2 Artificial Intelligence and Machine Learning in Integrated Diagnostic

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2.1 Background

High-quality patient care relies on the delivery of high-quality and comprehensive medical treatments, meeting the needs of each patient. It comprises a wide range of healthcare services, including diagnosis, treatment, and management of illnesses, as well as preventive care and health promotion. Physician's experience is a key factor in providing valuable standard of care and in taking accurate decisions. Obviously, this is a long process requiring both financial and time investments through practice and continuous education. Artificial Intelligence (AI) and Machine Learning (ML) can offer great support to the experienced physicians, by providing them with additional insights that otherwise they may not have had direct access to. AI can also help to automate routine tasks and identify potential issues early, assisting expert physicians in their diagnostic process and decision-making. If a radiologist may review approximately 225,000 magnetic resonance (MR) or computed tomography (CT) exams during his career [1], AI algorithms can process millions of scans in a short period; this leads to a higher probability to identify subtle abnormalities that may have been missed by radiologists. This high potential can be exploited in "integrated diagnostics," a term used to define the convergence of imaging, pathology, and laboratory tests with advanced information technology [2]. AI can contribute to creating new models, boosting the integration of these different data toward a more efficient and straightforward healthcare [3]. One of the main areas where AI is exploited in integrated diagnostics is in the analysis of medical images. AI algorithms can be trained to analyze images from multiple modalities, such as X-ray, CT, MR, positron emission tomography (PET), single photon emission computer tomography (SPECT), and ultrasound (US) images and detect phenotyping information that may not be obvious to the human eye.

AI is also used in the analysis of genomic data. The cost of sequencing a patient's genome has decreased over the years, with the consequent exponential increase of the available genomic data [4]. AI algorithms analyze these data and identify genetic variations that may be associated not only with cancers but also with common non-cancer diseases [5]. This can lead to the development of personalized precision medicine and a better understanding of the underlying causes of disease. AI can also be used in the analysis of electronic health records (EHRs). EHR includes information about a patient's health history, such as diagnoses, medicines, tests, allergies, immunizations, treatment plans, personalized medical care, and improvement of medical quality and

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L. Giovanella (ed.), *Integrated Diagnostics and Theranostics of Thyroid Diseases*,
https://doi.org/10.1007/978-3-031-35213-3_2

safety [6]. Through AI, it would be possible to accurately classify diseases, reclassify preexisting disease categories according to individual characteristics, quickly analyze images and medical data in EMR, and provide appropriate services [6]. In addition, AI assists in the interpretation of lab test results, such as pathology reports, and other diagnostic data. Digital image analysis in pathology can identify and quantify specific cell types quickly and accurately evaluating histological features, morphological patterns, and biologically relevant regions of interest [7, 8]. Quantitative image analysis tools also enable the capturing of data from tissue slides that may not be accessible during manual assessment via routine microscopy reducing the analysis time and avoiding human error [9, 10]. The power of AI to analyze large amounts of data quickly can significantly speed up the discovery of novel features that may help predict how a patient's disease will progress and how the patient will likely respond to a specific treatment [11–14].

2.2 Artificial Intelligence and Machine Learning

McCarthy and colleagues coined the term "Artificial Intelligence" during a conference in the 1950s and they referred to all the mathematical algorithms that attempt to perform tasks that normally require human cognitive abilities [15–17]. It encompasses a wide range of technologies and techniques, including machine learning, natural language processing, computer vision, and expert systems. AI systems can be trained using a variety of techniques, such as supervised learning, unsupervised and reinforcement learning. They can also be implemented using a variety of architectures, such as neural networks, decision trees, and genetic algorithms. In general, the first step in the creation of an AI model starts with collecting the data and checking for their goodness and lack of bias. The data has to be harmonized and only after they can be used to train the algorithm. The training phase consists of a set of iterations executing mathematical functions and is aimed to correlate the input of the endpoint of interest with a high level of probability. The accuracy of the created model has to be evaluated with another dataset called testing set, which allowed for adjusting the model parameters. Finally, the model has to be confirmed with internal and/or external validation datasets, in order to evaluate the performance with a new and independent dataset.

The most common types of AI in diagnostic medicine include:

1. Machine learning: ML algorithms are used to identify patterns and make predictions based on data by multiple layers of analysis. The models produced by ML algorithms are inferences made from statistical analysis of very large datasets, expressed as the likelihood of a relationship between variables [18]. According to how the ML algorithms are trained, they can be divided into supervised, unsupervised, and reinforcement learning. Supervised learning requires a set of input data as well as their corresponding output information, in order to identify a function linking inputs to outputs [19]. On the other hand, unsupervised learning does not need labels, since it searches for patterns that can separate the input data into subsets with similar characteristics [20]. The supervised learning algorithms can be broadly divided into regression and classification based on prediction of a quantitative or categorical variable [21]. Unsupervised learning is often used for feature extraction, while supervised learning is suitable for predictive modelling [22]. Different methods can be used for unsupervised learning. For example, clustering is one of the most famous methods in which data are split into groups according to their peculiarities [23]. The third category of AI algorithm is reinforcement learning, which learns by taking in feedback the result of its action. It consists of an agent that executes an action and the environment in which the action is performed. It is based on the concept of reward: an agent learns to interact with the environment aiming to achieve the best reward. The

environment sends a signal to the agent that performs a specific action. Once the action is performed, the environment reacts with a reward signal, so the agent can update and evaluate its last action. The cycle repeats until the environment sends a stop feedback. This workflow mirrors what happens in clinical situations, where a doctor has to adopt an action depending on the patient's condition [24]. Reinforcement learning can be used to design a decision support system in order to provide treatment recommendations to physicians [25].

