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Artificial Intelligence in Nephrology: Core Concepts, Clinical Applications, and Perspectives

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Artificial intelligence is playing an increasingly important role in many fields of medicine, assisting physicians in most steps of patient management. In nephrology, artificial intelligence can already be used to improve clinical care, hemodialysis prescriptions, and follow-up of transplant recipients. However, many nephrologists are still unfamiliar with the basic principles of medical artificial intelligence. This review seeks to provide an overview of medical artificial intelligence relevant to the practicing nephrologist, in all fields of nephrology. We define the core concepts of artificial intelligence and machine learning and cover the basics of the functioning of neural networks and deep learning. We also discuss the most recent clinical applications of artificial intelligence in nephrology and medicine; as an example, we describe how artificial intelligence can predict the occurrence of progressive immunoglobulin A nephropathy. Finally, we consider the future of artificial intelligence in clinical nephrology and its impact on medical practice, and conclude with a discussion of the ethical issues that the use of artificial intelligence raises in terms of clinical decision making, physician-patient relationship, patient privacy, and data collection.

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Introduction

Artificial intelligence (AI) is now used in almost every area of our daily lives. Smartphones take advantage of facial recognition algorithms, autonomous cars are driving in our streets, and human Go champions have finally been defeated by computers.[1]

AI is also being deployed in medicine. The US Food and Drug Administration has allowed clinicians to use AI in different medical fields; for example, AI can now routinely detect diabetic retinopathy without the need for an ophthalmologist to confirm the diagnosis made by the algorithm[2] (Table S1).

In this Perspective, we discuss the development of medical AI (MAI) relevant to the practicing nephrologist. We define AI, describe the applications of MAI already available in clinical nephrology, and consider whether it is time for nephrologists to get involved in MAI.

What Is AI?

In simple terms, AI can be seen as the study of computations that make it possible to perceive, reason, and act,[3] as stated in Box 1. AI can be used on its own to perform a variety of tasks, but another possibility is to take advantage of AI algorithms to enhance human intelligence rather than replace it; this concept is called augmented intelligence.

One of the prime branches of AI is called machine learning (ML). ML can be defined as a set of algorithms that have the ability to learn and improve from experience, without being explicitly programmed for a specific task. This property makes ML fundamentally different from classic computational approaches.

Popular examples of ML algorithms are random forest, support vector machine, artificial neural networks (ANNs), and deep learning; their functioning is described in Box 1. Because ANNs and deep learning are predominant in MAI, we discuss them in more detail.

What Are Neural Networks?

Overview

An ANN is simply a collection of artificial neurons organized in layers. ANNs have been developed since the middle of the 20th century, as shown in Box 2.[4-8]

Currently, the most widely used model of artificial neurons is called the sigmoid neuron[9] (Fig S1). The sigmoid neuron is an elementary unit that may be seen as a model of biological neurons. As such, the sigmoid neuron receives 1 or more weighted inputs that determine to what extent the neuron gets activated.

An ANN has 1 input layer, optional hidden layers, and 1 output layer (Fig S1). Each neuron of a layer is connected to every neuron in the next layer; for this reason, such networks are called fully connected ANNs. The optimal number of neurons in each layer, as well as the optimal number of layers, is determined empirically for each ANN.

The Learning Process

Before an ANN can be used for practical purposes, it has to be trained. The first step of the training is to select a proper architecture for the network[9]: an adequate number of hidden layers and an appropriate number of neurons in each layer have to be chosen.

The second step is related to data collection and organization. The amount of data required to train an ANN is proportional to the size of the network. Moreover, for technical reasons, each piece of data can only contribute to a very small part of the learning process. Because of this, it is common for data sets to comprise several hundred thousand items. Data have to be randomly split into a training batch and a testing batch. The former is used to

Box 1. Definitions of the Core Concepts Used in Medical Artificial Intelligence (MAI)

Algorithm: a set of rules that precisely defines a sequence of operations.

Artificial intelligence (AI): a set of algorithms that enable computations making it possible to perceive, reason, and act.

Augmented intelligence: an alternative conceptualization of artificial intelligence that focuses on enhancing human intelligence rather than replacing it.

Machine learning (ML): a branch of artificial intelligence in which algorithms have the ability to learn and improve from experience, without being explicitly programmed for a specific task.

Supervised learning: a set of machine learning algorithms that have the ability to learn from labeled data and make predictions.

