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ADMINISTRATION
CENTER FOR DEVICES & RADIOLOGICAL HEALTH

EXECUTIVE SUMMARY FOR THE PATIENT ENGAGEMENT ADVISORY COMMITTEE MEETING

Artificial Intelligence (AI) and Machine Learning (ML) in Medical Devices

October 22, 2020

INTRODUCTION

Technology has transformed how humans live, providing new opportunities for learning, shopping, connecting with others and performing complex tasks. The ubiquitous availability and increasing computing capacity have made it possible for intelligent machines to be used in our daily lives. Artificial intelligence (AI) defined broadly as the science and engineering of making intelligent machines is becoming more common. For example, online streaming entertainment sites analyze viewers' previous choices to make new viewing recommendations, continually updating with every new choice each viewer makes. In the past decade, as a result of expanding data availability, improvements in hardware, and novel machine learning (ML) algorithms, AI has shown great promise across a wide array of applications, ranging from digital advertising to self-driving cars to electronic trading platforms. Systems that imitate human intelligence are also integral to healthcare. AI is being used to detect eye conditions, recognize certain cell types, and evaluate human behaviors associated with mood disorders. Modern automated external defibrillators that can detect abnormal heart rhythms by analyzing heart waveforms and deliver the needed electrical charge have been in use since the 1970s, with continually improving performance. They have been designed and implemented to use the same process for detection as has been done by physicians. Compared to these technologies that aim to mimic the human decision process, modern AI technologies are data-driven in that they analyze large volumes of complex data in novel ways; discover new relationships between the information entered and the desired results from the available data; and can adapt their reasoning based on new data. In recent years, there has been an increased use of AI/ML in medical devices, especially for tasks that require the analysis of large volumes of data or the interpretation of complex information.

Most devices that rely on AI/ML fall into the category that the FDA calls Software as a Medical Device, or SaMD. SaMD is defined by the International Medical Device Regulators Forum (IMDRF) as "software intended to be used for one or more medical purposes that perform these purposes without being part of a hardware medical device".[1] In 2019, the FDA released a discussion paper proposing a regulatory framework for modifications to AI/ML-based SaMD.[2] In the discussion paper, the FDA highlights the potential for AI/ML-based devices to transform

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[1] IMDRF: Software as a Medical Device (SaMD): Key Definitions. 2013; Available from: http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-131209-samd-key-definitions-140901.pdf.
[2] Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) - Discussion Paper and Request for Feedback. Available from: https://www.fda.gov/files/medical%20devices/published/US-FDA-Artificial-Intelligence-and-Machine-Learning-Discussion-Paper.pdf.

healthcare due to the potential ability to learn from real-world feedback (training) and improve performance (adaptation). The FDA welcomes the iterative improvement power of AI/ML-based software as a medical device.

Adaptive AI/ML technologies, which have the potential to adapt and optimize device performance in real-time to continuously improve healthcare for patients, do not ideally fit the traditional paradigm of medical device regulation. The highly iterative, autonomous, and adaptive nature of these tools may better fit a new, total product lifecycle (TPLC) regulatory approach that facilitates a rapid cycle of product improvement and allows these devices to continually improve while providing effective safeguards. With the opportunities provided by new AI/ML devices to potentially advance healthcare, there are also challenges to be addressed to ensure safe use of the devices throughout their lifecycle.

WHAT IS MACHINE LEARNING AND HOW IS IT USED?

Machine learning (ML)– neural networks and deep learning
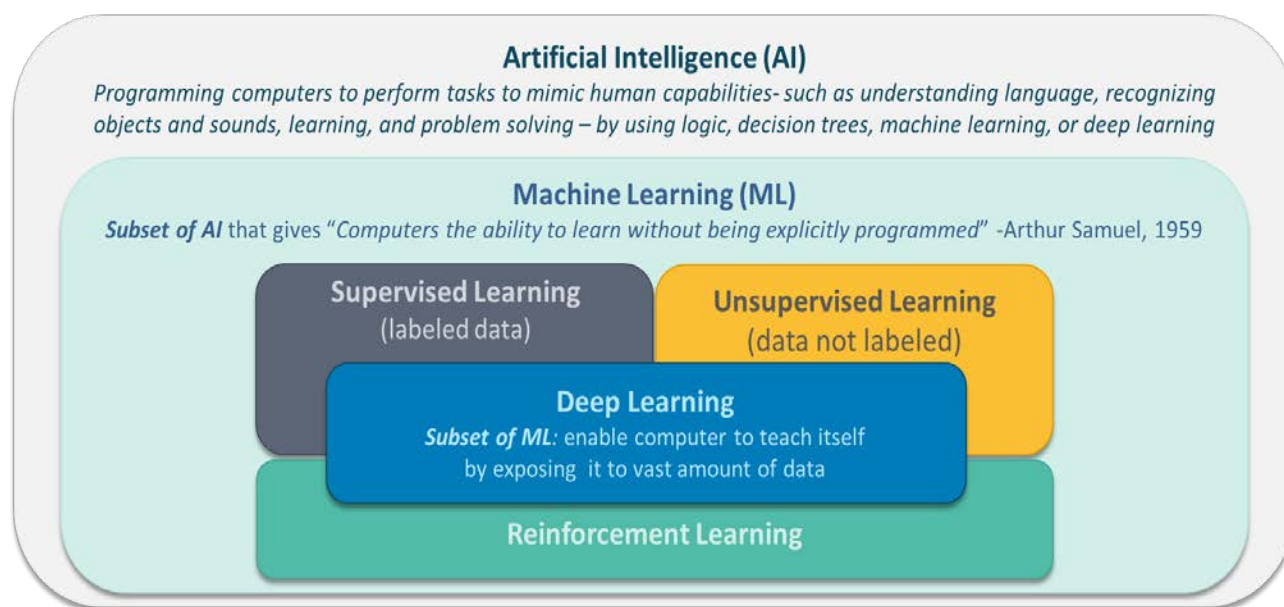

Figure 1. Artificial Intelligence and Associated Methods

Fundamental to the incorporation of AI in healthcare is ML which uses algorithms to find patterns in massive amounts of data which could include numbers, words, sounds, and images (**Figure 1**). Three major branches of machine learning have

emerged since electronic computers came in to use during the 1950s and 1960s: statistical methods, symbolic learning and neural networks.[3]

Neural networks, a commonly used form of AI/ML, is a technology that has been available since the 1960s and has been well-established in healthcare research for several decades.[4] It has been used for categorization applications like determining whether a patient will develop a particular disease. These neural networks typically consist of at least three layers of neurons: input layer (which receives information), hidden layer (responsible for extracting patterns and conducting the internal processing), and output layer (produces and presents the final network output).[5] These networks have been loosely likened to the way that neurons in the brain process signals.

A more complex form of neural network is deep learning which has many layers of computational nodes or neural networks that work together to process data and deliver a final result. This type of ML is scalable (can process large data sets using large models that can expand) and is hierarchical (perform automatic feature extraction from raw data called feature learning), building more complicated concepts from simpler ones. Deep learning allows the system to recognize patterns independently and make predictions, such as recognizing potentially cancerous lesions in radiology images.[6] Deep learning is increasingly being applied to data extracted by a method called radiomics, which can extract clinically relevant features in imaging data beyond what is perceived by the human eye.[7,8] Their combination may lead to greater accuracy in diagnosis than the previous generation of automated tools for image analysis, known as computer-aided detection or CAD.

