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REVIEW

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The clinical application of artificial intelligence in cancer precision treatment

Jinyu Wang[1,2], Ziyi Zeng[2,3], Zehua Li[4], Guangyue Liu[5], Shunhong Zhang[6], Chenchen Luo[7], Saidi Hu[8], Siran Wan[9] and Linyong Zhao[10*]

Abstract

Background Artificial intelligence has made significant contributions to oncology through the availability of high-dimensional datasets and advances in computing and deep learning. Cancer precision medicine aims to optimize therapeutic outcomes and reduce side effects for individual cancer patients. However, a comprehensive review describing the impact of artificial intelligence on cancer precision medicine is lacking.

Observations By collecting and integrating large volumes of data and applying it to clinical tasks across various algorithms and models, artificial intelligence plays a significant role in cancer precision medicine. Here, we describe the general principles of artificial intelligence, including machine learning and deep learning. We further summarize the latest developments in artificial intelligence applications in cancer precision medicine. In tumor precision treatment, artificial intelligence plays a crucial role in individualizing both conventional and emerging therapies. In specific fields, including target prediction, targeted drug generation, immunotherapy response prediction, neoantigen prediction, and identification of long non-coding RNA, artificial intelligence offers promising perspectives. Finally, we outline the current challenges and ethical issues in the field.

Conclusions Recent clinical studies demonstrate that artificial intelligence is involved in cancer precision medicine and has the potential to benefit cancer healthcare, particularly by optimizing conventional therapies, emerging targeted therapies, and individual immunotherapies. This review aims to provide valuable resources to clinicians and researchers and encourage further investigation in this field.

Keywords Solid tumor, Machine learning, Deep learning, Precision radiotherapy, Targeted therapy, Immunotherapy, Tumor microenvironment

*Correspondence:
Linyong Zhao
153795352@scu.edu.cn
[1]Department of Medical Genetics, West China Second University Hospital, Sichuan University, Chengdu, China
[2]Key Laboratory of Birth Defects and Related Diseases of Women and Children, Sichuan University, Ministry of Education, Chengdu, China
[3]Department of Neonatology, West China Second University Hospital, Sichuan University, Chengdu, China
[4]Department of Plastic and Burn Surgery, West China Hospital, Sichuan University, Chengdu, China
[5]Department of Anesthesiology, West China Hospital, Sichuan University, Chengdu, China
[6]Department of Cardiology, Panzhihua Iron and Steel Group General Hospital, Panzhihua, China
[7]Department of Outpatient Chengbei, the Affiliated Stomatological Hospital, Southwest Medical University, Luzhou, China
[8]Department of Stomatology, Yaan people's Hospital, Yaan, China
[9]Department of Gynaecology and Obstetrics, Yaan people's Hospital, Yaan, China
[10]Department of General Surgery & Laboratory of Gastric Cancer, State Key Laboratory of Biotherapy / Collaborative Innovation Center of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu, China

McCarthy J et al. coined "artificial intelligence" at the initiation of the 1956 Dartmouth summer research project, establishing the foundation of this field. This term, broadly defined as 'the approach to creating intelligent machines,' was based on the hypothesis that machines could emulate various aspects of learning and intelligence [1]. Briefly speaking, Artificial intelligence (AI) refers to a branch of computer science that emulates human intelligent behavior and addresses challenges such as reasoning, knowledge representation, automated planning, natural language processing, machine perception, robotics, etc [2–4]. AI predominantly encompasses machine learning and deep learning, although these three terms are sometimes used synonymously. Emerging as a subtype of AI, machine learning focuses on utilizing computational algorithms to identify patterns within data and fit predictive models to it [5]. Machine learning can be categorized as supervised learning, unsupervised learning, semi-supervised learning and reinforcement learning. Supervised learning uses human-labelled data for training and predicts outcomes through classification or regression. On the contrary, data-driven unsupervised learning are used for clustering or dimension reduction by training on unlabeled data. Semi-supervised learning is in between, using both labelled and unlabeled data for training [6]. Finally, reinforcement learning is a specific method that compares against a pre-defined goal in iterative interactions, corresponding to the generation of rewards or penalties, and is performed repeatedly [7, 8]. Each of these methods can be subdivided into different algorithms that are used individually or integrated. Deep learning is a subset of machine learning that typically does not require feature extraction. Its end-to-end learning capabilities significantly enhance the processing of natural raw data, a capability not present in traditional machine learning [9]. (Fig. 1) Focusing on deep neural networks (DNNs), deep learning uses algorithms composed of multiple hidden processing layers to integrate extensive datasets and explore complex relationships, greatly impacting fields including image identification, speech recognition, object detection, and natural language processing, especially when involving biomedicine [10].

According to GLOBOCAN 2020, it is expected that there will be 28.4 million cancer cases globally in 2040. Besides powerful advocacy for cancer prevention, optimizing cancer management is crucial in the current context. Obama launched the Precision Medicine Initiative as a revolutionary strategy for tailored cancer care in his 2015 State of the Union address. Since then, the world has been a shift towards cancer precision medicine

