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Review

Deep learning–driven multi-omics analysis: enhancing cancer diagnostics and therapeutics

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Abstract

Artificial intelligence (AI) excels at efficiently processing large volumes of data and extracting valuable insights. Deep Learning (DL), a subfield of AI, utilizes multi-layer neural network algorithms to analyze various types of data, mimicking the neural network architecture of the human brain. One of the most prominent features of DL is its end-to-end learning mechanism, which excels at automatic feature extraction and pattern recognition in data. As multi-omics technologies rapidly evolve, the volume of omics data from cancer samples has surged, presenting a significant challenge in managing this vast amount of information. Due to its strong data processing capabilities, DL is increasingly applied across a range of cancer research areas, such as early detection and screening, diagnosis, molecular subtype classification, discovery of biomarkers, and predicting patient prognosis and treatment responses. DL integrates high-dimensional data from fields such as genomics, epigenomics, transcriptomics, proteomics, radiomics, and single-cell omics, enhancing our understanding of cancer development and advancing personalized treatment approaches. This paper reviews various DL models and their roles in analyzing complex data patterns, providing a review of DL applications in cancer multi-omics analysis research and emphasizing its potential in early detection, diagnosis, classification, and prognosis prediction. As DL models are introduced continuously, we expect their application in cancer research to become more extensive, thus propelling the advancement of cancer medicine.

Keywords: artificial intelligence; deep learning; multi-omics; cancer early detection; tumor biomarker

Introduction

Artificial intelligence (AI) received its formal designation and definition at the 1956 Dartmouth Conference, signifying the formal inception of the AI discipline [1]. A subset of AI, machine learning (ML) is typically divided into supervised learning, unsupervised learning, and reinforcement learning. The essence involves utilizing algorithms to allow machines to autonomously learn from data and discover patterns, thus enabling decision-making or predictions. Deep learning (DL), a subset of ML, has existed in theory and algorithm since the 1980s, but it began to gain significant attention in 2006, driven by advancements in computational power and the availability of large datasets. DL employs multi-layer neural networks to mimic the way humans learn, enhancing prediction accuracy by learning the multi-layered representations of data. It has achieved remarkable success in fields like computer vision, natural language processing, and intelligent construction [2, 3].

The distinction between DL models and existing technologies primarily lies in the following aspects: feature extraction techniques, the requirements for data and computational resources, model interpretability, and approaches to solving problems. In terms of feature extraction methods, traditional techniques such as conventional computer vision methods require manual feature extraction. As the number of classification categories increases, feature extraction becomes increasingly cumbersome [4]. In contrast, DL models can automatically extract features without the need for manual selection of important features [3]. Regarding data and computational resource demands, DL requires access to large-scale datasets to surpass other methods, and training DL models necessitates high-performance computing units, robust Graphics Processing Units (GPUs), and significant storage capacity [5, 6]. In comparison, traditional technologies have relatively lower demands for data volume and computational resources. In terms of model interpretability, DL models are frequently criticized as "black boxes" due to their millions of parameters, each with intricate interrelations, making it very challenging to manually adjust the model parameters [7]. On the other hand, traditional techniques, such as conventional computer vision, offer full transparency. Engineers can assess whether a solution will work outside the training environment and can incorporate insights into the algorithm based on the problem [4, 6]. Regarding problem-solving approaches, traditional techniques like conventional computational imaging depend on physical models, limited by optical systems and imaging conditions. On the other hand, DL has revolutionized this "physics model-driven" paradigm, ushering in

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a "sample data-driven" approach to learning [8, 9]. Over the past few years, DL technology has demonstrated unique benefits in medical practice and has become an essential tool in oncology research.

The development and progression of cancer involves interactions across various levels such as the genome, epigenome, transcriptome, proteome, and metabolome. The integration of multi-omics data into cancer research assists us to improve a better understanding of the intrinsic framework of tumor development and lays the foundation for cancer diagnosis and personalized treatment. With the increasing volume of omics data, effectively integrating and analyzing these data amid noise and uncovering the potential information within vast amounts of data have become pressing challenges. DL, with its ability to handle high-dimensional, heterogeneous, and unstructured data, as well as its capability to discover complex relationships in multimodal data, offers a potential solution to this challenge [10, 11]. In recent years, DL technology has demonstrated its application potential in various stages of cancer management, including early detection and screening, diagnosis, molecular subtype classification, prognosis prediction, survival analysis, and treatment response assessment [12].