2. Deep learning (DL): DL, a term coined in 1986 by Rina Dechter [26], is a new type of ML method that uses advanced neural networks with multiple layers to analyze the data. A neural network is a set of simple computational units, also called nodes, highly interconnected. Nodes are then organized into layers, i.e., a structure that takes information from the previous layers and then passes it to the next layer. In general, there are input layers, hidden layers, and output layers. As the name suggests, the number of nodes and layers in DL algorithms can be very high. DL is particularly useful for analyzing images and other types of data that have complex structures and presents not simply linear relationships [27]. Different from traditional feature-based ML approaches (Fig. 2.1), DL is able to achieve diagnosis automation, avoiding human intervention [28]. In medical applications, DL algorithms are exploited, for example, in the detection and characterization of different tissues (normal vs pathological) as well as for the analysis of disease progression [26, 29].
3. Natural language processing (NLP): NLP is a branch of AI that is used to understand and interpret written and spoken human language. It can be used to extract information from unstructured data, such as medical records, clinical notes, and other free texts. Understanding human languages constitute some of the most challenging problems faced

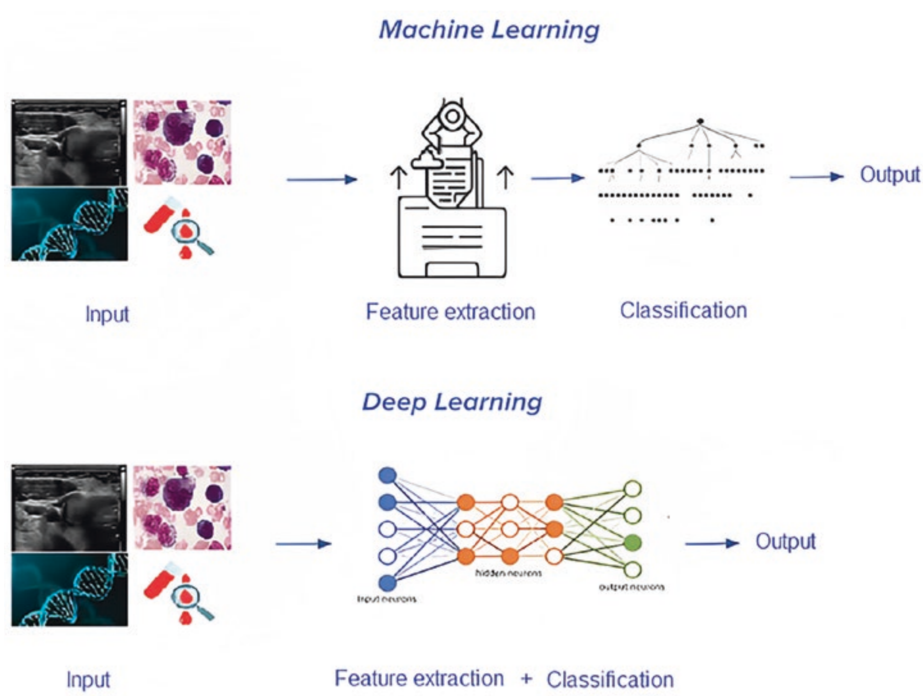

Fig. 2.1 Difference between ML and DL. In contrast to ML, DL does not need to define a priori a set of handcrafted features, but it is able to find complex correlations to predict the output

by AI [30]. As well as for the other AI methods, often the amount of available data is not sufficient and the effort to evaluate their goodness by the experts can be very huge and expensive. This is particularly true for Clinical NLP; in fact, it requires a very important amount of time for the revision of these unstructured data. Moreover, domain knowledge has also been shown to be important for understanding biomedical texts, such as in interpreting linguistic structures [31]. The knowledge is commonly represented as ontologies, that organize domain knowledge into structures that computers can read, and humans can understand. The size and extent of background knowledge needed to make inferences are great [31]. However, clinical NLP benefits from the availability of massive knowledge resources, such as, for example, medical vocabularies.

