CENTER FOR THE GOVERNANCE OF CHANGE

THE DATA CHALLENGE: FROM BIASES TO REGULATION

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Innovation, Sustainability, and the Future of Healthcare
Chapter 3

Algorithms based on machine learning and deep learning unlock the technological possibility of using aggregated healthcare data to produce powerful models that facilitate and improve the accuracy of diagnosis, tailoring treatments and targeting resources with maximum effectiveness.

However, there are **key ethical and technical challenges** that need to be evaluated before AI solutions can be widely implemented in the clinic – and often, the two are closely **intertwined**. Issues about ownership and control of confidential health data of patients, their privacy, public trust, accountability and responsibility about the application of an AI tool all require consideration; and ethical considerations naturally come to the fore. Two of the biggest technical barriers are data **standardization** and data sharing, both of which are essential to fight possible algorithmic biases. In turn, **data sharing** poses its own set of questions, including regulation, ownership of data and privacy protection, protection and cybersecurity, and accountability.

We have found that, although there have been **advances** in all these areas, they **remain insufficient**. The rapid development of the field is making it difficult for regulatory bodies to keep up – and similarly with the attempts to standardize data. There are increasing numbers of data-sharing initiatives such as **biobanks and international consortia** in the European Union and abroad, and frameworks focusing on interoperability and clinical translation. However, **current methodologies for anonymization and de-identification are often suboptimal**; and while there is a critical need to provide high-quality diverse data to train unbiased algorithms, maintaining patient privacy must always be carefully maintained.

These aspects are critical to the success of the whole field an-d will **require close collaboration** on a global scale.

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1. ORGANIZATIONAL AND TECHNICAL BARRIERS FOR HEALTH DATA USE FOR AI IN EUROPE

The development of AI algorithms in healthcare provision requires the availability of a massive amount of data, integration into complex existing clinical workflows, and compliance with regulatory frameworks [1]. AI techniques developed for clinical prediction, diagnosis and treatment have to learn from appropriate data, which may include demographics, healthcare provider notes, medical images, laboratory results, genetic testing data, and recordings from medical devices or wearable devices/sensors [2]. Similarly, several technology platforms may be involved in the generation or collection of such data, including network servers, personal computers, tablets/smartphones with apps, electronic health records, sequencing devices, and wearable devices and sensors. With an improved global connectivity via the internet and technology with cloud-based capabilities, data access and distribution have become easier [3]. Integration of big data concerning health and disease will provide unprecedented opportunities in the management of healthcare information at the interface of patients, physicians, hospitals, decision makers and regulatory institutions [4], [5].

However, despite the pervasive enthusiasm about the potential of AI-based healthcare, AI technology is not yet totally executable at the frontlines of clinical practice (see Table 1). Both policymakers and healthcare providers must demonstrate to patients why data sharing is a social benefit. A critical foundational relationship in healthcare interactions is trust between patients/public and doctors/healthcare providers. Patients frequently cannot predict their doctor's actions, but their trust is based on beliefs that doctors have appropriate knowledge and understanding of the patient's attitude. Similarly, the challenge in AI is to develop a system of data governance that protects the interests of patients, guarantees transparency, provides access for researchers, distributes the fruits of success fairly, and gains the confidence of the patients/public. Moreover, incentives to allow data to be shared are still demanded. Currently, there are few healthcare organizations that claim to have (or be close to having) the data infrastructure required to collect the sensitive data needed to optimally train algorithms and use them for patients' benefit [6], [7]. Particularly, there is a lack of studies that interrogate the data for biases to guarantee that the algorithms perform consistently across patient cohorts, especially those who may not have been adequately represented in the training cohort [8]. For example, an AI algorithm trained on one subpopulation will likely not have the same accuracy when applied to others [9].

Table 1. The current key research priorities in data sharing.

Validated methods for data anonymization / de-identification • Because privacy concerns are paramount when using clinical data, methods are needed to facilitate the aggregation of clinical imaging data for training ML algorithms.	**New image reconstruction methods** • They should efficiently produce data suitable for human interpretation from original source.
Automated labeling and annotation methods • Including information extraction from the report, electronic phenotyping, and prospective structured reporting that are needed to rapidly produce training data for ML research.	**New AI algorithms for clinical and imaging data** • Namely new methods for clinical and imaging data, such as tailored, pretrained model architectures and federated machine learning methods.

Table key: ML = machine learning

The percentage of health data collected digitally instead of analogically increased dramatically in the past two decades. Current estimations suggest a doubling of the total amount of data in the world every 2–3 years [2]. In radiology, the introduction of standardized data structure and communication with DICOM (Digital Imaging and Communication in Medicine) and the development of picture archiving and communication systems (PACS) [10] were the first steps of the digitalization of imaging which allowed the increase in digital data collection and lowered the threshold to acquire data, therefore allowing for higher sampling frequency with more comprehensive data. When conducting retrospective data collection from a PACS, the actual challenge is to include the relevant selection from the dataset acquired and generated that can be used for analysis and will lead to the required insight. What data to collect and at which frequency is still a human decision, and thus prone to error, variation and personal or institutional preferences. AI, however, needs to rely on those types of healthcare data collections of questionable quality [10]. Moreover, even when the correct cohorts are appropriately identified and the required ethics and legal approvals are obtained, the variability in the data collection can be enormous [2].

