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Artificial intelligence-based multi-omics analysis fuels cancer precision medicine

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ABSTRACT

With biotechnological advancements, innovative omics technologies are constantly emerging that have enabled researchers to access multi-layer information from the genome, epigenome, transcriptome, proteome, metabolome, and more. A wealth of omics technologies, including bulk and single-cell omics approaches, have empowered to characterize different molecular layers at unprecedented scale and resolution, providing a holistic view of tumor behavior. Multi-omics analysis allows systematic interrogation of various molecular information at each biological layer while posing tricky challenges regarding how to extract valuable insights from the exponentially increasing amount of multi-omics data. Therefore, efficient algorithms are needed to reduce the dimensionality of the data while simultaneously dissecting the mysteries behind the complex biological processes of cancer. Artificial intelligence has demonstrated the ability to analyze complementary multi-modal data streams within the oncology realm. The coincident development of multi-omics technologies and artificial intelligence algorithms has fuelled the development of cancer precision medicine. Here, we present state-of-the-art omics technologies and outline a roadmap of multi-omics integration analysis using an artificial intelligence strategy. The advances made using artificial intelligence-based multi-omics approaches are described, especially concerning early cancer screening, diagnosis, response assessment, and prognosis prediction. Finally, we discuss the challenges faced in multi-omics analysis, along with tentative future trends in this field. With the increasing application of artificial intelligence in multi-omics analysis, we anticipate a shifting paradigm in precision medicine becoming driven by artificial intelligence-based multi-omics technologies.

1. Introduction

The pathogenesis of cancer involves complex rearrangements at the genetic, transcriptional, proteomic, and metabolic levels that drive oncogenesis [1]. Thus, in-depth analysis of the genome, epigenome, transcriptome, proteome, and metabolism of tumors is imperative, which allows the comprehensive characterization of cancer biology and the dissection of tumor plasticity and heterogeneity. In recent decades, a variety of omics technologies have surged to systematically measure different aspects of tumor characteristics and interrogate biological networks at unprecedented levels.

Various omics technologies have tremendous potential in cancer research since they provide an unparalleled opportunity to portray cancer biology at different pathological and molecular levels. Indeed, omics technologies have led to ground-breaking discoveries and substantially deepened our understanding of tumor behavior. However, individual profiling using a single-omics approach only provides a partial landscape of complex molecular regulatory networks in tumors. Therefore, integration analysis of multi-omics data is an imperative step toward a deeper understanding of the inner mechanism of oncogenesis. Actually, integrative multi-omics analysis has greatly improved our views of the multifaceted nature of tumor biology, involving tumor evolution [2], tumor heterogeneity [3], tumor microenvironment [4], immune evasion [5], and drug resistance [6]. Moreover, integrative multi-omics analysis across various tumor cohorts has shed light on the complex dysregulation responsible for specific cancer phenotypes [7]. Multi-omics integration analysis across different molecular levels has promoted modern biological and medical studies and offers a full-scale cancer atlas to guide tumor precision therapy.

Beyond omics data, other modality data are also experiencing rapid

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growth in the clinical oncology care path, such as codified clinical information, molecular measurements, and radiographic and histopathologic data. Integration of these complementary digital assets with multi-omics data can provide a comprehensive description of the state of cancer and inform rational clinical decision-making. With available data becoming larger and broader, an ensuing technical challenge is how to integrate and synthesize these data. The computational algorithms and tools are required to tease out meaningful signals from noise. Artificial intelligence (AI), specifically deep learning (DL), is flexible and well-suited to address heterogeneous and unstructured data and has a high propensity to discover non-linear and high-dimensional relationships in multi-modal data [8,9]. Over the past few years, the field of AI has shifted from theoretical research to real-world applications. AI has been successfully applied to all stages of cancer care, from early risk prediction and prevention, screening, diagnosis, response assessment, and prognosis prediction to final treatment strategy formulation [9]. AI-assisted tools for clinical medicine can improve management decisions and ultimately promote precision medicine.

AI-driven multi-omics analysis not only dramatically improves the understanding of cancer biology but also has the potential to discover new druggable targets and develop biomarkers to optimize therapeutic benefits. In this review, we highlight state-of-the-art multi-omics technologies for cancer precision medicine and describe a workflow of integration analysis of multi-omics data and other modality data. We then comprehensively summarize the latest advances in AI-based multi-omics tumor profiling, focusing on the applications of AI-based multi-omics technologies on cancer diagnosis, classification, early cancer screening, response assessment, and prognosis prediction. Finally, the challenge of AI-based multi-omics analysis and future perspectives for their integration into cancer precision medicine are discussed. AI-based multi-omics analysis has great promise for precision medicine, providing new opportunities with tailored therapies for individual patients.

2. Multi-omics technologies

2.1. Bulk omics technologies: from genotype to phenotype

As high-throughput technologies flourish, diverse omics techniques have been developed to characterize different but complementary biological layers, including genomics, epigenomics, transcriptomics, proteomics, and metabolomics (Fig. 1). A variety of omics technologies enable the systematic, quantitative characterization of complex biological systems by describing nearly all biomolecules ranging from DNA to metabolites.

2.1.1. Genomics

The genome harbors hereditary information that determines the cell's architectural and functional machinery by regulating gene expression [10]. Genomics can examine DNA sequences and decipher the genetic information encoded in the genome, which is the basis for understanding the associations between human diseases and genomic alterations [11]. Whole-genome sequencing (WGS) and whole-exome sequencing (WES) are two major technologies for genomic studies. WGS covers almost the whole genome, including the gene regulatory regions, whereas WES is optimized to examine the exonic portion of the genome [12]. Compared with WGS, WES usually has a lower cost and a greater depth of coverage in target regions, although information on regulatory regions is lacking [13]. Recently, investigations of genomic variations have entered the pan-genomics era, followed by the rapid expansion of genomics data [14]. AI technologies have accelerated the transition of genomic analysis into clinical use in cancer management. Beyond the identification of genomic alterations, emerging applications of genomics assays in clinical practice include monitoring therapeutic responses and characterizing mechanisms of resistance to therapy [15].

