

Artificial Intelligence enabling improved patient treatment strategies – challenges and recommendations

Authors

Sara Zullino¹, Anna Niehues¹, Tanushree Tunstall¹, Celeste Oliveira², Sandra Caramujo-Balseiro², Ana Filipa Brito², Natália Lescura², Carolina Bezzi³, Samuele Ghezzi³, Katarina Gvozdanovic⁴, Roberto Mužić⁵, Jakov Vuković⁵, Josip Vrančić⁵, Fotis Psomopoulos⁶, Emanuel Brađašević⁵, Pero Ivanko⁵, Ivan Pristaš⁵, João Quintas², Luca Boldrini⁷, Carolina de la Pinta⁸, Maria Laura Garcia-Bermejo⁸, Luis Mendes⁹, Jan-Willem Boiten¹⁰, Ana Blanco¹¹, Almudena Fuster-Matanzo¹¹, Milana Truč¹², Merete Schmiegelow¹³, Karina Huberman¹⁴, Antonela Blazekovic¹⁵, Sarah Meglaj Bakrac¹⁵, Fran Borovecki¹⁵, Gary Saunders¹

¹ EATRIS ERIC, Amsterdam, the Netherlands

² Instituto Pedro Nunes, Coimbra, Portugal

³ Vita-Salute San Raffaele University, Milan, Italy

⁴ Croatian Agency for Medicinal Products and Medical Devices, Zagreb, Croatia

⁵ Croatian Institute of Public Health

⁶ Institute of Applied Biosciences, Centre for Research and Technology Hellas

⁷ Dipartimento di Diagnostica per Immagini, Radioterapia Oncologica ed Ematologia; Fondazione Policlinico Universitario “A. Gemelli” IRCCS, Roma, Italy

⁸ Biomarkers and Therapeutic Targets Group, Ramon y Cajal Health Research Institute (IRYCIS), Madrid, Spain

⁹ AIBILI- Association for Innovation and Biomedical Research on Light and Image, Portugal

¹⁰ Health-RI, the Netherlands

¹¹ QUIBIM, Spain

¹² European Patients' Forum, Belgium

¹³ EATRIS-Plus Patient Advisory Committee

¹⁴ European AIDS Treatment Group

¹⁵ University of Zagreb School of Medicine, Zagreb, Croatia

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Introduction

In the last decade, Artificial Intelligence (AI)-based technologies have been progressively adopted by and transforming different areas of society. Increased computing power, availability of extensive digital data, and development of new algorithms have led to the proliferation of AI technologies.

In medicine, the application of AI has emerged as a particularly transformative approach with the potential to revolutionize disease diagnosis, treatment planning, and patient management strategies. The promise of AI lies in its ability to mimic the capabilities of clinicians while analysing huge volumes of data, detect patterns normally invisible to the naked eye, and generate actionable insights that can support clinical decision-making and improve patient outcomes. AI tools in medicine can be broadly categorised into four classes: biomedical research, clinical practice, public health, and health administration. Examples include their use in optimising clinical trials by identifying suitable patients and predicting outcomes, surveillance of disease outbreaks, accelerating drug discovery processes, enabling personalised medicine approaches, utilising AI-powered surgical robots, and extraction of relevant information from health records. Moreover, AI applications, such as chatbots and virtual assistants enhance patient engagement and provide timely support and guidance, ensuring better patient satisfaction and adherence to treatment plans [1], [2]. These applications have the potential to augment the ability of humans and revolutionize healthcare by providing a faster, more accurate, and cost-effective way to diagnose and treat diseases [3]. While introducing AI to medicine holds great promise for revolutionising healthcare, this transition is not without its key translational challenges that need to be addressed to ensure the safe and effective integration of AI into the healthcare ecosystem. [4]–[7].

Despite the rapid advancement of AI technologies, their widespread adoption in patient care is still limited, delaying accurate assessment of their true impact [8]. Multiple challenges constraining the successful translation and integration of AI-enabled technologies into healthcare practice need to be addressed. An important framework for classifying and regulating AI-based applications in Europe will be the expected European Artificial Intelligence Act [9]. The translational medicine community includes diverse stakeholders including clinicians, researchers, patients, decision-makers, funders, and regulators, often organised in national and international community initiatives. They all play a role in ensuring that AI-enabled technologies applied in healthcare allow making informed decisions benefiting the patients while preserving their privacy.

Here, we review key challenges to AI implementation in clinical settings, highlight the best practices from our translational community and propose recommendations. Our intention is to stimulate dialogue among the relevant stakeholders involved in the translational process, encourage collaboration, attract investment, and drive further advancements in this rapidly evolving field.

Challenges and advancements

An independent high-level expert group on AI set up by the European Commission [10] suggested that trustworthy AI should be lawful, ethical, and technically robust. Poor implementation and validation could cause AI systems to make incorrect inferences, leading to flawed decisions potentially harming patients. Application of AI technologies in healthcare is associated with technical and regulatory challenges that are encountered by the translational medicine community. Overcoming these challenges requires the establishment of robust data governance frameworks, standardised data formats, secure data exchange protocols, and clear guidelines for consent and data usage. All these segments are important for fostering data-driven innovation and ensuring transparency and public trust.

