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AI IN IMAGING AND THERAPY: INNOVATIONS, ETHICS, AND IMPACT: REVIEW ARTICLE

AI and machine learning ethics, law, diversity, and global impact

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ABSTRACT

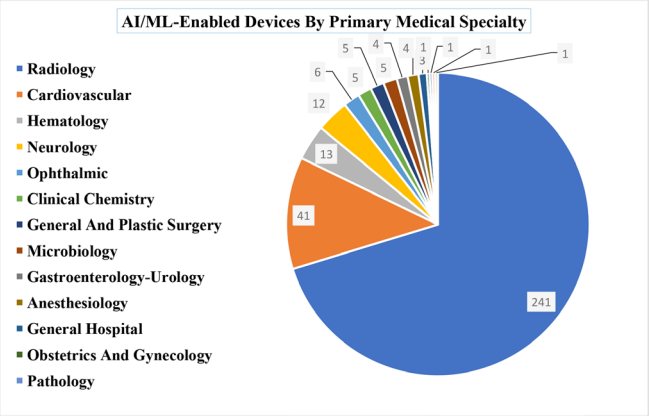
Artificial intelligence (AI) and its machine learning (ML) algorithms are offering new promise for personalized biomedicine and more cost-effective healthcare with impressive technical capability to mimic human cognitive capabilities. However, widespread application of this promising technology has been limited in the medical domain and expectations have been tampered by ethical challenges and concerns regarding patient privacy, legal responsibility, trustworthiness, and fairness. To balance technical innovation with ethical applications of AI/ML, developers must demonstrate the AI functions as intended and adopt strategies to minimize the risks for failure or bias. This review describes the new ethical challenges created by AI/ML for clinical care and identifies specific considerations for its practice in medicine. We provide an overview of regulatory and legal issues applicable in Europe and the United States, a description of technical aspects to consider, and present recommendations for trustworthy AI/ML that promote transparency, minimize risks of bias or error, and protect the patient well-being.

INTRODUCTION

Artificial intelligence (AI) and machine learning (ML) algorithms are currently transforming biomedical research, especially in the context of cancer research and clinical care. One of earliest major AI/ML initiatives in biomedicine was the MYCIN project at Stanford in the 1970s. MYCIN was a rule-based system to identify bacteria types that may cause infectious diseases and recommend antibiotics.[1] In a blinded evaluation by a panel of experts, it was able to achieve an acceptability rating of 65%.[2] However, wider implementations of AI/ML took place in radiological sciences starting in the 1980s with the emergence of computer-aided detection (CADe) and computer-aided diagnosis (CADx) systems. CADe/x provided radiologists with a computer output that acted as a "second opinion" to aid in making final clinical decisions.[3] A major success of these systems has been reported in the areas of breast cancer imaging.[4] These efforts resulted in the first Food and Drug Agency (FDA) approved CADe system known as R2 ImageChecker in 1998.[5] However, the application of this CADe system was also controversial in the literature with contradictory multi-institutional studies; some suggesting that it would reduce accuracy,[6] while others suggesting it would improve accuracy.[7] It would take nearly another two decades to approve the first CADx system in radiology known as QuantX in 2019, sounding the alarm early on the challenges and barriers associated with the application of AI/ML systems in medicine.

Recent advances in AI/ML software algorithms and availability of powerful computing hardware resources have resulted in tremendous expansion in the potential application of AI/ML into various areas of medicine.[8] In each of these medical areas, AI/ML is expected to reshape its practice with examples in radiological sciences,[9] cardiology,[10] hematology,[11] neurology[12] and ophthalmology[13] to name a few. Indeed, the FDA has been busy approving many AI-based systems recently.[14] Starting in April of 2019, the FDA has published several white papers on its regulatory process for considering AI/ML-based Software as a Medical Device (SaMD).[15] SaMD AI/ML could be categorized as class I, II, or III according to the amount of control that is necessary to ensure that the device is safe and effective for patients and providers. This classification determines the type of premarket processes that are required for the device. These generally could be 510(k) approvals (classes I and II), which are equivalent to an already approved device or could go through the *de novo* pathway, which is utilized

Figure 1. FDA approved SaMD devices by primary medical specialty between 04/2019 and 09/2022. AI, artificial intelligence; ML, machine learning; SaMD, Software as a Medical Device.



for devices that are proven safe but are different than any other device that had been previously marketed. To date, more than 300 SaMDs have been approved with radiology accounting for the greatest portion (70%) followed by cardiology, hematology, neurology, and ophthalmology accounting for 12%, 3.8%, 3.5%, and 1.7%, respectively, as represented in Figure 1. In addition to the primary medical specialty attributed to each device, the devices are also utilized in vast secondary specialties. Table 1 conveys the utilization of these tools in oncology and their overlap with other medical specialties. The majority of AI/ML powered devices have been approved through the 510(k) pathway, as summarized in Table 2.

