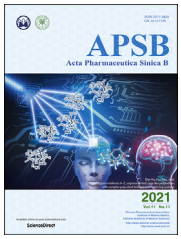
Acta Pharmaceutica Sinica B 2021;11(11):3393−3405

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com



REVIEW

Applying artificial intelligence for cancer immunotherapy

Zhijie Xu[a,†], Xiang Wang[b,†], Shuangshuang Zeng[b], Xinxin Ren[d], Yuanliang Yan[b,c,*], Zhicheng Gong[b,c,*]

[a]*Department of Pathology, Xiangya Hospital, Central South University, Changsha 410008, China*
[b]*Department of Pharmacy, Xiangya Hospital, Central South University, Changsha 410008, China*
[c]*Institute for Rational and Safe Medication Practices, National Clinical Research Center for Geriatric Disorders, Xiangya Hospital, Central South University, Changsha 410008, China*
[d]*Center for Molecular Medicine, Xiangya Hospital, Key Laboratory of Molecular Radiation Oncology of Hunan Province, Central South University, Changsha 410008, China*

Received 6 October 2020; received in revised form 7 December 2020; accepted 21 December 2020

KEY WORDS

Artificial intelligence;
Cancer immunotherapy;
Machine learning;
Diagnostics

Abstract Artificial intelligence (AI) is a general term that refers to the use of a machine to imitate intelligent behavior for performing complex tasks with minimal human intervention, such as machine learning; this technology is revolutionizing and reshaping medicine. AI has considerable potential to perfect health-care systems in areas such as diagnostics, risk analysis, health information administration, lifestyle supervision, and virtual health assistance. In terms of immunotherapy, AI has been applied to the prediction of immunotherapy responses based on immune signatures, medical imaging and histological analysis. These features could also be highly useful in the management of cancer immunotherapy given their ever-increasing performance in improving diagnostic accuracy, optimizing treatment planning, predicting outcomes of care and reducing human resource costs. In this review, we present the details of AI and the current progression and state of the art in employing AI for cancer immunotherapy. Furthermore, we discuss the challenges, opportunities and corresponding strategies in applying the technology

Abbreviations: AI, artificial intelligence; CT, computed tomography; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; DL, deep learning; ICB, immune checkpoint blockade; irAEs, immune-related adverse events; MHC-I, major histocompatibility complex class I; ML, machine learning; MMR, mismatch repair; MRI, magnetic resonance imaging; PD-1, programmed cell death protein 1; PD-L1, PD-1 ligand1; TNBC, triple-negative breast cancer; US, ultrasonography.

*Corresponding authors.
E-mail addresses: yanyuanliang@csu.edu.cn (Yuanliang Yan), gongzhicheng@csu.edu.cn (Zhicheng Gong).
†These authors made equal contributions to this work.

Peer review under responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2021.02.007

for widespread clinical deployment. Finally, we summarize the impact of AI on cancer immunotherapy and provide our perspectives about underlying applications of AI in the future.

1. Introduction

With the increasing development of biotechnology and continuous advances in characterizing the molecular mechanisms of tumors, immunotherapy is now playing a critical role in cancer treatment aside from standard chemotherapy, radiotherapy and surgery. Cancer immunotherapy can use the patients' own immune system to treat cancer, which has been regarded as the first broadly successful strategy for various cancers[1,2]. Immune checkpoints are a class of inhibiting receptors and suppressive signaling pathways that are exploited by tumors to block the function of T lymphocytes and thus engage in immune escape. Currently, programmed cell death protein 1 (PD-1), PD-1 ligand 1 (PD-L1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) are the dominant checkpoint molecules. In recent years, promising advances have been made in employing immunotherapy in the clinic, including immune checkpoint inhibitors, chimeric antigen receptor T cell therapies, tumor vaccines and adoptive immunotherapy[3]. Immunotherapy drugs, such as nivolumab (anti-PD-1), atezolizumab (anti-PD-L1), and ipilimumab (anti-CTLA-4), have provoked increasing concern regarding their profound anti-tumor activity[4]. However, the objective response rate to these therapies varies greatly among various patients. In addition, the high cost of these treatments and the high incidence of autoimmune-disease, such as immune-related adverse events (irAEs), are the main limitations of immunotherapy that need to be addressed[5]. Therefore, clinical satisfaction with immunotherapy might be enhanced by improving its diagnostic accuracy and by identifying patients most likely to respond to the drugs in addition to monitoring the outcomes of treatment.

The basis of artificial intelligence (AI) was firstly established in a Dartmouth conference sixty years ago and created to utilize the technology to complete jobs that included making decisions, interpreting language and applying visual perception that frequently required human intelligence. Notably, AI technology service providers have emerged with increasing frequency on the market, which has allowed vertical domain image algorithms and natural language processing to meet the requirements of the medical industry and created a hot spot for the application of AI in medicine[6]. With the amassing of data and related outcomes, AI approaches enable computers to become progressively better in conducting a specific task and then generating decision support systems, revealing promise in their accuracy of distinguishing diverse immunohistochemical scores, cancer subtypes, and biomarkers[7]. Furthermore, just as Thompson et al.[8] predicted, AI, with its advanced computing technology, may have the potential to rebuild the specialty through minimizing errors and improving such parameters as the specificity of patients' treatment and dosimetry regulation.

Although immunotherapy is a great breakthrough in the field of cancer treatment, the judgment of whether a particular patient can respond to the therapy is occasionally confusing. However, the appearance of AI increases the chance of successful cancer immunotherapy through forecasting the therapeutic effect based on the establishment of immunotherapy predictive scores, including immunoscore and immunophenoscore[9]. These two scoring systems were developed to predict the response to immune checkpoint blockade (ICB) therapy. Meanwhile, some limitations, such as unknown predictive power of individual biomarkers, difficulty of integrating diverse biomarkers into one system and lack of ICB response prediction models that can integrate different biomarkers, are the main barriers that warrant further study. A previous study showed that the integration of an AI-based diagnostic algorithm with physicians' interpretations can be positively related to improving diagnostic accuracy for indiscernible cancer subtypes[7]. AI technology obtains approximately 91.66% accuracy when recognizing major histocompatibility complex (MHC) patterns associated with immunotherapy response[10]. More importantly, AI can be applied to standardize assessments across institutions instead of depending on the interpretation of clinicians that occasionally is inherently subjective[11,12]. Therefore, the application of AI in cancer immunotherapy may lead to positive outcomes in patients (Fig. 1 and Table 1).

In this review, we mainly discuss the critical roles of AI in cancer immunotherapy as well as the advantages and limitations. In addition, we predict the impact of AI on cancer immunotherapy and provide our opinion about better acceptance of AI in the future.

2. Definition of AI in medicine

In the frame of this review, AI refers to the capacity of a machine to stand alone and model certain thought processes and intelligent behaviors of humans in taking an action to achieve a predetermined goal in response to its perceived environment; however, it should be noted that multiple definitions currently exist. Generally, AI is the process of building models with outstanding performed in training and testing datasets through the combination of computerized algorithms and high-throughput data[32]. Using radiomics as an example, the process includes three aspects. The first step commonly involves lesion segmentation, which is usually conducted by the image preprocessing steps covering skull stripping, intensity normalization, and alignment of image volumes from different modalities[33]. Currently, several methods have been applied for segmentation, including manual annotation and/or labeling, semiautomated methods and deep learning (DL) methods[34,35]. The next step of radiomics refers to the extraction of quantitative features, which contain basic size, shape, intensity metrics and some more complex features obtained from various statistical methods used for images, for example, texture-based features, DL features, spatial patterns, fitted biophysical models and histogram-based features[36]. Then, several different machine learning (ML) models can be used on intermediate quantitative features to "mine" them for critical connections, enabling them to forecast significant information about the tumor, such as

