Ageing and Alzheimer's Disease

Application of Artificial Intelligence in Mechanistic Studies, Diagnosis, and Drug Development

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Contents

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Abstract

Artificial intelligence (AI) implies the use of a machine with limited human interference to model intelligent actions. It covers a broad range of research studies from machine intelligence for computer vision, robotics, and natural language processing to more theoretical machine learning algorithm design and, recently, "deep learning" development. The application of AI in medical fields is booming, including the use of AI in data collection, analysis, mechanistic prediction, to clinical disease diagnosis and drug development. In this chapter, we focus on the challenges in the studies of aging and the age-predisposed Alzheimer's disease (AD) and summarize on how to use AI to help addressing these questions. We finally provide future perspectives on the use of AI in aging research and AD.

1 Introduction

Artificial intelligence (AI) is a generic concept that implies the use of a machine with limited human interference to model intelligent actions. It covers a broad range of research studies from machine intelligence for computer vision, robotics, and natural language processing to more theoretical machine learning algorithm design and, recently, "deep learning" development. In general, AI is recognized as having begun with the invention of robotics in the 1920s. There have been several waves of success and stagnancy over the years, most recently exemplified in the recent breakthrough powered by the development of more powerful graphics processing units (GPUs) and the outbreak of big data. Funding for both AI-based research studies and industrial innovation projects has further propelled progress and accelerated development.

In medicine, artificial intelligence (AI) research is growing rapidly with broad applications (Fig. 1). In 2016, healthcare AI projects attracted more investment in comparison with AI projects from other sectors of the global economy. In addition to conventional mathematical and statistical methods, AI techniques, in particular machine learning and deep learning approaches, draw significant attention to the analysis of medical data as medicine is becoming an increasingly data-centric discipline. The nature of evidence-based medicine is to guide therapeutic decision-making through learning from past data. Statistical approaches have historically addressed this challenge by characterizing correlations inside data through statistical equations, such as linear regression, indicating a "line of best fit." Through machine learning or deep learning, AI can reveal nuanced relationships, which cannot simply be deduced by an equation. AI can extract valuable details from the electronic footprint of a patient. This will initially save time and increase performance but can also explicitly guide patient management after appropriate research. Specialist diagnostic skills can now also be carried into primary care by AI-based technologies. Broadly speaking, there are three types of algorithms for machine learning including (1) unsupervised learning (capable of identifying patterns directly from data, e.g., activity recognition using smartphone sensors, clinical outcome prediction from the electronic health records, anomaly detection, and knowledge discovery), (2) (semi-)supervised learning (classification and inferencing based on previous examples, e.g., chemoinformatics and drug discovery, multifactorial omics analysis and biomarker identification, imaging, and data enhancement), and (3) reinforcement learning (synergy of reward and punishment sequences to form an operating strategy in a given problem space, e.g., therapy optimization, treatment management, and surgical robotics).

