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The primary aim of *Artificial Intelligence in Cancer* (*AIC*, *Artif Intell Cancer*) is to provide scholars and readers from various fields of artificial intelligence in cancer with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

AIC mainly publishes articles reporting research results obtained in the field of artificial intelligence in cancer and covering a wide range of topics, including artificial intelligence in bone oncology, breast cancer, gastrointestinal cancer, genitourinary cancer, gynecological cancer, head and neck cancer, hematologic malignancy, lung cancer, lymphoma and myeloma, pediatric oncology, and urologic oncology.

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MINIREVIEWS

Potential and role of artificial intelligence in current medical healthcare

Chao-Ming Hung, Hon-Yi Shi, Po-Huang Lee, Chao-Sung Chang, Kun-Ming Rau, Hui-Ming Lee, Cheng-Hao Tseng, Sung-Nan Pei, Kuen-Jang Tsai, Chong-Chi Chiu

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Abstract

Artificial intelligence (AI) is defined as the digital computer or computer-controlled robot's ability to mimic intelligent conduct and crucial thinking commonly associated with intelligent beings. The application of AI technology and machine learning in medicine have allowed medical practitioners to provide patients with better quality of services; and current advancements have led to a dramatic change in the healthcare system. However, many efficient applications are still in their initial stages, which need further evaluations to improve and develop these applications. Clinicians must recognize and acclimate themselves with the developments in AI technology to improve their delivery of healthcare services; but for this to be possible, a significant revision of medical education is needed to provide future leaders with the required competencies. This article reviews the potential and limitations of AI in healthcare, as well as the current medical application trends including healthcare administration, clinical decision assistance, patient health monitoring, healthcare resource allocation, medical research, and public health policy development. Also, future possibilities for further clinical and scientific practice were also summarized.

Key Words: Artificial intelligence; Machine learning; Potential; Limitation; Medical healthcare application; Coronavirus disease 19

Core Tip: In this review, we explored the potential of powerful artificial intelligence (AI) for a more comprehensive application in the healthcare setting. Moreover, we also pointed out the demerits and problems in the current application of AI in medicine.

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INTRODUCTION

McCarthy, one of the core founders of artificial intelligence (AI), defined AI as the science and engineering of making intelligent machines[1]. AI has come a long way since its conception in 1956[2]. AI research aims to establish a capable system with intelligence to overcome the Turing test, demonstrating intelligent behavior identical to humans. For the next 60 years, this specialty encountered several episodes of excitement and frustration with nearly no advancement. However, in 2010, deep learning achieved marked improvements. This achievement is a type of machine learning (ML) with multiple layers of nodes among the input and output layers, resulting in artificial neural networks capable of establishing excellent development in recognizing speech, classifying an image, and translating context[3].

AI has been applied to analyze complex and big data to deliver outputs beyond human input in diverse healthcare backgrounds[4]. Davenport *et al*[5] advocated that AI systems would not extensively take over human clinical professionals but would amplify their patient care achievements. In other words, the concept of professional advice from a digital helper is not better than the clinician, but the fusion and application of ML into clinical medicine would enhance accurate healthcare delivery[6]. Rather than traditional robotics, AI applications in current healthcare mainly affect clinicians and medical institutions accessing enormous data sets of crucial clinical knowledge. A scheme of medical information for patient care could use sophisticated algorithms to give real-time analysis[7], including diagnosis, management strategies and prognosis, recurrence and survival rates, and information collection rates of millions of patients, geographical distributions, and countless and sometimes interconnected health status of oncologic patients. This advanced computing power of AI can detect and analyze large and small trends from the available information, and even forecast through ML designed to classify possible health prognoses.

The importance of AI technology in medical healthcare provision and study is increasingly becoming apparent[8]. There is a rapid growth trend of related publications on this topic in the form of academic articles from medical professionals (Figure 1). Specialists have emphasized the effectiveness and

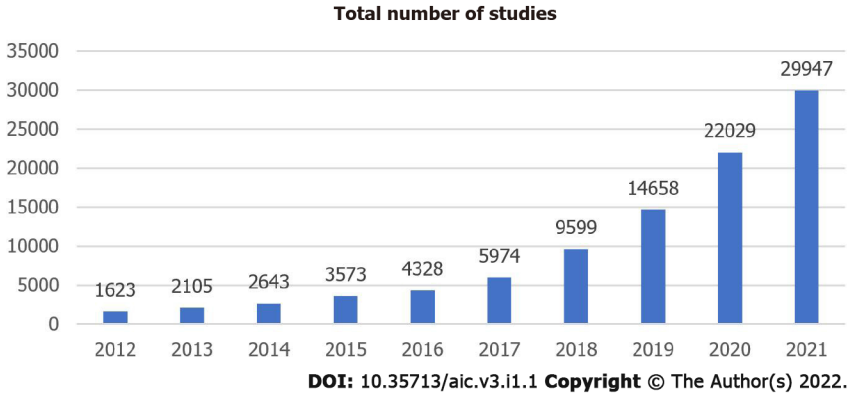

Figure 1 Number of medical artificial intelligence publications by year beginning in 2012 up to 2021, searched on Pubmed.com using the terms "machine learning" OR "deep learning".

capability of AI-empowered healthcare provision. Recently, more countries and private institutions have invested in this technological progress[9]. In addition, the United States Food and Drug Administration (FDA) has enthusiastically promoted AI-empowered instruments in the medical market[10].

In this study, the potentials of AI, its application in different fields of healthcare, and its current limitations will be discussed. Furthermore, we also investigated the advantages of clinicians over AI in clinical work and suggest different ways of cooperating with AI effectively.

RELEVANT POTENTIALS OF AI

AI is a collection of technologies consisting of abilities that could be applied in healthcare. Some particular AI technologies are paramount to healthcare (Figure 2).

Neural network and deep learning

Neural networks and deep learning are essential to ML, a statistical technology for fitting models to data and 'learning' by training models with data. The neural networks technology has been available since the 1960s for categorization applications[11]. A standard neural network comprises many simple, connected processors called neurons, each producing a sequence of real-valued activations[12]. It imitates the process of how neurons manage signals. It can determine if one person would suffer from a specific disease in his or her life. It views the disease based on the inputs, outputs, and weights of variables or parameters related to the inputs with outputs.

Deep learning is the most complicated form of ML, which involves neural network models with different levels of parameters to predict prognosis. Each character in a deep learning model usually has limited implications for clinical professionals. In other words, the explanation of the model's prognosis may be very challenging to interpret. Nowadays, the typical utilization of deep learning in healthcare involves the recognition of possibly cancerous lesions in radiologic imaging[13]. Currently, it is commonly applied to detect clinically specific features in imaging data, which is easily neglected by the human eye[14].

Natural language processing

Since the 1950s, AI researchers have strived to make sense of human language. Natural language processing aims to program machines to interpret human language as humans do. It comprises speech recognition, word analysis, sentence translation, and other intentions based on human language. Statistical natural language processing is related to deep learning neural networks. It has also contributed to increased recognition accuracy. A natural language processing system can duplicate patient interactions and operate conversational AI[15]. Furthermore, it has succeeded in scaling up partial roles of clinical decision-making, developing tools to stratify risks, and even identifying possible surgical complications from clinical records[16], and performing patient triage by identifying syndromes[17].

Rule-based expert systems

Expert systems could automatically alert patients and provide instructions according to the telemonitoring data. This is expected to increase patient self-care and improve clinical management[18].

In the 1980s, expert systems related to the 'if-then' rules were the primary technique for AI. Human experts and knowledge engineers were required to build up a set of guides in a specific knowledge domain. In the healthcare aspect, they were extensively applied to assist in making clinical decisions.

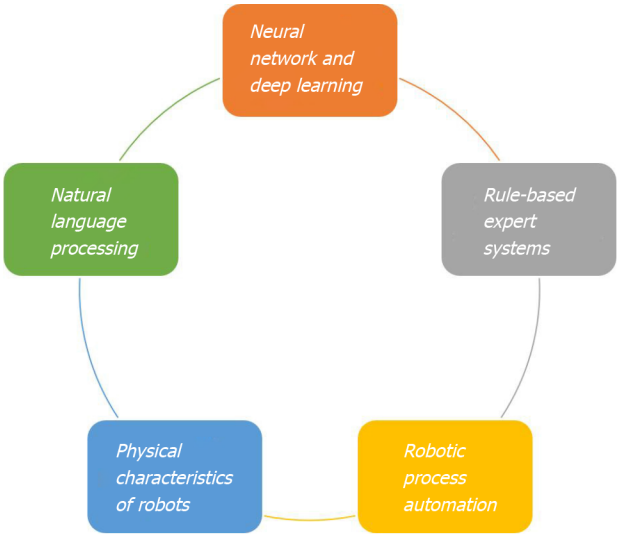

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Figure 2 Relevant potentials of artificial intelligence.

This system consisted of an expert system and a statistical analysis system linked to a patient database [19]. They have been used for the past decades, but are more extensively used nowadays[20]. However, they are proposed to be replaced by more advanced ML algorithms, possibly because of their static nature. As these expert systems are applied to clinical use, this demerit becomes accentuated by the rapid generation rate of new knowledge, the regional differences related to the expression of many diseases, and the change rate of patient demographics and disease incidence in the future[19].

Physical characteristics of robots

Physical robots are well-known for performing repetitive and precise pre-defined work, such as elevating, locating, welding, or collecting objects during hospital supply delivery. Since the 1980s, there has been an incremental development of minimally invasive surgeries. However, this was limited by the complexity of surgery due to the technical constraint of traditional laparoscopic instruments. Robotic technology provides a 3-dimensional view of the operating field, allows filtering of physiological tremor, and permits greater precision and control through its articulated arms. These advantages offer solutions to the limitation of traditional laparoscopic instruments[21]. The United States initially approved robot-assisted surgery in 2000. Robots empower the surgeons and provide a clearer vision to perform accurate and minimally invasive surgery resulting in smaller surgical wounds[22]. Robotic-assisted prostatectomy, cystectomy, pyeloplasty, nephrectomy, and partial nephrectomy are all becoming increasingly common techniques used by surgeons[23]. Moreover, robots are becoming more intelligent, as other AI facilities are being installed in the operating systems. Of course, dominant decision-making is still made by humans during surgery.

Robotic process automation

"Automation" is defined as the application of robotics, AI, ML, machine vision, and similar emerging and mature digital technologies to allow human work to be substituted by robots[24]. This technique executes structured digital works for organizational goals. Robotic process automation involves mere computer programs on servers. It hinges on a set of work assignments, business guidelines, and a 'presentation layer' combination with information systems to mimic a semi-intelligent system operator. In the medical field, it is usually applied to perform repetitive work, *e.g.*, updating patient records or billing, extracting data from images into transactional systems, *etc*[25].

According to the study by Willis *et al*[26], many forms of automation already exist in the healthcare setting. Not only do they increase the productivity of human employees, but they also do not remove human tasks entirely. Automation has even unexpectedly created more work for the medical staff. Although automation has allowed humans to process tasks more efficiently, it has resulted in more administrative work.

PRACTICAL FIELDS OF AI APPLICATION IN HEALTHCARE

During the global health emergency related to coronavirus disease 19 (COVID-19), experts have worked day and night to explore new technologies to mitigate the pandemic. Due to this, the trend of AI

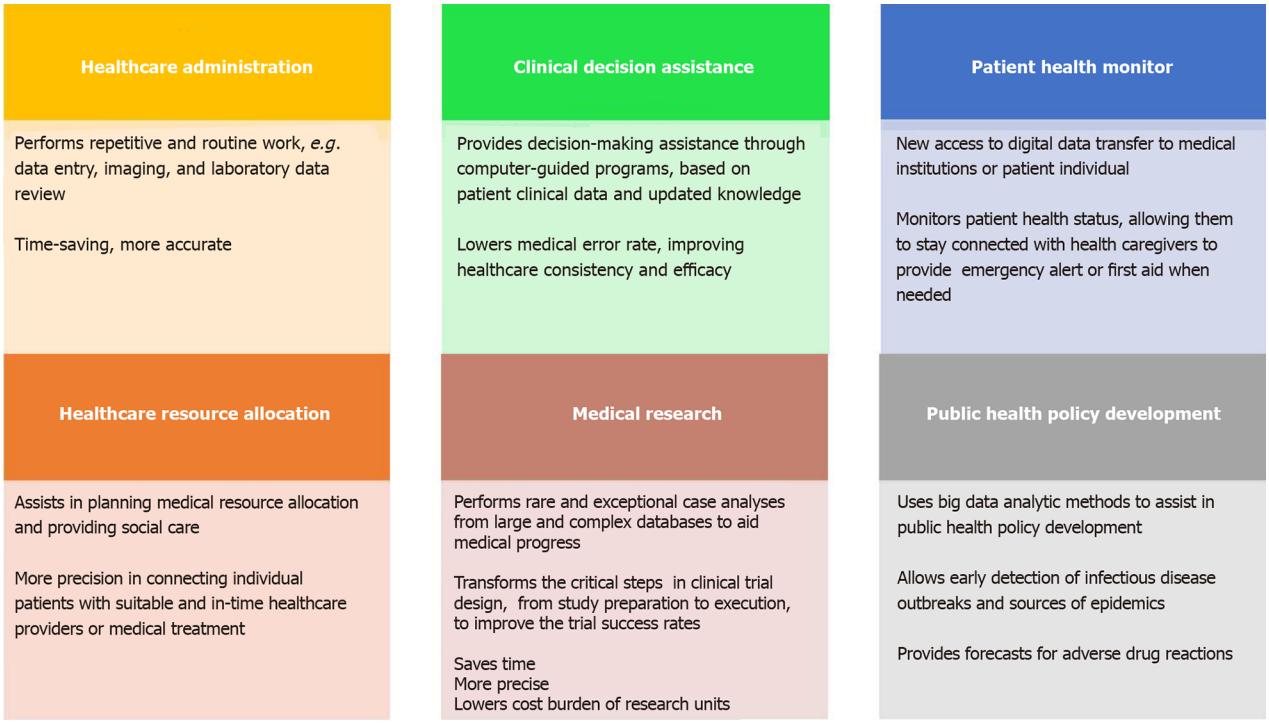

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Figure 3 Practical fields of artificial intelligence application in healthcare.

application in healthcare has grown rapidly[9], and has involved the development of sophisticated algorithms to perform complicated work efficiently and effectively[27]. Recent research has shown that AI could greatly enhance COVID-19 screening, diagnostics, and prediction, resulting in better scale-up, a timely response, a more reliable and efficient outcome. Furthermore, it was found that sometimes it outperforms humans in certain healthcare tasks[28].

In summary, AI-empowered healthcare delivery exerts a significant impact on healthcare administration, clinical decision assistance, patient health monitoring, healthcare resource allocation, medical research, and public health policy development (Figure 3).

Healthcare administration

AI could save time, which the clinical staff could use to care for patients, by performing repetitive and routine work, such as data entry, imaging, and laboratory data review[2]. The connection of ML algorithms with digital medical records could help clinical staff and administrators gain accurate patient data[29]. The accuracy and speed of data searches could be refined using ML and concept-based information retrieval systems. AI has already been applied to identify diseases even in the early stages. For example, AI-assisted diagnosis of breast cancer has significant advantages over those without AI assistance. It helps radiologists act as a second interpreter during data interpretation and patient screening. According to the American Cancer Society, it also reduces false-positive diagnosis rates, eliminating the need for unnecessary biopsy and lowering medical expenses[30]. It can finish reviewing and reporting the findings in just a few seconds. Although innovative methods have been established to diagnose and distinguish breast cancer, none of those methods could identify all cancer patients.

Clinical decision assistance

Clinical decision assistance systems are computer-guided programs that assist clinicians in their decision-making based on patient clinical data and updated knowledge[31]. AI is a powerful tool that lowers the medical error rate and improves healthcare consistency and efficacy.

The trend of AI application in clinical decision assistance is rising tremendously. For example, the case number of the COVID-19 global pandemic has overcome current medical facilities and obligated the clinical professionals, patients, and families to make crucial determinations based on limited information and within a short time. ML methods have been previously applied to assist in making clinical decisions. There is currently a demand for ML-supported decisions based on acquired vital signs, laboratory data, prescription orders, and complications from caring for previous patients. In clinical practice, AI-related precision medicine can predict patients' most suitable treatment protocols based on different patient characteristics and the treatment context[32]. AI can also make individualized treatment protocols for patients based on the large-scale database and updated information[33]. In addition, it is expected to guide inexperienced hospital frontline and healthcare providers to perform

appropriately with ample evidence under emergent situations[34].

Patient health monitoring

The popularity of smartphones and monitoring instruments has brought new access to digital data transfer to medical institutions. Using digital medical records also empowers the AI to monitor patient health status[29]. Through AI, patients with chronic diseases could be better informed about their health and stay connected with their health caregivers. Furthermore, AI-assisted home health monitoring instruments and techniques help low functioning and elderly patients to keep connected to assure that emergency medical technicians can immediately provide first aid when needed[35].

AI systems are also capable of following patient prognosis. For example, the National Institutes of Health has created the AiCure app to monitor medication used by patients. Moreover, those with hypertension or diabetes could benefit from AI's ability to track their health status through its clinically validated sensors and devices, effectively driving self-management[35]. Technology applications and apps boost more suitable actions in individuals and push one to follow a healthier lifestyle. In other words, it puts people in control of their health and well-being.

Healthcare resource allocation

Many governments use AI to plan medical resource allocation and provide social care services. AI could connect individual patients with suitable healthcare providers who could satisfy their needs based on their allocated medical budget.

Furthermore, AI could also design a specific treatment protocol and suggest more effective resource use for every patient[36]. For example, clinicians could identify potential risk factors associated with obesity using statistics, ML, and data visualization methods. AI systems can generate automated, personalized, contextual, and behavioral recommendations for obese patients during body weight control, including the suggestion of bariatric surgery, if indicated[37].