This paper reviews recent applications of multi-omics analysis combined with DL technology in cancer diagnosis and treatment. We present the basic concepts, workflows, and common strategies for DL data integration, and provide examples of several typical DL models. In addition, we discuss in detail the classification of multi-omics, the main data types in each omics, and the analysis techniques involved. Furthermore, we discuss the fundamental concepts of DL, various common DL models, the classification of multi-omics, and the foundational process of integrating multi-omics data using DL. Finally, we explore the specific uses of DL in the field of oncology, encompassing early detection and screening of cancer, diagnosis, subtype classification, discovery of biomarkers, and prognosis and treatment response prediction. Additionally, we summarize the current challenges and future outlook of DL technology.

An overview of deep learning

Introduction to deep learning

AI represents a cutting-edge technological advancement, possessing the ability to acquire knowledge and discern connections within datasets. It can effectively utilize this information to compute and produce results from new input data [13]. AI can process large-scale data efficiently and extract valuable information, patterns, and structures from it as well. ML is a subset of AI focused on data analysis, pattern recognition, and the construction of predictive models. DL, a subfield of ML (Fig. 1), draws inspiration from brain neural structures and utilizes multi-layer neural network algorithms to analyze various types of data and produce predictive outcomes [14]. The most prominent feature of DL is its end-to-end learning mechanism, which enables models to learn from raw data to final outcomes, bypassing manual feature engineering or intermediate processing steps. This characteristic not only conserves time in data analysis but also diminishes subjective errors in DL when dealing with complex issues, enhancing the efficiency and accuracy of the results [15]. Potential systemic errors, such as issues with data selection during the model training phase, can be mitigated by optimizing network architecture and selecting training samples to reduce their impact on model performance.

Thanks to the introduction of microarrays and high-throughput sequencing, the volume of biological data from cancer samples has increased dramatically [16], especially in omics fields affected by multiple factor interactions, such as genomics, epigenomics, transcriptomics, proteomics, metabolomics, and single-cell omics, which generate substantial data [17–20]. Besides, integrating these high-dimensional, heterogeneous multi-omics datasets presents a formidable challenge, requiring more sophisticated data processing technologies. Against this backdrop, DL provides modeling algorithms that can learn from numerous complex features, making DL-based approaches potent tools for biomedical data analysis. DL is superior to traditional statistical modeling and shallow ML, as it can learn nonlinear and hierarchical features from multimodal data, fit heterogeneous, high-dimensional data, and discern relevant granular features, offering meaningful insights. Lately, DL has emerged as one of the most efficacious methods for integrating multi-omics data analysis in cancer [14, 21].

Basic concepts, workflow, and common strategies of multi-omics data integration based on Deep Learning

Basic concepts of deep learning

DL models, central to data integration, typically consist of several core components: input layer, hidden layers, output layer, pooling layers, weights and biases, activation functions, loss functions, optimizers, and regularization. Subsequently, a general introduction to the roles and significance of these core components will be provided. The input layer serves as the starting point of the neural network, receiving the raw data (images, text, numerical values, etc.) for processing. The hidden layers comprise multiple layers of nonlinear processing units, including convolutional, recurrent, and fully connected layers, each transforming and extracting features from the previous layers. The design and function of the output layer depend on the type of task the model addresses, and its role is to convert the model's final features into prediction outcomes. The pooling layers perform dimensionality reduction and feature extraction on feature maps, merging semantically similar features to reduce subsequent computational load and alleviate overfitting during model training. Weights and biases are parameters in deep neural networks that can be adjusted through backpropagation to optimize model performance. Activation functions, incorporated into neural networks, introduce nonlinearity, empowering networks to fit complex relationships and dictate the output to subsequent neurons. Loss functions evaluate the gap between model predictions and actual outcomes, with common types including mean squared error and cross-entropy loss functions. Optimizers update parameters such as weights and biases during model training to minimize loss functions and enhance model performance. Regularization, aimed at reducing overfitting risk, involves in introducing extra information or constraints during model training to boost generalizability.

Workflow of data integration

The workflow for multi-omics data integration using DL mainly involves six key stages: data preprocessing, feature selection or dimensionality reduction, data integration, DL model construction, data analysis, and result validation (Fig. 2). Data preprocessing is the initial step in the entire workflow, mainly consisting of data cleaning and standardization procedures. In multi-omics data integration, issues such as missing values, noisy data, and duplicate information are often encountered, which can affect the quality of subsequent analyses. Therefore, it is essential to clean the data first, with common methods including filling in missing values, removing outliers, and standardizing the data