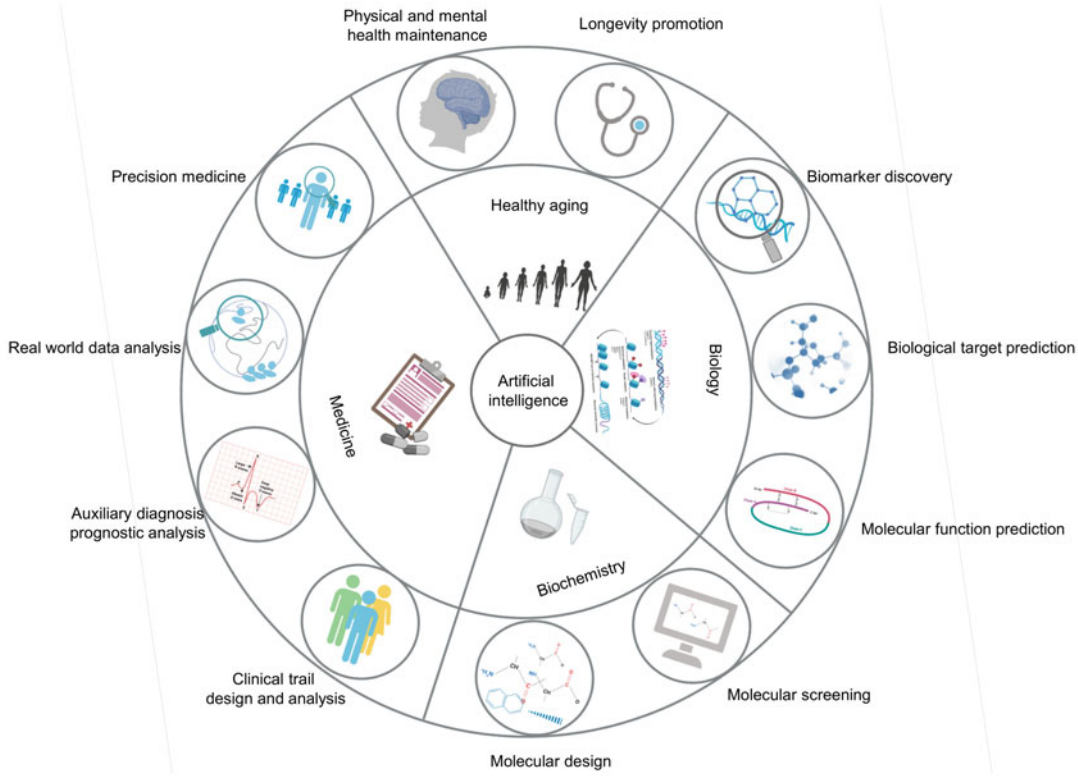

Fig. 1 The use of artificial intelligence (AI) in healthcare. The broad application of AI in healthcare consists of overlapping fields like biology, biochemistry, medicine, and healthy aging. For details see the text

In general, AI techniques have returned significant dividends by achieving outstanding performance in various applications especially for AI in medicine. There are a few key problems that need to be solved. For example, most current AI-based algorithms are typical black boxes. The end users can easily access high-performance AI, but the interpretability of the derived features and prediction is not clear. Therefore, explainable AI will be a major area for future research. Moreover, although current studies rely on a human operator's manual labelling, the ultimate goal will be "Taking the Human Out of the Loop." This encompasses future research directions including self-supervised learning, semi-supervised learning, and more advanced non-supervised learning methods. The first sections of this chapter will detail the historical development of AI in healthcare and in particular AI in biology, biochemistry, medicine, and healthy aging. The rest of the chapter will focus on the application of AI in clinical work for Alzheimer's disease including diagnosis, treatment planning, drug development, and prognosis. We will also shed a light on future perspectives.

2 AI in Healthcare

2.1 Historical Overview

Among the broad range of research studies covered by machine intelligence, medicine has been identified as one of the most important areas for AI applications. Since the advent of AI, applications of AI in medicine have been explosive and make it possible for more precise and personalized medicine. The progressive growth and development of the application of AI in medicine can be organized by specific periods.

2.1.1 From the 1950s to the 2000s

In the first 20 years of this stage, researchers in this field primarily focused on the development of decision-making systems that had the ability to make inferences or decisions that could be applied in the clinical setting. In this period, some clinical informatics databases and medical record systems were firstly built, which had established the foundation for future applications of AI in medicine [1]. The last 30 years of this period was referred to as the AI winter. During this time, research funding and interest in AI in general were significantly reduced, and accordingly there was slow progress in the field. Generally, two major historical limitations had led to this famous "winter" which was also reflected in its application in medicine. The first was the extensive cost of building and maintaining the expert-labelled databases and obtaining the necessary calculating power. The second was the perceived limitations of AI such as the efficiency of the algorithm. Although there was a lack of funding and interest from academia during this period, collaboration among pioneers in the field of AI and medicine continued. In 1973, the Stanford University Medical Experimental Computer-Artificial Intelligence in Medicine (SUMEX-AIM) project was founded to enhance the connectivity between computer scientists and biomedical researchers from several institutions [1]. In 1975, the NIH sponsored an AI in medicine workshop which was held in Rutgers University [2]. Those initial collaborations among the pioneers in the field facilitated AI's application to medicine at this stage.

In later years of this period (after the 1970s), research turned toward comparing the performance of computer-aided diagnostic systems with that of human physicians [3]. Some systems had also been shown to have the ability to interpret ECGs, diagnose diseases, choose appropriate treatments, provide interpretations of clinical reasoning, and assist physicians in generating diagnostic hypotheses in complex patient cases [4–6]. Scientists also put some research effort into the use of a computer to improve the detection and classification of the lesions in the vascular and integumentary systems using image analysis.

2.1.2 After the 2000s

As the development of computer hardware accelerated, the application of AI in medicine started to grow fast. Although the development of neural networks had begun in 1950, by the 1980s, it had progressed to such a point that it was now possible to create deep learning models (a phrase first coined by Rina Dechter in 1986) [7]. The development of deep learning (DL) marked important progress. Although deep neural networks had technically first been studied in the 1950s, their application to medicine had been limited by two problems for many years: first, insufficient computing capacity and second, the lack of available training data [8]. These limitations were overcome in the 2000s with increases in the availability of large data sources and significantly improved computing power. The large data sources included large-scale studies (e.g., UK Biobank), data-collection platforms (e.g., Broad Bioimage Benchmark Collection and the Image Data Resource), and electronic medical record (EMR) data [9, 10]. To highlight this increase, a national survey conducted in 2008 noted that only 13% of physicians reported having a basic EMR system, but by the end of 2012, 72% of physicians had adopted some type of EMR system [11, 12]. Since that time, the application of AI in medicine has been on the "fast track." With the advances came substantial progress in image classification tasks and innovations in the application of AI to other fields such as drug development.