Shi *et al*[38] and Shi *et al*[39] used an artificial neural network model for predicting the 5-year mortality after surgery for hepatocellular carcinoma using the administrative claims data obtained from the Taiwan Bureau of National Health Insurance (BNHI). Their studies demonstrated that surgeon volume was the most crucial factor influencing 5-year mortality, followed by hospital volume and Charlson co-morbidity index. These parameters could be addressed in preoperative and postoperative healthcare consultations to educate the patients for better recovery and prognosis after hepatocellular carcinoma surgery. In addition, the government could also adjust the policy of healthcare resource allocation in hepatocellular carcinoma surgery with the aid of the AI-empowered analysis results of the BNHI database.

Medical research

Clinicians could use AI to analyze rare and exceptional cases from large and complex databases faster and more precisely than previously[40]. AI could also search for related scientific studies and information from the literature and combine different data to aid in medical progress[41]. In clinical trials, inappropriate patient selection and recruiting techniques, paired with ineffective patient monitoring and coaching could lead to high trial failure rates. AI can transform the critical steps of a clinical trial design, from study preparation to execution, to improve the trial success rates, thus lowering the cost burden of the research units[42]. It is expected to select the most precise patient data for relevant clinical studies and establish a database with a large population for more studies in the future.

Kiely *et al*[43] applied real-world data to screen for idiopathic pulmonary arterial hypertension, and the initial report was published in 2019. Their initial AI analysis algorithm has been used to provide a lower-cost screening at a significant population level, facilitate earlier diagnosis, and improve diagnostic rates and patient outcomes.

There was no reliably effective vaccine or specific drug invented for COVID-19 until the end of September 2020. Specialists have proposed several vaccines and drugs for COVID-19 by utilizing AI-based approaches. For example, the Harvard T.H. Chan School of Public Health and the Human Vaccines Project declared that they are using AI models to accelerate vaccine development by utilizing state-of-the-art techniques in epidemiology, immune monitoring, and network biology to explain effective immunity in older populations[44,45].

Public health policy development

Nowadays, many medical and health-related institutions use AI to assist in the early detection of infectious disease outbreaks and sources of epidemics[46]. Moreover, AI could also forecast adverse drug reactions, which causes about 6.5% of hospital admissions in the UK[47]. This indicates that AI could use big data analytic methods to assist in public health policy development.

When AI applications are deployed mainly in high-income countries, their use in low-income regions remains relatively nascent. However, AI systems in such low-income countries could support healthcare management in several ways. First, medical expert systems can assist clinicians in disease diagnosis and treatment plan selection, as performed in developed countries. AI could act as a human clinician in

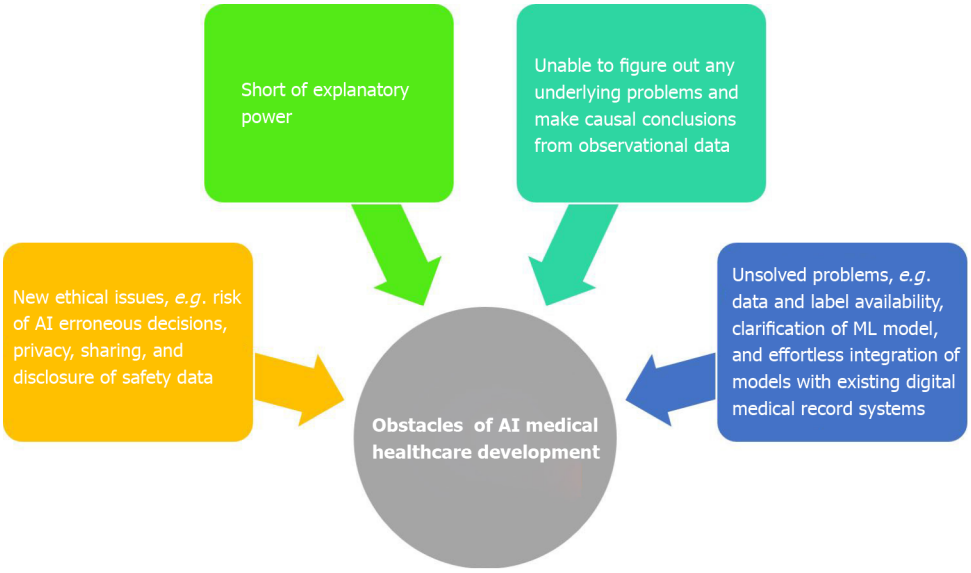

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Figure 4 Current limitations of artificial intelligence medical healthcare development. AI: Artificial intelligence.

initial disease diagnosis in poor communities if one is not readily available. The sick could then be transferred to a suitable institution with the relevant medical resources. Furthermore, AI has already been used to forecast the disease model and delay its spread in epidemic situations worldwide, even in resource-poor regions[48].

LIMITATIONS OF AI MEDICAL HEALTHCARE DEVELOPMENT

Deep learning is short in explanatory power; deep neural networks cannot interpret how a diagnosis is made, and prejudice characteristics are difficult to identify[7]. This means that ML cannot determine underlying problems and is unable to make causal conclusions from observational data. Algorithms are efficient in outcome prediction, but predictors are not causes[49]. Furthermore, there are still problems that need to be solved, such as data and label availability, clarification of the ML model, and effortless integration of these models with existing digital medical record systems[50].

With the advent of AI development, new ethical issues have also been encountered after it intervened in medical practice, *e.g.*, risk of erroneous decisions by AI, responsibility of using AI in support decision-making, difficulties in confirmation of AI outputs, constitutive data biases in AI system training, sensitive data security crisis, assurance of public trust in AI medical interventions, and the possibility of AI being used for malicious goals[51]. Among these issues, privacy, sharing, and disclosure of safety data relating to AI applications must be strengthened and solved first (Figure 4).

ADVANTAGES OF CLINICIANS OVER AI IN PATIENT CARE

AI cannot replace the clinician's role in healthcare because it intrinsically lacks articulation and cannot generate insights[4]. However, AI could assuredly assist in making better clinical decisions and even provide more accurate judgment in specific healthcare fields[52]. ML has already alleviated much of the workload of radiologists and anatomical pathologists in many medical institutions due to its massive imaging database, accompanied by advanced innovation in computer vision. With rapid progress in AI performance, machine accuracy can overcome that of humans[53]. The expanding availability of healthcare databases and the fast progression of big data analytic methods have led to the success and popularity of AI applications in the healthcare field. In addition, powerful AI techniques can discover new clinical information hidden in the extensive database, further assisting clinical decision-making[54-56]. However, there are no universally applicable healthcare rules. AI must be complemented with clinician confirmation in many instances. Furthermore, the clinician-patient relationship is guided by associative thinking and could affect real-life treatment decisions. The impact of psychosocial and emotional factors on disease prognosis falls outside the AI scope, which should always be considered. Thus, most AI experts believe that a blend of human experience and digital augmentation should be the natural settling point for AI in healthcare (Table 1).

Table 1 Collaboration of human and artificial intelligence characteristics aiming to provide an ideal healthcare delivery

Human factors	AI factors
Clinicians could regard their patient as a fellow mortal, vulnerable being and gain detailed knowledge of the patient's disease related to their lives	AI continually coordinates new knowledge and perfects itself more rapidly than humans do
Clinicians know about social relationships and norms and could establish a genuinely intimate and empathetic connection with their patients	Automation of routine work could save time, such as documentation, administrative reporting, or even triaging images
The clinician-patient relationship could be guided by human associative thinking and affect real-life treatment strategies	AI could provide reliable diagnosis and treatment strategies, issue reminders for medication, provide precise analytics for pathology and images, and predict overall health according to the current medical database and patient information
The impact of psychosocial and emotional factors on disease prognosis and patient compliance could benefit from a good and close clinician-patient relationships	AI could provide simple mental health assistance *via* chatbot, monitor patient health, and predict disease progression

AI: Artificial intelligence.

CONCLUSION

Clinical medicine always requires professional staff to manage enormous amounts of data, from patient physiologic information to laboratory and imaging results. The capability of this complex management has separated excellent clinicians from others. AI has been regarded as an essential tool for clinicians in their daily practice. The increased application of AI technologies does not lower the value of face-to-face interaction with patients. On the contrary, because of AI, it is expected that clinicians would move toward the tasks that uniquely need social skills such as empathy, persuasion, and big-picture integration. Integrating the human clinician's 'hardware' with the AI's 'software' could provide an ideal healthcare delivery that exceeds what either could do alone. Perhaps the experts who refuse to apply AI technology in their clinical practice would be regarded as non-professional in the next decade.

FOOTNOTES

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MINIREVIEWS

Artificial intelligence as a future in cancer surgery

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Abstract

Artificial intelligence (AI) is defined as the theory and development of computer systems able to perform tasks normally requiring human intelligence, such as visual perception, speech recognition, and decision-making. Machine learning and deep learning (DL) are subfields of AI that are able to learn from experience in order to complete tasks. AI and its subfields, in particular DL, have been applied in numerous fields of medicine, especially in the cure of cancer. Computer vision (CV) system has improved diagnostic accuracy both in histopathology analyses and radiology. In surgery, CV has been used to design navigation system and robotic-assisted surgical tools that increased the safety and efficiency of oncological surgery by minimizing human error. By learning the basis of AI, surgeons can take part in this revolution to optimize surgical care of oncologic disease.

Key Words: Artificial intelligence; Surgery; Robotic surgery; Machine learning; Pattern recognition; Cancer

Core Tip: Artificial intelligence (AI) has been applied in different fields of medicine to maximize the accuracy of diagnosis and treatment. AI-based navigating systems and surgical robots have helped surgeons to improve their results in terms of safety and efficacy in oncologic surgery. By learning the basis of AI, surgeons can take part in this revolution to optimize surgical care of oncologic disease.

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INTRODUCTION

Artificial intelligence (AI) is defined as the theory and development of computer systems able to perform tasks normally requiring human intelligence, such as visual perception, speech recognition, and decision-making. Machine learning (ML) is a subset of AI. It is based on algorithms inspired by neural networks, developed to be able to learn to solve problems as a human brain would do[1]. A part of ML is deep learning (DL), based on artificial neural networks (ANNs) (such as deep neural networks, deep belief networks, deep reinforcement learning, recurrent neural networks, and convolutional neural networks). In DL, multiple layers of processing are used to extract progressively an higher level of features from data, with the final purpose 'to learn through experience'[2]. AI, ML, and DL are having greater and greater impact in everyday life and health care providing. Being developed faster and more reliably, they are expected to gain a relevant position in diagnostic and thera-peutic processes.

Cancer is still one of the most common causes of death in developed countries, destined to increase due to the global aging of the population[3]. An enormous effort has been made and it is still going on to employ AI and its future developments in cancer diagnosis and treatment, as it is still a huge priority worldwide. Approximately 30 years ago, surgeons witnessed the birth of robotic surgery, which has been constantly improved with AI technologies to improve its efficiency and minimize human mistake. To be truly part of this revolution, surgeons must understand the foundation of AI technologies.

The purpose of this minireview is to show the basis of AI and its subfields and its role in cancer surgery.

METHODS

A MEDLINE search on PubMed was performed. We screened the resulting articles to identify key concepts and techniques within AI, especially leading innovation in the field of oncologic surgery. Thirty-four articles are cited in our minireview, including reviews and meta-analyses.

AI IN MEDICINE

At present, AI is applied to computers and medical robots to mimic human intelli-gence, assisting in drug design, clinical diagnosis formulation, and robotic surgery[4]. In addition, sophisticated AI software is used to produce medical statistical datasets and recognize tumoral cellular patterns for histological diagnoses, including cancer[5].

In medicine, AI has two main branches: Virtual and physical[6]. The virtual component applies DL information management to control electronic health records and guide physicians to take treatment decisions. The physical branch is represented by robots[7]. Robotic systems have been used in surgery since the late 90 s; also robotic assistants are also used in the care of elderly patients and nanorobots are currently being developed to deliver drugs to a specific target[8]. In the next future, this new way to administer chemotherapy will change cancer treatment, improving its efficacy by reducing global toxicity.

Nevertheless, as any new technology introduced in a critical field like healthcare providing, societal and ethical controversies of these new technologies need a special focus on their true utility, economic and environmental sustainability, and constant widening of their applications[9].

SUBFIELDS IN AI: ML, NATURAL LANGUAGE PROCESSING, ARTIFICIAL NEURAL NETWORK, AND COMPUTER VISION

To better understand AI and its role in oncologic surgery, it is crucial to discuss AI's principal subfields and their role in medicine.

ML allows machines to recognize specific patterns and, by doing that, automats can learn and make predictions. Actually, there are two types of ML: Supervised and unsupervised. Supervised ML utilizes partial labelling of the data to predict a known result or outcome. Unsupervised ML, instead, analyses the structure detected in the data itself to find patterns within data[10]. ML is particularly useful to

identify hidden patterns in large datasets. In fact, they can easily detect complex non-linear relationships and multivariate effects compared to conventional statistical analysis[11]. Also, part of ML is reinforcement learning, where accomplishing a task depends on previous success or failure.

Natural language processing focuses on machine's understanding of human language beyond simple word recognition including semantics and syntax. At present, it has been used to analyze large datasets in search of adverse events and postope-rative complications. Moreover, it has found an interesting use in surgery: By analyzing operative reports and postoperative notes, it has been able to elaborate an algorithm that predicts the anastomotic leak after colorectal surgery. Of interest, the software did not only include obvious data like the type of surgery and time to first oral feeding, but also could understand and codify how the patient was described by doctors (weak, irritated, at ease, *etc.*) and include this data in the analyses[12].

ANNs are the base of DL. They get their inspiration from human neural networks. These networks are made of many layers of connections and are able to learn from previous experiences. Based on previous feedbacks, in fact, in-put and out-put patterns change to complete the due task. In clinical practice, these technologies have been proved more accurate than traditional scores in predicting patients' outcomes[13].

Computer vision (CV) is the ability of computers to understand and process images. Its applications in clinical practice are huge and in continuous growth: Computer-aided diagnosis, image-guided surgery, and virtual colonoscopy are only few of the new technologies developed and introduced in everyday medical practice[14].

AI IN CANCER SURGERY

AI technologies, especially the field of DL, have a huge role in cancer diagnosis and treatment. At present, early detection is the key to preventing neoplastic affections to become incurable. The role of AI in the diagnostic field of oncologic affection is well known and widely described in the medical literature. As a matter of fact, DL has been applied to clinical radiology and histopathology to obviate the operator's sensitive level of precision. DL has proved great success rates in imaging pattern recognition, thus the expectations on its future clinical applications have grown exponentially in the last decade. Early results published in the literature showed how DL-based imaging recognition provided superior performances compared to traditional computer-mediated techniques, or in some cases, they were even more accurate than experienced physicians[15].

High impact examples of this are dermatologic software able to perform dermo-scopies to detect melanoma. In the literature, these technologies have been proved to have same accuracy as expert dermatologists[16]. CV has been extensively used in oncologic radiology. Recent studies have demonstrated that AI software is able to interpret mammographic images for breast cancer screening as an expert physician would do[17]. Moreover, computer aided-detection improved by ANN, generated a software program able to detect imaging alterations on computed tomography (CT), like enlarged lymph nodes and suspect colonic lesions for colon cancer early diagnosis[18].

Another interesting cancer-related field in great expansion is automatic histopa-thology analysis. Of interest, in cancer treatment, tissue biomarker positivity (expressed in scores) is essential to plan a chemotherapy schedule. Recently developed DL-based computational approaches can automatically score the presence of a specific biomarker. For example, a recent study demonstrated that the DL-mediated scoring of HER 2 in breast cancer samples was more accurate than the human-mediated scoring and lead to identification of few cases at high risk of misdiagnosis[19].

When explaining the role of AI in histopathology analyses, it is crucial to emphasize how ML-based increased accuracy can influence physicians' therapeutic choices and, therefore, a patients' history. In fact, DL models can recognize high risk cancer lesions at fine needle biopsy with greater accuracy than traditional methods. This can affect surgery too, since the diagnosis of a benign neoplasm can prevent or limit surgical excision, reducing patients' risk of developing complications or carrying impairing lesions. As an example, in an interesting study by Juwara *et al*[20], AI assistance significantly reduced mastectomies by 30.6% by increasing the detection of benign lesions at core biopsy, which usually were diagnosed only after extended surgery.

Surgical resection is often a crucial point in cancer treatment. AI subfield gets employed in computer assisted surgery (CAS), which has entered everyday clinical practice, and has improved its efficiency and efficacy in the management of oncologic diseases that need surgical attention[21]. CV is widely applied in image guidance and navigation, defined as a system designed to assist surgeons on the basis of pre-operative radiological CT images[22]. It is used to easily explore a patient's anatomy, recognize pathologic or noble structures, and plan their removal or sparing. Radiological imaging combined with specific tracking technologies installed in surgical instruments get set on the patient's coordinate system. The machine recognizes and indicates the structures of interest, even when they are hidden, helping surgeons to easily and safely find their way towards their operative targets[21]. At present, image guidance and navigation have found a prolific field of application in neurosurgery and orthopedic surgery, more in general in all kinds of surgery where anatomy do not get subverted by

tissue shifting and organ moving[23]. In these cases, computer-based navigation has found limited application. Great efforts have been made to apply AI surgical navigation techniques to surgeries where plane dissection generates anatomical subversion, like abdominal surgery. As a result, new techniques in study can give insights and orientation for hidden anatomical features, like showing the position of the aorta and the ureter in relation to the instruments in laparoscopic rectal surgery[24]. Another successful example is computer-assisted liver map creation in liver cancer surgery[25]. In future, more structures will be 'mapped' on CT images and will be available for image-guided abdominal surgery like the spleen, pancreas, and esophagus[26,27].

The most popular field of CAS is robotic-assisted surgery. Robotic surgery boasts a 50-year-long history. The use of robotics in the surgery field has been hypothesized around 1964, but it took more than 30 years to finally be approved in medical practice by the United States Food and Drug Administration[28]. Originally, abdominal robotic surgery was thought intended for long-distance trauma surgery in battlefield settings. Since the first 2000 s, when surgical robots became commonly used in worldwide operating rooms, robotic surgery gained more and more popularity. Its advantages, in fact, have been shown in medical studies, international randomised controlled trial, and meta-analyses, winning the trust of the more skeptical physicians[29,30]. At present, the well-known advantages of robotic surgery, like 3-D vision, the elimination of hand tremor, and the expanded degrees of freedom of its tools, led robot-assisted surgery to become frequently used in pelvic surgery, like in prostatectomy and hysterectomy. In recent meta-analyses, robotic prostatectomy was connected to improved urinary function, lower intraoperative complication rates, and improvements in positive surgical margins compared to laparoscopic technique[31]. Thus, there is a chance for robotic prostatectomy to become gold standard for surgical treatment of prostate cancer[32]. Huge expectations rely in the field of robotic surgery. In the next future, assistance systems are expected to be integrated with surgical robots. This imple-mented CV technologies will provide surgeons with answers to their doubts about anatomical structures and resection margins by comparing intra-operative data with millions of inventory images [33].

