15–16.

154 FDCA § 520(o)(1)(E)(iii), 21 U.S.C. § 360j(o)(1)(E)(iii).

> *for consideration* (e.g., missing, corrupted, or unexpected input data values) that will enable the HCP to independently review the basis for the recommendations and apply their judgment when making the final decision.
>
> In order to describe the *basis for the recommendations*, regardless of the complexity of the software and whether or not it is proprietary, the *software output or labeling should provide adequate background information in plain language on the input(s), algorithm logic or methods, datasets, and validation*. Relevant sources should be identified and available to the intended user (e.g., clinical practice guidelines with the date or version, published literature, or information that has been communicated by the CDS developer to the intended user) and understandable by the intended user (e.g., data points whose meaning is well understood by the intended user). In order to enable independent evaluation of its basis, the recommendation should be based on information whose meaning could be expected to be independently understood by the intended HCP user (e.g., the inputs used to generate the recommendations are identified, the recommendations are based on inputs that do not omit material information, and the quality and robustness of the datasets or clinical studies are described).[155]

In addition to the final CDS Guidance, the FDA has also recently launched a new Digital Health Policy Navigator that should help developers determine whether their software function is possibly the focus of the agency's oversight as a medical device.[156] This tool should also assist developers in identifying applicable legal requirements and FDA-specific recommendations.[157] It consists of seven steps with questions primarily based on the medical device definition in FDCA Section 201(h)(1), the categories of non-device software functions in FDCA Section 520(o)(E), and relevant FDA guidance documents.[158] Step 6 of this tool deals specifically with CDS software functions and, following the new CDS Guidance, asks the questions shown in Figure 6 to determine whether a developer's software function may be considered a device under the FDCA.[159]

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155 U.S. Food & Drug Admin., *supra* note 18, at 14 (emphasis added).

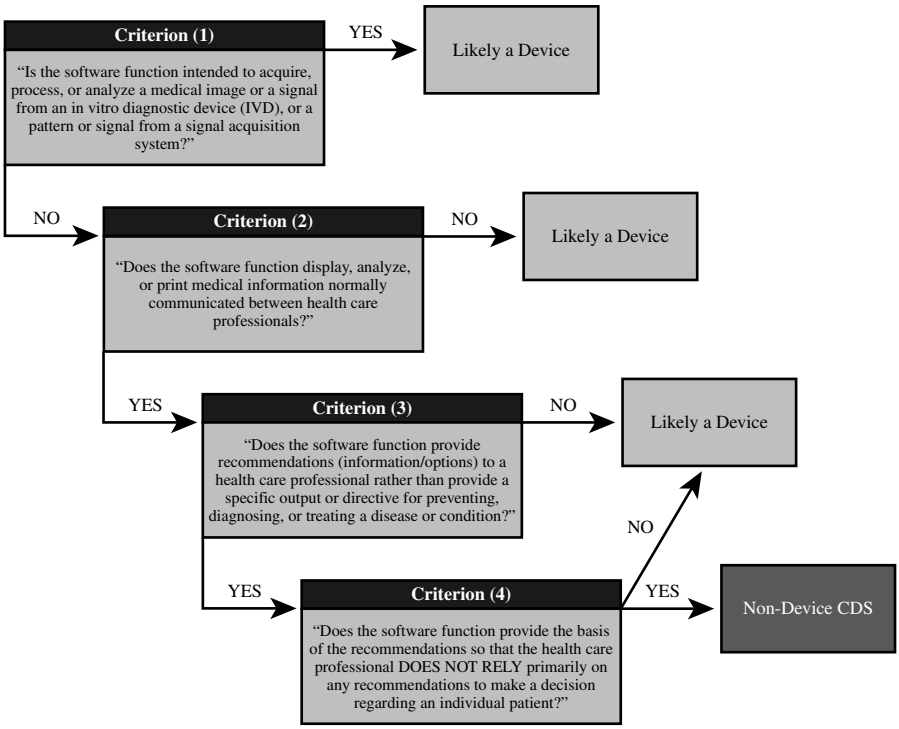
156 *Digital Health Policy Navigator*, U.S. Food & Drug Admin. (Dec. 14, 2022), https://www.fda.gov/medical-devices/digital-health-center-excellence/digital-health-policy-navigator [https://perma.cc/AP8F-7NWR].

157 *Id.*

158 *Id.* For the categories of non-device software functions, see *supra* Figure 5.

159 *Step 6: Is the Software Function Intended to Provide Clinical Decision Support?*, U.S. Food & Drug Admin. (Dec. 14, 2022), https://www.fda.gov/medical-devices/digital-health-

FIGURE 6. CLASSIFICATION OF WHETHER A SOFTWARE FUNCTION FALLS UNDER THE MEDICAL DEVICE EXCEPTION IN FDCA SECTION 520(O)(1)(E) AND THUS IS A NON-DEVICE CDS BASED ON THE FDA'S CURRENT THINKING IN ITS NEW CDS GUIDANCE OF SEPTEMBER 28, 2022, AND DIGITAL HEALTH POLICY NAVIGATOR[160]



3. *Criticism of the New CDS Guidance of September 28, 2022*

The new final CDS Guidance of September 28, 2022,[161] differs significantly from the previous CDS Draft Guidance of September 27, 2019.[162] Such a profound change without involving a reproposal was a massive surprise for stakeholders, such as CDS manufacturers and health care professionals.[163] Thus, it is not astonishing that the CDS Guidance has already been criticized significantly. For example, the final guidance has been called "truly a disaster" that "violates the law"

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center-excellence/step-6-software-function-intended-provide-clinical-decision-support [https://perma.cc/4VW8-KMJC].

160 *See id.*

161 U.S. FOOD & DRUG ADMIN., *supra* note 18.

162 *See* U.S. FOOD & DRUG ADMIN., *supra* note 140.

163 The CDS Draft Guidance of September 27, 2019, was already a reproposal of the first CDS Draft Guidance *Clinical and Patient Decision Support Software* of December 8, 2017, likely because the revised 2019 draft guidance differed significantly from the first 2017 draft guidance.

(i.e., the 21st Century Cures Act).[164] It has been argued that, particularly with its interpretation of criteria (2) and (3) of FDCA Section 520(o)(1)(E), the FDA wants to "reclaim jurisdiction over software that Congress declared is unregulated."[165]

Indeed, the FDA appears to intend a significant shift from its previous regulatory approach to CDS software functions, expanding its oversight over at least some of them. For example, AI algorithms that analyze a patient's medical information to detect sepsis and generate an alert to notify a health care professional have not been regulated by the FDA for years, despite their considerable safety and effectiveness concerns.[166] As seen above, the new CDS Guidance clearly articulates that this may change in the future because criterion (3) is not satisfied in cases where a software function is intended to provide a specific diagnostic directive or output, including an alert that supports time-critical decision making.[167]

Although the FDA's move to consider AI algorithms for sepsis alerts as medical devices seems commendable from a patient safety perspective, criticism of the new CDS Guidance cannot be dismissed easily. In particular, it has been argued that the FDA can interpret

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164 Bradley Merrill Thompson, *FDA's Final Guidance on Clinical Decision Support Violates the Law*, LinkedIn (Sept. 27, 2022), https://www.linkedin.com/pulse/fdas-final-guidance-clinical-decision-support-law-thompson-rac [https://perma.cc/TB54-TETF].

165 *Id.*; FDCA § 520(o)(1)(E)(i)–(ii), 21 U.S.C. § 360j(o)(1)(E)(i)-(ii). For more information on criteria (2) and (3), see *supra* Section II.B.2.

166 Casey Ross, *Epic's AI Algorithms, Shielded from Scrutiny by a Corporate Firewall, Are Delivering Inaccurate Information on Seriously Ill Patients*, STAT+ (July 26, 2021), https://www.statnews.com/2021/07/26/epic-hospital-algorithms-sepsis-investigation [https://perma.cc/UUG3-TMED] (highlighting concerns that Epic's algorithm for predicting sepsis "routinely fails to identify the condition in advance, and triggers frequent false alarms"); Andrew Wong, Erkin Otles; John P. Donnelly, Andrew Krumm, Jeffrey McCullough, Olivia DeTroyer-Cooley, Justin Pestrue, Marie Phillips, Judy Konye, Carleen Penoza, Muhammad Ghous & Karandeep Singh, *External Validation of a Widely Implemented Proprietary Sepsis Prediction Model in Hospitalized Patients*, 181 JAMA Internal Med. 1065 (2021); Casey Ross, *In New Guidance, FDA Says AI Tools to Warn of Sepsis Should Be Regulated as Devices*, STAT+ (Sept. 27, 2022), https://www.statnews.com/2022/09/27/health-fda-artificial-intelligence-guidance-sepsis [https://perma.cc/5B5X-5Z3Z]; Casey Ross, *A 'Disaster', or a 'Clear Path' Forward?: New FDA Guidance on AI in Medicine Sparks Strong Reactions*, STAT+ (Sept. 28, 2022) [hereinafter Ross, *A 'Disaster', or a 'Clear Path' Forward?*], https://www.statnews.com/2022/09/28/fda-artificial-intelligence-tools-regulation-oversight [https://perma.cc/BG9P-AVAC]; Casey Ross, *Epic Overhauls Popular Sepsis Algorithm Criticized for Faulty Alarms*, STAT+ (Oct. 3, 2022), https://www.statnews.com/2022/10/03/epic-sepsis-algorithm-revamp-training [https://perma.cc/LJQ7-HJW4] (revealing that Epic now has a new version of its sepsis prediction model, but it is still too early to say whether it will improve patient outcomes); Casey Ross, *Epic's Overhaul of a Flawed Algorithm Shows Why AI Oversight Is a Life-Or-Death Issue*, STAT+ (Oct. 24, 2022), https://www.statnews.com/2022/10/24/epic-overhaul-of-a-flawed-algorithm/ [https://perma.cc/4BS3-8RSC].

167 *See supra* Section II.B.2.; U.S. Food & Drug Admin., *supra* note 18, at 22.

ambiguous terms in the 21st Century Cures Act based on their typical meaning but cannot add novel concepts to the statutory language, which impacts what products are regulated as medical devices.[168] For example, it is questionable whether Congress limited criterion (2) ("*medical information about a patient*") to "the type of information that *normally* is, and generally can be, communicated between HCPs in a clinical conversation or between HCPs and patients in the context of a clinical decision, meaning that the *relevance* of the information to the clinical decision being made is *well understood and accepted*."[169] In addition, although the FDA's concerns about the risks of automation bias are understandable and valid, that doesn't change the issue that it is disputed whether Congress would agree with the FDA's interpretation of criterion (3) ("supporting or providing recommendations") to exclude software functions from the medical device exception in cases where they provide specific preventive, diagnostic, or treatment directives or outputs and in time-critical decision making.[170]

But even with regard to criterion (4) of FDCA Section 520(o)(1)(E) ("enabling such health care professional to independently review the basis for such recommendations"),[171] the final CDS Guidance falls short of expectations. Although it is positive that manufacturers are incentivized to improve their labels, particularly by listing information on the underlying algorithm development and validation, in order to be able to fall under the medical device exemption,[172] the FDA's latest interpretation of criterion (4) also brings with it many uncertainties for AI/ML manufacturers and safety concerns.

First of all, similar to the previous CDS Draft Guidance,[173] the final CDS Guidance does *not* distinguish between the different types of CDS using AI/ML ("AI/ML-based CDS")—i.e., black-box AI/ML, explainable AI/ML, and interpretable AI/ML. In fact, the FDA only

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168 Thompson, *supra* note 164.

169 U.S. Food & Drug Admin., *supra* note 18, at 9 (second, third, and fourth emphasis added); FDCA § 520(o)(1)(E)(i), 21 U.S.C. § 360j(o)(1)(E)(i); Thompson, *supra* note 164 (arguing that "Congress did not so limit this exemption").

170 FDCA § 520(o)(1)(E)(ii), 21 U.S.C. § 360j(o)(1)(E)(ii); U.S. Food & Drug Admin., *supra* note 18, at 10; Thompson, *supra* note 164 (arguing that "[n]one of this has any basis whatsoever in the statutory language" and "that language is nowhere found in the statute").

171 FDCA § 520(o)(1)(E)(iii), 21 U.S.C. § 360j(o)(1)(E)(iii). For more information on criterion (4), see *supra* Section II.B.2.

172 *See* Ross, *A 'Disaster', or a 'Clear Path' Forward?*, *supra* note 166 (citing the clinical data scientist Mark Sendak who applauded this aspect of the new CDS Guidance).

173 *See* U.S. Food & Drug Admin., *supra* note 140.

uses the term "AI/ML" once in its new CDS Guidance,[174] although many CDS being developed use AI/ML.

Second, this omission of any differentiation between the different types of AI/ML-based CDS leads to uncertainties for AI/ML manufacturers as it is unclear whether their products can meet criterion (4) in the first place. The new language in the CDS Guidance makes it even more difficult for manufacturers to predict whether—according to the FDA's interpretation—their AI/ML-based CDS is considered a medical device under FDCA Section 201(h)(1). The CDS Draft Guidance of September 27, 2019, still explained that "[i]n order to describe the basis for a recommendation . . . 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."[175]

In contrast, the new final CDS Guidance no longer uses the term "rationale" for manufacturers to describe "the basis for the recommendations."[176] Instead, the FDA now recommends that "the software output or labeling should provide adequate background information in plain language on the input(s), *algorithm logic or methods*, datasets, and validation."[177]

The previous CDS Draft Guidance suggested that *CDS using black-box AI/ML* were unlikely to fall under the medical device exception in FDCA Section 520(o)(1)(E).[178] In other words, according to the FDA's previous interpretation, CDS using black-box AI/ML were likely considered a priori Device CDS (i.e., CDS that are medical devices under FDCA Section 201(h)(1)) and thus generally the focus of the FDA's regulatory oversight). Many health AI/ML-based products that are available on the U.S. market use black-box AI/ML models—algorithms typically labeled as deep learning—such as the cloud-based software RhythmAnalytics, detecting over fifteen cardiac arrhythmias.[179] As mentioned previously, however, it is very difficult, if not impossible, for humans, such as software developers and users, to understand black-box AI/ML models.[180] Thus, applying the FDA's previous interpretation of criterion (4) of FDCA Section 520(o)(1)(E) laid out in its CDS Draft Guidance, CDS using black-box AI/ML were

174 U.S. Food & Drug Admin., *supra* note 18, at 14.

175 U.S. Food & Drug Admin., *supra* note 140, at 12 (emphasis added).

176 U.S. Food & Drug Admin., *supra* note 18, at 14.

177 *Id.* (emphasis added).

178 *See* U.S. Food & Drug Admin., *supra* note 140, at 12.

179 For more information see *supra* Section I.A.2.

180 *See supra* Section I.A.2.

likely considered Device CDS because, in most cases, manufacturers would not be able to describe the logic or rationale used by the algorithm to render a recommendation. In other words, users would likely not be able to "independently review the basis for such recommendations that such software presents" and thus would primarily rely on it.[181]

As explained earlier, to counter potential users' skepticism about noninterpretable black-box models, the new research field *explainable AI/ML* is emerging.[182] It is questionable, however, whether explainable AI/ML could help to describe the basis for rendering a recommendation under the FDA's previous interpretation in its CDS Draft Guidance and thus could fall under the medical device exception in FDCA Section 520(o)(1)(E). Explainable AI/ML uses a second explanatory algorithm, but this algorithm only approximates the outputs of the black box.[183] These post-hoc explanations may, in fact, provide a false truth. They give manufacturers and users as much information as if a group of prospective male customers was told that they would not be allowed into an iconic nightclub because they wore sneakers. In reality, however, the bouncer would not let them in because the club was looking for more female customers. Explainable AI/ML provides manufacturers and users with a false sense that they understand the logic or rationale of the black-box model better. But the provided explanation is only an "ersatz understanding" and should be used with caution against all the current enthusiasm for explainability in health care.[184] Hence, explainable AI/ML does not guarantee to give manufacturers and users the *correct* rationale used by the algorithm to render a recommendation. Under the CDS Draft Guidance, it was therefore likely that CDS using explainable AI/ML would *not* fulfill criterion (4) of FDCA Section 520(o)(1)(E) and would thus be considered Device CDS.

