

Computational healthcare: Present and future perspectives (Review)

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Abstract. Artificial intelligence (AI) has been developed through repeated new discoveries since around 1960. The use of AI is now becoming widespread within society and our daily lives. AI is also being introduced into healthcare, such as medicine and drug development; however, it is currently biased towards specific domains. The present review traces the history of the development of various AI-based applications in healthcare and compares AI-based healthcare with conventional healthcare to show the future prospects for this type of care. Knowledge of the past and present development of AI-based applications would be useful for the future utilization of novel AI approaches in healthcare.

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1. Introduction

'Big data', large datasets that are difficult to record, store and analyze with conventional data management systems, has been accumulating in various fields in recent years with regard to the development of communication and sensor technology. The advances in technology regarding big data have emerged that the use of big data is expected to create new avenues of research. However, the overall trend of big data is difficult to understand based on general information processing by humans; thus, information processing by artificial intelligence (AI) has also attracted attention (1). In general, industries have succeeded in improving sales and work efficiency and decreasing costs using big data and AI (2).

In healthcare, the creation of new knowledge and the improvement in diagnostic and therapeutic outcomes are expected through the utilization of big data pertaining to life science information and medical data (3). In fact, the implementation of AI in healthcare has been actively investigated; however, it has not been used in a widespread manner due to a number of problems (4).

The present review looks back at the history of AI and AI-based applications, compares the advantages and the issues of conventional healthcare and AI-based healthcare, and considers the future development of AI-based applications.

2. Historical view of the clinical application of computational support

In the 1950s, McCarthy *et al* (5) proposed AI as a prediction machine (hardware or software that exhibits behavior which appears intelligence by predicting associations between variables). Samuel (6) developed machine learning in 1959, which triggered the first AI boom (Fig. 1). In this period, the discrimination of cells in microscopic images started to be investigated using machine learning (7,8). In the 1970s, progress with AI was temporarily halted, as the AI was only able to solve simple problems. By contrast, in the same period, expert systems consisting of knowledge bases and inference engines were invented, and tools for diagnosis in specific fields such as MYCIN and INTERNIST-1 were developed (9,10). Subsequently, deep learning was proposed by Dechter (11)

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in 1986 and a convolutional neural network was proposed by LeCun *et al.* (12) in 1988, leading to the second AI boom. In this boom, to allow adaptation to real-world problems, experts in various fields educated AI using parameters, including marketing, healthcare and life science data. In addition, surgical robots began to flourish during this period. Among them, PUMA 200 was developed to automatically identify the appropriate location of lesions in computed tomography-guided brain tumor biopsies and was the first robot used for assisting human neurosurgery (13). AESOP was a breakthrough in robotic surgery when introduced in 1994, as it was the first laparoscopic camera holder to be approved by the FDA (14). Moreover, in 2000, the da Vinci Surgical System obtained FDA approval for use in general laparoscopic procedures and became the first operative surgical robot in the US (15). In 2005, a surgical technique for the da Vinci Surgical System was documented in canine and cadaveric models called transoral robotic surgery; this was the only FDA-approved robot to perform head and neck surgery at the time (16).

In addition, medications based on a computational analysis of the crystal structure of molecules were developed (17,18). The ROBODOC Surgical System was introduced and revolutionized orthopedic surgery by being able to assist with hip replacement surgeries. This was the first surgical robot to be approved for use in humans by the FDA in 2008 (19).

Thus, during the second AI boom, several tools were successfully developed. However, it was difficult for humans to provide the information that an AI needs to solve complex problems, and it was difficult for the machines of that time to learn the vast level of information available.

With the advent of deep learning in 2006 and the development of computers and communication equipment, the interest in AI was renewed (20,21). In particular, the historical victory of a deep learning program by utilizing a convolutional neural network, a deep learning method in image recognition, in an image recognition contest called the ImageNet Large Scale Visual Recognition Challenge (ILSVRC) triggered the third AI boom (22). As a result, image recognition has become the most applied AI-based technology in the clinical setting. When considering clinical applications based on image recognition using AI, IB Neuro is a diagnostic software used to detect brain tumors by MRI, and this was approved by the FDA in 2008 as the first AI-based application in humans (23). In addition, IntelliSite was approved by the FDA as the first whole-slide imaging system in 2017 (24,25). Thus, a number of AI-based applications were approved by the FDA in the third AI boom. The number of approved applications for diagnostics, mainly image recognition, increased from 11 in 2008-2015 to 135 in 2016-2020 (Table I) (23,26). In addition to applications for diagnosis, applications for treatment are also being approved by the FDA, with three AI-based applications to support treatment processes such as radiotherapy being approved in 2018-2019 (23,26).

Moreover, AI-based applications for follow-up of treatment progress are also being developed. In 2012, the BodyGuardian Remote Monitoring System was the first AI-based application for follow-up to be approved by the FDA (23). Subsequently, applications for follow-up are being actively developed and 13 applications were approved by the FDA in 2017-2020 (23,26). Similarly, computational support continues to contribute

to drug development, such as methylenetetrahydrofolate dehydrogenase 2 targeting one carbon metabolism (27).

AI is being applied to various processes in the medical field. Current AI and AI-based applications are often specialized for each field; however, applications that are widely available, such as IBM Watson (ibm.com/watson), have been also developed (28-30). These applications have been developed during each of the AI booms, each of which exhibited their own trends and problems. AI in the current boom is more developed than before, but there are also problems such as the lack of knowledge regarding the information that AI recognizes. The resolution of such problems is expected to further develop AI. Big data and AI will continue to support healthcare in numerous ways.