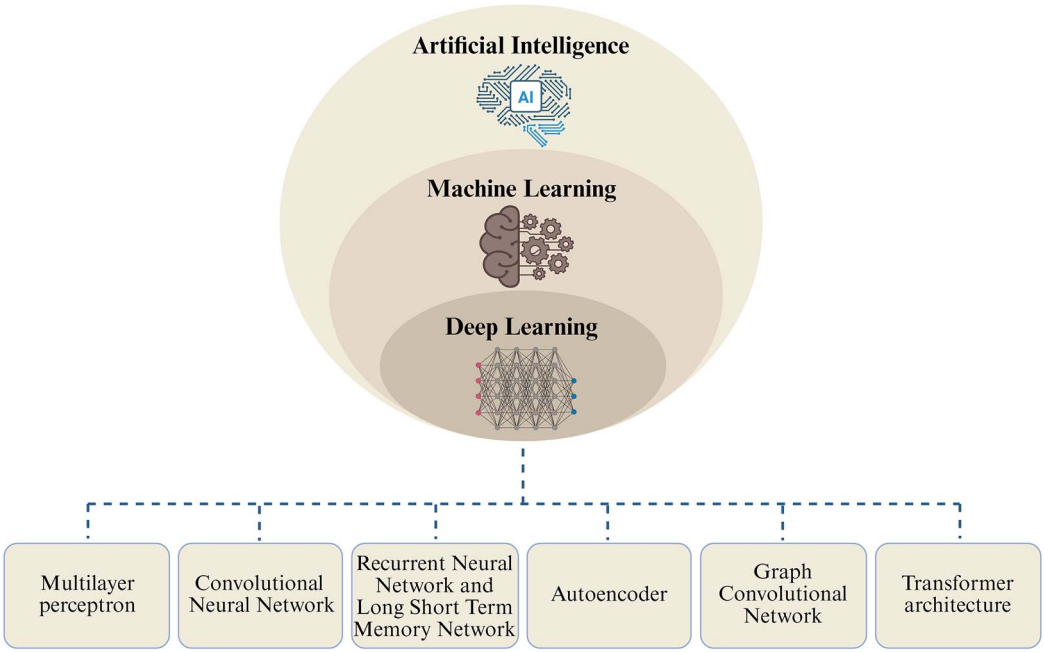

Figure 1. The connections among artificial intelligence (AI), machine learning (ML), and deep learning (DL), along with several types of neural network models in deep learning (by BioRender). AI is capable of simulating the informational processes of human consciousness and cognition, constructing models by learning and identifying patterns and relationships between inputs and outputs, and then computing and outputting results for new input data. AI excels at processing large datasets, efficiently identifying valuable information, patterns, and structures. Machine learning is a subfield of AI, typically divided into supervised learning, unsupervised learning, and reinforcement learning. ML allows machines to automatically learn from data and identify patterns through algorithms, enabling them to make decisions or predictions. DL, a subfield of ML, uses multi-layer neural network architectures to analyze various data types and generate prediction outcomes through an end-to-end learning process. The main deep learning models include multilayer perceptron, convolutional neural network, recurrent neural network and long short-term memory network, autoencoder, graph convolutional network, and transformer architecture (by BioRender).

(e.g. z-score normalization or Min-Max normalization) [22]. These steps aim to ensure data quality and improve the accuracy of data integration. During the data integration process, a large number of features or variables are often present, which may lead to high-dimensional data and thus increase computational complexity. To solve this problem, feature selection or dimensionality reduction techniques, such as principal component analysis (PCA) or autoencoders (AEs), are commonly employed. These techniques can effectively reduce redundant features and extract the most representative features for subsequent analysis. PCA maps the original data to a new coordinate system through linear transformations, retaining most of the information, whereas AE learns the low-dimensional representation of input data using a neural network. These dimensionality reduction techniques can improve the computational efficiency of the model and also reduce the risk of overfitting. Data integration involves merging data from different omics sources into a unified dataset for easier further analysis. Data integration strategies can be categorized into early, mid, and late integration [23]. Early integration refers to combining all omics data into one large multidimensional dataset before feature selection or dimensionality reduction; mid-term integration occurs after feature selection or dimensionality reduction, where data is integrated according to omics types; late-stage integration involves integrating the analysis results of different omics after each omics data has been analyzed separately. The selection of these integration strategies depends on the specific requirements of the task and the characteristics of the data. Effective integration strategies can facilitate the maximization of information sharing between datasets, thereby improving the accuracy and robustness of the analysis. Constructing the DL model is the core step in data analysis. Depending on the data type and analysis objectives (e.g. classification, regression, clustering), an appropriate DL model needs to be selected. Common DL models include Convolutional Neural Networks (CNNs), Recurrent Neural Networks (RNNs), and Autoencoders (AEs), among others. These models are capable of capturing complex nonlinear relationships and hierarchical structures within the data, extracting hidden information from various omics datasets [24]. For example, a CNN is typically used for image data processing, capable of extracting useful spatial features from images; an RNN is suitable for time-series data analysis, capable of handling temporal dependencies in sequence data. During the data analysis phase, the constructed DL model is used to analyze the integrated data for specific tasks. Common tasks include classification (e.g. disease prediction), regression (e.g. biomarker quantification prediction), clustering (e.g. patient subtype identification), and so on. By training the model, useful information can be extracted from complex multi-omics data, allowing for accurate predictions of target tasks. In the result validation phase, the performance of the model needs to be validated through a series of evaluation metrics. Common evaluation metrics include accuracy, F1 score, Mean Squared Error (MSE), and silhouette coefficient, with the specific metric choice depending on the task type and objective [25]. Accuracy is suitable for classification tasks, the F1 score accounts for class imbalance, MSE is suitable for regression tasks, and the silhouette coefficient is suited for clustering tasks. Through these evaluation metrics, the model's effectiveness can be quantified, providing a basis for further optimization [26].

