2 Artificial Intelligence and Digital Health: An International Biomedical Perspective

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Abstract

With the scientific and technological progress achieved through -omic sciences (e.g., genomics, proteomics) and the development of sophisticated Artificial Intelligence (AI)-based solutions, Personalized Medicine has reached new opportunities for patient prevention and care in a new clinical avenue called "Digital Health" (DH). Investments in this field are rapidly increased worldwide. The chapter shows how AI is used in DH by elucidating four principal applications reported by the literature. AI-based solutions can support in retrieving big data, in analyzing Real-World Data (RWD) to produce Real-World Evidence (RWE), in predicting prognostic outcomes and risks, in personalizing clinical diagnostics, while customizing therapy development and monitoring patients' adherence. The chapter finally summarizes some challenges that still need to be addressed by the stakeholders involved in the field of DH.

Keywords

Artificial Intelligence · Digital Health · Patient management · Predictive model · Virtual ward · Patient support program

2.1 Introduction

The scientific progress achieved with the -omics (e.g., genomics, proteomics, metabolomics, radiomics, etc.), and the technological advances brought by Information Technology (IT), bioinformatics, and data sciences have rapidly increased the prognostic and diagnostic opportunities for Personalized Medicine (PM), aiming at

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delivering "*the right treatment to the right patient at the right time*" (Cesario et al. 2021). The boost of innovation in biomedical research has rapidly increased life expectancy worldwide, leading healthcare systems to face a higher demand for their services and workforce, to meet patients' and citizens' specific needs. Several challenges affect this demand such as changes in patients' expectations, a shift in lifestyle choices, or the continuous innovation of services, technologies, and clinical possibilities (Spatharou et al. 2020). For example, it has been estimated that by 2050, one in four people in Europe and North America will be over the age of 65, meaning that the health systems will deal with more chronic and complex needs.

The management of such needs is therefore expensive and requires systems to transform their organizations in a more proactive and long-term way (Spatharou et al. 2020). To this aim, several investments have been made in the field of biomedicine regarding Artificial Intelligence (AI)-based solutions to address several challenges such as remote patient management and disease prediction. Consequently, biomedical infrastructures are going to integrate novel evidence-based AI solutions to promote a new clinical avenue called "Digital Health" (DH) that can potentially revolutionize this field by addressing some of the mentioned challenges (Cesario et al. 2022).

This chapter will introduce the role of AI in DH by giving an overview of the main global trends in using AI solutions for biomedical purposes, without neglecting current limitations and challenges that still need to be overcame.

2.2 The Role of Artificial Intelligence in Digital Health

Artificial Intelligence is a discipline that outlines how computers can simulate, reproduce, and eventually enhance human intelligence mechanisms. According to the Medical Subject Heading (MeSH) Browser, AI is defined as:

> Theory and development of Computer Systems which perform tasks that normally require human intelligence. Such tasks may include speech recognition, learning; visual perception; mathematical computing; reasoning, problem solving, decision-making, and translation of language (MeSH Browser 2022).

On the other hand, Digital Health is a discipline that includes digital and technological care programs to enhance the efficiency of healthcare delivery and make medicine more personalized and precise; it uses remote monitoring tools and AI-driven solutions to facilitate understanding of health problems and challenges faced by individual citizens and subpopulations of patients (WHO 2021).

To take a glance at the international framework, a search performed within the PubMed database on June 16, 2022, shows the trend represented in Fig. 2.1, for a total of 357 results. This trend is likely to increase exponentially.