Technical aspects

High-quality and interoperable data

With the growing role of AI in healthcare, there is an increasing demand for access to health data for both primary and secondary reuse [11]. When used for AI training, such data can become the foundation for applications used in diagnostics and treatments. Accurate and robust AI models require high-quality data. Since the data quality impacts the achievable performance of AI applications, it is essential to address potential bias, inaccuracy, or errors in the data before training AI models. Data quality measures [12]–[14] can help ensure that data used to train AI models is both diverse and representative of the target population to mitigate bias [15].

As healthcare data is often stored in different systems and formats, combining data from different sources can be challenging. The FAIR Guiding Principles [16] offer recommendations to increase findability, accessibility, interoperability, and reusability emphasising on the necessity of machine-actionability enabled through semantic interoperability. Since data FAIRification requires expert domain knowledge, FAIR practices can best be implemented at the source. Additionally, data publishing environments need to enable both manual and automatic data submission, search, sharing, and reuse [17].

Data standardisation is fundamental to interoperability and a critical factor to effectively employ AI technologies in medicine. It involves converting data into a format that can be interpreted by various tools and methodologies, facilitating seamless communication across diverse systems. For healthcare data, that is gathered using different methods, serving distinct purposes, and stored in varied formats through an array of databases and repositories, a challenge lies in optimising the reuse of existing

tools and resources to avoid redundant efforts and ensure the implementation of best practices. Technical differences between systems and a lack of awareness about available resources can hinder this process. Several initiatives focus on data standardisation in healthcare to enhance interoperability and facilitate data sharing across different medical domains. Selected standards and relevant communities are presented in Table 1.

Table 1: Health data, ICT and AI-related standards and initiatives.

Standard	Community/organisation	Purpose
Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) and standardised vocabularies [18]	Open community standard managed by the Observational Health Data Sciences and Informatics (OHDSI) [19] CDM Working Group	Standardise structure and content of observational medical data across various clinical domains
Systematized Nomenclature of Medicine (SNOMED) Clinical Terms (CT)	SNOMED International [20], a not-for-profit organisation developing SNOMED CT and offering the terminology to its members and licensees	Standardised clinical terminology providing a common language for health information sharing, promoting precise communication among healthcare providers and systems.
Digital Imaging and Communications in Medicine (DICOM) [21] / ISO 12052 [22]	The Medical Imaging & Technology Alliance (MITA), a division of the National Electrical Manufacturers Association (NEMA)	International standard for storing and transmitting medical images, ensuring consistent image formats and metadata for seamless exchange.
Various open-source standards, frameworks, and tools related to genomics data	The Global Alliance for Genomics and Health (GA4GH) [23]	The international consortium promotes genomic data sharing to benefit human health, specialising in standardising consent forms and ethical guidelines for responsible genomic data collection and utilisation.
	StandICT.eu and Stand4EU [20]–[22]	Collaborative efforts involving European ICT experts in defining European and global standards for AI-based solutions.
	EU Observatory for ICT Standardisation [23]	Monitors the global standardisation landscape, covering important ICT standards, working groups, and committees.
	IEEE Standards [24]–[27]	Develops standards for AI applications related to health and wellbeing, including models and approaches.
	ITU-T Standards [28]	Sets standards for AI and machine learning-based software as medical devices.
	ETSI Standards [29]	Leading specific standardisation efforts related to the application of AI in healthcare, such as eHealth data recording requirements.

Robust and ethical AI applications

There is a growing recognition of the need for standards to guide the development and use of AI in various domains, including translational medicine. Community recommendations like DOME [24], which provides guidance on how to report supervised machine learning-based analyses applied to biological studies, can be a step towards standardisation. Data and application standards (see Table 1) can help to ensure the quality and reliability of AI-based solutions, as well as to promote the responsible and ethical use of AI. However, there may be challenges in establishing and enforcing these standards, particularly in a rapidly evolving field like AI. In addition to a clear regulatory framework, it also requires a culture that embraces data sharing [25].

Privacy preservation

The European General Data Protection Regulation (GDPR) regulates the processing of personal data. Since the use of AI applications often involves handling sensitive personal data such as patient records, the preservation of patient privacy is an urgent priority. Anonymisation of patient data is a crucial first step to ensuring that information is exchanged securely. Data anonymisation transforms personal information into non-identifiable data, preserving patient privacy in healthcare research, while enabling valuable insights without revealing individual identities. However, the effectiveness of anonymisation methods and the potential for re-identification are subjects of debate. An alternative technical measure to protect personal data is pseudonymisation [26], [27]. Achieving a balance between privacy protection and data utility remains a complex challenge in the realm of data privacy and ethics, particularly in healthcare research and other fields dealing with sensitive data. The need to preserve privacy also adds to the requirements of computing environments.

In recent years, the European Member States have made progress in proposing regulatory frameworks around the management of health data, defining main stakeholders, data sources, processes and data protection rules and policies. There is a clear momentum in Europe with regards to sharing and (re)using the health data as a valuable input for achieving sustainable healthcare systems. Some of the main initiatives are depicted in Table 2. The challenges addressed by these initiatives can provide the foundation for the development of cutting-edge AI applications in healthcare in Europe.

Table 2: Initiatives addressing technical and regulatory challenges.

Initiative	Scope	Challenge addressed
European Health Data Space (EHDS) [28]	Regulation enabling individuals, communities, and companies to benefit from secure and seamless access to health data regardless of its location [29]. EHDS comprises rules, standards, infrastructures, and a governance framework.	Technical and Regulatory.
Health@EU Pilot [30]	Pilot version of the European Health Data Space (EHDS) infrastructure for the secondary use of health data.	Technical: IT infrastructure, data standardisation and interoperability. Regulatory: guidelines for compliance.
EU Joint Action Towards the European Health Data Space (TEHDAS) [31]	Define joint European principles for the secondary use of health [31].	Regulatory: ethical and legal compliance.