2.2 AI for Drug Discovery

The discovery of molecular structures with specifically required properties has been one of the most impactful scientific and industrial challenges. Normally, to develop a novel drug, the mean pre-tax expenditure is nearly $2.55 billion over 10–15 years [13]. In recent years as more and more big chemical datasets have become available, deep learning has been applied to those data to accelerate the process of drug discovery and reduce costs in the process. AI technology can be applied during several steps of the drug design

process, including virtual screening, activity scoring, quantitative structure-activity relationship (QSAR) analysis, de novo drug design, and in silico evaluation of absorption, distribution, metabolism, excretion, and toxicity (ADME/T) properties [14].

2.2.1 Virtual Screening

Virtual screening (VS) is defined as the use of algorithms to find bioactive molecules from known molecular libraries for a drug target, typically an enzyme or a protein receptor. It has proved to be a very effective approach to filtering out those compounds with unfavorable properties [15, 16]. Based on traditional computer-aided drug discovery (CADD), virtual screening usually uses 2D and 3D structural information from ligands and target proteins. Similarity searching of small molecules, pharmacophore-matching, and molecular docking are commonly used techniques in traditional virtual screening. All the abovementioned techniques depend on the knowledge of chemistry, physics, and biology. While the technology used to run these CADD methods for virtual screening is affordable and easy to learn, it is hard to master them to successfully find the bioactive molecule for a given target. Recently, deep learning has been applied to virtual screening [17]. As opposed to traditional knowledge-based methods, deep learning VS directly extrapolates the rules through examination of its training data. Using molecular features, it tries to predict the classes of bioactivity through the examination of many abstract and high-level features that are sometimes not immediately obvious to the human eye. Due to the high feature extraction ability and low generalization error of deep learning, it is especially well adapted for use in ligand-based virtual screening which does not rely on the 2D/3D structural information of proteins [18–21]. For example, traditionally, the sparse distribution of active compounds in the general database wasted a lot of time during the process of virtual screening [22]. DL methods have been used to address this issue through use of the long short-term memory (LTSM) network model. The model was based on the similarity between natural language and simplified molecular-input line-entry system (SMILES) which is a specification in the form of a line notation for describing the structure of chemical species using short ASCII strings [23]. Using AI for virtual screening may increase the chance of identifying new targets and make the process more rational. Another implementation of AI virtual screening is the use of abundant data from high-throughput experiments with gene expression profiles. For example, researchers tried to find potential drugs through measurement of the functional similarity of small molecules based on gene expression data [24].

2.2.2 Bioactivity Scoring

Activity scoring is one of the core components of molecular docking, a process that evaluates the potential binding affinities of drug-like molecules toward an interested target [25]. The DL-based methods perform well in this field due to their high nonlinear mapping ability and the fact that they could extract features efficiently from genomic, chemical, and physical force data [26]. For instance, some studies using convolutional neural networks (CNNs) to extract the features from protein-ligand interaction images were able to predict protein-ligand affinity [27]. A study using a 3D CNN model demonstrated prediction of binding affinities that was well matched with the experimental data [27]. Additionally, some studies used DLs to extract features from basic and primitive features. DeepVS was built with a CNN model and was designed to discern abstract features from basic chemical features (e.g., the atom context). DeepVS outperformed the traditional docking programs on area under the curve (AUC) and enrichment factor [28].

2.2.3 ADME/T Properties Prediction

It is vital to identify the molecules with poor chemical properties in the drug discovery pipeline. Early identification of ADME/T properties can reduce the risk of failure and save a large amount of time and money during development. Many DL-based methods were developed to address this issue [29]. One study utilized a CNN-ANN that extracted data from the molecular graph, and another study used the tensor-based convolutional embedding of attributed molecular

graphs method to predict the solubility of molecules [30, 31]. The two models both showed good predictive performance in their testing data. Some studies that focused on predicting drug absorption, the process by which drugs entered the blood from the site of administration, also applied DL-based methods. For example, a study with 1,014 molecules used the MLR model to predict bioavailability with structural fingerprints and molecular properties [32]. The model had a good predictive performance (correlation coefficient 0.71, MSE 0.24). The DL-based methods have also improved predictive performance in modelling drug distribution, metabolism, excretion, and toxicity. Recently, some multitask DL models for ADME/T prediction were also developed and showed good performance compared with other models targeted on predicting single property [33].