Again, computer imaging is currently used to create virtual models of surgical fields on which surgeons can be trained to acquire the psychomotor skills and surgical knowledge necessary before operating on real patients. This kind of technology is not only useful to train new generations of surgeons, but in future, 3-D operative simula-tors of patients' specific anatomies will be available. This will be revolutionary in oncologic surgery, allowing the deep anatomical understanding of hardly resectable tumors[34].

Looking at these new technological opportunities, it is easy to predict how the role of AI in oncologic surgery will grow fast and will be applied also to pre- and post-operative phases, aiming to a more patient-targeted type of health care that can minimize mortality and morbidity. As a result, surgeons have a key role in the application of ML and DL in the everyday surgical practice. By understanding the basis of AI, surgeons can be part of the designing process of new machine integrated with AI systems. In fact, by highlighting the surgical point of view and changing their skills to adapt to this new way of delivering clinical care, surgeons can be part of this new way to provide health care that will become more targeted, safer, and always more accurate, improving success rates and reducing mortality and postoperative morbidity.

LIMITATIONS

As a minireview, this article has potential limitations common to all reviews. These include potential bias, like the influence of the authors' personal viewpoints and gaps in literature searching that may lead to the omission of relevant data.

CONCLUSION

AI-based technologies, especially ML and DL, have entered the field of oncology, bringing new perspectives and improving accuracy in different fields. In surgery, new CV system and intra-operative image analyses are currently helping surgeons to be more accurate, reducing human error and improving survival. By learning the basis of AI, surgeons can take part in this revolution to optimize surgical care of oncologic disease.

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AIC mainly publishes articles reporting research results obtained in the field of artificial intelligence in cancer and covering a wide range of topics, including artificial intelligence in bone oncology, breast cancer, gastrointestinal cancer, genitourinary cancer, gynecological cancer, head and neck cancer, hematologic malignancy, lung cancer, lymphoma and myeloma, pediatric oncology, and urologic oncology.

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MINIREVIEWS

Usefulness of artificial intelligence in early gastric cancer

Alba Panarese

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Abstract

Gastric cancer (GC) is a major cancer worldwide, with high mortality and morbidity. Endoscopy, important for the early detection of GC, requires trained skills, high-quality technologies, surveillance and screening programs. Early diagnosis allows a better prognosis, through surgical or curative endoscopic therapy. Magnified endoscopy with virtual chromoendoscopy remarkably improve the detection of early gastric cancer (EGC) when endoscopy is performed by expert endoscopists. Artificial intelligence (AI) has also been introduced to GC diagnostics to increase diagnostic efficiency. AI improves the early detection of gastric lesions because it supports the non-expert and experienced endoscopist in defining the margins of the tumor and the depth of infiltration. AI increases the detection rate of EGC, reduces the rate of missing tumors, and characterizes EGCs, allowing clinicians to make the best therapeutic decision, that is, one that ensures curability. AI has had a remarkable evolution in medicine in recent years, moving from the research phase to clinical practice. In addition, the diagnosis of GC has markedly progressed. We predict that AI will allow great evolution in the diagnosis and treatment of EGC by overcoming the variability in performance that is currently a limitation of chromoendoscopy.

Key Words: Early gastric cancer; Artificial intelligence; *Helicobacter pylori*; Endoscopic submucosal dissection; Dysplasia; Computer-aided; Detection

Core Tip: Early diagnosis and treatment of gastric cancer (GC) can benefit from the introduction of artificial intelligence (AI) into endoscopic diagnostics of the upper digestive tract. AI improves endoscopic diagnosis because it overcomes the difficulty of diagnosis linked to the experience of the endoscopist. Improving endoscopic diagnosis will allow for better treatment, which is more likely to be curative, with submucosal endoscopic dissection or surgery. However, because research advances in this area continue to be rapid, prospective multicenter studies are needed on the application of AI to the diagnosis of early GC.

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THE RELEVANCE DIAGNOSIS OF GASTRIC CANCER

Gastric cancer (GC), the fourth leading cause of cancer in men and seventh in women, is still third for cancer-related deaths worldwide[1]. It's 5-year survival rate is less than 40%[2] and its prognosis is related to the stage at the time of detection. The 5-year survival rate of patients with early gastric cancer (EGC) is 91.5%, whereas it is 16.4% for patients in the advanced stage[2-4]. The screening programs are cost effective in high-incidence regions[1,5] and advanced endoscopic technologies allow endoscopists to diagnose EGC[6-8]; however, optical diagnosis requires a period of training[9].

Recently, the practice of medicine has changed with the development of artificial intelligence (AI) based on image recognition with deep learning (DL) using the convolutional neural network (CNN), which, in upper endoscopy, is trained with endoscopic images and detects GC accurately[10-14]. Several AI-assisted CNN computer-aided diagnosis (CAD) systems have been built, with diagnostic precision in the detection of GC based on different types of endoscopic images. AI helps endoscopists to achieve the accuracy needed for GC screening, surveillance of precancerous, as well as for detecting the depth of invasion of gastric lesions, and when applied to radiological imaging techniques, lymph node and peritoneal metastasis[11-14].

OPTICAL ENDOSCOPIC DIAGNOSIS OF EGC

While computed tomography, endoscopic ultrasound, and positron emission tomography are important for the diagnosis and staging of advanced GC, endoscopy plays an essential role in the early detection of EGC, as it allows the gastric mucosa to be examined directly. Endoscopy with targeted biopsies is the gold standard method for diagnosing EGC, and the accurate diagnosis of EGC through endoscopic imaging is a primary goal for improving the poor prognosis of patients[4,15-17]. Although the quality and accuracy of endoscopic detection are variable between centers and endoscopists, endoscopy is crucial because many early-stage tumors (*i.e.* intramucosal cancer) can be resected endoscopically in a curative manner, with an excellent prognosis at 5 years[4,18,19].

Unfortunately, few endoscopists are experts in advanced endoscopic imaging, and diagnostic accuracy depends largely on the clinical experience of the experts and is influenced by multiple factors, such as training and technologies[9,20]. Ultimately, early diagnosis and curative treatment are important for prognosis but can be difficult to achieve depending on the endoscopist[10,21]. The false negative rate of GC detected by esophagogastroduodenoscopy is 4.6-25.8[22-24], with higher values for inexperienced endoscopists[9,25]. The diagnostic capacity of endoscopists, due to the endoscopic appearance of EGC, which is usually very subtle, varies widely with regard to the differentiation between GC and gastritis, the prediction of the horizontal extension of GC and the depth of invasion [26].

As lesions of the gastric mucosa develop according to the Correa cascade, from atrophy to intestinal metaplasia, intraepithelial neoplasia and invasive neoplasia[27,28]; improving the accuracy of endoscopic diagnosis of precancerous lesions and EGC through screening and surveillance programs, is useful to reduce the incidence and mortality of GC[29-31]. The standard modality for the detection of EGC is endoscopy with white light imaging (WLI), but its overall sensitivity is not satisfactory (40%-60%)[32]. Magnified endoscopy (ME) with image-enhanced endoscopy techniques such as narrow-band imaging (NBI; Olympus Co., Tokyo, Japan), flexible spectral imaging color enhancement (FICE; Fujifilm Co., Tokyo, Japan), and blue laser imaging (BLI; Fujifilm), improve the accuracy of the detection of gastric lesions[26,33,34]. In particular, ME-NBI, the most frequent technology used in AI studies, achieves significantly better sensitivity, specificity, and accuracy than WLI, facilitating examination of the glandular epithelium in the stomach by observing the microvascular architecture and structure of the microsurface[32,35-39].

However, the virtual chromoendoscopic diagnosis of EGC requires considerable skill and experience [9,38,40,41]. The diagnostic effectiveness of endoscopists non yet trained in differentiating EGC from non-cancerous lesions with ME-NBI is disappointing[9,36,41]. Optical diagnosis can improve with AI-assisted CNN, which has been mainly applied to ME-NBI[14].

AI FOR THE DIAGNOSIS OF EGC

AI, which mimics human cognitive function[42] with its efficient computational power and learning capabilities, can be applied to GC because it processes and analyzes large amounts of data with systems that classify and recognize lesion images without the need to write complicated image processing algorithms[43]. Therefore, AI could help gastroenterologists in clinical diagnosis and decision-making. Technically, the DL method approximates complex information using a multilayer system (*e.g.*, CNN), in which neural layers connect only to the next layer (Figure 1), overcoming the limitation of the "black box" of previous systems because it shows the reasons for the decisions made[44]. Over the years, new CNN-based systems have been introduced to analyze lesions of the gastric mucosa, using higher quality images and image selection strategies based on evidence from previous experiences. CNN systems in the initial training phase take a few hours to generate the identification system, which can then be used repeatedly; and has a good adaptability as it can be used on multiple platforms for the real-time analysis of JPEG images or video captured by chromoendoscopy. Magnifying chromoendoscopic images can improve the speed and accuracy of CNN diagnostics compared to conventional endoscopy alone[45, 46]. Typically, training images are judged by experienced endoscopists and pathologically confirmed, and only endoscopic and chromoendoscopic images with appropriate magnification and typical manifestation for learning the CNN model are selected.

In recent studies, other important outcomes have been added to the main outcome to establish endoscopic resectability, namely the identification of the margins and depth of the lesion[47-49]. Gastric tumors of differentiated intramucous type (m) or infiltrating only the superficial layer of the submucosal (≤ 500 μm: Sm^1) can be resected endoscopically, while those that deeply invade the submucosal (> 500 μm: Sm^2) are surgically resected because of the risk of lymph node and distant metastases. The optical differentiation between m/Sm^1 and Sm^2 is often difficult[19].

Using PubMed, Embase, Web of Science, and Cochrane Library databases to search the literature on CAD systems for the diagnosis of EGC, we identified 26 relevant physician-initiated studies through November 2021. Table 1 summarizes the main characteristics of the studies (two single-center prospective[50,51], two multicenter prospective[49,52], and twenty-two retrospective[14,45-48,53-69]): Study design; endoscopic modality; main study aim; and subjects/lesions/images for validation. Table 2 describes the endpoints of the studies.

Selected studies included a diagnostic test on the application of AI in endoscopy for the diagnosis of EGC; the absolute numbers of true-positive, false-negative, true-negative and false-positive; clear information about data and number of images; the description of the algorithms and the process applied to the EGC diagnosis.

To form a training dataset, 11 studies used only WLI images[47,50-53,55-58,60,61], 9 only virtual chromoendoscopy images[48-49,59,63-68], 1 only WLI and chromoendoscopy images[54], and 5 WLI, chromoendoscopy and NBI images[14,45,46,62,69]. The identified studies were largely published in the last 3 years.

Overall, current CNN systems work quite well in detecting the endoscopic/chromoendoscopic characteristics of EGC and other gastric lesions and could provide diagnostic support to experienced and non-expert endoscopists in future practice. AI-assisted CNN CAD systems can avoid subjectivity during the processing and diagnosis of endoscopic/chromoendoscopic images; moreover, in the screening of GC, they work as a "confirmer" or "corrector," providing a second opinion to reduce the diagnostic errors committed by endoscopists and suggesting optimal treatment. Current studies by Asian authors[54,59] confirm that CAD systems detect EGCs and estimate the depth of infiltration and extension, overcoming the problem of operator training and the subjectivity of diagnosis. Moreover, if the first studies report comparable results between experts and CAD systems, the most recent ones show that AI has reached a sensitivity even higher than that of experts, with similar specificity[46]. Over time, images used for CAD system training have improved and, at present, advanced training strategies and videos are being used.

Namikawa *et al*[58] first reported the usefulness of AI systems in GC detection, developing the "original convolutional neural network (O-CNN)," with a relatively low positive predictive value (PPV). The same authors developed an advanced AI-based diagnostic system, "advanced CNN (A-CNN)", by adding a new training dataset to the O-CNN and evaluated its applicability for the classification of GC and gastric ulcer. The diagnostic performance of A-CNN was evaluated retrospectively using an independent validation dataset and compared to that of the O-CNN by estimating the overall accuracy of the classification. The sensitivity, specificity, and PPV rates of A-CNN for the classification of GC at the lesion level were 99.0%, 93.3%, and 92.5%, respectively, and 93.3%, 99.0%, and 99.1% for the classification of gastric ulcers. The overall accuracy of O-CNN and A-CNN in the classification of GC

Table 1 Studies involving computer-aided diagnosis for early gastric cancer detection

Ref.	Study design	Endoscopic modality	Main study aim	Subjects for validation
Kubota *et al*[53], 2012	Retrospective	WLI	Prediction of invasion depth	344 patients
Miyaki *et al*[63], 2013	Retrospective	ME-FICE	Differentiation of cancerous areas from non-cancerous areas	46 patients
Miyaki *et al*[64], 2015	Retrospective	ME-BLI	Differentiation of cancerous areas from non-cancerous areas	95 patients
Kanesaka *et al*[65], 2018	Retrospective	ME-NBI	Delineation of cancerous areas	81 images
Hirasawa *et al*[14], 2018	Retrospective	WLI, CE, NBI	Delineation of cancer	69 patients
Zhu *et al*[54], 2019	Retrospective	WLI, NBI	Prediction of invasion depth	203 lesions
Cho *et al*[50], 2019	Prospective validation dataset	WLI	Differentiation of cancerous areas from non-cancerous areas	200 patients
Ishioka *et al*[55], 2019	Retrospective	WLI	Detection of GC	62 patients
Yoon *et al*[56], 2019	Retrospective	WLI	Detection of GC	800 patients
Tang *et al*[57], 2020	Retrospective	WLI	Differentiation of cancerous areas from non-cancerous areas	279 patients
Namikawa *et al*[58], 2020	Retrospective	WLI	Differentiation of cancerous areas from non-cancerous areas	220 lesions
Li *et al*[66], 2020	Retrospective	ME-NBI	Detection of cancer	341 images
An *et al*[62], 2020	Retrospective	WLI, CE, ME-NBI	Delineation of EGC margins	355 images
Horiuki *et al*[67], 2020	Retrospective	ME-NBI	Differentiation of cancerous areas from non-cancerous areas	258 images
Nagao *et al*[45], 2020	Retrospective	WLI, CE, NBI	Prediction of invasion depth of GC	1084 GC
Wu *et al*[52], 2021	Prospective	WLI	Detection of Blind spotsAnd early gastric cancer	1050 patients
Ueyama *et al*[59], 2021	Retrospective	ME-NBI	Differentiation of cancerous areas from non-cancerous areas	2300 images
Ling *et al*[48], 2021	Retrospective	ME-NBI	Differentiation status and margins for EGC	139 + 58 + 87 EGCs
Ikenoyama *et al*[46], 2021	Retrospective	WLI, CE, NBI	Detection of cancer	140 lesions
Hu *et al*[68], 2021	Retrospective	ME-NBI	Detection of cancer	295 lesions
Oura *et al*[60], 2021	Retrospective	WLI	Missing GC and point out low-quality images	855 lesions + 50 lesions
Zhang *et al*[61], 2021	Retrospective	WLI	Detection of cancer	1091 images
Wu *et al*[51], 2021	Prospective	WLI	Screening gastric lesions	10000 patients
Hamada *et al*[69], 2022	Retrospective	WLI, CE, BLI	Depth of invasion of EGC	68 patients
Nam *et al*[47], 2022	Retrospective	WLI	Lesion detection, differentiation and depth	1366 patients
Wu *et al*[49], 2022	Prospective	ME-NBI	GC and EGC detection, EGC invasion depth and differentiation status	

BLI: Blue laser imaging; CE: Color enhancement; EGC: Early gastric cancer; ME-NBI: Magnification endoscopy; NBI: Narrow-band imaging; WLI: White light imaging.

and gastric ulcer was 45.9% (GC: 100%, gastric ulcer 0.8%) and 95.9% (GC: 99.0%, gastric ulcer 93.3%), respectively, at the lesion level. The A-CNN system can effectively classify GC and gastric ulcer. Yu *et al* [36] explored the diagnostic capacity of the CNN system with ME-NBI to distinguish EGC from gastritis. CNN accuracy with ME-NBI images was 85.3% (220 of 258 images correctly diagnosed). Rates of sensitivity, specificity, PPV, and negative predictive value (NPV) were 95.4%, 71.0%, 82.3%, and 91.7%, respectively. In total, 7 of 151 EGC images were identified as gastritis, while 31 of the 107 gastritis images were recognized as EGC. The overall test speed was 51.83 images/s (0.02 s/image). CNN with

Table 2 Endpoints of the extracted studies

Ref.	Main outcome
[45,53,54,69]	Accuracy rate of diagnosing the depth of wall invasion of gastric cancer
[64]	Detection rate of gastric cancer
[63]	Identification rate of cancerous lesions, reddened lesions and surrounding tissue
[48,62,65]	Detection rate of early gastric cancer and its margins
[14]	Identification rate of gastric cancer and gastric ulcer
[50]	Identification rate of advanced gastric cancer, early gastric cancer, high grade dysplasia, low grade dysplasia and non-neoplasm
[46,51,55,57,59,60,66,68]	Detection rate of early gastric cancer
[56]	Detection rate of early gastric cancer and its localization. Accuracy rate of diagnosing the depth of wall invasion of gastric cancer
[58]	Identification rate of early gastric cancer, advanced gastric cancer and benign gastric ulcer
[67]	Identification rate of early gastric cancer and gastritis
[52]	Identification rate of early gastric cancer and number of blind spots
[61]	Identification rate of early gastric cancer and other gastric lesions (high grade dysplasia, peptic ulcer, advanced gastric cancer, gastric submucosal tumors and normal gastric mucosa)
[47]	Identification rate of early gastric cancer, advanced gastric cancer and benign gastric ulcer. Accuracy rate of diagnosing the depth of wall invasion of gastric cancer
[49]	Detection rate of early gastric cancer. Accuracy rate of diagnosing the depth of wall invasion of gastric cancer

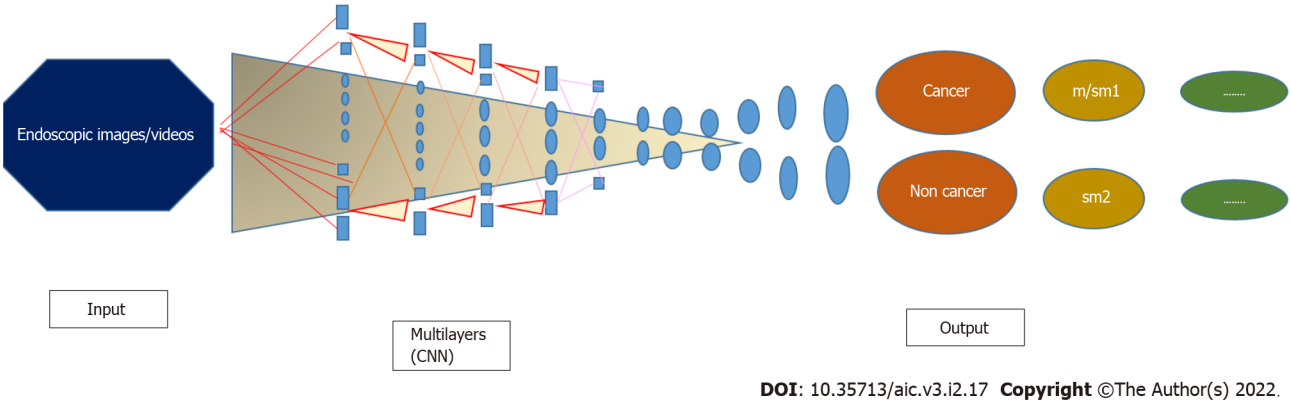

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Figure 1 The multilayer system in the diagnosis of early gatric cancer.

