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**FRONTIER**

- 2664 Cystic pancreatic lesions, the endless dilemma  
*Okasha HH, Awad A, El-meligui A, Ezzat R, Aboubakr A, AbouElenin S, El-Husseiny R, Alzamzamy A*

**REVIEW**

- 2681 Status quo and future prospects of artificial neural network from the perspective of gastroenterologists  
*Cao B, Zhang KC, Wei B, Chen L*
- 2710 Molecular alterations in pancreatic tumors  
*Visani M, Acquaviva G, De Leo A, Sanza V, Merlo L, Maloberti T, Brandes AA, Franceschi E, Di Battista M, Masetti M, Jovine E, Fiorino S, Pession A, Tallini G, de Biase D*
- 2727 Toward a new era of hepatitis B virus therapeutics: The pursuit of a functional cure  
*Tsounis EP, Tourkochristou E, Mouzaki A, Triantos C*

**MINIREVIEWS**

- 2758 Artificial intelligence in perioperative management of major gastrointestinal surgeries  
*Solanki SL, Pandrowala S, Nayak A, Bhandare M, Ambulkar RP, Shrikhande SV*
- 2771 Direct antiviral agents in hepatitis C virus related liver disease: Don't count the chickens before they're hatched  
*Compagnoni S, Bruno EM, Madonia G, Cannizzaro M, Madonia S*
- 2784 Rethinking the Barcelona clinic liver cancer guidelines: Intermediate stage and Child-Pugh B patients are suitable for surgery?  
*Romano F, Chiarelli M, Garancini M, Scotti M, Zago M, Cioffi G, De Simone M, Cioffi U*
- 2795 Potential risk factors for constipation in the community  
*Werth BL, Christopher SA*
- 2818 Requirements for implementation of artificial intelligence in the practice of gastrointestinal pathology  
*Yoshida H, Kiyuna T*

**ORIGINAL ARTICLE****Basic Study**

- 2834 Fecal microbiota transplantation ameliorates experimental colitis *via* gut microbiota and T-cell modulation  
*Wen X, Wang HG, Zhang MN, Zhang MH, Wang H, Yang XZ*

- 2850** Insight into molecular mechanisms underlying hepatic dysfunction in severe COVID-19 patients using systems biology

*Hammoudeh SM, Hammoudeh AM, Bhamidimarri PM, Mahboub B, Halwani R, Hamid Q, Rahmani M, Hamoudi R*

#### **Clinical and Translational Research**

- 2871** Survival-associated alternative splicing events interact with the immune microenvironment in stomach adenocarcinoma

*Ye ZS, Zheng M, Liu QY, Zeng Y, Wei SH, Wang Y, Lin ZT, Shu C, Zheng QH, Chen LC*

#### **Retrospective Study**

- 2895** Clinicopathological characteristics and prognosis of 232 patients with poorly differentiated gastric neuroendocrine neoplasms

*Han D, Li YL, Zhou ZW, Yin F, Chen J, Liu F, Shi YF, Wang W, Zhang Y, Yu XJ, Xu JM, Yang RX, Tian C, Luo J, Tan HY*

#### **Observational Study**

- 2910** Prediction of hepatic inflammation in chronic hepatitis B patients with a random forest-backward feature elimination algorithm

*Zhou JY, Song LW, Yuan R, Lu XP, Wang GQ*

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## Status quo and future prospects of artificial neural network from the perspective of gastroenterologists

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### Abstract

Artificial neural networks (ANNs) are one of the primary types of artificial intelligence and have been rapidly developed and used in many fields. In recent years, there has been a sharp increase in research concerning ANNs in gastrointestinal (GI) diseases. This state-of-the-art technique exhibits excellent performance in diagnosis, prognostic prediction, and treatment. Competitions between ANNs and GI experts suggest that efficiency and accuracy might be compatible in virtue of technique advancements. However, the shortcomings of ANNs are not negligible and may induce alterations in many aspects of medical practice. In this review, we introduce basic knowledge about ANNs and summarize the current achievements of ANNs in GI diseases from the perspective of gastroenterologists. Existing limitations and future directions are also proposed to optimize ANN's clinical potential. In consideration of barriers to interdisciplinary knowledge, sophisticated concepts are discussed using plain words and metaphors to make this review more easily understood by medical practitioners and the general public.

**Key Words:** Artificial neural network; Gastrointestinal disease; Diagnosis; Treatment; Prognosis; Endoscopy

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**Core Tip:** This review summarizes the current achievements and existing limitations of artificial neural networks (ANNs) used in gastrointestinal (GI) diseases. The future directions of ANNs are also discussed to provide references for promoting its clinical value. To make this review readable, we introduce the basic knowledge of ANN and illustrate the contents from the perspective of gastroenterologists. ANN is believed to play a critical role in clinical practice of GI diseases.

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## INTRODUCTION

The concept of artificial intelligence (AI) was first proposed at Dartmouth Conferences in 1956. Although definitions of AI vary, it is universally accepted that AI is designed to perform tasks that were previously fulfilled only by human intelligence. The debate on future directions of AI continues today. In the past few decades, AI has only been used to construct complex mathematical models. With the concurrent advancement of hardware, data, operation, and algorithm, AI has exhibited incomparable significance in many fields, such as fingerprint identification, information retrieval, and language translation. From 2016 to 2017, Robot AlphaGo driven by AI continuously defeated two world class Go grandmasters, which improved the connatural cognizance towards computer functions and drove us to reconsider the relationship between AI and human beings in the future.

As a branch of computer science, the integration of the cross-curricular interests of AI provides a strong boost for medicine. Many studies have focused on AI-aided screening, prevention, diagnosis, treatment, and health management. Since the MYCIN system was invented for clinical decisions with regard to infectious diseases in the 1970s[1], multiple systems supported by AI have been produced to meet the needs of medical care. For example, the AlmeHealthCoach system can automatically arrange medication regimens for patients at home. MedicalGraph can analyze the medical records and relevant laboratory tests to predict patients' disease risk. These productions also performed well in the field of medical robots, imaging diagnosis, and research on new drugs. Such progress has broken through unwavering predicaments of current medicine.

Artificial neural networks (ANNs) belong to a subtype of AI and have been used in many subspecialties of clinical medicine, including pathology[2], radiology[3], cardiovascular[4], neurology[5], orthopaedics[6], and gastroenterology[7]. Gastrointestinal (GI) tract disorders are diseases of the human digestive system and the therapeutic regimens of GI diseases strongly rely on imaging examinations. Mass image data are burdensome to radiologists, potentially increasing the odds of inaccurate clinical decisions. Compelling evidence has suggested that ANNs could effectively solve this problem[7-9]. Conversely, the rapid improvement of ANNs demands that clinicians enrich their knowledge and fully understand the strengths and pitfalls of ANNs.

This review focuses on the application of ANNs in GI diseases. We first introduce the basic knowledge of ANNs to help readers with a foundation for learning. The current achievements of ANNs are systematically summarized based on their applications. The characteristics, limitations, and future directions of research are then proposed from the perspective of gastroenterologists.

## OVERVIEW OF ANN

### Machine learning

Machine learning (ML) is a method that endows computers with the ability to actively analyze data. If AI is a metaphor for one person, ML is like the brain of that person. The birth of ML serves as the fruit of multidisciplinary crosstalk, including statistics, probability theory, approximation theory, and algorithm complexity. The intrinsic connection of variables can be deduced based on learning experiences, as with a reasoned detective to reconstruct the crime from known facts. The cultivation of a detective requires the accumulation of basic knowledge and experience in handling many experiences. The detective will be qualified to participate in cases only after he receives adequate training and passes exams. Similarly, ML algorithms receive many data with known answers, and the resulting operation formula can be constructed to manage specific problems. This process is defined as the training phase. Different from classical linear functions, ML is automatic and unobservable. After training, ML

algorithms will be tested with external datasets during validation phase, from which the test results are critical indicators of model efficiency and accuracy. Common algorithms for ML include ANNs, decision trees, naïve Bayes, support vector machines (SVMs), random forest, and expectation maximization.

Based on the learning approaches, ML can be typically divided into four subfamilies: (1) Supervised; (2) Unsupervised; (3) Semi-supervised; and (4) Reinforcement learning. Supervised ML is given a dataset with known correct output (*i.e.*, labelled data), and the accuracy of the models is gradually optimized *via* feedback of labelled data. For example, to construct a model for pathological classification between gastric cancer (GC) and normal tissues, the diagnostic results in the internal datasets should be labelled. Supervised ML aims to solve two primary tasks: (1) Classification, such as rapid review of chest X-rays; and (2) Regression, such as predicting the recurrence risk of cancer patients based on clinical indices. These two tasks are based on the exploration of potential rules among variables. Logistic regression, back propagation neural networks (BPNNs), and K-nearest neighbors are common ML algorithms. Notably, most studies involved in this review are supervised models.