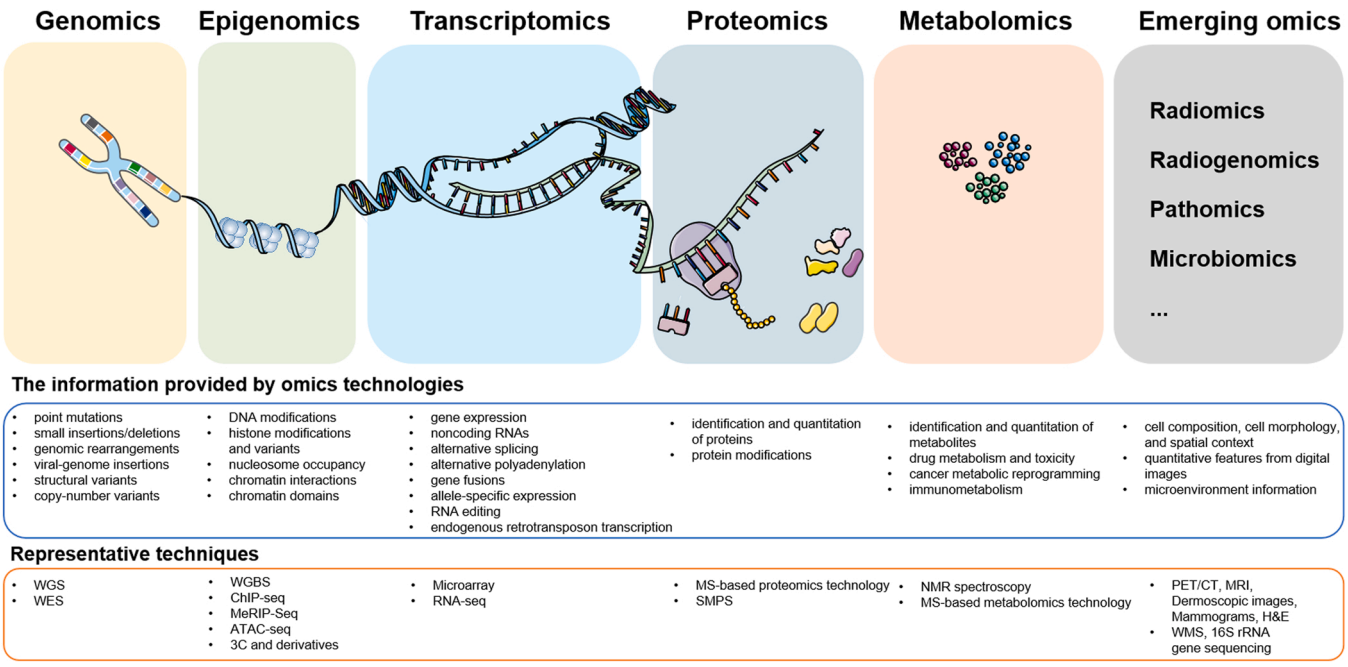

Fig. 1. Multi-omics technologies. Multi-omics technologies have been developed to profile genome sequences, epigenetic features, transcription expression, protein and metabolite abundance, and more. Additional information from an individual can be captured by emerging omics technologies, such as radiomics, pathomics, and microbiomics. The corresponding representative technologies are enumerated. Whole-genome sequencing (WGS), whole-exome sequencing (WES), whole-genome bisulfite sequencing data (WGBS), chromatin immunoprecipitation sequencing (ChIP-seq), methylated RNA immunoprecipitation sequencing (MeRIP-seq), assay for transposase-accessible chromatin using sequencing (ATAC-seq), chromosome conformation capture (3C) technology, mass spectrometry (MS)-based proteomics technology, single-molecule protein sequencing (SMPS) technologies, Nuclear magnetic resonance (NMR) spectroscopy, mass spectrometry (MS)-based metabolomics technology, positron emission tomography(PET)/computed tomography (CT) scans, magnetic resonance imaging (MRI), Hematoxylin and eosin staining (H&E), and whole metagenome sequencing (WMS).

2.1.2. Epigenomics

Epigenetic changes can affect gene expression and function *via* chemical modifications of nucleotides and proteins without changing the actual nucleotide sequence. Increasing evidence shows that epigenetic changes play fundamental roles in the initiation and progression of human cancer, primarily involving epigenomic modifications and chromatin accessibility [16]. The first epigenomic mark to gain attention is DNA methylation, which can be measured by numerous methods, such as affinity enrichment-based and bisulfite conversion-based techniques [17]. As the largest category among profiled chromatin marks, histone modifications have important roles in the emergence and maintenance of malignant cell phenotypes in various cancer types. Chromatin immunoprecipitation sequencing (ChIP-seq) is a commonly used method to profile histone modifications [18]. In RNA modifications, N^6-methyladenosine (m^6A) is the most prevalent internal RNA modification in eukaryotes. Many high-throughput sequencing methods can be used to detect m^6A, such as m6A/MeRIP-Seq [19], miCLIP [20], m6A-LAIC-Seq [21], DART-Seq [22], m6A-REF-Seq [23], and m6A-SEAL [24].

Chromatin accessibility is a widely studied characteristic of the eukaryotic genome that determines physical access to DNA and possesses an essential role in establishing and maintaining cellular identity [25]. Multiple biochemical methods have been developed to assess chromatin accessibility or nucleosome positioning, including deoxyribonuclease I (DNase I) hypersensitive site sequencing (DNase-seq) [26], assay for transposase-accessible chromatin using sequencing (ATAC--seq) [27], micrococcal nuclease sequencing (MNase-seq) [28], and several single-molecule chromatin accessibility profiling approaches [29]. In addition, distinct implementations of chromosome conformation capture assays are being used to investigate chromatin interactions, including chromosome conformation capture (3C) technology [30], 4C [31], 5C [32], Hi-C [33], chromatin interaction analysis with paired-end tag sequencing (ChIA-PET) [34] and promoter capture Hi-C (PCHi-C) [35]. By pursuing these epigenetic approaches, myriads of epigenomic features have been comprehensively profiled in cancer patients, which are involved in tumor initiation, growth, metastasis, and immune evasion [36,37]. Numerous epigenetic biomarkers and therapeutic strategies are starting to be incorporated into clinical practice [38,39].

2.1.3. Transcriptomics

As a transient intermediary molecule, RNA can convert genetic information stored in DNA into proteins. The emergence of noncoding RNAs expands the functional repertoire of the transcriptome [40]. Transcriptome can serve as an indirect indicator of protein expression and real-time imply genome activity. Generally, dynamic changes in the transcriptome reflect physiological remodeling in the body. Transcriptomic analysis can capture gene expression changes and has been instrumental in the understanding of cancer pathogenesis.

Several approaches are available to deduce and quantify the transcriptome, with the dominant techniques being microarrays and RNA-seq. Compared with microarrays, focused on a small number of genes, RNA-seq provides a far more precise measurement of transcript abundance and is particularly suitable for the identification of alternative isoforms and gene fusions [41]. The advantages of RNA-seq have promoted to form an unprecedented global view of the transcriptome. Studies using this method have already altered our view of the extent and complexity of eukaryotic transcriptome. An emerging area subject to intensive research is to dissect the organization and crosstalk of different cell types in multicellular organisms. Spatial transcriptomics combines the strengths of transcriptomic technology and in situ hybridization, which characterizes transcriptome profiles while retaining information about the spatial tissue context [42–44]. Spatial transcriptomics is becoming increasingly used in various fields of oncology, providing fundamental insights into cancer biology [45]. Transcriptomic technologies have broad utilities in biomarker discovery, cancer diagnosis and classification, and optimization of therapeutic schedules, paving the way for precision medicine [46,47].