3. Current AI applied in medicine

Diagnosis. Diagnosis requires the ability to process different types of information about patients and detect abnormalities with high accuracy and reproducibility. In conventional diagnosis, physicians process various pieces of patient information using their own knowledge and/or experience, and detect abnormalities in patients using their own senses or through diagnostic equipment. This method sometimes fails to detect abnormalities in patients or results in the wrong decisions being made. In addition, the diagnostic ability is dependent on the experience of the physician. Therefore, AI is expected to have diagnostic performance with reproducibility and accuracy equal to or better than that of skilled physicians, and to compensate for differences in physician experience. Current AI for diagnosis is actively being developed to perform diagnostic imaging with computed tomography and tissue sections. In particular, convolutional neural networks perform well in the ILSVRC every year; therefore, convolutional neural networks are the most used for diagnostic imaging and perform as well as or better than skilled physicians (31). Moreover, systems have been developed to predict radiation or anticancer drug sensitivity using convolutional neural networks (32,33). In addition to diagnostic imaging, AI is also being developed to diagnose diseases such as cancer via machine learning of blood components (34). However, limitations in measurement sensitivity and technical artifacts such as noise are barriers to diagnosis using blood components. The development of improved measurement technology and/or more advanced machine learning models would be required for a diagnosis that applies machine learning of blood components (35).

As aforementioned, the current application of AI for diagnosis mainly improves the accuracy of each test. By contrast, for the identification of a disease from various symptoms in a patient and the results of tests, a wide range of knowledge, not specific knowledge, and advanced information processing is necessary. To meet this demand, AI assistants such as Watson are also being developed that can learn the literature on a subject by enabling the processing of natural language, and can make complex decisions using expert systems (28,36).

Thus, for diagnosis, AI is mainly developed to improve the accuracy of each test and make appropriate decisions using the large quantity of related literature available, and different algorithms suitable for each process are applied.

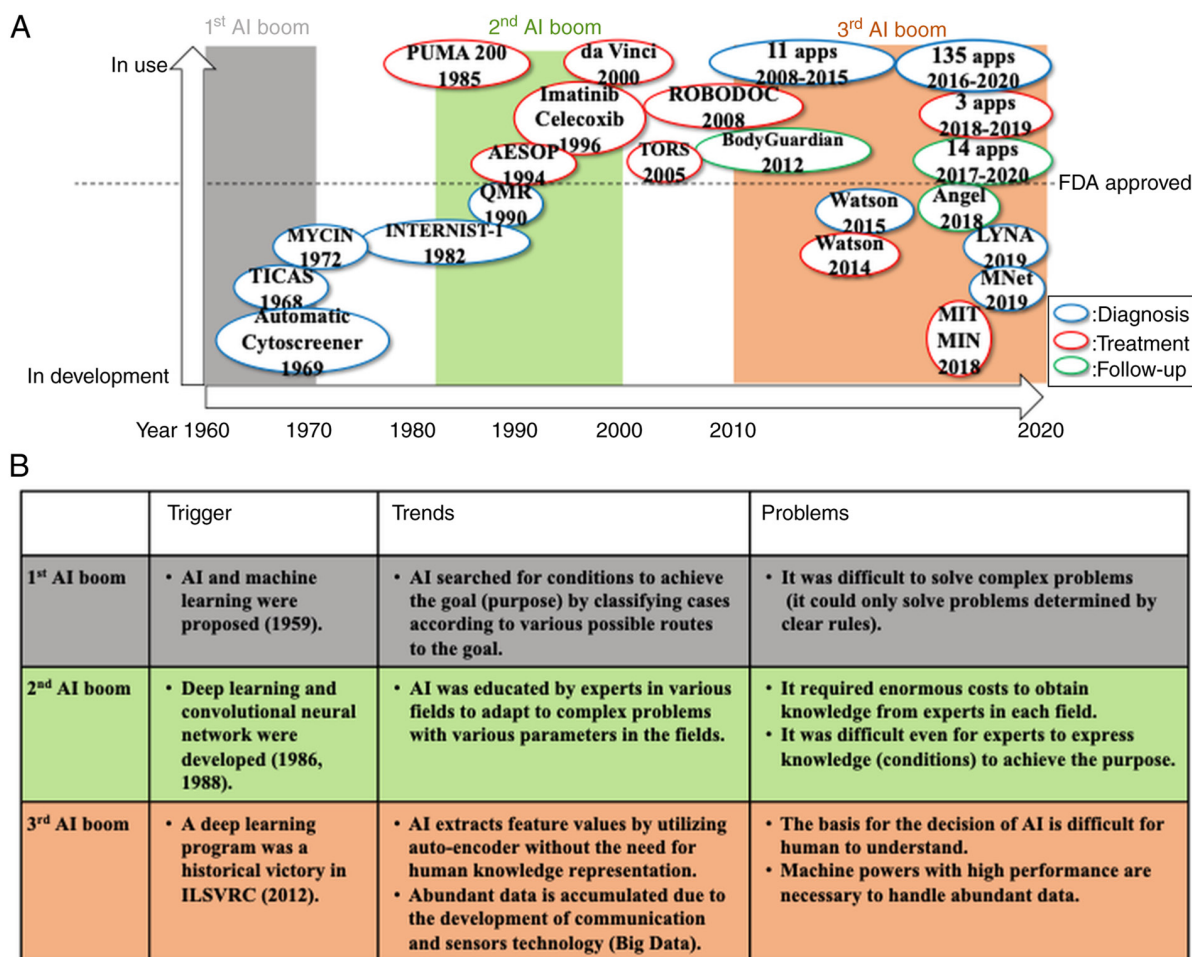


Figure 1. (A) Historical view of clinical applications with computational support. (B) Trigger, trends and problems of each AI boom. AI, artificial intelligence; ILSVRC, ImageNet Large Scale Visual Recognition Challenge.

Treatment. For treatment, surgical robots are mainly being developed. Surgical robots are suitable for detailed work with precise movements that is beyond the reach of human hands. In conventional surgical robot algorithms, classification and detection of objects required during surgery are performed by the developer manually creating features of the region of interest; however, with the advent of deep learning, convolutional neural networks are being applied for the classification and detection of objects (37,38). In addition, real-time predictions are also being made with recurrent neural networks (39). Conventional surgical robots are operated by a physician; however, surgical robots that work automatically without operation by a physician are also being developed (40). Thus, the development of AI has also led to the development of robots that support physicians during surgery.