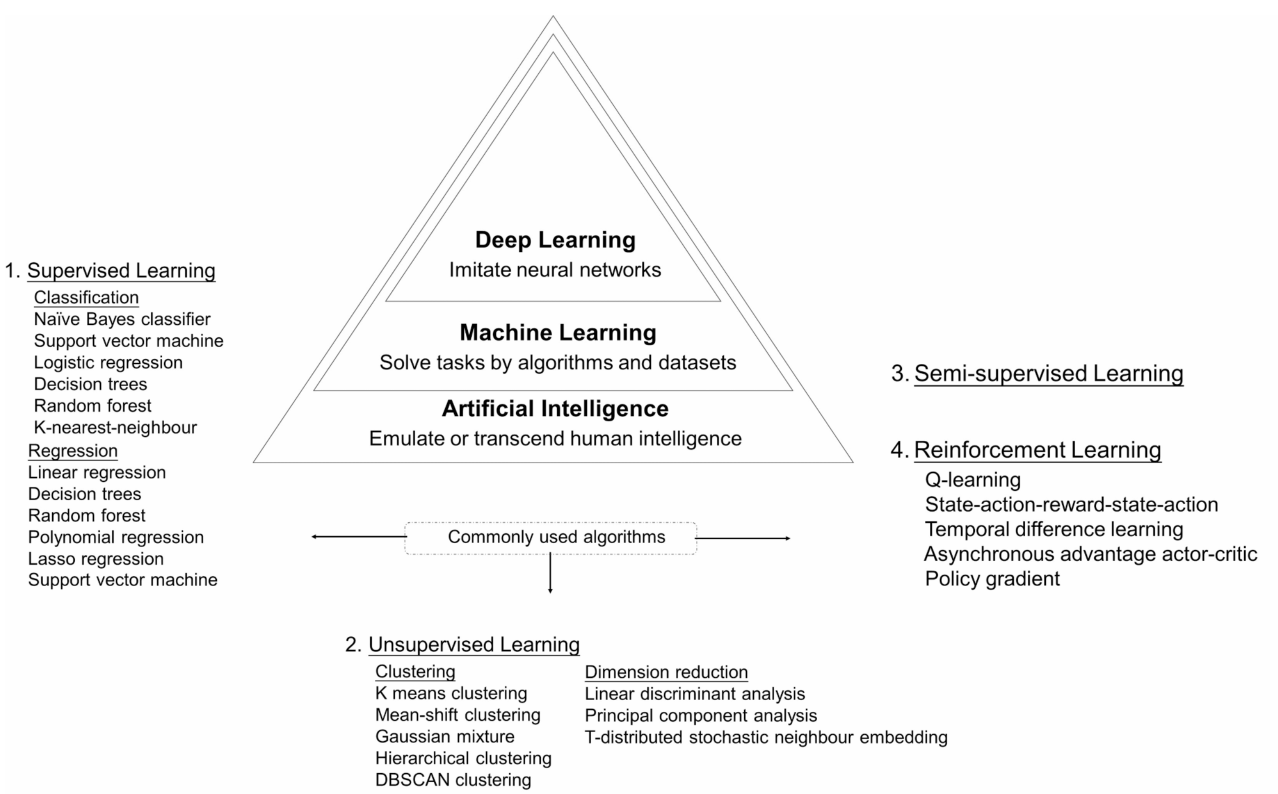

Fig. 1 The concise overview of artificial intelligence and its associated algorithms. Artificial intelligence encompasses machine learning, which includes deep learning. The terms may be used interchangeably despite distinct characteristics. Algorithms serve as the fundamental basis for artificial intelligence and are classified into various categories

(CPM) - individualized cancer care that places at its core the unique characteristics of patients [11, 12], including clinical records, health history, lifestyle, genome, epigenome, transcriptome, proteome, metabolome, medical image, histopathologic feature and new data streams that may develop as oncology research progresses [13, 14]. Diverse patient-specific data is experiencing explosive growth with medical technology advances and is constantly in flux during a patient's trajectory, which requires significant expertise and time for collation and utilization. Thus, the use of AI techniques has become progressively ubiquitous due to their ability to enhance efficiency and reproducibility through automation [5]. Furthermore, a single type of data is extremely limited in providing a comprehensive view of a tumor. AI is driving the development of multimodal data integration in oncology and enhancing the precision of its predictive models by combining complementary information from different modalities [13]. The integration of highly heterogeneous data can be effectively managed and analyzed by deep learning neural networks due to their capacity to include diverse raw data types and flexibility in data processing [15].

This review focused on the latest AI applications for CPM, particularly in the fields of optimizing conventional therapy, target prediction, drug selection, and personalized immunotherapy. (Fig. 2) Moreover, we discuss the current limitations and prospects in translating AI to clinical practice and present potential solutions to bridge the gap between AI and real-world medical practice.

Optimizing conventional therapy with AI techniques

Conventional treatments, such as surgery, radiotherapy and chemotherapy are still widely used in solid tumor management. To meet the demand for better outcomes, less risk, and more economical cost, achieving accuracy and individualization of conventional therapies is crucial. AI models have the ability to process, analyze and integrate datasets efficiently, allowing each aspect in conventional therapeutic areas to change from relatively uniform processes to individualized solutions. (Fig. 3)

AI in perioperative decision-making

Through AI algorithms, analyzing complex datasets supports accurate risk prediction, personalized surgical strategies and real-time adjustments, and leads to improved surgical outcomes and fewer complications. The combination of artificial intelligence and advanced imaging technologies continues to advance surgical precision and patient management [16]. Thus, AI has become an essential tool in the whole perioperative processes, including preoperative planning, intraoperative guidance, as well as postoperative care [17].

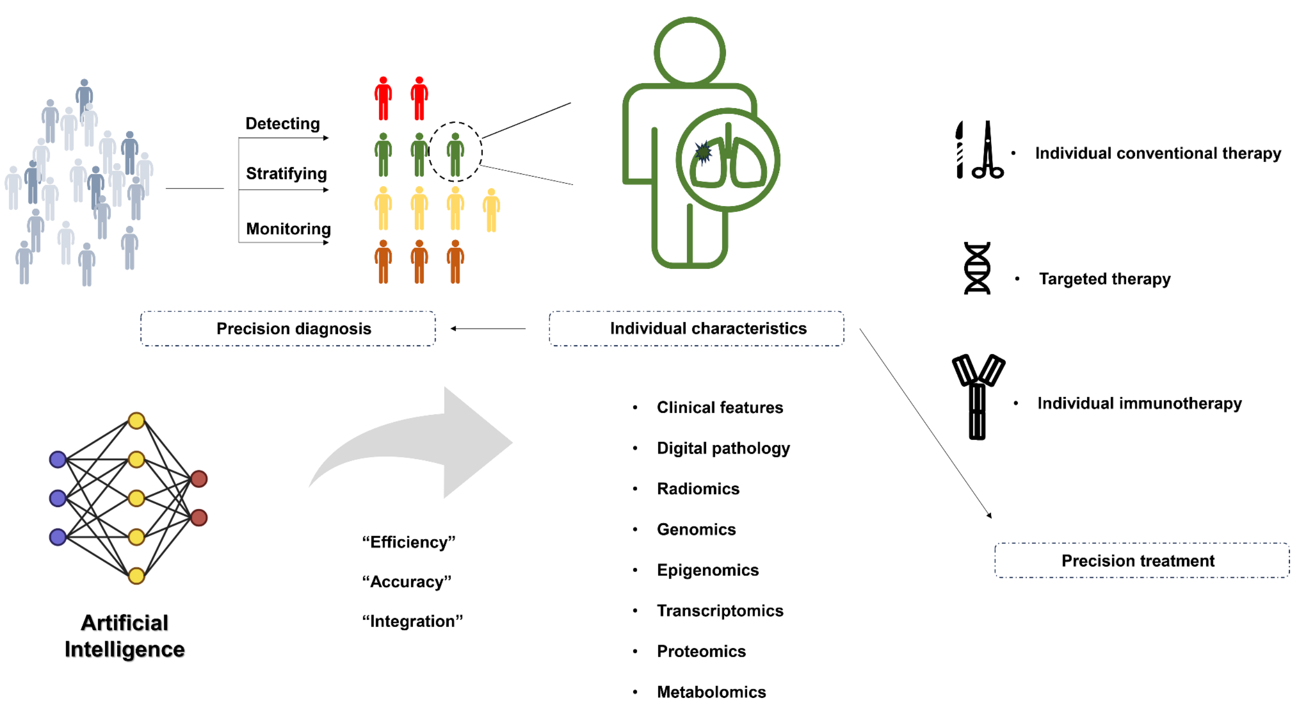

Fig. 2 The comprehensive flowchart illustrating the application of artificial intelligence in precision cancer treatment. With various algorithms at its core, artificial intelligence is gradually being involved in the field of oncology. Individual characteristics data, generated from the whole process of cancer management, can be seamlessly integrated and efficiently utilized by artificial intelligence systems to facilitate accurate precision diagnoses and subsequently advance the efficacy of precision treatment strategies