Unsupervised ML refers to a learning dataset without effective labels. This learning approach is typically used for disorderly and unsystematic data. Clustering is the representative use of unsupervised ML and can help uncover innate models and groups based on exploratory data. Taking next-generation sequencing as an example, tens of thousands of gene expression levels are listed. Genes will be clustered based on expression similarities and the process does not require prelabelled data. Additionally, unsupervised ML can be used to group and label datasets for next-step supervised algorithms.

Semi-supervised learning serves as an important helper for pattern recognition. It combines supervised and unsupervised approaches that flexibly use labelled and unlabeled data, thus integrating the advantages of both types. During semi-supervised learning, unsupervised parts can save the cost of human labor for labelling or classifying mass data, as well as decrease the difficulties of data handling, while the supervised part can guarantee model accuracy. Self-training, transductive learning, and transductive SVM are all types of semi-supervised learning.

Reinforcement learning is copied from the psychological process of acquired behaviors. Like training pets, any preset data are not required. Algorithms are gradually fed by signals in each layer and then receive “rewards” or “penalties” instantaneously after evaluating errors between true values and output data. The efficiency of algorithms can be adjusted during learning, and the core rules of reinforcement learning is maximizing rewards and minimizing penalties. How to obtain optimal balances and reliability allocation remains the most challenging problem for investigators. Currently, computers can independently solve complex problems based on reinforcement learning, as in Robot AlphaGo.

### **ANN history and fundamentals**

The concept of ANN was first proposed in 1943. The development of ANN models has complicatedly approached from then on. In the 1980s, the rapid progress of ANN algorithms boosted a modern revolution (Figure 1). The design of ANNs is based on the human brain’s neural network. An ANN is primarily composed of many neurons. The data flow (*i.e.*, the signal) is passed and programmed across neural nodes. Neurons in the different layers have their own missions to solve problems, which can be analogous to factory production lines. The deconstruction of missions for data analysis provides the ability to find the optimal solution within the shortest time. As a type of parallel distributed system driven by mass data, ANNs are free from the requirements of logical or mathematical associations known beforehand.

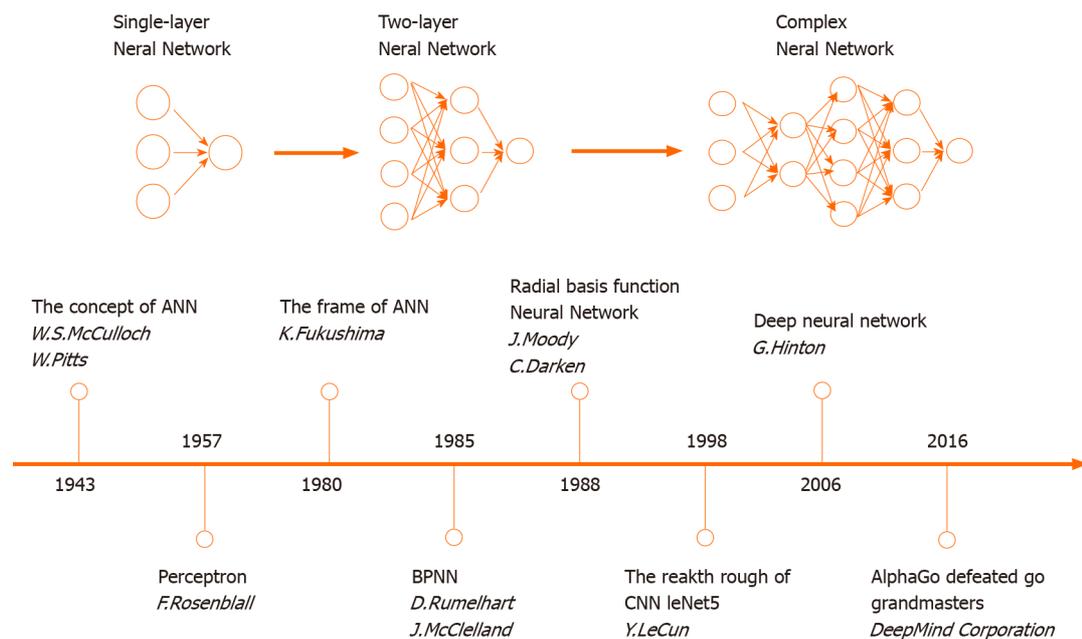
The structure of an ANN can be divided into three parts (Figure 2). First, input layers are responsible for receiving signals from specific datasets and serve as the “eye” of ANN to view the external environments. Second, hidden layers are predominant stages of ANNs and hinge on associations between input and output data. Raw data from input layers will be processed by neurons, and the numbers of hidden layers are always more than one. Missions for ANNs can be subtly disassembled and distributed into several layers. The multilayer structure promotes the efficiency of data analysis. Neurons in layers have serial connections based on settled sequences rather than parallel or parallel-series connections. Last, output layers make the final decisions and output results.

Common terms that describe shapes and capabilities of ANNs are listed (Table 1). The depth determines the efficiency of ANNs. The simplest ANN is a single-layer network (*i.e.*, a perceptron neural network) and has one input layer, one output layer, and one hidden layer. A single-layer network can only be used to describe a single

**Table 1** Terms commonly used to describe artificial neural network structures

Term of ANN	Specific meaning
Size	Number of neurons in the whole model
Width	Number of neurons in the one layer
Depth	Number of layers
Framework	Arrangement methods of layers and neurons
Capability	The reflection contents of reality by the specific model

ANN: Artificial neural networks.



**Figure 1** In the 1980s, the rapid progress of artificial neural network algorithms boosted a modern revolution. ANN: Artificial neural network; BPNN: Back propagation neural network; CNN: Convolutional neural network.

dichotomy based on a single factor, thus making most problems beyond its capabilities. Amplifying ANN depth can geometrically augment competence of fitting complicated features. Researchers began to create ANN models with multiple layers. Even in 2016, He *et al*[10] reported an ANN model with over 1000 layers[10]. However, excessive ANN depth may lead to system instability and loss of superficial learning abilities.

Each layer has a definite mission if the dataset volume and ANN depth are set. Width can be compared to the number of workers in a production line. Adequate workers will improve the qualities of tasks, while labor redundancy will yield negative effects. A broad ANN width enhances the access to different data features, while a narrow width leads to low efficiency of feature extraction and excessive hardware burden. The concept of size describes the accumulation of both depth and width, which is an important index when evaluating an ANN’s capability.

Additionally, ANNs can be divided into two major categories based on the directions of signal flow between hidden layers. There are many differences between the two types of ANNs (Table 2). In the feedforward neural network (FNN), data flow is unidirectional from the upper levels to the lower levels without feedback; no connections exist between neurons in any given layer. In terms of system learning, FNN is convenient for reprogramming and can process non-linear questions. The other one is feedback neural network. One neuron in feedback neural network can pass its output data to the other neurons in the same or upper layers. The algorithms will be simultaneously adjusted by signals from other neurons based on a pre-knowledge dataset. Repeated calibration contributes to the excellent robustness and

Table 2 Comparisons between feedforward and feedback neural network

Category	Feedforward neural network	Feedback neural network
Signal direction	Unidirectional	Unidirectional/bidirectional
Operation time	Short	Long
Feedback by output signal	No	Yes
Structural complexity	Simple	Complicated
Memory time	Short-term or none	Long-term
Applied ranges in medicine	Wide	Limited
Application	Perceptron network, back propagation network, radial basis function network	Recurrent neural network, Hopfield network, Boltzmann machine