In addition, in drug therapy, AI-based applications are being introduced in diagnosis and follow-up rather than in the treatment process. Various AI applications have been introduced in the drug development process to develop therapeutic drugs. In the drug development process, developers need to process an enormous amount of information to discover just a few promising compounds from millions to tens of millions of candidate compounds (41). Various types of AI play active roles in processing this information, as described in detail later in this review.

Thus, in the treatment process, surgical robots are mainly being developed to make the operation more accurate and reduce the burden on the physician, while in the drug development process, AI is being used to process large quantities of information.

Follow-up. In medicine, no matter what type of disease or what type of treatment is given, follow-up is more or less always necessary. In addition, life expectancy in the world has increased by 20 years in the last 50 years, and as the population ages, the risk of having chronic diseases increases. Against this background, wearable devices equipped with AI that can constantly monitor health conditions and immediately detect any abnormality in wearers are actively being developed. In particular, wearable devices are expected to be used in cardiology, where the condition of the patient may change rapidly and there is a direct link with mortality status. In fact, more than half of the applications for follow-up approved by the FDA in 2017-2020, including the ECG app on the Apple™ Watch, are wearable cardiology devices (23,26). A number of the algorithms in wearable devices are applied artificial neural networks or adaptive algorithms (42).

In addition to the wearable devices, automated communication systems have also been introduced for follow-up. For example, Pharmabot was a chatbot developed in 2015

Table I. FDA approved AI-based applications.

Applications	Company	Purpose	Medical specialty	FDA Cleared
IB Neuro	Imaging Biometrics, LLC	Diagnosis	Neuroradiology	2008
Pathwork Tissue of Origin Test Kit-FFPE	Pathwork Diagnostics, Inc.	Diagnosis	Pathology	2010
DeltaView Model 2.1	Riverain Technologies	Diagnosis	Radiology	2011
AlphaPoint Imaging Software	RadLogics, Inc.	Diagnosis	Radiology	2012
BodyGuardian Remote Monitoring System	Preventice	Follow-up	Cardiology	2012
ClearRead +Confirm	Riverain Technologies	Diagnosis	Radiology	2012
Temporal Comparison	Riverain Technologies	Diagnosis	Radiology	2012
cvi42	Circle Cardiovascular Imaging, Inc.	Diagnosis	Radiology	2014
Ahead 100	BrainScope	Diagnosis	Neurology	2014
AliveCor	AliveCor	Diagnosis	Cardiology	2014
Lung Density Analysis	Imbio LLC	Diagnosis	Radiology	2014
Vitre CT Lung Density Analysis Software	Vital Images, Inc.	Diagnosis	Radiology	2015
Stroke VCAR	GE Medical Systems	Diagnosis	Neuroradiology	2016
QbCheck	QbTech AB	Diagnosis	Psychiatry	2016
PixelShine	AlgoMedica	Diagnosis	Radiology	2016
Steth IO	Stratoscientific, Inc.	Diagnosis	General medicine	2016
ClearRead CT	Riverain Technologies	Diagnosis	Radiology	2016
Arterys Cardio DL	Arterys Inc	Diagnosis	Radiology	2016
CT CoPilot	ZepMed, LLC.	Diagnosis	Neuroradiology	2016
ClearView cCAD	ClearView Diagnostics Inc.	Diagnosis	Oncology	2016
Arterys Cardio DL	Arterys Inc.	Diagnosis	Radiology	2017
Cantab Mobile	Cambridge Cognition, Ltd.	Diagnosis	Neurology	2017
Lung Nodule Assessment and Comparison Option	Philips Medical Systems	Diagnosis	Radiology	2017
EnsoSleep	EnsoData, Inc.	Diagnosis	Neurology	2017
AmCAD-US	AmCad BioMed Corporation	Diagnosis	Radiology	2017
QuantX	Quantitative Insights, Inc.	Diagnosis	Radiology	2017
NeuroQuant	Cortechs.ai	Diagnosis	Neuroradiology	2017
LesionQuant	Cortechs.ai	Diagnosis	Neuroradiology	2017
Arterys Oncology DL	Arterys Inc	Diagnosis	Radiology	2017
Rooti Rx System ECG Event Recorder, Rooti Link APP Software	Rooti Labs, Ltd.	Diagnosis	Cardiology	2017
BioFlux	Biotricity, Inc.	Diagnosis	Cardiology	2017
CNeuro cMRI	Combinostics Oy	Diagnosis	Neuroradiology	2018
Idx	IDx LLC	Diagnosis	Ophthalmology	2018
WAVE Clinical Platform	Excel Medical Electronics, LLC	Follow-up	Hospital monitoring	2018
Insight BD	Siemens Healthineers	Diagnosis	Radiology	2018
Viz LVO (ContaCT)	Viz. AI, Inc.	Diagnosis	Neuroradiology	2018
DM-Density	Densitas, Inc.	Diagnosis	Oncology	2018
OsteoDetect	Imagen Technologies, Inc.	Diagnosis	Radiology	2018
Quantib Brain	Quantib BV	Diagnosis	Neuroradiology	2018
Guardian Connect System	Medtronic	Diagnosis	Endocrinology	2018
PowerLook Density Assessment Software	ICAD Inc.	Diagnosis	Radiology	2018
Viz CTP	Viz. ai, inc.	Diagnosis	Neuroradiology	2018
NeuralBot	Neural Analytics, Inc.	Diagnosis	Radiology	2018
OsteoDetect	Imagen Technologies	Diagnosis	Radiology	2018
EchoMD Automated Ejection Fraction Software	Bay Labs, Inc.	Diagnosis	Radiology	2018
MindMotion GO	MindMaze SA	Follow-up	Orthopedics	2018
LungQ	Thirona Corporation	Diagnosis	Radiology	2018

Table I. Continued.