Initiative	Scope	Challenge addressed
EUropean Federation for CAncer IMages (EUCAIM) [32]	Pan-European digital federated infrastructure of cancer-related images, for the development of AI tools toward Precision Medicine.	Technical: IT infrastructure, data standardisation and interoperability. Regulatory: ethical and legal compliance.
Genomic Data Infrastructure (GDI) [33]	Enable access to genomic and related phenotypic and clinical data across Europe by establishing a federated, sustainable, and secure infrastructure to access the data.	Technical: IT infrastructure, data standardisation and interoperability. Regulatory: ethical and legal compliance.
EOSC-Life [34]	Creation of an open, digital, and collaborative space for biological and medical research by the 13 Life Science 'ESFRI' research infrastructures (LS RIs)	Technical: data standardisation. Regulatory: ethical and legal compliance.
Testing and Experimentation Facility for Health AI and Robotics (TEF-Health) [35]	Support AI developers to bring trustworthy AI to the market more efficiently, and facilitate its uptake in Europe.	Technical: standards for AI applications.
The Data Spaces Support Centre (DSSC) [36]	Define common requirements and establish best practices to accelerate the formation of sovereign data spaces.	Technical: IT infrastructure.
Simpl [37]	Enable cloud-to-edge and support all major data initiatives funded by the European Commission, such as common European data spaces.	Technical: IT infrastructure.
Gaia-X [38]	Gaia-X enables a federated and secure data infrastructure linking many cloud service providers based on common rules defined by members of the Gaia-X association.	Technical/regulatory: infrastructure governance.
European Health Data & Evidence Network (EHDEN) [39]	Harmonise real world health data and develop a federated infrastructure across Europe.	Technical: IT infrastructure, data standardisation.
Data Analysis and Real World Interrogation Network (Darwin-EU®) [40]	Coordination centre established by EMA [41] and the European medicines regulatory network to support regulatory decision making by providing a catalogue of approved high-quality data sources.	Regulatory: healthcare databases for use in medicines regulation.
AI4Health.Cro [42]	Not-for-profit public-private consortium and European Digital Innovation Hub (EDIH) based in Croatia, focusing on AI applications in smart healthcare.	Technical and regulatory.
FUTURE AI [43]	International, multi-stakeholder initiative for defining and maintaining concrete guidelines that will facilitate the design, development, validation and deployment of trustworthy AI solutions in medicine and healthcare based	Technical: trustworthy AI

Initiative	Scope	Challenge addressed
	on six guiding principles: Fairness, Universality, Traceability, Usability, Robustness and Explainability	

Regulatory aspects

Regulatory policies (see, e.g., [44]) provide a framework for the development and application of AI-based technologies in healthcare. A key regulatory framework is the European AI Act, which was proposed by the European Commission in 2021 [9] and provisionally agreed upon in December 2023 [45]. An overview of European policies related to regulation of data usage and AI applications in a general or more specific health context is given in Table 3.

Table 3: European digital transformation programmes, policies and agreements.

<ul style="list-style-type: none"> • Digital Decade Policy Programme (2023) [46] • European Data Governance Act (2023) [47] • AI Act (provisionally agreed upon 2023) [9], [45] • Digital Health Uptake (DHU), project under the Digital Europe Programme (2022) [48] • EDITH. Ecosystem Digital Twins in Healthcare (2022) [49] • ARISA. European AI Skills Alliance (2022) [50] • Data Act (2022) [51] • Proposal for regulation of EHDS (2022) [52] • Digital Transformation. Cost of Non-Europe. EPRS_STU(2022)699475_EN (January 2022) [53] • 'Path to the Digital Decade': the EU's plan to achieve a digital Europe by 2030 (December 2022) • AI Act (proposal, 2021) [54] • eHealth Digital Service Infrastructure (eHDSI). European Commission (2021) [55] • Strategy for Data (2020) [56] • European Recovery Fund (2020)

While some regulatory developments related to privacy preservation and IT infrastructure processing health data are described above, regulation also needs to address challenges specific to AI-enabled Medical Devices.

Regulatory classification of for AI-enabled Medical Devices

Nowadays, it is common to find AI algorithms within Software as a Medical Device (SaMD), for example, enhanced medical imaging systems, smart robots, wearable technology, AI-based data analysis, simulation platforms and AI applications to improve the clinical decision-making process with the support of data analysis [57]–[59].

From a regulatory point of view, AI-based medical devices (AI-MDs), are treated as any other medical device. In the European Union (EU), MDs are regulated by Medical Device Regulation (MDR, Regulation 2017/745) and In Vitro Diagnostic Medical Device Regulation (IVDR, Regulation 2017/746) [60], [61]. In addition to MDR and IVDR, other guidelines and standards, which set specific requirements for software-based MDs, must be considered before putting these devices into the EU market [62].

Besides helping to improve the quality of patient care, AI-MDs are a potential cause for safety concerns. The regulators should address the complexities of MDs that incorporate AI capabilities. While there is no specific section in the EU regulations for MDs regarding AI-MDs, some requirements

for SaMD must be considered [60], [61]. Moreover, SaMD is primarily classified in the medium and higher risk classes, requiring an assessment from a notified body (NB).