2.2.4 De Novo Drug Design

The de novo molecule generation problem involves generating novel or modified molecular structures with desirable properties. Thus, generative AI models are usually coupled with the abovementioned predictive neural networks to generate new compound structures under the constraints of interesting molecular properties. For example, Mariya et al. proposed ReLeaSE which combined a molecular property predicting neural network with a molecular generative neural network to design chemical compounds with desired physical, chemical, and/or bioactivity properties [34]. However, Mariya et al. did not combine their generative AI model with bioactive experiments in their research. In silico medicine built the generative AI model GENTRL to auto-design novel inhibitors for kinase DDR1; their generated chemical compounds were identified as bioactive by their wet labs [35]. Additionally, because of the high generative ability of DL models, a study used data from the NCI-60 cell line assay to train an adversarial autoencoder model. This model could be used to generate the molecular fingerprints that were helpful in the search for potential anticancer agents.

2.3 AI in Biology

DL can be applied in the field of biology to answer some fundamental questions because it is suitable for dealing with high-dimension data from omics, such as genomics and proteomics.

2.3.1 Genetics

Currently, a massive amount of genomics data is produced using next-generation sequencing technology, and AI is applied in analyzing those data. There are an increasing number of studies using DL to examine the genome and functional genomics. For example, DL has been applied in: (1) predicting the sequence specificity of DNA-- and RNA-binding proteins, (2) methylation status, (3) gene expression, and (4) control of splicing [36]. Additionally, DL has been successfully applied in regulatory genomics. In this field, some architectures from computer vision or natural language processing were well suited after some genomic-specific modifications [36].

DL can also answer the question "how much RNA is produced from a DNA template in a particular cell" by building a model to predict gene expression from genotype data. It can be used for studying splicing-code models as well as for the identification of long noncoding RNAs. DL has been used for the interpretation of regulatory control in single cells [37], for example, the detection of DNA methylation in single cells, and for the identification of subgroups of cells through improvement of the representation of single-cell RNA-seq data. Additionally, predicting phenotypes is also one of the major interests of DL in genomics [36].

2.3.2 Proteomics

Proteomics aims to study the proteins' structure and function in biological systems and is gradually becoming a data-rich discipline. Accordingly, DL is warranted to interpret the huge amount of data, giving biological insights. In the field of proteomics, DL performed well in predicting protein structure, posttranslational modification, and MHC-binding peptide [38].

The function of a protein largely depends on its structure, and predicting the spatial structure from

an amino acid sequence plays a vital role in protein design and drug screening [39]. Currently, nearly 170,000 protein structures have been measured through a multicenter effort; however, it is a very time-consuming and high-cost process to directly measure the structure. Using DL to predict the structure may reduce the cost and accelerate the related research [38]. Recently, the performance protein structural predictive models was significantly improved through the application of AI, especially in those predictions without previously known homologous structures. After 11 rounds of Critical Assessment of protein Structure Prediction (CASP), the performance of DL in predicting protein structures increased quickly, especially in terms of development of residue-residue contact predictions [40]. In the most recent CASP14, the performance of AlphaFold2 achieved remarkably high improvement, and its success rate received considerable interest from both academia and the general public. Although the structure of AlphaFold2 has not been published yet, we know that its precursor AlphaFold has a highly complex, dilated residual neural network (ResNet) with 220 blocks to predict the Cβ distances of residue pairs given the amino acid sequence and many MSA-derived features [41].

2.4 AI in Medicine

2.4.1 Diagnosis

Image-based diagnosis has been regarded as the most successful application of AI in medicine. Its application scenarios in the hospital are widely used in radiology, ophthalmology, dermatology, and pathology to assist with image-based diagnoses [42].

In the department of radiology, the earliest application of computer-assisted diagnosis may date back to the 1970s [43]. Currently, with the development of methodology, AI was applied in the detection of lung nodules and the diagnosis of pulmonary tuberculosis and other common lung diseases using images from chest radiography [44, 45]. Additionally, breast-mass identification using mammography scans reached expert-level diagnostic accuracies [46, 47]. Currently, many clinical diagnostic AIs are seeking legal approval for clinical applications. For example, an AI system for cardiovascular disease diagnosis with MRI image was registered by the FDA in 2018.

In dermatology, physicians use AI to diagnose various skin lesions and further differentiate disease. A recent study suggested that in diagnosing skin malignancy, convolutional neural networks achieved dermatologist-level accuracy [48]. The DL model performed better than the dermatologist in a comparison of algorithm predictions to the assessments of 21 dermatologists given a set of photographic and dermoscopic images. Although the training phase of the deep learning model can be expensive and time-consuming, the final model can easily be used on mobile devices which is very convenient and fast for disease screening [48].