Common strategies for multi-omics integration

The core challenge of multi-omics data integration lies in how to effectively merge different omics data. These data vary in

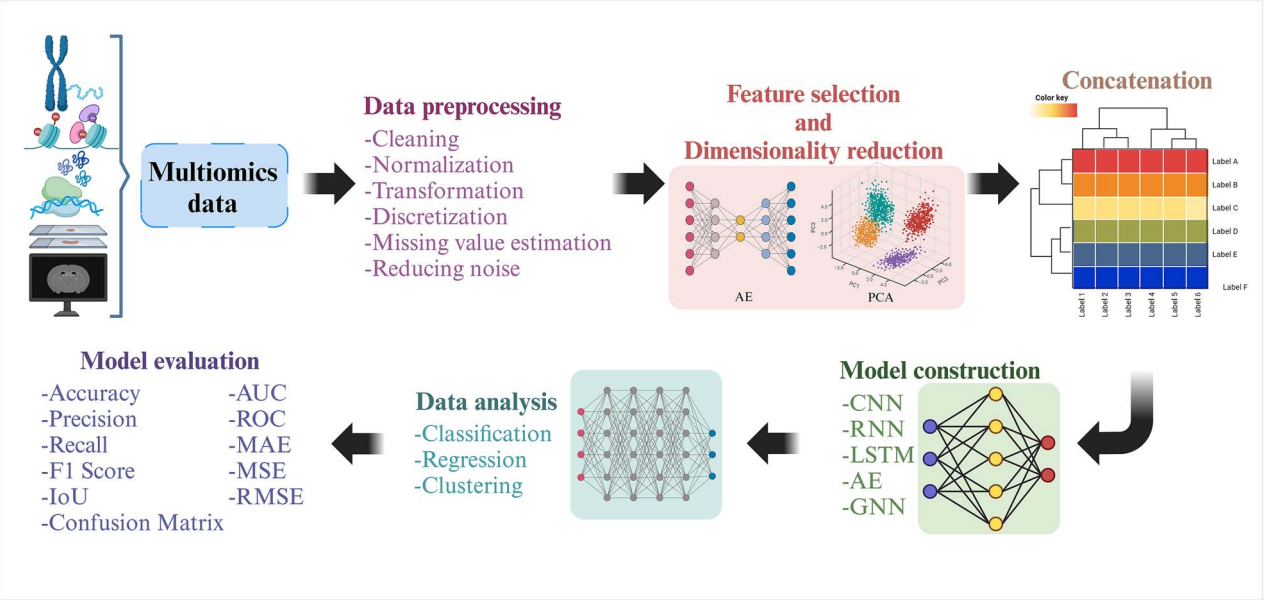

Figure 2. Workflow for integrating multi-omics data through DL. The complete workflow consists of six major steps: data preprocessing, feature selection or dimensionality reduction, data integration, deep learning model development, data analysis, and result validation. Initially, the multi-omics data undergoes cleaning, followed by feature selection and dimensionality reduction techniques to refine the dataset. Subsequently, the data variables from various omics need to be consolidated into a comprehensive dataset for further analysis. Following that, a suitable deep learning model is chosen according to the data type and task goals, and model training and parameter optimization are conducted. The trained model is utilized to conduct analysis tasks, including classification, regression, and clustering, on the integrated data. Lastly, relevant metrics are chosen to evaluate the model's performance (by BioRender).