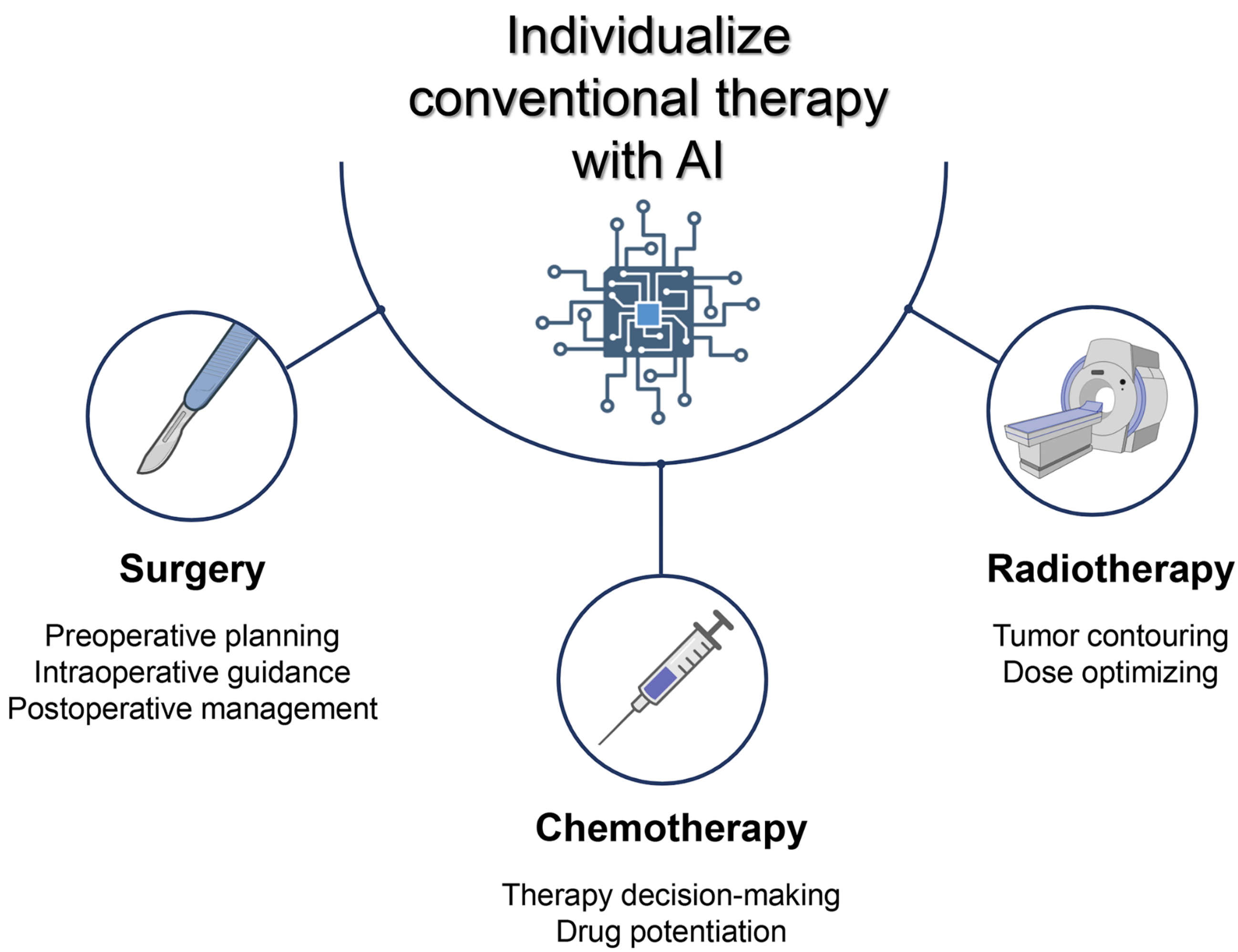

Fig. 3 Artificial intelligence makes conventional cancer treatment more individualized. AI is revolutionizing conventional cancer treatments such as surgery, radiotherapy, and chemotherapy. It enables greater individualization throughout the entire treatment process, including pre-treatment decision-making, real-time management during treatment, and post-treatment care. AI approaches maximize the effectiveness of traditional treatment methods within the framework of precision medicine, enhancing therapeutic outcomes while minimizing side effects

Preoperative planning

AI enhances preoperative strategies by providing surgeons with comprehensive insights into patient risk factors, tumor characteristics, and expected surgical outcomes. Especially, Lymph node metastasis (LNM) is critical in determining whether surgery is appropriate for patients with solid tumors. Machine learning significantly optimizes the decision-making for operation by predicting LNM [18]. In colorectal cancer, Song JH et al. used a deep learning model with H&E-stained endoscopic resection specimens to predict LNM. Compared to traditional methods using clinical and/or pathological features, this model performed better in predicting LNM for stage-T1 (AUC = 0.764 in validation set). It substantially reducing unnecessary additional surgeries compared to current guidelines (67.4% vs. 82.5%) [19]. Similarly in other digestive system cancers, researchers combined AI algorithms with other data modalities, including clinical variables [20, 21], histopathological images [22], and radiomics features [23–25], enhancing the prediction of LNM. Moreover, in solid cancers of other systems, AI models also show great potential to achieve the same goal, such as thyroid [26], lung [27], breast [28], and endometrial tumors [29]. For example, in a multicenter retrospective study, researchers proposed an AI-based model of outstanding performance that demonstrated high accuracy in predicting LNM in bladder cancer (AUC ranged from 0.978 to 0.998 in 5 validation sets). This diagnostic model outperformed senior pathologists in diagnostic sensitivity (0.983 vs. 0.947) [30].