In addition to detection or diagnosis, another common application of traditional machine learning is predicting what treatment protocols are likely to succeed on a

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[3] Kononenko I. Machine learning for medical diagnosis: history, state of the art and perspective. *Artif Intell Med* 2001; 23:89–109.

[4] Shahid N, Rappon T, Berta, W. Applications of artificial neural networks in health care organizational decision-making: A scoping review. *PLOS ONE* (2019) 14: e0212356. https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0212356&type=printable (Accessed on September 17, 2020).

[5] Shahid N, Rappon T, Berta, W. Applications of artificial neural networks in health care organizational decision-making: A scoping review. *PLOS ONE* (2019) 14: e0212356. https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0212356&type=printable (Accessed on September 17, 2020).

[6] Fakoor R, Ladhak F, Nazi A, Huber M. Using deep learning to enhance cancer diagnosis and classification. A conference -presentation. The 30th International Conference on Machine Learning, 2013.

[7] Vial A, Stirling D, Field M, et al. The role of deep learning and -radiomic feature extraction in cancer-specific predictive modelling: a review. *Transl Cancer Res* 2018;7:803–16.

[8] Davenport T and Kalakota R. The potential for artificial intelligence in healthcare. *Future Healthc J* 2019; 6: 94–8.

patient based on various patient attributes and the treatment context.[9] Machine learning can occur using two different methods—supervised or unsupervised. In supervised learning, the data is labeled and tells the machine what patterns it should identify. Most ML applications use supervised learning which require a training dataset for which the outcome variable (e.g., disease state) is known. Unsupervised learning does not have labeled data, so the goal is to infer the natural structure present within a dataset.

In addition to AI/ML being used to analyze large amounts of data, software powered by AI/ML is increasingly being used in robotics. Robotically-assisted surgical devices (RASD) support surgeons by improving their ability to see, help create precise and minimally invasive incisions, and assist with wound closure.[10] RASD are commonly being used to perform gynecologic, prostate, and head and neck surgeries. AI/ML devices with augmented reality could mimic the role of a super-assistant by performing tasks like highlighting a tumor during surgery to enhance the surgeon's medical decision making. While autonomous RASD are not yet a reality, there are many applications where AI could be used to augment the work of medical staff.[11] Despite the inclusion of RASD in surgical procedures, important decisions are still made by human surgeons.

WHAT DOES THE MACHINE USE TO LEARN?

Data is the most important ingredient for training AI/ML algorithms. AI/ML algorithms rely on computational power to make efficient algorithms, drawing connections between different pieces of data. However, in many instances the available training data for AI/ML devices are teaching the device a "worldview" but could be narrow in focus, particularly if the data does not represent a diverse set of patients. Historically, the datasets have leveraged retrospectively collected data to train and test the algorithms. Curated data sets that are robust and have both the breadth and depth for training a specific application are essential. The absence of curated and aggregated data sets means that the technology is being developed on limited data sets.

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[9] Lee SI, Celik S, Logsdon BA, et al. A machine learning approach to integrate big data for precision medicine in acute myeloid leukemia. *Nat Commun* 2018 9:42.

[10] Davenport TH, Glaser J Just-in-time delivery comes to knowledge management. *Harv Bus Rev*. 2002; 80:107-11, 126.

[11] Sturgis, K. How Artificial Intelligence is changing medical devices. Available from: https://www.mddionline.com/software/how-artificial-intelligence-changing-medical-devices. (Accessed on September 17, 2020).

Generalizability and External Validity

Generalizability is a term that refers to the accuracy with which results or findings can be transferred to situations or people other than those originally studied. In the setting of AI/ML, the device is generalizable to the wider population when it is developed with large, heterogenous, multicenter datasets. Important considerations for the data include ensuring that the data is obtained from a diverse segment of the population as well as across the spectrum of the condition. The devices on which the data (e.g., images) are obtained may also need to represent the spectrum of available devices in terms of models and versions within a given brand and potentially across different device brands. Hence, validation of the AI/ML device is best performed using data from an institution or institutions that differ from those that informed the training of the algorithm. This type of validation is called external validation. A systematic review found only 6% of 516 eligible published studies of AI algorithms designed to provide diagnostic interpretation of images performed external validation.[12] Hence, validation of the AI/ML device is best performed using data from an institution that differs from those that informed the training of the algorithm. It is generally agreed upon that the external validation approach will help ensure that diverse patient demographics and the spectrum of disease in the population on which the device will be used are adequately represented.

Examples of Demographic Considerations for Datasets

Sex/Gender

AI/ML SaMD using magnetic resonance neuroimaging has been suggested as a promising strategy to distinguish parkinsonian syndromes from multiple system atrophy by helping to better evaluate the cerebellum, brainstem, and putamen volume.[13] Broad regions of the brain are thicker in women than in men and ratios of grey to white matter also differ.[14,15] Some structures (such as hippocampus) are

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[12] Kim DW, Jang HY, Kim KW, Shin Y, Park SH. Design characteristics of studies reporting the performance of artificial intelligence algorithms for diagnostic analysis of medical images: results from recently published papers. *Korean J Radiol*. 2019;20:405–10.

[13] Scherfler C, Göbel G, Müller C, Nocker M, Wenning GK, Schocke M, et al. Diagnostic potential of automated subcortical volume segmentation in atypical parkinsonism. *Neurology*. 2016;86:1242.

[14] Luders E, Narr KL, Thompson PM, et al. Gender effects on cortical thickness and the influence of scaling. *Human Brain Mapping*. 2006;27:314.

[15] Allen JS, Damasio H, Grabowski TJ, Bruss J, Zhang W. Sexual dimorphism and asymmetries in the gray-white composition of the human cerebrum. *NeuroImage*. 2003;18:880.

larger in the female brain, others (such as amygdala, hypothalamus) are larger in the male brain relative to the overall brain size.[16] Inclusion of diverse patients in the datasets used to train the algorithm would be critically important to account for sex-based differences in neural anatomy.

Race and Ethnicity

AI/ML devices are being used to aid in the diagnosis of melanoma. Several studies have reported that deep learning devices for the classification of skin cancer images may perform better than some clinicians in the diagnosis of melanoma.[17 -23] However, the lack of the full spectrum of skin phenotypes and lesions in the training datasets is a limitation of many of these devices. Moreover, a real-world validation study is not yet available.

Age

AI/ML devices are being used to help diagnose cardiovascular conditions. Electrocardiogram (ECG) is a traditional tool used to diagnose thickening of the left muscle wall of the heart, also known as left ventricular hypertrophy (LVH). However, while ECG is relatively specific, it lacks sensitivity in diagnosing LVH in middle-aged to older individuals. In addition, false positives are more common in young or thin individuals whose voltage may exceed conventional thresholds. False negatives may occur in women, obese patients, chronic obstructive pulmonary disease and other comorbid conditions. Conversely, increased voltage is a common

[16] Goldstein JM, Seidman LJ, Horton NJ, et al. Normal sexual dimorphism of the adult human brain assessed by in vivo magnetic resonance imaging. *Cereb Cortex*. 2001;11:490.