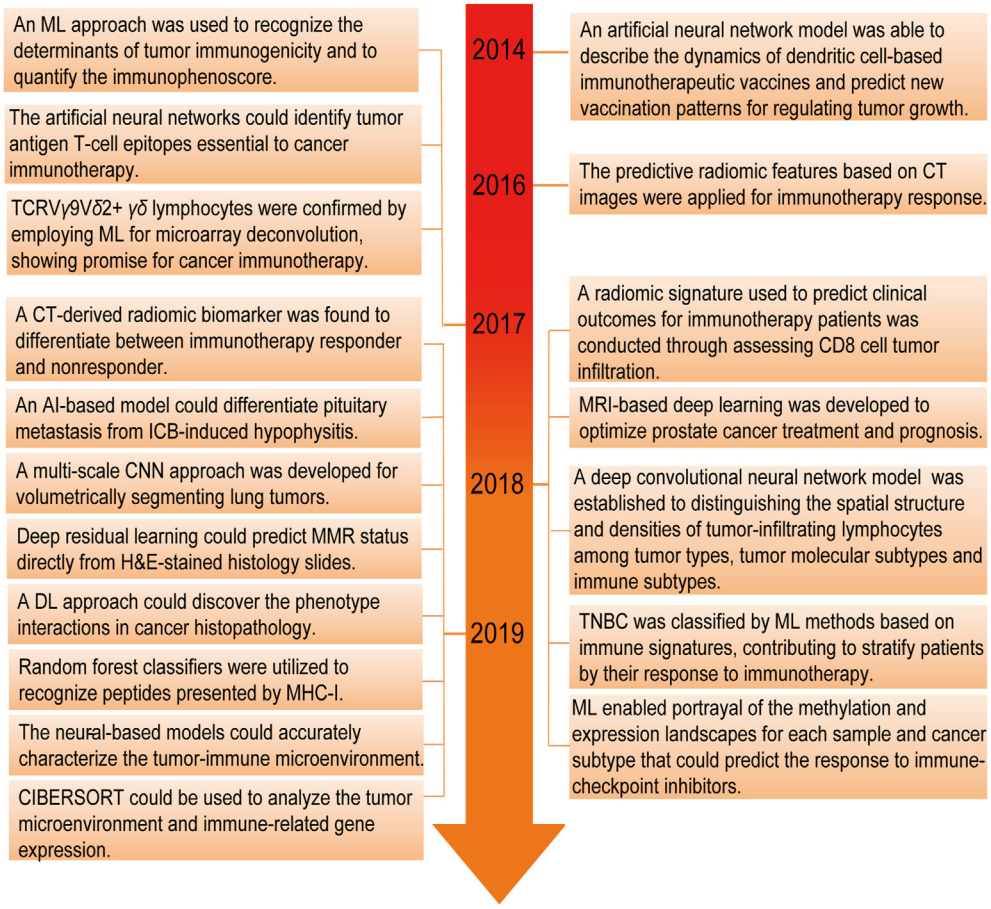


Figure 1 Timeline of key discoveries of AI applications in cancer immunotherapy. Landmark events and advances in the application of AI technology in cancer immunotherapeutic response. AI, artificial intelligence; CNN, convolutional neural network; CT, computed tomography; DL, deep learning; ICB, immune checkpoint blockade; MHC-I, major histocompatibility complex class I; ML, machine learning; MRI, magnetic resonance imaging; TNBC, triple-negative breast cancer.

molecular markers, infiltrating tumor margins and prognosis, which are related to treatment decision making[37]. Based on the above information, AI is good at identifying complex patterns in high-throughput data and can offer a quantitative evaluation in an automated manner. Therefore, more precise and repeatable assessments can then be established when AI is integrated in the clinical workflow as a method to assist physicians[38].

ML, a subfield of AI technology, can adjust the parameters of a model based on large quantities of exemplar training data by employing statistical methods instead of being explicitly programmed[39]. Based on its features, ML can be classified into handcrafted and non-handcrafted feature-based techniques, and supervised, unsupervised and reinforcement learning are three examples[40]. Handcrafted feature-based ML techniques are able to extract numerous explicit features, such as those based on what physicians typically search for in their diagnostic or decision processes that are prespecified in the dataset. Using heuristic methods that rely on developed and understood algorithms, such as edge detection in medical image processing or signals, these ML techniques can quantify the information in an automated manner from the samples[39]. However, non-handcrafted feature-based ML techniques can manage the raw medical data and then adjust to extract its own features beyond distinct labeling from the dataset to ameliorate the prediction error or other measures of classification performance. For example, DL methods remarkably improve the state of the art in medical image analysis, genomics and immunology[41]. Supervised learning depends on specific datasets that have been labeled by experts and algorithms, such as support vector machines, Naive Bayes classification and random forests. These algorithms are trained to measure the difference between the known labels and predicted labels, which finally optimizes the clinical responses error[42]. In contrast, unsupervised learning, such as principal component analysis, k-means clustering and autoencoders, divides the clinical samples into different classes according to the features of the training data alone without corresponding labels[43]. In addition, reinforcement learning, including model-free and model-based reinforcement learning, can be conducted to predict the detailed clinical features in the future, relying on the past and present clinical symptoms predicted by maximizing the expected return at each stage[44]. In conclusion, AI is widely used in the medical field, and its emergence provides better medical services to patients.

3. AI-based immune signatures

Cancer immunotherapy is a process of restoring the body's normal antitumor immune response to control and remove tumors through restarting the tumor-immune cycle, including tumor antigen release and presentation, activation of effector T cells, migration

Table 1 Application of AI-based technologies in cancer immunotherapy.

Medical field	Biomarker	Task	Outcome	Tumor	Immuno- therapy type	Ref.
Hematology	Immunogenomics	Identification the determinants of tumor immunogenicity and quantify the termed immunophenoscore	Positive	20 solid tumors	ICB	13
Hematology	Peptide presentation by MHC-I	Identification peptides presented by MHC-I	Positive	9 different cancer types	Tumor vaccine	14
Hematology	RNA-seq and imaging data	Characterize the tumor-immune microenvironment	Positive	4 Solid tumors	N/A	15
Hematology	Profiles of immune cell infiltration and immune-related genes	Explore the immune cells and immune-related gene expression	Positive	Colorectal cancer	N/A	16
Hematology	Tumor-specific T-cell epitopes	Discernment tumor antigen T-cell epitopes	N/A	Melanoma	N/A	17
Hematology	Tumor-infiltrating TCRVγ9Vδ2$^+$ $\gamma\delta$ lymphocytes	Recognization blood-derived TCRVγ9Vδ2$^+$ $\gamma\delta$ lymphocytes	N/A	50 types of solid and hematological malignancies	N/A	18
Hematology	Immunogenomic Profiling	Classification of triple-negative breast cancer	Positive	TNBC	ICB	19
Radiology	Radiographic Characteristics	Description of each lesion on the pretreatment contrast enhanced CT imaging data	Positive	NSCLC Melanoma	ICB	20
Radiology	CD8 cell infiltration level	Evaluation CD8 cell tumor infiltration	Positive	Advanced solid tumors	ICB	21
Radiology	MRI features	Management more layers of data and forms of data	N/A	Prostate cancer	N/A	22
Radiology	Radiomic features	Prediction radiomic features	N/A	NSCLC	N/A	23
Radiology	CT image-based features	Volumetrically segmenting lung tumors and accurate longitudinal tracking of tumor volume changes	Positive	NSCLC	ICB	24
Radiology	Image-based signature	Differentiating pituitary metastasis from ICB-induced hypophysitis	Positive	N/A	ICB	25
Pathology	MMR status	Prediction MMR status	Positive	Gastrointestinal cancer	ICB	26
Pathology	Tumor-infiltrating lymphocyte maps	Extraction information on the probability of tumor-infiltrating lymphocyte infiltration	Positive	13 different cancer types	ICB	27
Pathology	Phenotypic information	Exploration tumor immune cell interactions within the tumor microenvironment	Positive	Melanoma	ICB	28
Other	Volatile organic compound	Detecting volatile organic compound patterns in exhaled breath	Positive	NSCLC	ICB	29
Other	Gene expression and DNA methylation	Unraveling the interplay between gene expression and DNA methylation	Positive	Glioblastoma	ICB	30
Other	Vaccination profiles	Imitation the behavior of tumor growth in dendritic cell-based immunotherapy	Positive	Fibrosarcoma	Tumor vaccine	31

CT, computed tomography; ICB, immune checkpoint blockade; MHC-I, major histocompatibility complex class I; MMR, mismatch repair; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; TNBC, triple-negative breast cancer.

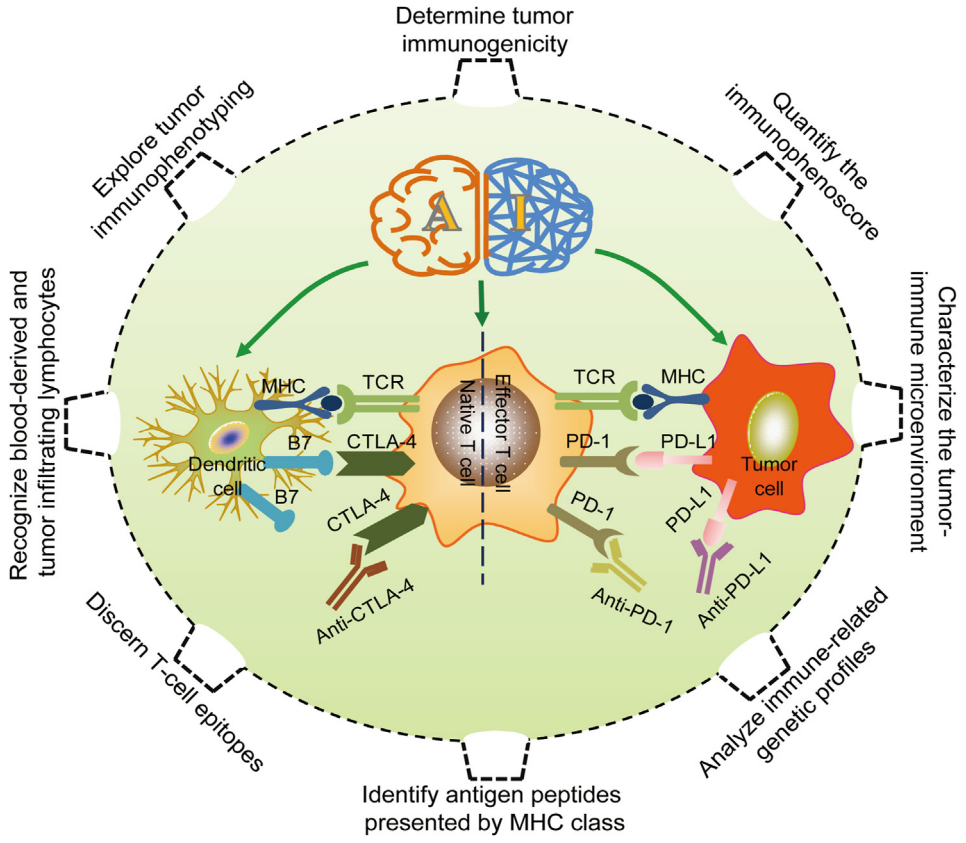


Figure 2 AI provides novel and promising strategies for evaluation of numerous immune signatures. AI-based technologies can be used to identify and quantify multiple aspects of immune-associated signatures, which are closely related to cancer immunotherapeutic response. AI, artificial intelligence; CTLA-4, cytotoxic T lymphocyte-associated antigen 4; MHC, major histocompatibility complex; PD-1, programmed cell death protein 1; PD-L1, PD-1 ligand1; TCR, T cell receptor.