In contrast, according to the FDA's previous interpretation in its CDS Draft Guidance, CDS using *interpretable AI/ML* (i.e., white-box models)[185] were likely able to fulfill criterion (4). These models create ex ante transparency, whereby they can generally be understood by humans with reasonable efforts and give clear reasons for how deci-

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181 FDCA § 520(o)(1)(E)(iii), 21 U.S.C. § 360j(o)(1)(E)(iii).

182 *See supra* Section I.A.2.

183 *Id.*

184 *Id.*; Babic et al., *supra* note 47, at 285.

185 For more information on interpretable AI/ML, see *supra* Section I.A.2.

sions are made.[186] According to the CDS Draft Guidance, CDS using interpretable AI/ML for the purpose of "supporting or providing recommendations to a health care professional" could thus fall under the medical device exception in FDCA Section 520(o)(1)(E).[187] In cases where the intended user is a caregiver or patient rather than a health care professional—similar to the current CDS Guidance—however, CDS using interpretable AI/ML were considered Device CDS under the CDS Draft Guidance even if the user could "independently review the basis for such recommendations that such software presents."[188]

Figure 7 below illustrates the likely interpretation of the "independently review the basis" part of criterion (4) according to the FDA's previous CDS Draft Guidance on FDCA Section 520(o)(1)(E) related to different types of CDS using AI/ML and classification as Device CDS/Non-Device CDS.

186 Babic et al., *supra* note 47, at 284, 286.

187 U.S. Food & Drug Admin., *supra* note 140, at 12; FDCA § 520(o)(1)(E)(ii), 21 U.S.C. § 360j(o)(1)(E)(ii).

188 U.S. Food & Drug Admin., *supra* note 140, at 8; FDCA § 520(o)(1)(E)(ii)–(iii), 21 U.S.C. § 360j(o)(1)(E)(ii)-(iii).

FIGURE 7. LIKELY INTERPRETATION OF THE "INDEPENDENTLY REVIEW THE BASIS" PART OF CRITERION (4) OF FDCA SECTION 520(O)(1)(E) ACCORDING TO THE FDA'S PREVIOUS CDS DRAFT GUIDANCE OF SEPTEMBER 27, 2019, RELATED TO DIFFERENT TYPES OF CDS USING AI/ML AND CLASSIFICATION AS DEVICE CDS/NON-DEVICE CDS[189]

Types of CDS	Can the User "Independently Review the Basis"? Part of Criterion (4) of FDCA Section 520(o)(1)(E)	Classification
Black-Box AI/ML	No	Device CDS
Explainable AI/ML	No	Device CDS
Interpretable AI/ML	Yes	Non-Device CDS (Intended User is a Health Care Professional)
		Device CDS (Intended User is a Caregiver or Patient)

In contrast, the new CDS Guidance of September 28, 2022,[190] suggests that the FDA has moved away from its previous thinking in its CDS Draft Guidance and the likely interpretation illustrated above in Figure 7. It appears that the FDA's new interpretation of criterion (4) no longer a priori excludes certain types of AI/ML from being able to fulfill the medical device exception in FDCA Section 520(o)(1)(E). In other words, according to the final CDS Guidance, it seems that all types of AI/ML—i.e., black-box AI/ML, explainable AI/ML, and interpretable AI/ML—can fulfill criterion (4) in principle, and thus potentially can fall under the medical device exception. It is likely that the FDA deliberately dropped the term "rationale" from its new CDS Guidance and replaced it with the word "methods."[191] In particular, as already seen, in order to fulfill criterion (4), the FDA recommends in its new CDS Guidance, among other things, that:

> c) The software or labeling provide a plain language description of the underlying algorithm development and valida-

189 *See* U.S. FOOD & DRUG ADMIN., *supra* note 140.

190 U.S. FOOD & DRUG ADMIN., *supra* note 18.

191 *Id.* at 14.

> tion that forms the basis for the CDS implementation, including:
>
> i. A *summary of the logic or methods* relied upon to provide the recommendations (e.g., meta-analysis of clinical studies, expert panel, statistical modeling, *AI/ML techniques*) . . . .[192]

The FDA explicitly lists "AI/ML techniques" as an example of the "summary of the logic or methods relied upon to provide the recommendations."[193] The FDA does not distinguish between the different types of AI/ML here, suggesting that even black-box AI/ML could potentially meet this FDA recommendation. Unfortunately, the FDA does not clarify further its current view on this point in its final CDS Guidance, which leads to considerable uncertainties for AI/ML manufacturers. In fact, the above quote is the only time the FDA uses the term "AI/ML" in its CDS Guidance.[194] This is surprising considering that more and more CDS currently available or under development in the U.S. market utilize AI/ML.

A recent interview with the new acting director of the FDA's Digital Health Center of Excellence, Brendan O'Leary, in *STAT* also supports the above analysis that the FDA has expanded its interpretation of criterion (4) in its new CDS Guidance and currently thinks that all types of AI/ML can potentially fall under the medical device exception in FDCA Section 520(o)(1)(E).[195] Speaking with *STAT* about the FDA's new CDS Guidance, Brendan O'Leary said that "one thing that's happened with this document through that notice and comment process is that we have gotten to that place where it is possible for certain artificial deep neural networks, artificial intelligence, and machine learning algorithms to meet the statutory criteria for exclusion from the device definition."[196] O'Leary also made a similar statement during an FDA webinar on the new CDS Guidance held on October 18, 2022, emphasizing that even the most complex algorithms, such as deep learning, can fulfill the medical device exception.[197]

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192 *Id.* (emphasis added).

193 *Id.*

194 The FDA also does not use the terms "artificial intelligence" or "machine learning" in its CDS Guidance. The FDA does not clarify this topic in its new Digital Health Policy Navigator. *See Digital Health Policy Navigator*, *supra* note 156; *supra* Section II.B.2.

195 Ross, *A 'Disaster', or a 'Clear Path' Forward*, *supra* note 166.

196 *Id.*

197 Brendan O'Leary, Acting Dir., Digit. Health Ctr. of Excellence, U.S. Food & Drug Admin., Remarks at FDA's Center for Devices and Radiological Health Webinar on Clinical Decision Support Software—Final Guidance 11 (Oct. 18, 2022), https://www.fda.gov/media/162880/download [https://perma.cc/9WHF-HNU4]; Ctr. for Devices & Radiological Health, U.S.

Consequently, this means that even a software function using deep learning that provides a health care professional with a list of treatment order options based on clinical guidelines for the treatment of patients presenting with pneumonia symptoms can be considered a Non-Device CDS according to the FDA's current thinking as long as the developer follows the agency's recommendations on criterion (4) in its CDS Guidance.[198] The FDA's new interpretation is highly questionable and problematic, however, because it is more than unclear, as discussed above, how black-box AI/ML (and even explainable AI/ML) can fulfill the statutory requirement of "enabling such health care professional to independently review the basis for such recommendations that such software presents."[199]

Third, the FDA's new approach is particularly concerning from a risk-based approach. The CDS Draft Guidance contained an entire section called "Application of IMDRF Risk Categorization," in which the FDA clarified its intention to leverage the IMDRF SaMD Framework[200] to apply a risk-based policy to its regulation of Device CDS software functions.[201] This section, however, no longer exists in the FDA's final CDS Guidance. The FDA only mentions briefly in its interpretation of criterion (3) of FDCA Section 520(o)(1)(E) that developers should read the IMDRF document *Software as a Medical Device: Possible Framework for Risk Categorization and Corresponding Considerations* "[f]or additional information regarding risk categorization and considerations that may apply to certain software functions."[202]

Even though the FDA's application of the IMDRF SaMD Framework to its regulation of Device CDS in its CDS Draft Guidance was far from perfect,[203] the FDA at least placed a large focus on risks asso-

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Food & Drug Admin., Webinar Presentation, Final Guidance on Clinical Decision Support Software (Oct. 18, 2022), https://www.fda.gov/media/162345/download [https://perma.cc/Z4XN-J9XT].

198 *See* U.S. Food & Drug Admin., *supra* note 18, at 14, 16.

199 FDCA § 520(o)(1)(E)(iii), 21 U.S.C. § 360j(o)(1)(E)(iii).

200 IMDRF SaMD Working Grp., *"Software as a Medical Device": Possible Framework for Risk Categorization and Corresponding Considerations*, IMDRF Doc. IMDRF/SaMD WG/N12FINAL:2014 (Sept. 18, 2014), https://www.imdrf.org/sites/default/files/docs/imdrf/final/technical/imdrf-tech-140918-samd-framework-risk-categorization-141013.pdf [https://perma.cc/9L4A-JKH4].

201 U.S. Food & Drug Admin., *supra* note 140, at 13–18.

202 U.S. Food & Drug Admin., *supra* note 18, at 13. For the IMDRF Framework, see *supra* note 200.

203 *See* Gerke, *Health AI*, *supra* note 10, at 453–60 (revealing the issues and inconsistencies with applying this approach and criterion (4)).

ciated with CDS software functions. This still appears to be the case for the agency's reinterpretation of criterion (3) of FDCA Section 520(o)(1)(E), but for criterion (4), this is highly questionable, especially considering that the FDA no longer excludes a priori certain types of AI/ML from being able to fulfill the medical device exception. The FDA's job is to ensure, among other things, that medical devices are reasonably safe and effective when placed on the market.[204] The agency's current thinking concerning criterion (4), however, focuses mainly on improved labeling to circumvent regulation rather than safety and effectiveness. Although improved labeling is great and imperative, it alone is not enough to protect patient safety. Labeling must be coupled with a robust regulatory pre- and postmarket framework for CDS software functions.[205]

At the moment, it appears that the FDA puts the burden mainly on health care professionals who should "assess whether the data is representative of their patient population . . . and assess if best practices were followed" and "assess the potential performance and limitations when applied to their patients" and "independently review the basis for the recommendations and apply their judgment when making the final decision."[206] Do we really want certain CDS using black-box AI/ML (and even explainable AI/ML) to be released on the market without being reviewed by the FDA for their safety and effectiveness? In other words, do we want to put the responsibility for assessing those CDS software functions, including the associated liability risks,[207] primarily on health care professionals who are already overburdened in their daily clinical practice? It is also not surprising that during the FDA webinar on the new CDS Guidance one stakeholder asked where health care professionals could obtain the training needed to assess these complex systems.[208] O'Leary simply clarified that the FDA does not regulate the practice of medicine and thus could not answer that question.[209]

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204 *FDA's Role in Regulating Medical Devices*, U.S. Food & Drug Admin. (Aug. 31, 2018), https://www.fda.gov/medical-devices/home-use-devices/fdas-role-regulating-medical-devices [https://perma.cc/RGV3-FSN2].

205 For more information, see *infra* Section III.C.

206 U.S. Food & Drug Admin., *supra* note 18, at 14.

207 *See, e.g.*, W. Nicholson Price II, Sara Gerke & I. Glenn Cohen, *Potential Liability for Physicians Using Artificial Intelligence*, 322 JAMA 1765 (2019).

208 Orest Boyko, Remarks at FDA's Center for Devices and Radiological Health Webinar on Clinical Decision Support Software—Final Guidance, *supra* note 197, at 15.

209 Brendan O'Leary, Acting Dir., Digit. Health Ctr. of Excellence, U.S. Food & Drug Admin., Remarks at FDA's Center for Devices and Radiological Health Webinar on Clinical Decision Support Software—Final Guidance, *supra* note 197, at 16.

The final CDS Guidance is not binding, but it does have a considerable impact in practice because it represents the FDA's current thinking on this topic.[210] AI/ML manufacturers should comply with the CDS Guidance to protect themselves from warning letters or other enforcement actions by the FDA. On the one hand, the many ambiguities in the new CDS Guidance make it even more difficult for AI/ML manufacturers to comply with the agency's recommendations. On the other hand, these uncertainties in the interpretation of the CDS Guidance also open doors for misuse of labeling to bypass regulation. Manufacturers likely have an interest in their AI/ML-based CDS being considered Non-Device CDS and thus not being reviewed by the FDA. To achieve this goal, manufacturers solely need to *intend* that their CDS is "for the purpose of enabling such health care professional to independently review the basis for such recommendations that such software presents."[211] Even if the FDA makes specific suggestions in its CDS Guidance on how the labeling of a Non-Device CDS should look, there is still a lot of leeway for manufacturers that they can use to their advantage.

Thus, although the FDA goes further in its new CDS Guidance than in its previous CDS Draft Guidance and now considers that all types of AI/ML-based CDS can generally fulfill the medical device exception in FDCA Section 520(o)(1)(E), including deep learning, the FDA simultaneously seems to expand its regulatory oversight over certain CDS software functions, such as sepsis tools, with its new interpretation of criteria (2) and (3). In general, the new CDS Guidance does not offer the long-awaited hope of clarity, but rather creates confusion among stakeholders, especially AI/ML manufacturers. This puzzlement of stakeholders could also be seen during the question and answer session of the FDA webinar on the new CDS Guidance.[212] In particular, there is no clear, consistent line apparent as to when a CDS software function is considered a Non-Device CDS or a device software function,[213] and frankly speaking, it seems to be an insurmountable task.

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210 U.S. Food & Drug Admin., *supra* note 18, at 4.

211 *See* FDCA § 520(o)(1)(E)(iii), 21 U.S.C. § 360j(o)(1)(E)(iii). For more information on the term "intended use," see *supra* Section II.B.1; *see also* Evans & Ossorio, *supra* note 10, at 243 (arguing that "[t]he software manufacturer merely needs to *intend* for the software to explain its recommendations transparently").

212 *See* sources cited *supra* note 197.

213 Leo Celi, a biostatistician at Harvard, told STAT+, "They come up with this (guidance) and it's not very clear where the line is between software as a medical device and a non-device."

To be fair, the FDA appears to be trying to fix a mistake Congress made in the first place when enacting the CDS software exception as part of the 21st Century Cures Act.[214] This decision reportedly was likely driven by lobbyists pushing relentlessly for proposals to vitiate regulatory hurdles facing health software.[215] This author has thus already argued in one of her other works in depth that Congress should amend the FDCA by deleting Section 520(o)(1)(E).[216] In other words, all CDS should be considered a priori device software functions.[217] This suggestion would be beneficial in three ways. First, it would eliminate the current blurry line between device software functions and Non-Device CDS and thus would contribute to greater clarity and legal certainty for AI/ML manufacturers.[218] Second, it would effectively prevent products from slipping off the FDA's radar because they are considered Non-Device CDS, although their functionality could bear a risk to patient safety if they were *not* to operate as intended.[219] Third, it could offer a safeguard against automation bias.[220] This suggestion would also entail that the FDA would still be free to exercise enforcement discretion over some device software functions that are lower risk.[221] With the release of the new CDS Guidance, calls are growing for "Congress to investigate what FDA is doing here to override the statute."[222] Consequently, now is the perfect time for Congress to act and use the CDS Guidance as an opportunity to correct its mistake in enacting the CDS software exception as part of the 21st Century Cures Act in the first place and thereby giving the FDA the statutory authority it needs to regulate CDS safely and effectively.

Ross, *In New Guidance, FDA Says AI Tools to Warn of Sepsis Should Be Regulated as Devices*, *supra* note 166.

214 21st Century Cures Act, Pub. L. No. 114–255, § 3060, 130 Stat. 1033, 1130-31 (2016) (codified at 21 U.S.C. §§ 321(h)(1), 360j(o)).

215 *See* Casey Ross & Ike Swetlitz, *IBM to Congress: Watson Will Transform Health Care, So Keep Your Hands off Our Supercomputer*, STAT+ (Oct. 4, 2017), https://www.statnews.com/2017/10/04/ibm-watson-regulation-fda-congress [https://perma.cc/U8TX-P2YS]; *see also* Gerke, *Health AI*, *supra* note 10, at 456–57 (discussing this scandal).

216 Gerke, *Health AI*, *supra* note 10, at 453–63.

217 *Id.* at 460.

218 *Id.* at 461.

219 *Id.* at 457–58, 463; *see* U.S. Food & Drug Admin., Policy for Device Software Functions and Mobile Medical Applications—Guidance for Industry and Food and Drug Administration Staff 2 (2022), https://www.fda.gov/media/80958/download [https://perma.cc/B9MM-6WMZ].