Applications	Company	Purpose	Medical specialty	FDA Cleared
HealthCCS	Zebra Medical Vision Ltd.	Diagnosis	Radiology	2018
EchoMD Automated Ejection Fraction Software	Bay Labs, Inc.	Diagnosis	Cardiology	2018
DenSeeMammo	Statlife	Diagnosis	Oncology	2018
DreaMed	DreaMed Diabetes, Ltd	Follow-up	Endocrinology	2018
ProFound™ AI Software V2.1	iCAD, Inc	Diagnosis	Radiology	2018
BriefCase- ICH	Aidoc Medical, Ltd.	Diagnosis	Neuroradiology	2018
AmCAD-UT Detection 2.2	AmCAD BioMed Corporation	Diagnosis	Endocrinology	2018
Arterys MICA	Arterys, Inc.	Diagnosis	Radiology	2018
ECG App	Apple, Inc.	Follow-up	Cardiology	2018
Volpara Imaging Software	Volpara Health Technologies Limited	Diagnosis	Oncology	2018
AI-ECG Platform	Shenzhen Carewell Electronics, Ltd.	Diagnosis	Cardiology	2018
FibriCheck	Qompium NV	Follow-up	Cardiology	2018
Irregular Rhythm Notification Feature	Apple, Inc.	Diagnosis	Cardiology	2018
RightEye Vision System	RightEye, LLC	Diagnosis	Ophthalmology	2018
Accipiolx	MaxQ-AI, Ltd.	Diagnosis	Radiology	2018
icobrain	Icometrix NV	Diagnosis	Radiology	2018
FluoroShield™	Omega Medical Imaging, LLC	Treatment	Radiology	2018
Vitre CT Brain Perfusion	Vital Images, Inc.	Diagnosis	Neuroradiology	2018
SubtlePET	Subtle Medical, Inc.	Diagnosis	Neuroradiology	2018
FerriSmart Analysis System	Resonance Health Analysis Service Pty, Ltd.	Diagnosis	Radiology	2018
Embrace	Empatica Srl	Follow-up	Neurology	2018
Quantib ND	Quantib BV	Diagnosis	Neuroradiology	2018
iSchemaView RAPID	iSchemaView, Inc.	Diagnosis	Radiology	2018
Study Watch	Verily Life Sciences LLC	Follow-up	Cardiology	2019
cmTriage	CureMetrix, Inc.	Diagnosis	Oncology	2019
Thoracic VCAR with GSI Pulmonary Perfusion	GE Medical Systems	Diagnosis	Radiology	2019
KardiaAI	AliveCor, Inc	Follow-up	Cardiology	2019
Loop System	Spry Health, Inc.	Follow-up	Hospital monitoring	2019
RhythmAnalytics	Biofourmis Singapore Pte, Ltd.	Follow-up	Cardiology	2019
Bone Vcar	GE Medical Systems	Diagnosis	Radiology	2019
Aidoc Briefcase- ICH and PE triage	Aidoc Medical, Ltd.	Diagnosis	Radiology	2019
Deep Learning Image Reconstruction	GE Medical Systems, LLC.	Diagnosis	Radiology	2019
eMurmer ID	CSD Labs GmbH	Diagnosis	Cardiology	2019
HealthPNX	Zebra Medical Vision Ltd.	Diagnosis	Radiology	2019
Aidoc BriefCase- CSF triage	Aidoc Medical, Ltd.	Diagnosis	Radiology	2019
ReSET-O	Pear Therapeutics, Inc.	Treatment	Psychiatry	2019
HealthICH	Zebra Medical Vision Ltd.	Diagnosis	Neuroradiology	2019
Advanced Intelligent Clear-IQ Engine (AiCE)	Canon Medical Systems Corporation	Diagnosis	Radiology	2019
Koios DS	Koios Medical, Inc	Diagnosis	Oncology	2019
DeepCT	Deep01 Limited	Diagnosis	Neuroradiology	2019
iNtuition-Structural Heart Module	TeraRecon, Inc.	Diagnosis	Radiology	2019
AI-Rad Companion (Pulmonary)	Siemens Healthineers	Diagnosis	Radiology	2019
ACR LAB Urine Analysis Test System	Healthy.io, Ltd.	Diagnosis	Urology	2019
Current Wearable Health Monitoring System	Current Health, Ltd.	Follow-up	Hospital monitoring	2019

Table I. Continued.