2.1.4. Proteomics

Proteins as the workhorses, carry out the vast majority of functions of the cell, from copying DNA, pushing genetic information transduction, and catalyzing metabolic reactions to driving cellular motion [48,49]. Proteins link the genotype with the phenotype and hence can better reflect the real state of cells than genome or transcriptome [50]. Proteome analysis can therefore provide vital information toward the understanding of biological processes and disease. Mass spectrometry (MS)-based proteomics technology has been the most frequently adopted approach for protein analysis for at least the past two decades [51]. Recent technological advances in MS technology have enabled proteomics to meet the requirements of high-throughput and repeatability for large-scale cancer analyses [7,52,53]. However, MS-based proteomics techniques are limited by their low resolution and insufficient dynamic range, resulting in the inability to characterize proteins in low-abundance. In recent years, some single-molecule protein sequencing (SMPS) technologies have been proposed to solve these drawbacks and revolutionized proteomics research [48,54]. SMPS technologies fall generally into three categories: a) sequencing by degradation: fluorosequencing [55], N-terminal-specific amino acid binders (NAABs)-based sequencing [56], and single-molecule mass spectrometry [57]; b) sequencing by transit: nanopore sequencing [58], electron tunneling [59], and ClpXP-based fingerprinting [60]; and c) sequencing by affinity, e.g., DNA nanotechnology [61]. These techniques have extreme sensitivity to detect low-abundance proteins and promote the realization of single-cell proteomics [62]. AI technologies have dramatically improved the quality and reliability of proteomics analysis and empowered precision oncology with increased chances to elaborate the complex mechanisms of carcinogenesis and identify new therapeutic targets and actionable biomarkers for clinical use [63,64].

2.1.5. Metabolomics

The metabolome, the collection of metabolites or small molecule chemicals involved in metabolism, can directly reflect functional readouts of biochemical reactions, thus providing insights into multiple aspects of cellular physiology [65]. In fact, metabolites are extremely sensitive to internal signals and external stimuli, which means that metabolome has the potential as the probe of biological phenotypes to reveal what is happening in cells [66]. Recent studies indicated that tumor cells can reprogram intracellular metabolism to support the demands of uncontrolled proliferation [67]. Meanwhile, metabolic rewiring is also essential for immune cell differentiation, function, and fate [68–71]. Thus, metabolome has been in the spotlight for cancer research. Metabolic dysregulation leads to characteristic metabolic phenotypes that can be used for earlier cancer diagnosis, monitoring, and/or as therapeutic targets in cancer [67]. Metabolomics can systematically identify and quantify all metabolites in biological samples at high-throughput and provide critical information about the cancer state that is not available in other omics technologies [67]. Metabolomics has emerged as a powerful tool to elucidate pathogenic mechanisms underlying various diseases.

Nuclear magnetic resonance (NMR) spectroscopy and MS-based technologies have been of extraordinary importance for metabolomic analysis. NMR spectroscopy is an essential analytical technique for metabolite identification, while its applicability in analyzing the fine structure of metabolites is curbed by the inherent requirement of sufficient high-purity samples [72]. MS, as an important tool for the detection and quantification of metabolites, has been fueled by strides in separation technologies, such as combining with gas chromatography (GC—MS) or liquid chromatography (LC—MS), thereby improving analyte resolution by increasing specificity and sensitivity [73,74]. Although these improvements allow the detection of more analytes with high specificity and sensitivity, MS-based technologies still face some challenges, including unknown metabolite identification, elimination of

exogenous contamination, chromatographic separation of isomers, and lacking complete reference databases [74]. The rise of advanced instrumentational, experimental, and computational tools has boosted the development of metabolomic technologies [75–78]. In particular, AI technology has been rapidly applied to solve the conundrum of metabolite characterization, revealing useful information for cancer research [72]. Metabolomics analysis has revealed novel therapeutic vulnerabilities for cancer treatment, and emerging therapy regimens have been proposed to target metabolic restrictions in cancer [79,80]. Moreover, abnormal metabolic phenotypes can be used for early cancer diagnosis and monitoring [67,81].

2.2. Single-cell omics: unprecedented resolution and scale

Tumors exhibit a remarkable degree of intertumoral and intratumoral heterogeneity, usually manifesting as phenotypically and functionally distinct cell populations [2]. However, bulk omics technologies mask important properties specific to diverse cellular subsets and only provide averaged measurements of multiple cells [82]. The advent of single-cell technologies offers robust solutions to investigate omics profiles at single-cell resolution, which capture biological information that is unobtainable from bulk omics data. With rapid advances in cell isolation and high-throughput sequencing technologies, single-cell omics technology has undergone a dramatic expansion, making it feasible to explore genomic alteration [83], DNA methylation [84], chromatin accessibility [85], gene perturbation [86], transcriptome dynamics [87], protein abundance [88], and metabolic reorganization [89] at unprecedentedly high resolution. Moreover, a variety of single-cell multi-modal omics technologies allow simultaneous profiling of multiple modalities in the same cell, providing comprehensive insights into cell behavior and identity [1]. For example, G&T-seq [90], SIDR [91], and TARGET-Seq [92] can simultaneously profile genome and transcriptome at the single-cell level, while CITE-seq [93] and REAP-seq [88] allow the multiplexed detection of transcriptome profiles together with protein abundance. Furthermore, higher-order single-cell multi-omics techniques have emerged to handle multiple information sources from distinct omics layers in the same single cell, such as ECCITE-Seq [94], Perturb-CITE-seq [95], and PHAGE-ATAC [96]. More importantly, an explosion in single-cell spatial technologies has enabled the simultaneous measurement of multiple modalities and spatial cellular context [97]. With advancements in various single-cell omics technologies, it is now possible to generate multi-modal data to answer various biological problems, such as intratumor heterogeneity, tumor microenvironment reprogramming, metastasis dissemination, and therapeutic resistance [98]. Thus, single-cell omics technologies have the potential to improve several areas of cancer medicine, including early detection, diagnostics and risk stratification, non-invasive monitoring, and drug target discovery [98,99].

2.3. Beyond classical omics

Considering the complex multifactorial nature of cancer etiology, cancer screening and diagnosis need to integrate information across multiple biological scales from molecular profiles to clinical phenotypes. In virtually all situations, medical imaging can provide crucial information for clinical decision-making. In the last decade, medical imaging techniques have evolved towards omics approaches, intending to quantify and characterize imaging features at a large scale [100]. As two major branches of medical imaging, pathomics and radiomics describe diverse characteristics of tumors at different biological scales. Pathomics comprehensively depicts the cell composition, cell morphology, and spatial context harboring the information of cellular interactions. Radiomics characterizes tumor properties at the macro-scales through the high-throughput generation and interrogation of a large number of quantitative features from digital images [100,101]. The application progress of pathomics and radiomics has been impressive in precision medicine. Pathomics and radiomics yield large-scale digital archives. AI has high utility in radiographic and histopathologic data. Most Food and Drug Administration (FDA)-approved AI applications for clinical oncology are mainly used to parse medical imaging data [9].

The rapid advancement in the field of medical imaging drives a need to interrogate the associations between image features, molecular signatures, and clinical outcomes. The recent advent of radiogenomics has accelerated the integration of medical imaging and genomics technology, which extends radiomics approach by investigating the correlation between imaging characteristics and genomic patterns [102,103]. Radiogenomics provides insights into the underlying mechanisms of disease progression and therapy response while allowing for biomarker discovery for precise diagnosis and management in a non-invasive manner [103]. AI strategies have been explored to integrate imaging features into multi-omics data sources and ushered in new directions in medical research.

Owing to the plethora of evidence highlighting the crucial role of microbiota in cancer, microbiome has become an area of increasing interest in cancer research [104]. Other diagnostic modalities, such as cell-free DNA (cfDNA) analysis and clinical laboratory serial testing, provide longitudinal readouts for monitoring tumor progression. In addition, clinical information as complementary data sources can provide meaningful information for diagnosis. AI-driven integrative analysis of multi-omics and multi-modal data can clarify the findings by extracting knowledge from complex data and thus provide new opportunities for patient-tailored therapy.