Fundus photography is a noninvasive procedure that uses retinal cameras to capture images of the retina, optic disc, and macula [49]. Images acquired by fundus photography can be used as another source of data for the AI-assisted diagnosis. Recently, a research team of computer scientists and clinicians trained convolutional neural network models to identify referable diabetic retinopathy and diabetic macular edema with 128,175 retinal images. In this study, the DL model had a good performance in two independent datasets (areas under the receiver operating characteristic curve > 0.99) [50]. Additionally, its performance was comparable to the performance of expert-level ophthalmologists. This study also demonstrated that DL could identify the underlying associations between the images and age, gender, systolic blood pressure, smoking status, or cardiovascular events, which indicated the ability of DL to elicit new knowledge from raw data [51]. Another study showed that the performance of a convolutional neural network exceeded in pre-specified sensitivity (85%) and specificity (82.5%); it was authorized by the FDA for use by healthcare providers to detect diabetic macular edema and moderate-to-severe diabetic retinopathy [52].

In the Department of Pathology, images from histopathological assessment are used with AI

algorithms to assist diagnosis. AI can be applied in the detection of various cancers and their metastases using biopsy specimens. For instance, DL models used in conjunction with normal clinical assessments can facilitate risk stratification of prostate and breast cancer patients [53]. In the USA, it is estimated that there will be a deficit of more than 5,700 pathologists in the next 10 years [54]. DL detection system may be able to mitigate this gap and provide a fast and accurate assessment from histopathological slides or other biopsy specimens, further improving the quality of care for cancer patients.

Overall, successful applications of AI in radiology, dermatology, ophthalmology, and pathology have been followed by the availability of large labelled datasets, improved computational power, and the development of deep learning methods. Currently, those applications are changing medical practice dependably.

2.4.2 Prognosis

As more and more longitudinal data and EHRs become available, the DL model can learn from the trajectories of a large number of patients and further predict their prognosis. For instance, whether the patient could go back to work in a short period or how long they may have before the disease progress could be predicted. Several large integrated health systems included a DL model to evaluate the risk of transferring to the intensive care unit for in-hospital patients [55]. Additionally, some studies built DL models to predict mortality, readmission, and length of hospital stay using data from EHRs, classifying the cancer patients with different responses to chemotherapy. At the large population level, the same type of forecasting could perform risk stratification and identify those patients who have a higher risk of readmission or may need more healthcare services. Such information could lead to a better healthcare resource allocation and provide evidence-based healthcare [56].

One limitation for such models is the integration of the health data. Building prognosis systems needs longitudinal data to provide a comprehensive view of the patients' disease course. The integrated data need to include outcomes such as mortality, readmission, and medical cost; however, those data are held by a variety of bodies such as hospitals, the local public health bodies, medical insurance departments, and public security bureau. To integrate those data from different sources, a better solution could be to put those data in the hands of patients through ID cards or other personal terminals. Additionally, standardization of the collected data is a vital issue for building such models [56].

2.4.3 Aging Biomarker Development

Aging is a gradual, multi-organ process that leads to multiple age-related diseases. Currently, some new experimental techniques have produced a huge amount of aging-related high-dimensional data. These data can evaluate the aging process precisely. AI technologies are suitable for the identification of the biomarkers of aging through patterns within in these high-dimensional datasets [35].

Some DL-based aging clocks have already been created using data from genomics, biochemistry, proteomics, and clinical imaging. Biological age is a more precise measure of aging compared to chronological age. Generally, changes in biological age can provide a more comprehensive and objective evaluation of general health status [57, 58]. Data from MRI has been used for the determination of biological age, which can serve as a biomarker of aging. A study using a deep neural network (DNN)-based DL method on T1-weighted MRI images was shown to outperform random forest- or ANN-based age prediction models, with the predicted age named the brain age gap (BAG) [59]. The results demonstrated that age could be accurately predicted using unimodal imaging in a young population using engineered features instead of raw images. Notably, the discrepancy between the BAG and chronological age could be regarded as a marker of aging speed, and BAG could be used as a biomarker for neurodevelopment and disease detection that could be easily interpreted. Additionally, the biological age also can be built with transcriptomic data using deep learning. Some studies built deep learning models using transcriptomic data were presented. In one study

using data from 545 transcriptomic samples from 12 datasets of human skeletal muscle, a deep feature selection (DFS) model was built and compared with several regression models. Linear regression was used as a baseline, and its performance was compared with other DL approaches. Although all models achieved a strong correlation between predicted and chronological age, SVM and DFS models clearly outperformed the other methods in age prediction (R^2 0.83/0.83, mean absolute error 7.20/6.24 years). Some studies also used clinical EMR data to estimate biological age using DL. One study used DNNs to predict human chronological age using 41 biomarkers extracted from thousands of blood biochemistry samples from patients undergoing routine physical examinations. The DNN model with the best performance had an R^2 of 0.80 with an MAE of 6.07 years. In the analysis of feature importance, albumin, glucose, alkaline phosphatase, erythrocytes, and urea were identified as the five most important variables. These five biomarkers could also be identified from within thousands of biomarkers by DL [35].

3 Application of Machine Learning in Clinical Work for Alzheimer's Disease

3.1 Etiology

Alzheimer's disease (AD) is a neurodegenerative disease. Patients experience a steady progression of dementia, finally losing the ability to respond appropriately to their environment.