and infiltration of T cells into tumor tissues, and finally recognition and clearing of tumor cells by T cells[45–47]. Although numerous immune signatures are connected with cancer immunotherapeutic responsiveness, the method used for signature identification and quantification is a major challenge. Nevertheless, advances in AI have provided a novel and promising strategy for this research (Fig. 2). Using an ML approach, Charoentong et al.[13] identified the determinants of tumor immunogenicity and quantifies the immunophenoscore, a distinctive predictor for recognizing the treatment response to anti-PD-L1 and CTLA-4, with an established scoring scheme. Boehm et al.[14] made random forest classifiers for identifying peptides presented by major histocompatibility complex class I (MHC-I) not only to further our understanding of immunopeptidomics but also to apply this information to neoantigen binding predictions for cancer immunotherapy. Neural-based models developed by Reiman et al.[15] accurately characterized the tumor-immune microenvironment of colorectal, breast, lung and pancreatic solid tumors, which is essential for patients' response to cancer immunotherapy, through integrating both RNA-Seq and imaging data in a clinical setting. The infiltration of immune cell types in the tumor microenvironment and immune-related gene expression in colorectal cancer were analyzed using a deconvolution algorithm named cell type identification by estimating relative subsets of RNA transcripts[16]. Moreover, ML-based artificial neural networks enable us to discern tumor antigen T-cell epitopes from melanoma patients, which are crucial to personalized cancer immunotherapy. Moreover, the method of ML for microarray deconvolution completes the task for recognizing blood-derived TCRVγ9V$\delta 2^{+}$ $\gamma\delta$ lymphocytes and evaluating their abundance as tumor infiltrating lymphocytes across 50 types of solid and hematological malignancies, which represent promising effectors for cancer immunotherapy[17,18]. Unsupervised and supervised ML methods were utilized to perform the classification of triple-negative breast cancer (TNBC) based on the conduciveness of immune signatures to the optimal stratification of TNBC patients regarding whether they will respond to immunotherapy, such as anti-PD-1/PD-L1[19]. Furthermore, unsupervised approaches are capable of stratifying luminal-A breast cancer into five subtypes based on cancer-associated heterocellular signatures and the enrichment of immune checkpoint genes and other immune cell types, indicating their potential response to cancer immunotherapy[48]. In addition, certain genomic or genetic features, such as PD-L1 expression, deficient DNA mismatch repair, neoantigen load and tumor mutation burden, are also relevant to immunotherapeutic responses that could be further researched and combined in an AI application[49–51]. The computation of genomic or genetic biomarkers is simple; moreover, their values can easily be identified from high-throughput data.

Neoantigens are newly formed peptides produced by somatic mutations that are able to induce tumor-specific T cell recognition, which can be used to develop personalized immunotherapy for

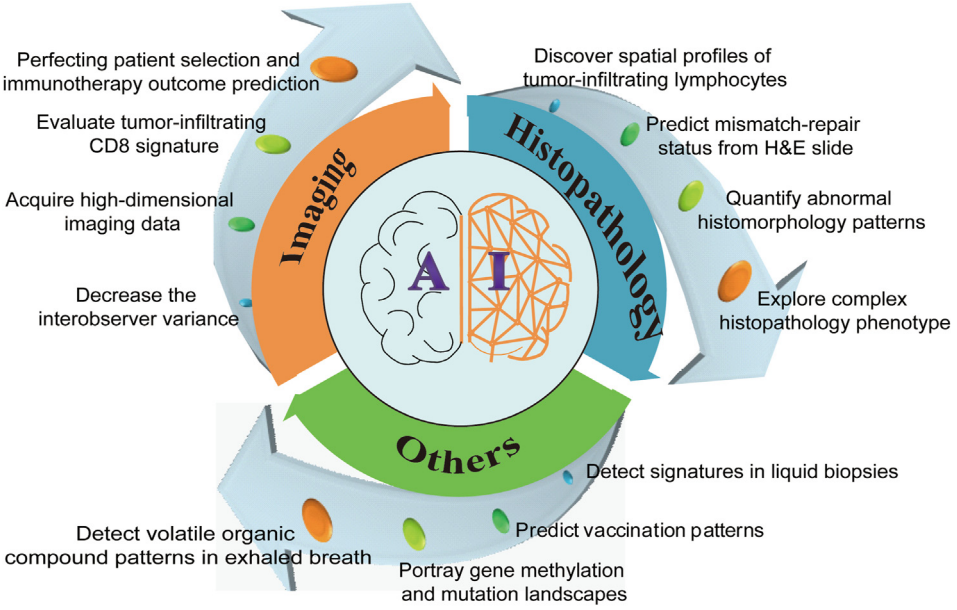


Figure 3 The application of AI-based technologies in immunotherapy and their potential clinical consequences. AI has served as a surprisingly developed method during the pursuit of computer-assisted cancer immunotherapy. Through analysis of clinical data in imaging, histopathology, etc., advanced AI methodologies can be used to provide effective clues on immunotherapy response in clinical practice. AI, artificial intelligence.

cancer treatment[52,53]. In general, the potential neoantigens can be predicted according to several steps, including somatic mutation identification, human leukocyte antigen (HLA) typing, peptide processing, and peptide-MHC binding prediction[53]. Recently, the advent of AI provides another promising approach to accurately identify the neoantigens. ML-based models can be applied to predict the binding of peptides to specific HLA class I allotypes. Accordingly, Mei et al.[54] found that ML-based algorithms can improve the prediction accuracy of immunogenic peptides through integrating HLA-binding properties with several immune-associated features, such as peptide transport into the endoplasmic reticulum, susceptibility to proteasome cleavage and T-cell receptor repertoire. In addition, some peptide-MHC-binding prediction algorithms play an essential role in the field of neoepitope prediction[55,56]. For example, MHCflurry, an open-source software for MHC I binding prediction, was recently developed to generate the separate predictions for binding affinity of MHC I epitopes and their peptide ligands[57]. Meanwhile, artificial neural networks have been performed with higher accuracy in acquiring the nonlinear relationship between peptide sequence and the binding affinity of homologous MHC molecules[58]. Even though the AI-based technologies have been confirmed for its biological importance in neoepitope predication, the further development of AI-driven algorithms in definitely identification of neoantigens requires more concerted efforts in clinical practice.

4. AI for predicting of immunotherapy responses

To date, most notable is the successful application of AI in immunotherapy in cancer research (Fig. 3). ML can match the pace with modern medicine regarding generated data and the detection of phenotypic varieties that sneak through human screening[59]. The range of machine screening can also be adjusted to detect only interested phenotype changes or to screen for broader phenotypes. Currently, AI-based methods have shown good results in the prediction of MHC-II epitopes on the strength of amino acid sequences and the development of vaccines targeting MHC-II immunopeptidome[60,61], which demonstrate the increasingly extensive application of AI in immunotherapy.

4.1. *AI-based imaging analysis*

Medical imaging is a technological process that creates visual representations of the interior of a body, and this technology is used in clinical practice and research, *i.e.*, computed tomography (CT) and magnetic resonance imaging (MRI)[62,63]. The remarkably complex descriptions of tumors and lymph nodes and the lengthy tasks conducted by radiation oncologists induce bottlenecks for effective radiation therapy and monitoring of treatment effects[64]. However, with the increasing application of AI in medical imaging, high-dimensional imaging data can be acquired to show macroscopic as well as molecular and cellular characteristics. AI-based medical imaging offers advantages in saving time and decreasing interobserver variance, which could improve current workflows in radiology, including directly impacting diagnoses, standardization of multiple images, image quality enhancement, database mining for study, content-based indexes and reports of generation and semantic error labeling[65].

Patient selection and predicting treatment responses represent main issues limiting the use of cancer immunotherapy. However, AI-based medical imaging biomarkers have revealed hopeful consequences in perfecting patient selection and outcome prediction through providing unparalleled perspectives into tumors and their microenvironment in a noninvasive manner[66]. Radiomics refers to AI-based characterization of radiology, which can offer more detailed characterization than that possible by eyes[67,68]. A CT-derived radiomic biomarker was developed and validated that distinguished immunotherapy responders from nonresponders both in non-small cell lung carcinomas (NSCLC) and melanoma patients by generating an AI-based feature description on the pretreatment contrast-enhanced CT imaging data[20]. This study found that lesions with more heterogeneous morphological

profiles, which had compact borders and non-uniform density patterns, were more likely to response to immunotherapy. Based on the above, medical imaging-based radiomics could provide credible noninvasive biomarkers for the prediction of therapeutic response to anti-PD1, suggesting that the AI-based models can be applied to evaluate the response to cancer immunotherapy[69,70]. Similarly, in a retrospective multi-cohort study, Sun et al.[21] established a radiomic signature to predict clinical outcomes in patients with advanced solid tumors after anti-PD-L1 or anti-PD-1 immunotherapy. Through combining RNA-seq genomic data from tumor biopsies and contrast-enhanced CT images, this radiomics approach provided a promising method to evaluate the tumor-infiltrating CD8 signature and infer clinical outcomes for cancer patients[21]. Thus, these studies suggested connections between immunotherapy response and radiomics characteristics, revealing uniform trends across cancer types as well as anatomical location.