Although AI can be incorporated into software MD requirements, there exists a regulatory gap regarding the specificities of AI-based products. The European Commission is expected to release an AI act specific to medical devices in 2025. Until then, manufacturers are required to continue developing their AI-MDs according to MDR and IVDR.

Cybersecurity for AI-based Medical Devices

The importance of cybersecurity in MDs is emerging, mainly because of the increase in cyberattacks and the requirements addressed to SaMD. For AI-MDs, the basis for compliance with European legislation is conformity with Annex I – General Safety and Performance Requirements (GSPR) of the MDR or the IVDR. GSPR clause 17 and GSPR clause 16 of the MDR [63] and IVDR [64], respectively, introduce new (cyber)security requirements.

Furthermore, in 2020, specific guidance on cybersecurity for medical devices has been published (MDCG 2019-16) [65]. This guidance, which centres on the Confidentiality, Integrity, and Availability (CIA) principle during the entire lifecycle of the MD, was issued to help manufacturers fulfil all the cybersecurity requirements described in MDR/IVDR Annex I [65], [66]. While this guidance is specific to medical devices, the principles and challenges discussed are pertinent to the broader field of AI in healthcare, as evidenced in the EMA Reflection Paper [67]. The Reflection Paper underscores the risks associated with AI systems, particularly the potential for personal data exposure with high-parameter models. Techniques such as regularisation, dropout, and random noise addition are emphasised for mitigating data memorisation risks in large language models. It also stresses the importance of maintaining the integrity of training data and adopting robust security measures to safeguard patient privacy and maintain data confidentiality before transferring AI models to less secure environments. MDCG 2019-16 also provides valuable information on the EU regulator's expectations concerning cybersecurity for MDs under the MDR and IVDR. It illustrates how different aspects and requirements of these regulations are connected through Post Market Surveillance (PMS) and Risk Management [65], [66].

Risk management is the core of cybersecurity. The GSPR of the MDR and IVDR [63], [64] further lays down that manufacturers are required to establish, execute, document, and maintain a risk management system. For AI-MDs, the security risk management process involves the same practices as a traditional safety risk management process according to ISO 14971 [68], and the recently published ISO/IEC 23894 [69]. This approach is based on documenting vulnerabilities, threats, and controls for the total product lifecycle. The process should also consider other standards, namely IEC 62304 [70], IEC 82304-1 [71], IEC 62443-4 (parts 1 and 2) [72], [73], IEC 81001-5-1 [74], IEC/TR 80002-1 [75], ISO/TR 24971 [76] and ISO/IEC 27000 series [77].

It should also be noted that, concerning cybersecurity, the regulatory structure is even more exhaustive. In addition to MDR/IVDR, the EU Cybersecurity Act (CSA) (Regulation (EU) 2019/881) [78], the reformed Network and Information Security System Directive 2 (NIS 2) (Directive (EU) 2022/2555) [79], the General Data Protection Regulation (GDPR) (Regulation (EU) 2016/679) [80] and the proposal of the Artificial Intelligence Act (AI Act) [9], [81] should also be considered.

Good Machine Learning Practice (GMLP) for Medical Device development

The use of Good Machine Learning Practice (GMLP) for MD development is a growing source of concern for regulators. Considering this, the U.S. Food and Drug Administration (FDA), Health Canada, and the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) have

collaborated to establish ten guiding principles which serve as the basis for the development of GMLP [82]. These principles aim to support the creation of efficient, safe, and high-quality MDs that incorporate AI and Machine Learning (AI/ML).

Although European organisations did not participate in the development of this document, and a similar document does not exist in Europe, practices are designed to ensure that MDs that use AI/ML are safe, effective, and of high quality. Currently, in the EU, alignment with these ten guiding principles means complying with the MDR [63] or IVDR [64], while also adopting relevant standards such as ISO 13485 [83], IEC 62304 [70] and IEC 82304-1 [71].

The supplementary material of this paper includes a table comparing the ten guiding principles identified by the FDA, Health Canada and MHRA, and the applicable parts of the MDR [63], IVDR [64], ISO 13485 [83], IEC 62304 [70], IEC 82304-1 [71], and other relevant standards or guidelines (Supplementary Material, Table 1).

There are requirements that manufacturers of AI-MDs must fulfil to comply with the applicable regulation. This is becoming more challenging for AI-MDs as necessary clear guidelines do not exist yet. The impact on economic operators, especially manufacturers, can be regulatory and economic. The regulatory requirements affected by the development of AI-MDs include quality management system (QMS), technical documentation, risk management, data management, cybersecurity, classification, pre-clinical verification and validation, and clinical evaluation (see Table 4). Regarding the financial considerations, the manufacturers of AI-MDs must evaluate the need to integrate or train collaborators with competence in AI and regulation. For example, persons responsible for regulatory compliance (PRRC). For medium or high-risk devices, such as AI-MDs, the costs also increase due to manufacturers’ legal responsibility and product liability.

Table 4: Regulatory requirements for AI-based Medical Devices and economic impact.