Intraoperative guidance

After personalizing the surgical plan, AI has also become a transformative approach in intraoperative care, which can significantly enhance precision, efficiency, and decision-making during surgical procedures. Firstly, AI provides real-time diagnosis and decision support through detection and localization using single dataset or multimodal datasets [31]. Based on digital pathology data, Sendín-Martín M et al. developed an automated approach using a deep learning algorithm with ex vivo confocal microscopy for rapid detection of basal cell carcinoma during Mohs surgery (AUC = 0.94 in validation set) [32]. Based on imaging data, in neuro-oncology, AI models have revealed its potential in detecting tumor boundaries [33, 34]. A deep learning model was used to identify the eloquent cortex from rs-fMRI connectivity before surgery [35], while an AI technique combining CNN and NIR-II fluorescence imaging (named FL-CNN) was similarly reported to enhance surgical safety by detecting glioma boundaries [36]. Besides using single data, real-time surgical decision support systems use multimodal AI to integrate patient-specific data to create dynamic dashboards that guide surgeons at critical moments [37]. These systems enhance situational awareness and inform decisions such as resection margins, biopsy necessity, or anatomical navigation. For example, Sturgeon, a patient-independent transfer-learning neural network, using rapid nanopore sequencing, allows rapid access to sparse methylation profiles during surgery, enabling accurate diagnosis of most samples within 40 min of starting sequencing [38].

In addition, AI-driven surgical robots are at the forefront of development [39]. They combine computer vision with machine learning algorithms to perform complex tasks such as tissue dissection, suture placement and real-time anatomical recognition [40–42]. These systems improve accuracy and reduce human error, and are particularly beneficial in minimally invasive surgery where precision is critical. Recently, Hani J Marcus et al. have presented the IDEAL framework for surgical robotics, providing guidelines for AI-driven surgical robots in clinical translational phases [43].

Moreover, predictive modelling has become an important tool, which assist in monitoring vital signs and physiological parameters during surgery. For example, the Hypotension Prediction Index System, which predicts the onset of intraoperative hypotension, enabling timely intervention and reduction of complications [44]. By analyzing time-series data from intraoperative monitoring systems, AI models– particularly one model based on recurrent neural networks (RNNs) - can also predict other complications such as hypoxia and excessive blood loss.(AUC = 0.94 in validation set of approximately 25000 patients) [45].

Furthermore, intraoperative AI has advantages in addressing non-technical aspects of surgery, such as optimizing surgical teamwork and promoting surgical skills education. An important development in improving surgical collaboration is the creation of an AI-powered mentor designed to detect how well a surgical team's mental frameworks are aligned, which could be vital for surgical outcomes [46]. Furthermore, Various non-skill data streams including physiological metrics like heart rate variability, staffing levels and equipment availability could be integrated into a system designed for automation and optimization. Common intraoperative challenges such as fatigue, communication breakdowns and turnover issues, and equipment shortages could be solved through this kind of AI-system [47, 48]. In terms of surgical education, traditional surgical education lack effective assessment of feedbacks of trainees and consumes a longer period of time [49]. Reliable feedback from automated analysis of data makes AI methods uniquely suited to training surgical skills [50]. Rafal Kocielnik et al. proposed a collaborative human-machine refinement process that uses unsupervised machine learning algorithms to discover categories of feedback in the surgical record that significantly enhance the prediction of behavioral change in trainees. This facilitates modification of trainee behaviors and more efficient skill acquisition [51].

Postoperative care and recovery

After surgery is conducted, AI holds promising potential in postoperative management by predicting complications, tracking recovery, and providing personalized follow-up. This approach reduces readmission rates, improves patient outcomes, and optimizes healthcare resources allocation. For example, to better predict major postoperative complications in patients undergoing cytoreductive surgery, Deng H et al. utilized US Hyperthermic Intraperitoneal Chemotherapy Collaborative Database to create an explainable machine learning model (AUC = 0.75 in validation set) [52], which proved more accurate than the published MLR model (AUC = 0.54). After other types of tumor surgery, Hassan AM et al. developed a random forest model for predicting mastectomy skin flap necrosis (AUC = 0.70 in validation set) [53]. In measuring cosmetic outcomes, Kim DY et al. evaluated them after reconstructed breast surgery, using a generative adversarial network [54].

AI in individual radiotherapy

Besides surgery, radiotherapy remains one of the primary treatment modalities for cancer. The processes of radiotherapy generate various kinds of data, including clinical variables, imaging data, biological samples, planning parameters, and machine data. AI approaches show advantages in integrating these data to support tasks such as accurate contouring and dose prediction, thereby enhancing individualized radiotherapy [55, 56].

Tumor contouring
Tumor contouring is usually the first step of radiotherapy procedure. Traditionally, contouring of gross tumor volume, clinical target volume and organs at risk have been performed manually by radiation oncologists, relying highly on expertise, which results in unavoidable intra-observer viability and significant time consumption. AI-mediated multistep integrated radiation therapy workflow has shown promising results in a single center [57]. Especially, deep-learning based systems has shown remarkable progress in this field [58]. A 3D U-Net, base on deep learning methods, has automated and standardized the process of segmentation, delineating tumor boundaries with high precision [59]. Additionally, Shi F et al. generated RTP-net, a deep-learning model for radiotherapy planning, showing high accuracy with average Dice score of 0.95 [60]. To compare AI-led and oncologist-led methods, Jordan W et al. evaluated deep learning based auto-segmented contours trained by a single oncologist and expert contours created by multiple oncologists, concluding that the former performed accurately in organs at risk and provided significant time savings [61].

Dose optimizing
Precision-dose radiotherapy helps to maximize the effect on tumors while sparing healthy tissue. In terms of dose predicting, an individualized auto-planning system is urgently needed, as current radiotherapy operators often determine the dose of radiation based on standard protocols, adjusting them iteratively to coordinate doses in different regions. The method of iterative trials limits the efficiency and precision of radiotherapy [62]. Systems based on AI algorithms has made considerable progress in accurately making dose prediction [63, 64]. For example, Florian M et al. generated a generative adversarial network model to predict dose distributions inside unknown phantoms accurately, with potential applications in novel radiotherapy techniques requiring high accuracy, such as synchrotron X-ray microbeam radiation therapy [65]. Furthermore, the combination of radiomics data and dosimetry data has been widely used in response and toxicity prediction. For example, Jin C et al. presented a multi-task deep learning approach that allows solid tumor radiotherapy response prediction [66]. The imaging-based model, integrated with blood-based tumor markers, substantially improves prediction accuracy with AUC = 0.97 in validation set.

AI in personalized chemotherapy
While chemotherapy is a fundamental treatment for many cancers, it is often associated with severe side effects and variations in patient response. AI has become an invaluable tool for optimizing chemotherapy in therapy planning and drug utilization.

Chemotherapy planning
AI methods were primarily used for decision-making in chemotherapy of different cancers. In gastric cancer, Sundar R et al. used a genomic-based random forest model to guide the selection of patients with gastric cancer who would benefit from paclitaxel [67]. In colorectal cancer, ssing deep learning and H&E-stained tissue sections, DoMore-v1-CRC provided a clinical decision support system that stratified patients with stage II and III colorectal cancer with favorable prognosis, helping to avoid unnecessary adjuvant chemotherapy [68]. Similar results were obtained when a machine learning framework was used to predict the response of neoadjuvant chemotherapy in muscle-invasive bladder cancer [69]. In ovarian cancer, a 2021 study showed that AI models trained on gene expression data could predict the efficacy of platinum-based chemotherapy with more than 80% accuracy [70]. These predictive models help oncologists to avoid ineffective treatments, minimize the risk of unnecessary toxicity, and select the best beneficiaries.