3. Artificial intelligence for multi-omics analysis across different modalities

With available data from cancer samples becoming 'bigger', there has been a resurgence of interest in AI implementation in precision oncology. The recent AI techniques have evolved from "shallow" to "deep" learning architectures. As an important branch of AI, machine learning (ML) can automatically learn to capture intricate patterns and make intelligent decisions based on data [105,106]. ML has very wide applications in cancer research and clinical oncology. In particular, DL-based approaches, belonging to a subfield of ML, have emerged as powerful tools for biomedical data analysis, driven by the rapid growth of multi-omics data. Classical statistical modeling and shallow ML generally struggle to fit unstructured, heterogeneous, and high-dimensional data, while DL has the ability to learn non-linear and high-dimensional relationships in multiple modality data and is particularly applicable for multi-omics analysis [9].

Based on the availability of labeling on data, ML methods can be divided broadly into two categories, supervised learning and unsupervised learning (Fig. 2). Supervised learning methods use label information from input data for model training, whereas unsupervised learning discovers intrinsic patterns directly from data without clear labels [105,107]. Several excellent reviews have surveyed different ML methods and provided clear navigation to researchers regarding the selection of suitable ML methods for specific applications [105,108]. Here, we briefly introduce the basic steps in ML workflow. ML workflows usually consist of three key steps to develop a computational model: data collection and preprocessing, selection of algorithm and model training, testing, and tuning, and external validation. Data collection and preprocessing is the first and key step of any ML workflow, as ML output is highly dependent on high quality data. It is necessary to inspect and correct possible noise to ensure high quality of input data. The data also need to be checked to alleviate the impact of possible biases or high variance that can lead to underfitting or overfitting the model, respectively [109]. Underfitting and overfitting are major issues in ML. In the case of underfitting, the model does not capture the underlying structure of a particular data set, resulting in low learning precision. In overfitting, the model learns from noise or

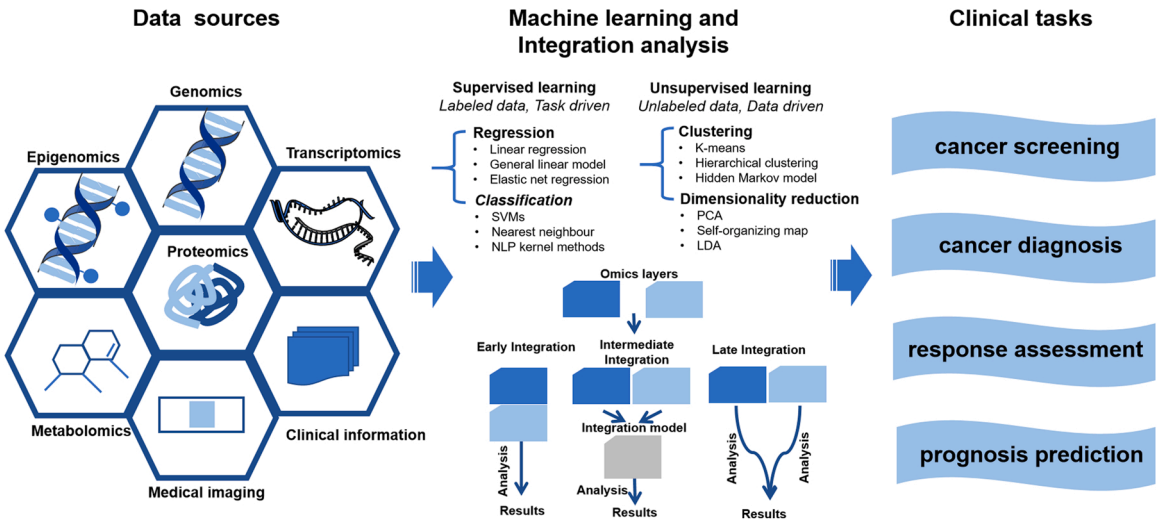

Fig. 2. Artificial intelligence support of multi-level biomedical data integration workflow. The data acquired in multi-omics studies can be integrated with other complementary modality data, including medicinal imaging, and clinical information (left panel). ML methods can be divided broadly into supervised learning and unsupervised learning. Representative ML methods are listed (middle panel). Data integration strategies for multi-omics include early, intermediate, and late integration (middle panel). AI-based multi-omics analysis has the potential to aid precision medicine. Key applications of AI-based multi-omics analysis in cancer precision medicine are shown (right panel). Support vector machines (SVMs), natural language processing (NLP) kernel methods, principal component analysis (PCA), and latent dirichlet allocation (LDA).

artifacts in the training data rather than the true signals, resulting in an ungeneralizable model [110]. Strategies such as increasing the sample size of the training set, cross-validation or bootstrapping, manually curating predictive features, and adopting ensemble approaches have been suggested to prevent overfitting [109].

Another critical phase of ML workflow is to select and optimize the model. The performance of a ML model needs to be balanced between sensitivity and specificity. Moreover, it is equally important to validate the model on independent external datasets to ensure model stability and generalizability. After deploying the model into clinical practice, the performance and application of the model should be constantly monitored, which is crucial to maintain model consistency and validity [109].

3.1. *Artificial intelligence approaches boost single-omics analysis*

The continuous improvement of omics technologies has generated plentiful omics data at an astonishing speed and scope. However, these data are usually high-dimensional and sparse, thus effective algorithms are urgently needed to capture dependencies in data and then derive rational biological hypotheses. The accumulation of omics data in cancer research has fostered lots of AI approaches, which in turn has promoted cancer research. In fact, all omics technologies have embarked on utilizing AI approaches to strengthen the analysis and extract high-content information from complex data (Fig. 3).

AI approaches have achieved remarkable success in different genomics fields [111], such as 3D genome structure prediction [112], modeling of epigenomic modification and chromatin accessibility [113], genome annotation [114], sgRNA design [115], and outcome prediction of genome editing [116]. Several comprehensive reviews summarized the ML methods for genomics analysis [105,111]. In the transcriptomics field, AI approaches have been widely used to investigate gene expression [117], alternative splicing [118], and transcription factor binding [119], promoting the discovery of the molecular mechanisms underlying disease progression. Notably, transcriptomics technology combined with ML can serve as an auxiliary diagnostic tool for early detection [120], cancer classification [121], as well as prognosis and recurrence prediction [122,123].