Regulatory requirements impact	Quality Management System (QMS)
	A manufacturer, to comply with the general obligations of manufacturers listed in Article 10 of the MDR/IVDR, must implement a QMS, preferably according to ISO 13485, as an NB is involved [63], [64], [83].
	Technical documentation
	The information listed in Annex II and III of the MDR/IVDR is compiled in a Technical Documentation file to demonstrate compliance with the GSPR listed in Annex I of MDR/IVDR [63], [64]. If compliance is verified, CE marking can be affixed, with or without the involvement of NBs (depending on device classification).
	Risk management
	Risk management is one of the core activities of the MDs development. Both the MDR/IVDR and ISO 13485 require the manufacturer to implement a risk management process, preferably according to ISO 14791. Risk management is a total product life-cycle process including identification of hazards, estimation and evaluation of risks, control and monitorisation of the effectiveness of control measures [63], [64], [68], [83].
	Data management

The input data used to develop the AI system is handled in a way that guarantees the confidentiality of information and data (articles 109 and 110 of MDR and articles 102 and 103 of IVDR). Also, GDPR and Regulation (EU) 2018/1725 apply to the processing of personal data. Furthermore, data submitted to the electronic system for clinical investigations and performance studies are subjected to the requirements of personal and commercial data protection (article 73 MDR and article 69 IVDR) [63], [64], [80], [84].

Cybersecurity

How AI-MDs interact with patients and users poses specific risks that need to be considered to prevent patient and manufacturer consequences. Cybersecurity is essential to protect the model and, consequently, the patients.

Classification

AI-MDs are usually class II or class III devices (see Annex VIII, MDR/IVDR, and MDGC 2019-11), with stricter requirements for regulatory approval. Classification is related to the intended purpose of the device, the medical indications and the claims defined by the manufacturer [63], [64], [85].

Pre-clinical verification and validation (V&V)

V&V activities generate the data to support the GSPR of MDR/IVDR. In the context of AI algorithms, V&V activities require special attention from manufacturers. Training and test data should be properly controlled to avoid bias in the dataset so that the model output is scientifically validated. It should also be noted that in the case of AI, usability principles should be applied so that it is possible to test to what extent human experts can recreate the model's decisions [63], [64].

Clinical evaluation

Enough data with sufficient quality is also required to demonstrate compliance with the GSPR of MDR/IVDR. The data sources include clinical (ISO 14155) and performance investigations, scientific literature, and PMS activities [63], [64], [86]. As AI-MDs are innovative, it is challenging to establish equivalence to other CE-marked devices. In Europe and until EUDAMED is fully functional, the search for CE-marked AI-MDs is greatly conditioned by the absence of a public database with information on approved devices and the confidentiality of information submitted to NBs and Competent Authorities. Thus, clinical and performance investigations are the primary source of clinical evidence. The results from the clinical evaluation are collected in the Clinical Evaluation Report for MDs and Performance Evaluation Report for in vitro diagnostic medical devices (Article 61 and Annex XIV, MDR; Article 56 and Annex XIII, IVDR; MDCG 2020-5 and MDCG 2020-6) [63], [64], [87], [88].

Economic impact

Costs

Besides the need for insurance and its related costs, medium and high-risk class AI-MDs are associated with the involvement of an NB in the conformity evaluation process. The costs of other certifications, for example, the QMS, also increase the budget needs.

Legal responsibility and product liability

Manufacturers shall also, in the scope of MDR and IVDR, in a manner that is proportional to the risk class, type of device and the size of the enterprise, have measures to provide financial coverage in respect of their potential liability (Article 10 of the MDR/IVDR) [63], [64]. As most AI-MDs are classified into medium and high-risk classes, the responsibilities regarding liability issues are also charged to the manufacturers.

Person responsible for regulatory compliance (PRRC)

This expertise should be included within the team must consider Article 15 of MDR and IVDR, requiring that manufacturers shall have available within their organisation at least one PRRC who possesses the knowledge of QMS for MDs and MDs regulation [63], [64].

Competence in AI

The manufacturers should hire experts with knowledge of AI, besides cybersecurity and MD regulation.

From the beginning of the development, top management and the development team must consider a regulatory roadmap and financial plan with the involvement of relevant organisations (competent authority, NB, consultancy teams) for support. This planning helps manufacturers to predict the financial burden and workload associated with their AI-MD.

Key stakeholders and recommendations

Various stakeholders including researchers from academia, industry and healthcare, clinicians, regulators at national and European level, patients, industry, and more are taking on the challenges described above. The diverse challenges require collaboration between them.

Education and Training

The successful implementation of AI in healthcare requires comprehensive education and training for clinicians, healthcare providers, researchers, patients, and policymakers encompassing the latest advancements in personalised medicine and AI, as well as the ethical and social implications associated with these advanced technologies.

Collaboration across disciplines and among stakeholders is crucial for the practical application of AI, requiring scientists from various fields to possess a fundamental understanding of AI concepts, methods, and potential applications. This collaborative effort relies on clinicians grasping the potential and practical implementation of AI, while data scientists need to comprehend the clinicians' requirements. Moreover, patients could provide important expertise on their conditions and offer valuable insights that would make patient needs and expectations easier to understand for healthcare professionals, researchers, and developers.

Core competencies in AI are essential for physicians to supervise and effectively use AI systems, but they are not comprehensively integrated into medical training. With the increasing use of AI in medicine, healthcare professionals must be capable of working with the growing number of different medical AI systems, including evaluating their performance and understanding their limitations.

Therefore, it is essential to formalize the teaching of AI concepts and possibilities to ensure successful integration into routine medical practice. Interestingly, medical students in Europe feel unprepared to work in a digitised healthcare system [89], emphasising the need for additional digital and AI competencies in their training. For instance, the results of a national-level survey on Croatian radiologists and radiology residents showed that almost 90% of research participants believe that there is a need to include AI education in medical curricula, regardless of age or subspecialty area [90].