Quality checks, standardization and curation of healthcare data

Since AI-based systems require large training datasets [11], healthcare, with its abundance of data, is in theory well-poised to benefit from it. However, variable completeness, quality of data entry, and interoperability between different providers remain a problem. Most health-related datasets are unstructured and not yet standardized [12], [13]. The lack of appropriately curated large datasets is one of the key obstacles to the introduction of AI systems in healthcare [14], [15], [16].

Without early efforts to optimize interoperability, the practical effectiveness of AI in healthcare will be severely limited. A set of standards would be necessary to allow for integration between these different algorithms and to allow them to be used in different centres, by different users, and on different equipment.

Reproducibility and reporting. The huge number of works published in medical literature on repeatability and reproducibility of medical reports in the last few decades illustrates the need for reproducible medical results in AI-based studies [2]. Although AI applications may improve and optimize diagnostic exams and procedures [17], [18] while reducing costs [19], one of the current limitations of AI systems is the lack of standardized data and protocols, probably due to the rapid growth of AI tools [20].

Shared guidelines could improve the quality of such database and make them useful for training AI algorithms: it is timely that existing standards for prediction model reporting (including development, validation, update, impact assessment and implementation reporting studies) are being updated specifically to incorporate standards applicable for this purpose [21].

As a full and clear reporting of information on all aspects of a prediction model is needed to adequately assess the risk of bias and potential usefulness of prediction models, statements like the "Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis" (TRIPOD) [22] and its related elaboration papers [23] were developed as a consensus guideline for reporting and discussing the significance of its major elements in regard to reproducibility and validity. TRIPOD includes 22 items (most of them are relevant to studies of both developmental and validation nature), which are summarized in an open-access checklist (http://www.tripod-statement.org/TRIPOD/TRIPOD-Checklists). Similarly, the "Preferred Reporting Items for Systematic Reviews and Meta-analyses" (PRISMA) [24] is a relatively mature guideline for systematic reviews of clinical trials which is being enforced by some scientific journal editors. Finally, the "Checklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies" (CHARMS) [25] was designed for critical appraisal of and information extraction in evidence synthesis from multiple published studies with the purpose to assess the applicability of a published model to a particular clinical problem. In the current AI era, with the technological progress in big data and data sharing, it becomes possible to develop, validate and update predictive models

using huge numbers of records collected either from electronic health records or accessing the individual cases in published models [26].

Healthcare datasets for AI algorithm training, testing and validation can be developed including statistical metrics for validation, parameters for clinical integration, and pathways for assessing algorithm performance in clinical practice. Thus, the likelihood of bringing safe and effective algorithms to clinical practice will increase dramatically [27].

Standardization. Standardization refers to the process of transforming data into a common format that can be understood across different tools and methodologies [28], [29]. As healthcare data has been shown to be more heterogeneous and variable than research data produced within other fields [27]) standardization is particularly crucial here.

With the complexity of healthcare data and the massive volumes of patient information, data standardization should occur at the initial development stage and not at the user end. Accordingly, the first step to reach a consistent and standardized practice is to standardize the techniques themselves [30], [31]. For instance, in radiology the size of a mass in organs can be compared best if the same imaging acquisition protocol is used [28]. Segmentation of the imaging data is even more challenging, because an appropriate segmentation of an index lesion in the training process of an AI system requires the most uniform images possible, and currently no widely accepted standard exists to store and communicate segmentation results between different tools from different vendors/sources [2], [32], [33]. The Annotation and Image Markup (AIM) standard and the DICOM Presentation State are the two main examples of high-quality standardized annotation methods [34], [35] that are not used much by software developers to report on annotations [10].

The second step is to reduce variations in terminology in medical reports: a common and international imaging lexicon, for instance, through structured reports, can provide a uniform method to share the information, which is important for an improved communication between different centres [30], [31], [36], [37]. Currently, the necessary information for training AI algorithms has to be extracted from a radiological report, a pathology examination report or surgical reports [10]. The value of such data relies both on the expertise of the observer describing the result, the accuracy of the description, and on the quality of the measurement methods; however, the accuracy of the results described by a physician is compromised by the fact that many reports are still free text without standardized lexicon or terminology resulting in multi-interpretable ambiguous reports with an abundance of synonyms. The American College of Radiology (ACR) proposed the Reporting and Data Systems (RADS) to provide a standardized framework for reporting on imaging findings and assessing probability of disease [38]: digitization of imaging datasets, in combination with structured radiological reports that contain scoring systems such as PIRADS, LIRADS or BIRADS (for prostate, liver and breast examinations, respectively) have paved the way towards developing algorithms that can contribute to image interpretation through machine learning (ML). However, researchers are currently poorly equipped to

translate such knowledge into international guidelines to reach standardized practice [39], [40]. A potential solution could be to use Natural Language Processing (NLP), which is a subfield of linguistics, computer science, information engineering and AI-science concerned with the interactions between computers/device and human/natural languages. In particular, it deals with how to programme computers to process and analyse large amounts of natural language data in situations where structured reporting and coding is not being used, as is still the case in most hospitals across the European Union [10], [29].