[17] Brinker TJ, Hekler A, Utikal JS, Grabe N, Schadendorf D, Klode J, et al. Skin Cancer Classification Using Convolutional Neural Networks: Systematic Review. *J Med Internet Res*. 2018;20:e11936.

[18] Hekler A, Utikal JS, Enk AH, Hauschild A, Weichenthal M, Maron RC, et al. Superior skin cancer classification by the combination of human and artificial intelligence. *Eur J Cancer*. 2019;120:114.

[19] Maron RC, Weichenthal M, Utikal JS, Hekler A, Berking C, Hauschild A, et al. Systematic outperformance of 112 dermatologists in multiclass skin cancer image classification by convolutional neural networks. *Eur J Cancer*. 2019;119:57.

[20] Marchetti MA, Liopyris K, Dusza SW, Codella NCF, Gutman DA, Helba B, et al. Computer algorithms show potential for improving dermatologists' accuracy to diagnose cutaneous melanoma: Results of the International Skin Imaging Collaboration 2017. *J Am Acad Dermatol*. 2020;82(3):622.

[21] Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, et al. Dermatologist-level classification of skin cancer with deep neural networks. *Nature*. 2017;542(7639):115.

[22] Brinker TJ, Hekler A, Enk AH, Klode J, Hauschild A, Berking C, et al. Deep learning outperformed 136 of 157 dermatologists in a head-to-head dermoscopic melanoma image classification task. *Eur J Cancer*. 2019;113:47.

[23] Haenssle HA, Fink C, Toberer F, Winkler J, Stolz W, Deinlein T, et al. Man against machine reloaded: performance of a market-approved convolutional neural network in classifying a broad spectrum of skin lesions in comparison with 96 dermatologists working under less artificial conditions. *Ann Oncol*. 2020;31:137.

normal variant, particularly in young adult males and in athletes.[24,25] A preliminary study utilizing AI/ML suggested that AI/ML approaches show promise in identifying LVH from the ECG more accurately than cardiologists using a variety of conventional ECG criteria.[26] The study was based on hospitalized patients, primarily middle aged to older adults, using transthoracic echocardiogram as the "gold standard." Additional studies will be important to determine the optimal approach to utilizing this (or a similar) technology in clinical practice[26,27] and to identify ECG or demographic features that can enhance the accuracy of conventional interpretative methods, including younger adults.

These examples highlight the importance of being inclusive when assembling datasets for training and validation of AI/ML devices.

WHAT IS THE 'BLACK BOX" OF AI/ML?

Some researchers group AI/ML-based devices on the level of "opacity", usually a metaphor for how transparently it draws conclusions from data, with the opaquest form sometimes referred to as "black box." Black box AI is sometimes defined as an AI system whose inputs and operations are not visible to the user or other interested parties. Professor W. Nicholson Price describes "black box" as follows:

> Algorithms can be opaque for multiple reasons. Sometimes, algorithms are nontransparent because, while they may rely on explicit rules, those rules are too complex for us to explicitly understand…….. In particular, these rules may be impossible to explain or to understand by following the process of scientific/medical discovery: mechanistic lab experiments followed by confirmatory clinical trials. Other times, the relationships used in a black box algorithm are literally unknowable because of the machine-learning techniques employed—that is, no one, not even those who programmed the machine-learning process, knows exactly what factors go into the ultimate decisions. A key distinguishing feature of black-box algorithms, as the term is used here, is that it refers to algorithms that are inherently black box (i.e.,

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[24] Goldberger AL, Goldberger ZD, Shvilkin A. *Goldberger's Clinical Electrocardiography: A Simplified Approach*, 9th ed, Elsevier/Saunders, Philadelphia 2017.

[25] Sharma S, Drezner JA, Baggish A, Papadakis M, Wilson MG, Prutkin JM, et al. International recommendations for electrocardiographic interpretation in athletes. *J Am Coll Cardiol*. 2017;69(8):1057.

[26] Kwon JM, Jeon KH, Kim HM, Kim MJ, Lim SM, Kim KH, et al. Comparing the performance of artificial intelligence and conventional diagnosis criteria for detecting left ventricular hypertrophy using electrocardiography. *Europace*. 2020;22:412.

[27] Kashou AH, Noseworthy PA. Artificial intelligence capable of detecting left ventricular hypertrophy: pushing the limits of the electrocardiogram? *Europace*. 2020;22:338.

their developers cannot share the details of how the algorithm works in practice)—rather than to algorithms that are deliberately black box (i.e., their developers will not share the details of how the algorithm works). Black-box algorithms are especially likely to evolve over time as they incorporate new data into an integrated process of learning-and-applying.[28]

The "black-box" nature of many algorithms, particularly those using deep-learning-based approaches, is a frequently mentioned area of concern. Some methods are being developed to create "explainable AI"; examples include techniques that help gain insight into the function of intermediate layers of deep neural networks and demonstrate what the network is perceiving to inform decisions.[29] This level of transparency is an important concept that is applicable not only to the methods and data used to develop the algorithm, but also interpretation of decisions or outcomes reached by the AI/ML device. One way to gain the trust of patients and providers in AI/ML today is to explain the "why" of the algorithm output as well as the "what". However, in some instances, the rules used by algorithms used in medical AI/ML may not be possible to explain. As implementation of AI/ML technology moves forward in healthcare, assurances of algorithm efficacy and safety with relevant limitations and warnings highlighted will be needed. The IMDRF risk categorization system may help calibrate the evidence needed for these assurances.

HOW IS AI/ML CATEGORIZED BASED ON RISK OF THE DEVICES?

The IMDRF provides a risk categorization system for SaMD based on the intended use of the device. The intended use is defined by the significance of information provided by the SaMD to the healthcare decision and the state of the healthcare situation condition.[30] These factors can be used to place the AI/ML-based SaMD into one of four categories, from lowest (I) to highest risk (IV), reflecting the risk associated with the clinical situation and device use (**Table 1**).

Table 1. SaMD IMDRF risk categorization.

Significance of information provided by the SaMD to healthcare decisions

[28] W. Nicholson Price II, Regulating Black-Box Medicine, 116 MICH. L. REV. 421, 430 (2017).

[29] W. Samek, A. Binder, G. Montavon, S. Lapuschkin, K.R. Müller Evaluating the visualization of what a deep neural network has learned. *IEEE Trans Neural Networks Learn Syst* (2017) 28:2660-2673.

[30] US FDA. Proposed regulatory framework for modifications to artificial intelligence/machine learning (AI/ML)-based software as a medical device (SaMD): Discussion paper and request for feedback. https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device (Accessed September 20, 2020).

State of healthcare situation or condition	Treat or diagnose	Drive clinical management	Inform clinical management
Critical	IV	III	II
Serious	III	II	I
Non serious	II	I	I

For example, a SaMD that performs diagnostic image analysis differentiating strokes that are due to oxygen deprivation (ischemia) from those due to bleeding (hemorrhagic) would be considered category IV. The information provided by the device would be used to inform time sensitive, life-saving treatments. In contrast, a SaMD that analyzes heart rate data intended to help a healthcare provider diagnose a non-life threatening arrythmia would be category II. The information provided by the device is for a serious medical condition (abnormal heart rate) but it is not time critical (not immediately life threatening) and may not require therapeutic intervention.[31]

To date, FDA has only cleared or approved AI/ML-based SaMD with algorithms that are "locked" prior to marketing. "Locked" algorithms are those that provide the same result each time the same input is provided. In contrast to locked algorithms, it is possible that an AI/ML-based SaMD could be adaptive. These AI/ML-based applications continuously learn, where the adaptation or change to the algorithm is realized after the SaMD is distributed for use and has "learned" from real-world experience. Following distribution, these types of continuously learning and adaptive AI/ML algorithms may provide a different output than what it would have provided in its initially cleared form.