Medical schools are increasingly introducing courses teaching basic AI competencies, which should ultimately become an integral part of the mandatory curriculum [91]. As medical training needs to adapt to the evolving healthcare landscape, an integrated review of current educational activities can guide educators and policymakers in shaping future medical training programs that are responsive to changing realities and patient needs [91]–[96]. Radiology will be significantly impacted by AI, necessitating a deep understanding of AI among postgraduate radiology students [96].

We are currently experiencing a unique opportunity for the exchange of knowledge and expertise in science, medicine, and academia. This ecosystem fosters multidirectional communication among various stakeholders, creating a natural foundation to promote the application and realisation of the full potential of innovative scientific concepts such as AI. This cooperation operates on multiple levels facilitating timely acquisition of knowledge, horizontal learning, and carries a strong possibility of producing highly motivated scientists. Through multinational cooperation, this collaborative approach cultivates a stimulating environment and create fertile ground for the successful, sustainable, and widespread integration of AI into routine clinical practice.

Pharmaceutical Industry

AI has revolutionised the world of the pharmaceutical industry, including healthcare companies, offering immense potential to improve clinical workflows, patient management and how healthcare is delivered. The AI in healthcare market is projected to grow from USD 14.6 Billion in 2023 to USD 102.7 Billion by 2028; it is expected to grow at a compound annual growth rate (CAGR) of 47.6% during the forecast period [97].

Particularly in the medical imaging domain, the number of AI-based applications using biomedical imagery has increased dramatically. This has been possible thanks to the intrinsic digitised nature of the whole imaging workflow, including image acquisition and reconstruction, image segmentation and image processing and by the advent of high-performance computing [98]–[104]. Interestingly, AI in medical imaging market size surpassed USD 1.5 Billion in 2021 and is anticipated to witness over 30% CAGR between 2022 and 2030 [105].

Remarkably, AI has fostered collaboration between industry, medical facilities, academia and research organisations, promoting knowledge exchange and open innovation in healthcare. Collaborative public-private partnerships can pool resources and expertise to develop AI-driven solutions for global health challenges. This cooperation and co-creation facilitate the translation of cutting-edge research into practical applications and accelerates the adoption of AI in clinical practice and their regulatory clearance, leading to the development of advanced imaging techniques, optimised diagnostic algorithms, and novel treatment strategies, ultimately benefiting patients and improving healthcare outcomes. Public-private partnerships can also face challenges related to data sharing and intellectual property. It is important to make sure that informed consent allow for data use in the public-private collaboration. Legal agreements need to be made based on how data is shared within the consortium. Several funding initiatives actively promote collaborations between industry and academia, such as the funding programmes for research and innovation Horizon Europe, both endorsed by the European

Commission. Particularly interesting is the Innovative Health Initiative (IHI) programme, the EU public-private partnership funding health research and innovation.

Despite the advantages of AI and the remarkable progress in its implementation, there are still several challenges to be addressed [106]. As discussed earlier, ethical concerns, data privacy, and security issues are critical considerations in utilising AI in medicine; ensuring the responsible and unbiased use of AI algorithms remains a priority. Additionally, the lack of standardised frameworks and regulations poses challenges in integrating AI systems into existing healthcare infrastructures. Moreover, the requirement for large amounts of high-quality labelled data for AI model training often limits widespread adoption [106]. Overcoming these challenges necessitates close collaboration between stakeholders, including regulatory bodies, healthcare providers, industry leaders, and academic institutions, to establish guidelines, ethical frameworks, and data-sharing protocols.

In summary, the implementation of AI in medicine has revolutionised healthcare and patient management and fostered public-private collaboration. While challenges exist, successful cases demonstrate the potential of AI in enhancing diagnosis, treatment, and patient outcomes. To realize the full benefits of AI, it is crucial to address current problems through interdisciplinary collaboration, regulatory frameworks, and ethical guidelines. By embracing AI technology responsibly, the healthcare industry can further advance patient care and revolutionize the field of medicine.

Patient engagement

Patients are increasingly interested in gaining a better understanding of their medical conditions and are seeking a more engaged and proactive role in managing their health and overall well-being. Through online access to their health data, health monitoring apps, telehealth, wearables, and digital medical devices, digital technologies offer significant opportunities for enabling patients to take a proactive approach in making the healthcare system more patient-centric.

There are numerous European initiatives established by representatives of patients with different pathologies. They seek trustworthy, in-depth, and evidence-based information on their diseases, treatment options, efficacy, and side effects [107]. This information will allow patients to discuss with their doctor and make informed decisions on the treatment and management plan, according to their preferences. In addition, the use of AI in medicine can help gather real-world information on the efficacy of different treatments, reducing the biases inherent in clinical trials due to the selection of very specific populations to be included. This selection is responsible for the fact that in some cases the extrapolation of the results of clinical trials is not valid. The information provided by AI would be a very useful tool for patients, contributing to their desirable autonomy. However, putting patients at the centre of digital health policies also requires their involvement in the design, testing and deployment of trusted digital health solutions that respond to their real needs and meet their expectations, as well as in the discussions regarding the ethical and safety standards regarding the use of AI in healthcare.