220 Gerke, *Health AI*, *supra* note 10, at 461.

221 *Id.*; *see also infra* Section II.C. (discussing the FDA's enforcement discretion).

222 Thompson, *supra* note 164.

C. *The FDA's Enforcement Discretion*

The FDA clarifies in its *Policy for Device Software Functions and Mobile Medical Applications* that the agency follows a risk-based approach, meaning that the agency focuses its *regulatory oversight* entirely on device software functions "whose functionality could pose a risk to a patient's safety if the device were to not function as intended."[223] An example of an AI/ML-based medical device subject to FDA's regulatory oversight is a software function that calculates dosage for radiation therapy based on patient-specific parameters.[224]

The FDA, however, also clarifies in this policy that the agency intends to exercise *enforcement discretion* if the software function is or may be a medical device under the FDCA and poses a *lower risk* to the public.[225] For instance, the FDA likely does not intend to enforce requirements under the FDCA in the case of an AI/ML-based software function that coaches patients with cardiovascular disease how to obtain optimal nutrition or maintain a healthy weight.[226]

The CDS Draft Guidance of September 27, 2019, still contained a comprehensive section explaining the policy for Device CDS functions and when the FDA intends to practice enforcement discretion.[227] The final CDS Guidance of September 28, 2022, no longer includes this enforcement discretion policy.[228] Instead, the CDS Guidance only states:

> some decision support software functions may be identified in other guidance documents as software functions for which, based on our current understanding of the risks of these software functions, FDA does not intend at this time to enforce compliance with applicable device requirements of the FD&C Act, including, but not limited to, premarket clearance and approval requirements.[229]

Thus, it is even less clear to developers than before when the FDA intends to exercise enforcement discretion over specific Device CDS functions. The FDA's new Digital Health Policy Navigator, however, contains at least some information on the agency's enforcement

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223 U.S. Food & Drug Admin., *supra* note 219, at 2, 11.

224 *See id.* at 13.

225 *Id.* at 2, 13–15.

226 *See id.* at 14.

227 U.S. Food & Drug Admin., *supra* note 140, at 16–18.

228 U.S. Food & Drug Admin., *supra* note 18.

229 *Id.* at 5.

discretion policies.[230] In particular, steps (3) and (7) of the Digital Health Policy Navigator, based on the FDA's General Wellness Guidance[231] and Policy for Device Software Functions and Mobile Medical Applications,[232] may help developers determine whether the FDA intends to exercise enforcement discretion over their device software functions or at least identify the relevant FDA policies. For example, according to the General Wellness Guidance, the FDA intends to exercise enforcement discretion over software functions that remind users to avoid direct sunlight exposure on their skin when the UV index is high to help decrease skin cancer risk.[233]

III. WHAT ARE THE CHALLENGES OF LABELING FOR AI/ML-BASED MEDICAL DEVICES?

Part III examines the challenges of labeling for AI/ML-based medical devices. It first provides an overview of labeling for medical devices, including relevant definitions, information on misbranding, labeling regulations for medical devices in Title 21 of the C.F.R., and IMDRF documents. This knowledge helps to better illustrate why the current labeling requirements are insufficient for AI/ML-based medical devices. Furthermore, this Part shows why AI/ML-based medical devices differ from traditional medical devices such as contact lenses. In particular, Part III argues that there is an urgent need for labeling standards for AI/ML-based medical devices, as such devices are increasingly used by a wide range of users, such as health care professionals and consumers. And many users are *not* sufficiently informed about the device's benefits, risks, and limitations. This even applies in the few cases in which the FDA has so far demanded specific labeling requirements on a case-by-case basis. This lack of knowledge can endanger patient health and lead to unnecessary treatment and biased care. Labeling standards would reduce these risks and help create certainty for manufacturers.

Part III also explores practical challenges and methods for implementing labeling standards for AI/ML-based medical devices. In particular, it suggests that the FDA could implement such new labeling standards either in the form of regulations or nonbinding recommendations through a guidance document. It would also be desirable from

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230 *Digital Health Policy Navigator*, *supra* note 156. For more information on this Navigator, see *supra* Section II.B.2.

231 U.S. FOOD & DRUG ADMIN., *supra* note 115.

232 U.S. FOOD & DRUG ADMIN., *supra* note 219.

233 U.S. FOOD & DRUG ADMIN., *supra* note 115, at 7.

a global harmonization standpoint if the IMDRF additionally dealt with this topic. Moreover, this Part argues that labeling for AI/ML-based medical devices must go hand in hand with other needed regulatory reforms.[234] A new regulatory framework for AI/ML-based medical devices, among other things, needs to ensure that labeling cannot be misused as an excuse to bring poorly designed devices—such as the one in the introductory example that missed Alicia's melanoma because it was trained only on images of people with white skin—to market.

A. Labeling for Medical Devices

Currently, manufacturers of those AI/ML-based medical devices that are the focus of FDA's regulatory oversight[235] need to comply with the labeling requirements for medical devices. This Section first explains the difference between the terms "label" and "labeling." It then briefly examines the issue of misbranding and the importance for manufacturers of knowing and complying with labeling requirements to shield themselves from civil enforcement proceedings and liability claims. Lastly, this Section discusses relevant labeling regulations for medical devices in Title 21 of the C.F.R. and pertinent IMDRF documents for medical device labeling, which demonstrate that there are currently no labeling standards for AI/ML-based medical devices.

1. Difference Between Label and Labeling

There are two essential terms that need to be distinguished from each other, namely "label" and "labeling."[236] FDCA Section 201(k) defines the term "label" as "a display of written, printed, or graphic matter upon the immediate container of any article."[237] An immediate container "does not include package liners."[238] The label usually consists of that portion of the display limited to the medical device itself.[239] Any statement, word, or other information that appears on the label must also appear on the outside wrapper or container (if there is

234 *See* Gerke, *Health AI*, *supra* note 10.

235 *See supra* Part II.

236 *Compare* FDCA § 201(k), 21 U.S.C. § 321(k), *with* FDCA § 201(m), 21 U.S.C. § 321(m).

237 FDCA § 201(k), 21 U.S.C. § 321(k).

238 FDCA § 201(l), 21 U.S.C. § 321(l).

239 U.S. Food & Drug Admin., Labeling: Regulatory Requirements for Medical Devices 2 (1989), https://www.fda.gov/media/74034/download [https://perma.cc/BWN5-GCN5].

one) of its retail package or must be easily readable through the outside wrapper or container.[240]

What does this mean for AI/ML-based medical devices? What kind of label do such devices have? The answer to these questions likely depends on whether the AI/ML-based medical device is SaMD or SiMD. As we have seen,[241] most AI/ML-based medical devices that are currently being developed or available on the U.S. market are SaMD and thus are stand-alone software. Consequently, in the absence of a physical form, SaMD typically has no physical label.[242] The label of an AI/ML-based SaMD is instead available electronically via the software itself or other easily accessible means such as the inclusion of a web address.[243] For example, the electronic label can be shown to clinicians when logging into a cloud-based software platform powered by AI. In contrast, SiMD has software and hardware components.[244] SiMD is integral to a medical device, which typically has a physical label.

FDCA Section 201(m) defines the term "labeling" as "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."[245] The term "accompanying" is understood broadly.[246] It does not only mean the physical association with the product, but it also includes, for example, tags, circulars, pamphlets, posters, brochures, direction sheets, booklets, and instruction books.[247] The term also extends to labeling that is united with the medical device after (delivery for) shipment in interstate commerce.[248] Consequently, labeling is an umbrella term that encompasses all labels as well as informational and descriptive literature, such as instructions for use, accompanying the AI/ML-

240 FDCA § 201(k), 21 U.S.C. § 321(k).

241 *See supra* Section II.A.

242 For example, SaMD could also be delivered on a physical medium, such as a CD or DVD, but in the modern world of technology, these media are "are dying out." For more information on physical media and unique device identification, see *infra* Section III.A.4.

243 *See* IMDRF Good Regul. Rev. Pracs., *Principles of Labelling for Medical Devices and IVD Medical Devices*, IMDRF Doc. IMDRF/GRRP WG/N52FINAL:2019, at 26 (Mar. 21, 2019), http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-190321-pl-md-ivd.pdf [https://perma.cc/6A72-3MT5].

244 For more information on SiMD, see *supra* Section II.A.

245 FDCA § 201(m), 21 U.S.C. § 321(m).

246 U.S. Food & Drug Admin., *supra* note 239, at 2; *Device Labeling*, U.S. Food & Drug Admin. (Oct. 23, 2020) [hereinafter *Device Labeling*], https://www.fda.gov/medical-devices/overview-device-regulation/device-labeling [https://perma.cc/3M77-F22Q].

247 *See* sources cited *supra* note 246.

248 *See id.*

based medical device.[249] Some promotion is also considered labeling.[250]

2. *Misbranding, FDCA Section 502*

FDCA Section 502 lists when a medical device is considered misbranded. For example, a "device shall be deemed to be misbranded . . . [i]f its *labeling is false or misleading in any particular.*"[251] The terms "false or misleading" are interpreted broadly.[252] The labeling is "misleading" if it is deceptive—i.e., it leads or creates a false impression in the reader's mind.[253] A "false impression" can arise not only from literally false statements, but also from statements that create ambiguities, misdirections, and those that fail to include relevant information for the reader and thus act deceptively.[254] Another example of a misbranded medical device that FDCA Section 502 lists is generally a device whose labeling does *not* bear adequate directions for use.[255]

It is important that manufacturers of AI/ML-based medical devices know and adhere to the labeling requirements for medical devices to shield themselves from civil enforcement proceedings for misbranding, including warning letters, recalls, or injunctions.[256] Moreover, manufacturers who create the AI/ML-based medical device's label may also face liability claims under tort law (products liability) as well as criminal penalties in severe cases.[257]

3. *Labeling Regulations for Medical Devices, Title 21 of the C.F.R.*

Six parts of Title 21 of the C.F.R. contain labeling requirements for medical devices, namely:

(1) General Device Labeling (Part 801),

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249 *See* U.S. Food & Drug Admin., *supra* note 239, at 2.

250 *See id.*; *see also Device Labeling*, *supra* note 246 (explaining that labeling often includes advertising). For more information on the distinction between the terms "label," "labeling," and "advertising," and the FDA's outer limits of jurisdiction over "labeling," see, for example, Peter Barton Hutt, Richard A. Merrill, Lewis A. Grossman, Nathan Cortez, Erika Fisher Lietzan & Patricia J. Zettler, Food and Drug Law 225–32 (5th ed. 2022).

251 FDCA § 502(a), 21 U.S.C. § 352(a) (emphasis added).

252 U.S. Food & Drug Admin., *supra* note 239, at 4.

253 *Id.*

254 *Id.* at 4–5.

255 FDCA § 502(f), 21 U.S.C. § 352(f).

256 *Misbranding Defense*, Oberheiden P.C., https://federal-lawyer.com/criminal-law/misbranding-defense [https://perma.cc/Q2RN-CWJC].

257 *Id.*

(2) In Vitro Diagnostic Products for Human Use (Part 809),
(3) Investigational Device Exemptions (Part 812),
(4) Good Manufacturing Practices (Part 820),
(5) Unique Device Identification (Part 830), and
(6) General Electronic Products (Part 1010).[258]

AI-based medical devices are categorized into three classes based on their risk (low, moderate, or high).[259] The regulatory controls increase the higher the classification of the device.[260] Class I devices are subject to general controls, Class II devices are subject to general and special controls (if available), and Class III devices are subject to general controls and premarket approval ("PMA").[261]

The General Device Labeling requirements laid down in 21 C.F.R. Part 801 (*see* Box 1 below) are an example of general controls and thus usually apply to all medical devices, including AI/ML-based ones.

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258 *See* 21 C.F.R §§ 801, 809, 812, 820, 830, 1010; *Device Labeling*, *supra* note 246.

259 *How to Study and Market Your Device*, U.S. Food & Drug Admin. (June 7, 2022), https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/how-study-and-market-your-device [https://perma.cc/SD8C-C7PC].

260 *Id.*

261 FDCA § 513(a)(1), 21 U.S.C. § 360c(a)(1). For more information on regulatory controls, see *Regulatory Controls*, U.S. Food & Drug Admin. (Mar. 27, 2018), https://www.fda.gov/medical-devices/overview-device-regulation/regulatory-controls [https://perma.cc/BC2V-MWR4].

Box 1: Overview of Relevant General Device Labeling Requirements (21 C.F.R. Part 801)

21 C.F.R. Part 801 consists of different Subparts (A–H).

- **Subpart A: General Labeling Provisions**
  - 21 C.F.R. § 801.1—Name and Place of Business
    - The name of business of the manufacturer, distributor, or packer shall be specified conspicuously on the label of a medical device in package form.[262] This also applies to the place of business, which includes the city, state, zip code, and usually the street address.[263]
  - 21 C.F.R. § 801.5—Adequate Directions for Use
    - "[D]irections under which the layman can use a device safely and for the purposes for which it is intended."[264] This includes statements of all conditions, uses, or purposes for which the device is intended, quantity of dose, preparation for use, as well as frequency, duration, time, and route or method of application or administration.[265]
  - 21 C.F.R. § 801.15—Use of Symbols in Labeling
    - This Section contains, among other things, labeling requirements for the use of symbols,[266] which were introduced by the FDA's final rule, "Use of Symbols in Labeling," and became effective on September 13, 2016.[267] The requirements only apply to those symbols utilized to convey information under the authority of or required by the FDCA to appear on the device's label or labeling.[268]

262 21 C.F.R. § 801.1(a).

263 *Id.* § 801.1(d).

264 *Id.* § 801.5.

265 *Id.* § 801.5(a)–(g).

266 *Id.* § 801.15.

267 Use of Symbols in Labeling, 81 Fed. Reg. 38911 (June 15, 2016). For more information on the final rule, see, for example, Antoinette (Tosia) Hazlett & Scott Colburn, *Using Symbols to Convey Information in Medical Device Labeling*, U.S. FOOD & DRUG ADMIN. (July 19, 2018), https://www.fda.gov/news-events/fda-voices/using-symbols-convey-information-medical-device-labeling [https://perma.cc/B6FB-D98B].

268 *Use of Symbols in Labeling: Frequently Asked Questions*, U.S. FOOD & DRUG ADMIN. (Mar. 22, 2018), https://www.fda.gov/medical-devices/device-labeling/use-symbols-labeling-frequently-asked-questions [https://perma.cc/A4A3-VTE8].

- Manufacturers have the choice of whether to use symbols on the label or labeling for a device.[269] If they decide to use symbols, they can use them with adjacent explanatory text or stand-alone symbols.[270] If they choose the latter, they need to make sure, among other things, that the symbols are established in a standard created by a standards development organization ("SDO") and explained in a symbols glossary.[271]

- 21 C.F.R. § 801.18—Standard Date Format
  - In general, dates provided on a medical device label (e.g., date of manufacturer, printed expiration date, etc.) must be presented in a specific format.[272] For example, February 23, 2021, must be presented as 2021-02-23.[273]

- **Subpart B: Unique Device Identification ("UDI") Labeling Requirements**
  - 21 C.F.R. § 801.20—Label to Bear a UDI
    - In general, the label and package of "every medical device shall bear a unique device identifier (UDI) that

269 *See* 21 C.F.R. § 801.15(c)(1)(i).

270 *Id.*

271 *Id.*; U.S. FOOD & DRUG ADMIN., *supra* note 268; *see also* Int'l Org. for Standardization [ISO], *Medical Devices—Symbols to Be Used With Information to be Supplied by the Manufacturer—Part 1: General Requirements*, ISO 15223-1:2021 (identifying requirements for symbols used in device labeling). The term "SDO" is defined as

> an organization that is nationally or internationally recognized and that follows a process for standard development that is transparent, (*i.e.*, open to public scrutiny), where the participation is balanced, where an appeals process is included, where the standard is not in conflict with any statute, regulation, or policy under which FDA operates, and where the standard is national or international in scope.

21 C.F.R. § 801.15(c)(1)(iii)(A). A symbols glossary is "a compiled listing of":

> (1) Each SDO-established symbol used in the labeling for the device;
>
> (2) The title and designation number of the SDO-developed standard containing the symbol;
>
> (3) The title of the symbol and its reference number, if any, in the standard; and
>
> (4) The meaning or explanatory text for the symbol as provided in the FDA recognition or, if FDA has not recognized the standard or portion of the standard in which the symbol is located or the symbol is not used according to the specifications for use of the symbol set forth in FDA's section 514(c) recognition, the explanatory text as provided in the standard.