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[31] IMDRF. Software as a medical device: Possible framework for risk categorization and corresponding considerations. 2014. http://www.imdrf.org/workitems/wi-samd.asp (Accessed September 25, 2020).
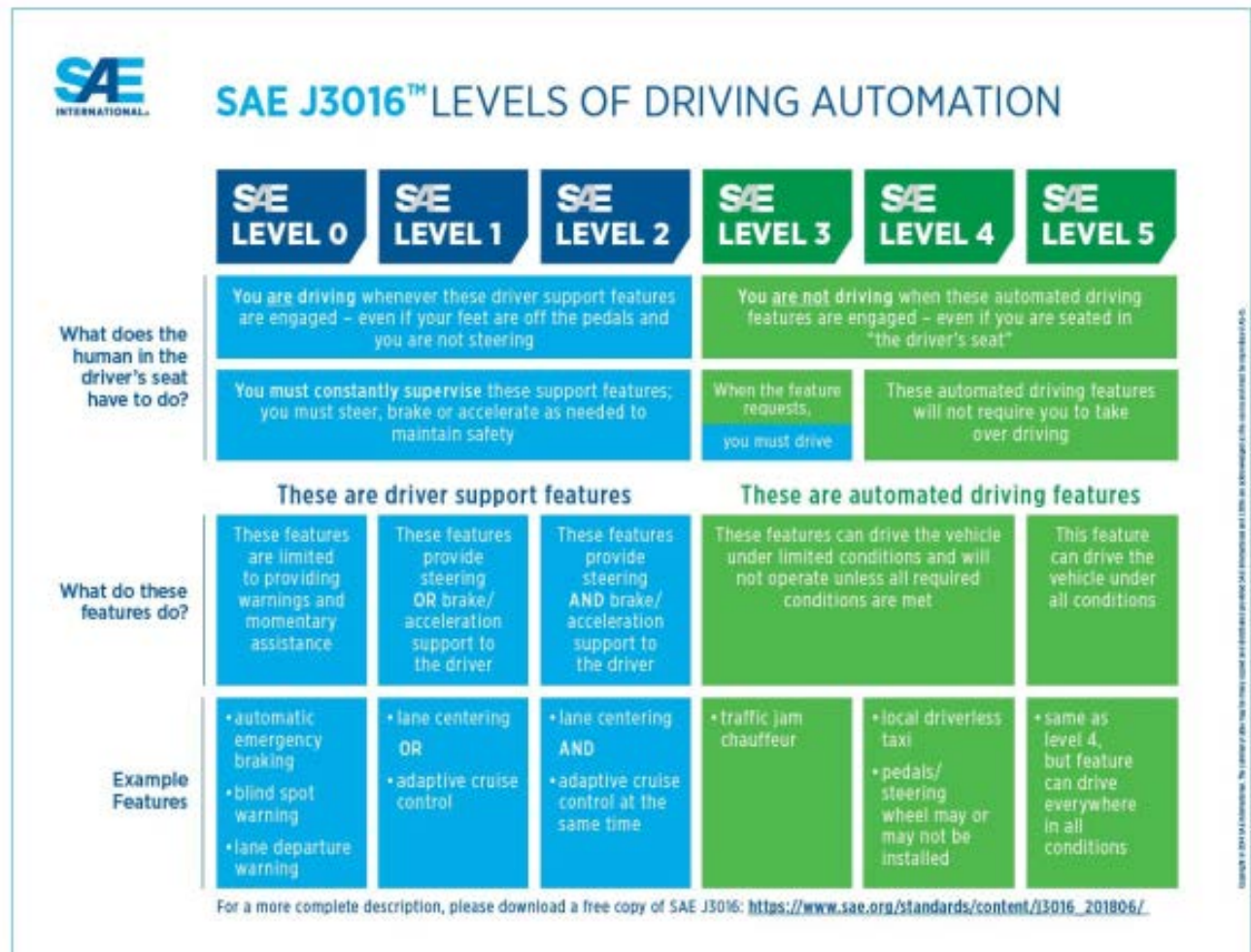
Level of Autonomy

Figure 2. The Society of Automotive Engineers International Levels of Driving Automation.

Some experts have adapted the Society of Automotive Engineers (SAE) classification for self-driving cars[32] to identify the six levels of autonomy in healthcare,[33,34] where the highest level indicates full autonomy with no requirement for human intervention or interaction (**Figure 2**). Most AI/ML systems currently being designed provide decision support where clinicians are still expected to provide oversight of algorithmic interpretations. The use of decision support

[32] Society of Automotive Engineers International. Taxonomy and definitions for terms related to driving automation systems for on-road motor vehicles. J3016_201806.

[33] JL Jaremko, M Azar, R Bromwich, A Lum, L Cheong, M Gibert, et al. Canadian Association of Radiologists white paper on ethical and legal issues related to artificial intelligence in radiology. *Can Assoc Radiol J*, 70 (2019), pp. 107-118.

[34] E.J. Topol. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med*, 2019;25:44.

software that provides the clinician real-time assistance to detect and classify lesions is a good example of an autonomy level 2 application. At level 3, the AI/ML device may complete specific tasks with the expectation that a clinician will intervene in certain scenarios. An example may be large-scale reading of capsule endoscopy reports primarily by AI/ML, with human observers only intervening when results are positive or indeterminate. As higher levels of autonomy are attained possibly in the future, the burden of responsibility may shift toward the stakeholders involved in AI/ML development and deployment.[35]

Autonomous AI/ML applications that can cause serious injury or harms (i.e., morbidity or mortality) to patients if they malfunction would be considered high risk. AI/ML software has vast capabilities to aid in clinical decision-making by detecting complex patterns that are not easily discernable by humans. However, these algorithms may have limited ability to take contextual information into account, which is normally referred to as clinician judgment for appropriate interpretation of the information. As the technology continues to evolve to potentially create greater access to care and greater efficiencies in healthcare delivery, these benefits will continue to be weighed against the risks associated the use of autonomous AI/ML.

INTUITIVE DESIGN: HOW DO HUMANS INTERACT WITH AI/ML DEVICES?

Innovative solutions employing AI/ML in medical devices have the potential to optimize and improve healthcare delivery to patients and empower patients with real-time information about their health. However, the widespread use of AI/ML devices by clinicians and patients brings with it questions about how the information is being perceived and used to achieve intended clinical needs. Intuitive designs that do not require user instructions or manuals may facilitate greater use of AI/ML across various populations irrespective of literacy. FDA evaluates how the information is perceived when reviewing human factors data for AI/ML medical devices.