Applications	Company	Purpose	Medical specialty	FDA Cleared
physIQ Heart Rhythm and Respiratory Module	physIQ, Inc	Diagnosis	Cardiology	2019
RayCare 2.3	RaySearch Laboratories AB	Treatment	Radiology	2019
Critical Care Suite	GE Medical Systems	Diagnosis	Radiology	2019
Biovitals Analytics Engine	Biofourmis Singapore Pte. Ltd	Follow-up	Cardiology	2019
Caption Guidance	Caption Health, Inc.	Diagnosis	Radiology	2019
AI-Rad Companion (cardiovascular)	Siemens Healthineers	Diagnosis	Radiology	2019
SubtleMR	Subtle Medical, Inc.	Diagnosis	Radiology	2019
StoneChecker	Imaging Biometrics, LLC	Diagnosis	Radiology	2019
BrainScope TBI	BrainScope Company, Inc	Diagnosis	Neurology	2019
ProFound AI Software V2.1	ICAD Inc.	Diagnosis	Oncology	2019
KOALA	IB Lab GmbH	Diagnosis	Radiology	2019
EchoGo Core	Ultromics, Ltd.	Diagnosis	Cardiology	2019
RSI-MRI+	HealthLytix	Diagnosis	Radiology	2019
HealthCXR	Zebra Medical Vision, Ltd.	Diagnosis	Radiology	2019
icobrain	Icometrix NV	Diagnosis	Neuroradiology	2019
QyScore Software	Qynapse	Diagnosis	Neuroradiology	2019
Aidoc BriefCase- LVO	Aidoc Medical, Ltd.	Diagnosis	Neuroradiology	2019
AutoMISar	Apollo Medical Imaging Technology Pty, Ltd.	Diagnosis	Neuroradiology	2019
TransparaTM	Screenpoint Medical B.V.	Diagnosis	Radiology	2019
ADAS 3D	Galgo Medical S.L	Diagnosis	Radiology	2020
QuantX	Quantitative Insights, Inc.	Diagnosis	Radiology	2020
Eko Analysis Software	Eko Devices, Inc.	Follow-up	Cardiology	2020
densitas densityai	Densitas, Inc.	Diagnosis	Radiology	2020
red dot	Behold.AI Technologies, Ltd.	Diagnosis	Radiology	2020
icobrain-ctp	Icometrix NV	Diagnosis	Neuroradiology	2020
Broncholab	Fluidda, Inc.	Diagnosis	Radiology	2020
Transpara	ScreenPoint Medical B.V.	Diagnosis	Oncology	2020
AI-Rad Companion (Musculoskeletal)	Siemens Healthineers	Diagnosis	Radiology	2020
Hepatic VCAR	GE Medical Systems	Diagnosis	Radiology	2020
MammoScreen	Therapixel	Diagnosis	Oncology	2020
RAPID ICH	iSchemaView, Inc.	Diagnosis	Neuroradiology	2020
AIMI-Triage CXR PTX	RadLogics, Inc.	Diagnosis	Radiology	2020
CuraRad-ICH	Keya Medical	Diagnosis	Neuroradiology	2020
NinesAI	Nines, Inc.	Diagnosis	Neuroradiology	2020
HealthVCF	Zebra Medical Vision, Ltd.	Diagnosis	Radiology	2020
Syngo.CT CaScoring	Siemens Healthineers	Diagnosis	Radiology	2020
MEDO ARIA	Medo.AI	Diagnosis	Orthopedics	2020
Auto 3D Bladder Volume Tool	Butterfly Network, Inc.	Diagnosis	Urology	2020
AI-Rad Companion Brain MR	Siemens Healthineers	Diagnosis	Neuroradiology	2020
qER	Qure.ai Technologies	Diagnosis	Neuroradiology	2020
BriefCase-IFG	Aidoc Medical, Ltd.	Diagnosis	Radiology	2020
CINA	AVICENNA.AI	Diagnosis	Neuroradiology	2020
Rapid ASPECTS	iSchemaView Inc.	Diagnosis	Neuroradiology	2020
EyeArt	EyeNuk, Inc.	Diagnosis	Ophthalmology	2020
InferRead Lung CT.AI	Beijing Infervision Technology Co., Ltd.	Diagnosis	Radiology	2020
Rapid LVO 1.0	iSchemaView, Inc.	Diagnosis	Neuroradiology	2020
HealthMammo	Zebra Medical Vision, Ltd.	Diagnosis	Oncology	2020
Caption Interpretation Automated Ejection Fraction Software	Caption Health	Diagnosis	Cardiology	2020

Table I. Continued.

Applications	Company	Purpose	Medical specialty	FDA Cleared
AI-Rad Companion Prostate MR	Siemens Healthineers	Diagnosis	Radiology	2020
FractureDetect (FX)	Imagen Technologies	Diagnosis	Radiology	2020
VIDAvision	VIDA Diagnostics, Inc.	Diagnosis	Radiology	2020
Accipiolx	MaxQ AI, Ltd.	Diagnosis	Neuroradiology	2020
Aidoc BriefCase for iPE Triage	Aidoc Medical, Ltd.	Diagnosis	Radiology	2020
Aview 2.0	Coreline Soft Co., Ltd.	Diagnosis	Radiology	2020
AVA (Augmented Vascular Analysis)	See-Mode Technologies Pte, Ltd.	Diagnosis	Cardiology	2020
THINQ	CorticoMetrics LLC	Diagnosis	Neuroradiology	2020
Cleerly Labs V2.0	Cleerly, Inc.	Diagnosis	Radiology	2020
Syngo.CT Neuro Perfusion	Siemens Healthineers	Diagnosis	Neuroradiology	2020
Quantib Prostate	Quantib BV	Diagnosis	Radiology	2020
AVIEW LCS	Coreline Soft Co., Ltd.	Diagnosis	Radiology	2020
Liver Surface Nodularity (LSN)	Imaging Biometrics, LLC	Diagnosis	Radiology	2020
WRDensity	Whiterabbit.ai Inc.	Diagnosis	Oncology	2020
Neuro.AI Algorithm	TeraRecon, Inc.	Diagnosis	Neuroradiology	2020
FastStroke, CT Perfusion 4D	GE Medical Systems	Diagnosis	Neuroradiology	2020
PROView	GE Medical Systems	Diagnosis	Radiology	2020
Genius AI Detection	Hologic, Inc.	Diagnosis	Radiology	2020
HALO	NiCo-Lab B.V.	Diagnosis	Neuroradiology	2020
HealthJOINT	Zebra Medical Vision, Ltd.	Diagnosis	Radiology	2020
HepaFat-AI	Resonance Health Analysis Service Pty, Ltd.	Diagnosis	Radiology	2020
SQuEEZ Software	Cardiowise, Inc.	Diagnosis	Radiology	2020
EchoGo Pro	Ultromics, Ltd.	Diagnosis	Cardiology	2020
AI Metrics	AI Metrics, LLC	Diagnosis	Radiology	2020
BrainInsight	Hyperfine Research, Inc.	Diagnosis	Neuroradiology	2021
HearFlow Analysis	HeartFlow, Inc.	Diagnosis	Radiology	2021
uAI EasyTriage-Rib	Shanghai United Imaging Intelligence Co., Ltd.	Diagnosis	Radiology	2021
Visage Breast Density	Visage Imaging GmbH	Diagnosis	Oncology	2021
CLEWICU System	CLEW Medical, Ltd.	Diagnosis	Hematology	2021
qp-Prostate	Quibim	Diagnosis	Radiology	2021
Lvivo Software Application	DiA Imaging Analysis, Ltd.	Diagnosis	Cardiology	2021
Veolity	MeVis Medical Solutions AG	Diagnosis	Radiology	2021
NinesMeasure	Nines, Inc.	Diagnosis	Radiology	2021
Optellum Virtual Nodule Clinic, Optellum Software, Optellum Platform	Optellum, Ltd.	Diagnosis	Radiology	2021
Imbio RV/LV Software	Imbio LLC	Diagnosis	Radiology	2021
Vbrain	Vysioneer, Inc.	Diagnosis	Neuroradiology	2021
Viz ICH	Viz. AI, Inc.	Diagnosis	Neuroradiology	2021
syngo.CT Lung CAD (VD20)	Subtle Medical, Inc.	Diagnosis	Radiology	2021
Saige-Q	DeepHealth	Diagnosis	Oncology	2021
MEDO- Thyroid	Medo.AI	Diagnosis	Endocrinology	2021
CINA CHEST	AVICENNA.AI	Diagnosis	Radiology	2021
Overjet Dental Assist	Overjet, Inc.	Diagnosis	Radiology	2021