AI approaches have also been well applied in proteomic and metabolomic analysis. AI approaches are applicable in aspects of MS-based proteomics analysis, especially in identifying unknown peptides, with high accuracy [124]. Moreover, AI approaches have also been used to parse protein-nucleic acid and protein—protein interactions, which are of great significance to a variety of biological processes [125,126]. Similarly, metabolomics studies are also highly dependent on AI approaches. The data processing and analysis of metabolomics have been further improved by using AI algorithms [127]. Another interesting application area of AI approaches in metabolomics studies is metabolic modeling, in which AI algorithms are often used in the optimization of parameters in the modeling process and metabolic network reconstruction [128]. The other applications of AI techniques in metabolomics have been well reviewed in the literature [105]. At present, AI approaches also undertake most of the tasks in single-cell omics analysis, including data denoising and imputation, batch effect correction, cell

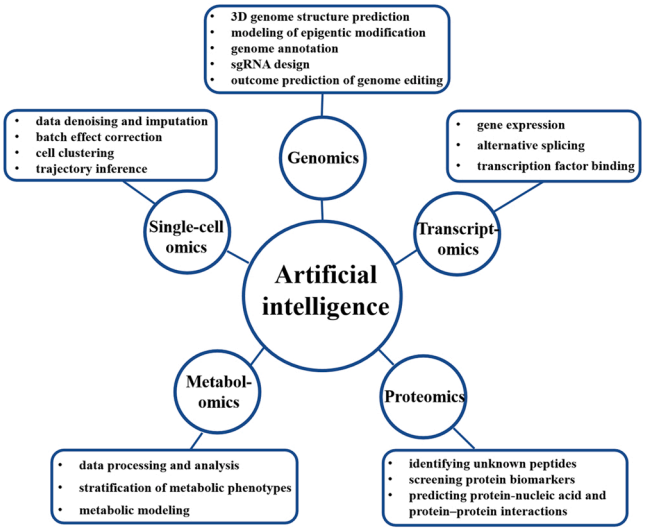

Fig. 3. The applications of AI technologies in single-omics analysis. The applications of AI technologies have largely boosted single-omics analysis, including genomics, epigenomics, transcriptomics, proteomics, metabolomics, pathomics, radiomics, etc.

clustering, trajectory inference, and so on. In recent years, AI approaches have also achieved unprecedented success in radiomics and pathomics analysis, enlightening us on the mechanisms of cancer development and progression. Meanwhile, AI-assisted radiomics and pathomics technologies can track disease state dynamics and aid the diagnosis, prediction, and treatment of cancer [129]. Together, AI approaches have made remarkable achievements in different omics studies and have largely advanced our insights into biological mechanisms.

3.2. AI-based integration analysis of multi-omics data

Multi-omics integration analysis can comprehensively explore biological characteristics and fully explain complex biological phenomena in depth while also inevitably bringing challenges for developing effective computational methods and tools for integrative analyses. There are three integrative strategies for multi-omics data, including early, intermediate, and late integration (Fig. 2). Early integration is the most straightforward strategy for integration analysis, which simply concatenates different features from each omics layer into one integrated dataset. However, it may lead to the "curse of dimensionality" due to the large feature space. In late integration, analyses are independently performed at each omics layer, and the results are then integrated at the end. Compared with the above two integrative strategies, intermediate integration can transform different modality data into appropriate intermediate representations using various transformation methods, enabling to capture more complementary information embedded in each omics and considering new interactions across omics layers [7].

Within the scope of multi-omics, a series of AI approaches, especially ML, have been widely applied to integration analysis of multi-omics data, which can systematically capture intricacies between multi-omics data and establish a more reliable linkage of multi-omics data. Moreover, AI methods can effectively solve the issues such as data heterogeneity, the "curse of dimensionality", missing data, big data scalability, and class imbalance [106]. In addition, the integration of multi-omics data and non-omics data by AI algorithms, such as clinical and electronic health record data and clinical lab tests, can offer an opportunity to link genotype and clinical phenotype and comprehensively profile the tumor state (Fig. 2). Thus, AI-based integrative analysis of multiple modality data is promising for clinical diagnosis and decision-making in precision medicine. With the development of multi-omics technologies and the emergence of new analysis approaches, AI-based multi-omics analysis will greatly promote the development of therapeutic strategies, especially for precision medicine.

4. Application of artificial intelligence-based multi-omics analysis in cancer precision medicine

The prerequisite of cancer therapy is accurately diagnosing the cancer subtype and proposing optimal treatment strategies, which would be expected to prolong the survival of patients. Currently, AI algorithms can integrate the data from multiple platforms, including genomics, epigenomics, transcriptomics, proteomics, metabolomics, pathomics, radiomics, etc., to endow the identification of cancer subtypes more precisely and provide robust tools for predicting cancer prognosis and treatment response [130–134] (Table 1).

4.1. AI-based multi-omics analysis in early cancer detection and screening

Early cancer detection has gained great concern because it contributed to decreasing the mortality of cancers through timely treatment. Although tissue biopsy-based cancer diagnosis is the main method to define cancers in solid tumors, its application is depressed in early detection and non-symptomatic cancers. In recent years, liquid biopsies, such as blood tests, have been demonstrated as a minimally invasive and favorable approach for early cancer detection and guiding treatment. Liquid biopsy biomarkers mainly include circulating tumor cells (CTCs), extracellular vesicles (EVs), cfDNA, and circulating tumor DNA (ctDNA). These biomarkers represent the intrinsic characteristics of the primary tumor. However, the amount of these circulating biomarkers is relatively low in blood, which limits their clinical application. AI-based multi-omics analysis, such as integrating genome alterations, transcriptome profiles, CTCs information, and serum markers, can significantly improve the sensitivity and accuracy of liquid biopsy (Table 1). In a multianalyte blood test, by integrating circulating protein expression and cfDNA mutation with AI, Cohen et al. developed CancerSEEK to detect early cancer and directly predict eight distinct cancer types [135]. CancerSEEK identified eight cancer types of organ origin with an accuracy of 70 % by utilizing a logistic regression model to analyze 61 amplicons of 16 mutation genes and eight plasma protein biomarkers. Then, five cancer types without available early detection tests were predicted with a sensitivity of 69–98 %, including ovary, liver, stomach, pancreas, and esophagus cancer. By using the microRNA profiles of serum exosomes and protein expression of hepatocellular carcinoma marker alpha-fetoprotein (AFP), Wang et al. developed a diagnostic model that distinguished liver cirrhosis from hepatocellular cancer with an AUC of 0.93 [136]. In another study, Chabon et al. [137] developed a cfDNA-based ML method, lung cancer likelihood in plasma (Lung-CLiP), that detected early-stage lung cancer using the plasma of cancer patients. The study first analyzed non-small cell lung cancer (NSCLC)-associated mutations in cfDNA using cancer personalized profiling by deep sequencing (CAPP-Seq) and estimated the correlation between cfDNA mutations and tumor features (e.g., disease stage, metabolic tumor volume, tumor histology). Then, the study developed the Lung-CLiP algorithm by incorporating tumor features with cfDNA mutation/fragment and trained the algorithm in a discovery cohort of 104 early-stage NSCLC patients and 56 risk-matched individuals. Finally, the Lung-CLiP algorithm was validated in a validation cohort comprising 46 early-stage NSCLC patients and 48 risk-matched individuals and achieved similar sensitivity to that of tumor-informed ctDNA analysis. The ML-developed Lung-CLiP algorithm is an eligible tool for detecting early stages of lung cancer and thereby increasing screening rates and patient survival. In another promising study, Moss et al. reported that ctDNA could be used to predict the microsatellite instability (MSI) status of endometrial cancer and guide immunotherapy [138]. Moreover, several studies revealed that AI algorithms were trained to extract cancer-associated information from pathological and radiological imaging data for cancer detection and screening, including prostate, breast, prostate, and liver cancer [139]. For example, Wentzensen et al. developed a deep-learning classifier to analyze p16/Ki-67 dual-stained (DS) slides, which accurately and efficiently screen cervical cancer patients from the trained cohort [140]. Altogether, with the development of AI algorithms, liquid biopsies, and multi-omics technology, we anticipate that AI integrating multiple data types will fuel early cancer detection and screening.