Optimizing drug efficacy
Even if the potential beneficiaries of chemotherapy can be identified, drug resistance largely limits the application of conventional chemotherapy. Machine learning can be used to accurately predict patients' resistance to chemotherapy drugs, potentially mitigating this issue. Sasaki K et al. integrated machine learning algorithms with CT images to predict neoadjuvant chemotherapy resistance in patients with advanced gastric cancer. The integrated model demonstrated better results than current clinical models (AUC > 0.752 in validation sets from three centers) [71]. The latest developments in AI methodologies and tools have also enhanced our understanding of cancer multidrug resistance. In response, Fu L et al. presented a new viewpoint on repurposing non-oncology small-molecule drugs as an attractive approach to improve cancer therapy [72].

AI in targeted treatment
Focusing on specific molecular targets involved in cancer progression, targeted therapy has become one of the most popular treatments in CPM [73]. Nevertheless, due to the limited understanding of carcinogenesis, obstacles remain in the development of targeted therapies, especially in the fields of target prediction and drug selection. Implementing the entire process from target identification to targeted drug therapy is challenging based on a single technique or single-omics data. Therefore, AI holds considerable potential to effectively integrate multiple datasets and explore interactions between genes

and gene products involved in tumorigenesis, thereby advancing the clinical application of targeted drugs [74]. (Fig. 4)

Prediction of emerging targets with AI

Precisely predicting drugs is the basis of targeted therapy. AI-driven algorithms primarily predict new druggable targets by combining omics data. Using nonparametric random forest to analysis genomics data, Zare A et al. reported an inflammatory breast cancer (IBC)-specific gene signature (G59) to show the molecular differences between IBC and non-IBC patients, paving the path for discovering therapeutic targets at the genomic level [75]. In addition, the combination of machine learning models and mechanistic information could help to demonstrate signal transduction network heterogeneity and identify potential therapeutic target. For example, Pham TH et al. integrated a machine-learning framework with chemicogenomics and transcriptomics data to identify YAP/TAZ dependency across cancers and propose a potential therapeutic target in Hippo pathway dysregulation [76]. Moreover, integrating multi-omics data, Xiao Y et al. used machine learning methods based on the polar metabolome and lipidome analysis to distinguish triple-negative breast tumors into two prognostic metabolomics subgroups (C2 and C3) [77]. They subsequently revealed that N-acetyl-aspartyl-glutamate is a critical tumor-promoting metabolite and might exist as a potential therapeutic target for high-risk C2 and C3 tumors.

AI in targeted drugs

After identifying potential therapeutic targets, AI could participate form drug generation to selection to utilization. With AI models, it is easier to generate and validate drugs that interact most effectively. Furthermore, drug repurposing and combination therapies can be realized through powerful analytical capabilities of AI, which are also of vital importance combating potential drug resistance and minimizing side effects.

Drug generation

For traditional drug generation, the industry and reasearch have often focused on the chemical aspects of compound generation while overlooking the biological consequences. In the stage of drug discovery, aberrant m6A regulators have emerged as popular drug targets in recent years. AI-assisted synthesis of FTO inhibitors and METTL3 inhibitors has greater advantages over natural compounds [78]. Using deep learning and molecular dynamics simulation-based drug screening, Zhang H et al. identified UM-164 as a potential TIPE2 inhibitor [79]. Despite only focusing on chemical aspects, following machine-learning-based virtual screening, surface plasmon resonance, molecular docking, and pharmacokinetic analyses identified two potential inhibitors of anti-apoptotic members of the Bcl-2 family in solid tumors [80]. In addition, knowledge of drug mode of action (MoA) is an important part of developing anti-cancer drugs. Mohamad Saoud et al. have successfully predicted

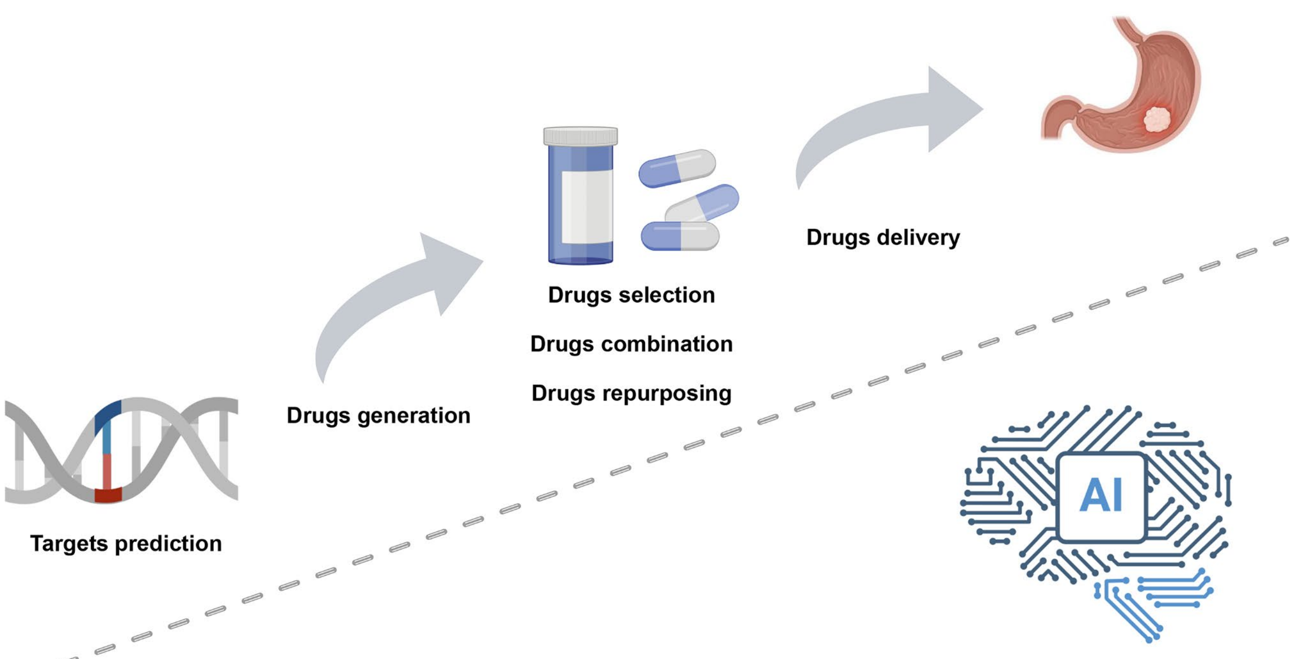

Fig. 4 Artificial intelligence involves throughout the targeted therapy process. AI plays an important role throughout the entire process of targeted therapy. From the identification of therapeutic targets and the development and utilization of targeted drugs to the precise delivery of these drugs, AI demonstrates significant potential at every stage of the targeted therapy workflow

MoA of novel drug candidates in prostate cancer cells using metabolomics data combined with machine learning, and the predicted results of MoA based on prostate cancer cell therapy was successfully validated in breast cancer and Ewing's sarcoma [81].