AI, artificial intelligence.

to assist in medication education for pediatric patients and their parents using a Left-Right parsing algorithm and Care

Angel, which applied an automated voice dialogue system to check on the condition of the person requiring care, to

Table II. Comparison between conventional and computational medicine.

Medicine	Conventional	Computational
Diagnosis	Doctors meet patients; patients are diagnosed using diagnostic equipment at the hospital; diagnostic accuracy depends on the experience of a doctor	AI can detect lesions with the same or better accuracy than a skilled doctor; AI support is used to avoid misdiagnoses; AI supports the decision of the doctor by processing of the medical literature
Treatment	Doctors perform surgery directly; doctors or nurses administer medications	Robotics support doctors in surgery; devices automatically administer medications based on time and symptoms
Follow-up	Doctors or nurses meet patients; patients are diagnosed using diagnostic equipment at a hospital	Devices, such as those that are wearable, can detect abnormalities at a very early stage; the AI can consult with patients about their medical conditions and medications
Advantages	Patients can meet their doctors and nurses; abstract expression is possible	AI decreases the burden on doctors and nurses; AI responds quickly in an emergency
Problems	The burden on doctors and nurses is heavy; sometimes it is not possible to respond immediately in an emergency	The process of outputting the data is incomprehensible to humans. Application cost is high. AI cannot take responsibility for mistakes.

AI, artificial intelligence.

detect abnormalities and to alert the caregiver to changes if necessary (43,44).

As aforementioned, AI-based applications are contributing to medicine in numerous ways. The characteristics of conventional medicine and AI-based medicine are summarized in Table II. In the current section, some examples of the applied AI-based applications have been introduced; however, it is difficult for AI-based medicine to classify diseases and symptoms that are still difficult to define, and to obtain the sense of security that is felt upon meeting a doctor or nurse directly. It would be possible to realize better medical care by solving the disadvantages of both and integrating the advantages of both.

4. AI in drug development as a foundation for drug therapy

Medications used in pharmacotherapy are discovered from among millions to tens of millions of candidate compounds after long years of research and after a huge amount of money has been expended. To evaluate each candidate compound, a number of key pieces of information are required for evaluation, such as *in vitro* and *in vivo* pharmacological activity, safety, target specificity, pharmacokinetics, physical properties such as molecular weight and solubility, stability in the body and during storage, and development cost. Therefore, drug development sites always generate enormous amounts of information. Developers need to extract the important information from this in order to discover optimal compounds. Therefore, it is expected that AI would improve the accuracy and efficiency of developers in drug development. AI was introduced to the field of drug development earlier than to the medical field (45). In conventional drug development, developers propose hypotheses for the treatment of a disease and focus on a target that can be used to develop a therapeutic drug within the hypothesis; this is followed by drug development. However, this process might miss crucial therapeutic targets and drugs for various

diseases. In AI-based drug development, AI can propose, and lead to the development of, important targets and candidate drugs for disease therapy (Table III). In particular, Watson is able to identify connections and relationships among diseases, drugs, genes and other factors, and can generate novel hypotheses by mining the scientific literature (28). This tool is useful not only for drug development, but also for drug repurposing. In addition, Watson is constantly and automatically updated. Automatic learning in AI is important, not only to decrease the effort involved, but also to create better methods to meet unmet needs in life sciences and medicine.

AI-based drug development can save time and money. In conventional drug development, screening is performed using millions to tens of millions of compound libraries, followed by synthetic development based on the candidate compounds obtained from the screening and the re-evaluation of their activities to identify those with promise. However, numerous identified compounds do not exhibit physical properties and safety profiles that are suitable for pharmaceutical applications; therefore, other compounds are often re-synthesized. To avoid such time and money loss, AI-based drug development can predict the activity, physical properties and safety of each compound using computers. Various AI-based applications have been developed to predict these parameters (Figs. 2 and 3) (28,46-62). Furthermore, applications have been developed that predict not only the properties of individual compounds, but also suitable routes of synthesizing pharmacological reagents or therapeutic compounds (61,62). The cost of drug development has been decreased by these applications; however, the accuracy of the AI prediction of the compound properties is not sufficient and further improvement of this factor is necessary. In particular, AI-based applications have been actively developed as screening steps, which require time and money. However, it is difficult to predict the affinities

Table III. Comparison between conventional and AI-based drug development.

Drug development	Conventional	AI-based
Driving factor	Target-driven	Data-driven
Targets	Easily druggable targets with known structure and interactions in cells	Meaningful targets extracted by machine learning using big data
Advantages	It is easy for humans to understand identified targets and compounds.	Saves time and money by predicting the activities and properties of compounds before synthesis; compounds that target un-druggable molecules may be identified
Problems	Targets are limited by the complex and/or un-known structures and interactions; the identification of promising compounds is time consuming (numerous synthesis-evaluation cycles).	A large amount of accurate data is necessary for learning; AI cannot understand whether compounds are meaningful for humans

AI, artificial intelligence.

between a target protein and compounds, for the following reasons: i) Difficulties in predicting protein flexibility; ii) ambiguity regarding the complexity of a protein in an actual environment, and iii) difficulties in assessing the solvent effects of an actual environment (63,64). To solve these problems, a number of experiments and new algorithms would be necessary.