ME-NBI can differentiate between EGC and gastritis with high sensitivity and NPV in a short period of time. Thus, the A-CNN system can complement current clinical practice of diagnosis with ME-NBI.

Nam *et al*[47] have developed and validated CNN-based AI models for lesion detection, differential diagnosis (AI-DDx), and depth of invasion (AI-ID; pT1a *vs* pT1b among EGC). AI-DDx is comparable to experts and outperforms novice and intermediate endoscopists in the differential diagnosis of gastric mucosal lesions. AI-ID performs better than endoscopic ultrasound to assess depth of invasion. Ling *et al*[48] have developed a system to identify in real time with precision with ME-NBI the state of differentiation and delineate the margins of the EGC, fundamental to determine a surgical strategy and achieve the curative resection. In the unprocessed videos of EGC, the system obtained a real-time diagnosis of EGC differentiation and its margins ME-NBI endoscopy. This system has achieved higher performance than experts and has been successfully tested in real EGC videos.

Zhu *et al*[54] represented a further step forward because they developed an algorithm capable of differentiating lesions with Sm^2 invasion depth from m/Sm^1. AI has presented 76% sensitivity and 96% specificity in identifying "Sm^2 or deeper" cancers, resulting in significantly higher sensitivity and specificity than those achieved through visual inspection of endoscopists. The specificity of 96% could minimize the overdiagnosis of invasion, which would contribute to a reduction of unnecessary surgeries for m/Sm^1 cancers.

Wu *et al*[52], in a prospective multicenter randomized controlled trial, developed a CNN system to monitor blind spots during esophagogastroduodenoscopy, updating the previous system

(ENDOANGEL), verifying efficacy in improving endoscopy quality, and pretesting performance in detecting EGC.

Ultimately, AI is even superior to endoscopists experienced in identifying and classifying ECC, eliminates interobserver variability, and can train inexperienced endoscopists. Yet, it must optimize the ability to recognize all lesions (PPV) and not interpret the inflammatory or benign aspects of the mucosa as neoplastic (NPV). Over time, CAD systems have improved image selection strategies with strict criteria, using high-quality data and videos, and eliminating overlearning and misdiagnosis. Videos improve the performance of AI[55] because they represent real-life scenarios, and compared to static images improve PPV and NPV. Regarding the selection of images, gastritis, that is, the presence of inflammation, reduces the performance of AI[14] and endoscopists[70]. The small (diameter ≤ 5 mm) and depressed EGCs, difficult to distinguish from gastritis even for experienced endoscopists, influence the rate of false negatives; and gastritis with redness, atrophy and intestinal metaplasia affects the rate of false positives. In dedicated studies, CAD systems detect *Helicobacter pylori (H. pylori)* infection (sensitivity 89%, specificity 87% and diagnostic time 194 s)[71,72], but, regarding the diagnosis of EGC with AI sistems, we propose to evaluate the gastric mucosa after the eradication of *H. pylori* to reduce the intensity of redness of gastritis.

Integrating in appropriate algorithms, through the intersection of engineering and medical expertise, high-quality image sets, poor images, and images from regular sites, will increase clinical effectiveness. Moreover, the products obtained through collaboration among centers specialized in the diagnosis and treatment of gastric lesions are reproducible and the limitation in applying AI to the diagnosis of EGC is the acquisition of new technologies, which requires investment. Finally, prospective multicenter trials are needed.

CONCLUSION

The application of AI to the clinical practice of the upper digestive tract increases the rate of EGC compared to all GCs, exceeding the subjectivity of the diagnosis and reducing the chance of missing EGCs. AI recognizes those lesions that not even the most experienced endoscopists can detect, as if "illuminating" the images with its third artificial eye. Of course, AI increases the accuracy of endoscopic diagnosis of EGC, especially when combined with the experience of endoscopists. However, since its introduction in this field is very recent, the results in clinical practice must be further validated, considering all possible aspects, both technical and technological concerning endoscopy, and organizational ones.

FOOTNOTES

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Learning models for colorectal cancer signature reconstruction and classification in patients with chronic inflammatory bowel disease

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Abstract

BACKGROUND

In their everyday life, clinicians face an overabundance of biological indicators potentially helpful during a disease therapy. In this context, to be able to reliably identify a reduced number of those markers showing the ability of optimising the classification of treatment outcomes becomes a factor of vital importance to medical prognosis. In this work, we focus our interest in inflammatory bowel disease (IBD), a long-life threaten with a continuous increasing prevalence worldwide. In particular, IBD can be described as a set of autoimmune conditions affecting the gastrointestinal tract whose two main types are Crohn's disease and ulcerative colitis.

AIM

To identify the minimal signature of microRNA (miRNA) associated with colorectal cancer (CRC) in patients with one chronic IBD.

METHODS

We provide a framework of well-established statistical and computational learning methods wisely adapted to reconstructing a CRC network leveraged to stratify these patients.

RESULTS

Our strategy resulted in an adjusted signature of 5 miRNAs out of approximately 2600 in Crohn's Disease (resp. 8 in Ulcerative Colitis) with a percentage of success in patient classification of 82% (resp. 81%).

CONCLUSION
Importantly, these two signatures optimally balance the proportion between the number of significant miRNAs and their percentage of success in patients' stratification.

Key Words: Inflammatory bowel disease; microRNA; Muti-group comparison; Machine learning; Colorectal cancer; Sparse partial least squares-discriminant analysis

Core Tip: This study provides an optimised strategy based on classic learning methods and multi-group variable selection combination from 2600 microRNAs of 225 patients with one chronic inflammatory bowel disease to identify the minimal signature of microRNAs associated with the development of colorectal cancer in these patients.

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INTRODUCTION

The emergence of high-through experiments, image-based analysis and massive sequencing techniques [1-3] has disrupted the way clinicians make decision on a disease therapy. Now the usage of the grade of expertise in their respective do- mains to decide a treatment, frequently considered as a subjective evaluation, is strengthened by an overwhelming capability of support. However, this overabundance of available information does not make their task that straightforward. In this context, the use of interpretable mathematical methods can decipher the underlying complexity of data, generating systemic hypothesis that really help practitioners with their treatment outcomes. In this study, we introduce a learning framework based on a combination between unsupervised hierarchical clustering and weakly supervised classification approaches. These methods are applied to the analysis of a pool with approximately 6000 miRNAs extracted from biopsies of 216 inflammatory bowel disease (IBD) patients with and without colorectal cancer (CRC).

IBD consist of various disorders that cause prolonged inflammation of the digestive tract. Its prevalence rises more and more in the western developed countries[4] largely affecting their health-care systems. Besides that fact, the treatment of such disorders requires an early assessment of the response to the medical treatment[5]. Thus, the finding of a reduced signature optimally predicting the strata a patient will be lying on is of paramount importance during therapy. The main goal of our methodology is using the above approaches to reconstructing a minimal network that stratifies patients with a chronic IBD[5,6] having developed CRC as indicated in[7,8].

Unsupervised hierarchical clustering[5] is a robust method successfully used in the comparison of more than two groups. Particularly, this method enables the identification of biologically meaningful biomarkers, *i.e.* miRNAs, reducing significantly the amount of data in the study. Powered by parse partial least squares discriminant analysis (sPLS-DA) this signature becomes minimal[9] in the description of the required CRC network in IBD. And the later application of random forests (RF)[10] and support vector machines (SVM)[11,12] to the adjusted signature of selected miRNAs ensures the classification of patients is less sensitive to data heterogeneity. Regarding the calibration of classifiers, the performance of each algorithm is assessed by means of leave-one-out (LOO) cross validation[13] and their confusion matrices[14]. Overall this methodology shortens clinicians' efforts, enhancing a reduced set of important features and avoiding unnecessary time delays prior to make any decision on the course of a disease therapy.

Motivation

There exist intra patient differences in miRNA expression between the inflammatory and healthy tissue, between the healthy tissue of an inflammatory and non-inflammatory patient and between the healthy tissue of a cancer and non- cancer colic patient. We want to identify a minimal miRNA profile of developing or not cancer in patients with a chronic inflammatory bowel disease. In other words, a miRNA profile of healthy tissue from patients with chronic IBD with (case) *vs* without cancer (control). In that way, provided a specific miRNA profile is of interest, this one could be prospectively validated, and its predictive marker maybe also developed. Ultimately, this would allow clinicians to in- crease the diagnosis colonoscopy pace in IBD patients where a miRNA profile of risk is detected and conversely

decreasing that pace in patients tagged as at lower risk.

MATERIALS AND METHODS

Samples and mi RNA extractions

Patients were recruited from various public French hospitals for this study. Our sample consists of 225 IBD patients with 75 cases developing dysplasia in colon. These cases matched with 150 controls, *i.e.*, patients with IBD who did not develop dysplasia, yielding a total ratio of 1 case for each 2 controls. The extraction of 6609 miRNAs in each sample resulted from the biopsies of 216 quantified patients. A posteriori, 10 out of these 216 patients were discarded because of their difficulty in extracting miRNAS.

Biological variability

At least 40 biopsies were extracted from each sample during diagnostic chromo-endoscopies in IBD. The anatomopathological grading of inflammation described in[15,16] is adopted on the Hematoxylin Eosin Saffron slide of each sample. To not get affected the miRNA signature by a mucosa inflammation, only the healthy mucosa (non-inflammatory nor dysplastic) corresponding to the grade 0 in GOMES classification was collected. Finally, the absence of histological inflammatory lesion in the mucosa has been considered in preference to the colic segments.

Quality control

Following the Affymetrix hybridisation standards[17], the intensity of miRNA was log2-transformed (Supplementary Figure 1). A first quality control on all miRNA was performed using a principal component analysis (PCA). PCA by[18] allows transforming a set of correlated data, herein their intensity in the gene-chip of Affimetrix GeneChip miRNA 4.0 chips, in a new data set, uncorrelated, by following the top ranked principal components. These components are used as axes of a new space where detect patients with an ambiguous score of intensity, *i.e.*, those intensity outputs generated by unsuitable experimental condition, and exclude them all. Just after one of the two RNA strands becomes functional the miRNA is prepared to participate in intricate biological processes within the cell. This maturation process leads the miRNA to a "steady-state" that provides a more valuable biological information. Thus, we opted for considering only mature transcript miRNAs defined in[19], noted by MIMAT, in the completion of this study. Those transcripts amount to 2578 miRNAs in total. In addition, miRNAs with an average intensity > 8 were also removed being considered as outliers of the overall expression profile.

Technical variability

The Affymetrix Genechip 4.0 encompasses around 36000 probes, more than 6000 of which are humans (each probe corresponds to a complementary sequence of nucleotides). Details on each miRNA and sample are provided by the Affymetrix database. The intensity values of 6609 miRNAs are considered from the 216 patients. Notably, both the RNA extraction and the miRNA technical analysis were performed twice with similar library sizes (see Supplemental Material) detecting a very low bias attributable to a defective sample collection or a poor miRNA quality.

STATISTICAL LEARNING ANALYSIS

Reconstruction of the miRNA signature

Differential expression using general linear models: A first signature of differentially expressed (DE) miRNAs is inferred from general linear models implemented in the limma R-package[20]. During this process we estimate variance for other miRNAs, weight to incorporate unequal variations in data, and pre-process to reduce noise.

Multiclass DE analysis: The signature identified by linear models returned an amount of miRNAs larger than expected to be considered in practice as biologically significant. We decided, then, to reduce the size of miRNA signature by means of a multi-group comparison strategy. Firstly, we cal- culated the mean expression of each miRNA according to the four analysed groups [*i.e.*, Ulcerative colitis (UC) and Crohn's disease (CD) cases and controls respectively]. Next, we construct the tree related groups. Thus, we assume an underlying tree structure to compare groups based on recursive binary splits along the tree. Then each mean expression was compared, using a simple *t* test as in[21]. Any miRNA with a significant *t* test (*i.e.*, threshold = 0.005) was included in the final model.

We propose different strategies to test in pairwise all the possible combinations of groups: (1) Use the CD patients or the UC patients exclusively; and (2) Use each one of the groups to construct the tree (Figure 1 and Table 1): (1) Strategy 1: Comparison between the CD controls and the three remaining leaves (UC controls, CD cases and UC cases), then UC controls compare to CD cases and UC cases, *etc.*;

Table 1 Possible comparisons to be made during the unsupervised (*i.e.*, we do not rely on the type of disease) global analysis of patients following the considered three different strategies

Strategy	Comparison
Strategy 1 (classic)	1 *vs* (2,3,4)
	2 *vs* (3,4)
	3 *vs* 4
Strategy 2 (1&1)	1 *vs* 2; 1 *vs* 3; 1 *vs* 4
	2 *vs* 1; 2 *vs* 3; 2 *vs* 4
	3 *vs* 1; 3 *vs* 2; 3 *vs* 4
	4 vs 1; 4 *vs* 2; 4 *vs* 3
Strategy 3 (pairwise)	1 *vs* (2,3,4)
	2 *vs* (1,3,4)
	3 *vs* (1,2,4)
	4 *vs* (1,2,3)

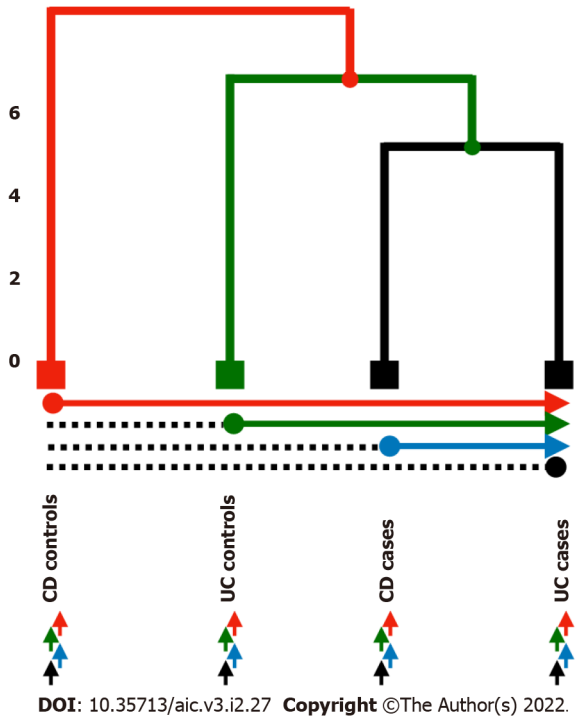


Figure 1 Pairwise leaves comparison to be tested. Hierarchical structure amounts to strategy 1 while horizontal and bottom arrows describe strategies 2 and 3 respectively. Highlighted in red, green, blue, and black the 4 possible comparisons amongst group of patients. UC: Ulcerative colitis; CD: Crohn's disease.

(2) Strategy 2: Comparison between each leaf and the others; CD controls compare to UC controls, CD cases and UC cases, then UC controls compare to CD controls and cases, and UC cases, and so on; and (3) Strategy 3: Comparison among leaves one by one; CD controls compare to UC controls, then CD controls compare to CD cases, and so on.

Upon setting the methodology, we analyse two related data set in tandem. Initially, we applied the method only to the miRNA labeled as MIMAT; to repeat the same approach, on a second occasion, with a set of 152 miRNAs previously selected by sparse PLS Discriminant Analysis (sPLS-DA).

In brief, PLS is an exploratory variable selection technique successfully proven in classification[22]. In particular, the sPLS-DA[9] is an extension of PLS applied in multi-class classification. It selects the most discriminant variables to classify patients, using Lasso penalization. By means of the mixOmics R package[23] three components of miRNAs were identified to predict cancer in all patients. The number of selected variables for each of the three components was chosen based on the lowest average balanced classification error rate with centroids after tuning of the sPLS-DA model using the selected number of

components and 5-fold cross-validation with 10 repeats. The linear programming problem associated with sPLS-DA may be succinctly described as:

Where $\min_{u_i,v_i}||M_i - u_i v\prime_i||_F^2 + P_\lambda\ u_i$, is applied component-wise in the vector $P_\lambda(u_i) = sign(u_i)(|u_i| - \lambda)_+$ (*i.e.*, the left singular vector from the Singular Value Decomposition (SVD) of the miRNA matrix expression M) and acts as the relaxed thresholding function that scales the Lasso penalty functions[24]. Thus, λ is the penalization parameter to tune.