4.2. AI-based multi-omics analysis in cancer diagnosis, classification, and grading

In the era of precision oncology, diverse omics technologies, such as genomics, transcriptomics, pathomics, and radiomics, have been extensively used to diagnose cancers and classify cancer subtypes. AI algorithms can process and integrate large volumes of data from multiple sources, helping clinicians diagnose and identify cancer types (Table 1). Deep neural networks (DNN) are powerful algorithms that can be applied to diagnose cancers, identify cancer grades, and distinguish cancer types by analyzing multi-omics data [130,141,142]. DNN-based models have exhibited excellent accuracy at identifying malignant tumors, such as distinguishing cancer cells from normal cells using digitized histopathology slides [143,144]. This approach accurately diagnoses cancer types and grades and distinguishes tumor and normal tissues. One of the most successful cases of this algorithm in tumor diagnosis is detecting metastases in lymph nodes of breast cancer using

Table 1
Summary of the application of AI-based multi-omics analysis in cancer precision medicine.

Application	Omics technology	AI algorithms	Representative results	Data sources
Early cancer detection and screening	cfDNA, proteomic data	CancerSEEK	Identification of multiple cancer types, including ovary, liver, stomach, pancreas, esophagus, colorectum, lung, and breast cancer.	Cohen et al. [135]
	miRNA, proteomic data	MedCalc	Model trained to distinguish cirrhosis and hepatocellular carcinoma.	Wang et al. [136].
	cfDNA	Lung-CLiP	Detecting early stages of lung cancer.	Chabon et al. [137]
	mRNA expression	SVMs, Random Forests	Identifying the cancer and normal tissues with an accuracy of 97.89 %.	Mohammed et al. [209]
	mRNA expression, Genomics, epigenomics	AMARETTO	Identify pan-cancer driver genes by analyzing the CNV, DNA methylation, and gene expression data.	Champion et al. [210]
	Pathology images	DNN	Screening cervical cancer.	Wentzensen et al. [140]
Cancer classification	WGS	DNN	Predicting cancer types by using somatic mutation patterns and driver genes.	Jiao et al. [211]
	mRNA expression, miRNA expression, methylation	Hierarchical integration deep flexible neural forest network	By integrating the multi-omics data to classify cancer subtypes. The accuracy of multi-omics data-based DL model is better than single transcriptome data.	Xu et al. [212]
	mRNA expression, proteomics, metabolomics	PROFILE	Classify the subtype of breast cancer.	Béal et al. [213]
	mRNA expression, DNA methylation, miRNA	Similarity network fusion (SNF)	Models trained mRNA expression, DNA methylation, and miRNA expression data to classify cancer subtypes.	Wang et al. [214]
	Pathology images	MSINet	Predicting the MSI status of colorectal cancer.	Yamashita et al. [149],
	Pathology images	Resnet18	Predicting the MSI status of gastrointestinal cancer.	Kather et al. [150]
Cancer diagnosis	Pathology images	Bladder4Net(CNN)	Model trained to diagnose bladder cancer and predict patient survival	Barrios et al. [144]
	Pathology images	DNN	Detecting breast cancer lymph nodes metastases.	Bejnordi et al. [145]
	Pathology images	Inception v3 algorithm (CNN)	Model trained to distinguish lung adenocarcinoma, lung squamous cell carcinoma, and normal lung tissue. Predicting lung cancer-associated gene mutations.	Coudray et al. [146]
	CT images	PMetNet algorithm	Predicting the peritoneal metastasis of gastric cancer.	Jiang et al. [153]
	CT images	3D ResNet algorithm	Predicting metastasis of colorectal cancer.	Yuan et al. [152]
	MRI images	3D DenseNet, V-Net, CNN	Distinguishing malignant cancer (e.g. nasopharyngeal carcinoma, prostate cancer, breast cancer) and benign disease.	Deng et al. [154], Wang et al. [155], McKinney et al. [156]
	^{18}F-FDG-PET/CT	EGFR-DLS	Detecting the EGFR mutation in non-small cell lung cancer.	Mu et al. [157]
	WES	DNN	By detecting the genomic point mutations from WES data, genomic-deep learning (GDL) model can identify 12 types of healthy and cancer tissues.	Sun et al. [159]
	DNA methylation data	random forest algorithm	DNA methylation-based classifier was used to diagnose central nervous system tumors	Capper et al. [160]
	mRNA expression, methylation	Random forest and different classifiers	Identify papillary renal cell carcinoma (PRCC) driven gene and distinguish early and late stages of PRCC.	Singh et al. [215]
	DNA methylation data	DNN	Identifying cancer types and origin.	Zheng et al. [162].
Prognosis prediction	mRNA expression	Decipher score	Predicting the early metastasis of prostate cancer and the survival of patient.	Erho et al. [165]
	mRNA expression	Molecular Prognostic Score (mPS)	Based on 23 prognosis-related genes mPS can precisely predicts the survival of breast cancer	Shimizu et al. [166]
	Methylation, mRNA, and miRNA expression	Deep learning	The DL model used to predict the survival of hepatocellular carcinoma and the concordance index is 0.68.	Chaudhary et al. [216]
	methylation, CNV, mRNA, and miRNA expression	Min-Redundancy and Maximum-Relevance (MRMR)	Predicting the survival of ovarian cancer by using multi-omics data.	El-Manzalawy et al. [217]
	mRNA expression, CNV, SNP	Group lass regularized Deep learning for cancer Prognosis (GDP)	Trained GDP on multi-omics data to predict the survival of pan-cancer, such as glioblastoma multiforme, kidney renal clear cell carcinoma, and bladder urothelial carcinoma.	Xie et al. [218]
	Pathology images	MesoNet	Predicting the overall survival of malignant mesothelioma patients from whole-slide images and without any pathologist assistance.	Courtiol et al. [164]
	Pathology images	DeepTILs	By analyzing the spatial distribution of lymphocytes in tumor tissues, the DeepTILs can predict the survival of colorectal carcinoma patients.	Xu et al. [175]
Treatment response prediction	Pathology images	DNN	The deep learning-based classifier was trained to detect the MSI status and predict immunotherapy of gastric cancer.	Muti et al. [180]
	Transcriptome, genomic, epigenomic, and proteomic data	Bayesian multitask MKL	Trained model to predict drug sensitivity from multi-omics data.	Costello et al. [219]
	Proteomics data	BEMKL model	The model trained on proteomic data to predict the drug sensitivity of cancer cells to chemotherapeutics and molecularly targeted anticancer compounds.	Ali et al. [220]
	Radiomics, laboratory data, baseline clinical data	Simple temporal attention (SimTA)	By integrating DL with serial radiomics, blood test data, and baseline clinical data to predict the response of NSCLC to anti-PD-1/PD-L1 immunotherapy.	Yang et al. [182]
	Radiology data	Deep natural language	The radiology text report based deep-learning model was developed to evaluate the overall response of PD-1 blockade and progression-free survival.	Arbour et al. [183]
	Histology data and clinical data	CNN	Predicting immune checkpoint blockade efficiency of advanced melanoma.	Johannet et al. [184]