One of the most difficult steps in the process of drug development is the prediction of adverse effects. It has been reported that computational modeling using machine learning is useful for predicting adverse effects (65). Moreover, it is possible to manufacture synthetic patients and data artificially by analyzing existing data using machine learning techniques (66,67). As there are no ethical concerns regarding the privacy and costs of using synthetic data, this would be a powerful tool for clinical studies that require a large number of patients and may be an effective alternative for preparing training data for machine learning algorithms. These fields of research could be further enriched by AI in the near future and would also contribute to the realization of personalized precision medicine.

5. Perspectives for AI-based medicine and drug development

AI has been used for clinical purposes and drug development. However, the current AI-based applications are only being developed for specific applications at each stage of pharmacological or medical applications. In particular, AI-based applications with a high accuracy for diagnosis have actively been developed. However, a diagnosis is not determined based only on the result of one diagnostic method, and should be performed by comprehensively combining various types of information, such as chief complaints and physical findings; a system that integrates the various specific diagnostic data would be necessary in the future (Fig. 3A). If the disease remained unclear based only on the acquired information, the system would be a present a diagnostic method to determine the condition. The system would avoid missing information and improve the accuracy of the diagnosis. In addition, the

system would not only be used for diagnosis, but also for monitoring the progress of treatment after surgery and drug therapy. At present, almost no AI-based application has been developed that predicts the therapeutic effect or proposes a therapeutic method. However, a system has been reported in basic research that predicts the sensitivity of anticancer agents and radiation therapy based on phase contrast image information (32,33). In the near future, AI may be able to predict the therapeutic effects of various therapeutic methods in advance and suggest an appropriate therapeutic method. Thus, clinical AI in the future should be a system that interprets and integrates various types of clinical information and considers the changes caused by each treatment, to promote the best flow toward the complete cure of the disease. In addition, by constantly collecting information on complaints and physical status, both inside and outside the hospital, AI systems should always support the ability of a patient to live without aggravating their condition.

In drug development, numerous specific AI-based applications are already in use. In particular, a number of applications for the simulation of the docking of compounds to target proteins have been developed (47-53). Moreover, in addition to having an excellent specific score (such as affinity for a target protein), a candidate compound needs to have comprehensive excellent safety and pharmacokinetics. Therefore, a system for identifying promising compounds by considering various characteristics, as well as learning specific scores, will be required in the future (Fig. 3B). Furthermore, in drug development, clinical trials impose a heavy financial and time burden. It is necessary to improve the efficiency of clinical trials by using portal devices, which configure and manage devices remotely over the network or via USB connection, and collecting and selecting applicable patients.

The most important key to solving the problems facing AI-based applications is making it possible for people to understand the judgment process of AI. AI-based clinical applications would be utilized in important aspects of future treatment decisions, such as the diagnosis and evaluation of treatment effectiveness. If the AI determination process is

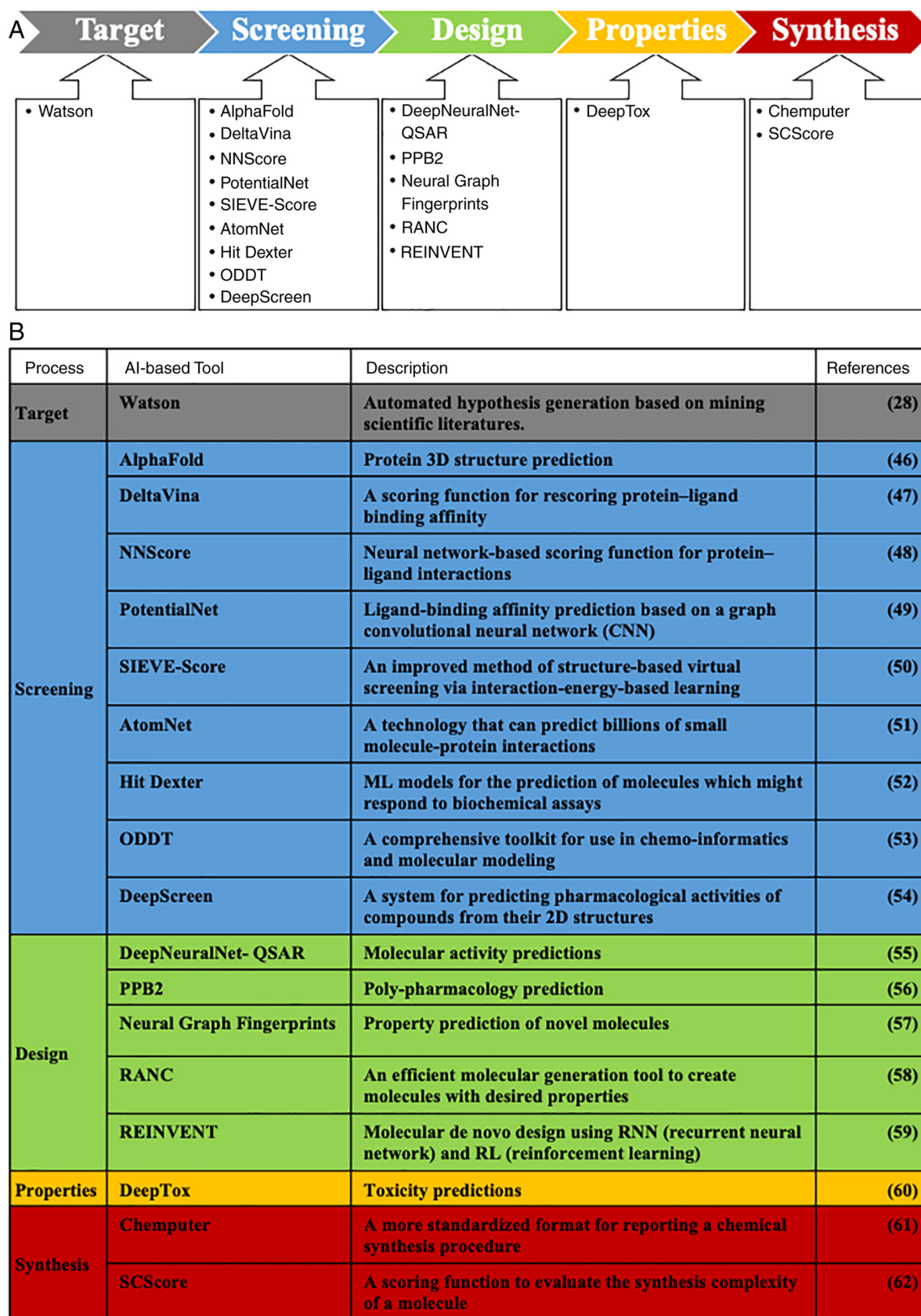


Figure 2. (A) AI-based tools in the drug development flow. (B) Description of AI-based tools in each process. AI, artificial intelligence.