Each sPLS-DA axe is constructed by a convex linear combination of a miRNA. Hence, the coordinate of any given patient on that axe is described by:

$$\sum_{i=1}^{N} \alpha_i \times\ miRNA_i$$

Then applying the majority vote criterion, any given individual having been calculated to have a probability > 0.5 in at least 2 out of 3 PLS-DA axes is considered misclassified.

Classification of patients

In an early exploratory classification, we based our results on the Euclidian distance of miRNA intensities across patients. Nevertheless, the high sensitivity of the Euclidean-based norm to heterogenous data and non-linearity produced a poor classification (Supplementary Figure 2). Anyway, this first classification definitively clued us in on the miRNA signature's optimisation. Next, to prevent the non-linear effect of our measurements in classification, we contemplated the employment of learning methods. Thus, the main purpose random forests and support vector machines pursue is the reconstruction of a minimal CRC network that could lead to optimally stratify the IBD patients evaluating the associated miRNA signature. These two methods are powerful tools to predict patients developing CRC that perform well in different classification issues. Briefly, RF is a machine learning method for classification based on decision tree and probabilities, introduced in[10], whereas SVM is a strong classifier with the aim of finding the optimal separation hyperplane of data by maximising the margin [25]. A total of 5,000 trees were conducted for RF analysis. The SVM was implemented using a linear kernel, *i.e.*, $\mathrm{K}(\mathrm{x}_i, x_j) = exp\left(\frac{-\|x_i - x_j\|^2}{2\sigma^2}\right)$ with bandwidth and including soft-regularisation with Sequential Minimal Optimization (SMO) as solver to find the optimal hyperplane well separating classes. The general out- put of a binary SVM classifier can be computed by the following expression:

$$y = sign\left(\sum_{i=1}^{N} \alpha_i y_i K(x_i, x_j) + b\right)$$

where $\alpha_i \geq 0$ are Lagrangian multipliers obtained by solving a quadratic optimisation problem, b is the bias, and K is the above defined kernel function. We evaluated the performance of each patient's classification using cross-validation with the LOO method. The RF classification was performed using the *randomForest* function of the *random-Forest* R-package[26]. Complementary, the variable importance (VIMP) of each miRNA for RF[27] was also calculated using the *varImp* and *varImpPlot* functions of the same pack- age. The Matlab© classification app implemented the SVM analysis and results are confirmed using *svm* function of the e*1071* R-package.

Performance evaluation of classification methods

We evaluate how optimal a miRNA signature is by means of its confusion matrix, using the *confusionMatrix* function of the *caret* R-package[28], and the so-called Receiver Operating Characteristic (ROC) curve along the calculus of its area under curve (AUC) using the *plotROC* R-package[29]. Percentage of true classification, sensibility, specificity, and the AUC were also calculated for each strategy using these two packages.

In summary, all the calculations of the statistical learning analysis were implemented using in-house scripts based on R and Matlab© (2014a, The MathWorks Inc., Natick, MA), and figures were depicted with *ggplot2* R-package.

RESULTS

A previous work of denoising is required if we want to reduce possible issues of bias and overfitting in our algorithms. Thus, the analysis was performed on 206 patients; excluding 4 patients considered as outliers, and 6 unmatched controls with cases. In addition, 101 miRNAs were removed since their expression was higher than 8. These miRNAs highly influenced to broke inconsistently down large clusters in the construction of tree and though considered as outliers. Yet, note that the unsupervised clustering can be biased by the lack of linearity in data. Hence, the way we use the hierarchical classification is limited to track a definite signature trend to be further learned by more robust methods. The best result was always obtained by the strategy 1. For clarity, we only show those results yielded by

Table 2 Summary of patients' classification predicted by random forests/support vector machines respectively. From left to right: Group of patients, amount of selected miRNA, percentage of success in true positive classification, sensitivity, specificity and their area under the curve

Methods	Nº miRNA	% True classification (95%CI)	Sensitivity	Specificity	AUC
All miRNA					
Strategy 1	56	69 (62-75)/69 (62-75)	0.25/0.43	0.93/0.83	0.76/0.74
CD	9	87 (78-93)/86 (77-92)	0.70/0.73	0.96/0.93	0.89/0.92
UC	30	72% (63-80)/76 (67-83)	0.45/0.55	0.86/0.87	0.77/0.81
miRNAs selected by sPLS-DA					
Strategy 1	11	69 (62-75)/68 (62-75)	0.36/0.36	0.87/0.86	0.72/0.74
CD	5	80 (70-88)/82 (67-86)	0.67/0.60	0.87/0.87	0.84/0.86
UC	8	73 (64-80)/81 (73-88)	0.48/0.57	0.86/0.93	0.73/0.81

AUC: Area under curve; CD: Crohn's disease; UC: Ulcerative colitis.

Table 3 All patients contingence matrix of the 56-selected miRNAs by means of random forests and support vector machines methods

Predicted by RF Predicted by SVM					
		Cases	Controls	Cases	Controls
True	Case	18	54	31	41
	Controls	10	124	23	111

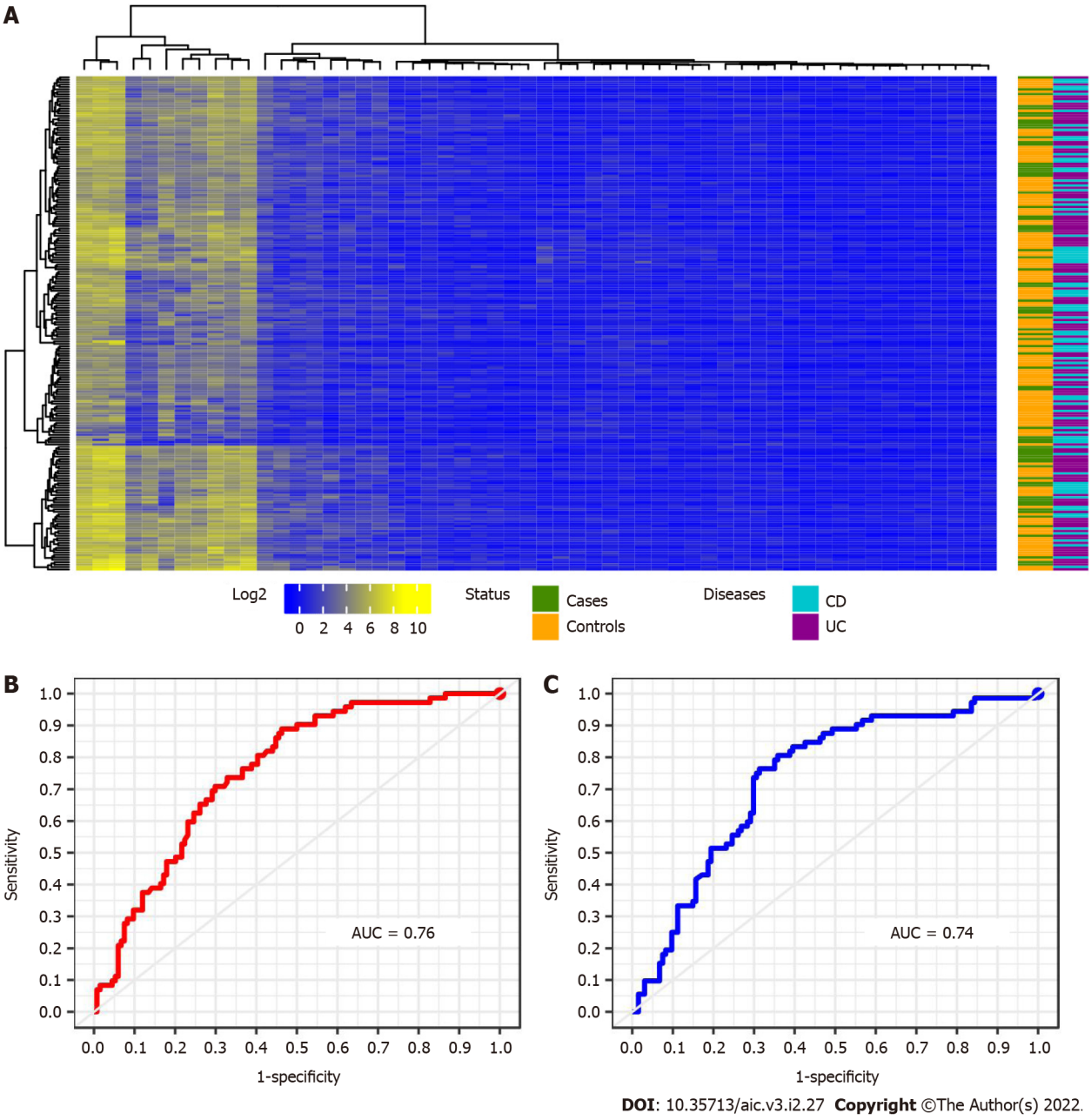
RF: Random forests; SVM: Support vector machines.

means of this strategy. We address to supplemental material for further details on the other two remaining strategies (Supplementary Figures 3-5 and 7-8). Naturally, the performance of this approach depends on each initial tree re- construction. The Table 2 summaries patients classification performed by all the methods using the strategy 1.

The overall signature associated with CRC

A priori, one would expect to find here a tree with two well separated branches making distinction between CD and UC patients. Nevertheless, the tree this first comparison returned describes a structure composed of three branches that mixes up cases with controls. Hence, the primary leaf groups the CD cases, the second one binds UC cases together, whereas the third leaf consists of control patients. See Supplementary Figure 1 to visualise the tree corresponding to the analysis of all the IBD patients.

Strategy 1: When this first strategy is considered, we are able to identify 56 miRNAs whose expression is differential between the CRC cases and controls. Those miRNAs are potentially good candidates to be associated with a CRC network that can achieve an optimal stratification of patients. A heatmap enhancing these miRNAs are depicted below in Figure 2. However, data heterogeneity and non-linearity negatively influence the measures captured by our multi-class strategy producing a poor stratification performance when re- constructing the sought minimal CRC network. To overcome such an obstacle, we keep using the selected miRNAs, but applied to classifiers such as RF and SVM which are more robust in presence of non-linear heterogeneous data. This combination enables better learning how patients stratify according to CRC. In that way, we attained to correctly classify the 69% of patients by means of RF and using linear SVM (see Table 2 and Figure 2B and C). However, the SVM performance overtakes at large that one given by RF in every case of patient stratification. Notice the large number of selected miRNAs in this first analysis. For clarity, the VIMP analysis shown in Supplementary Figure 6A only discloses the top 30 miRNA. The results obtained in the performance of patients' classification is represented as a confusion matrix in Table 3. In general control patients were correctly classified, but a remarkable number of cases was muddled with controls. This situation can be explained by the, pointed out in the literature, divergent genetic source of the two types of IBD. The ROC curve displayed in Figure 2B and C reported sensitivity-specificity ranges of 0.25-0.93 and 0.43-0.83 associated with RF and SVM respectively (Table 2).



DOI: 10.35713/aic.v3.i2.27

Figure 2 All patients hierarchical and leaning performance. A: Heatmap of the 56- selected miRNA intensity. Colour corresponding to the status of the patients: Purple: Ulcerative colitis patients; light blue: Crohn's disease patients; green: cases and yellow: Controls; B: Receiver operating characteristic curve for the classification using random forests analysis; C: Using L-SVM models for the 56 selected miRNA. AUC: Area under the curve.

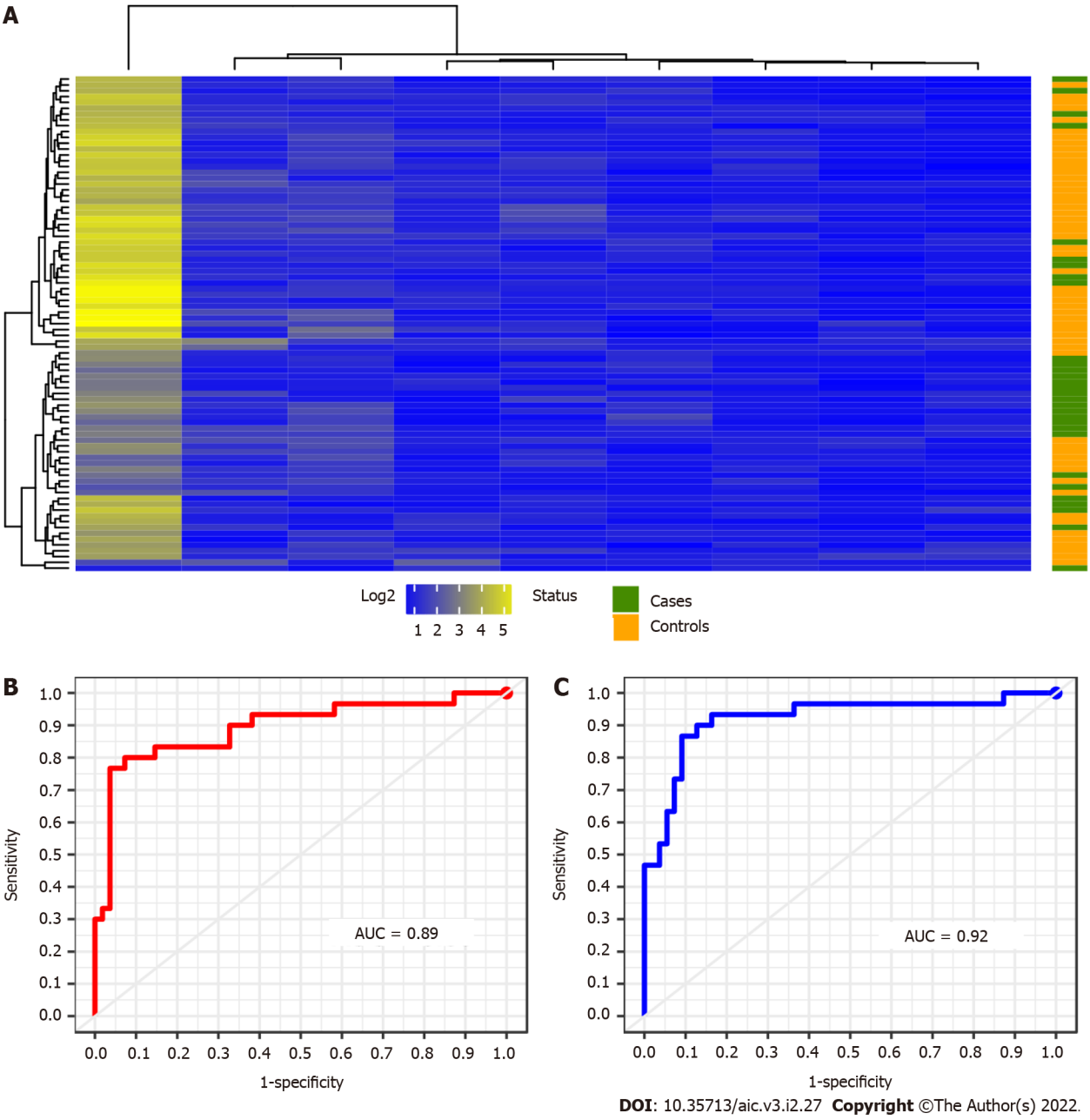
Constructing the local signature of CD patients

For this analysis we provide a sample data composed of 85 patients with CD, whose 30 are cases and 55 controls. As observed in panel (A) of Figure 3, we detect 9 miRNAs differentially expressed between cases and control in CD patients. But the use of the Euclidian distance misleads their percent- age of classification as occurred in the previous case-control study. The results obtained by the above indicated RF and SVM learning methods may be observed in Figure 3B and C and Table 2. The variable importance of each miRNA is also considered to simplify the calibration of the RF models (data not shown, see Supplementary Figure 6B). Moreover, their associated sensitivity-specificity ranges are 0.70-0.73 and 0.96-0.93 to RF and SVM respectively (Table 2). With these selected miRNAs, patients are correctly classified in the 87% and 86% of cases. These percentages are also shown in terms of a confusion matrix in Table 4. The adopted non supervised - supervised strategy returns rather good candidates to conform the network associate to CRC in IBD also providing the signature with an accurate predictive ability.

Table 4 Contingence matrix of the 9-selected miRNA and random forests methods for Crohn's disease patients

Predicted by RF		Predicted by SVM			
		Cases	Controls	Cases	Controls
True	Case	21	9	22	4
	Controls	2	53	8	51

RF: Random forests; SVM: Support vector machines.



DOI: 10.35713/aic.v3.i2.27

Figure 3 Crohn's disease patients hierarchical and leaning performance. A: Heatmap of the 9-selected miRNA intensity. Colour corresponding to the status of the patients: Purple: green: Cases and yellow: Controls; B: Receiver operating characteristic curve for the classification using random forests analysis; C: Using L-SVM models for the 9 selected miRNA. AUC: Area under the curve.

The local signature of UC patients

To identify a significant signature of UC patients we analysed a data set of 121 individuals. These patients are distributed in 42 cases and 79 controls respectively. Upon applying the previous approach to these samples, a signature of 30 miRNAs differentially expressed between cases and control in UC

was detected. The results derived from this calculation are plotted below in Figure 4.

As occurred with the two previous results, see Figure 2 and Figure 3, the presence of data heterogeneity hampers a right classification of patients when using the Euclidean norm across the expression profile of the detected 30 miRNAs. Additionally, the classification results yielded by the two learning methods used in this work are displayed by their ROC curves in Figure 4B and C. These curves attain a sensitivity-specificity ranges of 0.45-0.86 and 0.55-0.87 to RF and SVM respectively. And the miRNAs selected by multiple comparison of the annotated miRNAs achieved a percentage of success in classification of 76% across the mean expression of each group of patients. These amounts are slightly lower than in CD patients. Such a drop can be explained by a more scatter matching distribution among UC patients as well as a greater control-case ratio. The confusion matrix corresponding to this calculation is introduced above in Table 5.

Minimising the size of the overall signature by parse PLS discriminant analysis

Despite the relative low size of the prognostic signature identified so far, we wonder if it was possible to minimise the amount of miRNAs involved in the analysis without harming the overall classification performance. The statistical robustness of the parse PLS Discriminant Analysis in supervised feature selection makes us to consider its application before performing the unsupervised hierarchical clustering introduced in methods. The stratification of all patients is plotted in Figure 5A while Figure 5B describes the diseases tree architecture. The synergy between the two complementary statistical methods, supervised later unsupervised, still allow us to conclude the predictive power of the miRNAs minimal signature associated with CRC in IBD.