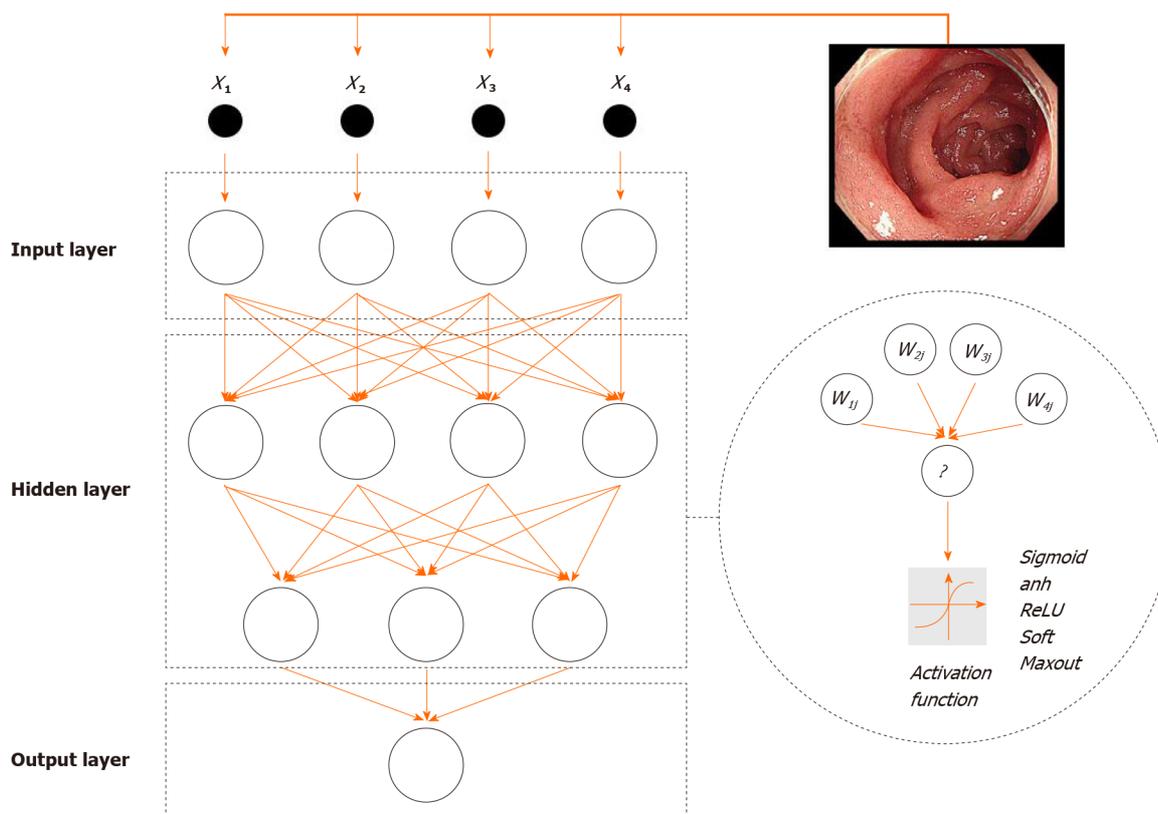


Figure 2 Structure of an artificial neural network.

accuracy of the ANN. A feedback neural network is typically used for image analysis, diagnosis, and outcome prediction.

Approaches of data processing in neurons can be defined as activation functions, and are like "all-or-none" principles of brain neurons. Activation functions primarily include sigmoid, relu, and tanh operations. Linear functions are excluded from activation functions because multiple overlays of linear functions can be compressed into one function. Accumulating studies have demonstrated that the nonlinear mapping ability of ANNs compensates for the boundedness of linear discriminant analysis. Otherwise, the "one-to-many" relationship between neurons guarantees the learning efficiency of the ANN. One neuron layer can simultaneously pass signals to more than one neuron. Importantly, signal flow is unequally allocated to each neuron in the next layer. The flow inequality makes the ANN adjustable to external environments. Before the computation of activation functions, data will be adjusted according to weight factors, each of which has a corresponding relationship with a specific neuron. Weight factors serve as the controllers of data flow. Larger weight factors have a greater influence on the output results. Conversely, setting a weight

factor equal to 0 can abrogate the functions of the corresponding neuron.

### **Categories of ANN**

There are a wide range of ANN categories used in basic and clinical medicine, and each contains a specific algorithm that has distinct advantages over the others. Comprehension and discrimination of ANN categories can provide a good command of research frontiers, and ensure that ANNs are used in the correct situations. Brief introductions of common ANN methods are as follows.

**Convolutional neural network:** Convolutional neural networks (CNNs) are the most popular type of neural network nowadays due to their additional convolutional layers and pooling layers. Convolution and pooling are complex concepts in computer science. Briefly, convolutional layers can extract features from a dataset because neurons in this layer are responsible for collecting and analyzing information located in specific areas. These neurons can be analogue to cells in the visual cortex of a human brain and act as windows that look out across the external environment. Data is then sent to the pooling layers after convolution, where the features of the dataset are filtered and compressed. Pooling layers reduce background and texture information at the cost of partial data loss. Then, the data will be processed in classic neural networks.

The number of CNN layers is relatively flexible. The accuracy and performance, however, are limited in CNNs with shallow structures. The majority of CNNs belong to deep CNNs. CNNs are applicable in numerous fields, such as image classification, objective recognition, and natural language processing. These applications require learning features from mass data and being able to generalize results. Also, fine-grained recognition of medical images is the core difficulty of CNNs for feature extraction and can be finished using handcrafted or unsupervised CNNs. The extraction efficiency of unsupervised CNNs outperforms handcrafted CNNs[11].

**BPNN:** BPNN is a type of multi-layer FNN. BPNN algorithms can be divided into two stages: Forward propagation and back propagation. For forward propagation, signals are handled from input layers to hidden layers and then to output layers. If errors between the real output and expected output are not acceptable, the error values will undergo back propagation, where the error values will be reversely transmitted layer by layer and then equally split into all involved neurons. Neurons automatically use revisions based on feedback signals; thus, BPNN can learn and apply mapping relations without clarifying mathematical derivation beforehand. The simplicity and accuracy of BPNNs have allowed them to be widely used in medicine, particularly for the diagnosis and prediction of patient outcomes.

**Bayesian neural network:** The training phase of the ANN requires a certain amount of data, and small training datasets tend to impair the efficiency and practicability of most ANNs. However, sufficient sample size is not always available. Bayesian neural networks (BNNs) have been designed for such situations. BNNs are based on weight factors that describe probabilistic ranges that are subject to Gauss distribution instead of being constants. The parameters optimized by back propagation are the means and variances of the weight factors, and can increase the confidence of each item of data, increasing the dataset robustness. Recently, BNNs have exhibited great potential in analyzing image features and constructing disease models.

**Recurrent neural network:** Data are frequently independent in a dataset, and the input sequence makes no difference in neural networks. However, there are sometimes internally logical relations between input information. For example, a set of computed tomography (CT) images contain many layers, and the observation of images in order can dynamically describe the sizes and shapes of lesions. Thus, treating these images as independent data would lose much information. Recurrent neural network (RNN) was invented to overcome this limitation. As introduced before, the values in hidden layers are under the control of weight factors. In RNNs, weights are regulated by not only values of this time, both at the current time step and the last time step; thus, the output values of RNNs are affected by the input sequence of the dataset. RNNs have been widely used to manage datasets with successional subjects.

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## **ACHIEVEMENTS OF ANN RESEARCH IN GI DISEASES**

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GI diseases primarily refer to acute and chronic disorders in the stomach and intestinal

tract. The diagnosis and prevention of GI diseases remain challenging for clinical practice based on three aspects: Anatomy, symptoms, and pathogenesis. First, regarding anatomy, the digestive tract is exposed to the external environment all the time; however, most of the digestive tract is beyond our visual observation. Thus, the GI tract is vulnerable to various irritants, but pathologic deterioration cannot be easily detected. Second, the symptoms of GI diseases are atypical. Patients with early-stage GI tumors tend to underestimate their disease severity and miss the best opportunities for treatment. Concurrently, symptoms are not qualified as critical indicators of diagnosis and outcome. Clinicians must use imaging examinations to further clarify disease conditions. Imaging interpretation is somewhat subjective, relying on experiences of radiologists. The rates of missed and delayed diagnosis remain high. Last, in terms of pathogenesis, GI diseases are multifactor diseases including heredity, food, microbes, and neuropsychic factors. Single preventive methods are ineffective for the treatment of GI diseases. However, the application of AI has gradually broken through this dilemma.

### **Pathological diagnosis**

Pathological diagnosis is the gold standard for GI diseases, which has significant implications for diagnosis, therapeutic directions, and outcome prediction. This work is highly dependent on the subjective judgement of pathologists. Accuracy is susceptible to cognitive capability, professional experience, and fatigue levels. The misdiagnosis of pathological images remains beyond clinical requirements. With the rapid development of digital pathological sections, the transformation from qualitative to quantitative analysis has become a research topic. ANN models are effective at computer-aided pathological diagnosis. Karakitsos *et al*[12] tried to explore the potential of ANNs to discriminate benign from malignant gastric cells, and their model accuracy reached 97%[12]. Despite concentrating on cellular morphology, the capability of interpreting pathological images has been revealed.

Haematoxylin-eosin (H&E) staining is the most common method for discriminating benign and malignant lesions. For GC, most studies used CNN models to construct diagnostic systems for H&E staining[13-17]. In 2017, Sharma *et al*[17] reported the first study about computer-aided classification in H&E staining of GC. Regretfully, their system exhibited an accuracy of only 69.9%, far from the clinical standard[17]. Rapid progress has been made during the past three years. A CNN model fed by over 2000 H&E slide images achieved a near 100% sensitivity and 80.6% specificity[13]. Such optimal sensitivity showed that this model has potential in preliminary screening of H&E staining. Kosaraju *et al*[14] developed a novel CNN model called Deep-Hipo, which could extract and capture features at both high and low magnification levels. The overall accuracy of Deep-Hipo was 93.7%[14]. Deep learning model was also constructed for the prediction of microsatellite instability in colorectal cancer. The model significantly outperformed pathologists[18]. Importantly, models detecting multiscale receptive fields can be extended for survival prediction, subtype classification of GC, and selection of sensitive drugs.