Unsupervised learning: a set of machine learning algorithms that have the ability to infer the structure of unlabeled data.

Support vector machine (SVM): a supervised machine learning algorithm that can classify data and detect outliers by constructing adapted hyperplanes, in which data belonging to different categories are linearly separated. SVM is fast but often not as accurate as other approaches such as deep learning.

Random forest algorithm (RF): a supervised machine learning algorithm that builds multiple decision trees to obtain a more precise prediction or classification: the output of the algorithm corresponds to the output of the majority of the trees. RF is a fast algorithm that performs well even if data are incomplete; however, RF interpretability is questionable.

Perceptron: historically, the first model of artificial neurons used in neural networks. Perceptrons are characterized by a finite number of weighted binary inputs and 1 binary output. If the weighted sum of the inputs exceeds an arbitrary threshold value called a bias, the neuron is activated and its output is 1; otherwise the output of the neuron is 0.

Sigmoid neuron: an improved model of artificial neurons based on perceptrons. Sigmoid neurons are characterized by input values between 0 and 1; their output, which also lies between 0 and 1, is the value of the activation function of the neuron, usually the sigmoid function. Contrary to perceptrons, sigmoid neurons in a neural network can take advantage of learning algorithms for the network to automatically learn from data sets.

Artificial neural network (ANN): a supervised or unsupervised machine learning algorithm based on a set of artificial neurons organized in layers, which can approximate complex functions involved in classification or prediction processes.

Deep learning: a supervised or unsupervised machine learning algorithm based on neural networks, often specialized in image recognition, which has multiple layers of nonlinear processing units for feature extraction and transformation.

Big data: refers to data sets that are too large or too complex for standard data processing techniques. Such data sets are encountered in large clinical trials or genomic studies (for example, DNA methylation or RNA sequencing results); these data sets can potentially be analyzed by artificial intelligence algorithms.

train the network; the latter allows to evaluate the performance of the network when training is complete.

During the learning step, the ANN progressively maps the input values it is fed to corresponding output values. To achieve such a mapping, the ANN must adequately set all the weights of all the neurons constituting it. This process is automatically performed using one of many available training algorithms, such as the gradient descent algorithm with backpropagation. After a proper training, each output neuron of an ANN will provide a relevant output value when the input neurons of the network are fed with appropriate values.

Using a Trained ANN

When a trained ANN is used, information flows from the input layer of the network to the output layer, the output of each neuron of a layer becoming one of the inputs of the neurons in the next layer. This processing of information is called the forward pass.

ANNs are popular because they are very efficient to approximate functions. A function is a relation that associates to each element of a set called the domain, a unique element of another set called the codomain. In 1989, Cybenko[10] showed that feedforward ANNs made of sigmoid neurons are universal approximators. This universal approximation theorem, later completed by Hornik,[11] demonstrates that any feedforward ANN with an appropriate architecture can approximate any function, including complex nonlinear functions.

Based on the universal approximation theorem, ANNs are used to approximate functions that take discrete values in classification problems. ANNs can also predict the value of continuous functions, which makes them good regression analysis tools.

In practice, ANNs are often the best option available to approximate complex nonlinear functions. However, simpler linear regression models should still be used to estimate simple functions because they need fewer computational resources and are more robust.

Clinical Applications of ANNs in Nephrology

Progressive immunoglobulin A nephropathy (IgAN) is a recognized cause of kidney failure. Unfortunately, it is difficult for the nephrologist to predict at the time of

Box 2. History of Artificial Neural Networks (ANNs)

The history of ANNs preceeds even the invention of modern computers. In 1943, McCulloch and Pitts,[4] a neurophysiologist and a mathematician, wrote the first known article on how artificial neurons might work, and modeled a simple ANN using electrical circuits. They showed that theoretically, their model could compute any logical function. In 1949, Hebb[5] pushed the concept further, proposing a learning law for the synapses of the neurons. A few years later, the famous Hungarian-American mathematician John von Neumann[6] laid the foundations for modern computer science and acknowledged that brain-inspired computers might be of interest. The first neuro-computer, called the SNARC, was constructed by Marvin Minski during the same period; it was the first working proof of principle confirming the new theories on artificial neurons, although this machine never carried out actual useful computations. In 1957, Rosenblatt developed the first successful neuro-computer, called the Mark I Perceptron, designed to improve pattern recognition. Nevertheless, researchers progressively shifted away from ANNs for 2 main reasons. First, the sudden craze for ANNs had led to a lack of experimental rigor that bothered many renowned scientists in the field. Second, many ANN researchers were carried away by their enthusiasm and made incredible claims. Based on Rosenblatt's declarations, the New York Times reported that the Perceptron was "the embryo of an electronic computer that [the Navy] expects will be able to walk, talk, see, write, reproduce itself and be conscious of its existence."[7] A temporary end was put to ANN research in 1969 by Minski and Papert,[8] who claimed that artificial neurons were unable to compute certain predicates; their work led scientists to consider ANNs as a dead end. However, by the early 1980s, neuro-computers and ANNs became once again an active research field as scientists improved the classical neural model and overcame its weaknesses, leading to the models of modern artificial neurons that are still in use today.