Reconstructing the overall signature: After having applied the proposed sPLS-DA to the miRNAs, the reconstruction of the tree structure based on the multi-class comparison strategy 1 improved the previous classification of patients between clusters (Figure 5B). The analysis of patients following such architecture resulted in a final signature composed by 11 miRNAs. Hence, these selected miRNAs correctly classified the 69% and 68% of cases (RF and SVM respectively). Both percentages are similar in accuracy to those obtained without the use of sPLS-DA, but with a signature consisting of only 11 out of initial 56 miRNAs. Nevertheless, the effect of the genetic drift of CD and UC origin could not have been prevented. We also provide the overall performance of the methods as a confusion matrix in the Table 6. For further details on the variable importance of this signature in the RF calculation see supplemental information (Supplementary Figure 9A).

Reconstructing the local signature of the CD patients: In this analysis 5 miRNAs were selected with the recursion cluster for CD patients. The SVM allows a better classification of true patients in the 82% of cases, and particularly the controls patients. The RF and SVM performances along their feature selection refining are presented in Figure 6B. See supplemental material for details on variable importance for each miRNA (Supplementary Figure 9B) of the RF computation. We also obtain their patients classification in a confusion matrix presented in Table 7. The accuracy and sensitivity are consistent with the above percentage of classification in CD patients reducing the signature in 4 miRNAs up to a final figure of 5 predictive profiles.

Reconstructing the local signature of UC patients: The overall signature of UC patients after making use of sPLS-DA was composed of 8 miRNAs. We also calibrated models by feature selection of these miRNAs, which results are shown in the Figure 6C. The attained percentage of success goes to the 81% upon computation of a SVM model across UC samples what improved the RF performance as had already occurred with previous counterpart calculations. For further details on the RF analysis see Supplementary Figure 9C. Strikingly the use of sPLS-DA enabled reducing the quantity of miRNAs required to predict UC patients developing or not CRC from 30 to 8 while increasing in a 5% the percentage of success. This may be due to the detection and later removal of features largely contributing to the dispersal form of the matching distribution among UC patients. Finally, the confusion matrix corresponding to this miRNAs signature is described below in Table 8.

DISCUSSION

The soundness of the signature has been improved accordingly to the incremental combination of learning methods presented in this study until attaint a sensitivity of 73% in CD and 57% in UC with a specificity of 87% and 93% in CD and UC respectively (see Table 2). These results are depending on the assumption of an initial hierarchical tree structure. The usage of PLS-DA decreases a bit its global sensitivity but gaining more in CRC signature optimisation. Noteworthy, the final overall signature is composed by only 5 miRNAs in CD and 8 in UC. These miRNAs are molecules extremely resistant and highly preserved. In general, low percentages of true classification are obtained is no difference on disease type is made on the IBD patients. This is in accordance with previous works that suggest the genetic divergence between CD and UC. However, if we consider the two types of the disease separately, the aim of classifying false controls, i.e., controls with a closer profile to cases and

Table 5 Contingence matrix of the 30-selected miRNA and random forests methods for Ulcerative colitis patients

Predicted by RF	Predicted by SVM				
		Cases	Controls	Cases	Controls
True	Case	19	23	23	19
	Controls	11	68	10	69

RF: Random forests; SVM: Support vector machines.

Table 6 Contingence matrix of the 11-selected miRNA and random forests methods for all patients

Predicted by RF	Predicted by SVM				
		Cases	Controls	Cases	Controls
True	Case	27	45	26	46
	Controls	18	116	19	115

RF: Random forests; SVM: Support vector machines.

Table 7 Contingence matrix of the 5-selected miRNA and random forests methods for Crohn's disease patients

Predicted by RF	Predicted by SVM				
		Cases	Controls	Cases	Controls
True	Case	20	10	20	10
	Controls	7	48	5	50

RF: Random forests; SVM: Support vector machines.

Table 8 Contingence matrix of the 9-selected miRNA and random forests methods for Ulcerative colitis patients.

Predicted by RF	Predicted by SVM				
		Cases	Controls	Cases	Controls
True	Case	20	22	24	18
	Controls	11	68	5	74

RF: Random forests; SVM: Support vector machines.

monitoring whether those samples are developing cancer can be approached now. Indeed, the introduced methodology would allow us to provide the identified molecular signature with predictive power. Additionally, the eventual availability of a second independent cohort could improve possibly the precision of results. Thus, we claim that in any case a clinician having this information will potentially benefit from an accurate prediction tool of prognosis rather than only using his or her own experience-based criteria[30,31]. This clinical scenario enhances the paramount importance of statistical learning-based applications in clinical practice since CRC is a feared life-threatening factor among patients with IBD[32,33]. In particular, the analysis of eventual miRNAs signatures associated with CRC in patients with IBD has been successfully proven previously in such contexts[34-36]. That way, these methodologies will contribute to shorten unnecessary delays prior to make any decision on a proper therapy in individuals with a IBD developing CRC[37,38].

CONCLUSION

In this study we provide a wise combination of statistical learning methods for patients' stratification

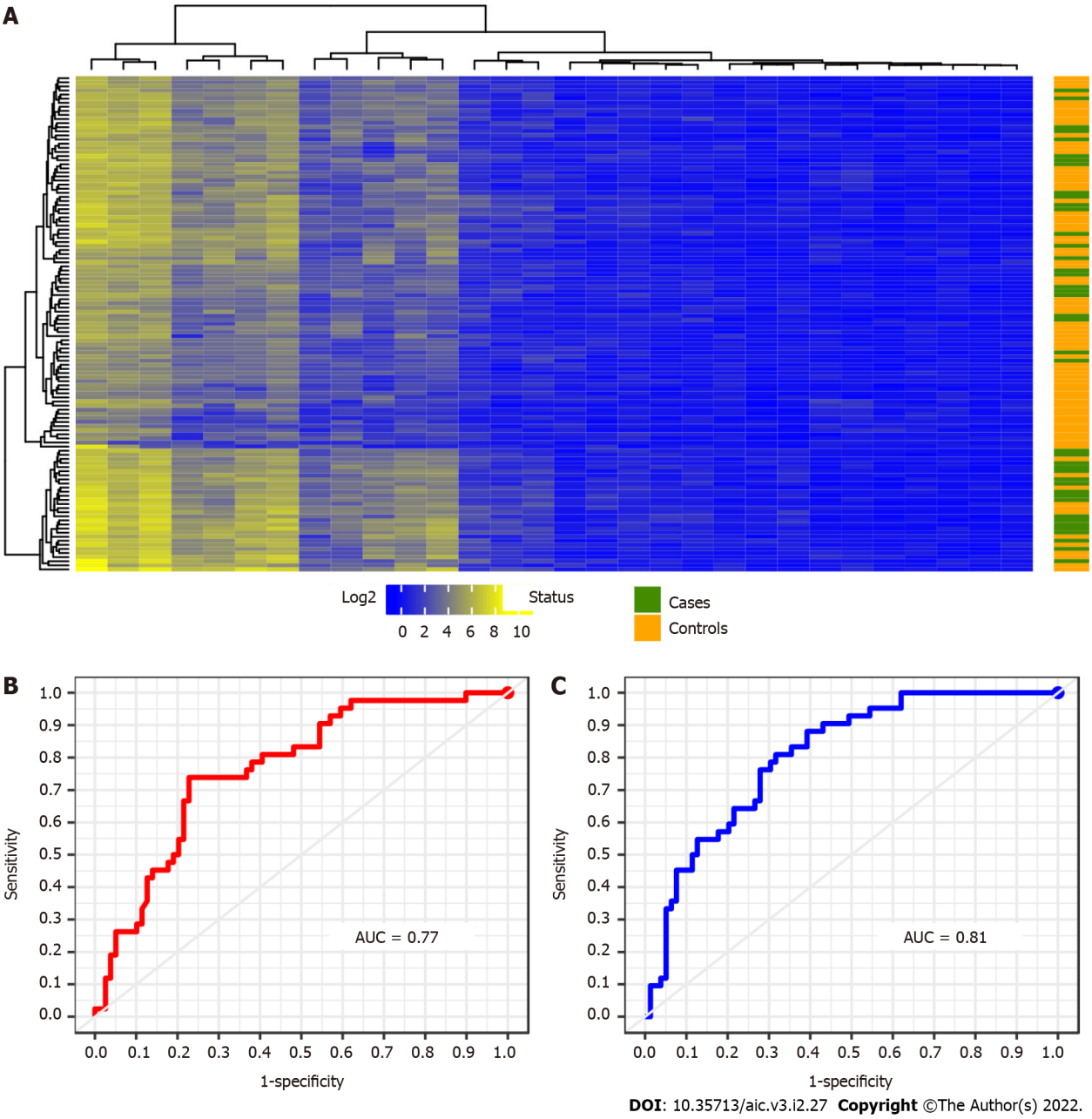


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Figure 4 Ulcerative colitis patients hierarchical and leaning performance. A: Heatmap of the 30-selected miRNA intensity. Colour corresponding to the status of the patients: Purple: Green: Cases and yellow: Controls; B: Receiver operating characteristic curve for the classification using random forests analysis; C: Using L-SVM models for the 30-selected miRNA. AUC: Area under the curve.

based on biologically meaningful characteristics, and its application in IBD based on a minimal miRNA network associated with CRC is demonstrated. The time constraint affecting the assessment of the response to the medical treatment indicates the interest of our method in improving the classification accuracy, minimising the signature of miRNAs required in the IBD patients' stratification, and avoiding unnecessary time delays. The findings are also consistent with the physio-pathological knowledge. Comparison with other existing classifying method shows that SVM makes our method yields better mean performances, using a reduced miRNA signature and reporting a much lower sensitivity to data heterogeneity. The application of the proposed method to a multi-class classification further points out the robustness and efficiency of our strategy particularly in the CD and UC group of patients. Additionally, the use of parse PLS Discriminant Analysis is also concluded for a minimal signature with accurate enough performances. In the next future, we will combine this method with other approaches such as deep learning methods enabling more intricate relationships between the elements of the signature and possibly another robust clinical data. Finally, we are convinced our methodology will be also instrumental for other diseases broadening the general framework herein provided.

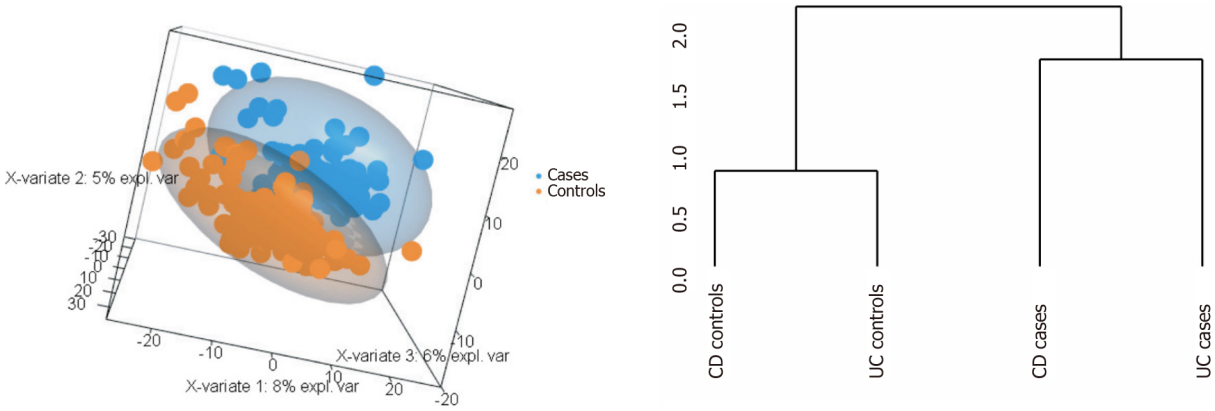

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Figure 5 Partial least squares discriminant analysis base. Left-hand side panel: Patient-control stratification (*i.e.* orange-blue) in three dimensional view with 152 miRNAs; Right-hand side panel: Classification tree with the 152 miRNAs selected by sPLS-DA.

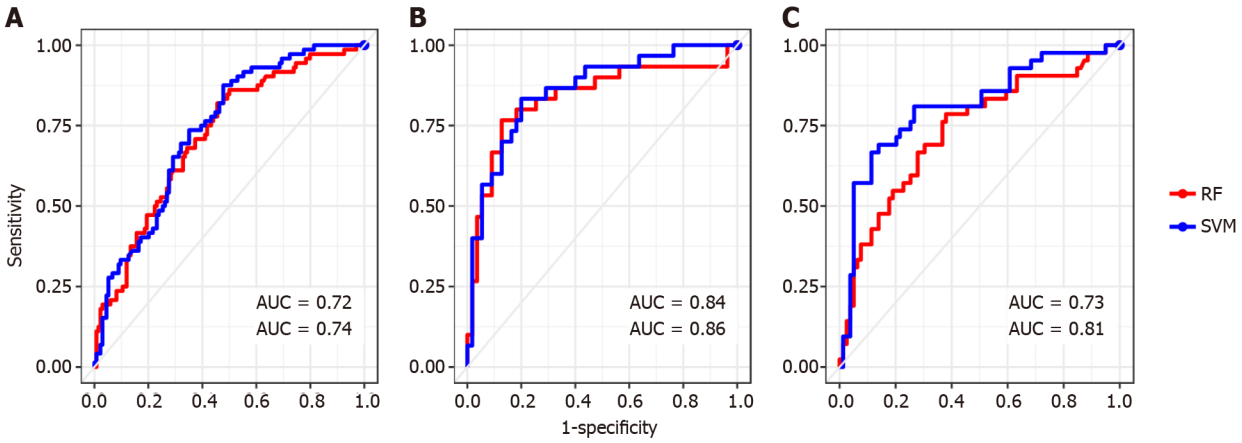

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Figure 6 Final performance of each reconstructed sub-signature. A: Receiver operating characteristic curve amounts to all patients learned classification by a signature corresponding to 13 selected miRNA; B: Similarly to the Crohn's disease patients classification of 5 selected miRNA; C: Ulcerative colitis patients classified according to 9 selected miRNA.

ARTICLE HIGHLIGHTS

Research background

Face the overabundance of information, it is not easy to clinicians discriminating amid biological indicators that potentially could be helpful during an inflammatory bowel disease (IBD) disease therapy.

Research motivation

There exist intra patient differences in miRNA expression between the inflammatory and healthy tissue, between the healthy tissue of an inflammatory and non-inflammatory patient and between the healthy tissue of a cancer and non- cancer colic patient. We want to identify a minimal miRNA profile of developing or not cancer in patients with a chronic inflammatory bowel disease. In other words, a miRNA profile of healthy tissue from patients with chronic IBD with (case) *vs* without cancer (control). In that way, provided a specific miRNA profile is of interest, this one could be prospectively validated, and its predictive marker maybe also developed. Ultimately, this would allow clinicians to in- crease the diagnosis colonoscopy pace in IBD patients where a miRNA profile of risk is detected and conversely decreasing that pace in patients tagged as at lower risk.

Research objectives

In this scenario, the identification of an optimal signa- ture, for example composed by microRNA (miRNA), associated with colorectal cancer (CRC) in patients with one chronic IBD is of vital importance.

Research methods
We provide a framework of well-established statistical learning methods (*i.e.*, RF, SVM, PLS-DA, ...) wisely adapted to reconstructing a CRC network leveraged to stratify these patients.

Research results
Our strategy provides an adjusted signature of 5 miRNAs with a percentage of success in patient classification of 82% in Crohn's disease (resp. 81% in Ulcerative Colitis).

Research conclusions
The application of the proposed method to a multi-class classification further points out the robustness and efficiency of our strategy particularly in the CD and UC group of patients. Additionally, the use of parse PLS Discriminant Analysis spots a minimal signature with accurate enough performances.

Research perspectives
In the next future, the combination of this method with deep learning models will enable more intricate relationships between the elements of the signature and possibly another robust clinical data. Finally, we are convinced our methodology will be also instrumental for other diseases broadening the general framework herein provided.

FOOTNOTES

Author contributions: Morilla I conceived and designed the computational experiments; Abaach M and Morilla I performed computational experiments, analyzed the miRNomic data, performed formal analysis; Morilla I wrote the original manuscript Abaach M and Morilla I reviewed and edited the manuscript.

Institutional review board statement: The protocols involving human participants conformed to the local Ethics Committee (CPP-Île de France IV No. 2009/17) and to the principles set out in the WMA Declaration of Helsinki, and the Belmont Report from the Department of Health and Human Services. Human ileal biopsies were obtained from the IBD Gastroenterology Unit, Beaujon Hospital and a written informed consent was obtained from all the patients before inclusion in the study.

Institutional animal care and use committee statement: The protocols involving human participants conformed to the local Ethics Committee (CPP-Île de France IV No. 2009/17) and to the principles set out in the WMA Declaration of Helsinki, and the Belmont Report from the Department of Health and Human Services. Human ileal biopsies were obtained from the IBD Gastroenterology Unit, Beaujon Hospital and a written informed consent was obtained from all the patients before inclusion in the study.

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The primary aim of *Artificial Intelligence in Cancer* (*AIC*, *Artif Intell Cancer*) is to provide scholars and readers from various fields of artificial intelligence in cancer with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

AIC mainly publishes articles reporting research results obtained in the field of artificial intelligence in cancer and covering a wide range of topics, including artificial intelligence in bone oncology, breast cancer, gastrointestinal cancer, genitourinary cancer, gynecological cancer, head and neck cancer, hematologic malignancy, lung cancer, lymphoma and myeloma, pediatric oncology, and urologic oncology.