Most studies concerning colorectal cancer (CRC) have also focused on distinguishing between benign and malignant tissues. Based on existing results, the accuracies or area under the curve (AUC) values of ANN-based models all exceed 80%[19-25]. Colon glands are important structures and indicators for pathological assessment[26]. However, the variation of glands in slides has been a barrier both for pathologists and algorithms. CNN models invented for it got excellent results about gland segmentation and classification[27-30]. Sirinukunwattana *et al*[31] showed a CNN model that automatically detects cell nuclei in CRC. The combination of spatially constrained CNN and softmax CNN might become a useful tool for exploring the tumor microenvironment[31]. Interestingly, a study investigated the correlation between genomic and epigenetic alterations in CRC. CNN algorithms were used to predict RNA expression classifiers from H&E images. This work lays the foundation for a comprehensive integration of morphology and molecular features[32]. Immunohistochemical staining and fluorescence microscopy belong to members of pathological examinations, and ANNs distinctly improved their diagnostic performance in GI tumors[33-35].

In addition to the auxiliary role of ANNs in pathological images, Wei *et al*[19] compared the accuracy of their model with that of pathologists and there was no significant difference between them[19]. The process from image input to result output could be finished within 2 s[20,36,37], and the time for ANN handling single image is evidently shorter than that for pathologists. ANNs can also complete repetitive processes with high-quality results. Based on the report of Yoon *et al*[20], the training time was only approximately 10 d[20], while the training time of a skilled pathologist

was based on the order of years. Thus, all evidence indicates the great potential of ANNs in fast pathological diagnosis.

### **Radiological examinations**

X-ray, CT, and magnetic resonance imaging (MRI) are common radiological examinations. CT is accepted as first choice for GI diseases due to its high image quality, convenience, and price[38,39]. The increasing clinical demand for examinations places great burdens on radiologists. Experience-based diagnosis has innate limitations in accuracy and efficiency. This dilemma requires novel computer-aided models with the support of new techniques. Compelling evidence indicates that ANNs can provide outstanding values in auxiliary diagnosis[40,41], and are not limited to this field.

At the end of the last century, an Austrian group investigated the potential of ANNs in single-photon emission CT[42]. Despite the lack of further validation, this innovative research launched a sharp increase in related studies. Many of them aimed to detect primary lesions in CT images[43-47]. For example, a CNN-based model was trained with 288 CT images for polyp detection and achieved a sensitivity of 97%[47]. Studies published in earlier years used multiple types of ANNs, including BPNNs, massive-training ANNs, and BNNs[45,48-50]. In recent years, investigators have collectively turned to using CNNs[43,51,52]. This tacit alteration suggests that CNNs have fewer complications in automatic CT interpretations. The combination of ANNs and CT has also been used in the diagnosis of cancer metastasis and invasion depth[53-56], which are also important indicators of patient prognosis. A study even reported that CNN-based systems could distinguish benign and malignant lesions by CT[57]. More possible development directions of CT were discussed. In brief, the diagnostic value of CT has been tremendously strengthened with the support of ANNs.

MRI has a superior definition of abdominal viscera and presents more information to radiologists than CT. Most studies focused on the promotion of MRI in CRC. A CNN-based system created by Trebeschi *et al*[58] reached up to an AUC of 99% for advanced rectal cancer[58], and other recent studies all performed well in this field[59-61]. Certain studies have tried to explore new applications of MRI. CNNs could increase the diagnostic capabilities of 3D reconstruction[62]. Faster Region-based CNN was trained with 240 cases for evaluation of circumferential resection margins and achieved a 95.6% specificity[63]. Chemosensitivity prediction by MRI was also achieved with the support of algorithms[64,65]. KRAS mutation is an important biomarker of CRC targeted therapy[66,67]. Genetic testing is the gold standard of detecting KRAS mutation. Two Chinese groups demonstrated that deep radiomics signature serves as a promising tool for the prediction of KRAS mutations[68,69]. The progression of algorithms could also elevate the sensitivities of 3D Stomach MRI[70]. These achievements suggested the feasibility of non-invasive detection for medication guidance of GI tumors. Otherwise, the importance of ANNs in inflammatory bowel disease (IBD) diagnosis has been shown[71].

### **Endoscopic detection**

Endoscopy is universally accepted as a revolutionary application in gastroenterology. Due to the unique advantages of the GI tract, endoscopists can visually observe diseased regions, obtain biopsies, and excise small lesions. The extensive application of endoscopy has effectively reduced mortality and economic burdens worldwide[72,73]. However, artificial discrimination and classification lead to a relatively high incidence of misdiagnosis. Conversely, endoscopy is widely used to screen and exclude diagnosis for health checks and suspected cases. Endoscopic sensitivity, therefore, must be improved. Thus, numerous studies have focused on the application of ANNs in endoscopy, and occupy the largest proportion of existing research.

The detection of GI tumors has become the mainstream direction of endoscopy. Many studies have developed endoscopic ANN-based systems. Like other methods of image analysis, investigators prefer CNNs to construct computer-aided models when managing endoscopic results[74-78]. For example, Hirasawa *et al*[74] trained a CNN model with 13584 endoscopic images and effectively captured GC lesions with a diameter of > 6 mm as well as all invasive GC[74]. Bagheri *et al*[79] proposed a CNN-based system to analyze the color levels during colonoscopies. The stratification of color levels significantly promoted diagnostic values, achieving a 93% precision and an 82% Dice score[79]. Otherwise, the fast speed is another advantage of ANN. Models can analyze thousands of images in a short time[74,80-83], which benefits from retrospective checks of images and facilitates real-time endoscopic diagnosis. For example, Zhang *et al*[80] developed a CNN model for the detection of gastric precancerous diseases in 2017[80]. After 2 years, they developed a novel CNN-based system

used for gastric polyps. This model achieved real-time analysis with 50 frames per second without a decline in diagnostic precision[84]. Intraoperative guidance and correction are urgently required. A deep CNN trained by 704 cases of colorectal adenomas, called ENDOANGEL, was published to help endoscopists monitor detection operations and avoid blind spots in real time[85]. This study is significant for computer-aided refinement of endoscopy.

Early screening has received much attention as people gradually attach importance to routine examinations. The atypical textures of lesions at an early stage pose a challenge for endoscopists. Numerous studies have aimed to improve the detection of GI polyps, precancerous lesions, and tumors at early stage using ANNs[9,78,86-92]. Interestingly, most research groups are from China and Japan, likely due to the regional characteristics of GI tumor incidence. The best performance of early detection was reported by Gao *et al*[78]. Their CNN system reached an overall accuracy of 98.7% and a specificity of 100%. ResNet50 stood out of five CNN models and performed the best in detecting CRC precancerous lesions with an accuracy of 93%[78]. Moreover, ANNs could assist in diagnosing *Helicobacter pylori* infection using the combination of blue laser imaging and linked color imaging[93-95]. This breakthrough undoubtedly expands the application ranges of endoscopy.

ANN application is not confined to traditional white-light endoscopy. Narrow-band imaging (NBI) is a new type of technique that can filter out broad-band spectrum in red, green, and blue colors, respectively. The concentrated layers of the GI mucosa can be altered by switching filtered wavelengths, endowing NBI endoscopy with unique strengths in detecting minor cancerous and even precancerous lesions. The integration of NBI and ANN has made amazing progress in early screening. Three studies respectively reported their models for the diagnosis of early GC[81,86,87]. For instance, Horiuchi *et al*[87] trained a CNN system that could differentiate between early GC and gastritis. This model achieved a high sensitivity but low specificity, yielding undesired accuracy[87]. In consideration of these fields of study, bias towards sensitivity is accepted. Trails concerning NBI colonoscopy were also performed and exhibited expectable results[7,96-98].

In recent years, wireless capsule endoscopy (WCE) has been developed for patient acceptance and the extension of detection zones. The small bowel, which is known as the blind spot of classical endoscopy, can be virtually examined only by WCE[99,100]. Thus, investigators use ANNs to enhance the capability of WCE diagnosis. A decade ago, Barbosa *et al*[101,102] began to develop an automatic detection system using a multilayer perceptron neural network[101,102]. Despite the limited size of the training dataset, this study proposed a novel direction for forthcoming models with great performance. With the development of WCE and algorithms, CNNs were shown to have sufficient potential to detect lesions in small-bowel WCE[8,83]. Particularly, Ding *et al*[8] trained a model with a large-sample dataset, achieving a sensitivity of 99.88%[8]. These achievements have changed the belief that the small bowel is the dead zone of GI tract examinations. However, two shortcomings of WCE still exist. First, WCE goes through a natural orifice, and its photograph angles are affected by GI peristalsis, body position, and contents within GI tract, presenting the possibility of losing sights. Second, during WCE movement, secreted mucus and chyme are likely to stick to WCE, decreasing image quality. ANNs may serve as an effective approach to solve these problems[103].

