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Artificial Intelligence in Diagnosis and Treatment

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Abstract

Artificial intelligence (AI) is a field within computer science that has vast applications and has transformed medical technologies. It is often regarded to be the branch of computer science that can handle complicated problems with minimal theory and many applications. AI is utilized to assist researchers in the analysis of large data sets, enabling precision medicine and assisting physicians in improving patient outcomes. New techniques in AI can bring together various types of data to make sense of new information obtained from multiomics datasets. Analyzing high-quality data combined with machine learning, a subset of AI, can help modify patients' unhealthy behaviors, predict risk or recurrence of chronic diseases after a surgical and curative treatment, prediction of progression and survival rates of patients with chronic diseases, therapeutic need, generation of improved clinical trial interpretations and identification of new targets. However, to effectively implement precision medicine in healthcare, a more user-friendly interface would be required. If AI technologies are applied correctly, fairly and robustly, in close cooperation with human intelligence, it is expected to open up new possibilities for effective and personalised healthcare services worldwide. In this review, the general outlines of AI technology, its application areas in healthcare and its future are overviewed.

Key words: *Artificial Intelligence, Explainable Artificial Intelligence, Machine Learning, Medicine, Drug Discovery*

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Introduction

The cost of healthcare is soaring everywhere. The rising prevalence of chronic illnesses, longer life expectancies, and the ongoing development of expensive new treatments all contribute to this trend. It is therefore not surprising that academics project a dismal future for the viability of healthcare systems globally. Artificial intelligence (AI) holds the potential to mitigate the effects of these advancements by enhancing and optimizing healthcare expenditures (1). When smartphones, wearables, sensors, and communication systems first appeared, medical technologies were primarily known as traditional medical devices (such as implants, stents, and prosthetic limbs). However, with the advent of these devices and their capacity to house AI-powered tools (like applications) in incredibly small forms, medical technology underwent a revolution. AI is a field within computer science that has vast applications and has transformed medical technologies. It is often regarded to be the branch of computer science that can handle complicated problems with minimal theory and many applications (2). AI is utilized to assist researchers in the analysis of large data sets, enabling precision medicine and assisting physicians in improving patient outcomes. AI algorithms can help doctors to make better decisions (“clinical decision support”, CDS), localize tumors in magnetic resonance (MR) images, read and analyze reports written by radiologists and pathologists, and much more. In the near future, reports that are legible by humans may also be produced with the aid of generative AI and natural language processing (NLP) systems like Chat Generative Pre-trained Transformer (ChatGPT) (3). AI includes various techniques such as machine learning (ML), deep learning (DL), and NLP. AI was still in its infancy and mostly the focus of scholarly research at the time. John McCarthy first used the phrase "Artificial Intelligence" in 1956 at the Dartmouth Conference. The modern AI era began with this occurrence. Expert and rule-based systems were the main topics of AI research in the 1960s and 1970s. But the lack of additional data and processing power made this strategy impractical. Artificial intelligence (AI) research turned to ML and neural networks in the 1980s and 1990s, enabling machines to learn from data and gradually improve their performance (4).

New techniques in AI can bring together various types of data to make sense of new information obtained from multiomics datasets. Analyzing high-quality data combined with machine learning, a subset of AI, can help modify patients' unhealthy behaviors (5), predict risk or recurrence of chronic diseases after a surgical and curative treatment (6), prediction of progression and survival rates of patients with chronic diseases (7), therapeutic need, generation of improved clinical trial interpretations and identification of new targets (8). The application of AI models for diagnostic and prognostic assessments is widely accepted in the context of some cancers (9). The ability of AI models to discover nonlinear patterns embedded within complex multivariate datasets could potentially lead to a better understanding of the complex mechanisms underlying carcinogenesis and cancer progression (10). In the last decade, there has been a massive increase in the number of large and complex omics datasets, especially thanks to large-scale consortium projects such as the Cancer Genome Atlas (TCGA), which has sampled multiomics measurements from more than 30,000 patients and dozens of cancer types (11, 12, 13). These rich omics data provide unprecedented opportunities to systematically characterize the underlying biological mechanisms in cancer evolution and understand how the tumor microenvironment (TME) contributes to this evolution (12, 14). However, the idea that AI is essentially an opaque "black box" that cannot be mechanically interpreted and therefore cannot meet the required high level of accountability, transparency and reliability in medical decision-making has led to major criticism of the incorporation of AI, especially deep learning, into medical fields. "Black box" AI models produce results with remarkable accuracy, but no one can understand and analyze how the algorithms arrive at their predictions (15). When AI suggests a decision, decision makers need to understand the underlying reasons. In recent years, AI researchers have been conducting extensive research to open this "black box" concept and transform it into a transparent system. At the forefront of this research is Explainable Artificial Intelligence (XAI), also referred to as the "white box" (16) (Figure 1). Explainability is the ability to explain AI decision-making in terms understandable to humans about how a decision is made (17). This system aims to achieve more transparent, more reliable and interpretable results by explaining to users what it has done, what it is doing and what it will do thanks to its developed algorithm (18). In the XAI method, the whole process can be analyzed retrospectively (15). Although studies on the use of AI in medicine have increased in recent years, XAI system studies using explainable algorithms have just started. Breast cancer is the leading cause of cancer-related deaths worldwide and is the most common type of cancer among women (19). Amoroso et al. used an

XAI modeling for breast cancer treatments and showed that XAI can summarize the most important clinical feature for oncological treatments designed for the patient and the patient (20).