Human factors engineering is the application of knowledge about human capabilities (physical, sensory, emotional, and intellectual) and limitations to the design and development of tools, devices, systems, environments, and organizations.[36] When applied correctly throughout the development of a medical device, the human factors engineering process can make medical devices more intuitive and easier to use. The technological era we find ourselves in brings complex medical products

[35] Ahmad OF, Stoyanova D, Lovat LB. Barriers and pitfalls for artificial intelligence in gastroenterology: Ethical and regulatory issues. *Techniques and Innovations in Gastrointestinal Endoscopy*. 2020;22:80-4.

[36] ANSI/AAMI HE75ANSI/AAMI HE75:2009/(R)2018 Human factors engineering - Design of medical devices

into clinics and into the home of patients and end users. These users desire products that do not require extensive training or lengthy reviews of user manuals. This is not to say that training and user manuals are not critical and often necessary to communicate important information; but with an intuitive design, training and user manuals may be simpler or even unnecessary, focus more on how the product can be used, and what the user can get out of the product as opposed to explaining technological details.

Intuitive Interface

A computer interface that is intuitive for its users, is one where they recognize a familiar situation and apply previous learnings to it. Intuitive interfaces allow users to easily navigate the system and focus on the task at hand, without much consideration to the interface itself. Activity theory is a theoretical framework that suggests the ways in which humans think cannot be separated from the physical and cultural environment that shapes our thinking.[37] Our experience with the physical environment is a global "language," accessible across different cultures. For example, one physical principle is that objects do not move on their own. Hence, an intuitive interface reflecting this principle would allow global users to move interface objects, which then remain where they are placed.[38] In addition, the cultural environment is also informative in intuitive design.

Figure 3. Example of Play button

For example, many people in the US are familiar with the image in **Figure 3** representing "play" for audio or video files. The cultural familiarity associated with this symbol makes its use on other devices, platforms or contexts intuitive.

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[37] McAvinia C. Chapter 3 Activity theory in Online Learning and its Users Lessons for Higher Education 2016, pp59-100. https://www.sciencedirect.com/science/article/pii/B9780081006269000034 (Accessed on September 20, 2020).

[38] Interaction Design Foundation. *Intuitive Design*. https://www.interaction-design.org/literature/topics/intuitive-design (Accessed September 20, 2020)

Creating AI/ML devices that are intuitive may increase its acceptability and integration into healthcare systems.

Experts have identified several features of a user-interface needed to convey an intuitive design: discoverability, affordance, comprehensibility, responsive feedback, predictability, efficiency, explorability and forgiveness.[39] In general, medical devices are encouraged to be designed such that features are easy to find when needed (discoverability) and the design adequately suggests how to perform a specific action for a given feature (affordance). The meaning and expected results from a particular action are most effective when they are well understood (comprehensibility) with results that are clearly and immediately conveyed to the user (responsive feedback) and meet expectations (predictability). An intuitive design avoids unnecessary interactions and repetition in the process of use (efficiency), allow users to use the medical device without fear of making a mistake (explorability), and easily recover from a mistake if made (forgiveness). These design features are incorporated through an iterative design process involving direct interactions or observations of the intended users and formative evaluations (e.g. cognitive walk-throughs, simulated use testing).

The incorporation of human factors principles in medical device design has many benefits to the end user: easier to comply with recommended usage of the technology, easier to understand the device output and functionality, reduced demand for customer support with more intuitive design, and quicker mastery of device operations and procedures.[40] Of the utmost importance is the safety of the end users.

Mitigating Risks for Safe Use

Through the application of human factors principles, risks to safety related to the use of a device employing AI/ML can be determined and appropriately mitigated. Determining risks to safety involves identifying potential use errors; however, predicting the types of errors that individuals will commit can be difficult given the complexity surrounding actual use situations and the uncertainty associated with an individual's goals, intentions, and attentional and affective states[41]. One method used to identify use-related risks associated with a medical device is a task analysis. A task analysis results from systematically breaking down the device use process into discrete sequences of tasks. The tasks are then analyzed to identify the user interface components involved, the use errors that users could make, and the potential results of all use errors. A task analysis can be used to study how

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[39] Intuitive Design: Eight Steps to an Intuitive UI by Everett McKay
[40] IEC/ISO TR 62366-2 Medical devices – Part 2: Guidance on the application of usability engineering to medical devices
[41] Salvendy, Gavriel. (2012). *Handbook of Human Factors and Ergonomics* (4th Edition). John Wiley & Sons.

users would likely perform each task and potential use error modes can be identified for each of the tasks. For each user interaction, the user actions can be identified using a common model called Perception, Cognition, Action (PCA), shown in **Figure 4**.[42]
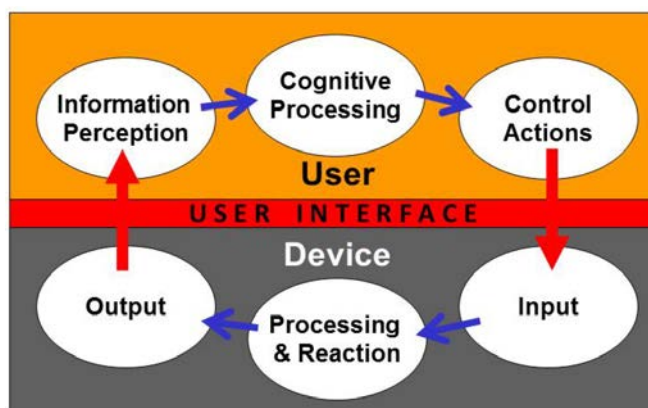

Figure 4. Device User Interface in Operational Context (adapted from Redmill and Rajan, 1997).[43]

The PCA model identifies user actions related to the perceptual inputs, cognitive processing, and physical or communicative actions involved in a task. Information from a device (i.e. device output) is perceived through our sensory system and subsequently provided some meaningful context based on our past experiences, knowledge, training, and understanding of the situation. This transformed information then informs the control actions to be taken either on the device itself (e.g. adjusting, pressing, etc.) or through communication with another person (e.g. requesting, querying, advising).[44]

Automation Bias

Automation bias is the tendency for users to exhibit greater trust in information from AI/ML technology without verification and can result in inappropriate decision-making due to overreliance on the output of the medical device.[45] There are two types of automation bias errors: automation bias omission and automation bias commission errors. Automation bias omission error occurs when users rely on the technology to inform them of a problem, but the technology fails to do so. Automation bias commission error occurs when users make choices based on incorrect suggestions or information provided by technology. Most AI/ML systems

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[42] 2016 FDA Guidance – Applying Human Factors and Usability Engineering to Medical Devices

[43] Redmill F, Rajan J. *Human factors in safety-critical systems*. University of Michigan; Butterworth-Heinemann, 1997.

[44] AAMI Applied Human Factors in Medical Device Design

[45] D. Lyell, E. Coiera. Automation bias and verification complexity: a systematic review. *J Am Med Informatics Assoc* 2016;24:423-31.

will be required to meet some threshold for reliability and accuracy, but these metrics do not provide insight into how patients/clinicians would react to inaccurate system output. It is important to understand how to detect automation bias in medical device users and best practices for mitigating this risk.