Finally, standardization of output interfaces is equally important. Radiologists, referring physicians and other healthcare providers use an array of electronic resources throughout the imaging cycle. Output from AI devices will eventually interface with existing clinical decision support systems for selecting the most appropriate examination as well as existing decision support tools for interpretation. Standardized interfaces for algorithm output into PACS worklists will be necessary as well, and AI tools will have to seamlessly interface with all of these resources [10].

Sharing standards. Developing open sources for coding and standardized interfaces for data transfer will ultimately affect the entire health information technology system, and developers of AI algorithms should avoid proprietary interfaces. In the United States there are islands of aggregated healthcare data in the intensive care units and in the Veterans Administration [41] that have predictably catalysed an acceleration in AI development. This is also thanks to the availability of some open-source standardized interfaces like the ACR's Computer Assisted Reporting Data Science platform [42], which is an authoring and reporting system that includes a definition format for representing radiology clinical guidelines as structured documents with a user-friendly reference implementation. However, without broader development of data infrastructure outside these islands it will not be possible to generalize these innovations.

In the European Union a multicentre cooperation for gathering and distillation of information is coordinated by the "European Innovation Partnership on Active and Healthy Ageing", which covers standards, technical reports and technical specifications, but also provides guidance documents, industry standards, databases and scientific methodologies and tools [29], [43]. There are some projects that are rapidly evolving worldwide for the purpose of clinical translation, like the Fast Healthcare Interoperability Resources (FHIR) framework [44], which utilizes a set of modular components that can be assembled into working systems that will facilitate data sharing as well as cloud-based communications [44], [45].

2. HEALTH DATA SHARING REGULATORY FRAMEWORKS IN EUROPE

Since data is needed not only for initial training but also for ongoing training, validation and improvement of DL algorithms, there may be a need for data to be shared across multiple institutions and nations for widespread implementation. At the same time, AI algorithms need to comply with regulatory frameworks when using personal data [2]. Accordingly, such data would need to be anonymized or deidentified; in the latter the informed consent processes would need to include the possibility of wide distribution [2], [46].

Therefore, the rules of patient privacy, notions of patient confidentiality and cybersecurity measures will be increasingly important in the current healthcare systems. Only collaboration between patients, healthcare operators and decision makers will be able to prevent the risks of inappropriate use of sensitive datasets, inaccurate or inappropriate disclosures, and limitations in deidentification techniques.

Although the current healthcare environment still holds little incentive for data sharing [47], European governments are starting to promote data sharing, similarly to what happened in the United States where the National Science and Technology Council Committee on Technology recommended that open data standards for AI should be a key priority for federal agencies [48]. Some have proposed creating anonymized benchmarking datasets with known diagnoses that are updated and calibrated at regular intervals using local data from the implementing institutions, similar to how clinical laboratories maintain a local reference standard for blood-based biomarkers [3]. To include in such an approach a local calibration (i.e. through a collaboration amongst different institutes across the European Union) is crucial because DL algorithms may capture local or cultural-specific parameters that may not be generalizable to different populations.

The following are examples of data-sharing efforts that include biobanks and international consortia for medical imaging databases and they represent an interesting step in the direction of an ideal open access database to anonymized medical images, coupled with information like histology, clinical history and genomic signatures:

- the Cardiac Atlas Project [49] that combines cardiac modelling and biophysical analysis methods developed by the University of Auckland (New Zealand) with structural database and probabilistic mapping infrastructure developed by the University of California, Los Angeles (United States) with contributions from some academic centres in Rome (Italy);

- the Visual Concept Extraction Challenge in Radiology Project [50] which executed a targeted benchmark framework to speed up progress towards the automated anatomy identification and pathology identification in 3D (MRI, CT) and 4D (MRI with a time component) radiology imaging and the similar case retrieval for these images and the reports associated with them. This project is supported by the European Commission under the Information and Communication Technologies Theme [50],coordinated by the Vienna University of Technology (Austria) and it involves the University of

Applied Sciences, Western Switzerland (Switzerland), the Medical University of Vienna (Austria), the ETH Zürich (Switzerland), the University of Heidelberg (Germany) and the Catalan Agency for Health Information (Spain);

- the Cancer Imaging Archive (TCIA) [51], which is an open-access service that de-identifies and hosts a large archive of medical images of tumours as DICOM files. Such data are organized as collections related by a common disease (for example, lung cancer), image modality or type (MRI, CT, digital histopathology, etc.) or research focus. This project is operated by the University of Arkansas for Medical Sciences (United States) and funded by the National Cancer Institute's Cancer Imaging Program (United States) that, together with the National Human Genome Research Institute (United States), also supports the following

- the Cancer Genome Atlas (TCGA) [52], which aims to list genetic mutations responsible for tumours, using genome sequencing and bioinformatics; and

- the UK Biobank [53], which is a national and international health resource based in England and involving centres in Wales and Scotland that are investigating the respective contributions of genetic predisposition and environmental exposure such as lifestyle and nutrition to the development of disease.