diagnosis which patients will develop kidney failure. However, the ability to identify these patients would be useful for prognostic and therapeutic reasons. Geddes et al[12] hypothesized that there exists a function that associates clinical and biological parameters measured at the time of IgAN diagnosis (namely age, sex, blood pressure, proteinuria, serum creatinine level, and anti-hypertensive treatments) to the probability of developing progressive IgAN. The authors designed and implemented an ANN to approximate this function. The results showed that their ANN could predict the occurrence of progressive IgAN more accurately than experienced nephrologists (correct predictions, 87% vs 69.4%; sensitivity, 86.4% vs 72%; and specificity, 87.5% vs 66%). Such approaches could be used in many progressive diseases to help clinicians in patient staging and management.

Other significant contributions of ANNs to clinical nephrology[12-20] are shown in Table 1.

What Is Deep Learning?

Overview

So far, we have discussed fully connected feedforward ANNs. For practical reasons, fully connected networks are limited to 1 or 2 hidden layers. However, deeper networks with more hidden layers can more easily approximate very complex functions. To overcome the limitations of shallow ANNs, a new model of networks was introduced: deep neural networks, used in deep learning. Here we consider convolutional neural networks (CNNs),[9] one of the most frequently used models of deep networks.

Basically, CNNs have the same architecture as fully connected feedforward ANNs. However, layers are not fully connected in CNNs; moreover, the number of neurons in CNN hidden layers progressively decreases as the network gets deeper (Fig 1). These particularities allow a decrease in the total number of weights, which in turn tremendously decreases the computational resources necessary to train or use the network. Therefore, CNNs can be deeper than ANNs and can approximate more complex functions.

CNNs are particularly efficient to analyze data that are spatially or temporally dependent, such as images or sounds. For this reason, CNNs are often a powerful approach to tackle image or speech recognition problems. They are also potentially efficient to analyze big data (Box 1).

Clinical Applications of CNNs in Medicine

Left ventricular dysfunction (LVD) is frequent in patients with chronic kidney disease, in particular in the hemodialysis population,[21] in which it is responsible for increased morbidity and mortality. Screening of LVD using echocardiography is possible but is critically volume dependent.

Attia et al[22] hypothesized the existence of a function associating data extracted from a 12-lead electrocardiogram to the risk for developing LVD. The authors trained a CNN on more than 40,000 patients; after training, the CNN was used to predict the risk for LVD on a different cohort of 50,000 patients. The CNN predictions had sensitivity of 86.3%, specificity of 85.7%, and accuracy of 85.7%. More interestingly, some patients with no clinical LVD were initially classified positively by the CNN; it was noticed later during follow-up that these patients were at 4 times the risk for developing LVD compared with patients with a negative AI screening (hazard ratio, 4.1; 95% confidence interval, 3.3-5.0). This study shows that CNNs trained with simple but relevant clinical data can already have a positive impact on the diagnosis and treatment of cardiovascular diseases.

Other significant contributions of CNNs to clinical medicine[23-38] are shown in Table S2.