Despite the hype and these anticipated potentials, application of AI/ML in daily clinical practice remains scarce. This can be attributed to technical challenges such integration into the clinical workflow but also to lengthy regulatory processes, and ethical issues regarding concerns that AI/ML driven technologies may exacerbate existing racial and gender inequity due to inherent bias in the training process and lack of prediction transparency.

The challenge of trustworthy AI

The notion of trustworthy AI has been highlighted in the European Commission description as well as by the FDA and the National AI initiative act of 2020 as a remedy to overcome skepticisms and fears concerning the application of AI in general and in healthcare specifically. These bodies advocate for more lawful, ethical, and robust application of AI from technological and societal perspectives.

Examples of AI failures

There have been numerous examples of AI failures or reported bias primarily related to social norms such as gender and race. The field of biomedicine has not been immune to these biases. For instance, an ML algorithm that was developed for predicting the risk of pneumonia, it counterintuitively suggested that patients with pneumonia and asthma will be at a lower risk of death than patients with pneumonia but without asthma.[16] Similar controversial examples were also noted in the case of skin cancer risk prediction, where the presence of a ruler in the image may have been a cue for the ML algorithm of high risk,[17] or in the case lung disease where the appearance of a tube in a chest X-ray was an indication of disease severity.[18] Covid-19 pandemic has also compounded this problem with many of the Covid-19 studies

Table 1. FDA approved SaMD devices with oncology applications from 04/2019 to 09/2022.

Primary medical specialty	Number of devices in primary medical specialty	Number of devices with oncology applications
Radiology	241	157
Cardiovascular	41	0
Hematology	13	10
Neurology	12	1
Ophthalmic	6	0
Clinical chemistry	5	0
General And Plastic Surgery	5	3
Microbiology	5	0
Gastroenterology-Urology	4	3
Anesthesiology	4	0
General Hospital	3	0
Obstetrics And Gynecology	1	0
Pathology	1	1
Dental	1	0
Orthopedic	1	0
Total	Total: 343	Total: 175

SaMD, Software as a Medical Device.

Table 2. FDA approved SaMD devices approvals between 04/2019 and 09/2022.

Pathway to approval by primary medical specialty			
Specialty	**510(K)**	***de novo***	**Total**
Radiology	237	4	241
Cardiovascular	37	4	41
Hematology	12	1	13
Neurology	9	3	12
Ophthalmic	5	1	6
Clinical chemistry	4	1	5
General and plastic surgery	5	0	5
Microbiology	4	1	5
Gastroenterology-urology	3	1	4
Anesthesiology	4	0	4
General hospital	3	0	3
Obstetrics and gynecology	1	0	1
Pathology	1	0	1
Dental	1	0	1
Orthopedic	1	0	1
Total	327	16	343

SaMD, Software as a Medical Device.

replicating each other with limited size data sets, unclear findings or a defined path towards clinical utility.[19] More recently, the electronic health records software, EPIC, implemented a tool for predicting sepsis that has been the subject of controversy in the field. In this case, a multi-institutional study found that the Epic implemented model predicted the onset of sepsis with an area under the curve (AUC) of only 0.63, which is significantly worse than the acclaimed performance by its developers.[20]

In spite of AI known potentials in radiological sciences,[9] issues related to data quality, pre-processing, independent testing, proper selection of AI/ML algorithms, and transparency of AI findings have inadvertently contributed to irreproducible and conflicting results in the literature.[21] Many of these algorithms are being evaluated for clinical trials selection, for deciding which treatment should be used, and are potentially applied to make life and death decisions. Therefore, there is a need to better validate and regulate the implementation of such AI/ML algorithms with their far-reaching impact. Towards this goal, there has been shifts toward developing more explainable/interpretable AI algorithms,[22] which would allow for better transparency, oversight, and accountability as discussed later.

ETHICAL CHALLENGES AND IMPACT ON SOCIETY

Fiduciary duty and the practice of medicine

The physician–patient relationship is one of fiduciary duty, in which there is asymmetric knowledge, competence, trust, and self-determination.[23] Assuming the role of the fiduciary, the physician has certain legal, professional, and ethical obligations towards the patient, including loyalty, acting in the patient's best interest, and providing patients with medical information and advice in such a way that allows them to make informed decisions about their health.[23]

The medical profession has numerous safety regulations in place designed to protect all actors involved in patient care. Noteworthy in the United States are state medical practice acts, which dictate who can prescribe or administer medication, treat or diagnose disease, and perform other functions typically regarded as reserved for physicians.[24] Key to this is the concept of the "practice of medicine,"[24] which begs the question: can and should AI/ML be allowed to practice medicine?