whole-slide images with hematoxylin-eosin (H&E) staining, exhibiting better efficiency and accuracy than diagnoses of pathologists [145]. In this competition, the area under the receiver operating curve (AUC) for the AI system was 99.4 %, which was significantly higher than the 81.0 % AUC yielded by the 11 pathologists. AI-based pathomics analysis has also been adopted to distinguish closely related cancer subtypes, such as adenocarcinoma and squamous cell carcinoma of lung tumors [134,146, 147]. Coudray et al. proposed an inception v3 algorithm that used whole-slide images from TCGA lung cancer to classify them into lung adenocarcinoma, lung squamous cell carcinoma, and normal lung tissue and achieved outstanding results (AUC=0.97) [146]. More importantly, this intelligence algorithm can link cancer gene mutations with pathology images. Several lung cancer-associated gene mutations, such as *STK11, EGFR, FAT1, SETBP1, KRAS,* and *TP53*, were predicted from H&E pathology images [146]. Other studies further confirmed that AI-based pathomics could predict clinically relevant genetic alterations and MSI status [148–150]. Recently, an AI-based multi-omics pan-cancer study revealed that driver gene mutations, whole-genome duplication, copy number alterations, and gene expression levels were closely correlated with histopathology features [151]. These studies show that AI-based pathology analysis can precisely diagnose cancer types and even predict genetic alterations in cancer.

Radiology technologies, such as magnetic resonance imaging (MRI), computed tomography (CT) scans, and positron emission tomography-CT (PET-CT) scans, are the most popular approaches to the diagnosis of cancers. Convolutional neural network (CNN)-based algorithms have presented remarkable accuracy in tumor diagnosis utilizing radiology images [132,152]. In a multicenter study, Jiang et al. used CT scans of gastric cancer patients to develop a DNN model that predicted occult peritoneal metastasis with an AUC of 0.946 [153]. Similarly, Yuan et al. utilized CT scans to develop a 3D ResNet algorithm that predicted occult peritoneal metastasis in colorectal cancer with an improved AUC of 0.922 compared to the AUC (AUC=0.791) yielded from clinical routine contrast-enhanced CT diagnosis [152]. Other studies used MRI image-based AI algorithms to distinguish malignant cancer from benign disease [154,155]. For example, Wang et al. developed a DNN model that distinguished prostate cancer from benign prostate diseases using MRI images from prostate cancer patients [155]. In a retrospective study, McKinney et al. proposed an AI system that uses mammograms from 28,953 women to identify breast cancer, and the achieved AUC was higher than the AUC of the radiologist [156]. Moreover, AI algorithms can associate genetic alterations with radiology image data. For example, the PET/CT-based DL model can predict EGFR mutation in -NSCLC with an AUC of 0.81 [157].

Apart from medical imaging data, omics data have also been used for cancer diagnosis, classification, and grading. With the development of high-throughput technologies, the classification of cancer has developed from traditional “morphological” into the new era of "molecular classification" [158]. Molecular features extracted from multi-omics technologies have been used to diagnose and classify cancer subtypes. However, data generated from multi-omics technologies often have large volumes and multidimensional information. DNN-based algorithms can efficiently process large volumes of data and integrate multiple data for cancer classification and diagnosis. For example, based on DNN algorithm, Sun et al. developed a genomic-deep learning (GDL) model that detected the genomic point mutations from WES data of 6083 tumor samples from 12 TCGA cancer types and 1991 healthy tissues [159]. By analyzing the cancer specific point mutation of WES data, the classifier can precisely distinguish the 12 cancer types and healthy tissues with an AUC of 0.94. In a promising study, Capper et al. developed a ML algorithm to classify tumor types based on DNA methylation profiles and compared the accuracy of diagnoses with histopathological diagnoses of pathologists [160]. In this study, 1104 test tumor cases that pathologists have diagnosed by histological or molecular techniques were used to evaluate the diagnosis accuracy of the AI algorithm. For 838 cases of these test cases, the ML-based classifier coincided with the pathologist’s classification, although a part of cases (15.5 %) was assigned to the subcategory of tumors. For 139 of the test cases, the diagnosis of the ML classifier un-match with the pathologist’s diagnosis. While further molecular analysis showed that, in fact, 93 % of those unmatched cases were accurately predicted by the classifier. A similar study also validated that DNA methylation and copy number-based classification using ML can be used for cancer diagnosis [161]. In addition, DNN algorithms have also been applied to identify the origin of cancers. Zheng et al. developed a DNN model to predict cancer origin and types by utilizing DNA methylation data of 7339 patients across 18 cancer types from TCGA [162]. Overall, these studies demonstrate the promising application of integrating AI with multi-omics data in cancer diagnosis, classification, and grading.

4.3. AI-based multi-omics analysis in predicting cancer prognosis and treatment response

Over the past years, AI algorithms have integrated multi-omics data, such as pathomics, radiomics, genomics, and transcriptomics, into risk prediction models for predicting tumor relapse risk and treatment response and guiding treatment [133,148,163] (Table 1). Classifiers, such as MesoNet [164], Decipher score [165], and molecular Prognostic Score (mPS) system [166], can provide more accurate and suitable treatment strategies for physicians. For example, Erho et al. demonstrated that a Decipher score genomic classifier trained exclusively on 22 genomic expression profiles could precisely predict metastasis of prostate cancer patients after prostatectomy [165]. Similarly, by screening 23 prognosis-related genes, Shimizu et al. established a universal molecular prognostic model based on AI methods, called the mPS system, that precisely predicted the survival of breast cancer patients [166]. Histopathology image data are also used to predict the risk of cancer recurrence and outcome. AI algorithms can extract prognosis-related information, such as lymphocyte count, the spatial distribution of lymphocytes, chromatin patterns, and proportions of cell subtypes, from whole-slide images for survival and outcome prediction. Courtiol et al. developed MesoNet, a deep convolutional neural network-based model that can independently (without the aid of pathologists) predict mesothelioma patient overall survival using digital whole-slide images [164]. Other studies further validated that AI algorithms, combined with data from whole-slide images, could produce accurate risk scores in multiple malignancies, including colorectal cancer [167], brain tumor [168], hepatocellular carcinoma [169], gastric carcinoma [170], breast cancer [171], etc. The infiltration and spatial distribution of lymphocytes is closely correlated with the response and outcomes of immunotherapy. Using H&E-stained histology images, Yuan et al. developed an automated image analysis tool to analyze the spatial distribution of lymphocytes in tumor tissues of triple-negative breast cancer (TNBC) [172]. Based on this tool, they found that the ratio of intratumor lymphocytes was associated with the survival of TNBC and was closely correlated with the expression levels of cytotoxic T lymphocyte protein 4. By integrating AI algorithms with pathology images, other researchers [173–176] also found that calculating the spatial distribution of tumor-infiltrated lymphocytes could predict the prognosis and recurrence of cancer.