Currently, the pathogenesis of AD is still unclear although it is thought to be caused by an interaction between genetic and environmental factors [60, 61], with genetic factors contributing approximately 70% [62–65]. One of the prevalent theories of AD pathogenesis is the amyloid hypothesis which holds that different factors cause an imbalance between β-amyloid production and clearance which leads to β-amyloid accumulation in the brain. In turn, this accumulation leads to the formation of neurofibrillary tangles and neuroinflammation. As a result, the neurons may eventually become dysfunctional and die. Recently, the mitophagy pathway has also been found to contribute to AD [66], but the detailed pathology is still unclear [62].

Etiological studies are aiming to discover the environmental and genetic factors causing disease, and these can be clues for researching both the prevention and treatment of AD. Recently, the development of AI technology has made it possible to achieve this goal using big data and ultra-complex models that exceed human brain processing capabilities [67–69]. AI provides a new way to model neuronal biological components using pathophysiologically functional modules that can be embedded to model the complex dynamics influencing neuropsychiatric disorder phenomenology [70]. Because genetic factors contribute to approximately 70% of AD cases, they have been the main focus of AD pathogenesis research. In recent years, wide use of microarray and next-generation sequencing technologies has allowed research using genetic data to grow explosively. AI technology is becoming urgently required. Currently, genetic research on AD with AI is continuously growing.

In the population, individual genetic variations include (1) aneuploidy or polyploidy; (2) chromosome rearrangements including duplication, deletion, and inversion as well as translocations; (3) large segment deletions and duplications; (4) small insertions and deletions; (5) tandem repeat variations; and (6) single nucleotide variations (SNVs) [71]. There are approximately 3.2×109 base pairs (bp) in the genome of human beings, but 99% of those form noncoding regions. These regions have important cellular regulatory functions and are associated with regulatory elements, such as promoters, enhancers, silencers, and insulators. This region can produce microRNAs, ribosomal RNAs, and transfer RNAs and form structural elements of the chromosome, such as telomeres, and satellite DNA [72–74]. Now, four strategies have been applied in the AD field to discover genetic variations in the human genome including genetic linkage analyses, candidate gene/pathway association studies, genome-wide association studies (GWAS), and next-generation sequencing (NGS)-based association studies [75].

For example, three mutations in genes, presenilin 2 (PSEN1), presenilin 2 (PSEN 2), and amyloid precursor protein (APP), were suggested to be causative in early-onset familial AD using genetic linkage analyses. Besides, the apolipoprotein E gene (APOE) alleles were identified as risk factors for late-onset AD by candidate gene/pathway approaches [76]. The International Alzheimer's Disease Project (IGAP) has collected many patients' samples to conduct large GWAS samples of LOADs [77, 78]. This strategy has also confirmed that APOE 4 is the most important genetic risk for AD [64, 75, 79]. To discover the extremely rare variants in AD, NGS was used to complement GWAS which requires large samples. Susceptibility loci, such as *ZNF655*, *ZBTB4*, *TTC3*, *TM2D3*, *PLD3*, *NOS1AP*, *NCSTN*, *IGHG3*, *GRN*, *FSIP2*, *CSFIR*, *CHMP2B*, and *ARSA*, were missed by GWAS but have been found to be related to AD development by NGS in very small population [80–83].

In order to better understand AD etiology, it might be necessary to consider additive or multiplicative effects, as well as the interaction of genes with the environment. However, more information is still needed, such as how genetic variations and environmental risk factors interact and mitochondrial genetic variation.

3.2 Diagnosis

Mental capacity and cognition preservation play an important role in the maintenance of autonomy in elderly people. Early detection of pathological cognitive impairment facilitates early, more effective treatment interventions focused on restoration and prevention. However, early detection of cognitive decline is a challenge due to the insidious symptoms, which are usually initially diagnosed as normal age-related cognitive decline [84, 85]. Requiring a longitudinal follow-up using multiple diagnostic criteria, mild cognitive impairment is often misdiagnosed as various different forms of dementia [86].

While magnetic resonance imaging (MRI) and genetic tests are the most common methods used in the clinic for the diagnosis of AD, there is currently no method available to detect early AD. Later-stage diagnostics are usually time- and money-consuming, and most importantly, they are not especially suitable for early detection and screening of large populations in a short time. As a result, an ideal diagnostic tool, sensitive enough to detect early disease, with a high specificity is needed. AI, being noninvasive and practical, could be an appropriate candidate.