In addition to GI tumors, ANNs play an important role in the diagnosis of other acute and chronic GI diseases. Many studies concerning GI bleeding focused on WCE. The imaging features of serious GI bleeding are relatively distinct, while small lesions with bleeding are likely to be missed, particularly in WCE. The authors used CNN, BPNN, and probabilistic neural network (PNN) to optimize the WCE capabilities of instant diagnosis, which covered the stomach, small bowel, and colorectum. These ANN models were all reported to perform well[104-109]. Different from GI bleeding, progress on using ANNs to diagnose chronic atrophic gastritis is slow, likely because of atypical features and low rates of early screening. Two recent studies indicated the tremendous potential of CNNs in this field and showed that CNNs outperformed the expert endoscopists in identifying GI bleeding[110,111]. IBD is another indication of colonoscopy, and ANN was also used to improve the diagnostic value of endoscopy[112,113].

### **Prediction of risks and survival**

A research group conducted a retrospective study of 521 GC patients in 2005. Three mining techniques, including ANN, decision tree, and Logistic regression, were used to analyze clinical information and predict postoperative complications. ANN outperformed the other two methods[114]. Since then, many studies have focused on the

clinical potential of ANNs in risk prediction. In particular, a large number of relevant reports have emerged in recent years, which is reflected in the rapid improvement of ML algorithms. ANN models for predicting cancer risks commonly include dozens of categorical variables, such as age, sex, oncology indicators, radiological tests, and therapeutic regimens[115-118]. Two Japanese groups combined clinical indicators and endoscopic images using CNNs to predict GC risks[94,119]. Genetic and microbial factors function as important regulators in carcinogenesis. Genomics and microbiome can exhibit the deep roots of GI tumors. Dadkhah *et al*[120] trained ANN models with the gut microbiome of 218 subjects to identify risks for colorectal polyps. Classification accuracy exceeded 75% based on home stool samples[120], which is expected as a novel method for convenient screening of colorectal polyps. mRNA profiles also have referential value in predicting the odds of malignant transformation[121,122]. The fruits of high-throughput screening techniques combined with deep analysis can depict the landscape of carcinogenesis. Subsequent etiology-based tests will contribute to revolutionary progress in precise prediction.

Metastasis is a critical index of therapeutic regimens and long-term prognosis. CT and MRI have detective limitations and only positive lymph nodes with swelling shapes can be observed, as well as distantly metastatic lesions. The results, however, always fall behind the real condition, misguiding surgical strategies and reducing survival benefits. Investigators have tried to use the advantages of ANNs to elevate the accuracy of the metastatic conditions in GI cancer. A German group used an FNN to predict lymph node metastasis of GC early in 2005[123], but the performance is poor, partly due to unadvanced algorithms and computers. With the development of ANNs, models included larger amount and more subtypes of clinical indicators. Their predictive efficiency has been augmented to reach clinical standards[124-127]. Two studies investigated ANNs used in identifying metastatic risks of CRC patients at T1 stage[128]. Although cases with metastatic T1 tumors are rare, the underlying mechanisms may be uncovered with the support of ANN. Kurokawa *et al*[128] first used BNN to construct a predictive model that involved a novel molecular target from basic medicine and showed great potential value[128]. The growth of novel biomarkers has recently provided more choices for GI diagnosis and prediction; however, few studies have emphasized the integration between these newly found targets and classical tumor biomarkers. Future development requires more investigation of ANNs to maximize the significance of existing fruits.

Survival time and quality of life are important factors that both patients and doctors consider. No efficient approaches have been developed to date, which is typically explained by disease heterogeneity, subpopulation differences, and medical experiences. These problems are likely based on one reason: Deficiency of data integration. Investigators rest their hopes for an accurate diagnosis on the excellent capabilities of information screening and automatic decision making. They used ANNs to weight many kinds of factors to quantify the survival outcome of cancer, GI bleeding, and IBD patients[106,129-133]. For GI cancer, certain studies compared ANN with TNM stage and models constructed by other ML methods. ANN typically exhibited better performance than Logistic regression, TNM stage, and even clinicians[134-136]. Competitions between different types of ANNs were also performed and the results were not consistent[137-139].

In addition to classical types of clinical information, certain novel biomarkers combined with ANNs have potential value in the prediction of GI disease risks and prognosis. Altomare *et al*[140] created a panel composed of exhaled volatile organic compounds (VOCs) from CRC patients. A PNN was used to synthetically analyze the levels of exhaled VOCs. This model could effectively identify CRC patients and predict the survival benefits from curative CRC surgery[140,141], which was a quantum leap in non-invasive screening. Several immune markers, including CD8, CD20, and CD68, combined with the proliferation marker Ki-67 by CNN showed great prognostic value in GC[135]. DNA aneuploidy, tumor-stroma ratio, and RNA sequencing were also proven to have great value in clinical prediction that were evacuated by ANN[142-144]. Otherwise, the guiding capabilities of ANNs in the prediction of both inpatient and outpatient services have been gradually revealed[145-148]. With the deep crosstalk between ANNs and medical needs, clinical tasks that were previously regarded as impossible or difficult are becoming feasible and easy.

### **Clinical decision support**

Clinical decision making plays a conclusive role in the process. Numerous clinicians and scientists have been striving to promote standardized, precise, and individualized treatment. As the primary adjuvant regimens of GI cancer, chemotherapy should consider many factors, such as patient tolerance, pathological sensitivity, concrete

dosage, and regimens. Accumulating evidence has showed that ANNs could help overcome the therapeutic limitations caused by individual differences and mass data. Evaluation of chemotherapeutic sensitivity with ANN models is a hot topic. To establish reliable prediction systems for locally advanced and metastatic CRC, several ANN models have been used to integrate clinical indicators[149,150]. Their accuracies were significantly better than those of clinicians. Moreover, deep learning of radiological images exhibited its potential value in assessing chemosensitivity[64,65,151]. For example, a CNN system was trained using 202 cases with colorectal cancer liver metastases and was validated to have good accuracy for predicting responses to FOLFOX combined with bevacizumab regimens based on CT information[151]. The practicability of radiotherapy, anti-integrin therapy, traditional Chinese medicine, and immunotherapy could also be improved with the support of ANNs[152-155].

The quality control of surgical guidance and supervision is highly dependent on the skills of clinical teachers. It is difficult to cultivate doctors who receive normalized training and guarantee surgical processes free from interference of uncertainties. Kitaguchi *et al*[156,157] created a novel CNN-based deep learning approach fed by intraoperative videos. It could automatically recognize the surgical phase and action with high accuracies of 81% and 83.2%, respectively[156,157]. These achievements will initiate a novel field of ANN application. Clinicians, especially young surgeons, will reap benefits from these technological innovations. Regrettably, few studies have been reported due to ethic restriction and complicated surgical situations. More attention and investment should be paid for developing efficient guiding systems that precisely match skills and customs of surgeons.

### **Translation of basic medicine**

Basic research is the frontier where ANNs have been widely used. Inherent logic and correlation between variables can be easily shown by ANNs, which may be too difficult for human intelligence. Many repetitive tasks can be finished within a short time. In the past 10 years, the rapid progress of ANNs has launched another wave of research (Table 3). Existing studies can be divided into three aspects: (1) Elucidation of mechanisms of GI carcinogenesis; (2) Guidance of drug selection; and (3) Integration of fundamental research data. First, high-throughput screening is the fundamental method for selecting critical molecules and pathways of GI cancer. High-throughput techniques will produce extremely large amounts of raw data. It is impossible to precisely choose potential targets only by manpower. Bidaut *et al*[158] began to use ANNs to characterize stomach stem cells based on microarray experiments[158]. This technique showed great value in the basic research of GI physiology. A protein-based ANN classifier was successfully constructed to identify the origins of tumor samples[159], which may promote the application of mass spectrometry in precise tumor diagnosis. Cell counting serves as a fundamental task in basic and clinical research. The low efficiency of classical manual detection cannot meet the requirement of many experiments. CNNs can significantly improve cell counting technology on their own merits[160]. A CNN-based cell counter has already been commercialized. Moreover, CNN showed great performance in discovering lncRNA-disease associations[161,162].