Additionally, while predictive radiomic features using CT images have been validated by Coroller et al.[22] for application to predicting treatment responses, an MRI-based DL algorithm capable of employing more layers of data is being used to optimize prostate cancer treatment and prognostication[23]. Based on the DL models, two multiple resolution residually connected networks are developed for volumetrically segmenting lung tumors and accurate longitudinal tracking of tumor volume changes, which was necessary for monitoring tumor response to pembrolizumab (anti-PD-1) in NSCLC patients[24]. Furthermore, an image-based signature accomplishing the best performance in differentiating pituitary metastasis from ICB-induced hypophysitis was developed by employing a multivariable prediction model based on a random forest tree algorithm, and this methodology can be used by clinicians for enhanced decision-making in cancer patients undergoing ICB therapy[25]. Therefore, the imaging biomarkers obtained from AI-based medical imaging analysis could be useful for predicting clinical outcomes and the prognosis of patients treated with immunotherapy, which could further promote the application of cancer immunotherapy in the clinic.

4.2. *AI-based histopathology analysis*

Solid tumors are generally always diagnosed by histopathologists, and these diagnoses are primarily based on hematoxylin and eosin (H&E)-stained slides[71]. The successful application of AI to pathology slides offering a wide variety of information has revolutionized our understanding of cancer histology. In a seminal paper in 2016, Sirinukunwattana et al.[72] demonstrated that a spatially constrained convolutional neural network combined with neighboring ensemble predictor accurately accomplished the detection and classification of the nucleus in routine colon cancer histology images, which benefited the pathological practice in terms of quantitative analysis of tissue constituents with respect to whole-slide images. These findings provide powerful proof that AI-based methods might have potential application in the location and identification of abnormal histomorphology patterns in routine whole-slide images of cancer patients. Accordingly, ML techniques based on histopathology analysis could provide new opportunities to predict the response to cancer immunotherapy[73]. Studies have proposed that defective mismatch repair (MMR) machinery caused by mutations in MMR genes that lead to an increasing number of somatic mutations in the genome is significantly related to the ICB response[74]. In support of these results, Le et al.[75] found that the immune-related objective response rate was 40% and 0% for MMR-deficient colorectal cancers and MMR-proficient colorectal cancers, respectively, indicating that MMR status could be used to predict the clinical response of patients treated with immune checkpoint inhibitors. Notably, Kather et al.[26] confirmed that deep residual learning could predict MMR status directly from H&E-stained histology slides in gastrointestinal cancer patients. In this report, they demonstrated that deep residual learning ultimately enables efficient identification of microsatellite instable patients, allowing the benefits of cancer immunotherapy to be demonstrated to a broader target population. In addition, the ratio between the total amount of intratumoral lymphocytes and cancer cells is significantly related to the expression of the immunotherapy target CTLA-4[76]. Moreover, many studies have confirmed that higher T cell infiltration levels and increased tumor-infiltrating lymphocyte numbers are related to better immune-checkpoint blockades[77]. Then, Saltz et al.[27] discovered that the spatial structure and densities of tumor-infiltrating lymphocytes, which are significantly associated with immunotherapy and obtained from H&E scanned images by employing a deep convolutional neural network model, are differentially enriched among tumor types, tumor molecular subtypes and immune subtypes. In addition, Effland et al.[28] developed a DL approach utilizing variational networks to explore complex phenotype interactions in melanoma histopathology that could be predictive of response to immunotherapy. Furthermore, co-development of purpose-built AI in parallel with computational pathology might benefit harmonizing immunotherapy companion diagnostics by facilitating easy sharing and standardizing of image analysis algorithms.

Therefore, exploring the functional roles of AI-based theologies in predicting immunotherapy response in cancer patients might open a novel important approach to provide a better understanding the therapeutic efficiency of ICB. However, some advantages and disadvantages should be better addressed in future research. First, the radiographic images are mainly obtained digitally and can be switched to a completely digital workflow with minimal information loss; conversely, tissue sections may contain more information than might be acquired in a digital image. However, the lack of fine detail plus worries that digital slides need more time to review than glass slides has decreased the charm of AI to pathologists[78]. Moreover, an excess of pathological sections and interference from artifacts, such as air bubbles and tissue folding, and the high cost of scanning and storing images are exacerbating this trend. In addition, there is vigorous debate among pathologists with respect to the potential capabilities of AI to surpass humans in diagnostic accuracy and treatment efficacy judgment as well as the future role of human experts in these areas[79,80]. Nevertheless, in considering these problems, we should keep in mind the inherent inaccuracy of technological prognostication and the role of perspectives and biases in affecting private opinions[81].

4.3. *Others*

Numerous other studies have applied AI to similar tasks in cancer immunotherapy. Using AI software, a device named “electronic nose” or “eNose” was trained by the researchers that could precisely predict whether NSCLC patients would response to anti-PD-1 therapies. In the study, the device was able to accurately distinguish responders from non-responders, which outperformed immunohistochemistry, through detecting volatile organic compound patterns in exhaled breath related to NSCLC patients’ responses to the checkpoint inhibitors pembrolizumab and

nivolumab[29]. Moreover, ML models using gene mutation features might serve as biomarkers for immunotherapy prognosis and guidance[75,82,83]. In addition, Hopp et al.[30] verified that a method based on self-organizing maps ML could be used to portray the methylation and expression landscapes for each sample and cancer subtype in glioblastoma, and this information is useful for the prediction of response to immune-checkpoint inhibitors. However, methylation and expression did not change simultaneously in subtypes of G-protein coupled receptors, such as cytokine receptors influencing immune response functionalities, which warrant further study. In addition, a model based on artificial neural networks was employed to analyze the dynamics of dendritic cell-based immunotherapeutic vaccines and predict vaccination patterns for managing fibrosarcoma growth[31]. Nevertheless, the simulation results and predicted profiles were not validated by experiments and require further confirmation. Therefore, these AI-based approaches should be carefully designed, integrated and further explored.

At present, liquid biopsy, particularly circulating tumor cell DNA, reveals better tumor heterogeneity with greater accuracy compared with tumor biopsy given its properties in a convenient and dynamic analysis[84−86]. In immunotherapy, liquid genetic biomarkers are increasingly being developed for use in predicting the therapeutic effect of ICB[87]. Moreover, some biomarkers, such as plasma cytokine interleukin and circulating tumor cell DNA, can be used to exclude hyperprogressive or pseudoprogressive disease after immunotherapy[88]. Thus, the use of potential biomarkers for liquid biopsy may contribute to the recognition of patients who would benefit the most from immunotherapy. In addition, AI has already been used as a potential strategy to automatically discover and detect molecular signatures in liquid biopsies[89]. Thus, in the future, AI will hopefully provide a range of information to evaluate immunotherapy response through liquid biopsy.

5. Application of AI in current challenges of immunotherapy

Immunotherapy has substantially changed the clinical strategy for treating cancer. With the development of treatments in the clinical and preclinical setting, the quantity of immunotherapy drug approvals, mainly belonging to the class of immune checkpoint inhibitors, has been increasing[90−92]. Currently, aside from numerous novel therapies targeting other prospects, treatments targeting T cell immunoreceptors with immunoglobulin and ITIM domains, the lymphocyte activation gene 3 and T cell immunoglobulin and mucin-domain 3, are in clinical trials or under development for cancer immunotherapy. PD-1, PD-L1 and CTLA-4 are the three main inhibitory molecules targeted by United States Food and Drug Administration approved drugs, such as pembrolizumab, avelumab and ipilimumab[93−96]. Unfortunately, although numerous molecular targets and their corresponding drugs have been developed with excellent therapeutic effect, only 20%−50% of patients respond to treatment. The mechanisms of immune checkpoints resistance have become a focus of attention. Arlauckas et al.[97] found that tumor-associated macrophages quickly removed anti-PD-1 monoclonal antibodies from T cells, thereby impairing the cytotoxic T cell responses. Other mechanisms include insufficient generation and effector function of anti-tumor T-cells and impaired formation of T-cell memory[98]. Therefore, developing methods to identify patients who are most likely to respond to immunotherapy is strongly warranted. On the other hand, irAEs have appeared as continual complications of checkpoint blockade, revealing a major clinical challenge to safely manage the use of these inhibitors[5]. Some irAEs, such as colitis or rash, emerge rapidly after employing immune checkpoint inhibitors, while others, such as hypophysitis or liver toxicity, develop slowly[99]. However, other irAEs, such as dermatitis or pneumonitis, are largely reversible owing to the intrinsic regenerative ability of the concerned organ, while others generate long-term tissue damage, such as adrenal corticosteroid and insulin deficiency, due to the destruction of endocrine organs[99]. Additionally, the severity and frequency of irAEs increase significantly during combination-treatments. Wolchok et al.[100] discovered that up to 60% of patients treated with anti-CTLA-4 plus anti-PD-1 were experiencing serious irAEs, including heart and nervous system inflammation. These clinical manifestations are probably attributable to the physiological function of checkpoint pathways in regards to modulating adaptive immunity and averting autoimmunity. Thus, understanding what drives these irAEs and how to avoid them are becoming increasingly important issues. Excitingly, a highly exact, standardized database of irAEs has been built to comprehensively detect and understand biological mechanisms of irAEs[101]. The extracted irAEs can act as the gold standard to assess automatic irAE extractions from other data resources and lay the foundation for developing computational methods to know the irAEs, which eventually to ensure safe cancer treatment. Finally, the high cost of the therapy could lead to massive individual spending, as well as financial burdens on the national medical insurance system.