Regulatory issues and policy initiatives

One further issue of AI in healthcare is the gap between the advances in technology and the lack of social and political preparation to make the most of these opportunities. To reach a real innovation embraced by both patients and healthcare providers/practitioners, it is essential to build a robust architecture of trust, accountability and security at a time when, generally, technical innovation is going through a period of breakdown in public trust [4].

Recently, researchers from Imperial College London and Google Health showed that DeepMind's medical AI system can outperform radiologists on identifying breast cancer from x-ray images [54]. Authors claimed that their robust assessment of the AI system paves the way for clinical trials to improve the accuracy and efficiency of breast cancer screening. If they are correct, it will be vitally important to harness the potential ahead of us through solid investments, research and international cooperation. The key question for radiology, alongside the rest of medicine, is therefore how to wrap accountability and trust around AI innovation: how do we address the legitimate concerns that digitization has not only brought exponential growth in data generation but also concentrated the power and means to turn that data into precious knowledge in the hands of a few powerful private companies? A good employment of AI may be powerful, helpful and valuable. On the contrary, a bad or unethical use of this cutting-edge technology may be dangerous, and patients, physicians and regulatory authorities must work together to prevent this [34].

In all the European countries, healthcare is highly regulated by national and international governing bodies to invest in technological development and to promote quality while ensuring patient safety and privacy [4]. This is particularly important as the new AI systems do more than just processing information and assisting humans to make decisions of consequence, providing sensitive services that require training and certification [12], [13], [55], [56], [57].

AI as a medical device. AI systems do more than process information and assist officials to make decisions of consequence. Many systems — such as the software that controls an airplane on autopilot or a fully driverless car — exert direct and physical control over objects in the human environment [57]. Other systems, including medical and radiological devices, provide sensitive services that, when performed by physicians, require training and certification [12], [13], [55], [56], [57]. These applications raise additional questions concerning the standards to which AI systems are held and the procedures and techniques available to ensure those standards are being met [58].

Since unambiguity is one of the pillars of any legislation [32], the first aspect policymakers need to address when regulating is whether to consider AI software used in healthcare as a medical device for legislation purposes. Currently, the European Union need to clarify which AI algorithm used in healthcare is to be considered as a medical device. The only official definition is relatively old and it is provided by Article 1(2) of Directive 93/42/EEC [59]: "the term 'medical device' is applied to any instrument or other tool intended by the manufacturer to be used for human beings for the purpose, among others, of diagnosis, prevention, monitoring, treatment, or alleviation of disease".

This definition has been endorsed by the Medical Device Academy, a non-legally binding guideline drafted by the European Commission to guide stakeholders in complying with legislation related to medical devices [60]. Notably, in the United States the 21st Century Cures Act [61] of 2016 defined the medical device differently, as a tool "intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or intended to affect the structure or any function of the body of man or other animals" [62].

Therefore, both the European Union and the United States have their own criteria for identifying healthcare and AI devices; however, not all DL algorithms used in healthcare may be deemed to be medical devices. Indeed, the Food and Drug Administration (FDA) and the International Medical Device Regulators Forum (IMDRF) have recently recognized that AI technologies are distinct from traditional medical devices. The IMDRF is a voluntary group of medical device regulators including the European Union, the United States, Canada, Australia, Brazil, China, Japan, Russia, Singapore and South Korea, working toward harmonizing international medical device regulation. The collaboration between IMDRF and FDA has defined a new category called Software as Medical Device (SaMD) pointing out for the need for an updated regulatory framework [3], [63] which takes into account the fact that

AI systems have to face additional safety challenges in the forms of complex environments or periods of learning (during which the system's behaviour may be unpredictable); this may result in significant variation in a system's performance [63]. Their guidance recommends a continuous iterative process based on real-world performance data and states that low-risk SaMD may not require independent review [3].

In the European Union the regulatory framework is composed of the Medical Devices Regulation (MDR) [64] and the new In Vitro Diagnostic Medical Device Regulation (IVDR) [65] (see Table 2). Both came into force on 25 May 2017; however, the MDR will apply from 26 May 2020 while the IVDR will apply from 26 May 2022. Such reforms will update regulatory framework trying to address the above-mentioned issues. Their main characteristics will be: extended scope to include a wider range of products; extended liability in relation to defective products; strengthening of requirements for clinical data and traceability of the devices; more rigorous monitoring of notified bodies; and improved transparency through making information relating to personal data used for developing and training AI algorithms public [66].