The Council of Europe outlines six areas where AI may impact the physician–patient relationship: (1) inequality in access to high quality healthcare; (2) transparency; (3) risk of bias; (4) patient well-being; (5) automation bias, deskilling, and displaced liability; and (6) privacy.[25]

In the USA, the American Medical Association (AMA) is clear that physicians will retain their primacy in healthcare as AI/ML continues to infiltrate the clinic. Using the term augmented intelligence (rather than artificial intelligence), the AMA focuses on AI's assistive role in enhancing and scaling human intelligence rather than replacing it.[26] Many stakeholders assert that physicians should remain in the loop (so called human-in-the loop (HITL), continuing to be present and active participants in patient care and having the ability to override AI/ML decisions. HITL may actually still be a necessity to achieve better

performance rather than an option as pure data-driven AI algorithms are still evolving, as discussed later. Even in cases where AI is substituting for physicians, the workflow should include a healthcare provider to monitor the process as quality controller such identifying misbehavior, providing accountability,[27] avoiding giving AI/ML unintended authority, mitigating bias, and avoiding an echo chamber effect in which medical discovery slows or halts as all medical data comes from machines.[28]

How AI/ML will change the practice of medicine: automation bias, deskilling, and reliance

As AI/ML becomes increasingly prominent in healthcare, it raises a myriad of concerns about its impact on how physicians practice medicine. The problems of automation bias and deskilling are at the forefront of these concerns. Automation bias occurs when clinicians over rely on AI/ML and leads to a reduction in their personal efforts to verify the machine's outputs,[29] creating concerning patient safety risks. Haupt asserts that physicians using AI in radiology may only give a cursory review of the outputs, making them more likely to overlook certain cancers (particularly in trickier cases) and overall degrading the performance of expert readers.[23] Additionally, a study conducted by Lyell et al showed that even when warned about the potential errors in a clinical decision support tool, medical students still committed omission (failure to notice problems because not alerted to them) and commission (complying with incorrect recommendations) errors due to an overreliance on the technology.[29] Participants also changed their answers a significant amount of times from correct to incorrect after being provided with incorrect advice by the technology.[29] Thus, while AI/ML can be an asset in reducing clinician error when correct, physicians should maintain caution around AI/ML generated results and remain vigilant when reviewing its outputs, consciously taking care not to fall victim to the *looking-but-not-seeing effect* or *inattentional blindness*.[23,29] As with other medical advice, physicians must determine if AI/ML results are applicable in their specific context and decide whether they must gather additional data or information to make a fully-informed, accurate decision.[23]

AI/ML may also generate unfortunate changes in physicians' skill sets. Deskilling—another consequence of overreliance on AI/ML—will have reverberating effects on current medical practice, the training of future doctors, and will possibly lead to an irreplicable loss of medical knowledge. For instance, when AI/ML displaces doctors in a particular specialty, there will naturally be less demand and thus less training opportunities for this specialty, leading to a reduction in human capacity in this field over time.[28] Eventually, human knowhow may decrease to a point where physicians act as a simple check on the machine and lose the ability to catch and correct AI/ML errors.[30] At this point, society could become stuck in a world where AI/ML is entirely responsible for healthcare outcomes and physicians and patients alike must follow it blindly. It is inevitable that AI/ML will sometimes fail. Physicians must be able to take over a procedure manually, particularly in an emergency. It is thus crucial that physicians maintain the same level of expertise currently demanded by the profession to mitigate damages when AI unavoidably and foreseeably fails.[31]

Ironically, deskilling also leads to obstacles in the continuing improvement of AI/ML and makes it harder to train new AI/ML algorithms.[28] Once new diagnostic sensors are available, such as an imaging machine producing higher quality images than before, AI/ML will need to be entirely retrained, as these images represent new data. There must still be human experts in the field who can work to generate this new training data for the AI/ML.[28] As the legal standard of care evolves alongside AI/ML, it will need to change in such a way that incentivizes physicians to use the technology but avoids encouraging an overreliance on the machine as a strategy to avoid malpractice. There are countless theories as to what would be an appropriate change to the standard of care once AI/ML has proven superior to humans in certain tasks, many of which are beyond the scope of this section.[28,31] One hopeful possibility is that the standard of care becomes one that requires the use of AI/ML plus meaningful review by a human doctor.[28] This standard could help attenuate the ramifications of a machine-controlled healthcare environment, such as automation bias and deskilling.