Drug selection

Turing from drug generation to practical clinics, drug selection is essential for individualized therapy. Based primarily on the chemical information of drugs, Su R et al. proposed a deep learning network named Siamese Response Deep Factorization Machines to directly rank the drugs for helping each patient receive the most effective drugs [82]. Additionally, at the single-cell sequencing data level, Chen J et al. developed a deep transfer learning model called scDEAL to predict and select drugs [83]. Other investigators have also obtained the goal with using AI to integrate data from different modalities. For example, Liu X et al. predicted drug response to guide anti-cancer drug selection by GraphCDR, a contrastive learning neural network based on multi-omics profiles and chemical structure of drugs [84].

Drug utilization

In the area of targeted drug utilization, AI contributes to drugs combination, repurposing, and delivery. Multi-targeted drugs combination is an emerging theme due to the increased understanding of intra-tumor heterogeneity, which is an important attempt in precision medicine. However, identifying multi-targets and selecting co-suppressive patient-specific therapies is difficult, as it is challenging in terms of both efficacy and toxicity. Researchers have proposed the AI-driven model scTherapy in conjunction with single-cell transcriptomics data to priorities multi-targeted therapeutic options for tumor patients. In a pan-cancer analysis of five cancer types, 19% of the therapeutic regimens generated by the system were patient-specific [85]. Using multi-omics data, Li X et al. also integrated cancer informatics algorithms and machine learning methods to develop a system called REFLECT [86]. It could optimize therapeutic benefits by choosing proper drug combinations. To improve drug repurposing, Cui C et al. integrated drug-exposure expression profiles and drug-drug links, using a graph neural network to develop a breast tumor drug repurposing strategy [87]. In addition, given the heterogeneity of delivery among drugs, using AI to enhance nanomedicine design for improved drug delivery efficiency represents a promising development [88, 89].

AI in personalized immunotherapy

Cancer immunotherapy represents a transformative approach in cancer treatment, restoring the normal anti-tumor immune response to control and eliminate tumors by restarting the tumor-immune cycle [90]. However, the effectiveness of immunotherapy varies significantly among patients. With integrating multimodal data, AI has emerged as a key tool to better understand tumor microenvironment (TME) and tumor immunology. Specially, AI models help to predict patient responses to immunotherapy, guide the discovery of neoantigens and tumor vaccines, and understand new concerns in tumor immunity such as LncRNA. (Fig. 5)

AI in predicting immunotherapy response

Immune checkpoint inhibitors(ICIs) are the most widely used approach in the field of tumor immunotherapy, and predicting its biomarkers is extremely important to enable personalized immunotherapy. Analyzing genomics, transcriptomics, epigenomics, radiomics and digital pathology data derived from high-throughput sequencing, AI is promising in predicting biomarkers for immunotherapy, including the most common biomarkers for ICIs, novel biomarkers, and predictive tools to be mined from TME [91, 92].

Through prediction of common biomarkers of ICIs

PD-L1 is one of the most important biomarkers in ICIs. Assessment of PD-L1 is crucial for treatment stratification and predicting immunotherapy outcomes. Combining digital pathological images [93, 94] or radiomics data [95, 96], AI models have significantly enhanced the ability to predict PD-L1 expression in solid tumors. For example, in non-small cell lung cancer, Choi S et al. developed an analyzer for PD-L1 tumor proportion score using whole-slide images [97]. Comparing the accuracy of manual evaluation and AI-assisted evaluation, they found that AI assistance increased the overall concordance rate among pathologists to 90.2% (compared to 81.4% for manual evaluation) with statistical significance ($P < 0.001$). In terms of multimodal data integration, Vanguri R S et al. also integrated AI and pathology with CT images, demonstrating an AUC of 0.80 in validation set for their model in predicting ICIs response in lung tumor [98].

In addition to PD-L1, other biomarkers are also potentially useful for predicting ICIs response with the aid of AI algorithms [99]. For example, Gong X et al. developed a machine-learning model and demonstrated that HLA gene expression is able to predict the immune subtypes of patients receiving ICIs [100]. Tumor mutational burden is another key feature that has been extensively studied. To evaluate tumor mutational burden and predict response to immune checkpoint blockade, researchers respectively combined AI algorithms with transcriptomics [101], radiogenomics [102], and digital pathology [103–105], demonstrating potential clinical benefits.

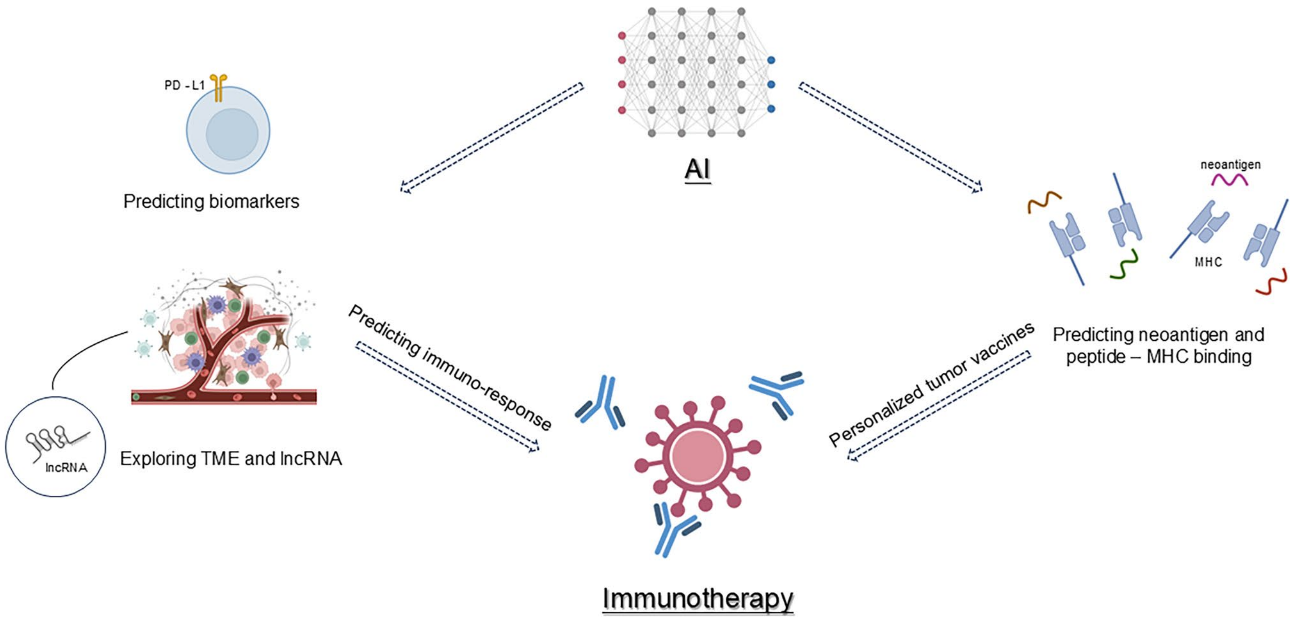

Fig. 5 Artificial intelligence's promising role in personalized immunotherapy. AI holds significant promise in personalized immunotherapy by contributing to key aspects of cancer immunotherapy, including predicting immune responses and generating tumor vaccines. This means that AI not only enhances the precision of widely used immunotherapeutic approaches, such as immune checkpoint inhibitors, but also exhibits great potential in the development of future individualized immunotherapy strategies