Table 2. Regulatory framework in the European Union on medical devices.

Directive 93/42/EEC •Directive on medical devices •Will be replaced by MDR on 26 May 2020	**MEDDEVS** •Non-binding guidelines on legislation related to medical devices
MDR •Regulation on medical devices •Applies from 26 May 2020 •Repeals Directive 93/42/EEC	**IVDR** •Regulation on in vitro diagnostic medical devices •Applies from 26 May 2022

Table Key: MDR = Medical Device Regulation; IVDR = In Vitro Diagnostic Medical Device Regulation; EEC = European Economic Community

Regulating a rapidly changing arena. Tsang et al. [67] pointed out that "programs that analyse large amounts of data to develop knowledge about a disease or condition, rather than to decide on treatment options for an individual patient, may not necessarily be considered as having a medical purpose, and hence as a medical device". It is the basic distinction between those research programmes that enhance medical knowledge from those that promote changes in healthcare. How will the latter systems be regulated by policymakers? Two approaches, described by Thierer et al. [68], may be interchangeably adopted and combined at the same time. The "precautionary principle approach" imposes some limits or sometimes outright bans on certain applications due to their potential risks: this means that these systems are never tested because of what could happen in the worst-case scenarios. Conversely, the "permissionless innovation approach" allows experimentation to proceed freely: the issues that do arise are addressed as they emerge.

The somewhat "black-box" nature and the rapid growth of machine/deep learning applications will make it difficult for regulators to approve all the new medical devices that are continuously developed in a timely fashion, given the volume and the complex nature of testing and verification involved. An example was the introduction of computer-assisted detection (CAD) software for mammography in 1998 [69] that took many years and extensive lobbying to obtain clearance from the FDA to be used as a second screening reader [70]. For this reason, developers nowadays present AI systems as aid tools for radiologists rather than as a tool that substitutes them [71]. However, a recently developed FDA programme called the "National Evaluation System for Health Technology" (NEST) is intended to shorten the time to market for new technology healthcare products by developing a system for more robust post-market surveillance, demonstrating also a high level of cooperation with international regulatory bodies [72].

Nowadays, companies understand the potential of deep learning and are continuously collecting new types of data to analyse and exploit [73]. In an environment like the technology world and AI, which changes quickly and unpredictably, regulations need to be timely to be relevant. As a result, they are often controversial and subject to the vagaries of guidelines and subjective interpretations by the authorities [4], [74].

Generally, in the United States the AI technology sector prospered in a permissive innovation policy environment and in the European Union decision-makers adopted a different policy for this revolutionary technological branch [68]. Certainly, swifter approval of AI software helps generate revenue for manufacturers, and physicians may benefit from having more tools at their disposal.

There have recently been large amounts spent developing machine learning technologies across the private and public sector, and not only in healthcare.

The Care Quality Commission (CQC), which regulate and inspect healthcare and medical devices in the United Kingdom, recently proposed a regulatory sandboxing as a new approach

to working collaboratively with private (or public) providers and government organizations that have an interest in policy development with AI in healthcare [75]. The related expected benefits for patients is to get access to more effective clinical outcomes while having more assurance that services using AI medical devices are going about that in the right way, as potential risks related to the technologies employed will be better monitored and controlled. Benefits to health providers will be to clarify the regulatory pathways for AI based services, and the dimensions of quality and standards for delivery. Another project in the United Kingdom is the AI Lab led by NHSX, which brings teams from the Department of Health and Social Care and the National Health Service (NHS) together into one unit to drive digital transformation in healthcare [76]. The aim of such a project is to facilitate cross-government, industry and academic collaborations for developing and for regulating deployment of AI in healthcare by a network of experts comprised of technicians, policymakers, physicians, patient representative groups, regulators, academics and data ethicists.

In general, the European Union's approach represents the view that the collective goal should be to improve prevention, diagnosis, treatment and prognosis of diseases with a potential positive impact on patient outcome and that, therefore, policymakers should provide pathways to market for important innovations while also ensuring that patients are adequately protected.

Ownership and control of the data

Before discussing the accountability of data sharing and AI applications, a more fundamental issue must be addressed: who owns health data; who can use it; and which strategies are required to guarantee their protection?

Currently, the worldwide healthcare organizations are the de-facto owners and guardians of patient data generated in the healthcare system, although informed consent from patients is formally required [4]. Some argue that patients themselves should be the owners and guardians of their health data and subsequently consent to their data being used to develop AI solutions [77], but governance would be needed to provide the appropriate regulations and surveillance.