Human aspects of the physician–patient relationship

While AI/ML can greatly benefit healthcare, it cannot replace critical components of the physician–patient relationship—the core tenets of which are trust, knowledge, regard, loyalty,[32] and empathy. Empathic, emotionally engaged physicians have been shown to have greater therapeutic efficacy by encouraging trust, eliciting fuller histories, decreasing patient anxiety, and promoting patient engagement in their own health.[33] As impaired physician–patient relationships have been associated with worse health outcomes,[32] it is imperative to preserve this relationship as a central value throughout AI/ML development and integration.

The practice of medicine is characterized by an abundance of intangible qualities that the human physician will always excel at relative to machines. These include empathy, compassion, touch, eye contact, and picking up nuanced social cues such as tone of voice.[31,34] People want to be cared for by other *people*, and it is vital to recognize the power of human interaction such as a hand on the back during a difficult conversation or a facial expression of genuine sorrow—actions which can sometimes communicate care better than words. When there is little more that scientific knowledge can do for a patient, a doctor can continue to provide care through practicing the "art," or the human aspects, of medicine.[31] While AI/ML certainly attempts to mimic qualities such as empathy, it is unlikely that machines will ever be able to substitute for the sacred bond that comprises the physician–patient relationship. Additionally, physicians have a non-linear working method that is not only an advantage in medical decision-making, but also infuses the physician–patient relationship with levels of personalization not allowed for by a data-driven or machine-only regime. Diseases may have similar features that AI/ML can easily recognize, but patients and their lifestyles are vastly different. Diagnoses and treatments thus require creativity and problem-solving skills that machines do not possess.[35] AI/ML learns off documented, structured data, but humans often do not fit into such neat boxes. Indeed, physicians make care

decisions based on more than data points in the patient chart: they use clinical intuition, years of experience, and context.[31] This last point—context—is of particular significance. Patients have different priorities and preferences, and part of the physician–patient relationship rests on the doctor's sensitivity to and incorporation of patient values into healthcare decisions. In an AI/ML world, physicians must have the ability to adjust an algorithm's optimization criteria and incorporate additional variables to refine the decisions in accordance with a specific patient's needs and desires.[28]

The patient–physician relationship is one of critical importance. As we move forward, we must not ask the question of how to replace physicians with machines, but rather, how we can ensure that AI/ML will enhance this relationship, and therefore healthcare itself.

SAFETY AND RELIABILITY OF AI/ML

Current literature provides several strategies to anticipate and address issues of safety and reliability of AI/ML.[36–42]

Identify the value proposition of AI/ML linked to performance metrics

Anticipating safety and clinical performance begins during product development prior to testing or implementation in the clinical setting.[37,41,43] The UK Department of Health & Social Care Guidance and experts recommend that developers articulate a clear value proposition.[37,41,43] This should address: what problem or need the product is designed to solve (such as improving efficiency, workflow, diagnostic certainty); how the product meets the specific need (including cost effectiveness and sustainability over time); and identifying outcome metrics for success and key performance indicators.[37,41,43] Mahadevaiah et al assert that implementing AI/ML should be part of a wider, coherent quality improvement strategy.[37] Clinicians and health professionals should assess areas where there is a clinical quality gap relating to processes or patient outcomes, and ensure data exist to suggest that implementing the AI/ML would reduce the quality gap. These assessments should compare performance metrics such as time saved, diagnostic accuracy, health outcomes, or process improvement from physician practice alone to physicians using AI/ML.[37,43]

Potential errors in AI/ML and patient safety

Current literature describes a variety of errors in AI/ML.[29,39,44,45] This may include problems with the data used to develop the algorithm, choices the developers make in building or training the model, or how the AI/ML program is eventually deployed.[46]

Errors in AI/ML can cause unintended adverse consequences and pose risks to patient safety. Inappropriate or erroneous AI/ML algorithm can reduce the quality of patient care such as providing false positives, false negatives, incorrect or unsafe recommendations.[37,39,45] The UK Department of Health & Social Care Guidance recommends that developers should clarify how risks to patient safety and health will be mitigated and limited.[43] As Price aptly notes, AI/ML errors are different from other errors in medicine because they can potentially impact thousands of patients, resulting in mass injuries.[30] Understanding the functioning of complex AI/ML requires technical knowledge that is not common among clinicians. Most physicians do not have training to identify errors and glitches, or recognize when AI/ML is providing a suboptimal or faulty recommendation.[36] The potential for errors combined with impact to patient safety leads many experts to caution against automation bias, maintain vigilance while using AI/ML, and emphasize the importance of ongoing validation and performance assessment of AI/ML algorithms.[23,28,29,40]