Through prediction of novel biomarkers

Many novel biomarkers have been confirmed with the assistance of AI [92]. Through genomics data, loss of heterozygosity status in human leukocyte antigen and genomic intra-tumor heterogeneity were identified to be associated with ICIs efficacy by Wang et al. with ML-based methods in non-small-cell lung cancer patients [106]. Using epigenomic data, artificial intelligence-driven approaches have identified a number of DNA methylation indicators as biomarkers for ICIs in different solid tumors [107, 108]. Through radiomics data, Dercle et al. used random forest algorithm to analysis 575 patients with melanoma treated with ICIs in KEYNOTE-002 and KEYNOTE-006 trials. They identified a radiomic biomarker composed of volumetric growth (absolute tumor volume difference), tumor volume, quantitative representation of tumor spatial heterogeneity, and quantitative representation of tumor edge phenotype, achieving precisely predicting OS (AUC = 0.92) [109].

The application of AI to integrate multimodal data to predict biomarkers has been a hot topic in recent years [110]. Through AI-driven multi-modal data integration, researchers have proposed a number of unique classifications to be used as biomarkers for immunotherapy, some of which have achieved good results [111]. For example, Shen et al. used ML-based methods to establish an immune cell phenotype with three classifications based on data from multiple sources, and identified that the LAG-3 + CD8 + T-cell population can be a novel biomarker for poorer OS and PFS in patients with melanoma and uroepithelial carcinoma(OS: $P < 0.001$; PFS: $P = 0.004$) [112]. Similarly, in bladder cancer, Shuai Ren et al. used the Graph Neural Networks model to integrate multi-omics data to generate a simple linear scoring model, responseScore, to predict immunotherapy response and identify key pathways. The model had an AUC of 0.839 in the validation set [113]. However, it is important to notice that multi-data integration brings higher challenges on the quality of input data. In addition, the validation datasets of these published multi-modal data integration AI systems are limited, so the evaluation of these AI procedures needs to be cautious.

Through exploration of TME

TME is the living space surrounding the tumor cells, including various types of cells, factors and matrix. AI techniques can accurately predict the status of TME and improve understanding of factors impacting immunotherapy efficacy. Along with the study of TME, some biomarkers, including neutrophil-lymphocyte ratio and tumor stemness showed potential predictive effects. With the help of support vector machine classifiers and random forests analysis, Raman spectroscopy shows potential for predicting response to ICIs in TME [114].

The tumor immune microenvironment (TIME), which represents the immune context of TME, has been proven to be associated with carcinogenesis, tumor progression, and identification of potential therapeutic targets [115, 116]. Tumor-infiltrating immune cells in TIME were widely researched. Based on biomarkers of tumor-infiltrating lymphocytes (TILs), Park S et al. used AI models and whole-slide images to predict the efficacy of ICIs and defined three immune phenotypes for predicting tumor response [117]. Similarly, Ao Z et al. developed a TILs score analyzer with clinical data and machine-learning algorithms. Using this analyzer, they evaluated the efficacy of drugs and selected an epigenetic drug called LSD1i which could enhance the therapeutic benefit of ICIs [118]. Furthermore, understanding T cell exhaustion (TEX) heterogeneity also helps to evaluate immunotherapies. Zhang Z et al. developed a machine learning-based gene signature to model the hierarchical TEX stages and optimize immunotherapy [119]. Similarly, Using unsupervised deep learning algorithms and analyzing spatial transcriptomics data, Chia-Kuei Mo et al. increased understanding of TME and proposed enhanced markers of immune depletion [120].

Using AI to target new tumor antigens

The search for tumor antigens as well as the developing of tumor vaccines are emerging strategies in immunotherapy. Somatic cancer mutations expressed especially in cancer cells, and these gene products could become neoantigens after breaking down and be targeted. Recognized by CD4 + or CD8 + T cells without being subject to central tolerance, neoantigens have great potential as targets for T cell-based immunotherapies [121]. As neoantigens are mostly unique for each patient, this therapeutic method is inherently personalized.

Neoantigen identification

Neoantigens are essentially the products of gene mutations in tumor cells. The development of AI techniques has promoted the discovery of mutations by analyzing high-throughput sequencing data [122–124]. Based on single data modality, by processing and analyzing transcriptome data, a machine-learning computational pipeline named EasyFuse developed by Weber D et al. to could help to detect cancer-associated gene fusions, potential sources of highly immunogenic neoantigens [125]. Integrating multimodal omics data including genomics, transcriptomics and proteomics data, the researchers developed an advanced ML-driven computational framework program called NeoDisc. This procedure was shown to outperform conventional methods in accurately prioritizing immunogenic neoantigens [126].

Prediction of MHC-antigen binding

Since neoantigens are presented on major histocompatibility complex (MHC) before bonding T cells, predicting peptide-MHC binding, is as crucial as predicting neoantigens and important in generating tumor vaccines [127]. Using label-agnostic protein sequence data, a transfer learning model called MHCRoBERTa was employed to address this task [128]. Using machine learning methods, the integrated model called Anthem combined mass spectrometry with machine learning, and particularly predicted HLA-I binding [129]. Similarly, Haodong Xu et al.so generated a DL-based system called ImmuneApp to predict HLA-I binding [130]. For the accurate prediction of HLA-II binding, Racle J et al. also realized it with a machine-learning framework [131].

Designing of personalized tumor vaccines

By simulating interactions with the immune system, AI contributes to the design and optimization of vaccines. It helps guide researchers in selecting the most promising personalized vaccines for further development and improves the efficiency and effectiveness of the vaccine development process [132]. Powderly JD et al. and Xu Y et al. designed mRNA vaccines and peptide vaccines with the help of AI, respectively, and conducted phase I clinical trials in different cancer areas [133, 134]. In addition, adjuvants play a crucial role as an essential component in the development of effective cancer vaccines that enhance the body's immune response to cancer cells and improve the effectiveness of cancer vaccines [135]. AI is involved in the development of tumor vaccine adjuvants in five ways: preliminary design, virtual screening, property prediction, and reuse [136]. For example, Sajjad Haider et al. successfully predicted three potent CXCL12 inhibitors that could potentially act as adjuvants using a ligand-based virtual screening tool [137].