Even if the AI's impact and efficacy for DH is still at its roots, we could expect interesting evolutions by looking at the pipeline of industrial and academic ideas on

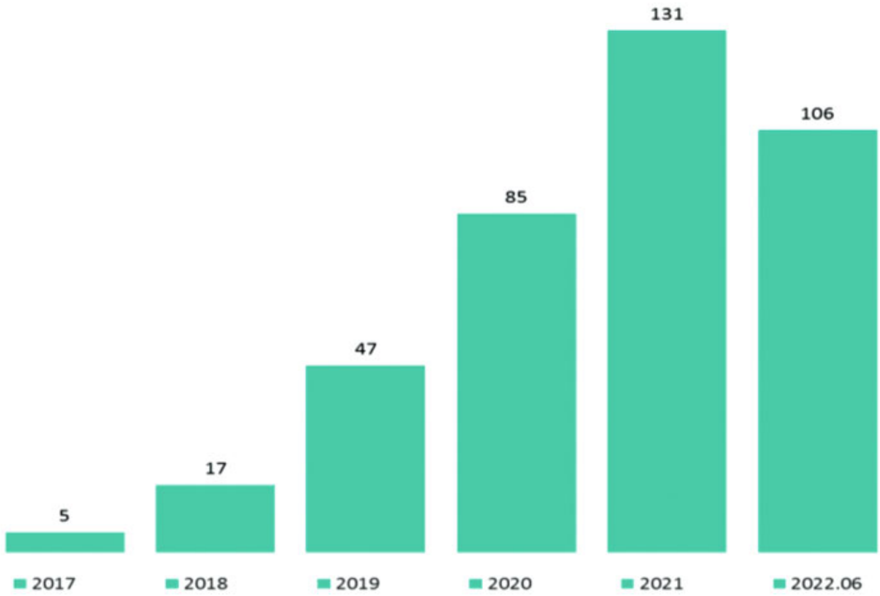

Fig. 2.1 Trend of scientific publications on PubMed for the query "artificial intelligence" [Title/Abstract] AND "digital health" [Title/Abstract], without setting any filter for year, language, or publication type

the global market. Currently, we envision four main directions of using AI solutions within the international medical field:

a. Support for prognostic outcomes and risk prediction
b. Support for clinical diagnostic personalization
c. Support for therapy development or improvement
d. Support for data collection and analysis [synthetic data, Real-World Data (RWD), Real-World Evidence (RWE)]

These directions will be elucidated in the following paragraphs.

2.2.1 Prognostic Outcomes and Risk Prediction

Prognostic outcomes and risk prediction is a process that involves the classification of individuals with certain characteristics or conditions and their classification according to stage, severity, and other clinical variables (European Parliament 2022).

One of the first fields in which AI-aided detection and prediction is applicable (but not limited to) is medical imaging. For example, starting from a database containing a considerable number of images of a neoplasm that are then compared with images of healthy cells and tissues, AI algorithms can be trained to early detect cancer by comparing images among them (Bi et al. 2019). The comparison of massive information allows the algorithm to identify if key features of that specific neoplasm are present within the patient's diagnostic images. The recognition helps anticipating the risk of disease manifestation/recurrence. Algorithms can therefore develop a "predictive model" (e.g., probabilistic and/or statistical analysis) that help doctors in creating a dedicated preventive path. In Part II of this book, several chapters will provide specific examples.

A sophisticated way in predictive modeling is the creation of Human Digital Twins (HDTs), computerized avatars that simulate the information ecosystem of the patient (although it represents a sampling of data and not the totality of his/her health), by connecting the medical history (including family history, if available) with current illnesses and symptoms (Valentini and Cesario 2021). HDT are important for clinicians and patients because they give a comprehensive overview of the clinical history to develop a personalized plan. Some interesting reflections will be reported in this book regarding the identity of the patient and the ethical aspects (see Manto and D'Oria, *infra*). Currently, HDTs are expected to compare the patient specimen with those of others to achieve stratified clusters of subpopulations in predictive medicine, to anticipate disease onset or exacerbation.

2.2.2 Clinical Diagnostics Personalization

AI-based algorithms show their greatest utility in multifactorial analyses of big data and RWD to create accurate predictive models for diagnostics and the reduction of clinical errors (Miller and Brown 2018). Predictive modeling starts from large datasets (based on the information retrieved from a patient, subpopulations with related characteristics, populations with the same disease, or seemingly distinct populations), whose data are classified according to similarities, rules, connections, neural networks, statistics, or probabilities.