TECHNICAL ASPECTS OF AI/ML IMPLEMENTATION

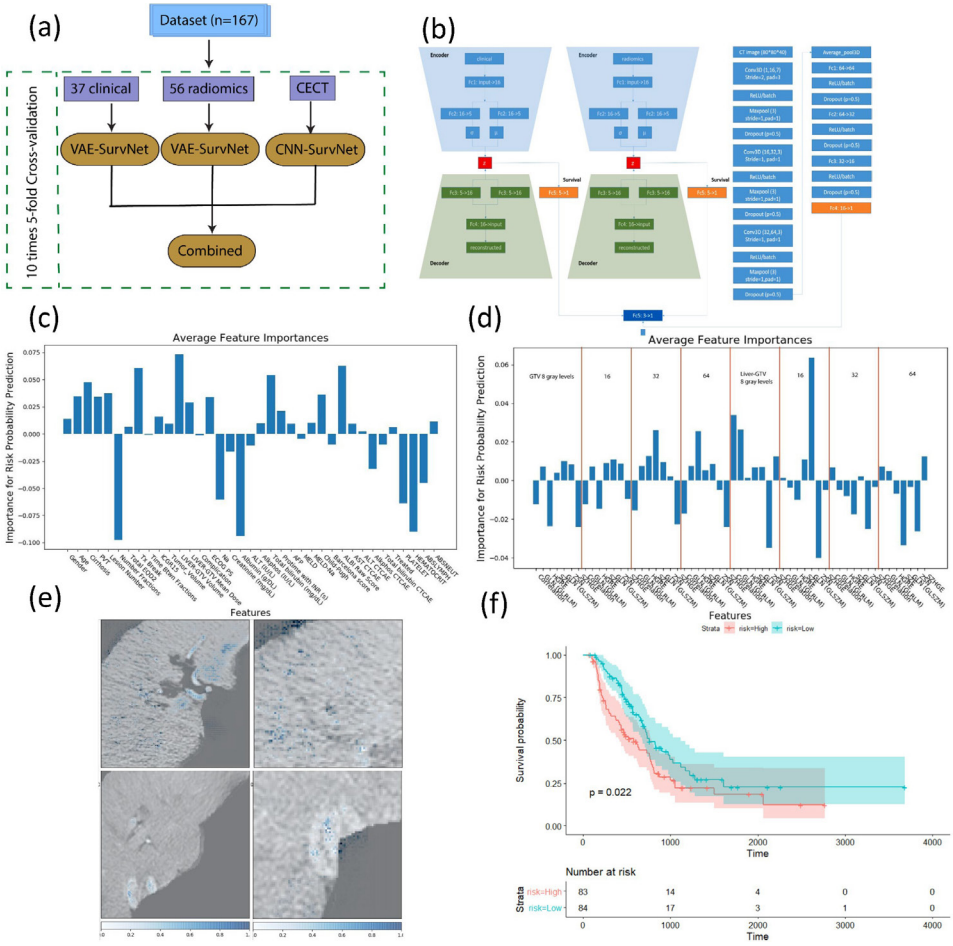
AI/ML validation approaches

Typically, AI/ML algorithms are validated through retrospective analyses on shelved data sets. The goal is to evaluate the predictive power of these algorithms on a specific medical task such as deciding what treatment is best for a current patient by predicting possible outcomes from past treatments.[47] Interestingly, such AI/ML models could be applied to patients who were not pre-selected for the treatment regimen in question. Hence, it could provide evidence to base a change in clinical practice and provide an insight into designing a new clinical protocol or a prospective study.[48] However, the reproducibility of AI/ML models predictions have been a challenge raising red flags and concerns regarding their accuracy on unseen data.[49] More recently, several societies have started developing recommendations for AI/ML applications in their respective field such as the checklist for AI in medical physics (CLAMP)[50] with the goal of ensuring rigorous and reproducible research of AI/ML in the field. However, recent evidence also suggests that retrospective validation alone is insufficient for addressing the complexity of decision making in clinical practice or mimicking the non-linear nature of physician–patient relationship. Moreover, evidence has shown that physician interaction with AI/ML algorithms seems to vary from conducting a retrospective simulated study to that when there is a patient laying in the bed.[51] Hence, there may be need for multitier prospective validation strategies to evaluate a pre-existing AI/ML model on a newly collected data from a prospective clinical trial.[52]