Table 1. Recent Studies Using ANNs in Clinical Nephrology

Clinical Issue	Reference	AI Algorithm	Algorithm Inputs	N	Prediction	Results	Limitations
Clinical Nephrology							
Prediction of GFR decline rate in ADPKD	Niel[14]	ANN	5 consecutive GFR values over 2 y	12	GFR value at 5 y	Predicted GFR is comparable to actual GFR at 5 y	Retrospective study, limited no. of pts
Evaluation of risk for progressive IgAN	Geddes[12]	ANN	Age, sex, BP, proteinuria, Scr, antihypertensive treatments	54	Risk score for progressive IgAN	Predicted risk score for progressive IgAN is more accurate than risk evaluated by experienced nephrologists	Retrospective study
Kidney Transplantation							
Estimation of Tac AUC in transplant recipients	Niel[15]	ANN	Tac blood concentration at 3 h postdose	53	Tac AUC	Predicted Tac AUC is comparable to actual value	Retrospective study
Prediction of Tac bioavailability in transplant recipients	Thishya[16]	ANN	Age, sex, BMI, Scr, CYP polymorphism	129	Trough level/Tac dose ratio	Predicted Tac bioavailability is comparable to actual value	Many samples needed
Hemodialysis							
Improvement of anemia management in HD pts	Barbieri[17]	ANN	19 clinical and biological parameters	752	Optimal EPO doses	Predicted EPO doses increase on-target Hb values, decrease Hb fluctuations, decrease EPO consumption	Many predictors needed
Prediction of adequate dialysis time to reach target urea removal	Akl[18]	ANN with RBF	SUN, weight, solute removal rate	30	Optimal dialysis time	Predicted dialysis time is comparable to actual time required to reach target urea removal	Many samples needed
Evaluation of PCR in HD pts	Gabutti[19]	ANN	Albumin, SUN, UF, phosphate, Kt/V, PCR	84	Follow-up PCR	Predicted PCR is more accurate than PCR determined by clinicians	Limited no. of pts
Estimation of optimal dry weight in HD pts	Niel[13]	ANN	Markers of hydration, blood volume reduction, and BP	14	Optimal dry weight	Predicted dry weight improves CV tolerance compared to dry weight determined by experienced nephrologists	Limited no. of pts
Peritoneal Dialysis							
Identification of pathogens responsible for bacterial infections in PD pts	Zhang[20]	RF, SVM, ANN	Set of cytokines and chemokines relevant in infectious processes	83	Pathogen identification	Predicted pathogens correlate with actual pathogens responsible for bacterial infections	Many predictors needed

Note: N denotes number of patients.
Abbreviations: AI, artificial intelligence; ADPKD, autosomal dominant polycystic kidney disease; ANN, artificial neural network; AUC, area under the concentration over time curve; BMI, body mass index; BP, blood pressure; CV, cardiovascular; CYP, cytochrome P450; EPO, erythropoietin; GFR, glomerular filtration rate; Hb, hemoglobin; HD, hemodialysis; IgAN, immunoglobulin A nephropathy; PCR, protein catabolic rate; PD, peritoneal dialysis; pt, patient; RBF, radial basis function; RF, random forest; SUN, serum urea nitrogen; Scr, serum creatinine; SVM, support vector machine; Tac, tacrolimus; UF, ultrafiltration.

What Are the Main Limits and Disadvantages of ANNs?

ANNs have 3 main inherent limits.[9] First, training ANNs requires a lot of data; this can be a limiting factor to the use of AI in patients with rare diseases. Second, ANNs need good predictors to correctly approximate functions; in other words, networks need to be fed with measurable data that are strongly correlated to the function to approximate. Third, training ANNs, in particular CNNs, requires a lot of computational resources.

Lack of interpretability is probably the main disadvantage of most ML algorithms, including ANNs. In other words, it is not possible to understand precisely how a network approximates a particular function. A direct consequence of this "black box" behavior is that it is impossible to predict how a small variation in the inputs will affect the prediction capabilities of a network. It has been shown that imperceptible modifications of pictures used as inputs to a CNN could lead to a dramatic decrease in the performance of the network. Conversely, major alterations of the same pictures, to a point at which the