Studies on patients' attitudes towards the use of AI in medicine have primarily focused on specific subspecialties or diagnostic procedures [108]–[110]. Most of these studies suggest that patients generally accept the use of AI in medicine. Moreover, a recent survey conducted by the European Patients' Forum [111] in Spring 2023 highlighted patient organisations' enthusiasm for the potential benefits of AI [112]. The respondents particularly welcomed the potential of AI to improve the accuracy of diagnosis and enhance the quality and efficiency of research and innovation in healthcare, and the support that AI can provide to healthcare professionals in delivering more personalised care. Another potential benefit highlighted by the survey respondents was the promotion of patients' self-management and adherence to treatments with the help of AI powered digital tools.

While recognising the potential benefits of AI to patients and the functioning of the healthcare system, patient organisations have also worked to highlight the risks and ethical concerns that must be thoroughly addressed to prevent potential harm. These include the risk of discrimination due to non-representative and biased data, unequal access to AI-supported solutions, insufficient digital literacy skills among both patients and healthcare professionals, as well as safety issues. Moreover, patient organisations believed it crucial that AI solutions are designed to assist and support human actors, and not to replace them. Human oversight is needed to identify and address additional biases and unintended consequences, and it allows for better accountability. Additionally, it is important to establish and maintain clear communication and transparency with the public regarding the benefits, risks, and intended uses of AI solutions.

Furthermore, 82% of survey respondents believed that patients and healthcare professionals should be significantly involved in some aspects of the development and deployment of AI-powered tools and technologies [112]. Patient involvement in AI research ensures that AI systems are designed and implemented to address the needs and concerns of patients, and the benefits and risks of AI technologies are balanced in a way that maximizes patient outcomes.

Patient involvement can be facilitated by patient-representative organisations, which can be involved in AI research in several ways. Firstly, they can establish patient advisory boards or focus groups to provide feedback on AI system design and implementation and identify areas where AI can have the most significant impact on patient outcomes. Secondly, they can help develop patient-centred AI systems that prioritize patient needs and preferences and are tailored to different patient populations. Thirdly, they can disseminate and translate in lay language the information about AI technologies and their potential impact on patient outcomes, educating patients to make informed decisions about their healthcare and advocate for their needs and preferences. The inclusion of patients in regulatory decision-making and in post-marketing surveillance also ensures patient-centred decisions and continuous assessment of the risks/benefits of the products based on patients' experiences. Such a meaningful involvement would contribute to the responsible implementation of AI in clinical routines, would ensure patients' acceptance and cooperation and result in an increased understanding of digital health solutions, which in turn could positively affect patients' trust in such tools [112].

EATRIS made patient involvement a priority to support effective multi-stakeholder collaboration and a patient-centred approach to translational research. The EATRIS strategy to accelerate patient involvement in academic research has been developed in close collaboration with European partners, and includes the following objectives: fostering patient education, training researchers in meaningful patient involvement, and co-creating research with patients. The European Patients' Academy (EUPATI) [113] is a European initiative created to inform and educate on the process of innovation, research and development of novelties in the field of healthcare with the main objective of fostering citizen participation by promoting outreach and communication, brokering, initiative development, and training and mentoring [114]. EUPATI was born in 2012 as a consortium made up of representatives of patient organisations, the pharmaceutical industry and academic institutions. It was created and is supported by the European Patients' Forum, comprises 30 organisations from 12 countries, and is integrated into the Innovative Medicines Initiative [115], [116]. EATRIS and EUPATI signed a partnership agreement in 2020, demonstrating the commitment of both organisations to provide translational research education and training opportunities for patient advocates, and strengthen the capabilities of academic researchers to effectively engage patients in their research. Recently EATRIS launched the Patient Engagement Resource Centre (PERC) [117], a platform co-created with the European Patients' Forum (EPF) and the European AIDS Treatment Group (EATG) to

assist researchers in effectively involving patients in their research [118]. This platform will play a significant role in engaging patients in the development of AI in Europe.

Co-creation across technical and clinical experts

To achieve the full potential of AI in translational medicine, it is crucial that researchers, clinicians and patients work together in a collaborative and interdisciplinary manner. This interaction is often hindered by a lack of understanding among the various actors in the process, who possess very distinct skill sets, knowledge and expertise with minimal overlap [119]. We strongly believe in the need for a process of co-creation, where AI researchers, healthcare professionals, and patients work together to design and implement medical AI research tools (see Box 1). The goal of co-creation is to ensure that all stakeholders' needs and perspectives are considered and incorporated into the research process. It is also essential to build trust and create the conditions for the final adoption of the results in clinical practice.

The process of co-creation should be applied to all the steps of the process in the generation of AI medical device(s): design, regulatory decision-making as needed, implementation and dissemination/adoption. Moreover, as machine learning models are developed and improved through an iterative process involving several rounds of data collection, model training, model validation, model improvement and implementation, it is essential that all the players are involved throughout the whole process.

Box 1: Co-creation – roles of clinicians and biomedical researchers.

1. Work with AI experts to clearly define the clinical problem(s) that the AI project is meant to solve, starting from the medical needs and including the specific outcomes and metrics that are of interest.
2. Help identify the types of data that are relevant to the clinical problem and available for use in the AI project. Moreover, they can provide knowledge on the quality and reliability of the data, as well as on their specificity, which could affect results.
3. Provide critical insights on the design of the machine learning model as they can give input of what could be the kind of interpretability that would warrant its actual use.
4. Validate and provide feedback on AI model performance: Clinicians can validate the performance of the AI model by testing it in clinical practice in accordance with regulatory requirements for clinical investigations and performance studies. They can also provide feedback on its interpretability and practical utility.