There are typically three recommended approaches to mitigating use-related risks: inherent safety by design, protective measures in the device, and/or information for safety[46]. Safety by design is considered the gold standard with information safety being the approach of last resort. For over-the-counter medical devices employing AI/ML technology that provides the user with information on which they base medical decisions and actions, the protective measures (e.g. warning statements and alerts) and information for safety (e.g. instructions for use or onboarding material for apps) become critical aspects to the device-user interface to mitigate skill degradation and automation bias. With an understanding of the potential risks and the incorporation of human factors principles into the design and development process, the device-user interface for AI/ML systems can be designed such that these residual risks are minimized.

WHAT TYPES OF MODIFICATIONS ARE MADE TO AI/ML DEVICES?

The traditional pathways for medical device regulation were not designed to account for the rapid cycles of iterative modification for software-based devices. AI/ML-powered therapeutic or diagnostic devices by design will continue to evolve, with software updates (e.g., security patches), the addition of new features or functionalities, and algorithm updates for performance improvement.[47] AI/ML-based devices can present unique challenges when they adapt and continuously learn in real time. The FDA AI/ML in SaMD discussion paper proposes a new regulatory framework for modifications to AI/ML based software as a medical device.[48] The discussion paper proposes a total product lifecycle regulatory approach that incorporates the iterative improvement process that AI/ML algorithms may use. Along the iterative cycles of algorithm development, there are common principles to consider including the quality and applicability of the dataset used for testing, the algorithm training methods, and the test methods. Confidence in the function and

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[46] ANSI/AAMI/ISO 14971:2007/(R)2016 - Medical devices— Application of risk management to medical devices
[47] Kuan R. Adopting AI in health care will be slow and difficult. HBR October 18, 2019.
[48] US FDA. Proposed regulatory framework for modifications to artificial intelligence/machine learning (AI/ML)-based software as a medical device (SaMD): Discussion paper and request for feedback. https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device (Accessed September 20, 2020).

performance of the algorithm can be supported with appropriate validation, transparency and claims after the modification.[49]

Three categories of modification have been identified following initial approval of the SaMD based on the following characteristics (**Table 2**):

- clinical and analytical **performance**;
- **inputs** used by the algorithm and their clinical association to the SaMD output; and/or
- **intended use.**

Table 2. Possible Modifications to AI/ML-based SaMD.

Modification Type	Description	Intended use	Input	Example
Improve Analytical and/or Clinical Performance	Retraining with new data sets, change in AI/ML architecture	unchanged	unchanged	• Increased sensitivity of SaMD at detecting breast lesions suspicious for cancer in digital mammography
Change Inputs	Changes to algorithm so it may be used with new types of input signals or same type of input signals from different sources	unchanged	changed	• Support compatibility with CT scanners from different manufacturers • Expand to using oximetry data in addition to heart rate to diagnose atrial fibrillation
Change Intended Use	Change from "aid in diagnosis" to "definitive diagnosis"	changed	Potentially changed	• Expand algorithm to detect multiple types of cancer • Expand use to children when initially intended for adults

[49] US FDA. Proposed regulatory framework for modifications to artificial intelligence/machine learning (AI/ML)-based software as a medical device (SaMD): Discussion paper and request for feedback. https://www.fda.gov/medical-devices/software-medical-device-samd/artificial-intelligence-and-machine-learning-software-medical-device (Accessed September 20, 2020).

WHAT ARE THE POTENTIAL SOURCES OF ERROR IN AI/ML MEDICAL DEVICES?

Errors are inevitable in any healthcare delivery mechanism. Taking careful steps during the early development stage of AI/ML can ultimately help improve patient safety. Engagement with clinical users and patients is key during the development of any AI/ML device to ensure that potential risks are identified early before they become embedded in the delivery of care. AI/ML algorithms have the potential for a bias and "brittleness" (tendency to be easily fooled) including the following:

- not generalizable to different populations,
- propagating unintentional biases in clinical practice, and
- accidentally fitting confounders rather than true signal.[50]

Not generalizable to different populations

Advances in science show us that the attributes of sex, age, and race are contained within the chromosomal complement of every cell and alter physiology at the molecular, cellular, and macro-organism level. In addition, these attributes along with gender and ethnicity affect behavior, perception, and health; and this has implications for biomedical research, intervention, and all of health care. It is important to include all populations, including underrepresented populations to refine artificial intelligence algorithms, and drive development of innovations that perform best in all populations for which the intervention was intended. It is about improving data quality, strengthening the science, and enriching patient information.

Kelly et al classifies algorithmic bias in to three components: (1) model bias (model selected to represent the majority); (2) model variance (inadequate data from minority groups); and (3) outcome noise (unobserved variables interacting with model predictions). Careful analysis of AI/ML device performance in diverse patient populations (e.g., sex, gender, age, race, ethnicity disease spectrum) may help identify the impact of these biases on the delivery of care. This type of analysis requires representative data from different sub-populations and the collection of such data is contingent upon multiple factors.

Increasingly, legal considerations across jurisdictions are being considered when compiling a curated data set needed to train and test the algorithms. Assembly of and access to curated datasets may be challenged by privacy concerns and other

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[50] Kelly CJ, Karthikesalingam A, Suleyman M, et al. Key challenges for delivering clinical impact with artificial intelligence. *BMC Med* 2019;17: 195. https://doi.org/10.1186/s12916-019-1426-2.

legal provisions (e.g. European Union General Data Protection Regulation (GDPR) and US Health Insurance Portability and Accountability Act (HIPAA) as well as record identification concerns. Current European data protection laws and data governance models such as GDPR aim to give control to individuals over their personal data. Individual patients must not only consent to the collection of the data but also to each use of the data. The absence of a broad consent that would allow for generalized data use limits the creation of databases that multiple developers could use. In addition, developers must be able to explain in plain language how their data will be used (explainability) as part of the consent process and with some AI/ML devices that can be challenging.[51] Without access to sensitive medical records, it is challenging to optimize the algorithms to be representative and generalizable. Differential sharing of patient data impacted by other extrinsic factors (e.g., competitive advantage, commercial considerations) may also lead to systematic biases in the algorithm.[52] This tension highlights the balance between patient privacy and better user experience achieved by using personal data to refine algorithms.

Propagating Biases

Because algorithms in AI/ML are trained using data from historical datasets, they may mirror human biases in decision making. Health care delivery is known to vary by race and ethnicity; therefore, it is possible that these same biases may be inadvertently introduced into the algorithms. Medical records of some of the most vulnerable groups might be poorly collected or digitized resulting in sample size disparity.[53] Hence, the available raw data could reflect and expand existing bias, leading to unfair impacts on members of different groups based on gender, race, age, and ethnicity.[54] The use of historical data to train algorithms may lead to inaccurate conclusions in different racial and ethnic groups. [55,56,57] For example,

[51] Geis J, Brady A, Wu CC, et al. Ethics of artificial intelligence in radiology: summary of the joint European and North American multisociety statement. *Insights into Imaging* 2019;10:101.
[52] Schönberger D. Artificial intelligence in healthcare: a critical analysis of the legal and ethical implications. *Int J Law Info Tech* 2019;27:171–203.

[53] Schönberger D (2019) Artificial intelligence in healthcare: a critical analysis of the legal and ethical implications. *Int J Law Info Tech* 2019;27:171–203.
[54] Obermeyer Z, Emanuel EJ (2016) Predicting the future—big data, machine learning, and clinical medicine. *N Engl J Med* 2016;375:1216–9.