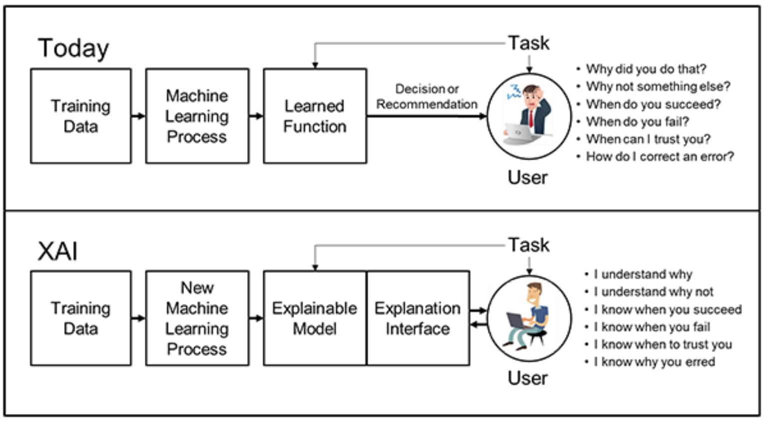

Figure 1. AI concepts (21).

In this review, the general outlines, application areas, future and possible ethical problems of artificial intelligence technology in healthcare are discussed.

Artificial Intelligence Applications in Medicine

AI in Pathology image processing

Digital pathology is becoming an increasingly important technological requirement in the laboratory setting and plays a crucial role in contemporary clinical practice (22). Histopathologists can now handle digital slide photos with greater ease and flexibility than they could ten years ago. They can also exchange images for telepathology and clinical use because to advancements in processing power, more rapid networks, and less expensive storage. Whole slide imaging (WSI), which enables total slides to be photographed and permanently saved at high resolution, has evolved during the last 20 years in pathology digital imaging (23). The FDA has approved digital pathology's WSI system, ushering in a new era for digital image analysis in the field (24, 25). AI has primarily been utilized in radiology and cardiology for image-based diagnosis up to now. With multiple research organizations and committed businesses, the field of active research on its application to pathology is growing. The images produced by WSI are an abundant supply of information; their size (100k x 100k is not uncommon) makes them more complex than many other imaging techniques; they also have color information (H&E and immunohistochemistry); there is no obvious anatomical orientation as in radiology; information is available at multiple scales (e.g., 4x, 20x); and there are multiple zstack levels (each slice contains a limited thickness and depending on the plane of focus, it will result in various images). It is obvious that an ordinary reader cannot possibly extract all visual information (23, 24). WSI is currently in use for training at tumor boards, conferences, online seminars, and presentations (22). With WSI capabilities, AI tools can aid in the continued education of the upcoming generation of pathologists by offering standardized, interactive digital slides that are available for sharing at anytime, anywhere, to numerous users (22, 26).

Based on histological characteristics, AI can be utilized to forecast prognosis and treatment outcomes. Important information might be succinctly provided by directly connecting images of various tumor characteristics, the surrounding microenvironment, and genetic data with survival outcomes as well as response for adjuvant/neoadjuvant therapy (27). Wang et al. used H&E stained tissue microarray slides to build a machine learning model that predicted recurrence in early-stage non-small cell lung cancer (NSCLC) based on nuclear orientation, nuclear shape, texture, and tumor architecture. In two validation cohorts, the prediction of their model proved to be an independent prognostic factor, with 82% and 75% accuracy for recurrence prediction, respectively (28). In 2018, Saltz et al. brought attention to the prognostic implications of AI tools. They employed a convolutional neural network to enhance pathologist feedback for the automated identification of the spatial organization of tumor-infiltrating lymphocytes in images obtained from The Cancer Genome Atlas. According to their research, this characteristic can predict the course of 13 different cancer subtypes (29). Similar research by Yuan et al. provided a model to examine the lymphocytes' spatial distribution in relation to tumor cells on triple-negative breast cancer white matter irradiation. They discovered a clear relationship between the spatial distribution of immune cells in ER-positive breast tumors and late recurrence, in addition to identifying three distinct types of lymphocytes (30).