Interpretability and explainability of AI/ML models

The interpretability and explainability of AI algorithms are also crucial for the transition of AI-based models into clinics. This is due to the fact that proper clinical implementation may require considering human–machine interactions in a practical setting.[22] Interpretability is noted as a weaker concept than explainability, which only requires that a clinician to discern that the prediction is scientifically sound without going into the details of the underlying mechanisms of the model prediction. There are two main types of interpretability approaches: (1) approaches that tend to be specific to particular ML methods (*e.g.* Gini index in decision trees or random forests), and (2) approaches that tend to be model agnostic, which are widely used especially with complex deep learning networks (*e.g.* class activation map (CAM)[53] and grad-CAM,[54] Local surrogate models (LIME),[55] SHapley Additive exPlanations (SHAP))[56,57]. An example of

Figure 2. Deep learning example for predicting actuarial risk (survival) in liver cancer. (a) Study design of combing three categories of variables (clinical, radiomics and raw CT images). (b) Different neural network architectures were used (VAE-SurvNet and CNN-SurvNet) for data representation. Clinical and radiomics features were input to the VAE as shown in the left sub-networks. 3DCT patches were fed into the CNN as shown in the rightmost sub-network. Numbers in parenthesis represent kernel dimensions. (c) Clinical features importance using integrated gradients method for the VAE network. (d) Radiomics features importance using integrated gradients method for the VAE network. (e) Model response interpretation using and integrated gradient method. Top shows images for a patient who died in 264 days. Bottom row shows images for a patient that survived 760 days (right censored). The blue dots show the critical pixels for the prediction of the neural network. (f) Kaplan–Meier plot of high and low risk groups for overall survival (p-value = 0.022). CNN, convolutional neural network; VAE, variational autoencoder.



such model agnostic interpretability is demonstrated in the context of image analytical modeling of liver cancer survival. In this study, discrete features from clinical demographics, manually extracted image features along with deep learning features from CT were used for prediction of liver cancer patient survival post-radiotherapy, as shown in Figure 2.

Additional approaches for improving AI/ML models robustness

In addition to above-mentioned interpretability approaches based on visualization, the newer techniques for intelligence augmentation or human in the loop as noted previously, where the algorithm design incorporates human expertise as part of its development process. This approach seem to improve model credibility (*i.e.* acceptance by experts) as well as its performance generalizability of model to unseen data.[58,59] More recently, approaches based on quantum computing in combination with machine learning have been suggested to improve data representation and robustness to noise in complex adaptive decision-making settings.[60,61]

REGULATORY AND LEGAL ASPECTS

Regulatory and legal structures provide a framework to ensure the introduction and use of AI/ML minimizes risks of bias or error, protects patient well-being, safeguards privacy, and promotes accountability. Three main areas of law apply to the development and use of AI/ML in healthcare, which include: regulation of medical devices, health data privacy laws, and liability for harm resulting from faulty, erroneous, or unsafe AI/ML devices or recommendations.

UK medicines and healthcare regulatory agency software as a medical device regulation

In the UK, the Medicine and Healthcare Regulatory Agency (MHRA) is responsible for ensuring products meet applicable safety, quality, and efficacy standards. MHRA states that many types of AI/ML used in clinical practice will meet the definition of software as a SaMD.[62–64] MHRA exempts certain products from this definition, such as software that merely organizes and displays diagnostic information or displays published clinical guidelines for a disease.[65] New devices are classified into four categories based on level of risk: Class I, Class II(a), Class II(b) and Class III and must obtain a UK Conformity Assessed Mark and product registration prior to marketing the device.[64]

In 2021, MHRA published Software and AI as a Medical Device Change Programme, which outlined its planned regulatory framework for AI/ML that included risk classification guidelines, premarket requirements, monitoring SaMD performance, change management processes, and noted that developers must also address cybersecurity issues, which can result in compromising device safety.[66] Gerke et al elaborates by noting that cybersecurity threats can translate to physical risks that harm or disrupt the delivery of medical services.[67] Examples include: corrupted or infected algorithms that provide erroneous recommendations; tampering with diagnostic tools; or interfering with smart pills or implanted medical devices that compromise patient safety.[67,68] In 2022, MHRA published the outcome of a consultation relating to proposed changes for medical devices in the UK.[68] MHRA plans to tailor oversight of SaMD through updated guidance modeled on International Medical Device Regulators Forum (IMDRF) SaMD risk categorizations are designed to ensure adequate pre-market scrutiny of safety, quality, and performance.[68,69] MHRA also encourages developers to engage in ongoing performance evaluation as outlined by IMDRF.[68,69]