Both the GDPR in the European Union and the California's Consumer Privacy Act in the United States regulate the ownership of health data [4]. The GDPR requires explicit and informed consent before any collection of personal data. Informed consent has been a long-standing component of medical practice (unlike in social media or online based marketing) but having to obtain informed consent for any collection of data still represents a higher bar than obtaining consent for specific items, such as procedures or surgical interventions. Indeed, the GDPR allows processing of anonymized health data without explicit patient

consent in the interest of healthcare in the European Union [78], but at the same time it is yet unclear as to whether or not this also applies to ML for AI development.

In the last decade two new issues have complicated the health data ownership scenario. First, the healthcare system shows a slow movement from a hospital-centric data model to a more patient-centric data model [5]. This model also includes integration of new information obtained from wearables, devices designed to collect the data of users' personal health and exercise. Second, the model of open data is increasingly being advocated by governments, resulting in huge collections of data mostly available in the cloud and establishing sandbox environments to be used by anyone to train and validate their algorithms [3], [50]. There is a risk in losing control of the data and in uploading health-related information into a variety of dispersed non-connected and non-standardized cloud solutions [3], [79].

Therefore, healthcare operators and regulatory bodies are called to closely protect patients' health data, and the development of large patient datasets incorporating wide ranges of clinical, imaging data and pathologic information across multiple institutions for the development of AI algorithms will necessitate a thorough re-examination of issues surrounding patient privacy and informed consent [4]. What type of data is considered personal for an individual patient or participant in a clinical trial, and who owns the data that is produced by an AI algorithm? Will informed consent be required only for patient data in the development of deeply annotated AI datasets? How will conformed consent be addressed if a patient's data is used in assessing an algorithm in routine clinical practice, and then used to retrain the algorithm? What mechanisms are in place to protect individuals who opt out?

The question of the ownership of health data requires a discussion about the different challenges posed between original, deidentified, anonymized and processed data [80].

The problem of anonymization

In the AI scenario the debate over the proper balance between privacy and better care outcomes, achieved via usage of personal data, is particularly important in healthcare. AI algorithms should use deep learning to provide data about patients without requiring their personally identifiable information in exchange. Therefore, the anonymization or, at least, the deidentification (true anonymization is an irreversible process, and it is challenging to achieve) has to be performed such that the scientific research value of the data is retained in the deidentified dataset while still removing all personal information [81].

However, current methodologies for anonymization and deidentification are often suboptimal [82]. There are currently no available certifications for tools and methods for anonymization and it is difficult to estimate when a general certification can be expected. The great challenge and difficulty in the evaluation of anonymization is that no known method can guarantee 100% data protection. If data is made anonymous, its information

content is inevitably reduced and distorted. To ensure that raw data retain their significance in an analysis, the data can only be changed to a certain extent.

The conflict between usability and security in data anonymization means that so far, no European data protection authority has extensively evaluated or certified technologies and methods for data anonymization outside specific use cases. New solutions are demanded to conceal identities effectively in such a way that the privacy of the individual is protected while maintaining the full value of the data for AI algorithms.

Current repositories of research data such as the TCIA [51] still have a workflow in place where curators visually check and when needed correct every DICOM file (image and header) entered into their database to ensure data privacy and correct handling of the data. The challenge here is the fact that DICOM headers may contain proprietary information that is not part of the standard DICOM but could include information on the acquisition or nature of the imaging data enclosed that is vital for adequate post-processing of the data. However, these private tags may also include references to personal health information which could violate the privacy of the subject. The same holds for the comment fields that are available in the DICOM header; the content of these fields is free text, and their use often vary per hospital or even per modality within a hospital [10].

An additional specific issue in the field of radiology is that facial features can easily be obtained from imaging datasets of the head: by performing surface or volume rendering reconstruction of those datasets, the face of the subject involved becomes visible. Studies have shown that facial recognition technology is able to match the data to actual photographs (for example from social media) of individuals in research studies and therefore to identify the imaged subject [83], [84]. This suggests that the current standard of removing only metadata in medical images may be insufficient to prevent reidentification of participants in research [84].

Nowadays, the deidentification/anonymization, the privacy protection and the data value seem to work against each other with opposing requirements and struggle with variability in data content and lack of standardization, thus hampering the automation of this process [10]. An urgent solution is needed as this is a major issue in the development of AI-based research collaborations with different institutions, at least within Europe, and to create trust in medical AI amongst the patient population [1].

Data protection and cybersecurity implications

The circulation of confidential information in vast number of copies between many unregulated companies is increasingly risky [68], [85], and the legal obligation to protect the privacy of data, especially health data, should be a crucial priority for governments. As access to huge amounts of medical data is needed to provide training material for AI algorithms [16],

[34], policies should prevent such sensitive data either to be harvested illicitly or collected from unknown sources [86]. Although in the last decade personal data regulation is increasing and privacy concerns are growing [87], we still face a lack of unique and clear regulations in data protection and cybersecurity [88], [89].