Commentation of Biochemical and Clinical Tests with Artificial Intelligence

Artificial intelligence (AI) has been also more and more empiercing into the world of health science applications. The foremost areas are biochemical and clinical tests. Because both the patients and clinicians always expect to get the most accurate and smooth results from the laboratories, the hand of AI could provide not only an opportunity for accelerating the process for obtaining results, but also annihilate the erroneous laboratory results at the best. Moreover, AI has been also being used for proper selection of sample in clinical trials and detection of very early signs of adverse effects or toxicity (31).

Biochemical tests have been displaying a great diversity and there are lots of parameters which could be handled successfully by AI software. For instance, oxidative stress parameters and anti-oxidative capacity have been attempted to commit in order to predict certain neurodegenerative diseases such as Alzheimer’s and Parkinson diseases (32). In clinical tests, as we mentioned that AI could be very useful for contemplating a clinical trial at the very beginning, there also have been lots of ventures to be able to use the AI for interpretation of biochemical or clinical test results. For instance, according to the one of previous studies, software algorithms are proved to have been producing more rapid and precise diagnosis in comparison to pathologists themselves (33).

Artificial Intelligence in Precision Medicine and Genomics

Precision medicine, also known as personalized medicine, is an innovative approach to prevent or treat diseases by taking into account differences in an individual's genetic history, environment and lifestyle. Precision medicine recognises the critical fact that not all patients respond in the same way to the same treatment. It takes a patient-centred approach by analysing clinical, genomic and pharmacogenomic data, rather than a symptom-centred approach. In the conventional healthcare system, clinicians tend to plan treatment on the basis of symptoms. Since the symptoms can vary greatly among individuals, genomic, metabolic and clinical data should be utilized together in order to create a more personalised treatment plan. In this way, the quality of healthcare services can be improved through the application of personalised precision medicine approaches rather than the symptom-based approach of the traditional healthcare system.

Artificial intelligence can be used in medicine in two different ways: virtual and physical. The virtual use of AI includes applications ranging from electronic health records to neural networks that guide patient treatment. Physical machines, such as artificially intelligent prosthetics for the disabled and robots that assist in surgery, are the physical subset of artificial intelligence. The most common applications of precision medicine are genetic screening for disease prediction and diagnosis, and pharmacogenomics for drug response prediction (34). Artificial intelligence and machine learning techniques have been shown to be useful in calculating genetic risk for diseases and in determining 'polygenic risk scores' to identify individuals at high genetic risk for certain diseases. Predictive algorithms can identify disease groups not recognised by clinicians and can guide the selection of personalised treatment options for these patients. Another option is to monitor people with a genetic predisposition to the disease on an ongoing basis, allowing early diagnosis at the onset of the disease. This would avoid the need for complex treatments. By applying artificial intelligence techniques to new generation sensors, such monitoring can be further developed.

Genomic studies and the next-generation sequencing have progressed at an exponential rate from the first descriptions of DNA by Watson, Crick and Franklin in 1953. Sequencing technologies have reached a stage where the entire genome can be sequenced in one day. While whole genome sequencing (WGS) covers the entire genome, whole exome sequencing (WES) focuses only on the protein-coding regions and both produce massive amounts of genomic data to analyse. It is important to help scientists understand how genetic variation is linked to a disease by affecting critical cellular processes such as cell development, cell differentiation, metabolism and DNA repair (35). Several deep learning models have been developed to analyse large genomic datasets and identify genetic variants within a whole genome, for example DeepVariant is an analysis pipeline, a deep convolutional neural network model (36). DeepVariant can call genetic variants from next-generation DNA sequencing data, enabling patient stratification based on statistically significant variants associated with a disease phenotype.

DeepSEA is another deep learning algorithm that can specifically identify functional effects of non-coding variants with single-nucleotide sensitivity, which is a difficult task due to the large number of these variants throughout the genome. DeepSea has been trained on regulatory sequences, chromatin profiles that play an important role in epigenetics and gene regulation at the transcriptional level, to predict changes, especially SNPs with a functional difference that are associated with a particular disease or phenotype (37).

Epigenomics is responsible for the regulation of gene expression without altering the DNA sequence, adding another layer of complexity to the genome. Recently, machine learning models have emerged to identify epigenetic changes. For example, DeepBind has been developed to analyse disease-associated genetic variants that can alter transcription factor binding and alter gene expression. It is based on deep convolutional neural networks and is designed to predict the sequence specificity of DNA and RNA binding proteins (38). Other tools for identifying histone protein modifications are DeepHistone and DeepChrome (39, 40). These tools were developed to predict epigenetic changes, specifically histone modifications that regulate gene expression (41).