Id. § 801.15(c)(1)(iii)(B).

272 21 C.F.R. § 801.18(a).

273 *See id.*

meets the requirements of this subpart and part 830 of this chapter."[274]

- A UDI helps to identify medical devices through use and distribution. It usually consists of two components:
  1. A *device identifier* ("DI")—i.e., "a mandatory, fixed portion of a UDI that identifies the specific version or model of a device and the labeler of that device"; and
  2. A *production identifier* ("PI")—i.e., "a conditional, variable portion of a UDI." When included on the device label, it identifies different information (e.g., serial number, expiration date, manufacturing date, lot, or batch).[275]

- 21 C.F.R. § 801.40—Form of a UDI
  - The UDI needs to comply with the technical requirements of 21 C.F.R. § 830.20 and be presented in two forms:
    1. "Easily readable plain-text," and
    2. "Automatic identification and data capture (AIDC) technology."[276]

- 21 C.F.R. § 801.50—Labeling Requirements for Stand-Alone Software
  - Special labeling requirements apply for "[s]tand-alone software that is not distributed in packaged form (e.g., when downloaded from a Web site)."[277] Such software "is deemed to meet the UDI labeling requirements . . . if it complies with the requirements of paragraph (b) of this

274 *Id.* § 801.20(a). Exceptions to the general rule are listed in 21 C.F.R. § 801.20(b). For example, in general, a medical device required to bear a UDI "on its label must also bear a permanent marking providing the UDI on the device itself if the device is intended to be used more than once and intended to be reprocessed before each use." *Id.* § 801.45(a). There is also the possibility to request an alternative to or exception from a UDI. *Id.* § 801.55. If requesting an alternative to a UDI, one would need to show why such alternative "would provide for more accurate, precise, or rapid device identification than the requirements of this subpart or how the alternative would better ensure the safety or effectiveness of the device that would be subject to the alternative." *Id.* § 801.55(a)(4). If one requested an exception from a UDI, one would need to explain why the requirements "are not technologically feasible." *Id.* § 801.55(a)(3).

275 *Id.* § 801.3. The UDI of Class I medical devices is not required to contain a PI; for this exception, see *id.* § 801.30(d). Moreover, the Universal Product Code ("UPC") on the label and packages of Class I medical devices can serve as the UDI. *Id.* § 801.40(d). The UPC is "the product identifier used to identify an item sold at retail in the United States." *Id.* § 801.3.

276 *Id.* § 801.40(a). The term "AIDC" is defined in 21 C.F.R. § 801.3 as "any technology that conveys the unique device identifier or the device identifier of a device in a form that can be entered into an electronic patient record or other computer system via an automated process."

277 *Id.* § 801.50(a).

section and conveys the version number in its production identifier."[278]

- ➢ According to paragraph (b) of this Section, there are two ways in which stand-alone software classified as a medical device must provide its UDI:
  1. "An easily readable plain-text statement displayed whenever the software is started;" or
  2. "An easily readable plain-text statement displayed through a menu command (e.g., an 'About * * * ' command)."[279]

  This requirement applies regardless of whether such software is distributed in packaged form.[280]
- ➢ Stand-alone software may be identified with the same DI when it is distributed in both forms (i.e., packaged and not packaged).[281]

- o Enforcement Discretion
  - ➢ The FDA has faced some policy and technical challenges to ensure the utility and quality of UDI data.[282] The agency recently published its final Guidance for UDI, in which the FDA clarifies, among other things, its compliance policy concerning the Global Unique Device Identification Database ("GUDID") submission requirements (21 C.F.R. § 830.300) for particular Class I medical devices.[283]
- o **Subpart C: Over-the-Counter Device Labeling Requirements**

278 *Id.*

279 *Id.* § 801.50(b).

280 *Id.*

281 *Id.* § 801.50(c).

282 *See* U.S. Food & Drug Admin., Unique Device Identification: Policy Regarding Compliance Dates for Class I and Unclassified Devices, Direct Marking, and Global Unique Device Identification Database Requirements for Certain Devices 4 (2022), https://www.fda.gov/media/110564/download [https://perma.cc/8BLE-97KA].

283 *Id.* at 2, 6–8. According to 21 C.F.R. § 830.300, the labeler must usually submit key information concerning the medical device required to bear a UDI to the GUDID. *See Unique Device Identification System (UDI System)*, U.S. Food & Drug Admin. (July 22, 2022), https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/unique-device-identification-system-udi-system [https://perma.cc/3HPC-W6MA]. GUDID contains basic identifying elements for medical devices, including the DI (but not the PI). *See UDI Basics*, U.S. Food & Drug Admin. (Aug. 17, 2022), https://www.fda.gov/medical-devices/unique-device-identification-system-udi-system/udi-basics [https://perma.cc/X3LL-5Z3C].

- **Subpart D: Exemptions from Adequate Directions for Use**
- 21 C.F.R. § 801.109—Prescription Device
  - A prescription device is "[a] device which, because of any potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use is not safe except under the supervision of a practitioner licensed by law to direct the use of such device."[284]
  - Such a device shall thus be exempt from "adequate directions for use" if certain conditions are fulfilled.[285] For example, the device must be in the possession of a licensed practitioner, or another lawfully engaged person, who prescribes the device's use in the course of her professional practice.[286] The label must bear the "Rx only" or "℞ only" statement and the methods of its use or application.[287] The labeling within or on the package must usually bear information for use, including routes, duration and frequency of administration, methods, effects, and indications, and any contraindications, side effects, relevant hazards, and precautions under which the licensed practitioner can safely use the device for the intended purpose.[288] All labeling bearing information for device use (except cartons and labels) must also bear the issuance date or the date of the newest revision of the labeling.[289]
- **Subpart E: Other Exemptions**
- **Subpart H: Special Requirements for Certain Medical Devices** (e.g., hearing aid devices[290])

Title 21 of the C.F.R. does not contain specific labeling requirements for AI/ML-based medical devices. As shown in Box 1, only with regard to the bearing of a UDI, there are special requirements for stand-alone software that are relevant for AI/ML-based SaMD.[291]

Manufacturers of AI/ML-based medical devices need to ensure that their premarket submission contains all required information, in-

284 *Id.* 21 C.F.R. § 801.109.

285 *Id.*

286 *Id.* § 801.109(a).

287 *Id.* § 801.109(b).

288 *Id.* § 801.109(c).

289 *Id.* § 801.109(e).

290 *Id.* § 801.420.

291 *Id.* § 801.50.

cluding proposed labels and labeling.[292] There are four relevant types of premarket submissions:

> (1) 510(k) Premarket Notification (for Class I or Class II devices, unless they are exempt),
> (2) PMA (for Class III devices),
> (3) Humanitarian Device Exemption (for Class III devices for rare conditions or diseases), and
> (4) De Novo Classification Request (for novel low- to moderate-risk devices).[293]

So far, most AI-based medical devices have been cleared via the 510(k) pathway.[294] Eighteen of 521 AI-based medical devices have received marketing authorization via the De Novo pathway and only three devices via PMA.[295] A 510(k) requires the sponsor to demonstrate that its medical device is "substantially equivalent" to a predicate device (i.e., a legally marketed device) concerning the intended use and technological characteristics or performance testing.[296] In particular, the 510(k) submission must contain, among other information, "[p]roposed labels, labeling, and advertisements sufficient to describe the device, its intended use, and the directions for its use. Where applicable, photographs or engineering drawings should be supplied."[297]

The FDA can require special label requirements through special controls.[298] The agency, however, typically only requests those for Class II medical devices in the De Novo process, a pathway focusing on particular novel medical devices with no predicate device.[299] As seen, however, only a tiny fraction of AI/ML-based medical devices have actually been reviewed via the De Novo process.[300]

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292 S*ee, e.g.*, U.S. Food & Drug Admin., *supra* note 259.

293 *Id*.

294 *See* U.S. Food & Drug Admin., *supra* note 7.

295 *Id.*

296 FDCA § 513(i)(1)(A), 21 U.S.C. § 360c(i)(1)(A); U.S. Food & Drug Admin., *supra* note 259. For more information on the 510(k) process, see, for example, *Premarket Notification 510(k)*, U.S. Food & Drug Admin. (Mar. 13, 2020), https://www.fda.gov/medical-devices/premarket-submissions/premarket-notification-510k [https://perma.cc/9LQ9-9YTN].

297 21 C.F.R. § 807.87(e).

298 U.S. Food & Drug Admin., *supra* note 261.

299 U.S. Food & Drug Admin., *supra* note 259. For more information on the De Novo process, see, for example, Gerke, *Health AI*, *supra* note 10, at 470–71.

300 *See Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices*, *supra* note 7.

4. IMDRF Documents

The IMDRF has published four documents that are particularly relevant for medical device labeling, including labeling for AI/ML-based medical devices:

(1) *Principles of Labelling for Medical Devices and IVD Medical Devices*,[301]
(2) *UDI Guidance*,[302]
(3) *Unique Device Identification system (UDI system) Application Guide*,[303] and
(4) *Software as a Medical Device (SaMD): Clinical Evaluation*.[304]

The purpose of the first IMDRF document, *Principles of Labelling for Medical Devices and IVD Medical Devices*, published on March 21, 2019, is "to provide globally harmonized labelling principles for medical devices, including in vitro diagnostic (IVD) medical devices."[305] The IMDRF document provides guidance on three elements of medical device labeling:

(1) the label,
(2) the instructions for use ("package insert"), and
(3) the information intended for patients.[306]

This document only gives an overview of the general labeling principles, which are globally harmonized; regulatory authorities may demand additional labeling requirements.[307] It does contain, however, three labeling principles for SaMD and medical devices containing software.[308] First, such devices should have a unique identifier (e.g., version, date of build release/issue, revision level) that should usually

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301 IMDRF Good Regul. Rev. Pracs., *supra* note 243.

302 IMDRF UDI Working Grp., *UDI Guidance*, IMDRF Doc. IMDRF/UDI WG/N7FINAL:2013 (Dec. 9, 2013), http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-131209-udi-guidance-140901.pdf [https://perma.cc/PC27-GPVT].

303 IMDRF UDI Working Grp., *Unique Device Identification system (UDI system) Application Guide*, IMDRF Doc. IDMRF/UDI WG/N48FINAL:2019 (Mar. 21, 2019), http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-190321-udi-sag.pdf [https://perma.cc/NTB2-2LH2].

304 Software as Med. Device Working Grp., *Software as a Medical Device (SaMD): Clinical Evaluation*, IMDRF Doc. IMDRF/SaMD WG/N41FINAL:2017 (Sept. 21, 2017), http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-170921-samd-n41-clinical-evaluation_1.pdf [https://perma.cc/9JWU-GQY3].

305 IMDRF Good Regul. Rev. Pracs., *supra* note 243, at 4.

306 *Id.*

307 *See id.* at 5.

308 *See id.* § 8.

be accessible to the intended user.[309] Second, the identifier does not have to be on the outside of the device in cases where software is incorporated into a medical device.[310] Third, the label may be presented electronically for SaMD without a packaging or physical form.[311] Manufacturers need to make sure that users have easy access to the electronic label via the inclusion of a web address, via the software itself, or by other means.[312]

The second relevant IMDRF document is the *UDI Guidance*, which was published on December 9, 2013, to provide a nonbinding framework for those regulatory authorities that aim to develop their UDI Systems.[313] It provides a high-level overview of how a globally harmonized UDI System intended for the identification of medical devices should work.[314]

This IMDRF Guidance also contains nonbinding rules for specific medical device types, including SaMD.[315] For example, it specifies when a SaMD would require a new UDI-DI or UDI-PI.[316] A new UDI-DI would be needed in cases of complex or significant changes affecting the effectiveness and original performance or the intended use or safety of the SaMD.[317] Such changes may include database structures, new or modified algorithms, operating platforms, new channels for interoperability, or new user interfaces.[318] A new UDI-PI would be needed in cases of minor SaMD revisions, such as those associated with usability enhancements (not for safety purposes), bug fixes, operating efficiency, or security patches.[319] The IMDRF *UDI Guidance* also contains UDI placement criteria for SaMD.[320] For example, the UDI applied to the physical medium, such as a DVD or CD, (if any) and its packaging (if existing) must be identical to the

309 *Id.* § 8.1.

310 *Id.* § 8.2.

311 *Id.* § 8.3.

312 *Id*.

313 IMDRF UDI Working Grp., *supra* note 302, at 3.

314 *Id.*

315 *Id.* § 10.

316 *Id.* § 10.6.1.

317 *Id.*

318 *Id.*

319 *Id.*

320 *Id.* § 10.6.2.

UDI given to the system level SaMD.[321] SaMD without a physical medium does not need to carry an AIDC representation of the UDI.[322]

The IMDRF also published on March 21, 2019, the *Unique Device Identification system (UDI system) Application Guide*, which is a supplement to the IMDRF *UDI Guidance*.[323] It aims to provide the specifications and details to ensure consistency for facilitating a harmonized UDI system application.[324] This Guide contains additional information on the UDI placement criteria for SaMD.[325] For example, it clarifies that SaMD without a physical data carrier, such as a CD or DVD, will not be required to carry an AIDC.[326] Appendix I of this Guide also contains examples of UDI assignment for software.[327]

Finally, the IMDRF document *Software as a Medical Device (SaMD): Clinical Evaluation*, published on September 21, 2017, provides a path for regulators to make SaMD clinically meaningful for users.[328] It also contains a few considerations on labeling for SaMD.[329] First, this document recommends that manufacturers properly review the collected postmarket information of their SaMD to assess whether any labeling changes are needed concerning warnings, contraindications, precautions, or instructions for use.[330] Second, it points out that the labeling of the SaMD should identify, in end-user-friendly language, device limitations relevant to the interpretation of its output and its clinical performance.[331]

In summary, the IMDRF documents do not contain specific labeling standards for AI/ML-based medical devices. They do, however, contain some information on SaMD that is relevant for AI/ML-based SaMD. Such information, however, is mainly limited to topics such as the format of labeling, labeling changes, and the UDI assignment and placement criteria. General information on the content or type of information that should be included in the labeling for SaMD is almost entirely missing.

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321 *Id.*

322 *Id.* For more information on AIDC, see Box 1 *supra* Section III.A.3.; *see also supra* note 276.

323 IMDRF UDI Working Grp., *supra* note 303, at 5.

324 *Id.*

325 *Id.* at 34–35.

326 *Id.* at 35.

327 *Id.* at 58–68.

328 Software as Med. Device Working Grp., *supra* note 304, at 4.

329 *Id.* at 20.

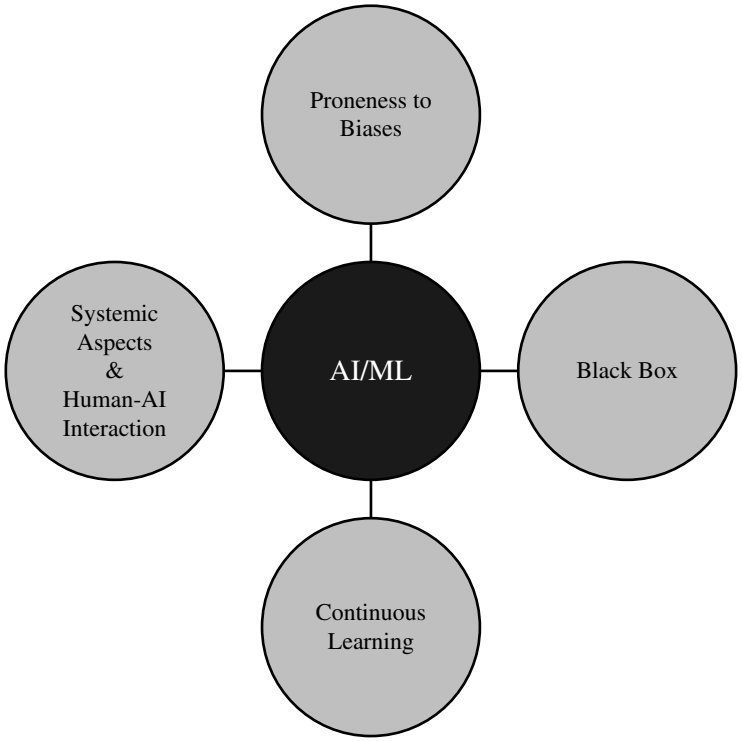
330 *Id.*

331 *Id.*

B. Why Do AI/ML-Based Medical Devices Differ from Traditional Medical Devices?

There are several reasons why AI/ML-based medical devices differ from traditional medical devices, such as contact lenses. Figure 8 illustrates four of them, which will also be discussed below.