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MINIREVIEWS

Building and evaluating an artificial intelligence algorithm: A practical guide for practicing oncologists

Anupama Ramachandran, Deeksha Bhalla, Krithika Rangarajan, Raja Pramanik, Subhashis Banerjee, Chetan Arora

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Abstract

The use of machine learning and deep learning has enabled many applications, previously thought of as being impossible. Among all medical fields, cancer care is arguably the most significantly impacted, with precision medicine now truly being a possibility. The effect of these technologies, loosely known as artificial intelligence, is particularly striking in fields involving images (such as radiology and pathology) and fields involving large amounts of data (such as genomics). Practicing oncologists are often confronted with new technologies claiming to predict response to therapy or predict the genomic make-up of patients. Understanding these new claims and technologies requires a deep understanding of the field. In this review, we provide an overview of the basis of deep learning. We describe various common tasks and their data requirements so that oncologists could be equipped to start such projects, as well as evaluate algorithms presented to them.

Key Words: Artificial intelligence; Precision medicine; Radiomics; Deep learning

Core Tip: Designing projects and evaluating algorithms require a basic understanding of principles of machine learning. In addition, specific tasks have specific data requirements, annotation requirements, and applications. In this review, we describe the basic principles of machine learning, as well as explain various common tasks and their data requirements and applications in order to enable practicing oncologists to plan their own projects.

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INTRODUCTION

Artificial intelligence (AI) has touched many areas of our everyday life. In medical practice also, it has shown great potential in several studies[1]. The implications of use of AI in oncology are profound, with applications ranging from assisting early screening of cancer to personalization of cancer therapy. As we enter this exciting transformation, practicing oncologists in any sub-field of oncology are oftentimes faced with various studies and products claiming to achieve certain results. Verifying these claims and implementing these in clinical practice remain an uphill task.

This is an educational review, through which we will attempt to familiarize the reader with AI technology in current use. We first explain some basic concepts, in order to understand the meaning of techniques labelled as AI, and then move into explaining the various tasks that can be performed by AI. In each we provide information on what kind of data would be required, what kind of effort would be required to annotate these images, as well as how to assess networks based on these tasks, for the benefit of those oncologists wishing to foray into the field for research, or for those wishing to implement these algorithms in their clinical practice.

WHAT IS ARTIFICIAL INTELLIGENCE: BASIC PRINCIPLES

AI is a broad, non-specific term referring only to the "intelligence" in a specific task performed, irrespective of the method used. Machine learning (ML) is a subgroup of AI, and deep learning (DL) is a further subgroup of ML, which are data-driven approaches. Unlike traditional software engineering where a set of rules is defined upon which the computer's outputs are based, ML involves learning of rules by "experience" without "explicit programming"[2,3]. What this means is that given large amounts of data which includes a set of inputs and the ideal outputs (training data), the task of ML is to understand a pattern within this set of inputs which results in outputs closest to the ideal output (Figure 1). The process of training the model is explained in Figure 2.

To understand this in medical terms, say the task of an AI system is to predict the survival of patients, given the stage of a particular tumour. If we were to use traditional software engineering, we would have to feed the median survival for each stage into the model, and teach the model to output the number corresponding to a particular stage. Whereas in case of a ML model, we would simply give as input, the stage and survival information of a few thousand patients. The model would learn the rules involved in making this prediction. While in the former case, we defined the rules (that is if stage= X then survival= Y), in the latter we only provided data, and the ML model deciphered the rules. While the former is rigid, that is, if a new therapy alters the survival, we would have to change the rules to accommodate the change, the latter learns with experience. As new data emerges, the ML model would learn to update the rules so that it can dynamically make accurate predictions. In addition, the ML model can take multiple inputs, say level of tumour markers, age, general condition, blood parameters into account, in addition to the stage of the patient, and personalise the survival prediction of a particular patient.

The above example also illustrates why ML models are data intensive. A good model needs to see a large amount of data, with adequate variability in parameters to make accurate predictions. For the same reason, AI has bloomed in disciplines which have large amount of digital data available, and these include ophthalmology, dermatology, pathology, radiology, and genomics. However, as curated digital data emerges in all fields, it is likely to touch and transform all fields of medical practice.

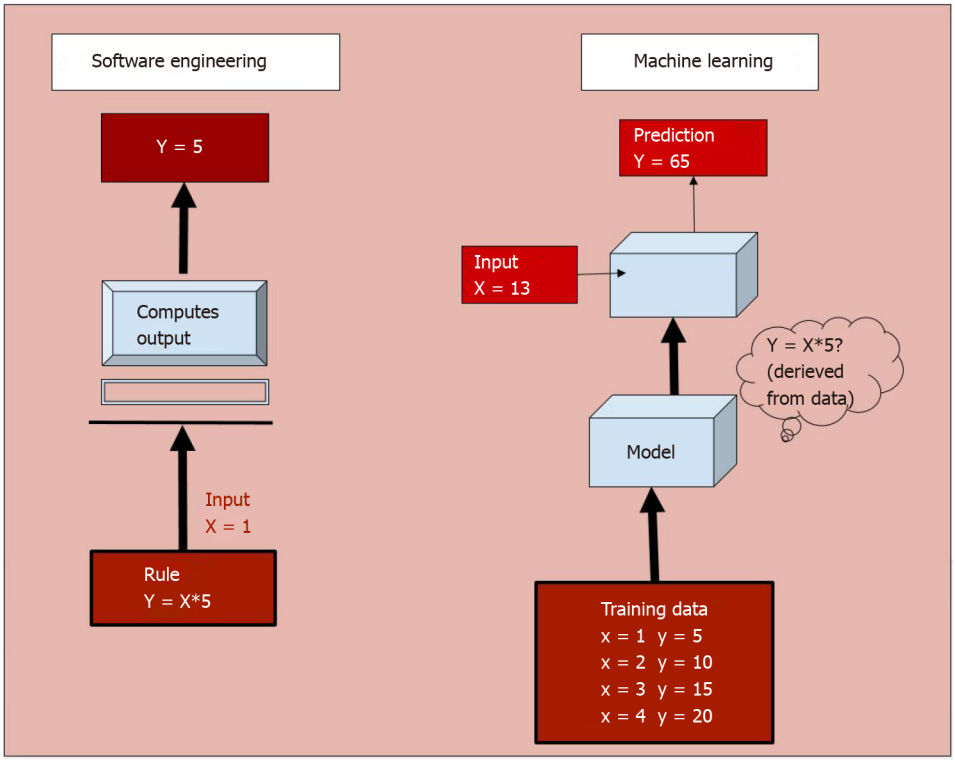

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Figure 1 Functioning of a software engineering process *vs* a machine learning model. In the former, a rule is programmed into the system based on which it computes output for a given input. Whereas in a machine learning model, the system learns from a large training dataset, and deciphers the rule to predict output.

WHAT ARE NEURAL NETWORKS?

A particular kind of ML algorithm, called neural network, has been particularly effective in performing complex tasks. A neural network takes inspiration from a biological neuron, where it receives several inputs, performs a certain calculation, and goes through an activation function, where similar to a biological neuron, a decision on whether it should fire or not is made. When there are a number of layers of these mathematical functions, the network is known as a "deep neural network" (DNN), and the process is called "Deep Learning" (Figure 3). A DNN is capable of handling a large amount of data, and defining complex functions, which explains its ability to perform complex classification tasks and predictions.

A specific kind of DL, called convolutional neural network (CNN), has performed particularly well in image-related tasks. CNNs use "filters" which are applied to images, similar to the traditional image processing techniques. "Convolving" with a filter (a mathematical operation) results in highlighting certain features of an image. Given an input set of images, a CNN basically learns what set of filters highlights features of a particular image, most relevant to a given task. In other words, a CNN is learning the features of an image that may be crucial to making a decision. For example, in case of mammography, a CNN is trying to answer what features of a mammogram are most predictive of the presence of a cancer within.

RADIOMICS AND RADIOGENOMICS: SHIFT TOWARD PERSONALIZED PATIENT CARE

Images contain information far beyond what meets the eye. While radiologists can interpret some of these features with the naked eye (such as margins, heterogeneity and density), pixel-by-pixel analysis of these images can yield significant amounts of hidden information. Studies have shown that these may be successfully correlated to outcomes such as patient survival and genomic mutations[4]. More specifically, it was shown by Choudhery *et al*[5] that in addition to differentiating among the molecular subtypes of breast cancer, texture features including entropy were significantly different among HER2 positive tumors showing complete response to chemotherapy. Other parameters such as standard deviation of signal intensity were found predictive in triple negative cancers. A similar study by Chen *et al*[6] in patients with non-small cell lung cancer treated with chemoradiotherapy showed that the 'radiomics signature' could predict failure of therapy. Therefore, using non-invasive imaging, it is thus

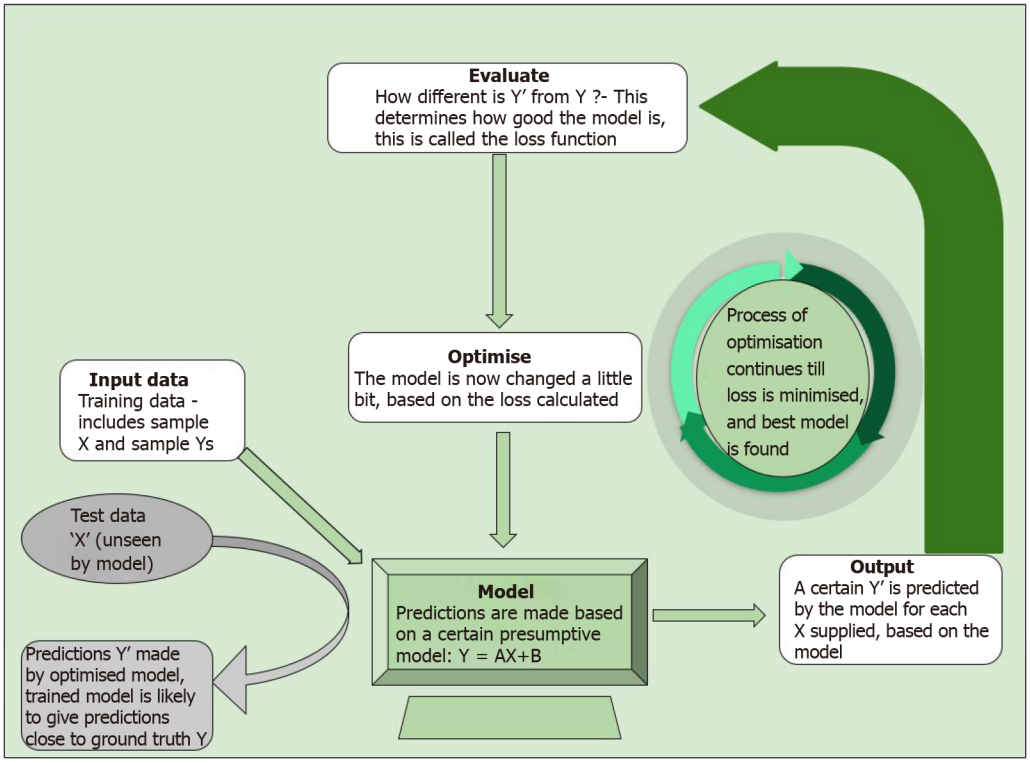

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Figure 2 Process of training a machine learning model. Following the initial training dataset, the model is tested on unseen data. The predicted output is compared to desired output, and changes are incorporated into the model till the predicted output is sufficiently close to desired output.

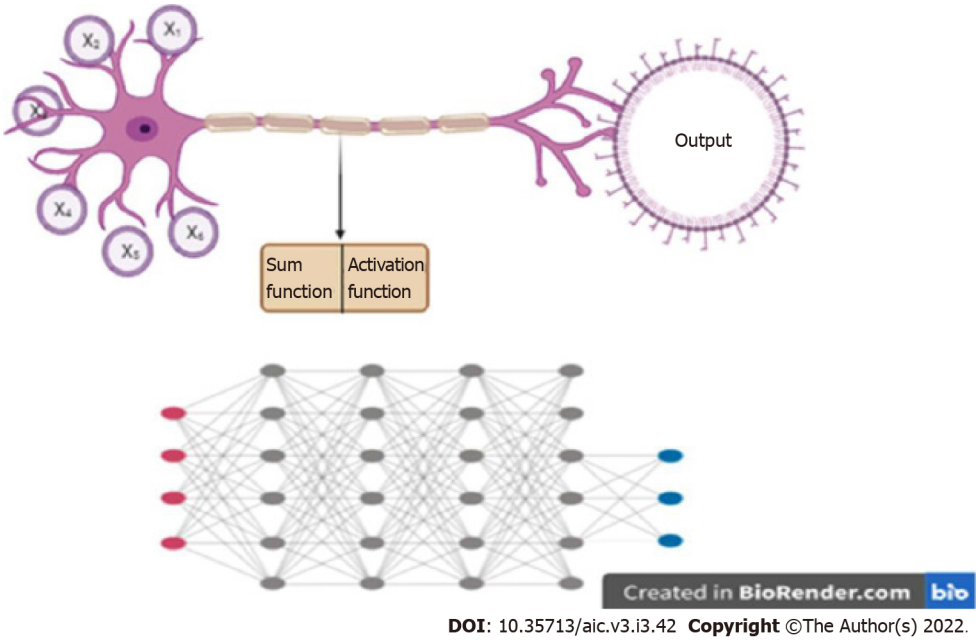

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Figure 3 Deep learning. A: Artificial neural networks take input from a number of channels (x1....xn), perform a mathematical function, and decide on 'firing' based on activation function; B: Deep learning involves multiple layers of such neural networks with many nodes. Each node communicates with all nodes of the connecting networks. Created with BioRender.com.

possible to predict the mutations, response to specific drugs and best site of biopsy. Thus potentially, the therapy of the patient can be guided by markers mined from non-invasive imaging, making precision medicine a true possibility.

DISCUSSION

Common applications of AI in oncology

Most applications of AI in oncology are currently in the field of radiology and pathology, given the abundant digital data available in these fields. These tasks may be classified into specific categories (Figure 4). For readers wishing to foray into the field, an explanation of each kind of task, as well as data requirements and some examples of applications of these tasks is given below.

Classification

A classification task is one in which the AI algorithm classifies each image as belonging to one of several target categories. These categories are given at the level of image or patient. For instance, whether a particular mammogram has cancer or not.

Data requirement: Training the network requires input images (mammograms in the above example), and an image level ground truth label (presence or absence of cancer in the above case). These are relatively easy to obtain if reports are available in a digital format, since automated extraction of diagnosis from free-text reports may be performed. Usually thousands of such images are required for training. Large public datasets of labelled natural images exist, such as "ImageNet" with over 14 million images[7], and several classification networks trained on these databases also exist, such as Alexnet, Inception and ResNet. These networks trained on these large public databases can be adapted to the medical domain, a process called "transfer learning".

Classification tasks can be evaluated by calculating the area under the receiver operating characteristic curve (AUROC) and by drawing a confusion matrix from which accuracy of classification can be calculated.

Applications: Some examples of classification tasks include breast density categorization on mammograms[8], detection of stroke on head computed tomography (CT) in order to prioritize their reading[9], and prioritising chest radiographs based on presence of pneumothorax in them[10].

Advantages: The most advantageous use of classification networks is for triage. These can be used to classify images that need urgent attention, or those that need a re-look by a reporting radiologist, pathologist, or ophthalmologist. This helps to reduce workload and effectively divert resources where required.

Disadvantages: When a classification task is performed by an algorithm, it simply classifies an image into a certain category, say 'benign' or 'malignant' for a mammogram, or 'COVID' or 'non-COVID' for a chest radiograph. It does not indicate which part of the image is used for classification, or indeed, if multiple lesions are present, which lesion is classified. This translates to reduced 'explainability' of such a model, where the results cannot be understood logically.

Detection

A detection task is one in which the network would predict the presence as well as location of a lesion on an image. Unlike a classification task, which is performed at the image or patient level, the detection task is performed at the lesion level. For example, if the network draws a box around a cancer on a mammogram, the task is a detection task.

Data requirement: Training requires images as input, and the ground truth needs to be provided as a box (called a bounding box) around each lesion, with their labels mentioned. This would typically have to be done prospectively, as this is not performed in the routine work-flow of most departments. In the above example, each mammogram would have to be annotated with bounding boxes by an expert radiologist (usually by multiple radiologists to avoid missing/misclassifying lesions), and each box would have to be assigned a label (as benign/malignant or with a BIRADS score, depending on what output is expected). Several publicly available datasets such as the COCO dataset[11] exist for natural images, with several networks trained on these datasets for object detection (such as RCNN, faster-RCNN and YOLO).

Detection tasks are evaluated by calculating the intersection over union between a predicted box and a ground truth box, that is, by calculating how close a predicted box is in comparison to the ground truth box. All boxes over a certain cut-off are considered a correct prediction. A free-response operating curve is drawn and sensitivity of the network at specific false positivity rates can be computed and compared.

Applications: The most prominent applications in oncology are detection of nodules on chest radiographs[12] and CT scans of the lungs[13-15], and detection of masses and calcifications on mammography[16].