unclear, the medical staff could not evaluate the validity of the AI determination, which would lead to the distrust of AI. To solve the uncertainty of AI, ‘Explainable AI’ has been

actively researched (68). The development of Explainable AI would be essential for the widespread use of AI-based applications in healthcare.

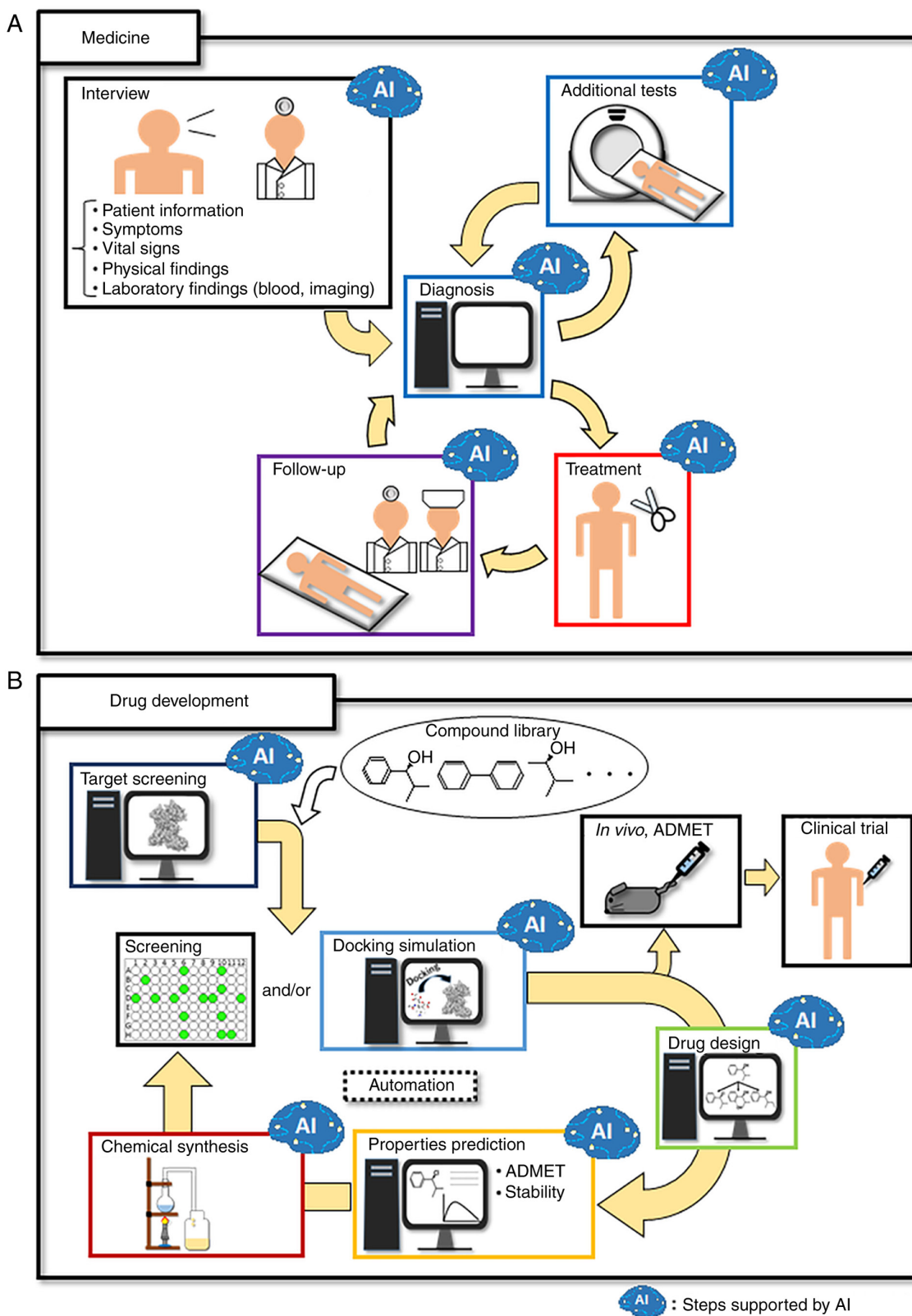


Figure 3. Perspectives for AI-based (A) medicine and (B) drug development. AI, artificial intelligence. ADMET, Absorption Distribution Metabolism Excretion Toxicity.

In addition, as AI-based healthcare would accumulate a greater amount of medical information than the current healthcare system, it would be necessary to prepare an infrastructure and security systems to handle large amounts of information. Futuristic clinical AI might monitor not

only medical information, but also the tasks of patients and medical staff, and might forecast workflow bottlenecks.

As aforementioned, the implementation of AI could facilitate more accuracy and greater efficiency in various fields of healthcare; however, it has some issues and limitations. Both

medical staff and developers would need to understand the issues and limitations, and then the coexistence of humans and AI could lead to better healthcare.

6. Conclusion

AI has evolved with the times and has been utilized in applications in drug development and healthcare. These applications are steadily producing results, and the use of AI is becoming established. The implementation of AI in society will need to overcome issues such as how to develop leading companies and train data scientists. However, company development may still face some obstacles, such as implementing AI, employment and cost. In the future, to improve human health, we should not only develop AI, but also think about the coexistence of humans with AI.

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Authors' contributions

HI, MT and AV conceptualized the study. AA, MK and HI wrote the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

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