FIGURE 8. CHALLENGES OF AI/ML-BASED MEDICAL DEVICES



1. Proneness to Biases

In contrast to typical medical devices, such as surgical gloves or crutches, many, if not all, AI/ML-based medical devices are prone to biases. The term "bias" is often used differently in various fields.[332] For example, according to a technical definition, bias means "systematic difference in treatment of certain objects, people, or groups in comparison to others."[333] In contrast, in law, the term is frequently

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332 A.I. Med. Devices Working Grp., *Machine Learning-Enabled Medical Devices: Key Terms and Definitions*, IMDRF Doc. IMDRF/AIMD WG/N67, at 10 (May 6, 2022), https://www.imdrf.org/sites/default/files/2022-05/IMDRF%20AIMD%20WG%20Final%20Document%20N67.pdf [https://perma.cc/Z8YV-5XNJ].

333 Int'l Org. for Standardization, *Information Technology—Artificial Intelligence (AI)—Bias in AI Systems and AI Aided Decision Making*, ISO/IEC TR 24027:2021. The term "treat-

associated with the meaning "unfair or unfairly prejudiced/partial."[334] There are different types of biases, including the following four:

(1) bias in the training data,
(2) label choice bias,
(3) contextual bias, and
(4) unconscious bias.

First, in general, algorithms should learn from diverse data sets to ensure that they will perform well for all patient communities, including racial and ethnic minorities, thus promoting equity and inclusion. According to the motto "garbage in, garbage out," the use of training data sets that lack diversity, such as in terms of gender, race/ethnicity, (dis)ability, etc., may result in biased AI/ML-based medical devices.[335] This, in turn, can lead to two undesirable scenarios. In the first scenario, the most vulnerable patient communities in our society, in particular, would be excluded from benefiting from such innovative technologies in their care from the outset. In the second scenario, AI/ML-based medical devices would be used in the care of patients who were underrepresented in the training data set, and the devices' recommendations or decisions could put their health at risk. As the introductory example shows, an AI/ML dermatology tool designed to diagnose specific skin diseases, including cancer, will be biased when predominantly trained on white skin images. Such a tool would likely make improper recommendations for people of color. For instance, if the AI/ML dermatology tool missed serious skin cancer in a Black patient, as was the case with Alicia's melanoma, late cancer treatment would potentially have severe consequences for that patient, including death. Thus, it is essential that manufacturers have access to and utilize diverse training data sets that were developed in compliance with ethical principles.[336] Regulators like the FDA should require AI/ML manufacturers to disclose detailed information on the used data sets, such as gender and race/ethnicity breakdowns. In general, they should

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ment" is defined in ISO/IEC TR 24027 broadly as "any kind of action, including perception, observation, representation, prediction or decision." *Id.* § 3.2.2.

334 A.I. Med. Devices Working Grp., *supra* note 332, at 10.

335 *See* Sascha Eder, *How Can We Eliminate Bias in Our Algorithms*?, FORBES (June 27, 2018, 8:00 AM), https://www.forbes.com/sites/theyec/2018/06/27/how-can-we-eliminate-bias-in-our-algorithms/?sh=cba7198337eb [https://perma.cc/93KA-3AJR].

336 For more information on health AI ethics and ethical principles, see, for example, Gali Katznelson & Sara Gerke, *The Need for Health AI Ethics in Medical School Education*, 26 ADVANCES HEALTH SCI. EDUC. 1447 (2021); Craig M. Klugman & Sara Gerke, *Rise of the Bioethics AI: Curse or Blessing?*, 22 AM. J. BIOETHICS 35 (2022). For the FAIR (Findable, Accessible, Interoperable, Reusable) principles, see Mark D. Wilkinson et al., Comment, *The FAIR Guiding Principles for Scientific Data Management and Stewardship*, 3 SCI. DATA 160018 (2016).

focus on promoting diversity, equity, and inclusion by ensuring that AI/ML-based medical devices that receive marketing authorization benefit everyone in our society, especially the most vulnerable ones.

Second, another major concern is label choice bias. A famous example is a widely used algorithm in the U.S. to guide health decisions.[337] Ziad Obermeyer, Brian Powers, Christine Vogeli, and Sendhil Mullainathan found that the algorithm exhibited a significant racial bias against Black patients.[338] The issue with this algorithm was that it predicted health care costs instead of illness.[339] As a consequence, because fewer Black patients have access to health care, the algorithm falsely assumed that white patients are much sicker than similarly ill Black patients.[340] The outcome was that many Black patients were denied extra care despite their needs.[341] Unfortunately, this is not an isolated incident. Biased algorithms are used throughout the health care system, guiding not only operational workflows and policy decisions but also clinical care.[342] Thus, it is important that C-suite leaders, technical teams working in health care, policymakers, and regulators critically define, measure, and reduce racial bias in live algorithms.[343] Obermeyer and others have recently published an algorithmic bias playbook that describes four steps—(1) Inventory Algorithms, (2) Screen for Bias, (3) Retrain Biased Algorithms, and (4) Prevent Future Bias—that can be taken to promote this goal.[344]

Third, there is the risk of contextual bias.[345] An example is an AI/ML-based medical device that is deployed in a specialist clinic in the U.S. and then used at a rural hospital in Africa.[346] This transfer from one context to another may potentially harm patients because the recommendations made by the AI/ML-based medical device—even if the device is trained on a diverse data set—may not be suitable for a rural

337 *See* Ziad Obermeyer, Brian Powers, Christine Vogeli & Sendhil Mullainathan, *Dissecting Racial Bias in an Algorithm Used to Manage the Health of Populations*, 366 SCIENCE 447, 447 (2019).

338 *Id.*

339 *Id.*

340 *Id.*

341 *Id.*

342 ZIAD OBERMEYER, REBECCA NISSAN, MICHAEL STERN, STEPHANIE EANEFF, EMILY JOY BEMBENECK & SENDHIL MULLAINATHAN, CHI. BOOTH CTR. FOR APPLIED A.I., ALGORITHMIC BIAS PLAYBOOK 1 (June 2021), https://www.chicagobooth.edu/-/media/project/chicago-booth/centers/caai/docs/algorithmic-bias-playbook-june-2021.pdf [https://perma.cc/4CCQ-AYPH].

343 *Id.*

344 *Id.* at 4.

345 Price, *Medical AI and Contextual Bias*, *supra* note 10, at 67–68.

346 *See* Minssen et al., *supra* note 10, at 17.

hospital in Africa. For instance, the AI/ML-based medical device may recommend a high-risk surgery that requires a team of experts, a resource that is likely not available in the rural hospital, and therefore, in the worst-case scenario, may kill the patient when performed.[347] Consequently, it will be essential to incentivize stakeholders and policymakers to build an infrastructure in low- and middle-income countries that promotes both data collection and use in health care.[348] AI manufacturers also need to be incentivized to develop AI/ML-based medical devices that are specifically designed to address respective countries' needs with the regional context in mind.[349] The importance of context has also been demonstrated in a recent study that showed a significant drop-off in model performance when a model was evaluated at only one U.S. clinical site and then evaluated at another location.[350] This issue again highlights the imperative need for algorithms to perform well across representative patient populations and to conduct assessments at multiple clinical sites.

Lastly, developing reasonably safe and effective AI/ML-based medical devices is even more complicated because there are unconscious or hidden biases. For instance, computer scientists may unconsciously introduce bias through their engineering decisions, such as during feature engineering or when selecting the algorithm.[351] Consequently, bias is a real and significant risk associated with AI/ML-based medical devices which may harm patients and generally is not present in traditional medical devices such as contact lenses.

2. Black-Box AI/ML Models

Another complexity is that many high-performing AI/ML-based medical devices are opaque (so-called "black boxes").[352] An example is the cloud-based software RhythmAnalytics, designed to detect over fifteen cardiac arrhythmia types with the use of deep learning.[353] Using black-box models instead of white-box models (interpretable AI/

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347 *Id.*

348 *See, e.g.*, Oluyemi E. Adetoyi & Olayanju A. Raji, *Electronic Health Record Design for Inclusion in Sub-Saharan Africa Medical Record Informatics*, 7 SCI. AFR., no. e00304, 2020, at 1.

349 *Id.*

350 Eric Wu, Kevin Wu, Roxana Denshjou, David Ouyang, Daniel E. Ho & James Zou, *How Medical AI Devices Are Evaluated: Limitations and Recommendations from an Analysis of FDA Approvals*, 27 NATURE MED. 582, 583 (2021).

351 A.I. Med. Devices Working Grp., *supra* note 332, at 10.

352 For more information on black boxes, see *supra* Sections I.A.2., II.B.3.

353 *See Biofourmis' RhythmAnalytics™ Platform Receives FDA Clearance for AI-Based Automated Interpretation of Cardiac Arrhythmias*, *supra* note 50.

ML)[354] can be especially beneficial to health care in cases where accuracy is critical. At the same time, black-box AI/ML models also raise considerable concerns among users because it is very difficult, or even impossible, for humans to understand them.[355] Humans are usually in the dark concerning the logic or rationale used by the algorithm to render its recommendation or decision.[356]

Black boxes are not unique to AI/ML. They sometimes exist in drugs when their mechanisms of action are unknown, such as in the case of acetaminophen.[357] Black boxes typically do not exist in traditional medical devices such as syringes, tongue depressors, and catheters, but they are prevalent in AI/ML-based medical devices.[358]

As analyzed earlier, explainable AI/ML is unlikely to help address the black box's criticisms and concerns.[359] Explainable AI/ML only provides an ersatz understanding and does not ensure that users are given the correct rationale used by the algorithm to render a recommendation or decision.[360]

User trust in black-box AI/ML models will be essential to promote their uptake in health care. Fostering this trust requires, among other things, that black-box AI/ML models be shown to be reasonably safe and effective in representative populations before their launch on the market. For example, clinical trials—unfortunately still rare in the health AI/ML field—are one tool that could be used more often to achieve this goal.[361] As seen in the pharmaceutical field, even though the mechanisms of action for some drugs like acetaminophen are still unclear, patients use such drugs all the time because they have been proven to be reasonably safe and effective.[362]

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354 For more information on interpretable AI/ML, see *supra* Sections I.A.2., II.B.3.

355 *See supra* Section I.A.2.

356 *See supra* Section II.B.3.

357 *See* Gerke, *Health AI*, *supra* note 10, at 493; K. Toussaint, X.C. Yang, M.A. Zielinski, K.L. Reigle, S.D. Sacavage, S. Nagar & R.B. Raffa, *What Do We (Not) Know About How Paracetamol (Acetaminophen) Works?*, 35 J. CLINICAL PHARMACY & THERAPEUTICS 617, 617 (2010); Grzegorz W. Przybyła, Konrad A. Szychowski & Jan Gmiñski, *Paracetamol—An Old Drug with New Mechanisms of Action*, 48 CLINICAL & EXPERIMENTAL PHARMACOLOGY & PHYSIOLOGY 3 (2021).

358 *See* Benjamens et al., *supra* note 7, at 3–4.

359 *See supra* Section II.B.3. For more information on explainable AI/ML, see also *supra* Section I.A.2.

360 *See supra* Section II.B.3.

361 Gerke, *Health AI*, *supra* note 10, at 491–96.

362 *Id.* at 493.

3. Ability to Continuously Learn

AI/ML-based medical devices currently marketed in the U.S. typically include so-called "locked" algorithms.[363] The FDA defines a "locked" algorithm as "an algorithm that provides the same result each time the same input is applied to it and does not change with use," such as decision trees, complex classifiers, or static look-up tables.[364] Most AI/ML algorithms, however, have the ability to continuously learn from real-world experience,[365] which makes them completely different from typical medical devices. In particular, such "adaptive" algorithms may provide different outputs compared to the ones initially cleared or approved for a given set of inputs.[366] The term "continuous learning" can also be defined as "[t]raining that leads to change of an [AI/ML-based medical device] with each exposure to data that takes place on an ongoing basis during the operation phase of the [AI/ML-based medical device] life cycle."[367]

Currently, manufacturers must submit a new 510(k) premarket notification in cases where the legally marketed device "is about to be significantly changed or modified in design, components, method of manufacture, or intended use."[368] Under 21 C.F.R. § 807.81(a)(3), significant changes or modifications that require a 510(k) premarket notification constitute:

> (i) A change or modification in the device that could significantly affect the safety or effectiveness of the device, e.g., a significant change or modification in design, material, chemical composition, energy source, or manufacturing process.
> (ii) A major change or modification in the intended use of the device.[369]

For example, another 510(k) is required when the modification introduces a significant change to the algorithm of a legally marketed AI/ML-based medical device.[370] With a new 510(k) also comes the

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363 U.S. Food & Drug Admin., *supra* note 55, at 3.

364 *Id.* at 3 n.7.

365 *Id*. at 3.

366 *Id.*

367 A.I. Med. Devices Working Grp., *supra* note 332, at 11.

368 21 C.F.R. § 807.81(a)(3).

369 *Id.*; *see also* U.S. Food & Drug Admin., Deciding When to Submit a 510(k) for a Software Change to an Existing Device—Guidance for Industry and Food and Drug Administration Staff 2 (2017), https://www.fda.gov/media/99785/download [https://perma.cc/9M4T-5XEM].

370 *See* U.S. Food & Drug Admin., *supra* note 55, at 3.

need for manufacturers to adjust their labeling.[371] Because it is time-consuming and expensive to undergo another or multiple premarket reviews, however, manufacturers may *not* carry out significant updates, and this failure to do so can jeopardize patient safety.[372]

To address this update problem, the FDA is currently exploring a new total product lifecycle ("TPLC") approach for modifications to AI/ML-based SaMD that aims to allow such devices to continuously learn and optimize their performance in real-time while providing effective safeguards.[373] In particular, during the initial premarket review of their device, manufacturers could voluntarily submit a modification plan (a so-called "predetermined change control plan"), composed of the anticipated modification types and the methodology being used to implement such modifications.[374] Such a new approach would require manufacturers to ensure accurate labeling changes.[375] In the FDA's new action plan on AI/ML-based SaMD, the agency announced that the cardiac ultrasound software device Caption Guidance, which received marketing authorization via the De Novo pathway on February 7, 2020, is pioneering because the manufacturer uses a predetermined change control plan for future changes.[376] The issue with using a predetermined change control plan, however, is that manufacturers often do not know in advance what updates are needed.[377] Thus, the FDA should focus particularly on implementing a continuous risk monitoring approach to ensure that AI/ML-based SaMD with adaptive algorithms remain safe and effective while continuously learning and adapting to new conditions.[378]

4. Systemic Aspects and Human-AI Interaction

AI/ML-based medical devices come with different types of intelligence (assisted, augmented, or autonomous) and different levels of

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371 For more information, see *supra* Section III.A.3.

372 *See* Babic et al., *supra* note 10, at 1202; Gerke, *Health AI*, *supra* note 10, at 496.

373 U.S. Food & Drug Admin., *supra* note 55, at 3.

374 *Id.* at 10. For more information on the TPLC approach and predetermined change control plan, see Gerke, *Health AI*, *supra* note 10, at 498–500.

375 *See* U.S. Food & Drug Admin., *supra* note 55, at 14. For more information on the need for a "dynamic" label, see also *infra* Section IV.A.

376 U.S. Food & Drug Admin., Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) Action Plan 2 (Jan. 2021), https://www.fda.gov/media/145022/download [https://perma.cc/2ZQS-YLNF]. For more information on Caption Guidance, see *supra* Section I.B.1.

377 *See* Babic et al., *supra* note 10, at 1204; Gerke, *Health AI*, *supra* note 10, at 500–01.