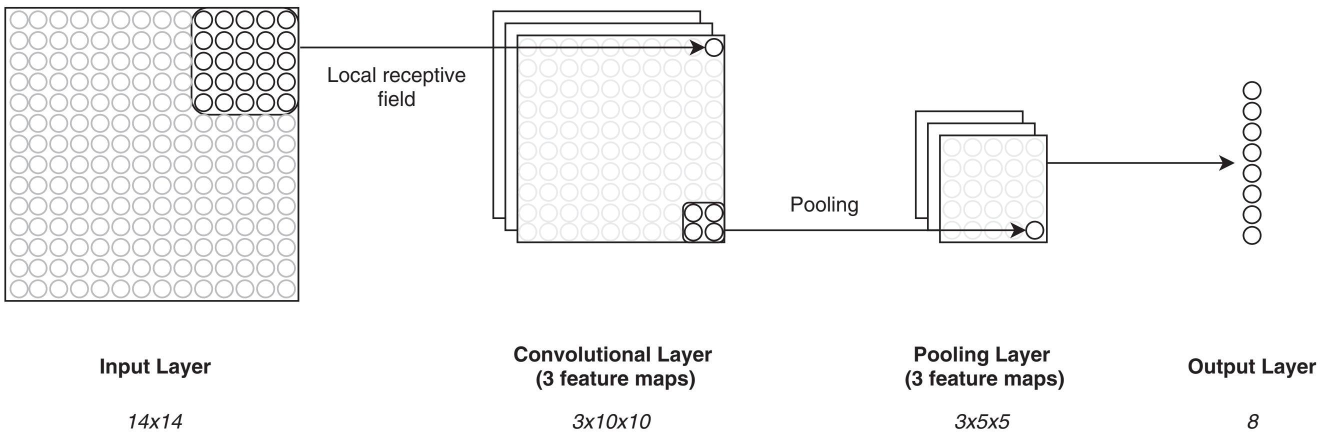

Figure 1. Architecture of artificial neural networks: deep convoluted neural networks. The input layer is divided into small regions called local receptive fields, which consider adjacent input values together. Each local receptive field is connected to a single neuron in the following convolutional layer. Convolutional layers comprise 1 or more feature maps; each feature map can only detect 1 input pattern; to detect several different input patterns, a corresponding number of feature maps have to be created inside the convolutional layer. The pooling layer creates a condensed feature map for each feature map of the convolutional layer, reducing further the number of neurons in the network. Several structures associating a convolutional layer and a pooling layer can be used consecutively. Finally, output neurons classify the inputs into one of the output categories.

human eye could not recognize them anymore, did not modify the way the CNN classified the images.[39-41] In practice, when ANNs are used instead of linear models, the gain in prediction performance should balance the loss of interpretability.

Another disadvantage of ANNs is that inputs and outputs of the network are often surrogates for clinical or paraclinical situations. Surrogates should therefore be particularly relevant to maximize the correlation between the prediction of the network and the clinical situation. This correlation may not always be optimal. Therefore, neural networks should preferentially be used on large and complex data sets when simpler linear methods do not provide accurate results.

What Will be the Impact of AI on Clinical Medicine?

Impact of AI on Clinical Decision Making

Clinical decision making (CDM) is a complex process[42] that can be modeled by the dual process theory, originally developed in cognitive sciences. The dual process theory states that 2 different pathways are involved in CDM: the first is intuitive and is usually described as subconscious, nonverbal, and autonomous, and the second is analytical and is depicted as conscious, verbal, and deliberate. Some characteristics expected from physicians involved in CDM, such as rationality, critical thinking, reflection, and communication skills, belong to the analytical pathway. Other characteristics related to the intuitive pathway (such as cognitive and affective biases) can pose a threat to clinical judgment when they are not properly understood and managed. Interestingly, it has been shown that poor CDM can result in diagnostic failure and ultimately leads to the death of up to 80,000 patients annually in the United States.[42]

AI could be a valuable tool to assist physicians in CDM, particularly because medical courses dedicated to CDM and problem solving are rare or nonexistent during medical training in most countries. AI could not only guide clinicians throughout their reasoning, but also help them be more aware of their cognitive and affective biases.

AI as a Change of Paradigm

Besides CDM, the use of AI in clinical medicine poses a more theoretical question about the very essence of medicine. In early civilizations, healers were also priests[43]; medicine was entangled with religion. Later, in European countries, medicine grew apart from religious beliefs, becoming an art aimed at restoring and maintaining health. During the 20th century, as a result of the advances in science and technology, medicine became both an art and a science. A good illustration of this dual identity is that evidence-based medicine, despite its wide acceptance, is still complemented by expert opinions. Nowadays, the emergence of MAI fundamentally connects medicine to hard sciences in general and to mathematics and computer sciences in particular.

What Will be the Impact of AI on Patients?

Privacy and Data Protection

ANN training requires a lot of valid data, which raises 2 types of issues. First, studies[44] have shown the existence of a dilemma between individual and collective interests in terms of data sharing. On the one hand, the individual interest of most patients is to protect their privacy and the confidentiality of their data by limiting data access and sharing or by providing anonymized or incomplete data. On the other hand, the collective interest is in favor of better health performance, which implies that complete data have to be collected and shared between clinicians and researchers. Multiple countries are amending their respective legislations in different ways to handle data protection and sharing.