US food and drug administration software as a medical device regulation

In the USA, the FDA intends to regulate many AI/ML products as medical devices, which corresponds to a set of regulatory requirements prior to product marketing and use.[15] Most products that are medical devices that use AI/ML are classified as SaMD.[15] For medical products, FDA regulates according to a risk-based classification system, based on the device's intended use and level of risk to patients if the device is inaccurate or harmful.[15,46] Similar to the UK, US law set forth in the 21st Century Cures Act excludes certain software functions from the definition of medical device if they meet four criteria, such as software that displays medical information or clinical guidelines.[15,46] New devices are classified into three categories based on level of risk: Class I, Class II, Class III, and Class IV devices, which each correspond to a specific regulatory pathway to obtain product clearance or approval prior to marketing.

In 2019, FDA issued Guidance on Clinical Decision Support Software that applied FDA's risk-based device framework with a matrix of device categories and corresponding regulatory pathways.[15] FDA also plans to regulate devices that are not CDS, such as software that uses patient imaging to create an individualized treatment plan for radiation or surgical modeling.[15] Rather than reviewing individual devices, FDA plans to offer a Software PreCertification Program to evaluate the developer's qualifications, processes to produce safe and effective devices, whether the developer can demonstrate compliance with Good ML Practices (GMLPs), and provide a Predetermined Change Control Plan.[15,70]

In 2021, FDA issued the Software as a Medical Device Action Plan that further outlined plans to increase transparency to users and patients, address algorithmic bias, and assess real-world performance.[70] Specifically, the action plan included intended actions of the FDA including to develop an updated regulatory framework for AI/ML-based SaMD, strengthen standardized and ethical development through publishing GMLPs, support efforts to address transparency, support regulatory science and methods tasked to improve algorithms, and to increase real-world performance pilots in order to provide guidance on what a real-world evidence generation program would look like for AI/ML-based SaMD.

Later in 2021, the FDA released a document entitled, "Good Machine Learning Practice for Medical Device Development: Guiding Principles", in collaboration with Health Canada and the UK's Medicines MHRA.[71] 10 guiding principles were identified which exist to encourage safe, effective, and high-quality SaMDs utilizing AI/ML. The FDA proposes that other collaborative bodies, such as the IMDRF can utilize the principles when regulating and providing guidance to other stakeholders in such devices. The principles include: multidisciplinary expertise is leveraged throughout the total product life cycle, good software engineering and security practices are implemented, clinical study participants and data sets are representative of the intended patient population, training data sets are independent of test sets, selected reference datasets are based upon best available methods, model design is tailored to the available data and reflects the intended use of the device, focus is placed on the performance of the human-AI team, testing demonstrates device performance during clinically relevant conditions, users are provided clear and essential information, and deployed models are monitored for performance and retraining risks are managed.

Medical device regulation in the EU and across jurisdictions

Muehlematter et al found many developers market devices across multiple countries, such as across the European Union (EU) and in the USA.[72] Developers who plan to market their device should also become familiar with regulatory requirements applicable to the EU.[72]

EU general data protection act and UK data protection act 2018

Building AI/ML relies on health-related data extracted from medical records, individual user data (such as wearables or applications), and research results.[24,73] In the UK, developers are responsible for complying with both the EU General Data Protection Act and the UK Data Protection Act 2018.[43,73] These laws categorize health data as "sensitive data," which requires specific,

informed consent to process (this excludes fully anonymized data), prohibits decisions based on automated processing, integrating privacy by design into data processing, and performing a data protection impact assessment.[74–76] Several authors suggest this may require that the physician disclose using AI/ML and maintaining a physician in the loop.[67,74,77] Schneeberger asserts these provisions demonstrate regard for human rights, human dignity, and the principle that people should not be fully subject to technical systems where a physician could miss special features and the context of human thinking and interaction.[74] The Information Commissioner's Office provides further guidance for compliance.[76]

US Health Insurance Portability and Accountability Act

The Health Insurance Portability and Accountability Act (HIPAA) in the USA differs significantly.[78] While the law sets forth specific requirements for collecting and using "protected health information" such as patient medical records, the law only applies to covered entities and business associates (such as hospitals and insurance companies), which generally excludes private technology companies.[24,67,78] Moreover, HIPAA permits research use of deidentified information, which would allow certain types of research using health information without consent. Several authors assert these gaps do not adequately protect privacy.[24,67,73]