[55] Char DS, Shah NH, Magnus D. Implementing machine learning in health care—addressing ethical challenges. *N Engl J Med* 2018; 378:981-3.

[56] Pesapane F, Volonte C, Codari M, et al. Artificial intelligence as a medical device in radiology: ethical and regulatory issues in Europe and the United States. *Insights Imaging*. 2018;9:745-53.

[57] Crawford K, Calo R. There is a blind spot in AI research. *Nature*. 2016;538:311–3.

studies have shown that algorithms designed to classify skin lesions performed similar to that of board-certified dermatologists on patients with light-colored skin but underperformed on patients with darker skin tones.[58,59] AI/ML algorithms in non-medical areas have made similar errors. A program designed to aid in sentencing by predicting the defendant's risk of recidivism showed a propensity to discriminate based on race and ethnicity.[60] In another example, a twitter-based chatbot was taught by a user community to make racially offensive comments which underscored the importance of quality data being used to inform AI/ML systems.[61]

Fitting confounders

Errors in AI/ML can occur when confounding factors are correlated with pathologic entities in the training datasets rather than actual signs of the disease. For example, an AI/ML device that detects pneumonia on chest radiographs may base the diagnosis of pneumonia on where the chest radiograph was taken and using what equipment, learning an association with a portable x-ray machine and pneumonia instead of the image markers of the disease. Because individuals who receive portable chest radiographs are usually very ill and have a high likelihood of having a pneumonia, the device capturing the image is inappropriately associated with the diagnosis.[62] To help mitigate diagnostic errors, many professional societies are recommending that AI/ML devices become more transparent, clearly identifying the specific features being learned by the neural networks.[63] This information will be critical when AI/ML devices are used in multiple healthcare settings and informed by images obtained from multiple different devices.

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[58] Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, et al. Dermatologist-level classification of skin cancer with deep neural networks. *Nature*. 2017;542:115–8.

[59] Haenssle HA, Fink C, Rosenberger A, Uhlmann L. Reply to "Man against machine: diagnostic performance of a deep learning convolutional neural network for dermoscopic melanoma recognition in comparison to 58 dermatologists." *Ann Oncol*. 2019. https://doi.org/10.1093/annonc/mdz015.

[60] Angwin J, Larson J, Mattu S et al. *Machine bias*. (2016) https://www.propublica.org/article/machine-bias-risk-assessments-in-criminal-sentencing

[61] Hammond K.(2016). 5 unexpected sources of bias in artificial intelligence https://techcrunch.com/2016/12/10/5-unexpected-sources-of-bias-in-artificial-intelligence/

[62] Zech JR, Badgeley MA, Liu M, Costa AB, Titano JJ, Oermann EK. Variable generalization performance of a deep learning model to detect pneumonia in chest radiographs: a cross-sectional study. *PLoS Med*. 2018;15:e1002683.

[63] D Schiff and J Borenstein. How should clinicians communicate with patients about the roles of artificially intelligent team members? *AMA Journal of Ethics* 2019; 21:E138-145.

Biased training data, inconclusive correlations, lack of intelligibility, inaccuracy, unfair outcomes, and other key concerns impact the trust users have in the decision-making capacity of AI/ML devices.

WHAT ARE OTHER CONSIDERATIONS FOR AI/ML MEDICAL DEVICES?

Data ethics are central to AI/ML, specifically informed consent, privacy and data protection, ownership, objectivity, transparency, and access.[64] It is important for patients to understand the benefits, risks and limitations of medical devices that incorporate AI/ML. Transparency about the function of and modifications to AI/ML-based medical devices that may learn and change over time is a key aspect to ensure their safety. The agency heard from stakeholders as part of feedback received from the AI/ML discussion paper that manufacturers should make the following information available: (1) clear description of data that were used to train the system, (2) the relevance of the input to the algorithm, (3) the logic employed by the application and (4) the evidence of its performance. This information may be important to foster trust in AI/ML, facilitate the patient provider decision-making process, and generate improved patient outcomes.

Trust

In May 2019, the United States joined with more than 40 other countries to endorse the Organization for Economic Co-operation and Development (OECD) AI Principles.[65] Recognizing that the trustworthiness of AI/ML systems is a key factor for the diffusion and adoption of AI/ML devices, the document set forward the following principles for responsible stewardship of trustworthy AI/ML:

- Inclusive growth, sustainable development, and well-being;
- Human-centered values and fairness;
- Transparency and explainability;
- Robustness, security, and safety; and
- Accountability.

Currently, there is a trade-off between performance and explainability. The best performing models (such as deep learning) are often the least explainable, whereas models with poorer performance (such as linear regression, decision trees) are the most explainable. If 'black box' algorithms are to be used in healthcare, they need to be used with knowledge, judgement, and responsibility. Explainable AI/ML approaches are likely to facilitate faster adoption of AI systems into the clinical

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[64] Geis JR, Brady A, Wu CC, et al. Ethics of artificial intelligence in radiology: summary of the joint European and North American multisociety statement. *Insights into Imaging* 2019;10:101.

[65] *Recommendation of the Council on Artificial Intelligence*. 2019; Available from: https://legalinstruments.oecd.org/en/instruments/OECD-LEGAL-0449.

healthcare setting and will help cultivate transparency and trust with their users. The use of AI/ML devices in clinical care raises questions around accountability, transparency, permission, and privacy.[66]

AI algorithms could also be subject to programming in a way to guide users toward clinical actions that would generate increased profits for purchasers such as recommending treatments, tests, or medical devices in which they hold stake or by altering referral patterns which may not necessarily result in better care.[67] Transparency may help garner trust among healthcare providers who use these devices.

AI/ML devices are also transforming the home environment. Wearable AI/ML biometric monitoring devices (BMDs) enable the remote measurement and analysis of patient data in real time. A recent study with adult patients with chronic conditions in France, "Community of Patients for Research" (ComPaRe) evaluated the potential benefits and dangers of wearable devices.[68] Some of these included AI/ML used to screen for skin cancer, remote monitoring of chronic conditions to predict exacerbations, smart clothes to guide therapy, and AI/ML chatbots used to answer emergency calls. While 20% of the ComPaRe participants felt that the benefits of the technology (improved reactivity in care and reduced burden in treatment) outweighed the dangers of the technology (inadequate replacement of human intelligence in care, risks of hacking, misuse of private patient data by caregivers, insurance companies, etc.), 35% of the patients refused to integrate at least one existing or soon-to-be available intervention using BMDs and AI/ML-based tools in their care. Additionally, even among the ComPaRe patients who were amenable to using technology in their care, they preferred AI/ML as a complement – and not as a replacement – for human care for situations related to sensitive topics (cancer) or those that involved lasting interventions (monitoring for chronic conditions).[69] The specific application of these general principles to AI/ML in

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[66] Davenport T and Kalakota R. The potential for artificial intelligence in healthcare. *Future Healthc J* 2019; 6: 94–8.

[67] Pesapane F, Volonte C, Codari M, et al. Artificial intelligence as a medical device in radiology: ethical and regulatory issues in Europe and the United States. *Insights Imaging*. 2018;9(5):745-53.