Emerging evidence has indicated that AI-based technologies can be used in cancer research and treatment. AI approaches the problems as a doctor handling a residency would, beginning with patient observation, utilizing algorithms to screen variables and searching combinations for predicting outcomes dependably. AI-based strategies have been used for tasks in multiple medical specialties, most widely pathology and radiology, and in some situations, these methods have achieved capability equivalent to that of human experts[102]. For example, integration of AI into pathology will generate an advanced diagnostics and improved workflow, empowering clinicians to review and share images quickly, and employ computational algorithms to assess valuable insights for acquiring a more informed and detailed cancer diagnosis[103,104]. Moreover, these algorithms could exploit data extracted from medical images that would not be obvious through human analysis that can be informative in regards to diagnosis, treatment sensitivity and prognosis[105]. In a retrospective study, Wang et al.[106] developed a semisupervised DL method, extracting effective CT-based data, to predict the risk of recurrence of high-grade serous ovarian cancer. Additionally, the application of AI in immunotherapy is becoming increasingly extensive, such as searching for biomarkers for diagnosis and prognosis and describing the phenotypic information of tumor cells[107]. Effland et al.[28] used variational networks for joint image reconstruction and segmentation based on a DL approach to illustrate the direct interactions between immune cells and melanoma cells. AI also has the potential to predict the response to ICB through focusing on the antigen presenting pathway[108]. In addition, AI provides us a promising method to solve the deficiencies of cancer immunotherapy, including the low rate of patient response, irAEs and expensive hospitalization cost. Houy et al.[109] imported AI techniques in immunotherapy to optimize the therapy schedule, which might be conducive to decreasing irAEs through using lower doses, as well as making the treatments more affordable. In addition, ML-based phenotyping method could recognize patients

with irAEs from numerous clinical notes and ML-based predictive analytics was a feasible approach for predicting onset and continuity of patient-reported symptoms in patients with ICB therapies. These studies are inspiring and illustrated that AI-based models could be further applied to the early detection of ICB-dependent toxicities. Finally, the further development of AI-driven algorithms in cancer immunotherapy can accelerate progress in terms of developing accurate biomarkers and governance algorithms for predicting the response to treatment, evaluating drug resistance, predicting patient survival and analyzing minimal residual disease, which enables clinicians to more precisely provide patients with the most effective standard of care, providing a supreme advantage for each patient[110−112].

6. Perspectives and opportunities of AI in immunotherapy

Learning from a large set of data and identifying patterns that could be applied to definite purposes, such as mutation annotation or diagnosis, is the greatest strength of AI[113,114]. For example, the International Business Machines Watson Oncology system trained on the available data, was an avant-courier in the AI field and provided evidence-based, individualized therapeutic regimens for the majority of blood and solid cancers[115]. However, there are some limitations obstructing the progress of AI in cancer immunotherapy. One barrier is the insufficient amount of available data. ML models usually function best when these models are trained on large amounts of training data, but few public databases are currently available[7]. In addition, some stakeholders might be loath to exchange data among each other due to various reasons, such as misaligned commercial purposes or responsibilities related to personal privacy laws[116]. Thus, encouraging data sharing among hospitals and institutes around the country or even around the world, such as The Cancer Imaging Archive and Quantitative Imaging Network project, are essential for meeting the requirements of utilizing large and diverse datasets to enhance the accuracy of AI approaches[117,118]. Another barrier is the current decentralized and fragmented state of medical records. Patient records obtained from hospitals and data centers exist in various forms, such as recorded speech, free text and medical images, and are rarely properly organized for computational analysis[119]. Furthermore, cultural and language bottlenecks are also factors involved in the fragmentation of medical records[120]. Therefore, establishing a standardized system including the use of inclusion and exclusion criteria could solve the need for a large amount of well-organized high-quality data for the application of AI in immunotherapy prediction[119,121]. Finally, ML models operate as a "black box" that is invisible and impalpable, leading clinical experts to be distrustful of them[122,123]. Moreover, trust between physicians and patients should be considered and built in when AI approaches are applied to immunotherapy[124]. Fortunately, many researchers have proposed methods for visualization of DL features and prediction models, which could potentially decrease the black box perception[125].

AI is an innovative and rapidly growing field with the potential to improve immunotherapy outcomes, as reported in many studies. However, at present, there are several problems in the literature. First, we discover that relevant prospective studies and randomized clinical trials of AI in immunotherapy are limited. Moreover, most non-randomized studies are not prospective, and a high risk of bias and deviation from existing reporting standards are noted[126]. Second, the reproducibility of AI is difficult to evaluate due to the limited availability of code and datasets, which might be solved by encouraging code and data sharing across scientific disciplines[127−129]. Additionally, overpromising language is found in many articles despite obvious limitations in terms of design, transparency, reporting and risk of bias[126,130]. Therefore, we should improve the reporting and transparency, strengthen the real-world clinical relevance, decrease the risk of bias and adjust the conclusion appropriately to reduce research waste, protect patients and avert hype.

Alternatively, a prevalent issue in numerous ML studies is the lack of proper "held out" validation samples, and this phenomenon also occurs during the learning process of models[33]. The overfitting shows that the trained model works well on the training set but poorly on the testing set. In general, data deficiency and complex models are the main causes of the phenomenon. Therefore, to avert overfitting (namely memorizing training sample cases instead of studying related pattern), data augmentation is required, and the dataset can be divided into three parts, including the training set, cross validation set and testing set, which can be used to preferably evaluate model performance[20,131]. In addition, several approaches, such as random forests, support vector machines and Bayesian networks, can be used to decrease model complexity through definitely engineered intermediate features and usually involve a feature simplification procedure[25,132].

AI methods have the ability to recognize patterns and combine information in ways that humans cannot, demonstrating substantial promise for the future of immunotherapy[133]. An ideal AI-based model used for immunotherapy would include all related data with clinical information and biomarkers to make accurate predictions regarding whether patients will benefit from immunotherapy[134]. In terms of the integrity, objectivity and speed of getting information, AI, such as radiomics, can exceed the clinicians' visual assessment[122]. However, AI differs from human intelligence in many aspects, and excelling in one area does not indicating outstanding performance in other areas, which needs to be clearly noted. In addition, there is no law that can be used to solve the liability issue if something goes wrong, such as who should be held responsible when an error in ML occurs or a diagnosis is missed[135]. Thus, the promise of up-and-coming AI approaches in immunotherapy should not be overstated, and AI does not replace clinicians at present because we all know that immunotherapy monitoring and strategies are quite complicated. Finally, we think that AI and clinicians should cooperate and learn from each other to better serve patients' immunotherapy.

Although AI approaches have strong potential in cancer immunotherapy, integrating AI techniques into the delivery of healthcare faces a number of obstacles. For example, overlooked assumptions in the primary data and models could result in dangerous suggestions, undiscerning to local care processes, being delivered by the AI system[136,137]. Problems with extensively used software might quickly impact many patients[138]. Furthermore, the intervention of AI in therapy monitoring might endanger some types of medical jobs, resulting in deskilling and possible technical errors[137,139]. To effectively manage these disadvantages, developing corresponding strategies is necessary. First, comprehension and investigation of the forms of sociotechnical threats that might be introduced by AI techniques into different fields of healthcare is important to build a consistent map of the safety landscape[111]. Second, establishing models of sociotechnical safety and related analytical methods is suitable for governing and explaining the patient safety venture produced by AI systems[140]. Third, we should understand the perspectives of the patient, practitioner and public in regards to the acceptability, benefits and

risks of AI approaches in successful immunotherapy, as well as in establishing institutional and social mechanisms deserving acceptance and trust[141,142]. Finally, building on higher level principles, testing the actual regulatory functions and specific management mechanisms will allow for guaranteeing the safety of emerging AI systems while adjusting to the particular challenges of governing technologies with the characteristics of constantly and autonomously adapting and learning[143,144]. Moreover, novel reliable computational models with the integration of various biomarkers are needed to improve immunotherapy response prediction. Recently, we developed a platform including the whole biochemical indexes of cancer patients, biomarkers and radiography data to provide some alternative methods for further optimization of AI-based approaches[145].

7. Conclusions

AI has served as a surprisingly developed method during the pursuit of computer-assisted cancer immunotherapy. With the increasing of clinical data and advanced AI methodologies, it has the potential to increase the functional roles in immunotherapy response; however, the technique is still far from widespread use in applications in clinical practice. We look forward to the promising not-too-distant future where AI will likely alter the practice of cancer immunotherapy and ultimately improve patient safety and healthcare quality.

Acknowledgments

The study was supported by the grants from National Natural Science Foundation of China (81803035), Natural Science Foundation of Hunan Province (2020JJ5934 and 2019JJ50932, China), China Postdoctoral Science Foundation (2020M672521), and Fundamental Research Funds for the Central Universities of Central South University (2019zzts345 and 2019zzts800, China).