The main tasks of these algorithms for diagnostics are as follows:

- Risk prediction and diagnosis of several diseases in their types, features, and levels of complexity (Kourou et al. 2014).
- Integration of omics and multi-omics data for complex diseases personalized diagnostics (Fornecker et al. 2019).
- Discovery of novel associations between diseases, including comorbidities and multimorbidities (Deparis et al. 2018).
- Observation of different pathology-specific therapeutic outcomes to identify key instances (e.g., mutations or genetic alterations) that originate new cancers (Zhang et al. 2017).

AI-based algorithms are prevalently used for disease prevention and therapeutic outcome prediction in several fields (e.g., radiology, radiation therapy, ophthalmology, dermatology (Naylor 2018), gastroenterology, gynecologic oncology, senology (Kourou et al. 2014), hematology (Radakovich et al. 2020), and infectious diseases

(Peiffer-Smadja et al. 2020; Ozsahin et al. 2020). Specifically, their use helps personalizing preventive diagnostics and therapeutic choices by gathering interpersonal features within the same cluster of patients, and therefore identify discordance from intrapersonal variability.

2.2.3 Therapy Development or Improvement

Another example that demonstrates how AI is utilized in the biomedical field regards the development/improvement of drugs and therapies to predict their outcomes (including the assessment of possible toxicity or the onset of adverse events) and personalize them according to each patient's characteristics (Bhinder et al. 2021). Such models, like those based on quantitative structure–activity relationship (QSAR) approaches (Golbraikh et al. 2012; European Parliament 2022), can help predicting large numbers of new compounds for various biological end points. These models can further facilitate greater understanding of molecules' behavior (e.g., potential antimicrobial activity) by screening a large volume of molecules and virtually test them to identify antibacterial compounds structurally distant from known antibiotics (Stokes et al. 2020; European Parliament 2022).

Besides, the current way of manufacturing pharmaceutical products and related existing logistic solutions is not mature for this revolution, since one of the current challenges is cybersecurity. A potential solution could be the envisioned in the concept of "cryptopharmaceuticals" elaborated by Nørfeldt et al. (2019), where pharmaceutical products are connected in a patient-specific blockchain of individual dosage units for personalized medication and, potentially, avoid counterfeit products.

AI-based models are also used for randomized controlled trials (RCTs) design, to increase the success rates or personalize patients' enrollment (Harrer et al. 2019), or to assess the risks and benefits of medical interventions. Sometimes, undertaking a RCT is not always possible under certain clinical conditions; therefore, Machine Learning (ML)/Deep Learning (DL) algorithms can be used in designing *in silico* clinical trials (ISCTs), computerized simulations often customized on HDTs that study the development or regulatory evaluation of a virtual drug, a device or a therapeutic intervention (the chapter of Surendran and colleagues—*infra*—elucidates very well the approaches to generating virtual patient cohorts in oncology). To this aim, studies with real patients may be reduced in favor of sophisticated simulations that predict, for example, the safety and efficacy of a treatment on a specific patient [the so called "N-of-1 clinical trials" (Lillie et al. 2011)], or a subset of patients with similar clinical pathophenotype.

2.2.4 Deep Data Collection and Analysis

AI solutions in clinical practice must be based on RWE from clinical trials, especially to implement clinical decision-support tools. Important preconditions for AI to deliver its full potential in global medicine and healthcare are the integration of broader data sets across organizations, a strong governance to improve data quality, and a greater confidence from practitioners, and patients in AI solutions and the ability to manage the related risks. Recently, many studies have been published in the field of synthetic data generation for healthcare, which can be applied and applied across a variety of domains (Goncalves et al. 2020). Indeed, generative neural networks—AI models that produce realistic data from a training dataset—are listed between the most innovative ideas proposed in the last decades (Laino et al. 2022). They represent promising tools in protecting patient privacy, diversifying datasets, for training and educational purposes, and in accelerating clinical research (Arora and Arora 2022). Synthetic data could help in any field of healthcare in coping with the data lack, anonymity, and quality (Elazab et al. 2020). Furthermore, when applied to medical imaging, generative neural networks have proven to be useful in many fields, such as:

– The generation of different images within the same modality [i.e., generating T1 images from T2 images at Magnetic Resonance (MR)] or from different modalities [i.e., producing MR from Computed Tomography (CT) scans], which could lead to a reduction in radiation exposure and an improvement in image interpretation (Kossen et al. 2021).
– The reconstruction of images, with reduction of artifacts and improvement of image quality, which could help in reducing CT radiation exposure and MR acquisition time.
– The data augmentation and the improvement of data availability and quality at a low cost, which is especially helpful for rare diseases (Laino et al. 2022).

However, since the type and quality of generated data are strictly dependent on the training dataset, and since it carries a lot of problems for their implementation in the clinical practice—as hallucination, deepfake, misdiagnosis of medical conditions (Laino et al. 2022)—the generation of synthetic data finds at the moment few clinical applications, while remaining a very active topic in biomedical research (Sorin et al. 2020).

2.3 Digital Health for Personalized Patient Compliance and Flow Management

Two main applications of DH can improve and personalize the clinical experience:

a. Monitoring patients' symptoms and adherence to therapy
b. Digitalization of clinical pathways

Both applications will be described below and require the integration of AI solutions with the hospital and home settings, specifically when DH focuses on several specialties (e.g., oncology, cardiology, neurology) to provide a holistic care.

2.3.1 Monitoring Patients' Symptoms and Adherence to Therapy

Patients can actively provide healthcare professionals with some information regarding their daily biometrics (e.g., hours of sleep, heart rate, and steps taken in a day), as well as their psychological state through dedicated questionnaires. This kind of information, obtainable through apps, sensors, and wearable devices (e.g., electronic bracelets), is known as "Internet-of-Medical-Things" (IoMT)—a subset of information deriving from the broader Internet-of-Things (IoT)—and represents the patients' data ecosystem to facilitate remote and real-time monitoring of certain parameters which, otherwise, could not be retrievable except with a physical visit.

According to Al-kathani and colleagues (Al-Kahtani et al. 2022), many technologies are rapidly evolving in healthcare to assist patients, and to collect/interpret data such as: "ambient intelligence communications technologies" with embedded human–computer interaction (HCI); remote monitoring with wearable devices (including smartphones, necklaces, etc.); Augmented Reality (AR) technologies for immersive medical education and training; smart robots to automatize some routinary activities of the patient or to transport the patient from a location to the another in the hospital. The urgency of remote monitoring has been accelerated during the COVID-19 pandemic (Khan et al. 2021), since social distancing required healthcare professionals to find alternative and smart solutions to communicate with patients, to transmit clinical data in a secure way, while improving the accuracy of care. A comprehensive example of patients remote monitoring is represented in the chapter of Kyriazakos and colleagues in this book [see *infra*].

2.3.2 Digitalization of Clinical Pathways

DH solutions are likely to address repetitive and largely administrative tasks that absorb significant time of doctors and nurses, optimizing healthcare operations and increasing their adoption. For example, they can facilitate the transition from hospital-based to home-based care toward virtual assistants, remote monitoring, and personalized alerts since patients are progressively increasing ownership about their care. Embedding AI in clinical workflows through a proactive engagement of several stakeholders (e.g., regulatory bodies, healthcare providers) requires combining well-designed DH solutions with the existing and the newest technologies, as well as managing cultural change and capability building within the organization.

a. *Virtual wards.* Virtual wards are a remote care experience to follow patients who cannot go to the hospital remotely (Hutchings et al. 2021). If a cancer patient is unable to travel from home (for example, due to an infection such as COVID-19), he/she can still be followed by doctors by checking his/her own biometric parameters (e.g., oxygen levels) after being adequately informed and trained for the correct use of the measuring instruments. Information is delivered (via video call, call, or messaging) to healthcare professionals who are in daily contact with the patient, offering telemedicine services and recalling him/her to the hospital for observation or treatment if necessary. Algorithms can support in data processing to predict the future course of the patient's condition and help the physician to make more personalized data-driven decisions.