Development of new drugs is an important direction of research. Computer-aided target selection has gradually replaced inefficient artificial experiments. Joo *et al*[163] aimed to screen compounds targeting dysfunction proteins to find new drugs for CRC. Preliminary selection was performed using ANN, and then a benzimidazolone compound was selected out for further cell toxicity tests. This study provides a good example for subsequent studies that explore novel medications. A CNN-based model, DeepIC50, was trained with 27756 features at molecular levels. It was proven to effectively predict three drug responsiveness classes for GC patients[163]. Further validation is required to determine whether the applicable ranges of DeepIC50 can extend to other types of tumors. Furthermore, tankyrase inhibitors have been verified as potential anticancer drugs. To confirm the activity ranking of tankyrase inhibitors in CRC treatment, Berishvili *et al*[164] developed an affinity prediction model based on CNN. The Spearman correlation of the model achieved 0.73, which was superior to those of the other three virtual screening approaches[164].

With the development of molecular biology, many types of high-throughput screening techniques have been widely used, including RNA-seq, protein mass spectrometry, metabolomics, microbiome, and noncoding RNA chips. Diverse types of ANN were employed to evacuate efficient targets from sequenced datasets[120,144,165,166]. Most studies have focused on their diagnostic value. Bao *et al*[167] constructed an ANN model to identify expression profiles of a microsatellite

**Table 3 Summary of studies concerning artificial neural network translation of basic achievements**

Ref.	Disease	Type of data	ANN technique	Application direction	Outcome
Bao <i>et al</i> [167], 2020	CRC	Microsatellite instability from TCGA database	Multi-layer perceptron network	Prognostic prediction	100% accuracy
Coppedè <i>et al</i> [189], 2015	CRC	DNA methylation	AutoCM	Identification of connections between DNA methylation and CRC	A strong connection between the low methylation levels of the five CRC genes
Liu <i>et al</i> [190], 2004	CRC	Gene signature from GEDatasets	Multi-layer network	Identification of latent marker genes of CRC	91.94% accuracy
Berishvili <i>et al</i> [164], 2019	CRC	Approximately 4000 complexes for which the data on the target binding constants	CNN	Screening filter for compound prioritization	73% Spearman rank correlation coefficient
Bloom <i>et al</i> [159], 2007	CRC and GC	MS	Multi-layer network	Differentiation between 6 common tumor types	87% accuracy
Dadkhah <i>et al</i> [120], 2019	colorectal polyp	Gut microbiome	ANN developed by Orange data mining tool	Early screening using collected stool	> 75% accuracy
Chang <i>et al</i> [166], 2011	CRC	miRNA profile	Not mentioned	Exploration of association between specific miRNAs and clinicopathological features	100% accuracy of miRNA panel
Chen <i>et al</i> [191], 2004	CRC	MS of serum protein pattern	Multi-layer perceptron network	Differentiation between CRC and healthy control	91% sensitivity; 93% specificity; 0.967 AUC
He <i>et al</i> [121], 2020	CRC and gastroesophageal cancer	Gene signature from TCGA database	Multi-layer network	Differentiation between types of cancer	CRC: 98.06% sensitivity; 96.88% precision. Gastroesophageal cancer: 94.89% sensitivity; 96.33% precision
Hu <i>et al</i> [192], 2015	CRC	Gene signature from database of NCBI NLM NIH	S-Kohonen neural network	Prediction of recurrence using gene expressions	91% accuracy
Kurokawa <i>et al</i> [128], 2005	CRC	Gene signature of nodal metastasis	BNN	Prediction of metastatic potential of CRC at stage I	88.0% sensitivity; 86.6% specificity; 0.904 AUC
Liu <i>et al</i> [160], 2019	Cancer cell	Synthetic microscopic images from two publicly datasets	CNN	Automated counting of cancer cells	-
Ronen <i>et al</i> [193], 2019	CRC	Gene signature from TCGA database	BNN	Stratification of CRC subtypes	-
Bilsland <i>et al</i> [194], 2015	CRC	A virtual library of compounds	Perceptron network	Screen of Benzimidazolone inhibitors for CRC treatment	CB-20903630 was selected out for further validation of CRC treatment
Maniruzzaman <i>et al</i> [195], 2019	CRC	Gene signature from patients	Fuzzy neural network	CRC classification	99.84% sensitivity; 99.75% specific; 99.81% accuracy; 0.9995 AUC
Inglese <i>et al</i> [196], 2017	CRC	3D MS	Deep neural network (unsupervised)	Identification of metabolic heterogeneity	Up to 0.6991 Pearson's correlation
Shi <i>et al</i> [197], 2020	CRC with liver metastasis	CT	ANN	Prediction of KRAS, NRAS and BRAF status	0.95 AUC
Jiang <i>et al</i> [198], 2020	GC	Two drug datasets	deep neural network	Prediction of drug-disease associations	17 kinds of drugs that were screened out by ANN had been confirmed as anti-tumor drugs
Bidaut <i>et al</i> [158], 2009	Stomach stem cell	Stemness signature	Perceptron network	Characterization of stem cells	-
Jing <i>et al</i> [168], 2019	Calibration of laboratory markers	CA-724	Radial basis function neural network	The effects of geographic factors on CA-724	CA724 reference values show spatial autocorrelation and regional variation

Xiao <i>et al</i> [122], 2018	GC	RNA-seq	Probabilistic neural networks (semi-supervised)	Diagnosis of cancer	96.23% accuracy; 99.08% precision
Hang <i>et al</i> [144], 2018	GC	MSI	Multi-layer perceptron network	Prognostic prediction	0.81 AUC
Xuan <i>et al</i> [161], 2019	GC	LncRNA profile	CNN	Prediction of GC	0.977 AUC
Joo <i>et al</i> [163], 2019	GC	Potential drugs from databases	CNN	Exploration of new drugs targeting	ANN-based model accurately predicts drug responsiveness as models previously reported
Liu <i>et al</i> [165], 2010	GC	MS from GC patients	Supervised neural network	Early screening	100% sensitivity; 75% specificity
Que <i>et al</i> [199], 2019	GC	MS from GC patients and clinicopathological parameters	Single-layer neural network	Prediction of long-term survival	0.82 AUC
Li <i>et al</i> [200], 2021	GC	Gene Expression Omnibus database	ANN	Differentiation between GC and healthy tissues	0.946 AUC

TCGA: The Cancer Genome Atlas; CRC: Colorectal cancer; GC: Gastric cancer; CNN: Convolutional neural network; BNN: Bayesian neural network; AUC: Area under the curve; MS: Mass spectroscopy; MSI: Microsatellite instability; ANN: Artificial neural networks; CT: Computed tomography; IHC: Immunohistochemistry; NCBI: National Center for Biotechnology Information; BRAF: V-raf murine sarcoma viral oncogene homolog B; NLM: Nonlinear-mirror.

status-related gene signature, which showed an accuracy of 100% in predicting the prognosis of CRC patient response to immunotherapy[167]. In addition to these novel targets, ANNs can optimize the diagnostic efficiency of clinical tumor biomarkers. According to the validation results of ANN, CA724 reference values are susceptible to geographical environmental factors, such as temperature, sunshine, and humidity[168]. This study suggested that indicators require precise calibration and ANN may become an effective tool. Briefly, ANNs have promising functions to integrate classical biomarkers and novel targets with optimum diagnostic weights.

### **ANN and GI noncancerous diseases**

Although most studies paid their attentions to ANNs in GI cancer, the functions of ANNs in noncancerous GI diseases were also revealed. IBD is a collective name, covering ulcerative colitis and Crohn's disease. Recent studies manifested the potential value of ANNs applied in clinical practice of IBD (Table 4), which preliminarily focused on the following two parts: (1) Differential diagnosis. ANNs could help distinguish between IBD, irritable bowel syndrome, and healthy controls. The sensitivities reported by the studies were all over 75%[169-172]. The data suggested the translational potential in diagnostic assistance of ANNs; and (2) Prediction of therapeutic efficacy. Surgery, hormone therapy, immunosuppressors, and targeted drugs are alternative regimens for IBD therapy. ANN models were proved to predict the efficacies of classical drugs, infliximab, vedolizumab, and enterectomy by analyzing huge numbers of clinicopathological variables[154,173-175].

Moreover, ANNs exhibited remarkable detective abilities for GI bleeding and atrophic gastritis. These two distinct diseases have one similarity: Early detection has critical value while delayed diagnosis can lead to a poor prognosis. However, the rates of missed diagnosis for GI bleeding and atrophic gastritis are relatively high. ANNs may overcome this dilemma. According to the existing evidence, the detection accuracies of endoscopy were significantly elevated under the assistance of ANN models[111,176-178]. Collectively, these studies indicate the role of ANN in the clinical practice of GI noncancerous diseases.