In summary, involving clinicians, biomedical researchers and patients in the project from its beginning, will increase their understanding of the results and their motivation for implementation, as well as build trust in the results. Of course, to be able to interact, all the different actors will need to have some knowledge outside their field, and for this, training would be crucial. The goal should be to strike a balance between leveraging the expertise of each group and ensuring that the results are relevant, trustworthy, and useful for the clinical community.

Table 5: Summary of challenges and recommendations to implement AI-based technologies in healthcare.

Challenge	Current Status	Recommendations	Example(s)
Lack of high-quality and standardised healthcare data	Significant progress in data sharing and interoperability, but challenges remain in	Implementation of gold-standard and approved clinical information standards for healthcare data.	Health information exchanges (HIEs) facilitating data sharing between healthcare providers. Research collaborations

Challenge	Current Status	Recommendations	Example(s)
	data quality and privacy protection.		leveraging large-scale patient data for AI models.
Limited interpretability of AI models	Ongoing research in explainable AI to enhance transparency and trust in AI-based treatment strategies.	Develop explainable AI techniques	Development of interpretable machine learning models, such as decision trees and rule-based systems. Use of techniques like LIME and SHAP to provide explanations for AI model predictions.
Ethical considerations and biases in algorithms	Increasing focus on ethical AI practices and bias mitigation, but more work needed to address algorithmic biases in healthcare.	Incorporate diverse data and perspectives	AI fairness and bias audits to identify and mitigate biases in healthcare algorithms. Efforts to include diverse representation in AI development teams and stakeholder engagement processes.
Regulatory and legal complexities	Regulatory frameworks are evolving to accommodate AI applications in healthcare, but challenges remain in ensuring compliance and patient safety.	Regulatory frameworks that enable ethical, legal, and societal challenges to be overcome in application of AI powered solutions across national borders	EU's General Data Protection Regulation (GDPR), Data ACT, AI Act addressing data privacy concerns. FDA's Digital Health Software Precertification Programme to streamline regulation of AI-based medical devices.
Integration with existing healthcare systems	Efforts are being made to integrate AI systems with existing healthcare systems, but standardisation and compatibility issues persist.	Invest in interoperability infrastructure	Integration of AI algorithms into electronic health record (EHR) systems. Use of healthcare data interoperability standards like HL7 FHIR.
Limited access and affordability of AI solutions	AI solutions becoming more accessible, but issues of cost, resource allocation, and equity need to be addressed for widespread implementation.	Promote accessibility and affordability	Cloud-based AI platforms enabling cost-effective access to AI tools. Initiatives to provide AI resources to underserved regions and communities.
Trust and acceptance by healthcare professionals	Increasing awareness and education initiatives to familiarise healthcare professionals with AI capabilities and foster trust in AI-based treatments.	Key technical resources that enable co-creation of AI and ML clinical services developed across technical and clinical experts	A training and capacity building programme to develop the skills and workforce required for routine the application of AI powered solutions in the personalised medicine domain.
Privacy and security concerns	Advancements in privacy-preserving AI techniques, but ongoing challenges in	Implement robust data protection measures	Differential privacy techniques to protect patient privacy when analysing sensitive healthcare data.

Challenge	Current Status	Recommendations	Example(s)
	securing patient data and preventing unauthorised access.		
Patient engagement	The adoption and acceptance of AI technologies among patients vary, with factors such as digital literacy, trust, and privacy concerns influencing engagement levels. AI still seen as a black box, the lack of transparency and interpretability of AI models can hinder patient understanding and trust in the technology.	Frameworks to enable meaningful patient engagement in the application of AI powered solutions in the healthcare domain.	PERC [117], https://patient-engagement.eu/
Industry - Public-Private-Partnerships (PPP)	Difficulty in understanding PPPs the specific relationships between stakeholders, which are different and go well beyond the traditional customer-provider relationship.	Demonstrate value of PPPs example, regulatory impact, improved endpoints, prediction biomarkers, patient segmentation, technology tracking, and insights gained from analyses of big data.	BigData@Heart platform [120], COVID-19 Data Repository [121]

Conclusion

In conclusion, our main arguments underscore the transformative potential of Digital Transformation (DT) and AI in upgrading global health systems. These technologies promise to enhance the care model, public health policies, system organisation, and overall efficiency, resulting in a more patient-centric healthcare ecosystem. Furthermore, our discussion highlights the empowerment of patients through DT, leading to improved quality of life and substantial resource savings, such as reduced medical consultations, hospital admissions, and unnecessary medications.

The application of AI within a socio-health approach ensures personalised care for the patient. Importantly, our analysis suggests that AI's role in healthcare is not one of dehumanisation but rather augmentation. By streamlining tasks and processes, AI provides healthcare professionals with more time for meaningful patient interactions and actively involving patients in decision-making. As we conclude, we reiterate our recommendations for the adoption and integration of AI and DT in healthcare systems worldwide. It is imperative to emphasise the necessity of adapting to these technological advancements to drive improvements in patient care, system efficiency, and overall healthcare delivery.

Looking ahead, numerous open questions deserve attention. These questions include how to address unique healthcare challenges, manage ethical, privacy, and security concerns, seamlessly integrate AI

and DT into healthcare workflows, and ensure that these technologies reduce healthcare disparities rather than exacerbate them. Collaboration between healthcare providers, biomedical researchers, technical AI experts, and policymakers is essential in creating a regulatory framework that fosters innovation while safeguarding patient rights and data privacy. The future of healthcare holds great promise with the continued evolution of AI and DT, provided these challenges are met with thoughtful solutions.

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