2.3 AI in Integrated Diagnostic: Challenges and Future Prospects

Recent reports confirm that approximately 86% of healthcare organizations use ML solutions, and more than 80% of healthcare organization leaders have an AI plan for the future [32, 33]. Looking at the articles published in the last 10 years, it is possible to estimate the growing interest and effort in the application of AI in healthcare (Fig. 2.2). The integrated diagnostic field is included in this big picture. In fact, the integration of the different diagnostic information, e.g., from pathology, imaging, EHRs, and its analysis by AI systems is expected to improve diagnostic precision and the therapeutic path [34]. Until now, many AI models have been used in the mentioned disciplines to detect cancers [35], cardiovascular diseases [36], neurological disorders [37], orthopedic conditions [38], pulmonary diseases [39, 40], skin diseases [41], sequencing genomic [42, 43], drug interactions and side effects [44, 45], and so on.

Unfortunately, the integration of the totality of diagnostic information into a clinical routine is limited by the lack of a suitable information technology infrastructure, the absence of high-quality unbiased data, and difficulties to access and exchange data [34]. AI methods need a very large database in order to avoid overfitting; however, this can be challenging, especially in small institutions or in the case of rare diseases. Additionally, the data must be as good as possible; in fact, the model will be a mirror of the type of data used to train it. Moreover, it can be possible, especially in clinical datasets, to have class imbalance negatively affecting the AI algorithms' performance. For example, if an AI system is trained on a dataset that is mostly composed of images from a certain race or gender, it may not perform well on images from other populations. This particular

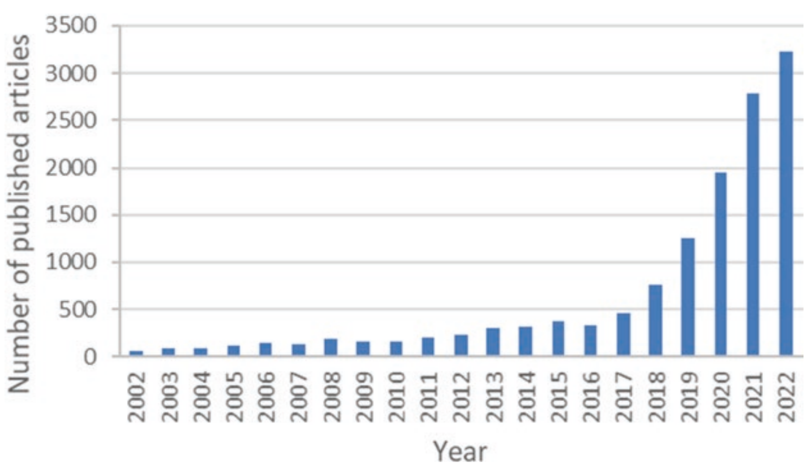

Fig. 2.2 Number of articles retrieved in PubMed by using the search terms "Artificial Intelligence" and "healthcare," grouped by year of publication. A search performed at the end of January 2023

aspect put light on the necessity of AI to be ethical: the performance of the AI solutions must be the same independent of race, gender, and age.

Explainability and transparency are other big problems of AI methods; AI-based systems can be difficult to interpret and understand, making it challenging to explain the taken decisions to patients and physicians. This can lead to uncertainty and a lack of acceptance of the technology. That is why there is a growing interest in developing AI systems that can provide explanations for their decisions, known as "explainable AI" or "XAI" [46].

AI-based diagnostic systems should be clinically validated and approved by regulatory agencies before they are used in clinical practice to ensure safety and efficacy [47]. A recent literature review reported that most studies assessing AI did not include the recommended design features for the robust validation of AI [48]. There is, therefore, a need to develop frameworks for the robust validation of the performance and safety of AI with reliable external datasets [49, 50]. The regulatory environment for AI in healthcare is still evolving and there are currently no clear guidelines for the development, validation, and deployment of AI-based diagnostic systems [51]. Additionally, there is a lack of standardization in the field, which can make it difficult for different systems to communicate and work together. It is a very difficult task, especially considering the dynamism of this technology. ML algorithm can be re-trained and improve its performance as soon as additional data are at disposal; but regularization system does not allow that a medical device changes without first undergoing a reauthorization process. Moreover, there is a need to protect patient privacy: strong privacy protection is realizable when institutions are structurally encouraged to cooperate to ensure data protection [52]. Commercial implementations of healthcare AI can be manageable for the purposes of protecting privacy, but it introduces competing goals. Manufacturers may not be sufficiently encouraged to maintain privacy protection if they can monetize the data or otherwise gain from them, and if the legal penalties are not high enough to offset this behavior. Because of these and other concerns, there have been calls for systemic oversight of big data health research and technology [51, 53].

2.4 Conclusions

In conclusion, AI is playing a growing role in the diagnosis and management of diseases through integrated diagnostics. By analyzing images, blood test results, and genomic data, AI algorithms can assist in the detection and diagnosis, leading to more accurate and personalized treatment plans. However, there are also limitations to consider, including the need for large amounts of data to train AI algorithms and the need for more research to validate the use of AI. Nevertheless, the future of AI in integrated diagnostics is promising and holds great potential to improve patient outcomes. For the broad implementation of AI and integrated diagnostics, central organizations (at the national or even international level) that ensure common structures, standards, and data safety have to be set up.

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