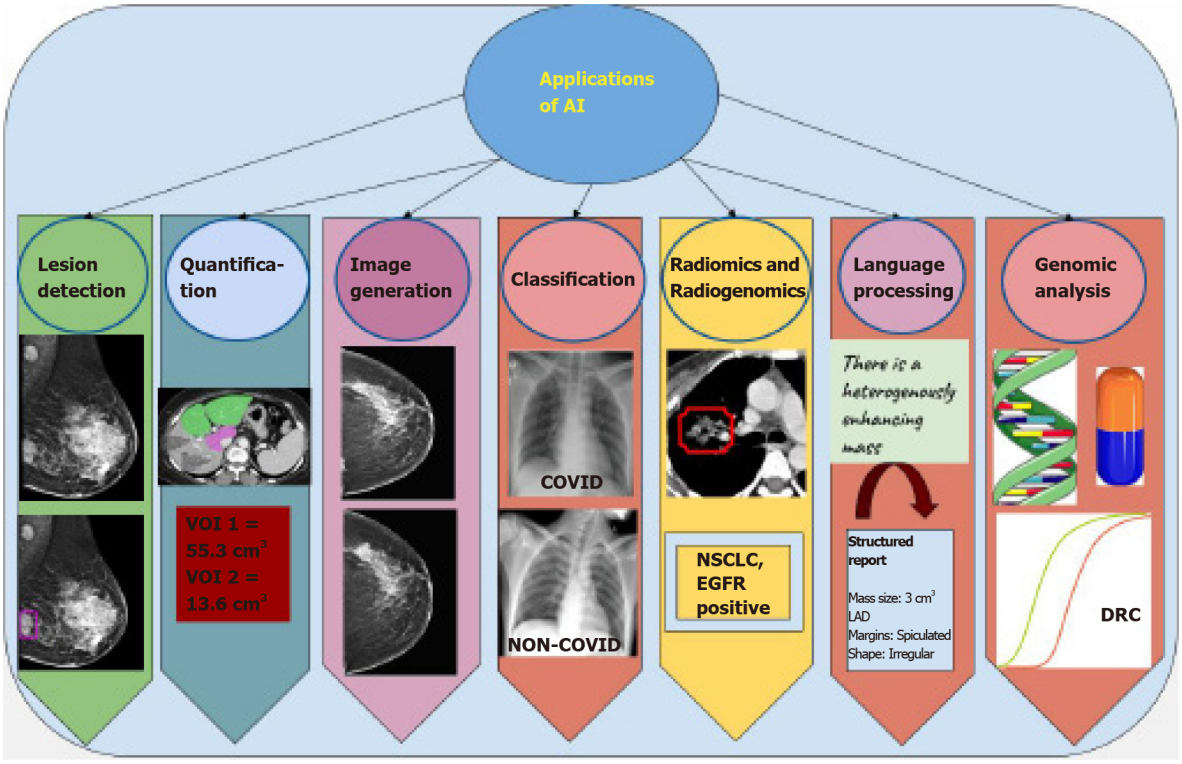

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Figure 4 Summary of tasks performed by artificial intelligence networks. The applications are diverse and range from lesion detection, *i.e.*, automatic identification of the area of pathology in a particular image, to segmentation of defined areas and quantification of area, volume, or percentage segment involved. Synthetic images may also be generated by artificial intelligence (AI) networks that closely resemble natural images. Further, it performs classification tasks, wherein images are placed into one of two or three categories. Analysis of texture features and correlation with genetic mutations is also possible using AI. Newer applications include language processing, from free flow to structured reports with standard, reproducible terminology. Genomic analysis of large amounts of DNA to determine drug response and susceptibility to drugs is also an evolving application. AI: Artificial intelligence; VOI: Volume of interest; NSCLC: Non-small cell lung carcinoma; EGFR: Epidermal growth factor receptor; LAD: Long axis diameter; DRC: Dose response curve.

Segmentation and quantification

A lesion segmentation task essentially involves classifying each pixel in the image as belonging to a certain category. So unlike a classification task (image or patient level) or detection task (lesion level), a segmentation task is performed at the pixel level. For instance, classification of each pixel of a CT image of the liver as background liver or a lesion would result in demarcating the exact margins of a lesion. The volume of these pixels may then be calculated to give the volume of the right lobe and left lobe of the liver separately.

Data requirement: Here, exact hand annotation of the lesion in question by the expert is required. This involves drawing an exact boundary demarcating the exact lesion in each section of the scan. Since this is routinely performed for radiotherapy planning, such data may be leveraged for building relevant datasets. Datasets like the COCO dataset exist with pixel level annotations for natural images.

These algorithms are evaluated with segmentation accuracy, IOU with the ground truth annotations (described in the previous section), or Dice scores[17].

Advantages: There is a tremendous advantage to the use of AI for segmentation, particularly quantification, in terms of increasing throughput and reducing the man-hours required for these tasks. In some cases such as quantification of extent of emphysema, which is particularly tedious for human operators, ready acceptance of AI may be found.

Applications: Automated liver volume calculations (liver volumetry) is an important application which can significantly reduce the time of the radiologist spent in the process[18,19]. Segmentation of cerebral vessels to perform flow calculations[20] and segmentation of ischemic myocardial tissue[21] are other such applications.

Image generation

Image generation refers to the network "drawing" an image, based on images that it has seen. For instance, if a network is trained with low dose CT and corresponding high resolution CT images, it may learn to faithfully draw the high-resolution CT image, given the low dose CT. The most successful

neural network to perform this task is called a generative adversarial network (GAN), first described by Ian Goodfellow[22]. This involves training two CNNs- a generator, which draws the image, and a discriminator, which determines whether a given image is real or generated. The two CNNs are trained simultaneously, with each trying to get better than the other.

Data requirement: This kind of network is usually trained in an "unsupervised" manner, that is, no ground truth is required. Therefore, no expert time is required in annotating these images. Only curated datasets of a particular kind of images are required.

This kind of network is difficult to evaluate, since no objective measure is typically defined. Evaluation by human eyes is generally considered the best.

Applications: GAN has found use in several interesting and evolving applications. This includes CT and magnetic resonance imaging (MRI) reconstruction techniques to improve spatial resolution while reducing the radiation dose or time of acquisition, respectively. GANs can also be trained to correct or remove artifacts from images[23]. An interesting application of GAN has been in generating images of a different modality, given an image of a certain modality. An example is generation of a positron emission tomography (PET) image from a CT image[24], a brain MRI image from a brain CT image[25], or a T2 weighted image from T1 weighted image[26].

Advantages: An interesting application of GAN has been used for simulation training for diagnostic imaging[27,28]. Students may be trained to recognise a wide variety of pathology using the synthetic images generated from these networks. This may be particularly important in certain scenarios such as detecting masses in dense breasts.

Disadvantages: These networks seem to possess a supra-human capability. The generated images cannot be verified for authenticity of texture or indeed even representation and thus may lead to an inherent mistrust of 'synthetic' images.

Natural language processing

Natural language processing (NLP) refers to understanding of natural human language. While processing structured information is relatively easy, most data in the real world is locked up in the form of sentences in natural language. For example, understanding what is written in radiology reports would require processing of free-text, and this task is called NLP.

Data requirement: Large publically available datasets such as the "Google blogger corpus" (text) and "Spoken Wikipedia corpuses" (spoken language) are available, over which networks can be trained to understand natural language. However, large medical corpuses with reports pertaining to specific tasks are needed for tackling specific medical problems. With more robust electronic medical records (EMR), integrated Hospital and Radiology Information Systems (HIS and RIS), as well as recorded medical transcripts, this field is likely to grow rapidly.

Applications: The applications of NLP range from extraction of clinical information from reports and EMR to train deep neural networks, to designing chatbots for conversing with patients.

Predictive modelling, radiomics, and radiogenomics

Predictive modelling has been at the core of medical practice for decades. While initial attempts were centered at developing scoring systems, or metrics that could be calculated from a few lab parameters, predictive modelling can be much more complex today because of the number of variables that ML systems can analyse.

A simple example of such a model is the "cholesterol ratio" (total cholesterol/HDL) which is used to estimate the risk of cardiac disease. As our models are capable of processing many variables, in fact capable of processing whole images, predictive models can be much more nuanced. Radiomics and radiogenomics are in fact an extension of the same, built to predict survival, response to therapy, or future risk of cancer, with more complex feature extraction and analysis from radiology images.

Data requirement: Building such models requires longitudinal data. Simple ML models would require lesser data in comparison to DL models. The amount of data required essentially depends upon which level ML is used at. For instance, if lesion segmentation is performed manually, feature extraction is performed with routine textural features, and feature selection is performed by means of traditional tools such as simple clustering or principle component analysis, then ML model would only use these selected features to make the desired prediction, and the amount of data required is relatively small. However, if DL is used end-to-end, the data requirement is much higher.

Predictive models are also assessed through AUROC and confusion matrices from which accuracy of prediction can be calculated.

Radiomics involve four steps: (1) Segmentation; (2) Extraction of features; (3) Selection of features; and (4) model building for prediction (Figure 5). Segmentation involves drawing a margin around a lesion. This may be performed by an expert manually, or automatically. Features of the lesion are then

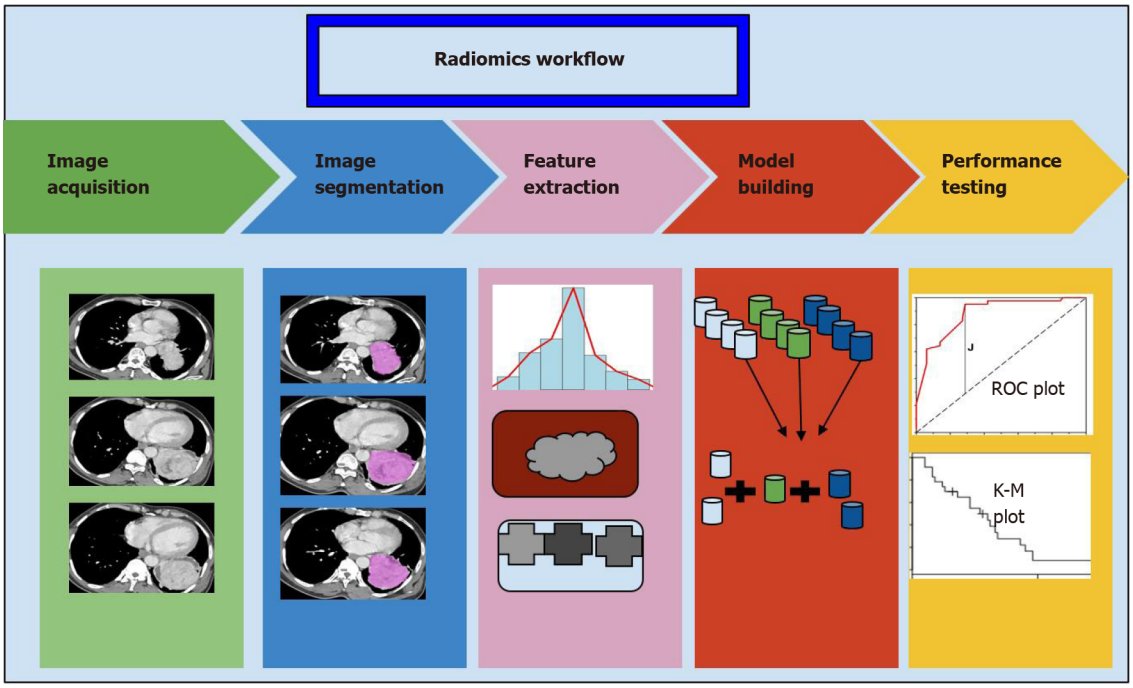

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Figure 5 The process of radiomics begins with segmentation of the region of interest from the image volumes, which may be manual or automatic. Following this, a series of features both histogram based and pixel based are extracted, and a set of these are chosen as classifiers for the discriminator model. The performance of this model is tested on a different set of data using statistical methods. ROC: Receiver operating characteristic; K-M: Kaplan-Meier

defined. These may be semantic, that is defined by an expert, such as tissue heterogeneity, spiculated margins, or quantitative features (such as mean, median, histogram analysis, and filter-extracted features). This may yield several 100 features, of which overlapping features should be removed before analysis. Subsequently, a few selected features may then be fed into a ML model along with the outcomes that are to be predicted. ML or DL may also be applied at the initial stages, for segmentation and feature extraction itself, rather than at the last step.

Applications: Predictive models are extremely useful in oncology. Studies have shown that features extracted from images can be used to predict the response to various kinds of therapies. Morshid *et al* [29] and Abajian *et al*[30] showed good accuracy in predicting response to transarterial chemoembolisation. Studies have also correlated the imaging features extracted with genomic information, for example, several studies have shown that imaging features can accurately predict EGFR mutation status in patients with lung cancer[31-34]. Segal *et al*[35] showed that 28 CT texture features could decode 78% of the genes expressed in hepatocellular carcinoma. More recent work also shows that DL models can predict future risk of development of cancer. Eriksson *et al*[36] studied a model that identified women at a high likelihood of developing breast cancer within 2 years based on the present mammogram. All these pave the way towards more personalised management of patients with cancer.

Genomic data analysis

The next generation of personalised medicine is undoubtedly 'genomic medicine', wherein not just targeted therapy but also diagnostic procedures are tailored as per the genetic make-up of an individual.

In addition, there is a growing effort towards population based studies for pooling of large scale genomic data and understanding the relationship between genomics, clinical phenotype, metabolism, and such domains. The challenges with these techniques are the huge amounts of data obtained from a single cycle, and the computational requirements in its processing and analysis. Thus, both ML and DL are ideally suited to deal with each step of the process starting from genome sequencing to data processing and interpretation.

For instance, a DL model that combined both histological and genomic data in patients with brain tumors to predict the overall survival, was able to show non-inferiority compared to human experts[37].

Data requirement: The essential in this field is not the data, but rather the ability to process the data. Since the human genome contains approximately 3 billion base pairs and thousands of genes, the data becomes extremely high dimensional. CNNs and recurrent neural networks (RNNs) have been proven to be the best approach to evaluate multiple DNA fragments in parallel, similar to the approach used in next generation sequencing (NGS)[38]. RNN models have also been used to perform microRNA and

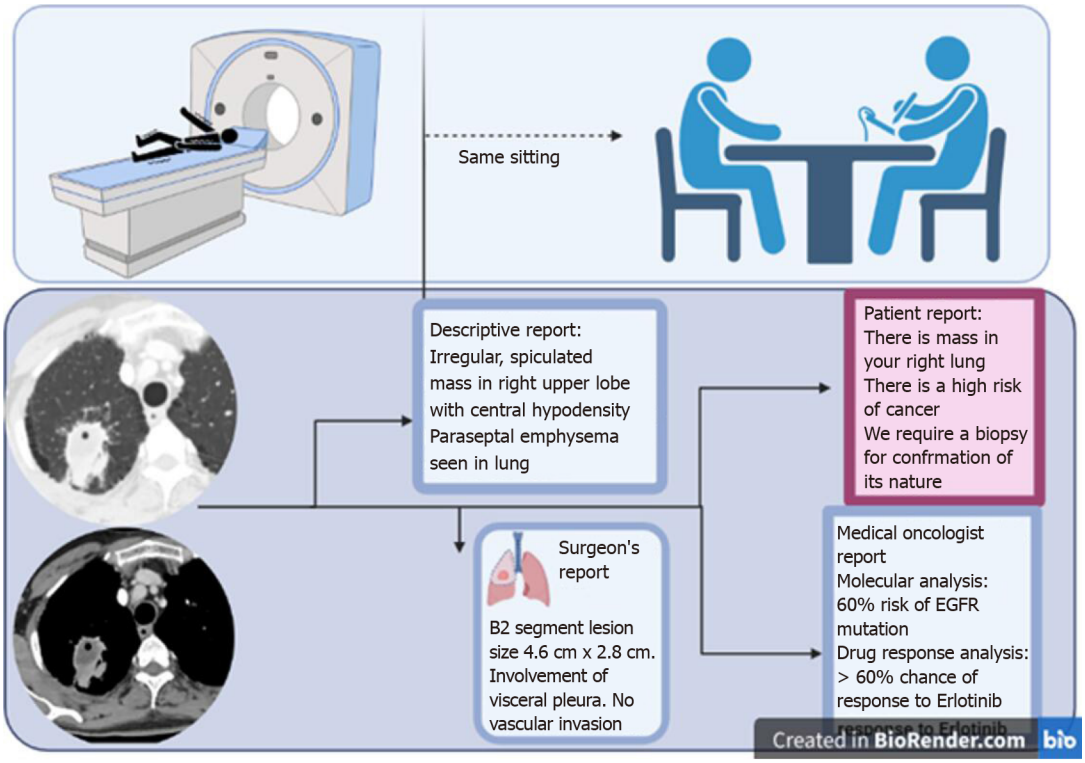

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Figure 6 Artificial intelligence enables the transition into the era of personalised medicine, where the assistance of artificial intelligence allows a radiologist to interact with the patient, correlate the findings with the clinical setting, and potentially issue a report in the same sitting as an imaging scan. Multiple different formats of report may be created based on the target audience, which enable clear communication and enhanced information exchange.

target prediction from gene expression data[39].

Applications: In addition to the applications detailed above, AI has also found use in variant identification, particularly Google's 'deep variant' which has shown superior performance to existing methods despite not being trained on genomic data[40]. Other studies have also used ML to identify disease biomarkers and predict drug response[41,42].

ENABLING PATIENT-CENTRIC ONCOLOGY CARE

Much of medical care today is moving away from patients, with focus shifting towards interpreting digital data in the form of blood reports, imaging data, pathology reports, genomic information, *etc.* The sheer amount of data has rendered face to face patient care less important, as synthesizing this information takes significant time and effort.

ML and DL have, however, ushered in a new era with endless possibilities. For instance, in a field like radiology, where AI is likely to have maximum impact, the onco-radiology reporting room of the future is likely to be dramatically different from where we are currently. AI, by reducing the amount of time spent in preparing a report, may pre-prepare images and sample reports, allowing a radiologist to spend time with the patient, examine the clinical files, and provide the report immediately after the examination (unlike in current practice where a radiologist sees the images, never meets the patient, and gives them a report about 24 h later). This report can potentially be transcribed into several reports simultaneously - for instance a patient friendly report, in easy to understand non-medical language, a physician report with important sections and lesions marked on the image, and a traditional descriptive radiology report. In fact, the radiology report is likely to have much more information than currently considered possible, including the possibility of a particular mutation, possibility of response to a particular therapy, and even reconstructed images translated to different modalities which may help determine the most important site of biopsy.

While Amara's law for new technology may well apply (which says that any new technology is overestimated early on, and underestimated later[43]), the potential of AI and the vistas that it opens up cannot be ignored. As the technology evolves, many of the changes it brings about will enable a leap towards the era of personalised medicine (Figure 6).

CONCLUSION

AI thus holds great potential. The most significant advantage of AI rests in the fact that since it is data-driven, it holds the potential to derive inferences from very large databases, in a short span of time. It brings with it the possibility to standardize clinical care, reduce interpretation times, and improve accuracy of diagnosis, and may help enable patient centricity in cancer care.

Like any new technology, however, AI must be used with care and only after thorough clinical tests. The most significant disadvantage derives from the fact that it is a "black-box", with little explainability. Little is known about the reasons behind the decisions taken by neural networks, making it imperative for the decisions to be seen and approved by human experts.

In summary, there is tremendous scope of AI in cancer care, particularly in the image related tasks. With the development of neural networks capable of performing complex tasks, the era of personalised medicine seems a reality with AI. Thus, judicious use must be encouraged to maximise the long term benefits that outlive the initial enthusiasm of discovery.

FOOTNOTES

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