AI can detect prognostic signals from data that can be easily collected such as MRI data, and electronic health records (EHRs). These signals enable the screening of aging populations prospectively. Currently, test results analyzed and interpreted by trained people may lead to delay in diagnosis. However, these delays can be reduced by using the AI approach. There remains much room for improvement, but applying AI to diagnose AD is already growing at an amazing speed [87–89]. For example, one study applied an artificial neural network (ANN) model to the diagnosis of AD within a cohort of 2482 community-dwelling people aged 60+ over 3 years. The study aimed to establish an early warning ANN model with high accuracy and diagnostic efficiency and to find a biomarker which was sensitive to early exploration. This model could be used as a low-cost, practical tool for the early detection and diagnosis of AD [90].

Physicians currently rely on subjective self-reported clinical measurements to diagnose and detect response to therapeutic intervention due to a lack of appropriate biomarkers [91]. Machine learning models can be used to identify the biomarkers of response to treatment from clinical trials. In fact, large publicly funded databases, namely, the ADNI, have set biomarker identification as one of their major objectives. We summarize **possible applications of AI in AD diagnosis and drug development (**Fig. 2**).**

3.3 Therapy

There are no effective treatments for AD; however, the large pharmaceutical companies have slowed their work in this field because of the high failure rate of clinical trials [92–95]. For

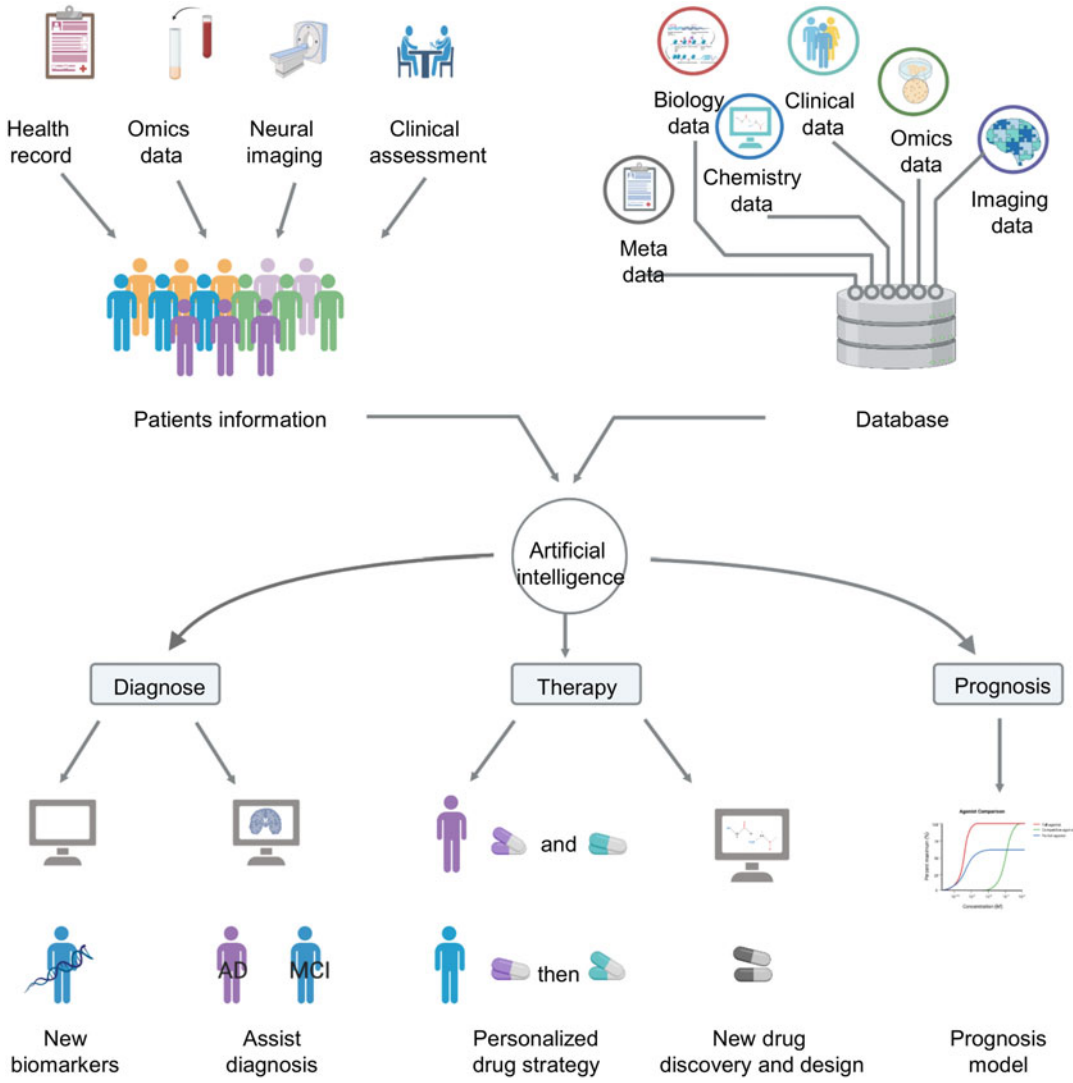

Fig. 2 Possible applications of AI in AD diagnosis and drug development. Through the use of patients' information and big databases, AI could improve diagnosis, treatment, and prediction of prognosis. For details see Sect. 3

example, from 2002 to 2012, more than 400 clinical trials for treating AD were performed, but only 1 drug was approved [96]. This highlights the complexity of developing personal drug strategies and provides the opportunity to use new approaches to design and discover new drugs.