Author contributions

Yuanliang Yan, Zhicheng Gong, Zhijie Xu and Xiang Wang collected the related papers. Zhijie Xu, Xiang Wang and Xinxin Ren drafted and wrote the manuscript. Zhijie Xu, Xiang Wang, Shuangshuang Zeng and Yuanliang Yan revised the manuscript. All authors have read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Looi CK, Chung FF, Leong CO, Wong SF, Rosli R, Mai CW. Therapeutic challenges and current immunomodulatory strategies in targeting the immunosuppressive pancreatic tumor microenvironment. *J Exp Clin Cancer Res* 2019;**38**:162.
2. Fu Y, Liu S, Zeng S, Shen H. From bench to bed: the tumor immune microenvironment and current immunotherapeutic strategies for hepatocellular carcinoma. *J Exp Clin Cancer Res* 2019;**38**:396.
3. Nishino M, Ramaiya NH, Hatabu H, Hodi FS. Monitoring immune-checkpoint blockade: response evaluation and biomarker development. *Nat Rev Clin Oncol* 2017;**14**:655−68.
4. Soularue E, Lepage P, Colombel JF, Coutzac C, Faleck D, Marthey L, et al. Enterocolitis due to immune checkpoint inhibitors: a systematic review. *Gut* 2018;**67**:2056−67.
5. Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. *JAMA Oncol* 2018;**4**:1721−8.
6. Tang Z, Chuang KV, DeCarli C, Jin LW, Beckett L, Keiser MJ, et al. Interpretable classification of Alzheimer's disease pathologies with a convolutional neural network pipeline. *Nat Commun* 2019;**10**:2173.
7. Rajkomar A, Dean J, Kohane I. Machine learning in medicine. *N Engl J Med* 2019;**380**:1347−58.
8. Thompson RF, Valdes G, Fuller CD, Carpenter CM, Morin O, Aneja S, et al. Artificial intelligence in radiation oncology: a specialty-wide disruptive transformation?. *Radiother Oncol* 2018;**129**:421−6.
9. Angell H, Galon J. From the immune contexture to the immunoscore: the role of prognostic and predictive immune markers in cancer. *Curr Opin Immunol* 2013;**25**:261−7.
10. Li Y, Niu M, Zou Q. ELM-MHC: an improved MHC identification method with extreme learning machine algorithm. *J Proteome Res* 2019;**18**:1392−401.
11. Thust SC, Heiland S, Falini A, Jager HR, Waldman AD, Sundgren PC, et al. Glioma imaging in Europe: a survey of 220 centres and recommendations for best clinical practice. *Eur Radiol* 2018;**28**:3306−17.
12. Okada H, Weller M, Huang R, Finocchiaro G, Gilbert MR, Wick W, et al. Immunotherapy response assessment in neuro-oncology: a report of the RANO working group. *Lancet Oncol* 2015;**16**:e534−42.
13. Charoentong P, Finotello F, Angelova M, Mayer C, Efremova M, Rieder D, et al. Pan-cancer immunogenomic analyses reveal genotype-immunophenotype relationships and predictors of response to checkpoint blockade. *Cell Rep* 2017;**18**:248−62.
14. Boehm KM, Bhinder B, Raja VJ, Dephoure N, Elemento O. Predicting peptide presentation by major histocompatibility complex class I: an improved machine learning approach to the immunopeptidome. *BMC Bioinf* 2019;**20**:7.
15. Reiman D, Sha L, Ho I, Tan T, Lau D, Khan AA. Integrating RNA expression and visual features for immune infiltrate prediction. *Pac Symp Biocomput* 2019;**24**:284−95.
16. Ge P, Wang W, Li L, Zhang G, Gao Z, Tang Z, et al. Profiles of immune cell infiltration and immune-related genes in the tumor microenvironment of colorectal cancer. *Biomed Pharmacother* 2019;**118**:109228.
17. Schmidt J, Guillaume P, Dojcinovic D, Karbach J, Coukos G, Luescher I. *In silico* and cell-based analyses reveal strong divergence between prediction and observation of T-cell-recognized tumor antigen T-cell epitopes. *J Biol Chem* 2017;**292**:11840−9.
18. Tosolini M, Pont F, Poupot M, Vergez F, Nicolau-Travers ML, Vermijlen D, et al. Assessment of tumor-infiltrating TCRVγ9Vδ2 $\gamma\delta$ lymphocyte abundance by deconvolution of human cancers microarrays. *OncoImmunology* 2017;**6**:e1284723.
19. He Y, Jiang Z, Chen C, Wang X. Classification of triple-negative breast cancers based on immunogenomic profiling. *J Exp Clin Cancer Res* 2018;**37**:327.
20. Trebeschi S, Drago SG, Birkbak NJ, Kurilova I, Calin AM, Delli Pizzi A, et al. Predicting response to cancer immunotherapy using noninvasive radiomic biomarkers. *Ann Oncol* 2019;**30**:998−1004.
21. Sun R, Limkin EJ, Vakalopoulou M, Dercle L, Champiat S, Han SR, et al. A radiomics approach to assess tumour-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study. *Lancet Oncol* 2018;**19**:1180−91.
22. Coroller TP, Agrawal V, Narayan V, Hou Y, Grossmann P, Lee SW, et al. Radiomic phenotype features predict pathological response in non-small cell lung cancer. *Radiother Oncol* 2016;**119**:480−6.
23. Miyahira AK, Soule HR. The 24th annual prostate cancer foundation scientific retreat report. *Prostate* 2018;**78**:867−78.

24. Jiang J, Hu YC, Liu CJ, Halpenny D, Hellmann MD, Deasy JO, et al. Multiple resolution residually connected feature streams for automatic lung tumor segmentation from CT images. *IEEE Trans Med Imag* 2019;**38**:134−44.
25. Mekki A, Dercle L, Lichtenstein P, Nasser G, Marabelle A, Champiat S, et al. Machine learning defined diagnostic criteria for differentiating pituitary metastasis from autoimmune hypophysitis in patients undergoing immune checkpoint blockade therapy. *Eur J Cancer* 2019;**119**:44−56.
26. Kather JN, Pearson AT, Halama N, Jager D, Krause J, Loosen SH, et al. Deep learning can predict microsatellite instability directly from histology in gastrointestinal cancer. *Nat Med* 2019;**25**: 1054−6.
27. Saltz J, Gupta R, Hou L, Kurc T, Singh P, Nguyen V, et al. Spatial organization and molecular correlation of tumor-infiltrating lymphocytes using deep learning on pathology images. *Cell Rep* 2018; **23**:181−193 e7.
28. Effland A, Kobler E, Brandenburg A, Klatzer T, Neuhauser L, Holzel M, et al. Joint reconstruction and classification of tumor cells and cell interactions in melanoma tissue sections with synthesized training data. *Int J Comput Assist Radiol Surg* 2019;**14**:587−99.
29. Abbasi J. "Electronic Nose" predicts immunotherapy response. *J Am Med Assoc* 2019;**322**:1756.
30. Hopp L, Loffler-Wirth H, Galle J, Binder H. Combined SOM-portrayal of gene expression and DNA methylation landscapes disentangles modes of epigenetic regulation in glioblastoma. *Epigenomics* 2018;**10**:745−64.
31. Mehrian M, Asemani D, Arabameri A, Pourgholaminejad A, Hadjati J. Modeling of tumor growth in dendritic cell-based immunotherapy using artificial neural networks. *Comput Biol Chem* 2014; **48**:21−8.
32. Kantarjian H, Yu PP. Artificial intelligence, big data, and cancer. *JAMA Oncol* 2015;**1**:573−4.
33. Rudie JD, Rauschecker AM, Bryan RN, Davatzikos C, Mohan S. Emerging applications of artificial intelligence in neuro-oncology. *Radiology* 2019;**290**:607−18.
34. Litjens G, Kooi T, Bejnordi BE, Setio AAA, Ciompi F, Ghafoorian M, et al. A survey on deep learning in medical image analysis. *Med Image Anal* 2017;**42**:60−88.
35. Shen D, Wu G, Suk HI. Deep learning in medical image analysis. *Annu Rev Biomed Eng* 2017;**19**:221−48.
36. Hagiwara A, Fujita S, Ohno Y, Aoki S. Variability and standardization of quantitative imaging: monoparametric to multiparametric quantification, radiomics, and artificial intelligence. *Invest Radiol* 2020;**55**:601−16.
37. Langs G, Rohrich S, Hofmanninger J, Prayer F, Pan J, Herold C, et al. Machine learning: from radiomics to discovery and routine. *Radiologe* 2018;**58**:1−6.
38. Hosny A, Parmar C, Quackenbush J, Schwartz LH, Aerts H. Artificial intelligence in radiology. *Nat Rev Cancer* 2018;**18**:500−10.
39. Deo RC. Machine learning in medicine. *Circulation* 2015;**132**: 1920−30.
40. Goldenberg SL, Nir G, Salcudean SE. A new era: artificial intelligence and machine learning in prostate cancer. *Nat Rev Urol* 2019; **16**:391−403.
41. LeCun Y, Bengio Y, Hinton G. Deep learning. *Nature* 2015;**521**: 436−44.
42. Lazarovits J, Sindhwani S, Tavares AJ, Zhang Y, Song F, Audet J, et al. Supervised learning and mass spectrometry predicts the *in vivo* fate of nanomaterials. *ACS Nano* 2019;**13**:8023−34.
43. Tshitoyan V, Dagdelen J, Weston L, Dunn A, Rong Z, Kononova O, et al. Unsupervised word embeddings capture latent knowledge from materials science literature. *Nature* 2019;**571**:95−8.
44. Uehara S, Mawase F, Therrien AS, Cherry-Allen KM, Celnik P. Interactions between motor exploration and reinforcement learning. *J Neurophysiol* 2019;**122**:797−808.
45. Liu J, Liu X, Han Y, Zhang J, Liu D, Ma G, et al. Nanovaccine incorporated with hydroxychloroquine enhances antigen cross-presentation and promotes antitumor immune responses. *ACS Appl Mater Interfaces* 2018;**10**:30983−93.
46. Xiao X, He X, Li Q, Zhang H, Meng J, Jiang Y, et al. Plasma exchange can be an alternative therapeutic modality for severe cytokine release syndrome after chimeric antigen receptor-T cell infusion: a case report. *Clin Cancer Res* 2019;**25**:29−34.
47. Aguilera TA, Rafat M, Castellini L, Shehade H, Kariolis MS, Hui AB, et al. Reprogramming the immunological microenvironment through radiation and targeting Axl. *Nat Commun* 2016;**7**:13898.
48. Poudel P, Nyamundanda G, Patil Y, Cheang MCU, Sadanandam A. Heterocellular gene signatures reveal luminal-A breast cancer heterogeneity and differential therapeutic responses. *NPJ Breast Cancer* 2019;**5**:21.
49. Diaz Jr LA, Le DT. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 2015;**373**:1979.
50. Rizvi NA, Hellmann MD, Snyder A, Kvistborg P, Makarov V, Havel JJ, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 2015;**348**:124−8.
51. Van Allen EM, Miao D, Schilling B, Shukla SA, Blank C, Zimmer L, et al. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. *Science* 2015;**350**:207−11.
52. Chen F, Zou Z, Du J, Su S, Shao J, Meng F, et al. Neoantigen identification strategies enable personalized immunotherapy in refractory solid tumors. *J Clin Invest* 2019;**129**:2056−70.
53. Richters MM, Xia H, Campbell KM, Gillanders WE, Griffith OL, Griffith M. Best practices for bioinformatic characterization of neoantigens for clinical utility. *Genome Med* 2019;**11**:56.
54. Mei S, Li F, Leier A, Marquez-Lago TT, Giam K, Croft NP, et al. A comprehensive review and performance evaluation of bioinformatics tools for HLA class I peptide-binding prediction. *Brief Bioinform* 2020;**21**:1119−35.
55. Holtstrater C, Schrors B, Bukur T, Lower M. Bioinformatics for cancer immunotherapy. *Methods Mol Biol* 2020;**2120**:1−9.
56. Mosch A, Raffegerst S, Weis M, Schendel DJ, Frishman D. Machine learning for cancer immunotherapies based on epitope recognition by T cell receptors. *Front Genet* 2019;**10**:1141.
57. O'Donnell TJ, Rubinsteyn A, Bonsack M, Riemer AB, Laserson U, Hammerbacher J. MHCflurry: open-source class I MHC binding affinity prediction. *Cell Syst* 2018;**7**:129−132 e4.
58. Zhao W, Sher X. Systematically benchmarking peptide-MHC binding predictors: from synthetic to naturally processed epitopes. *PLoS Comput Biol* 2018;**14**:e1006457.
59. Vandenberghe ME, Scott ML, Scorer PW, Soderberg M, Balcerzak D, Barker C. Relevance of deep learning to facilitate the diagnosis of HER2 status in breast cancer. *Sci Rep* 2017;**7**: 45938.
60. Moghram BA, Nabil E, Badr A. Ab-initio conformational epitope structure prediction using genetic algorithm and SVM for vaccine design. *Comput Methods Programs Biomed* 2018;**153**:161−70.
61. Degoot AM, Chirove F, Ndifon W. Trans-allelic model for prediction of peptide:MHC-II interactions. *Front Immunol* 2018;**9**:1410.
62. Liu F, Jang H, Kijowski R, Bradshaw T, McMillan AB. Deep learning MR imaging-based attenuation correction for PET/MR imaging. *Radiology* 2018;**286**:676−84.
63. Geis JR, Brady AP, Wu CC, Spencer J, Ranschaert E, Jaremko JL, et al. Ethics of artificial intelligence in radiology: summary of the joint European and North American multisociety statement. *Radiology* 2019;**293**:436−40.
64. Sharp G, Fritscher KD, Pekar V, Peroni M, Shusharina N, Veeraraghavan H, et al. Vision 20/20: perspectives on automated image segmentation for radiotherapy. *Med Phys* 2014;**41**:050902.
65. Dey D, Slomka PJ, Leeson P, Comaniciu D, Shrestha S, Sengupta PP, et al. Artificial intelligence in cardiovascular imaging: JACC state-of-the-art review. *J Am Coll Cardiol* 2019;**73**:1317−35.
66. Diem S, Schmid S, Krapf M, Flatz L, Born D, Jochum W, et al. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell

lung cancer (NSCLC) treated with nivolumab. *Lung cancer* 2017;**111**:176−81.
67. Su X, Chen N, Sun H, Liu Y, Yang X, Wang W, et al. Automated machine learning based on radiomics features predicts H3 K27M mutation in midline gliomas of the brain. *Neuro Oncol* 2020;**22**:393−401.
68. Aerts HJ. The potential of radiomic-based phenotyping in precision medicine: a review. *JAMA Oncol* 2016;**2**:1636−42.
69. Forghani R, Savadjiev P, Chatterjee A, Muthukrishnan N, Reinhold C, Forghani B. Radiomics and artificial intelligence for biomarker and prediction model development in oncology. *Comput Struct Biotechnol J* 2019;**17**:995−1008.
70. Yan Y, Zeng S, Wang X, Gong Z, Xu Z. A machine learning algorithm for predicting therapeutic response to anti-PD1. *Technol Cancer Res Treat* 2019;**18**: 1533033819875766.
71. Tosta TAA, de Faria PR, Neves LA, do Nascimento MZ. Color normalization of faded H&E-stained histological images using spectral matching. *Comput Biol Med* 2019;**111**:103344.
72. Sirinukunwattana K, Ahmed Raza SE, Yee-Wah T, Snead DR, Cree IA, Rajpoot NM. Locality sensitive deep learning for detection and classification of nuclei in routine colon cancer histology images. *IEEE Trans Med Imag* 2016;**35**:1196−206.
73. Martins J, Magalhaes C, Rocha M, Osorio NS. Machine learning-enhanced T cell neoepitope discovery for immunotherapy design. *Cancer Inform* 2019;**18**. 1176935119852081.
74. Asaoka Y, Ijichi H, Koike K. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 2015;**373**:1979.
75. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. *N Engl J Med* 2015;**372**:2509−20.
76. Fehlings M, Simoni Y, Penny HL, Becht E, Loh CY, Gubin MM, et al. Checkpoint blockade immunotherapy reshapes the high-dimensional phenotypic heterogeneity of murine intratumoural neoantigen-specific $CD8^+$ T cells. *Nat Commun* 2017;**8**:562.
77. Fridman WH, Pages F, Sautes-Fridman C, Galon J. The immune contexture in human tumours: impact on clinical outcome. *Nat Rev Cancer* 2012;**12**:298−306.
78. Griffin J, Treanor D. Digital pathology in clinical use: where are we now and what is holding us back?. *Histopathology* 2017;**70**:134−45.
79. Granter SR, Beck AH, Papke Jr DJ. AlphaGo, deep learning, and the future of the human microscopist. *Arch Pathol Lab Med* 2017;**141**:619−21.
80. Sharma G, Carter A. Artificial intelligence and the pathologist: future frenemies?. *Arch Pathol Lab Med* 2017;**141**:622−3.
81. Granter SR. Reports of the death of the microscope have been greatly exaggerated. *Arch Pathol Lab Med* 2016;**140**:744−5.
82. Yu J, Hu Y, Xu Y, Wang J, Kuang J, Zhang W, et al. LUADpp: an effective prediction model on prognosis of lung adenocarcinomas based on somatic mutational features. *BMC Cancer* 2019;**19**:263.
83. Yarchoan M, Hopkins A, Jaffee EM. Tumor mutational burden and response rate to PD-1 inhibition. *N Engl J Med* 2017;**377**:2500−1.
84. Patel H, Okamura R, Fanta P, Patel C, Lanman RB, Raymond VM, et al. Clinical correlates of blood-derived circulating tumor DNA in pancreatic cancer. *J Hematol Oncol* 2019;**12**:130.
85. Li J, Han X, Yu X, Xu Z, Yang G, Liu B, et al. Clinical applications of liquid biopsy as prognostic and predictive biomarkers in hepatocellular carcinoma: circulating tumor cells and circulating tumor DNA. *J Exp Clin Cancer Res* 2018;**37**:213.
86. Ikeda S, Schwaederle M, Mohindra M, Fontes Jardim DL, Kurzrock R. MET alterations detected in blood-derived circulating tumor DNA correlate with bone metastases and poor prognosis. *J Hematol Oncol* 2018;**11**:76.
87. Iinuma H. Genomic analysis and immunotherapy by liquid biopsy. *Gan To Kagaku Ryoho* 2019;**46**:1361−6.
88. Yan Y, Chen X, Wei J, Gong Z, Xu Z. Immunotherapy combinations in patients with small cell lung cancers. *J Thorac Oncol* 2019;**14**:e244−5.
89. Ko J, Baldassano SN, Loh PL, Kording K, Litt B, Issadore D. Machine learning to detect signatures of disease in liquid biopsies—a user's guide. *Lab Chip* 2018;**18**:395−405.
90. Akinleye A, Rasool Z. Immune checkpoint inhibitors of PD-L1 as cancer therapeutics. *J Hematol Oncol* 2019;**12**:92.
91. Zhao Z, Zheng L, Chen W, Weng W, Song J, Ji J. Delivery strategies of cancer immunotherapy: recent advances and future perspectives. *J Hematol Oncol* 2019;**12**:126.
92. Kruger S, Ilmer M, Kobold S, Cadilha BL, Endres S, Ormanns S, et al. Advances in cancer immunotherapy 2019—latest trends. *J Exp Clin Cancer Res* 2019;**38**:268.
93. Rotte A. Combination of CTLA-4 and PD-1 blockers for treatment of cancer. *J Exp Clin Cancer Res* 2019;**38**:255.
94. Seebacher NA, Stacy AE, Porter GM, Merlot AM. Clinical development of targeted and immune based anti-cancer therapies. *J Exp Clin Cancer Res* 2019;**38**:156.
95. Li A, Yi M, Qin S, Chu Q, Luo S, Wu K. Prospects for combining immune checkpoint blockade with PARP inhibition. *J Hematol Oncol* 2019;**12**:98.
96. Wang H, Kaur G, Sankin AI, Chen F, Guan F, Zang X. Immune checkpoint blockade and CAR-T cell therapy in hematologic malignancies. *J Hematol Oncol* 2019;**12**:59.
97. Arlauckas SP, Garris CS, Kohler RH, Kitaoka M, Cuccarese MF, Yang KS, et al. *In vivo* imaging reveals a tumor-associated macrophage-mediated resistance pathway in anti-PD-1 therapy. *Sci Transl Med* 2017;**9**: eaa13604.
98. Jenkins RW, Barbie DA, Flaherty KT. Mechanisms of resistance to immune checkpoint inhibitors. *Br J Cancer* 2018;**118**:9−16.
99. Boutros C, Tarhini A, Routier E, Lambotte O, Ladurie FL, Carbonnel F, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nat Rev Clin Oncol* 2016;**13**:473−86.
100. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall survival with combined nivolumab and imumab in advanced melanoma. *N Engl J Med* 2017;**377**:1345−56.
101. Wang Q, Xu R. Immunotherapy-related adverse events (irAEs): extraction from FDA drug labels and comparative analysis. *JAMIA Open* 2019;**2**:173−8.
102. Levine AB, Schlosser C, Grewal J, Coope R, Jones SJM, Yip S. Rise of the machines: advances in deep learning for cancer diagnosis. *Trends Cancer* 2019;**5**:157−69.
103. Niazi MKK, Parwani AV, Gurcan MN. Digital pathology and artificial intelligence. *Lancet Oncol* 2019;**20**:e253−61.
104. Tizhoosh HR, Pantanowitz L. Artificial intelligence and digital pathology: challenges and opportunities. *J Pathol Inform* 2018;**9**:38.
105. Kim DW, Jang HY, Kim KW, Shin Y, Park SH. Design characteristics of studies reporting the performance of artificial intelligence algorithms for diagnostic analysis of medical images: results from recently published papers. *Korean J Radiol* 2019;**20**:405−10.
106. Wang S, Liu Z, Rong Y, Zhou B, Bai Y, Wei W, et al. Deep learning provides a new computed tomography-based prognostic biomarker for recurrence prediction in high-grade serous ovarian cancer. *Radiother Oncol* 2019;**132**:171−7.
107. Johnson DR, Guerin JB, Ruff MW, Fang S, Hunt CH, Morris JM, et al. Glioma response assessment: classic pitfalls, novel confounders, and emerging imaging tools. *Br J Radiol* 2019;**92**:20180730.
108. Huemer F, Leisch M, Geisberger R, Melchardt T, Rinnerthaler G, Zaborsky N, et al. Combination strategies for immune-checkpoint blockade and response prediction by artificial intelligence. *Int J Mol Sci* 2020;**21**:2856.
109. Houy N, Le Grand F. Optimizing immune cell therapies with artificial intelligence. *J Theor Biol* 2019;**461**:34−40.
110. Wang G, Zhao D, Spring DJ, DePinho RA. Genetics and biology of prostate cancer. *Genes Dev* 2018;**32**:1105−40.
111. Shameer K, Johnson KW, Glicksberg BS, Dudley JT, Sengupta PP. The whole is greater than the sum of its parts: combining classical