While AI is being used to develop personalised medicine, there are limitations to consider. When predicting trends in a target individual's health data that may indicate a change in health status, based on data collected from a large number of individuals, it is important to remember that the data collecting from each individual is not ergodic. It has been argued by Fisher et al. important individual-level relationships are often missed by big data analyses, which combine information about many individuals to identify patterns that reflect population-level relationships between data points (42). Inferences based on group-level data can only be generalised to individual experience or behaviour for ergodic processes. However, medical data are unlikely to be ergodic as they vary between individuals and change over time. Therefore, in order to predict the target individual's health trajectory, more data points should be collected for each individual and the prediction should rely more on the existing data points for that target person rather than the population level data. It has been suggested that researchers across the medical sciences should clearly test the equivalence of processes at the individual and group levels (42).

Machine Learning In Pharmacogenomics

Pharmacogenomics (PGx) involves understanding how a patient's genetic profile affects how they respond to drugs, predicting how an individual metabolises drugs and potential side effects. It is well known that genetic variations can affect drug response, particularly variations in genes involved in the absorption, distribution and metabolism of drugs, all of which affect the pharmacodynamics and pharmacokinetics of a drug. The aim of the pharmacogenomics is to prescribe the most effective drug at the correct dose, minimising the risk of side effects, increasing treatment efficacy and enabling personalised medicine by identifying a patient's genetic variations. FDA released a guidance in 2013 for pharmaceutical industry and the researchers engaged in drug development to provide recommendations on when and how genomic information should be utilised (43). Pharmacogenomics assessment is recommended to implement in early phase clinical trials to identify populations based on genetic effects on drug exposure, dose-response, common adverse reactions and early efficacy should receive lower or higher doses of a drug or longer titration intervals. Although this approach has not yet been widely adopted by pharmaceutical companies, applications of artificial intelligence methods for patient stratification using clinical and genomic data are emerging and are expected to grow rapidly. Patient stratification involves the complex integration of heterogeneous sociometric, demographic and biomedical data to classify patients into subpopulations for clinical practice and clinical trial design. In order to identify better treatment options, electronic health records-linked DNA biorepositories have successfully used in predictive modeling with the integration of pharmacogenomic and sociometric data such as gender, age etc. Here are the some examples of recently published open source deep learning softwares applying artificial intelligence to patient stratification and healthcare coordination: Deep Patient is an unsupervised deep learning method for augmenting clinical decision systems and deriving patient representations. Hierarchical regularities and dependencies have been captured in the aggregated electronic health records of approximately 700,000 patients. Deep Patient can predict the likelihood of patients developing various diseases (44). DeepCare is another deep dynamic memory model for predictive medicine. This model uses electronic health record data, including medication codes, diagnoses and procedures, to predict unplanned readmissions and high-risk patients for mental health and diabetes patient cohorts (45).

Drug Discovery and Repurposing

Drug design is generally recognised as a specific stage in the drug discovery process. It focuses on the development, optimisation and refinement of potential drug compounds. Drug repurposing is a faster and more cost-effective process than developing new medicines from scratch. It is focused on the discovery of novel pharmaceutical uses for drugs that were originally developed for specific medical indications. In silico studies involve many tasks performed on computer to assist drug screening, drug design and repurposing via investigating the interactions between targets and drugs. Computational drug design is not a new concept. However, with advances in hardware and software, the use of computational approaches, AI and machine learning models has increased rapidly. Deep learning models, including neural networks, have been developed to study drug-drug interactions, drug-target interactions, protein-protein interactions, DNA-protein interactions and examining disease mechanisms. Experimental methods for studying these interactions are labour-intensive, time-consuming and expensive. AI models have great potential to reduce the time and cost required for such analysis and subsequently for drug discovery. Studies focusing on drug-drug interactions try to understand how a drug works when it’s given simultaneously with another drug and how this might change the way the drug works. A detailed examination of all AI-based software and tools used for drug discovery is beyond the scope of this review. However, we can give AlphaFold2 developed by Google DeepMind, DeepChem, DeepBind as examples of the most commonly used AI-based softwares for drug development, discovery and analysis (46, 47, 48). Interested readers are referred to the excellent review by Qureshi et al. (49).

Concluding Remarks and Future Perspectives

Healthcare is moving towards more personalised and targeted approaches to diagnosis, treatment and prevention. Artificial intelligence, clinical genomics, big data and pharmacogenomics are therefore critical to the future development of precision medicine. By harnessing the power of genomic and molecular data, precision medicine will help healthcare professionals and researchers access larger amounts of medical data and make more accurate diagnoses. There is currently no system that can simultaneously compare multi-omics data to predict more accurate and personalised outcomes. To effectively implement precision medicine in healthcare, a more user-friendly interface would be required. If AI technologies are applied correctly, fairly and robustly, in close cooperation with human intelligence, it is expected to open up new possibilities for effective and personalised healthcare services worldwide.

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