Second, adequate structures for collecting and sharing an increasing amount of data have yet to be created, nationally and internationally. One way to accommodate both patient anxiety about data confidentiality and clinical need for data sharing may be to involve patients in data collection and data registries.[45]

Physician-Patient Relationship

Using AI in clinical practice has a further consequence that is worth mentioning: modification of the physician-patient relationship. This dyad can be defined as a mutually agreed on relationship in which the patient knowingly seeks the physician's help and in which the physician knowingly accepts the individual as a patient.[46] The physician-patient relationship is mainly based on trust, knowledge, regard, and loyalty. It should be noted that this relationship has a documented impact on health outcomes[47]; a poor physician-patient relationship can significantly impair patients' health. The deployment of AI in clinical nephrology will necessarily modify the physician-patient relationship in ways that are complicated to predict but have to be taken into account for optimal patient care.

What Are the Challenges for the Deployment of MAI?

Recently, several major companies have invested in MAI. DeepMind Health, a subsidiary of Google, is working in partnership with the National Health Service in England to deploy AI solutions in several hospitals in London. One of their projects, called Streams,[48] is a secured mobile telephone application that aims to address failure to rescue in hospitalized patients. Watson Health, a subsidiary of IBM, is also involved in MAI. In oncology, Watson suggestions have been reported to be concordant with the tumor board recommendations in 93% of breast cancer cases, at least under laboratory conditions.[49]

The involvement of private corporations in MAI research is an opportunity to accelerate the deployment of AI in clinical practice. However, some issues have to be highlighted. First, the partnership between clinicians working in public hospitals and private corporations involved in MAI research should be balanced. A model of public-private partnership in which clinicians would only provide data and private corporations would be solely responsible for developing AI algorithms would involve the risk that clinicians may be forced to use AI tools that they do not fully understand or approve. On the contrary, a well-balanced partnership could more easily ensure that patients are treated by well-trained clinicians assisted by optimal technology.

Data protection is also an issue. In an era in which major private corporations such as Google or Facebook specialize in the monetization of personal data, precautions have to be taken to ascertain that medical data are processed ethically. Several scandals have recently taken place in well-known institutions that have allowed private AI companies to access years of hospital data.[50]

To address these issues, several solutions have been proposed. For example, DeepMind Health has asked independent reviewers to evaluate its strategy in terms of ethical impact. In their report published in 2018,[51] the reviewers noted that the activities of DeepMind Health lead to a risk for a monopolistic situation. However, the efficiency of independent ethic board recommendations on corporate policies still has to be assessed in the field of MAI.

A double-edged sword for MAI is that it can easily be used remotely. Thus, it has the potential to help developing countries gain access to cutting-edge diagnosis and prognosis tools. However, efforts have to be made to ensure that the most vulnerable people will effectively benefit from advanced medicine.

Medical training is another challenge that has to be met in the deployment of MAI. Physicians need to develop a proper understanding of AI algorithms to safely use them in clinical practice. However, in-depth comprehension of AI algorithms requires the use of advanced mathematical tools, which are not necessarily available to physicians. For this reason, a modification of medical training and continuing medical education should be discussed.

Conclusions

The deployment of AI in clinical medicine opens a vast field of opportunities for patients and clinicians. However, several challenges have yet to be met, in terms of ethics, medical training, regulation, and liability.

In particular, we believe that actions should be taken to govern the use of AI in clinical practice. First, Good Clinical Practice guidelines should be updated to take into account the use of ML algorithms, to protect patients' data while supporting clinical research.

Some fundamental principles should be emphasized: MAI algorithms used in clinical research should be evaluated in multicenter, double-blinded, randomized, prospective studies with external validation data sets when possible to ensure that their performance will be reproducible in a relatively heterogeneous target population. Individuals running studies should be adequately qualified and trained in medicine and AI. Moreover, postmarketing performance of MAI algorithms should be continuously monitored; adverse events should be reported to MAI vigilance units.

These measures will ensure that AI is optimally deployed in clinical medicine so that patients and physicians can safely take advantage of its potential.

Supplementary Material

Supplementary File (PDF)

Figure S1: Architecture of ANNs: fully connected feedforward neural networks and sigmoid neurons.

Table S1: Artificial intelligence algorithms approved by the FDA for use in clinical practice.

Table S2: Recent studies using deep learning in clinical medicine.

Article Information

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