The concept of confidentiality strictly requires that a physician withholds information from the medical record [90]. Once a clinical decision based on AI algorithms is integrated into clinical care, withholding information from electronic records will become increasingly difficult [90]. Currently, the use of AI raises two issues relating to the data collected by the devices. On the one hand, data must be protected from the same bodies collecting it by establishing rules (such as those of anonymization and ethical behaviour) that prevent misuse and unethical use. On the other hand, the same data is threatened by cyberattacks to these bodies as well as to the devices themselves. While there is critical need to provide high-quality and geographically diverse data to developers for testing and training, patient privacy must be carefully maintained.

In the European Union regulators updated the legislation concerning data protection and cybersecurity substituting the European legal framework for data protection as set out by Directive 95/46/EC (91) with GDPR. Accordingly, all data processing and use should be opt-in, and consumer consent for data use should be clear, prohibiting in that way the current data marketing based on third-party non opt-in personal data. The GDPR is a more suitable instrument to regulate AI because it has an extended territorial scope and wider rights for data subjects. For instance, it includes enhanced notification requirements (under Article 33, personal data breaches must be notified to the supervising authority within 72 hours), and rights to compensation for material or non-material damage and additional liability for data controllers (who determine the purposes for and the way in which personal data is processed) and processors (who actually process the data) (Article 88) [92].

With its Cybersecurity Directive [93], the European Union sets out a number of requirements for European Union Member States which aim to prevent cyberattacks and keep their consequences under control. Among other duties, Member States are required to ensure that operators of essential services take appropriate measures to prevent and minimize the impact of incidents and to preserve service continuity (Articles 14(2) and 16(2)), and to ensure that supervisory authorities are notified of incidents without undue delay (Articles 14(3) and 16(3)) [93].

In the United States, the Health Insurance Portability and Accountability Act (HIPAA) is a compliance focus for what concerns health information [67] defining standards and safeguards that protect patients' health records as well as personal health information that apply to all healthcare providers, insurers and other healthcare entities. This Act includes elaborate rules requiring, among other things, the formulation of policies and the setup of training systems for those who have access to sensitive data [67]. HIPAA does not hinder the action of individual states where it protects further the individuals' right to privacy, but

establishes national standards to protect individuals' electronic personal health information that is created, received, used or maintained by a covered entity [67]. Cybersecurity is dealt with by the FDA, which requires providers to report only a limited number of risks their devices present and the corresponding actions taken to minimize the vulnerability [67].

Considering the current amount of data collected and that with an increased presence of AI applications this can only grow, regulatory actions regarding cybersecurity will face continuous challenges [86]. In particular, even the tightest data protection rules may struggle to control our current technologies, which allow spreading of personal data at large scales [94]. A possible solution could come from blockchain technology (BCT), an open-source software (which can be either public or private) that enables the creation of a large, decentralized and secure public databases, containing ordered records arranged in a block structure [95]. Different blocks are stored digitally in nodes composed of the computers of the blockchain network members themselves, who are both users and maintainers of the entire system. The information on all transactions, present and past, are stored in the nodes [96]. Although the best-known use of BCT is in the field of economics (i.e. cryptocurrencies), its usefulness is extending to other fields, including health data, due to its emphasis on sharing, distribution and encryption [96]. In particular, as BCT can be used to validate the provenance of data and facilitate its distribution without compromising quality, it shows a great potential for healthcare. In the clinic, BCT may help patient data management. In this era of personalized medicine [97], the access to complete medical records is essential to adapt the treatment for patients, and BCT can provide a structure for data sharing as well as security. Healthcare providers may collect information from the patient and store them in the organization's existing databases and/or on cloud computing systems, then create a hash of each source of data which is redirected to the blockchain along with the patient's public ID. Finally, through an application programming interface, healthcare stakeholders may query the blockchain that provides the location where the data can be found without revealing patient identity [98]. Potentially, patients can share their medical record (including wearables data) to any stakeholder, being able at the same time to decide to whom to give access and on which conditions. In research, BCT may help clinical trials, in which abundant data is produced and large groups of people are involved, making it difficult to track and control everyone. BCT may also reduce the risk of data fraud, and trustworthy protocols and results can be published, thus facilitating the replication of the study and collaboration in the scientific community. Shared databases can be created to collect data from medical institutes around the world. As the blocks are impossible to change, it is impossible to delete or to modify anything without leaving a trace, and this is critical in the case of sensitive data such as medical information. Moreover, since there will be no centralized infrastructure to hack into, BCT is a leakage-free system, which can help secure the privacy of the patients/participants [99].

Accountability and responsibility

Alongside the AI regulations and data protection issues, there are other legal implications of AI and its use in healthcare: one of these is accountability. As soon as AI starts making autonomous decisions about diagnoses and treatments, stopping from only being a support tool, the question arises of whether its developer can be held accountable for the decision.