378 *See* Babic et al., *supra* note 10, at 1204; Gerke, *Health AI*, *supra* note 10, at 500–03.

human involvement (none, little, some, or high).[379] For example, they can be CDS software, make autonomous decisions, such as IDx-DR for detecting more than mild diabetic retinopathy in diabetic adult patients, and may even begin to interact with health care professionals dynamically in the future.[380]

Human factors and how AI/ML-based medical devices interact with their environment may increase variance.[381] Therefore, AI/ML-based medical devices can perform differently in an actual practice setting versus the artificial testing environment, where there is less variance.[382] Thus, once marketed, the performance of many AI/ML-based medical devices is likely less predictable than that of typical medical devices. Consequently, regulators like the FDA need to adopt a system view considering the environment in which these devices are used.[383]

C. The Urgent Need for Labeling Standards for AI/ML-Based Medical Devices

This Article argues that there is an urgent need for labeling standards for AI/ML-based medical devices. As seen above, AI/ML-based medical devices differ in many ways from traditional medical devices such as crutches or contact lenses.[384] Still, Title 21 of the C.F.R. does not contain specific labeling requirements for AI/ML-based medical devices.[385]

There are several further arguments pertaining to why labeling for AI/ML-based medical devices is important, as represented in Figure 9 and discussed below.

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379 *See supra* Section I.A.2.

380 *See id.*; Gerke et al., *The Need for a System View*, *supra* note 10, at 2.

381 Gerke et al., *The Need for a System View*, *supra* note 10, at 2.

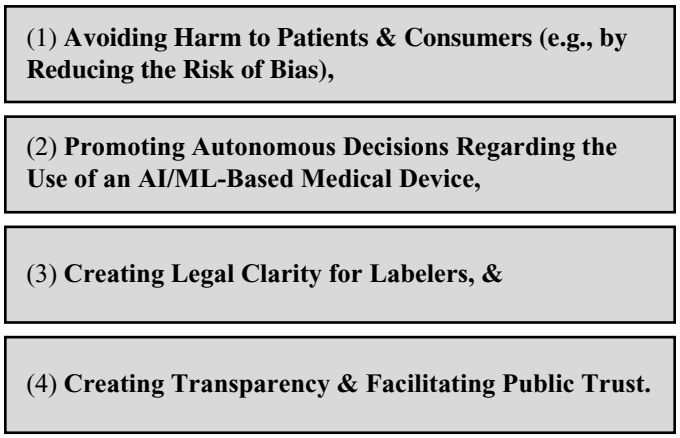
382 *Id.*

383 For more information on the system view, see *id.* at 1 and Gerke, *Health AI*, *supra* note 10, at 503–10. For example, the FDA could require more often that manufacturers conduct rigorous human factors testing to show that intended users can use their AI/ML-based medical device correctly based exclusively on reading its label. *See infra* Section IV.B.

384 *See supra* Section III.B.

385 *See supra* Section III.A.

FIGURE 9. BENEFITS OF LABELING FOR AI/ML-BASED MEDICAL DEVICE



First, labeling is helpful as it can ensure that users know how to use AI/ML-based medical devices correctly, thus avoiding harm to patients and consumers. It can contribute to the safety of patients and consumers by preventing device-related user errors that may result in severe injury or even death. Labeling can also help reduce the risk of bias. For example, suppose the labeling provides physicians with demographic information on the training data set. In that case, they could better assess whether the AI/ML-based medical device should be used in a specific patient's care, thus reducing bias risk and preventing harm.

A recent study showed that out of a total of 161 legally marketed AI-based medical devices in the U.S., only seven provided publicly available race/ethnicity information, and only thirteen disclosed gender information.[386] In addition, most manufacturers did not report information on the amount of data used to validate the device's performance or the geographic breakdown.[387] Thus, this study clearly confirms that the current labeling requirements for medical devices in Title 21 of the C.F.R. are insufficient. Without labeling standards for AI/ML-based medical devices, many users are left in the dark about important information, such as gender, race/ethnicity, and geographic breakdowns of the data sets used. Without this information, patients' health may be jeopardized by unnecessary treatment or biased care.[388]

386 Ross, *supra* note 7; Casey Ross, *Explore STAT's Database of FDA-Cleared AI Tools*, STAT+ (Feb. 3, 2021), https://www.statnews.com/2021/02/03/fda-artificial-intelligence-clearance-products [https://perma.cc/65X6-DFC3].

387 *See* sources cited *supra* note 386.

388 *Id*.

Even in the few cases in which the FDA has required special labeling requirements through special controls,[389] those are not enough. As mentioned earlier,[390] the FDA typically requests special controls for Class II medical devices in the De Novo process, but only eighteen marketed AI/ML-based medical devices out of 521 have undergone such a process.[391] Moreover, the majority of AI/ML-based medical devices that went through the De Novo process did *not* report gender and race/ethnicity breakdowns.[392] An example of such a device is BrainScope, which is used by emergency physicians to assess patients with head injuries for concussions.[393] The FDA required the following special labeling requirements through special controls:

> The labeling and training information must include:
>
> a. A warning that the device is not to be used as a stand-alone diagnostic.
> b. A detailed summary of the clinical performance testing, including any adverse events and complications.
> c. The intended use population and the intended use environment.
> d. Any instructions technicians should convey to patients regarding the collection of EEG data.
> e. Information allowing clinicians to gauge clinical risk associated with integrating the EEG interpretive assessment aid into their diagnostic pathway.
> f. Information allowing clinicians to understand how to integrate the device output into their diagnostic pathway when the device is unable to provide a classification or final result.[394]

These requirements are something, but it unfortunately appears that BrainScope did *not* provide gender and race/ethnicity breakdowns and there is no public data available on such information.[395]

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389 For more information on special labeling requirements through special controls, see *supra* Section III.A.3.

390 *See supra* Section III.A.3.

391 *Id.*

392 *See* Ross, *supra* note 386 (download XLS file; then filter for "De Novo" under "Approval Type") (showing data of fourteen AI/ML-based medical devices that went through the De Novo process).

393 BRAINSCOPE, *supra* note 65.

394 Letter from Jonette Foy, Deputy Dir. Eng'g & Sci. Rev., Off. Device Eval., Ctr. Devices & Radiological Health, U.S. Food & Drug Admin., to Michael Singer, President & CEO, BrainScope Co., Inc. 5 (Nov. 17, 2014), https://www.accessdata.fda.gov/cdrh_docs/pdf14/DEN140025.pdf [https://perma.cc/QN63-YML5].

395 *See* Ross, *supra* note 386 (download XLS file; then filter for "Ahead 100" under "Product").

Consequently, the FDA's case-by-case approach for particular AI/ML-based medical devices through special controls is also insufficient. Even if the FDA were to always require such a disclosure through the De Novo special controls, almost all AI/ML-based medical devices would be cleared through the 510(k) process and thus usually only would have to comply with the labeling requirements in Title 21 of the C.F.R.[396]

This brings us to the second benefit of labeling for AI/ML-based medical devices: because adequate labeling can inform users, among other things, about the benefits, potential risks, and limitations of the AI/ML-based medical device, it can promote autonomous decisions on whether to use the device. For instance, physicians need to know what the AI/ML-based medical device does, for whom its use is intended, and when and how to use it. In the case of DTC medical AI/ML apps, consumers should receive this information in a user-friendly manner (e.g., in plain language). This is crucial for them to properly understand the device's benefits, risks, and limitations, including when to seek medical care.[397]

Third, standards of labeling for AI/ML-based medical devices also can create legal clarity for labelers (i.e., in most cases, manufacturers). In particular, these standards will help avoid misbranding, such as misleading or false labeling, thereby protecting manufacturers from FDA enforcement actions.[398]

Fourth, proper labeling creates transparency to users and thus can help facilitate public trust in new digital health technology. In its action plan on AI/ML-based SaMD, the FDA announced it would organize a public workshop on how labeling fosters transparency to users.[399] In October 2021, the agency fulfilled this plan and virtually discussed how transparency through labeling might improve the safety and effectiveness of AI/ML-based medical devices.[400] This workshop

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396 For more information on Title 21 of the C.F.R., see *supra* Section III.A.3.

397 For more information on DTC medical AI/ML apps, see *supra* Section II.B.1.

398 *See* FDCA § 502, 21 U.S.C. § 352. For more information on misbranding, see *supra* Section III.A.2.

399 U.S. Food & Drug Admin., *supra* note 376, at 4–5.

400 *Virtual Public Workshop—Transparency of Artificial Intelligence/Machine Learning-Enabled Medical Devices*, U.S. Food & Drug Admin. (Nov. 26, 2021), https://www.fda.gov/medical-devices/workshops-conferences-medical-devices/virtual-public-workshop-transparency-artificial-intelligencemachine-learning-enabled-medical-devices [https://perma.cc/4B7D-QYA7]; U.S. Food & Drug Admin., Transcript of Virtual Public Workshop—Transparency of Artificial Intelligence/Machine Learning-Enabled Medical Devices (Oct. 14, 2021), https://www.fda.gov/media/154423/download [https://perma.cc/G9MH-V39B].

was a welcomed attempt to gather stakeholder input and promote public trust in AI/ML-based medical devices.

In summary, labeling standards are urgently needed because the current labeling requirements for medical devices and the FDA's case-by-case approach for a few AI/ML-based medical devices are insufficient. Labeling for AI/ML-based medical devices is a valuable tool to avoid harm to patients and consumers, such as reducing the risk of bias in AI/ML-based medical devices. It fosters autonomous decisions regarding the use of AI/ML-based medical devices, creates transparency, and enhances public trust in innovative technology. Labeling standards for AI/ML-based medical devices will also create legal clarity for labelers.

D. Practical Challenges and Methods for Implementation

This Article argues that criticism such as "why do you care; no one reads labeling anyway" should be rejected.[401] Even if it is true that not a single person—which is doubtful—reads drug or device labeling, one still has the choice—i.e., to read or not read the label, instructions for use, etc. From a libertarian perspective, especially considering the new challenges raised by AI/ML-based medical devices, it is important to make users at least aware of the peculiarities, especially the potential risks and limitations of the device. What matters is that if users want to read this information, they can. Without labeling standards, some of the information about AI/ML-based medical devices would otherwise not be publicly available or would only be available to users with considerable effort and difficulty.

Nicholson Price expresses some skepticism about the usefulness of medical AI labeling, but such skepticism is limited to solving contextual bias issues and deterring off-label uses.[402] Labeling is not the panacea that solves all issues raised by AI/ML-based medical devices. In particular, labeling must be coupled with other needed regulatory reforms for AI/ML-based medical devices.[403] A new regulatory frame-

401 *See, e.g.*, Dr. Jack Resneck, Remarks, *in* U.S. Food & Drug Admin., *supra* note 400, at 49 (for AI/ML-based medical devices); Mari Serebrov, *If No One Reads It, What's the Purpose of a Drug Label?*, BioWorld™ (Mar. 29, 2018), https://www.bioworld.com/blogs/1-bioworld-perspectives/post/247-if-no-one-reads-it-what-s-the-purpose-of-a-drug-label- [https://perma.cc/Z2J7-GA3B].

402 *See* Price, *Medical AI and Contextual Bias*, *supra* note 10, at 104, 106–07.

403 This author has written extensively about the need for a new regulatory framework for AI/ML-based medical devices. She suggests what such a framework could look like to better ensure that these devices are reasonably safe and effective when brought to the U.S. market and stay so throughout their life cycle. *See* Gerke, *Health AI*, *supra* note 10; *see also* Kristin M.

work for AI/ML-based medical devices, among other things, needs to ensure that devices, like the AI dermatology tool that failed to detect Alicia's melanoma because it was primarily trained on images of people with white skin, do not receive market authorization in the first place. Labeling has limits and must not be used as an excuse to bring a poorly designed device into the market.

Nonetheless, labeling is a necessary piece of the puzzle for successfully implementing AI/ML in health care. As noted above, there are several arguments in favor of labeling, including patient and consumer safety/prevention of harm, promoting autonomous decisions, creating legal clarity and transparency, and facilitating trust.[404] It also serves as an obvious tool for regulators like the FDA to leverage risk mitigation. Moreover, the design of the label is crucial and may influence whether users read the label and thus may prevent at least some off-label uses. Even if labeling failed to solve the contextual bias issues in their entirety, as correctly pointed out by Price—and AI developers need to be better incentivized to build AI/ML tools for low- and middle-income countries—labeling could inform and motivate some developers to show cross-context efficacy.[405]

Regulators, like the FDA, should take up the challenge—with the help of stakeholders—and develop labeling standards as soon as possible, even if such standards would certainly need to be updated on a regular basis as new information about AI/ML in health care emerges. More than 520 AI/ML-based medical devices have already been cleared or approved by the FDA and many more devices are being developed.[406] Without labeling standards for AI/ML-based medical devices, there is a high likelihood that such devices are deployed without providing users with the full package of information they should have to make informed decisions. This lack of knowledge can harm patients and consumers. Moreover, those standards will give labelers, especially AI/ML manufacturers, certainty about what will be expected from them.

Kostick-Quenet, I. Glenn Cohen, Sara Gerke, Bernard Lo, James Antaki, Faezah Movahedi, Hasna Njah, Lauren Schoen, Jerry E. Estep & J.S. Blumenthal-Barby, *Mitigating Racial Bias in Machine Learning*, 50 J. L. MED. & ETHICS 92, 98 (2022) (arguing for a robust regulatory framework to AI/ML).

404 *See supra* Section III.C.

405 *See* Price, *Medical AI and Contextual Bias*, *supra* note 10, at 107 (admitting that "[l]abeling may still have *some* benefit"). For more information on the contextual bias issues and the need for incentives, see *supra* Section III.B.1.

406 *Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices*, *supra* note 7.

Consequently, it will be essential for the FDA to develop adequate labeling standards for AI/ML-based medical devices that are easily accessible to users and designed in a manner that helps promote the benefits mentioned above. In particular, different audiences (e.g., health professionals, patients, consumers) need to be considered when developing labeling standards for AI/ML-based medical devices.

There are two options for the FDA to execute the new labeling standards. The first option is that the agency could implement the new standards in the form of regulations, such as through an amendment to Title 21 of the C.F.R., after receiving public feedback. The second option is that the FDA could publish nonbinding recommendations as a guidance document. On the one hand, regulations have the advantage of being published in the Federal Register and are legally binding. On the other hand, releasing guidance documents is less time-consuming than regulations, and guidance documents are more flexible; they can be changed easily and can be adapted to new technological developments. Regardless of which option the FDA ultimately chooses, it is crucial that the agency develop and implement specific labeling standards for AI/ML-based medical devices as quickly as possible to prevent harm to patients and consumers, promote autonomous decisions, create clarity and transparency, and promote trust. The FDA's virtual public workshop on transparency of AI/ML-based medical devices, focusing on labeling,[407] is certainly a step in the right direction, but more needs to be done promptly.

In addition to developing national labeling standards, from a global harmonization perspective, it would be desirable for the IMDRF to become an active participant on this topic. For example, the IMDRF could either update its *Principles of Labelling for Medical Devices and IVD Medical Devices*[408] to include specific standards for AI/ML-based medical devices or develop a separate guidance document.

IV. SUGGESTIONS

Part IV contains suggestions on how to move forward in developing labeling standards for AI/ML-based medical devices. It first focuses on the types of information that should be included on the label of all AI/ML-based medical devices, namely: (1) Model Identifiers; (2) Model Type; (3) Model Characteristics; (4) Indications for Use;

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407 *Virtual Public Workshop—Transparency of Artificial Intelligence/Machine Learning-Enabled Medical Devices*, *supra* note 400.

408 IMDRF Good Regul. Rev. Pracs., *supra* note 243.

(5) Validation and Model Performance; (6) Details on the Data Sets; (7) Preparation Before Use and Application; (8) Model Limitations, Warnings, and Precautions; (9) Alternative Choices; (10) Privacy and Security; and (11) Additional Information. This list is intended to serve as a useful starting point for the FDA to develop the urgently needed labeling standards for AI/ML-based medical devices. During the development process, the FDA should maintain an ongoing dialogue with all stakeholders, including patient and consumer representatives. In addition to developing *general* labeling standards for AI/ML-based medical devices, the FDA should also investigate, with input from all stakeholders, whether additional labeling standards are needed for *specific types of AI* and/or *intended users*. Moreover, this Part argues that the suggested labels should be "dynamic" and not static for adaptive algorithms, meaning they should be continuously updated.