statistical and machine intelligence methods in medicine. *Heart* 2018;**104**:1228.
112. van den Heuvel ER, Vasan RS. Statistics in cardiovascular medicine: there is still gold in the old. *Heart* 2018;**104**:1227.
113. Stephansen JB, Olesen AN, Olsen M, Ambati A, Leary EB, Moore HE, et al. Neural network analysis of sleep stages enables efficient diagnosis of narcolepsy. *Nat Commun* 2018;**9**:5229.
114. Doescher J, Laban S, Schuler PJ, Brunner C, Hoffmann TK. Immunotherapy for head and neck cancers: an update and future perspectives. *Immunotherapy* 2019;**11**:561−4.
115. Kohn MS, Sun J, Knoop S, Shabo A, Carmeli B, Sow D, et al. IBM's health analytics and clinical decision support. *Yearb Med Inform* 2014;**9**:154−62.
116. Rabbani M, Kanevsky J, Kafi K, Chandelier F, Giles FJ. Role of artificial intelligence in the care of patients with nonsmall cell lung cancer. *Eur J Clin Invest* 2018;**48**:e12901.
117. Treiber JM, Steed TC, Brandel MG, Patel KS, Dale AM, Carter BS, et al. Molecular physiology of contrast enhancement in glioblastomas: an analysis of the Cancer Imaging Archive (TCIA). *J Clin Neurosci* 2018;**55**:86−92.
118. Yankeelov TE. The quantitative imaging network: a decade of achievement. *Tomography* 2019;**5**:A8.
119. Liu Z, Wang S, Dong D, Wei J, Fang C, Zhou X, et al. The applications of radiomics in precision diagnosis and treatment of oncology: opportunities and challenges. *Theranostics* 2019;**9**:1303−22.
120. Li X, Wang H, He H, Du J, Chen J, Wu J. Intelligent diagnosis with Chinese electronic medical records based on convolutional neural networks. *BMC Bioinf* 2019;**20**:62.
121. Yu KH, Beam AL, Kohane IS. Artificial intelligence in healthcare. *Nat Biomed Eng* 2018;**2**:719−31.
122. Limkin EJ, Sun R, Dercle L, Zacharaki EI, Robert C, Reuze S, et al. Promises and challenges for the implementation of computational medical imaging (radiomics) in oncology. *Ann Oncol* 2017;**28**:1191−206.
123. Hutson M. Has artificial intelligence become alchemy?. *Science* 2018;**360**:478.
124. Nundy S, Montgomery T, Wachter RM. Promoting trust between patients and physicians in the era of artificial intelligence. *J Am Med Assoc* 2019;**322**:497−8.
125. Challen R, Denny J, Pitt M, Gompels L, Edwards T, Tsaneva-Atanasova K. Artificial intelligence, bias and clinical safety. *BMJ Qual Saf* 2019;**28**:231−7.
126. Nagendran M, Chen Y, Lovejoy CA, Gordon AC, Komorowski M, Harvey H, et al. Artificial intelligence *versus* clinicians: systematic review of design, reporting standards, and claims of deep learning studies. *BMJ* 2020;**368**:m689.
127. Camerer CF, Dreber A, Holzmeister F, Ho TH, Huber J, Johannesson M, et al. Evaluating the replicability of social science experiments in *Nature* and *Science* between 2010 and 2015. *Nat Hum Behav* 2018;**2**:637−44.
128. Ebrahim S, Sohani ZN, Montoya L, Agarwal A, Thorlund K, Mills EJ, et al. Reanalyses of randomized clinical trial data. *J Am Med Assoc* 2014;**312**:1024−32.
129. Wallach JD, Boyack KW, Ioannidis JPA. Reproducible research practices, transparency, and open access data in the biomedical literature, 2015−2017. *PLoS Biol* 2018;**16**:e2006930.
130. Kappen TH, van Klei WA, van Wolfswinkel L, Kalkman CJ, Vergouwe Y, Moons KGM. Evaluating the impact of prediction models: lessons learned, challenges, and recommendations. *Diagn Progn Res* 2018;**2**:11.
131. Sinigaglia M, Assi T, Besson FL, Ammari S, Edjlali M, Feltus W, et al. Imaging-guided precision medicine in glioblastoma patients treated with immune checkpoint modulators: research trend and future directions in the field of imaging biomarkers and artificial intelligence. *EJNMMI Res* 2019;**9**:78.
132. Zaharchuk G. Fellow in a box: combining AI and domain knowledge with bayesian networks for differential diagnosis in neuroimaging. *Radiology* 2020;**295**:638−9.
133. Jabbari P, Rezaei N. Artificial intelligence and immunotherapy. *Expet Rev Clin Immunol* 2019;**15**:689−91.
134. Collins FS, Varmus H. A new initiative on precision medicine. *N Engl J Med* 2015;**372**:793−5.
135. Chang K, Balachandar N, Lam C, Yi D, Brown J, Beers A, et al. Distributed deep learning networks among institutions for medical imaging. *J Am Med Inf Assoc* 2018;**25**:945−54.
136. Crawford K, Calo R. There is a blind spot in AI research. *Nature* 2016;**538**:311−3.
137. Cabitza F, Rasoini R, Gensini GF. Unintended consequences of machine learning in medicine. *J Am Med Assoc* 2017;**318**:517−8.
138. Topol EJ. High-performance medicine: the convergence of human and artificial intelligence. *Nat Med* 2019;**25**:44−56.
139. Verghese A, Shah NH, Harrington RA. What this computer needs is a physician: humanism and artificial intelligence. *J Am Med Assoc* 2018;**319**:19−20.
140. McCartney M. Margaret McCartney: AI in medicine must be rigorously tested. *BMJ* 2018;**361**:k1752.
141. Esteva A, Robicquet A, Ramsundar B, Kuleshov V, DePristo M, Chou K, et al. A guide to deep learning in healthcare. *Nat Med* 2019;**25**:24−9.
142. Stilgoe J. Machine learning, social learning and the governance of self-driving cars. *Soc Stud Sci* 2018;**48**:25−56.
143. Winfield AFT, Jirotka M. Ethical governance is essential to building trust in robotics and artificial intelligence systems. *Philos Trans A Math Phys Eng Sci* 2018;**376**:20180085.
144. Macrae C. Governing the safety of artificial intelligence in healthcare. *BMJ Qual Saf* 2019;**28**:495−8.
145. Zeng S, Wang D, Yan Y, Zhu M, Liu W, Gong Z, et al. Single-center analysis of the potential inappropriate use of intravenous medications in hospitalized patients in China. *Clin Ther* 2019;**41**:1631−1637 e4.