Promoting the use of long non-coding RNA in immunotherapy with AI

Long non-coding RNA (lncRNA), which regulates transcription, epigenetic modifications, and other post-transcriptional mechanisms, is closely associated with cancer immunity regulation and the TME [138]. AI helps to elucidate its various mechanisms and its role in tumor immunotherapy. It is documented in several types of cancer that lncRNA interacts with RNA-binding protein, and the use of machine learning methods revealed details of the mechanism and the potential of RNA-based therapeutics [139]. Given the importance of TILs in immunotherapy mentioned above, Zhou M et al. and Zhang N et al. respectively explored the tumor-infiltrating immune cell-associated lncRNA in low-grade glioma and tumor-infiltrating B lymphocytes [140]. Integrating machine learning algorithms and clinical profiles, they found that the tumor-infiltrating immune cell-associated lnc signature could select potential beneficiaries of immunotherapy. Liu Z et al. used an integrative procedure of machine learning to validate the clinical significance of lncRNA in colorectal tumors [141]. They constructed a consensus immune-related lncRNA signature to predict clinical outcomes, finding that the low-risk group benefited more from bevacizumab, whereas the high-risk group was better suited for fluorouracil-based chemotherapy. A consensus machine learning-derived lncRNA signature developed by Liu Z et al. reached a similar conclusion [142]. It was even further found to play a role in tumor recurrence prediction.

Limitations and challenges of AI in oncology

While AI has been widely studied in tumor management and has potentially shown a game-changing impact in this field, barriers remain in translating algorithms and research into clinical applications that require further discussion and investigation.

Quality and bias

Data bias could exist at every step of the process for AI applications [143, 144]. The greatest source of data used for training AI models is electronic health records from clinical activities, but unstructured and inconsistent records limit their usability, necessitating structured data organization [145]. Moreover, while data heterogeneity across institutions is common, evaluating external cohorts is crucial. Although more studies recently use training data from multiple centers, the representativeness of the target is still limited by biases that cannot be eliminated in gender, ethnicity, research interest, funding etc., potentially resulting in poor generalization of models and even increasing of health-care discrimination [146].

Interpretability and transparency

AI algorithms, especially black-box deep-learning models, often generate outputs without explaining the intermediate steps, resulting in a lack of interpretability [147]. This limitation in intelligibility challenges the collaboration between different clinicians or between AI systems and clinicians, partially limiting their real-world medical utility [148]. It is crucial for clinicians to understand AI models and relate them to human medical knowledge. In the era of precision oncology, this contributes to improved diagnostic accuracy and efficiency [149]. Biological network models in natural systems have the potential to enhance the cognition of how AI system works and improve its transparency [150]. Meanwhile, greater involvement of clinicians in data collection, bias mitigation, and technology application is needed to establish an efficient human-computer hybrid system rather than applying AI in isolation [151].

Security and privacy

Data security and privacy are also being challenged in the age of AI. Many AI systems, especially those connected to networks, face potential security risks, including malicious hacking that could compromise patient data privacy. Data breaches could lead to severe consequences, including the possibility of algorithm tampering to favor certain stakeholders. To address these risks, robust security measures, along with comprehensive laws and regulations, are essential for ensuring the safe deployment of AI applications.

Regulation and ethics

The regulatory framework for AI in healthcare is still evolving. Although some AI tools have been approved for clinical use by regulatory bodies like the FDA, the process of approving AI algorithms remains complex and time-consuming. The major ethical problem in this field is determining who should take responsibility for AI decision-making. Undeniably, clinicians providing medical advice, manufacturers of AI products, employers of clinicians, and health systems are all stakeholders in AI applications and should be held accountable if AI leads to suboptimal or adverse outcomes [152]. Under the current liability system, clinicians may hesitate to use AI especially when facing its opaqueness. Therefore, specialized adjudication systems together with special compensation systems funded by relevant people's taxes or fees might be able to replace the traditional liability system in medical disputes involving AI [152].

Future prospects and conclusions

AI in oncology holds great prospects and has the potential to transform cancer treatment by enabling more precise, personalized and efficient interventions. Firstly, understanding the cancer biology will always be a focus and a challenge in the field of oncology, and integrating and analyzing an increasing number of multimodal datasets is the most effective means of addressing this issue. As the field of AI develops, it is becoming more and more capable of integrating data through ever-refined algorithms [153, 154]. Besides today's most commonly used datasets from modern medical activities, including genomics data, imaging genomics data, TME-based data, and electronic health records, it is even possible to integrate potentially exploitable datasets such as facial and tongue visual diagnosis data generated from traditional Chinese medicine diagnosis and treatment [155]. This could better reveal the complex patterns of tumor behavior and treatment response and facilitate personalized tumor therapy. It is worth noting that most of the existing data used to train AI systems are derived from clinical studies. While this somewhat reduces bias, it undoubtedly makes AI systems less externally accessible. Therefore, compared to the limited amount of data originating from clinical studies, the larger and more complex real-world data is "an ocean" of lesser-explored data waiting to be integrated and utilized by AI [156]. In addition, the impact of AI on equality in oncology goes in both directions [157]. The ideal AI system is instead one of the best ways to address equality in oncology if its impact on health equality is considered in the early stages of its development, including integrating different datasets, addressing algorithmic bias, ensuring fair validation across different demographic and geographic contexts, and prioritizing fair outcomes. This is mainly in terms of removing implicit bias from clinicians' subjective assessments [158]. AI provides tools to reduce disparities in cancer care by increasing access to diagnostics, treatments, and clinical trials across populations. In short, individualized patient information is used as the most important basis for decision-making. At the same time, AI has the potential to tailor tools for resource-limited settings, such as portable imaging devices and simplified diagnostic approaches, from which lower-income populations can still have access to advanced cancer treatments. Finally, the value of large-scale language models (such as ChatGPT and systems based on it) in oncology remains to be developed [154]. They can provide simplified communication and knowledge acquisition, enhance opportunities for patient engagement, and thus improve the efficiency of the entire cancer care process. In conclusion, it is undeniable that AI algorithms have great potential in tumor treatment, and promote the management of tumors in the era of precision medicine. However, gaps remain between AI models and their clinical implementation. With research fervor in this area extremely high, However, gaps remain between AI models and their clinical implementation. Large-scale prospective clinical trials are expected, and in particular, AI-driven cancer precision medicine should not be pursued cautiously to maintain cost-effectiveness. Future research should focus on improving security and interpretability to enhance coordination between AI and clinicians, making AI more applicable.

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