## **FEATURES, LIMITATIONS, AND FUTURE PERSPECTIVES**

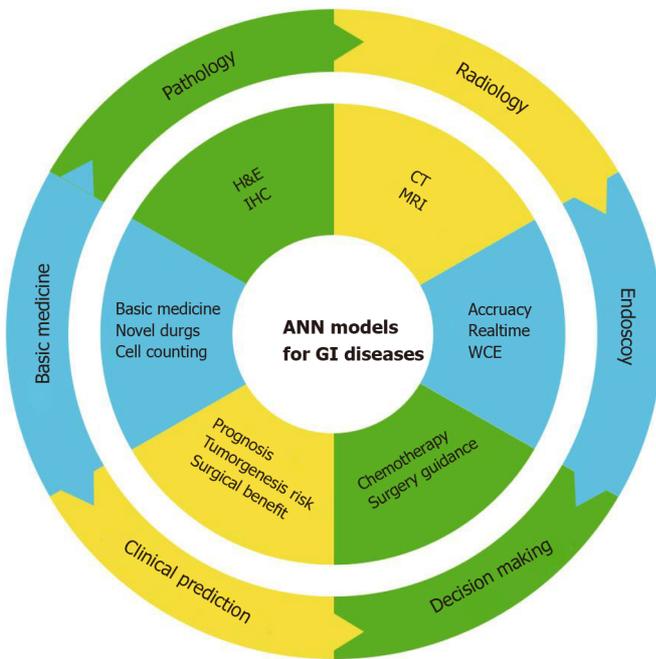
### **Features of ANN**

As mentioned above, accumulating studies have demonstrated that ANNs might have remarkable potential in diagnosis and treatment of GI diseases (Figure 3). ANN-based models commonly have optimal accuracies and AUC values. Some evaluation indexes

**Table 4** Summary of existing studies of artificial neural networks applied in inflammatory bowel disease

Ref.	Disease	Aim	Number of samples	ANN technique	Included variables	Outcome
Ahmed <i>et al</i> [169], 2017	CD	Diagnosis	144 CD patients; 243 HC individuals	BPNN	103 variables	Accuracy 97.67%; sensitivity 96.07%; specificity 100%
Ananthakrishnan <i>et al</i> [154], 2017	UC and CD	Predicting treatment response to vedolizumab	43 UC patients; 42 CD patients	vedoNet	Gut microbiome	AUC of CD 88.1%; AUC of UC 85.3%
Anekboon <i>et al</i> [201], 2014	CD	Predicting single nucleotide polymorphisms	144 CD patients; 243 HC individuals	Multi-layer perceptron network	103 SNPs	Accuracy 90.4%; sensitivity 87.5%; specificity 92.2%
Dong <i>et al</i> [173], 2019	CD	Predicting the risk of surgical intervention in Chinese patients	83 patients with surgery; 83 patients without surgery	ANN	131 variables	Accuracy 90.89%; precision 46.83%; F1 score 0.5757
Fioravanti <i>et al</i> [202], 2018	IBD	Classification of metagenomics data	222 IBD patients; 38 HC individuals	CNN	Gut microbiota	-
Hardalaç <i>et al</i> [203], 2015	IBD	Predicting the effect of azathioprine on mucosal healing	129 IBD patients	BPNN	Age, age at diagnosis, usage of other medications prior to azathioprine use, smoking, sex, UC-CD	Accuracy 79.1%
Kirchberger-Tolstik <i>et al</i> [170], 2020	UC	Diagnosis	227 Raman maps with 567500 spectra	CNN	Images of Raman spectroscopy	sensitivity of 78%; specificity 93%
Klein <i>et al</i> [204], 2017	CD	Predicting the clinical phenotype	47 B1 patients; 19 B2 patients; 39 B3 patients	Two-layer FNN	H&E	B1 vs B2 phenotype: sensitivity 81%, specificity 74%, accuracy 75%, AUC 0.74; B1 vs B3 phenotype: sensitivity 69%, specificity 76%, accuracy 70.5%, AUC 0.78; B2 vs B3 phenotype: sensitivity 67%, specificity 72.5%, accuracy 69%, AUC 0.72
Lamash <i>et al</i> [71], 2019	CD	Visualization and quantitative estimation of CD	23 pediatric CD patients	CNN	MRI	DSCs of 75 ± 18%, 81 ± 8%, and 97 ± 2% for the lumen, wall, and background, respectively
Le <i>et al</i> [174], 2020	IBD	Predicting IBD and treatment status	68 CD patients; 53 UC patients; 34 HC individuals	Neural encoder-decoder (NED) network	Gut microbiota	CD vs HC: 95.2% AUC; UC vs HC: 92.5% AUC; CD vs UC: 81.8% AUC
Morilla <i>et al</i> [175], 2019	UC	Predicting treatment responses to infliximab for patients with acute severe UC	47 patients with acute severe ulcerative colitis	Deep neural network	MicroRNA profiles	84% accuracy; 0.82 AUC
Ozawa <i>et al</i> [112], 2019	UC	Identification of endoscopic inflammation severity	841 patients	CNN (GoogLeNet)	Colonoscopy images	0.86 AUC of Mayo 0; 0.98 AUC of Mayo 0-1
Peng <i>et al</i> [205], 2015	IBD	Predicting the frequency of relapse	569 UC patients; 332 CD patients	ANN	Meteorological data	High accuracy in predicting the frequency of relapse of IBD (MSE = 0.009, MAPE = 17.1 %)
Shepherd <i>et al</i> [171], 2014	IBD	Differential diagnosis between IBD and IBS	59 UC patients; 42 CD patients; 34 IBS patients; 46 HC individuals	Multi-layer perceptron neural network	Gas chromatograph coupled to a metal oxide sensor in stool samples	76% sensitivity, 88% specificity, 76% accuracy
Takayama <i>et al</i> [132], 2015	UC	Predicting treatment response to cytoapheresis	90 UC patients	Multi-layer perceptron neural network	13 clinical variables	96% sensitivity; 97% sensitivity
Tong <i>et al</i> [172], 2020	CD, UC and ITB	Differential diagnosis between CD, UC and ITB	5128 UC patients; 875 CD patients; ITB 396 patients	CNN	Differential features of endoscopic images between UC, CD and ITB	The precisions/recalls of UC-CD-ITB when employing the CNN were 0.99/0.97, 0.87/0.83, and 0.52/0.81, respectively

IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease; ITB: Intestinal tuberculosis; IBS: Irritable bowel syndrome; CNN: Convolutional neural network; BPNN: Back propagation neural network; FNN: Feedforward neural network; MSE: Mean square error; MAPE: Mean absolute percentage error; HC: Healthy control; AUC: Area under the curve; ANN: Artificial neural networks; SNPs: Single nucleotide polymorphisms; MRI: Magnetic resonance imaging; H&E: Haematoxylin-eosin.



**Figure 3 Artificial neural networks might have remarkable potential in diagnosis and treatment of gastrointestinal diseases.** ANN: Artificial neural networks; GI: Gastrointestinal; CT: Computed tomography; MRI: Magnetic resonance imaging; IHC: Immunohistochemistry; WCE: Wireless capsule endoscopy; H&E: Haematoxylin-eosin.

of ANN models even achieved an accuracy of 100% [81,179]. For further validation of ANN metrics, comparisons were also performed and can be divided into three aspects based on the compared objects. First, regarding experts, studies involving comparisons with experts aimed at showing ANN superiority over artificial diagnosis [8,86,136]. The majority of ANNs exhibited faster speed and better accuracy than expert clinicians. Therefore, certain authors claimed that ANNs would become excellent tools for clinicians and scientists, perhaps even replacing humans in this capacity. Second, different ANN models have been studied. Researchers used several ANN algorithms that were trained with the same dataset and underwent validation phases [144,150,180]. The models with the best fitting degree were then selected out to process for further exploration. The comparisons exhibited the capabilities of different models in handling with clinical problems. Last, other reported data have shown that literature learning is another approach to determine the efficiency of developed models [106,181]. However, this type of comparative method is not reliable due to the inconsistency of research baselines, such as differences in datasets, hardware performance, and running time. These undefined bias may also affect comparative results. This method is thus not recommended for follow-up studies to further verify the advantages of their models. Generally, compelling evidence indicated that ANNs can lead the classification and deep analysis of GI clinical practice compared to linear statistical models and human labor.

Computers outperform humans in data processing, as shown in medical studies. The comprehensive diagnosis of GI diseases requires many types of examinations. GI clinicians must integrate clinical indicators to make diagnosis. However, existing guidelines and expert consensus cannot help GI clinicians manage the majority of complex diseases. ANNs can mitigate this limitation. Many types of patient characteristics and clinical indicators can be included in predictive models. Data stored in pictures is geometrically above that of textual data. CNNs can interpret radiological and endoscopic images. The analytic speed of CNNs is even fast enough to make real-time detection achievable. Some studies simultaneously included clinical indicators and picture information to analyze patient situations. This novel combination exceeds

the limitations of human capacity and provides optimal diagnostic and predictive accuracies.