After exploring the label content, Part IV discusses design questions of the label and argues that "nutrition facts labels" known from food products, with their eye-catching design, are a promising label design for AI/ML-based medical devices. With the help of such labels, users should be able to quickly get an overview of all important information about AI/ML-based medical devices. Education campaigns will also be essential to ensure users can properly read the AI/ML-based medical device labeling. Lastly, this Part also discusses other labeling questions, namely instructions for use for health professionals and laypersons.

A. Key Types of Information to Be Included on the Label

What are the essential components of a label for AI/ML-based medical devices? The answer to this question is not easy but is key for developing labeling standards for AI/ML-based medical devices. This Section carves out some essential types of information that should be included on the label of an AI/ML-based medical device. These suggestions are not exhaustive. Rather, they are a helpful tool to initiate this important discussion and the overdue development of labeling standards. It will be crucial for the FDA to have an ongoing dialogue with all stakeholders, including patient and consumer representatives, to ultimately determine the essential ingredients to be included on the label of an AI/ML-based medical device.

To identify the standard content of the label, another factor that will be important to consider is the audience of the label. As already

stated,[409] AI/ML-based medical devices are utilized by different users. For example, users include health professionals, nonexperts in a particular medical specialty,[410] and patients and consumers. Moreover, hospitals that buy and implement AI/ML-based medical devices and insurance companies will likely be interested in the label. It may be unrealistic, however, to expect labelers to develop a separate label for each potential audience. Rather, the label is addressed to the primary users—target audience or intended users—of the AI/ML-based medical device. For example, the intended users of the prescription device OsteoDetect, used to detect distal radius fractures, are clinicians, and the intended users of Apple's over-the-counter ECG app are consumers aged twenty-two and older.[411]

Consequently, when developing labeling standards for AI/ML-based medical devices, the FDA could follow three steps with input from all stakeholders. As a first step, the FDA could develop *general* labeling standards for AI/ML-based medical devices—i.e., identify the essential ingredients of the label that are needed for all AI/ML-based medical devices regardless of the type of AI/ML or target audience. In a second step, the FDA could assess whether additional information would need to be included on the label depending on the *type of AI* in question, such as whether it is a black-box model versus an interpretable model or an AI/ML-based SaMD versus SiMD.[412] In a third step, the FDA could analyze whether further additional information needs to be included on a label depending on the *intended users* in question, such as health professionals versus laypersons. The additional labeling standards related to specific types of AI or intended users could then be included as additional sections in the guidance or regulations, depending on how the FDA ultimately decided to implement the labeling standards for AI/ML-based medical devices.[413]

As discussed previously, modifications to a legally marketed AI/ML-based medical device require a new 510(k) premarket notification if they introduce, for example, a significant change to the algorithm.[414] A new 510(k) also would require manufacturers to adjust their label-

409 *See supra* Section I.B.

410 For example, the cardiac ultrasound software device, Caption Guidance, can also be used by nurses as nonexperts in ultrasonography. *See supra* Section I.B.1.

411 U.S. Food & Drug Admin., *supra* note 61, at 2; Letter from Angela C. Krueger to Donna-Bea Tillman, *supra* note 69, at 1. For more information on both devices, see *supra* Section I.B.1.–.2.

412 For more information on the types of AI, see *supra* Section I.A.2.–II.A.

413 For FDA's implementation options, see *supra* Section III.D.

414 *See supra* Section III.B.3.

ing.[415] As mentioned, however, the long-term plan of the FDA is to routinely implement a TPLC approach for modifications to AI/ML-based SaMD that particularly aims to allow these devices to continuously learn and optimize their performance.[416] This would provide manufacturers with the option of submitting a predetermined change control plan.[417] Consequently, the FDA will need to ensure that when manufacturers use a predetermined change control plan for these adaptive algorithms, the label is "dynamic" and not static, meaning it is continuously updated. The continuous update of the label will be crucial to ensure a clear line between on- and off-label uses of the AI/ML-based medical device. In this context, it will also be of paramount importance that the intended users are made aware of the label update, such as through a notification by phone or email.

With the help of the label, the intended users should be able to quickly get an overview of the AI/ML-based medical device, its indications for use, as well as its benefits, risks, and limitations. The label should be eye-catching and no more than one page to prevent information overload.[418] The details can be included in the instructions for use.[419] Furthermore, once labeling standards are established for AI/ML-based medical devices, education will be crucial to ensure intended users can read the label and understand the basics of AI/ML, especially the potential risks such as bias.[420]

Box 2 below lists the types of information that should be included on the label of all AI/ML-based medical devices.

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415 *See supra* Section III.B.3.

416 *See supra* Section III.B.3.

417 *See supra* Section III.B.3.

418 For more information on the design, see *infra* Section IV.B.

419 For more information on the instructions for use, see *infra* Section IV.C.

420 For more information on the importance of education, see *infra* Section IV.C. For information on bias risks, see *supra* Section III.B.1.

Box 2: Key Types of Information that Should be Included on the Label of AI/ML-Based Medical Devices
(1) MODEL IDENTIFIERS
(2) MODEL TYPE
(3) MODEL CHARACTERISTICS
(4) INDICATIONS FOR USE
(5) VALIDATION & MODEL PERFORMANCE
(6) DETAILS ON THE DATA SETS
(7) PREPARATION BEFORE USE & APPLICATION
(8) MODEL LIMITATIONS, WARNINGS & PRECAUTIONS
(9) ALTERNATIVE CHOICES
(10) PRIVACY & SECURITY
(11) ADDITIONAL INFORMATION

The first key type of information that should be included on the label is the *Model Identifiers*. These should generally include the brand name, name and place of business, model version, clearance/approval date of the AI/ML-based medical device, the FDA premarket submission number, and the UDI. This information will provide the intended users with an overview of all essential model identifiers.

The second essential component of the label is the *Model Type*. This includes, for example, information on whether the model is an interpretable model or a recurrent neural network.[421] This knowledge can help intended users understand whether they are dealing with a white- or black-box model and whether they can independently review the basis for its recommendations.[422] In the case of an adaptive algorithm, for instance, the intended users would also be informed that the algorithm is continuously learning and adapting to novel situations, or in the case of autonomous AI, that there is no human supervision of the device's decision.

The third key type of information on the label of an AI/ML-based medical device is the *Model Characteristics*. This information should help clarify whether this device is, for example, a prescription device or an over-the-counter device.

The fourth essential ingredient is the *Indications for Use*. This includes a description of what disease or condition the AI/ML-based

421 For the different types of AI, see *supra* Section I.A.2.

422 For more information on white-box and black-box models and whether one can independently review the basis of their recommendations, see *supra* Sections I.A.2., II.B.2.– II.B.3.

medical device will diagnose, cure, mitigate, treat, or prevent.[423] The label should include information on the benefits of the device and a description of the target population, as well as information relating to race/ethnicity and gender.[424] As previously mentioned, however, the label should not be an excuse to market AI/ML-based medical devices that have not been trained on a diverse data set, and regulators like the FDA should generally deny their marketing authorization in the first place.[425] Moreover, the label should clearly describe the role intended to be fulfilled by the algorithm's output.[426] This information is important so that the intended users know in which situations and for which target populations the AI/ML-based medical device should be used. It also helps identify potential off-label uses.

The fifth information type is *Validation and Model Performance*. The label should provide an overview of the validation and performance results.[427] In particular, it should list all of the model's cross-site performances to enable users to appraise its reliability. Recent research has shown that deep learning models that were evaluated at only a single clinical site can have weaknesses and may perform worse across clinical sites.[428] Moreover, the label should clearly articulate whether the AI/ML-based medical device underwent retrospective or prospective studies. Unfortunately, until now, almost all AI/ML-based medical devices available on the U.S. market have undergone retrospective studies.[429] Prospective studies are needed to fully assess the impact of such devices on clinical practice, especially whether they improve patient outcomes.[430] Consequently, in addition to establishing

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423 *See PMA Labeling*, U.S. Food & Drug Admin. (Sept. 27, 2018), https://www.fda.gov/medical-devices/premarket-approval-pma/pma-labeling [https://perma.cc/AT4E-M8TB]. For the definition of the term "device," see FDCA § 201(h)(1), 21 U.S.C. § 321(h)(1); *supra* Section II.A.

424 *See PMA Labeling*, *supra* note 423.

425 *See supra* Section III.D.

426 U.S. Food & Drug Admin., *supra* note 376, at 5 (mentioning stakeholder's express wishes on labeling needs).

427 *See* Mark P. Sendak, Michael Gao, Nathan Brajer & Suresh Balu, *Presenting Machine Learning Model Information to Clinical End Users with Model Facts Labels*, 3 npj Digit. Med., no. 41, 2020, at 1, 3 (for a sepsis ML model).

428 *See* Wu et al., *supra* note 350, at 582. For more information on this study, see *supra* Section III.B.1.

429 Wu et al., *supra* note 350, at 582.

430 *Id.* at 583; Xiaoxuan Liu, Samantha Cruz Rivera, Livia Faes, Lavinia Ferrante di Ruffano, Christopher Yau, Pearse A. Keane, Hutan Ashrafian, Ara Darzi, Sebastian J. Vollmer, Jonathan Deeks, Lucas Bachmann, Christopher Holmes, An Wen Chan, David Moher, Melanie J. Calvert & Alastair K. Denniston, *Reporting Guidelines for Clinical Trials Evaluating Artificial Intelligence Interventions Are Needed*, 25 Nature Med. 1467, 1467 (2019).

labeling standards for AI/ML-based medical devices, the FDA should consider two things: first, requiring the evaluation of such models at multiple sites before permitting their marketing; and second, requiring prospective studies, at least for high-risk AI/ML-based medical devices, as a premarket requirement.

Details on the Data Sets comprise the sixth essential label component for an AI/ML-based medical device. Where possible, this includes information about the training data, validation data, and test data. Although training data is used to train the model, test data is used to assess the generalization error of the final selected model, and validation data is used to estimate the prediction error for model selection.[431] For example, where does the training data come from? Electronic health records, wearables, etc.? In particular, information should be provided on the diversity of the data sets and the input data type.[432]

In addition to developing labeling standards, with input from stakeholders, the FDA could create a checklist for AI/ML developers that lists what is minimally required to show during premarket review in terms of identifying, assessing, and mitigating risks of bias.[433] For example, the default should be to establish that the AI/ML-based medical device works well across representative populations.[434] As discussed earlier, many AI/ML-based medical devices that have received marketing authorization from the FDA have not reported gender breakdown, race/ethnicity breakdown, and geographic breakdown, and also have not provided information on the validation data.[435] Manufacturers should not only report such data, but also have a reasonable justification when they cannot show a demographic representation of the data sets. An example of such a justification could be that the training data set does not include data from women because the AI/ML-based medical device is intended for diagnosing a disease that only exists in men, such as prostate cancer.[436]

The seventh key ingredient of the label is *Preparation Before Use and Application*. All things should be listed here that need to be done

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431 CHANG, *supra* note 38, at 70.

432 *See* Sendak et al., *supra* note 427, at 3 (for a sepsis ML model).

433 For more information on bias, see *supra* Section III.B.1.

434 *See* Wu et al., *supra* note 350, at 583.

435 *See* Ross, *supra* note 7; Ross, *supra* note 386. For more information, see *supra* Section III.C.

436 For more information on prostate cancer, see, e.g., *Prostate Cancer*, MAYO CLINIC (Oct. 1, 2022), https://www.mayoclinic.org/diseases-conditions/prostate-cancer/symptoms-causes/syc-20353087 [https://perma.cc/LBT8-C8CS].

by the intended users—who should also be clearly named[437]—before using the AI/ML-based medical device. For example, this could include a note that the validity of the AI/ML-based model must be confirmed first within the local setting before use or that user training is recommended.[438] Moreover, the label should contain information about the general application of the device. For example, it should say in a few words where to attach a patch that comes with the software on the patient's body or how to interact with the device. The details can then be explained in the instructions for use supplied by the manufacturer.

The eighth type of essential information that must be included on the label is *Model Limitations, Warnings, and Precautions*. Everything about the AI/ML-based medical device that should be brought to users' immediate attention must be listed. For example, the label needs to list all known risks and potential biases associated with using the AI/ML-based medical device. In the case of a DTC device, for instance, it would be essential to inform consumers about the potential risk of false positives and negatives and when to seek medical care.[439] If the algorithm is adaptive, users should be warned that it needs to be continuously assessed for its safety and effectiveness.[440] Depending on the AI/ML-based medical device, a warning should be added that variance may increase through human factors.[441] Contraindications must also be clearly listed, for example, in cases where the AI/ML-based medical device is *not* intended to provide a diagnosis or is *not* generalizable across application sites.[442] Using clear symbols may also be an option, with more detailed information included in the instructions for use.[443]

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437 *See* U.S. Food & Drug Admin., Computer-Assisted Detection Devices Applied to Radiology Images and Radiology Device Data—Premarket Notification [510(k)] Submissions— Guidance for Industry and Food and Drug Administration Staff 23 (2022), https://www.fda.gov/media/77635/download [https://perma.cc/7MKN-JFZ6].

438 *See* Sendak et al., *supra* note 427, at 2 (for a sepsis ML model); Letter from Robert Ochs to Sam Surette, *supra* note 67, at 3 (for Caption Guidance); Gerke, *Health AI*, *supra* note 10, at 505.

439 *See, e.g.*, Sara Gerke, Carmel Shachar, Peter R. Chai & I. Glenn Cohen, *Regulatory, Safety, and Privacy Concerns of Home Monitoring Technologies During COVID-19*, 26 Nature Med. 1176, 1178 (2020).

440 *See* Babic et al., *supra* note 10, at 1202.

441 *See* Gerke et al., *The Need for a System View*, *supra* note 10, at 2.

442 *See* Sendak et al., *supra* note 427, at 3 (for a sepsis ML model).

443 *See* IMDRF Good Regul. Rev. Pracs., *supra* note 243, at 18; *see also supra* Section III.A.3.

The ninth key ingredient of the label is *Alternative Choices*. It would be helpful for users to learn about alternative choices—if any—that they can consider instead of using the AI/ML-based medical device in question (e.g., an alternative treatment option). Given that AI/ML developers are likely to be hesitant to list alternative choices on the label as this can create a competitive disadvantage, a compromise could be to state on the label that alternative choices can be found on the FDA's website. For example, the 510(k) summary of an AI/ML-based medical device always lists the predicate device used to demonstrate substantial equivalence and is published on the FDA's website.[444] Indeed, while it would be much easier for the consumer to have a list of alternative options—if any—right on the label, a link to the FDA's website could balance the competing interests. It would still allow users to access this information and promote innovation in new AI/ML-based medical devices.

Privacy and Security is the tenth essential component of the label. It should contain essential information, such as whether the AI/ML-based medical device complies with the applicable privacy laws. The label should also say whether a privacy policy is publicly available, and if so, where to find it and when it was last updated.[445] It should also state security safeguards, such as encryption, and other practices, such as whether there is a publicly available "Coordinated Vulnerability Disclosure" policy.[446] This information could help potential users assess whether the privacy of individuals is adequately protected.

In the digital age, the FDA is increasingly finding itself in this relatively new situation of evaluating data-driven technologies for their safety and effectiveness, including AI/ML-based medical devices. The FDA enforces the FDCA, but it is the U.S. Department of Health and Human Services's ("HHS") Office for Civil Rights ("OCR"), for example, that is responsible for enforcing the Privacy and Security Rules of the Health Insurance Portability and Accountability Act ("HIPAA").[447] Both the HIPAA Privacy Rule and the HIPAA Secur-

444 *See Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices*, *supra* note 7 (listing the submission numbers of AI/ML-based medical devices marketed in the U.S. with hyperlinks to further information about the specific device, including usually a link to its summary).

445 *See* Andrea Coravos, Megan Doerr, Jennifer Goldsack, Christine Manta, Mark Shervey, Beau Woods & William A. Wood, *Modernizing and Designing Evaluation Frameworks for Connected Sensor Technologies in Medicine*, 3 NPJ DIGIT. MED., no. 37, 2020, at 1, 8 (for connected sensor technologies in medicine).

446 *See id*. at 6.