[68] Tran, V.-T., C. Riveros, and P. Ravaud, *Patients' views of wearable devices and AI in healthcare: findings from the ComPaRe e-cohort.* NPJ digital medicine, 2019. **2**: p. 53-53. https://www.nature.com/articles/s41746-019-0132-y (Accessed on September 20, 2020).

[69] Tran, V.-T., C. Riveros, and P. Ravaud, Patients' views of wearable devices and AI in healthcare: findings from the ComPaRe e-cohort. *NPJ digital medicine,* 2019. **2**: p. 53-53. https://www.nature.com/articles/s41746-019-0132-y (Accessed on September 20, 2020).

medical devices requires input from all stakeholders, including patients and caregivers, clinicians, device developers/manufacturers and regulators.

Validation

Major questions regarding validation revolve around the composition of the validation data set, the criteria used for determining whether the device recommended the correct diagnosis or action, and whether the use of the device was compared to a control arm. The ability of AI/ML-based devices to learn and re-learn in an iterative way also raises new questions such as what the changes are and how the changes in device performance will be measured and communicated to the user in the most effective way.

As Ploug and Holm[70] suggest, any patient wanting to contest the diagnoses of an AI/ML diagnostic device requires the availability of different types of information about the AI/ML device's use of data, the device's potential biases, device performance, and the division of labor between the device and the healthcare professionals. It is important that AI/ML devices are taught how to recognize various differences between people, provide personalized decisions tuned to individuals and not present a perspective from a homogenized composite, which may be representative of a very small subset of the patient population.[71] This transparency is an essential element supporting user's trust in the recommendations and output of these devices.

Real-world Application

The translation of AI/ML to clinical practice may be facilitated by more prospective studies to show how the AI/ML devices perform in the real-world. In addition, the publication of these studies in peer-reviewed journals are transparent means of sharing the information to engender trust and adoption of AI/ML.[72] Publishing data can illuminate whether specific AI/ML devices lead to improvements in patient and public health. For example, an unmasked, randomized clinical trial of a device used to provide automated interpretation of fetal heart rates during the labor of pregnant women found no improvement in clinical outcomes for mothers or the babies.[73] This study illustrates the "AI chasm" a term reflecting how accuracy does not

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[70] Ploug, T. and S. Holm, The four dimensions of contestable AI diagnostics – A patient-centric approach to explainable AI. *Artificial Intelligence in Medicine*, 2020; **107**: 101901.

[71] Sturgis, K. *How Artificial Intelligence is changing medical devices*. Available from: https://www.mddionline.com/software/how-artificial-intelligence-changing-medical-devices.

[72] Kelly CJ, Karthikesalingam A, Suleyman M, et al. Key challenges for delivering clinical impact with artificial intelligence. *BMC Med 17*, 2019;195. https://doi.org/10.1186/s12916-019-1426-2.

[73] Brocklehurst P, Field D, Greene K, Juszczak E, Keith R, Kenyon S, et al. Computerised interpretation of fetal heart rate during labour (INFANT): a randomised controlled trial. *Lancet*. 2017;389:1719–29. https://doi.org/10.1016/s0140-6736(17)30568-8.

necessarily represent clinical benefit.[74] This gulf between a scientifically sound algorithm and its usefulness in the real world could impact adoption and integration into clinical workflows.

Informed Consent & Patient Perspectives on AI/ML

The novelty and recent integration of AI/ML devices in clinical care place unique challenges on the informed consent process. Unlike traditional health-related software, patients are often not aware that their "chat", diagnosis, or treatment recommendation, is coming from an AI/ML-based device. Informed consent to use AI/ML devices in the care of patients can be complex given the uncertainties, fears or possible overconfidence about the performance of AI/ML.[75] Patients have voiced concerns about the credibility of AI/ML devices, data privacy and the loss of human interactions.[76] In a survey of 2000 US adults, college graduates (57%) were more likely to support developing AI than those with a high school or less education (29%).[77] A qualitative survey of 155 patients on their views of AI/ML in diagnostic radiology showed that the level of trust in the AI system was associated with the level of education.[78] Vulnerable patients, including racial and ethnic minorities, the underinsured or uninsured, economically disadvantaged and those with chronic health conditions could be at risk for improper consent for use of AI. A 2017 population survey of 2200 adults showed that those who claimed to know not much or nothing at all about AI were more likely to have an annual income of less than $50,000 (49%) and no college education (52%).[79] Given the complexity of the technology, it may be important for healthcare providers to have clear conversations about the use of the technology in their diagnoses and care as appropriate.

Skill degradation

If the clinical decision-making choices are provided at every decision point across the care continuum or consistently executed by automation, in time, the device user will not be as skilled in seeking or processing information, making decisions, or

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[74] Keane PA, Topol EJ. With an eye to AI and autonomous diagnosis. *Npj Digital Medicine* 2018;1:40. https://doi.org/10.1038/s41746-018-0048-y

[75] Schiff D, Borenstein J. How should clinicians communicate with patients about the roles of artificially intelligent team members? *AMA J Ethics* 2019;21:E138-145.

[76] Nelson CA, Perez-Chada LM, Creadore A, et al. Patient perspectives on the use of artificial intelligence of skin cancer screening : a qualitative study. *JAMA Dermatol* 2020 online

[77] Zhang B, Dafoe A. *Artificial intelligence: American attitudes and trends*. Oxford, UK: University of Oxford; 2019.

[78] Ongena YP, Haan M, Yakar D, et al. Patients' views on the implementation of artificial intelligence in radiology: development and validation of a standardized questionnaire. *Eur Radiol* 2020;30:1033-40.

[79] Morning Consult. *National tracking poll 170401*. Survey report. Updated October 22, 2018. https://morningconsult.com/wp-content/uploads/2017/04/170401_crosstabs_Brands_v3_AG.pdf

executing on choices. This may lead to failure to recall critical knowledge and skill decay. This problem can be attributed to a lack of practice or engagement. Skill degradation is mainly a concern for clinicians who utilize AI/ML technology to perform clinical tasks or make decisions. For example, you may consider whether the ability of a radiologist to detect, characterize, and monitor disease based on radiographs deteriorates if the decisions were facilitated by AI/ML. Degradation of clinical decision management skills in patients may also follow prolonged use of AI/ML devices. For example, type 1 diabetic patients using an automated glycemic controller device capable of automated insulin dosing management may experience a decay in skills necessary to manage their disease such as insulin dose or insulin-to-carbohydrate ratio calculation, carbohydrate counting, and adjustment of treatment protocol to physical exercise.[80]

CONCLUSIONS

Over the past decade, AI/ML has opened new diagnostic and therapeutic horizons but has also introduced novel ethical and methodologic challenges. As we seek to proactively develop nimble regulatory approaches for this technology, protecting health equity, increasing transparency, and fostering trust and acceptability of the technology also remain priorities. This new frontier requires insights from all stakeholders to ensure a reasonable assurance of safety and effectiveness so that the devices positively impact clinical outcomes and quality of care.

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[80] A. Quintal, V. Messier, R. Rabasa-Lhoret, E. Racine, "A critical review and analysis of ethical issues associated with the artificial pancreas" *Diabetes & Metabolism*, 2019;45: https://doi.org/10.1016/j.diabet.2018.04.003.