Cost is also an important factor for clinical practice. Cultivating a qualified doctor demands considerable time and economic and social costs. However, ANN learning is a relatively simple process. Based on current reports, training ANN models with large-sample databases requires only several days[20]. ANNs can comprehensively analyze data features and adjust the weight values within an extremely short time. Furthermore, hardware is the basic requirement to run ANN algorithms, specifically graphics cards and central processing units, the two important data-processing elements. High-performance hardware costs a few thousand dollars, which is far cheaper than training a doctor. Collectively, the time and economic cost of training ANN models is much smaller than that of training doctors. It is believed that ANN will play a critical role in clinical practice in the near future.

### **Limitations and challenges**

The application of ANNs appears to be a way to overcome existing problems for GI doctors. However, certain limitations should be taken seriously. First, training methods affect the efficiency of ANN models. Most research groups have performed small-sample studies with fewer than 1000 cases. For endoscopic detection, although the number of freezing frames could reach ten thousand, some were from the same video[8,182]. Thus, frame repeatability impaired their representativeness. The small size of dataset led to a higher likelihood of overfitting, which refers to models that receive too much training and overly fit the characteristics of internal datasets. Rigid observation of internal datasets will naturally reduce the model's flexibility to manage external data. For example, if the model is trained with a dataset of patients from country A, patients from country B may not be well described by this model due to various factors. Otherwise, retrospective datasets should be used as the primary sources of ANN training. Similar to common retrospective studies, biases also exist and affect the application of models. Selection bias is the most important factor. Patient data from medical histories could be selected based on research programmes. However, some studies used public databases to train their models[167,183]. The information of registered cases is inflexible, which means that researchers cannot exclude potential bias as they expected.

Second, the compromise between interpretability and accuracy should be emphasized. Models with optimal accuracy typically lack interpretability (*i.e.*, explainability). Conversely, models with nearly perfect interpretability are less accurate, like linear regression. During ANN training, algorithm modulation and data feedback are blind. Researchers do not know the activation functions in hidden layers, which are similar to a machine that hides its circuit in the box and places only switches and displays outside; this feature is called as "black box". For important medical decisions, doctors and patients both have the right to know how decisions were made. An inability to understand how the model makes decisions will naturally reduce the patients' and doctors' confidence. Conversely, lack of explainability makes researchers unable to describe the deduction processes of ANN models, decreasing their referential value.

Third, sociological issues should be carefully considered for ANN applications, which could be divided into three aspects. First, regarding medical liability, mistakes and medical negligence are likely, despite the outstanding ANN performance in the validation phase. Thus, who should be responsible for decisions and how to distribute liability to pay for compensation are difficult to determine. Doctors, patients, and programmers are all seemingly innocent, and accidents primarily result from inherent shortcomings, not human carelessness. Second, regarding confidentiality, the operation of ANN models requires many types of data, some of which concern patient privacy. Doctors who betray privacies will receive punishment. However, ANN models are connected to the Internet or company intranets. It is difficult to distinguish the origins of a privacy disclosure. Furthermore, the capabilities of data extraction by ANNs are incomparable. The ranges of consent exemption thus require further argument. The balance between ANN research and patient privacy remains a challenge. Last, regarding legislation, multiparty participation is an important characteristic of ANNs, which should include hospitals, patients, product providers, and insurance companies. Regrettably, the rules of ANNs used in medical practice are still obscure. Existing legal norms cannot support the application and prospective studies of ANNs.

### **Future directions**

The goal of ANN applications is to maximize medical benefits for patients, doctors, and society. To provide GI diagnosis and recommended treatment, ANNs must be further improved to bring them in line with clinical standards and inherent characteristics. Future directions are described below.

**Enlargement of application ranges:** ANNs have been used for GI diagnosis, prognosis and risk prediction, and therapeutic guidance, achieving relatively high accuracies. Significance is limited to constructing more models that have been proposed in the same fields[184,185]. Future studies should focus on expanding ANN application ranges. Treatment decisions and surgical guidance are two representative aspects of future development. They require including more factors and presupposing more complex situations. ANNs may become a promising tool to overcome the difficulties. Epidemiology is another field burdened with large quantities of data. Training ANN-based models will help investigators have a deep and quick command of epidemiologic features.

**Development of unsupervised learning:** Supervised learning is the mainstream direction of medical research. ANN models are primarily based on labelled datasets, which require considerable time and manpower. Future studies should try to use unsupervised and semi-supervised learning to reduce the training cost and develop comprehensive decision-making models. The unique advantages of unsupervised learning can break classical thoughts of clinical trials. It can automatically reveal the internal structures of mass data without grouping and statistical analysis. Also, unsupervised learning is “clear box” and can produce visual information that can be comprehended by humans, providing more convenient parameter adjustment and systematic optimization. Unsupervised ANN-based models should be created for data pre-treatment and association screening. Mature unsupervised systems for basic research are also required to find more diagnostic biomarkers and therapeutic targets.

**Improvement of datasets:** Large-sample prospective studies and real-world studies are encouraged. However, these studies will require high-quality datasets, including normalized inclusion criteria, number of cases, detailed degree, and rigorous check. Optimal sources of data can reduce the bias of ANN systems. Otherwise, larger sample sizes do not mean that enrolled cases should cover as many races and countries as possible. Heterogeneity is ubiquitous in medical care. There remains a lack of evidence that ANNs, perhaps even all AI algorithms, have the potential to generalize disease features throughout the world. It should be temporarily accepted to construct ANN models with functional, regional, or subpopulation characteristics rather than wide application. The qualities of the datasets determine the performance of the constructed models. More efforts should be paid to build full equipped registry systems and provide complete data for model training, which is typically neglected by constructors.

**Emphasis on legislation:** The nature of AI is totally different from human intelligence. It cannot accept liability by its own. Decision-making methods are still based on learning and experience. Also, ANNs are unable to correctly address problems that are beyond their knowledge. That is why commercial AI products are slightly clumsy when managing complex situations. The “black box” feature of ANNs means that all participants are precluded from the decision-making process. Once ANN models make mistakes, how to rationally distribute responsibilities should be carefully answered by legislation. The absence of reasonable rules also slowed clinical trials. Judgment criteria must be outlined to allow clinical trials to be launched. Problems that emerge will then guide legislation. Positive feedback will promote the progress of ANN application.

**Progress in ethics:** ANNs have been created to solve the specific problems, which naturally forms result-oriented operation patterns. However, this process is not always suitable for making decisions independently, particularly for GI diseases. For example, for an old patient who had severe ulcerative colitis and underwent many partial enterectomies, ANN models may show that he can benefit from the next surgery. Conversely, doctors will persuade patients to accept expectant treatment due to their tolerance, age, and emotion. The absence of empathy will make an ANN’s decision “perfect” but impersonal, which is partially why ANNs cannot become a substitute for human decision makings. Regarding the substitutability of human labor, arguments on this topic have never been stopped. ANNs have gradually taken over simple tasks. Similar to the aforementioned statement, many models outperformed experts in

endoscopy, radiology, pathology, and gastroenterology[8,19,56,186]. Then, concerns about ANNs taking jobs from gastroenterologists in the future become more common. We hold the opposite view: The development of ANN techniques can reverse the transmission of pressure to improve the competence of gastroenterologists. Only in this way can pressure and injustice fundamentally be solved. Some issues of ethics and society will be answered by further application of ANNs.

**Avoidance of overestimation:** A misleading saying is that ANNs automatically produce analytic results after being fed raw data. Many studies emphasize construction methods but neglect the importance of data cleaning and conversion. Insufficient data pre-processing has serious impacts on the qualities of models. Rigorous criteria of data pre-processing should thus be developed. Coincidentally, ANNs have advantages regarding data labelling and classification. ANN models should be developed to help construct other ANN models for decision making. Although results showed that ANNs outperformed other AI methods, certain studies also highlighted their limitations[187,188]. An internal comparison between different ML methods is required.

## CONCLUSION

The relationship between AI and medicine has received much attention. In this review, we introduced the basic knowledge of ANN, a primary method of AI and its application in the diagnosis, risk prediction and treatment of GI diseases. Considering interdisciplinary difficulties, the contents of this review were written from the perspective of gastroenterologists. Many vivid metaphors and brief conclusions reduced the comprehension threshold of GI clinicians and scientists. The characteristics, current limitations, and future directions were then illustrated. Undoubtedly, ANNs provide excellent value in clinical practice and even outperform GI experts and other types of AI techniques. However, there are still certain problems that hinder ANN applications, which require additional exploration in many fields. It is believed that ANN will become one of the most efficient tools for GI clinicians and benefit all participants in the future.

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