Compared with prognosis, AI algorithms predict the response to drug treatment with more clinical relevance, which helps clinicians make better treatment recommendations. During the past two decades, immunotherapy and targeted therapy have become the most prevalent treatment strategies for cancer patients and have achieved exciting clinical outcomes [177,178]. However, due to complex tumor heterogeneity and genetic alterations, different patients respond differently to specific therapies. Providing an accurate treatment regimen is beneficial for prolonging patient survival. Recently, several studies have proven that AI-based multi-omics analysis efficiently predicted the response to immunotherapy and targeted therapy. Genomics-based MSI test is an indicator for predicting the response to immunotherapy. Cancer genetic

alterations are correlated with specific histopathological phenotypes, such as MSI tumors harboring high levels of lymphocyte infiltration and mucinous differentiation. Many researchers have integrated histology imaging data from tumor tissues of malignancies, such as colorectal, gastric, and endometrial cancer, with AI to predict MSI for cancer patients who have not undergone genetic testing [149,179–181]. In a multi-center retrospective study, Muti et al. developed a DL-based classifier that detected the MSI status from H&E stained resection slides of 2823 gastric cancer patients [180]. The classifier could detect MSI status with an AUC ranging from 0.597 to 0.836, which can be used to predict immunotherapy response in gastric cancer. Yang et al. developed a simple temporal attention (SimTA) module that integrated DL with serial radiomics, blood test data, and baseline clinical data to predict the response of NSCLC to anti-PD-1/PD-L1 immunotherapy [182]. Similarly, based on the radiology data of patients with NSCLC treated with PD-1 blockade, Arbour et al. developed a DL model that directly predicted the best overall response and progression-free survival [183]. In another example, Johannet et al. used histology data and clinical data of melanoma patients to develop a multivariable classifier that predicted immune checkpoint inhibitor treatment outcomes with an AUC of 0.80 [184]. Most excitingly, Xu et al. developed an artificial intelligence-derived gene signature (AIGS) to predict the clinical outcome of bladder cancer [185]. The results showed that AIGS accurately distinguished patients who were sensitive to immunotherapy or other treatment strategies. In addition, based on the multi-omics data analysis, some gene mutations and copy number variations were also characterized by AIGS, which provided potential therapeutic drugs for bladder cancer patients. These studies demonstrated that AI algorithms integrating multi-omics data have shown prospects in evaluating responses to immunotherapy for patients with malignancies.

In recent years, single-cell sequencing is becoming a powerful tool to guide cancer precision therapy. A growing body of research reveals that single-cell sequencing is emerging to be an effective approach for dissecting intratumor heterogeneity, clonal evolution, tumor microenvironment, underlying mechanisms of tumor metastasis, and response to cancer-related therapies [186,187]. The data from single-cell sequencing have been used to improve clinical decision-making for cancer-targeted therapy and immunotherapy. For example, Zhang et al. employed scRNA-seq to reveal the immune cell dynamics in TNBC patients who received anti-PD-L1 atezolizumab and paclitaxel treatment. They found that $CXCL13^{+}$ T cells are important for anti-PD-L1 therapy, and paclitaxel may diminish immunotherapy efficacy by impairing this unique T cell subtype [188]. Since single-cell sequencing data are commonly big and complicated, disentangling these big data is a major challenge for researchers. To solve this problem, several AI algorithms, such as density clustering and residual neural network, have been developed to improve the readability of single-cell sequencing data [186,189–191]. With the emergence of the single-cell omics era, AI will further promote single-cell omics-based cancer precision.

5. Challenges and future directions

AI approaches have successfully tackled the complexity and heterogeneity of multi-omics data and are widely used in various touchpoints along the clinical oncology care path, as described in the previous sections. Although great progress has been made with AI-based multi-omics analysis, its application in precision medicine still faces many challenges.

5.1. Data scarcity

In general, AI approaches rely on large collections of data to guarantee adequate robustness. However, access to sufficient high-quality data in precision oncology is often difficult to achieve, which may induce implicit biases. The applications of accurate sampling methods are conducive to accessing high-quality samples, such as image-guided tissue extraction [192] and three-dimensional molds based on tumor morphology [193]. However, there are still challenges before these methods are scaled up. High-throughput technologies and interinstitutional data sharing may be the most straightforward ways to achieve large-scale and remedy the deficiencies of data scarcity. Cross-institutional data sharing can significantly reduce the need to carry out new experiments but may introduce biases due to data heterogeneity that can lead to limited interpretability of the results. Also, heterogeneity between cross-institutional data is a major reason for the failure of AI systems in clinical trials [194]. Meanwhile, it is important to note that the central premise of interinstitutional sharing is to ensure patient privacy [107]. Furthermore, recent research interest in transfer learning aims at improving the performance of specific learners by transferring the existing, generalizable knowledge from other different but relevant learners [195,196]. Transfer learning offers an excellent alternative to circumvent data scarcity and has been successfully applied to enhance cancer diagnoses and classification, as well as therapeutic response prediction [197–199].

5.2. High heterogeneity and complexity of multi-modal data

Despite numerous important advances, AI-based multi-omics analysis has mainly been applied to integrate data from genomics and transcriptomics. Additional layers of information still need to be added to expand the scope of insight to tackle complex biological problems underlying oncology diseases, such as multilayer regulatory programs mediated by various epigenomic modifications, transcription factors, and non-coding RNAs. In addition, recent spatial omics approaches preserve tissue architecture, further empowering investigators in pursuit of a comprehensive understanding of cellular neighborhoods and intercellular interactions [200]. Efforts are underway to create comprehensive multi-modal data resources available to investigators, such as Cancer Moonshot Research Initiatives, aiming to collect various omics and non-omics data to construct a comprehensive database to accelerate cancer research [201]. The ensuing technical challenge is how to explicitly model intermodal relationships [107]. Another crucial challenge is how to spatially accurately match *in vivo* imaging with *ex vivo* data, which is especially important to explore the biological correlation of multi-modal features [202]. These challenges promote the innovation of novel AI methodologies for handling heterogeneity and complexity inherent in multi-modal data.

5.3. Lacking interpretability and repeatability

Another tricky challenge is the lack of interpretability and repeatability in AI-based multi-omics analysis, which is a key component for promoting clinical usability [203]. While complexities underlying cancer, inherent discrepancies between modalities, and AI's black-box nature still hamper our understanding of how AI-based models make such predictions [204]. This issue obstructs the clinical translation of AI-based multi-omics approaches from bench to bedside. Fortunately, increasing efforts have been made to augment the interpretability, and several techniques have been proposed to elucidate AI prediction rationale, such as saliency maps, hidden-state analysis, variable importance metrics, and feature visualizations [9,205–207]. These techniques will help to offer meaningful explanations for patient-specific predictions and gain mechanistic insights into complex AI-based models. For repeatability, several strategies try to solve this problem, e.g., adopting a more complex algorithm or obtaining averaging results from several models, but this does not seem to fundamentally solve this problem [203]. Following the standard guidelines, by contrast, can guarantee the reproducibility, transparency, and methodological rigor of AI model to a certain extent [208].

In conclusion, multi-omics technologies hold particular promise for the field of precision oncology, as comprehensive profiling measured by multi-omics provides a holistic view of cancer behavior. AI can harness

information content from various sources, thereby opening new horizons for our understanding of cancer biology and providing opportunities for accurate cancer diagnosis and developing more precise therapeutic strategies. Although many challenges remain, there are substantial ongoing efforts to address these issues and promote the clinical translation of AI-based multi-omics analysis. With multi-omics data increasingly being generated in clinical practice, we evasion that AI technologies will provide meaningful information to guide clinical decisions, ultimately driving innovation in precision cancer management.

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Author contributions

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Conflict of interest statement

The authors declare that there are no conflicts of interest.

Data Availability

No data was used for the research described in the article.

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