The use of machine learning techniques for developing personal drug strategies is becoming more and more popular because the whole data of an individual including clinical history, transcriptomic, and neuroimaging as well as biomarker data can be fed into an algorithm of neurodegeneration disease [97]. Using deep learning by unsupervised models may be one approach to stratifying patients to reduce dimensionality in high-dimensional labelled data and to classify patients' outcome. Patients with different endotypes or subtypes of AD which are not obvious using traditional diagnostic methods may be identified [98]. These subtypes provide evidence for further development of personal drug strategies. For example, using this evidence, physicians may

prescribe single drug or combination drugs to an individual patient to improve treatment effects.

AI could also be a new way to design and discover new drugs for AD. As mentioned before, AD pathology involves a vast array of mechanisms. How to explore the data related to these pathways in an efficient, holistic, and thorough manner is key to understanding AD. However, this can be a challenge for individual researchers. AI can help make sense of or even predict or design new drugs. Knowledge graphs, which link genes, diseases, and drugs, are built from the integration of different data types including ChEMBL, Ensembl, OmniPath, KEGG, and PubMed [99, 100]. This approach can highlight the less-obvious links between drug targets and AD. However, the downside is lack of granularity in biological relationships, which leads to reductions in specific predictions [101]. Several relational inference methods have been published for AD. In contrast to knowledge graphs, machine learning enables a more detailed biological specification. By extracting gene expression data from healthy control and individual patients' gene expression data, molecular networks can visualize biological processes that change in different disease stages. For instance, a combination of Bayesian inference, clustering, and co-regulation was used to analyze transcriptomic data collected from the brain tissue of individuals with late-onset AD and non-AD controls [102]. A group of microglial-specific genes coding the TYROP protein and immune-related genes were found to be highly expressed in late-onset AD patients. After further verifying the function of TYROP in the AD mouse model, researchers found a deficiency of this protein, showing a neuroprotective function [103, 104].

3.4 Prognosis

Prognosis is as important as diagnosis because it quantifies the potential disease progression, and therefore how to predict when MCI converts to AD is also a hot research topic. Among the studies, some have focused on the roles of different imaging modalities in the prediction of MCI conversion [105]. Compared to this kind of early study, an atypical approach using multiple modalities was able to concatenate features into a combined feature set that was further used to build up a classifier. Because of the high dimensionality of the combined feature set, researchers built a logistic regression model with 71.6% accuracy in classifying MCT conversion rate over 4 years [106]. Another line of research which encapsulated each modality feature could better keep intramodal integrity and reveal intramodal differences. One common approach was multiple kernel learning (MKL), which achieved classification with 76.4% accuracy, 81.8% sensitivity, and 66% specificity [107]. Besides using baseline multimodal imaging data alone, some researchers tried to use longitudinal multimodal image data. For example, imaging and Neuropsychological Status Exam Score (NPSEs) data, both at baseline and development stages, were used for AI-based prediction; in this way, the accuracy, sensitivity, and specificity reached 81.40%, 79.69%, and 83.08%, respectively [108]. Finally to increase the accuracy, researchers used florbetapir-PET, together with MRI, FDG-PET, and ADAS-cog scores, which increased accuracy to 86.05% with 81.25% sensitivity and 90.77% specificity [109].

4 Future Perspectives and Concluding Remarks

As the quality of life and clinical technologies improve in the twenty-first century, a dramatic increase of lifespan, and correspondingly an increased aging population on Earth, is expected. Since the elderly population is more susceptible to disease, infection (e.g., COVID-19), and neurodegenerative diseases (AD), we foresee pressure on society and the healthcare system [110–112]. Thus, it is timely and necessary to apply AI for clinical use. In recent years, AI applications have been widely used in precision medicine, including AI diagnosis, prognosis, and drug development. AI-aided medical applications have not only supported the doctors, researchers, and scientists to increase inefficiency and provide decision-making support but have also accelerated the development of the medical and healthcare industry. With more and more

breakthroughs such as DeepMind's AlphaFold 2, we can foresee that AI will be able to revolutionize the drug development and disease diagnosis industry in the near future.

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Declaration of Interests

E.F.F. has CRADA arrangements with ChromaDex. E.F.F. and G.Y. are consultants to Aladdin Healthcare Technologies. E.F.F. is a consultant to the Vancouver Dementia Prevention Centre and Intellectual Labs. Z.N, X.J and B.T are affiliated with MindRank AI ltd.

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