447 *See HIPAA Enforcement*, U.S. DEP'T HEALTH AND HUM. SERVS. (July 25, 2017), https:/

ity Rule aim to protect certain individually identifiable health information.[448] In addition, privacy laws at the state level may help protect health information that falls outside of HIPAA's scope.[449] In addition, the Federal Trade Commission ("FTC") is the key federal agency on privacy policy and enforcement, with the FTC Act as its primary statute.[450] The Office of the National Coordinator for Health Information Technology ("ONC"), based within the Office of the Secretary for HHS, is the principal federal entity responsible for coordinating nationwide efforts to use and implement advanced health information technology, with a focus on establishing expectations on data sharing.[451]

Consequently, there would be an urgent need for the FDA, OCR, FTC, ONC, and possibly other entities, such as the U.S. Department of Commerce's National Institute of Standards and Technology ("NIST"),[452] to come together and discuss, in the context of AI/ML-based medical devices, how one can best ensure data protection and compliance with the applicable laws. It would be desirable to check compliance with privacy and security provisions upfront (i.e., premarket) rather than only intervening once the breach has already occurred. In this context, the agencies would need to decide what content should appear on the label of an AI/ML-based medical device in terms of privacy and security. An alternative option could also be for this information to be outsourced and included on an extra label dedicated solely to privacy and security, the development of which would be spearheaded by one of the other federal agencies in consultation with the FDA. In any case, this important discussion about labeling standards for AI/ML-based medical devices concerning privacy and

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/www.hhs.gov/hipaa/for-professionals/compliance-enforcement/index.html [https://perma.cc/8PH4-5S6M].

448 *See, e.g.*, U.S. DEP'T HEALTH AND HUM. SERV'S, SUMMARY OF THE HIPAA PRIVACY RULE 1 (2003), https://www.hhs.gov/sites/default/files/privacysummary.pdf [https://perma.cc/2EA9-NABP]. For more information on the HIPAA Security Rule, see, for example, *The Security Rule*, U.S. DEP'T HEALTH AND HUM. SERVS. (Oct. 20, 2022), https://www.hhs.gov/hipaa/for-professionals/security/index.html [https://perma.cc/V4SB-3LYX].

449 For more information on new state privacy laws, such as in California, Virginia, and Colorado, see, for example, Gerke & Rezaeikhonakdar, *supra* note 68, at 3.

450 *Protecting Consumer Privacy and Security*, U.S. FED. TRADE COMM'N, https://www.ftc.gov/news-events/topics/protecting-consumer-privacy-security [https://perma.cc/44BX-Q5BW]; Gerke & Rezaeikhonakdar, *supra* note 68, at 2.

451 *About ONC*, OFF. NAT'L COORDINATOR FOR HEALTH INFO. TECH. (Sept. 8, 2022), https://www.healthit.gov/topic/about-onc [https://perma.cc/VWF7-PEWQ].

452 *See* NAT'L INST. STANDARDS & TECH., U.S. DEP'T COM., https://www.nist.gov [https://perma.cc/DS6N-VP2M].

security between the federal agencies needs to occur as soon as possible.

The last key ingredient on the label is *Additional Information*. For example, this can include contact information and website addresses. The label should also contain the information regarding when it was last updated.

B. "Nutrition Facts Labels"

The design of the label will be important to ensure that the content of the label is presented in a way that is accessible and easy to understand for the intended users. The FDA should work closely with design experts to create an optimal design for a label for AI/ML-based medical devices that encourages reading. "Nutrition facts labels," known from food products,[453] are a promising label design for AI/ML-based medical devices. The key types of information—which should be included on the label of all AI/ML-based medical devices[454]—could be presented similar to nutrition facts labels on food products. Several scholarly groups have shown the design advantages of, for example, a "model card," a "nutrition label," a "nutrition-label-type visualization," and a "model facts" label in different contexts, such as for trained machine learning models,[455] for connected sensor technologies in medicine,[456] and for a sepsis machine learning model.[457] Such labels have the benefit of creating a visual ("eye-popping") representation for users that should help them easily understand essential facts about

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453 *See* 21 C.F.R. § 101.9. The FDA has also recently updated the nutrition facts label; for more information on the new label design, see, for example, *The New Nutrition Facts Label: What's in It for You?*, U.S. Food & Drug Admin. (Apr. 13, 2022), https://www.fda.gov/food/nutrition-education-resources-materials/new-nutrition-facts-label [https://perma.cc/GR5U-9DRJ].

454 *See supra* Section IV.A.

455 Margaret Mitchell Simone Wu, Andrew Zaldivar, Parker Barnes, Lucy Vasserman, Ben Hutchinson, Elena Spitzer, Inioluwa Deborah Raji & Timnit Gebru, *Model Cards for Model Reporting* (2019) (unpublished manuscript presented at 2019 ACM Conference on Fairness, Accountability and Transparency) (available at https://arxiv.org/pdf/1810.03993.pdf [https://perma.cc/M7N7-9ARG]).

456 Coravos et al., *supra* note 445.

457 Sendak et al., *supra* note 427; *see* Erin Brodwin, *With 'Nutrition Labels' and an Anthropologist's Eye, Duke Pioneers a New Approach to AI in Medicine*, STAT (Oct. 5, 2020), https://www.statnews.com/2020/10/05/duke-artificial-intelligence-hospital-medicine [https://perma.cc/ALA3-W4PR]. A few scholars have also suggested prescription drug labels as a possible design option, but most scholars are trending toward nutrition facts labels. *See* Barbara Barry, Collaborative Scientist, Robert D. & Patricia E. Kern, Ctr. for the Sci. of Health Care Delivery, Presentation at the Virtual Public Workshop, *in* U.S. Food & Drug Admin., *supra* note 400, at 44.

the AI/ML-based medical device.[458] A "nutrition facts label" also has the advantage that its design is familiar to users.

To improve the visibility of such labels, they could be shown to users immediately as the first thing they see when opening the software (typically in the case of SaMD) or be placed on the front and center of the physical device (typically in the case of SiMD).[459] Studies also suggest that putting the most important information up at the top (rather than at the bottom) will increase users' likelihood of reading them.[460] Ultimately, it would be valuable if extensive research (e.g., from a social science perspective) were conducted on how the label could effectively communicate the key types of information suggested above.[461] To increase transparency, the FDA could additionally make the labels available on its website. For example, the agency could easily link them to its publicly available list of AI/ML-based medical devices marketed in the United States and update such a list at regular intervals.[462]

It will also be important that the intended users, such as health care professionals, patients, and consumers, of the AI/ML-based medical devices know how to read the label. Thus, education campaigns across multiple channels, including videos, social media, advertising, and user-friendly educational materials, similar to current nutrition facts label campaigns, will be imperative.[463] Moreover, the FDA could require manufacturers of all AI/ML-based medical devices subject to premarket submission to show that intended users know its benefits, risks, and limitations and how to use it solely by reading its label.[464] Indeed, the FDA required a similar demonstration for Apple's ECG app; the agency asked for usability and human factors testing to demonstrate that users know how to use the app correctly based exclusively on reading the labeling.[465] But the FDA could standardize

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458 *See* Coravos et al., *supra* note 445, at 7.

459 It has been shown for nutrition labels that consumers would be more likely to read them if they were put on the front and center of the box. *See* Meredith Melnick, *Study: Why People Don't Read Nutrition Labels*, TIME (Oct. 24, 2011), https://healthland.time.com/2011/10/24/study-why-people-dont-read-nutrition-labels [https://perma.cc/5TYX-DCJG]. For more information on SaMD and SiMD and their labels, see *supra* Sections II.A., III.A.1.

460 *See, e.g.*, Melnick, *supra* note 459.

461 *See supra* Section IV.A.

462 For this list, see *Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices*, *supra* note 7.

463 *See* U.S. Food & Drug Admin., *supra* note 453.

464 Gerke, *Health AI*, *supra* note 10, at 504.

465 Letter from Angela C. Krueger to Donna-Bea Tillman, *supra* note 69, at 2, 3. For more information on the app, see *supra* Section I.B.2.

the request for performing such tests to mitigate risks such as device-related user errors.[466] Awareness campaigns and human factors testing are particularly important for DTC medical AI/ML apps like Apple's ECG app, which many consumers see as "diagnostic apps" but are actually just informational tools that are "not intended to replace traditional methods of diagnosis or treatment."[467]

C. Instructions for Use

With the consultation of all stakeholders, including patient and consumer representatives, the FDA should also develop standards for what should be or must be included in the additional information (besides the label) provided by the labeler, who is usually the manufacturer of the AI/ML-based medical device. An important element is the instructions for use, which should be supplied to users in an easily accessible form (e.g., electronic form, paper, or both).[468]

The target audience must be given special consideration when creating the instructions for use. For example, in the case of a DTC medical device, the instructions for use should be written in plain language to maximize consumers' understanding and the likelihood of reading the instructions. Sentences should be short and concise.[469] Some AI/ML-based medical devices may also provide different information for different users, such as health care professionals and laypersons.[470]

In general, it will be crucial that the instructions for use contain an in-depth explanation of all the above-suggested information on the label.[471] This enables users to read more about a specific topic of their choice and learn more about the pros and cons of the particular AI/ML-based medical device. Moreover, the instructions for use may help users better understand when and how to correctly use the AI/ML-based medical device and thus mitigate risks.

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466 *See* Gerke, *Health AI*, *supra* note 10, at 504.

467 Letter from Angela C. Krueger to Donna-Bea Tillman, *supra* note 69, at 1; Ashley N.D. Meyer, Traber D. Giardina, Christiane Spitzmueller, Umber Shahid, Taylor M.T. Scott & Hardeep Singh, *Patient Perspectives on the Usefulness of an Artificial Intelligence–Assisted Symptom Checker: Cross-Sectional Survey Study*, 22 J. MED. INTERNET RSCH. e14679 (2020).

468 *See* IMDRF Good Regul. Rev. Pracs., *supra* note 243, § 5.3.4.

469 U.S. FOOD & DRUG ADMIN., *supra* note 239, at 40–41.

470 *See* IMDRF Good Regul. Rev. Pracs., *supra* note 243, § 5.3.1.

471 *See supra* Section IV.A.

Conclusion

Although AI/ML-based medical devices are increasingly used in clinical care and offered directly to consumers, very little has been written on labeling for AI/ML-based medical devices. This is surprising given how important labeling is to avoid harm to patients and consumers. This Article is the first to identify and thoroughly analyze the significant challenges of labeling for AI/ML-based medical devices and provides solutions to address them. Although this Article focuses on devices, it also holds lessons for AI/ML-based products that are not subject to FDA regulation. What follows are the author's central findings and claims.

First, the long-awaited final CDS Guidance falls short of expectations. It seems to violate the 21st Century Cures Act, creates significant uncertainty for AI/ML manufacturers regarding whether their product is considered a medical device, and raises safety concerns. In particular, the FDA has expanded its interpretation of criterion (4) of FDCA Section 520(o)(1)(E) and currently thinks that all types of AI/ML—i.e., black-box AI/ML, explainable AI/ML, and interpretable AI/ML—can generally fall under the medical device exception and thus outside of FDA regulation. This is concerning because it is more than unclear how black-box AI/ML (and even explainable AI/ML) can fulfill the statutory requirement of "enabling such health care professional to independently review the basis for such recommendations that such software presents."[472]

Second, regarding criterion (4) of FDCA Section 520(o)(1)(E), the FDA currently appears to be primarily focused on improved labeling to circumvent regulation rather than safety and effectiveness. While improved labeling is key, it alone is not enough to adequately ensure patient safety. Labeling must go hand in hand with a robust regulatory framework for CDS software functions. Currently, the responsibility for assessing the safety and effectiveness of Non-Device CDS—which the FDA thinks can even be an artificial deep neural network—rests mainly with health care professionals who use the CDS in question, including the associated liability risks for patient injury. In addition, the many ambiguities in the final CDS Guidance create confusion among stakeholders. To its credit, the FDA attempts to accomplish the impossible task of finding a clear, consistent, and even line between Non-Device CDS and device software functions. Congress needs to act and fix its mistake in enacting the CDS software

472 FDCA § 520(o)(1)(E)(iii), 21 U.S.C. § 360j(o)(1)(E)(iii).

exception as part of the 21st Century Cures Act in the first place. The deletion of FDCA Section 520(o)(1)(E) would contribute to greater clarity and legal certainty by considering all CDS software functions a priori as medical devices. It would also effectively prevent products whose functionality could bear a risk to patient safety from absconding from the FDA's oversight and could serve as a safeguard against automation bias. This suggestion would also entail that the FDA would still be free to exercise enforcement discretion over some device software functions that are lower risk.

Third, there are currently no standards of labeling for AI/ML-based medical devices. This Article has shown, among other things, that Title 21 of the C.F.R. does not contain specific labeling requirements for AI/ML-based medical devices. This is concerning because AI/ML-based medical devices differ in many aspects from traditional medical devices such as contact lenses. For example, AI/ML-based medical devices can be biased. There are different types of biases, including bias in the training data, label choice bias, contextual bias, or unconscious bias. Some AI/ML-based medical devices also rely on black-box algorithms, which are usually impossible for humans to understand, and/or are adaptive and can continuously learn from novel data. Furthermore, the more human-AI interaction takes place, the more difficult it is to predict how AI/ML-based medical devices will perform in the real world once launched on the market.

Fourth, labeling standards for AI/ML-based medical devices are urgently needed because the current labeling requirements for medical devices and the FDA's case-by-case approach for a few AI/ML-based medical devices are insufficient. The FDA has already permitted marketing of more than 520 AI/ML-based medical devices, and many of them do *not* provide users with important information, such as gender, race/ethnicity, and geographic breakdowns of the data sets used. This lack of knowledge can ultimately harm patients and consumers. Labeling is crucial for users to understand, inter alia, the benefits, risks, and limitations of the specific AI/ML-based medical device and to empower them to assess when to use the device and how to use it correctly. It creates legal clarity for manufacturers, transparency to users, and can help facilitate public trust in new digital health technologies. The FDA could implement these new labeling standards either in the form of regulations, such as via an amendment to Title 21 of the C.F.R., or nonbinding recommendations through a guidance document. From a global harmonization perspective, it would also be desirable if the IMDRF dealt with this topic as well and either updated its

Principles of Labelling for Medical Devices and IVD Medical Devices or developed a separate guidance document on labeling for AI/ML-based medical devices.

Fifth, regulators like the FDA need to figure out what such labeling standards for AI/ML-based medical devices could look like, with input from all stakeholders, as soon as possible. This author suggested eleven key types of information that should be included on the label of all AI/ML-based medical devices, namely: (1) Model Identifiers; (2) Model Type; (3) Model Characteristics; (4) Indications for Use; (5) Validation and Model Performance; (6) Details on the Data Sets; (7) Preparation Before Use and Application; (8) Model Limitations, Warnings, and Precautions; (9) Alternative Choices; (10) Privacy and Security; and (11) Additional Information. In addition to creating general labeling standards for AI/ML-based medical devices as a first step, the FDA should also consider, in a second and third step, whether additional labeling standards are needed in the regulations or guidance document for specific types of AI and/or intended users.

Sixth, "nutrition facts labels," known from food products, are a promising label design for AI/ML-based medical devices. The design is familiar to users and allows them to get a quick overview of all key information. If the user needs more information on a specific topic, the instructions for use can be consulted for this purpose. For adaptive algorithms, the label should also be "dynamic" (rather than static), meaning it needs to be continuously updated. This is important to maintain a clear line between on- and off-label use.

Finally, labeling for AI/ML-based medical devices must be coupled with educational campaigns and other needed regulatory reforms for AI/ML-based medical devices. A new regulatory framework for AI/ML-based medical devices is essential to ensure, for instance, that devices such as the one in the introductory example—which likely missed Alicia's melanoma because it was primarily trained on images of people with white skin—do not receive marketing authorization in the first place. Labeling has limits and must not be misused as an excuse to launch poorly designed AI/ML-based medical devices that have not been trained on diverse data sets. For example, the FDA should require AI/ML manufacturers to disclose the gender, race/ethnicity, and geographic breakdowns of the used data sets. In general, the agency should have a special focus on promoting equity, diversity, and inclusion and ensuring that AI/ML-based medical devices benefit us all.