b. *Patient Support Programs* (PSP). A broader way through which provide care continuity to patients beyond the outpatient setting are PSP. By making use of multiple remote monitoring tools (apps, wearable devices, questionnaires, etc.) provided to the patient, healthcare professionals can check his/her health status in real time, be in constant contact with him/her, and intervene when appropriate. PSP are based on AI algorithms that can predict the risk of relapse (either physical or psychological), and they are specifically designed to monitor patients in the time distances between two clinical encounters (i.e., when he/she is not physically present in the hospital and may live outside the region). Patients are trained in using properly the monitoring tools and have access to apps/portals for educational materials on disease management. Additionally, they can request virtual coaching sessions with dedicated health professionals (psychologist, nutritionist, etc.).

Both solutions can strengthen patients' adherence to treatments (Su et al. 2022), and could also improve the therapeutic alliance with the whole team of experts that follows the patient.

2.4 Investments in the AI and DH Environment

The race to build and adopt AI tools as well as investing in AI start-ups is fast growing, with commercial uses of AI becoming an important reality worldwide (Mou 2019). Companies in every sector—from retail to agriculture—are more and more including AI software into their products or administrative management. This explains why AI is actually leading technology investments. The landscape of healthcare AI startup companies is progressively expanding with solutions aimed to solve some of the industry, hospital, or healthcare providers' most pressing problems (Young 2022).

This growing significance of AI and DH solutions to deliver precise and effective healthcare solutions has promoted the number of venture capital investors along with start-ups to invest in healthcare. Enormous potential and wide range of application in this sector could enhance patient management while minimizing costs, thus expediting market growth. For example, in the first half of 2022, Digital health ventures headquartered in Europe captured US 2.43 billion across 124 deals, with an average deal size of US 19.6 million.

In the future, the global market size of AI for healthcare is expected to reach US $45 billion by 2026 and 67.4 billion by 2027 [Artificial Intelligence in Healthcare Market Worth $45.2 Billion by 2026 (Markets and Markets 2020)]. On the other hand, AI integration in daily life will have a significant impact on major economic sectors, leading to the need to confront the possibility of job losses and rearranging our life habits (Mou 2019).

2.5 Further Considerations

According to the Organization for Economic Co-operation and Development (OECD) "*High expectations must be managed, but real opportunities should be pursued*" when considering the potential of AI in medicine and healthcare (OECD 2020). Indeed, some dimensions must be carefully examined to achieve sustainable goals for all patients and communities.

For example, although DH and AI can enable rapid and inexpensive information sharing, some concerns about privacy and personal health data still exist. Regulatory challenges go from data to privacy protection (see Giorgianni, *infra*), touching the framework on Digital Therapeutics (see Recchia and Gussoni, *infra*), and the approval of Regulatory Bodies about the introduction of medtech for personalized patient treatment (see Neumann et al., *infra*).

Another concern regards the possibility of augmenting the digital divide among minority groups in using and trusting DH systems, and therefore delivery jeopardized access to PM opportunities. The gap between low- and high-income populations should be managed effectively by fostering digital health literacy skills. In facts, it is not guaranteed that the healthcare professional and the patient would be able to master and understand DH tools, hence education about the technologies and the wording of the world of AI is a pivotal asset to consider. Specific programs on DH could be implemented to empower communities to embrace digital transformation with AI and IoMT in a sustainable manner (WHO 2021; Lin and Wu 2022).

Third, risk prediction should be considered as a "probability" and not a "prophecy": HDTs do not represent "the patient" but a sampling of the information available about the person (Valentini and Cesario 2021). Besides, every result coming from the calculation of an algorithm—even when precise, evident, and fully accurate—must always be contextualized and carefully explained by the healthcare professional to patients to increase their understanding and awareness. This perspective cannot be separated from the promotion of a transparent communication between all the stakeholders involved in this field that elucidate the real benefits that these technologies can bring to patients.

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