Errors in AI mainly appear when confounding factors are correlated with pathologic entities in the training datasets rather than actual signs of disease. When AI devices decide, their decision is based on the collected data, the algorithms they are based on, and what they have learnt since their creation. Conclusions of AI algorithms may be unpredictable for humans [100] as they are capable of analysing a much more exhaustive configuration space; their decisions therefore do not in general share a common basis with humans [14], [15], [55], [56], [73], [101], [102].

Although the evolving complexity of AI technology makes it inevitable that some of its inner workings will appear to be a black box [86], that does not mean accountability is out of the question: since AI will play an increasingly important part over the next years in the healthcare scenario, it will need to be bound by core ethical principles, such as beneficence and respect for patients [90].

A complicating factor to determine the legal classification of an AI system is that it is not so easy to tie to a breakdown of legal persons and legal objects. The artificial legal person that is a company can be an object too, it can be sold, and it can be divided, but it can also be held responsible for its actions. Personhood in a legal sense is not carved in stone; there is elasticity of the concept due to the evolution of societal needs, dependent on what is deemed acceptable within certain social, cultural, political and geographical parameters [10].

Some authors argued that accountability for an AI output may be a simple matter, as ultimately ethical and legal responsibility for decision making will remain in the natural intelligence of physicians [13], [55], [68], [71], [103]. From this viewpoint, it is probable that multidisciplinary boards will take the responsibility in difficult cases, considering relevant but not always conclusive what the AI provided [4].

Public-private partnerships for patient data sharing for AI

As it is now unthinkable that a developed nation would not have sanitation infrastructure, we should remember that in the past governments and regulators debated about whether such infrastructure was worthy of investment and whether it was a public or private good [85]. A similar debate has been simmering for some time regarding health data infrastructure, defined as the hardware and software to securely aggregate, store, process and transmit healthcare data in the AI era [5], [85], [104].

Panch et al. [85] proposed a paths base on a social compact around healthcare as a public good, the tolerance to public-private partnership, and the public's trust in both governments and the private sector to create a generalized data infrastructure with due care and attention in the face of both commercial and political perverse incentives. Existing initiatives such the above mentioned FHIR (44) – that create a common data schema for storage and transfer of healthcare data as well as AI enabled technology innovations – will accelerate progress and ensure that legacy data are included [85]. However, there are several complex problems still to be solved including how to enable informed consent for data sharing, and how to protect confidentiality yet maintain data fidelity, as we discussed above.

Nowadays, specific contracting instruments are needed to ensure that data sharing involves both the necessary protection as well as fair material returns to healthcare organizations and the patients they serve [21], [105]. Recently, the NEST Coordinating Center has chosen Lung-RADS Assist (Advanced Radiology Guidance, Reporting and Monitoring), sponsored by the ACR, as one of their demonstration projects for AI algorithms [72]. This is a method for validating and monitoring AI algorithms built for detection and classification of lung nodules in lung cancer screening: it uses use real-world data to assess the end-to-end workflow, from deployment of an AI algorithm in a radiology reporting system through to the capture of performance metrics within a national registry. This is an example of a public-private partnership that can be monitored in clinical practice to ensure ongoing patient safety while establishing a pathway to increase the efficiency of such a collaboration.

However, considering the thousands of algorithms that will likely be developed, governmental regulatory agencies are ill equipped to perform regulations in this field [57]. Moreover, the sheer number of algorithms that will likely be submitted for regulatory approval could place a considerable burden on the regulatory reviews process. Therefore, public-private partnerships between regulatory agencies and trusted organizations such as medical specialty societies could play an important role in the validation of AI algorithms, collecting the real-world evidence (for example, through wearable devices) that would support ongoing efficacy and safety of AI algorithms in clinical practice [29], [85].

In conclusion, all the solutions proposed require a multidisciplinary team which includes AI developers, health providers, regulators, governments, patients/public and physicians. Such a community needs to work together with a common, public aim of improving care and trust-creating infrastructures that enable the responsible use of patients' health data to facilitate the development of AI tools that will improve population health. Should this fail, data breaches and other data disasters could set the industry back decades [10].

3. CONCLUSIONS

The innovations of AI in healthcare face several challenges such as issues around the ownership and control of data, regulations of data sharing, protection of sensitive data through anonymization and cybersecurity, intense debate over the special accountability and responsibility requirements, and questions about the fiduciary public-private partnership for patient data sharing.

A good employment of AI may be helpful and valuable for both patients (better experience and better outcome) and healthcare staff (work optimization and more time to devote to patients in a reachable personalized medicine scenario). On the contrary, a bad or unethical use of this cutting-edge technology may be dangerous, and policymakers and healthcare practitioners must work together to prevent this. Governments have recently attempted to regulate this field, for example with the GDPR, and such regulations may facilitate implementation over the long term by promoting public trust and patient engagement. To ensure both humane and regulated (and, therefore, responsible) care of the patients, policies will need to provide security, privacy and ethical use of the sensitive information on which healthcare AI algorithms are based.

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