Data privacy requirements in the USA are less extensive than in the UK or across the EU. However, health providers and developers who intend to use patient health records for AI/ML research or product development should be aware that these requirements apply even to entities in other jurisdictions that collect health data from subjects in the UK or EU.[67]

Liability

Regulatory standards are designed to balance innovation to facilitate the delivery of useful products into the marketplace against potential risks. Even appropriately registered (in the UK), cleared, or approved (in the USA) devices can contain flaws or errors that result in patient harm. In the event that AI/ML provides a recommendation that compromises patient safety and results in harm, the physician, hospital, or even SaMD developer could be held liable.[23,28,31,67,79] A full discussion of claims such as malpractice, corporate liability, and products liability is outside the scope of this review. The types of claims, potential responsible parties, and methods of compensation differ between the UK and the USA, which several authors describe in more detail.[23,28,31,67,79] In theory, the liability system is designed as a critical component of healthcare and medical device safety because it provides incentive to uphold a standard of care that prioritizes patient safety, provides deterrence against introducing risky or unreliable devices into the market, and promotes accountability and fairness.[67,79]

Future developments in law and ethics: theragnostic cases

Our previous discussion has primarily focused on the application of AI/ML in context diagnostics and therapy separately. However, an emerging field in personalized medicine is theragnostic technologies, where therapy and diagnostics are combined. Example applications include nanomedicine,[80,81] nuclear medicine and interventional radiology.[82,83] For instance, in the case of interventional radiology, the interventionist performs minimally invasive procedure which replaces surgery and becomes fully responsible for both diagnosis and treatment. This may lead to multiple scenarios in which the AI/ML model can be utilized in the diagnosis portion only, the treatment portion only, or for both diagnostic and therapy.[84,85]

Table 3. Recommendations for trustworthy and ethical AI/ML.

Recommendation	Sources
Ethical requirements (IRB/HIPAA) are monitored in data aggregation and annotation	UK Data Protection Act 2018[43,73] EU General Data Protection Act[43,73] HIPAA[78] Mittelstadt 2021[25]
Transparency of training data characteristics, augmentation methods and ensuring proper inclusion of underrepresented groups (across age gender and race)	CLAIM, Consort-AI, CLAMP[50]
Transparency of training data model developments (architecture, loss function, optimization parameters)	CLAIM, Consort-AI, CLAMP[50]
Multilevel evaluation process (internal and external)	TRIPOD/Equator network[47]
Mitigation of explicit and implicit data leakage between training and testing	El Naqa et al, 2021[50]
Evaluation of human factors in evaluating real-world implementation and conduct prospective clinical trials if necessary	Luo et al. 2019[22] Mahadevaiah et al. 2020[37] Char et al. 2020[41] UK Department of Health and Social Care[43]
Continuous quality assurance and monitoring of deployed AI/ML models and live data incorporation	US FDA guidance[15] UK MHRA guidance[66] IMDRF[69]

AI, artificial intelligence; ML, machine learning.

Gurgitano et al describes multiple compound steps during this process that may be aided by AI/ML, such as selection of tools (*e.g.* size of catheter) and medical devices (*e.g.* type of stent), automating the dose of radiation, and using 3D images to guide therapies.[84] The ethical and liability aspects presented above still apply here, however, the associated risks for liability and patient safety are notably higher when each use of the model relies and builds upon previous information about the patient.

RECOMMENDATIONS

Meeting the need of accurate but trustworthy AI/ML with ethical and regulatory constraints may seem mired with challenges or contradictory requirements. However, there is a path that can be paved by deploying necessary technology and advance the legal requirements as distilled from the existing literature and summarized in Table 3.

CONCLUSIONS

To reap the promises of AI/ML for the betterment of clinical care, emerging ethical challenges and concerns regarding patient privacy, legal responsibility, trustworthiness, and fairness need to be addressed. Ethics are expected to be at the forefront and an essential component of the development and deployment cycle of AI/ML methods. In this review, we described these emerging ethical challenges created by AI/ML and discussed their potential impact on clinical care and biomedical research. There are several technical means to balance innovation with ethical applications of AI/ML that may allow for mitigating potential clinical implementation failures. Some of these techniques discussed here may include the implementation of better interpretability and explainability methods, and the incorporation of recent advances in intelligence augmentation and robust computing. We also provided an overview of regulatory and legal issues applicable in Europe and the United States and their evolving nature to meet the requirements of safe AI/ML. Subsequently, we recapitulated our recommendations for trustworthy AI/ML that aims to promote transparency, minimize risks of bias or error, and protect the well-being of patients and the society at large.

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