scale, resolution, and nature, and direct integration can result in data mismatches, noise interference, and scale inconsistencies. DL, leveraging its strong end-to-end learning framework, enables feature extraction and pattern recognition, enhancing integration performance. Common integration strategies include cascading strategies, dimensionality reduction and embedding learning, cross-modal attention mechanisms, and multi-modal representation learning. The cascading strategy processes different omics data in stages, first extracting features independently and then gradually integrating them, often using hierarchical structures [27]. Dimensionality reduction techniques, like PCA and AEs, reduce data complexity by mapping high-dimensional data to lower-dimensional spaces, helping models recognize the relationships between different types of data. In recent years, cross-modal attention mechanisms have advanced significantly. Attention-based DL models, such as Transformer, can automatically learn and assign importance across different modalities, guiding the model to focus on the interconnected parts of various omics data. Multi-modal representation learning achieves joint analysis by learning a shared embedding space, mapping different types of data into the same space. Joint embedding technologies, like multi-modal variational autoencoders (VAEs) and joint embedding networks, utilize similar mathematical structures to achieve joint representations, facilitating information sharing and cross-modal fusion, which significantly enhances model expressiveness, especially for complex biological data. Traditional integration methods, such as simple cascading or dimensionality reduction, primarily achieve data integration through single feature extraction and subsequent fusion. On the other hand, DL, with its hierarchical feature learning approach, can more flexibly address the heterogeneity of multi-omics data and reveal underlying complex patterns between different omics layers [28]. For instance, cross-modal attention mechanisms can assist the model in adaptively selecting important features and optimize integration performance through attention allocation strategies. Some studies attempt to improve integration effectiveness by using modified DL architectures. For example, cross-modal attention mechanisms can allocate different weights to different data types within the same network structure, promoting the flow of important information. Compared to traditional methods, this mechanism can integrate information at multiple levels, avoiding the loss of information in simple cascading approaches. The application of multi-modal representation learning is also an important advancement. Through techniques such as joint embedding, models can find shared representation spaces across multiple modalities, achieving efficient information fusion. This method, by learning joint features across omics, can extract common features without explicit labels, enhancing the model's universality and generalizability. Future research should further explore the deep relationships between different omics data, particularly how to leverage advanced mechanisms in DL, such as cross-modal attention mechanisms and multi-modal representation learning, to achieve more refined and efficient multi-omics data integration. These methods not only address data heterogeneity and enhance model accuracy and reliability, but also transform the approach to multi-omics data analysis, allowing complex biological data to be integrated by DL models in more flexible and varied ways [29].

Interpretability of deep learning

Note that DL models are typically seen as "black box," making it challenging to clearly elucidate their reasoning or decision-making processes, thus having low interpretability. As computing power increases, DL models become more complex and more difficult to explain. The complexity stems from intricate interactions within the model's multiple layers of nonlinear data processing and vast datasets, posing a considerable challenge in tracing and understanding its decision-making pathways. To

tackle the challenge of interpretability in DL models, researchers have implemented methods such as Local Interpretable Model-Agnostic Explanations (LIME) and SHapley Additive exPlanations (SHAP) to provide clearer insights into the workings of these models [30, 31]. However, these tools have their limitations, for instance, LIME's local explanations and instability, which cannot capture the overall behavior of the model, and using the same parameters and methods for repeated explanations may yield entirely different results [32]. To enhance model interpretability, explainable artificial intelligence (XAI) was developed to assist doctors and patients in understanding the reasoning behind AI decisions [33]. XAI aims to improve the transparency of AI models, making their decision-making process easier to understand, particularly for complex DL models, addressing the "black-box" problem [34]. The application of XAI in cancer research is becoming increasingly widespread, primarily through techniques such as feature visualization, heatmaps, LIME, and SHAP values (Shapley values) to improve model interpretability [35]. Feature visualization techniques like Grad-CAM can intuitively display the image regions that the model focuses on, helping doctors understand the tumor recognition process [36]. LIME and SHAP provide more transparent decision-making by analyzing the contribution of features to the prediction outcomes, enhancing the reliability and transparency of AI systems. Specific applications of XAI in cancer research include tumor detection and classification, cancer biomarker prediction, and patient survival prediction. For example, in tumor imaging analysis, XAI can help doctors understand why the model classifies an image as malignant or benign, assisting in accurate diagnosis. In personalized therapy, XAI identifies which patient characteristics have the greatest impact on treatment decisions, helping to design tailored treatment plans. Additionally, XAI enhances the transparency of cancer treatment decisions, driving the development of personalized medicine [37]. In the future, as technology continues to evolve, XAI is expected to drive the standardization of medical AI systems while addressing ethical issues such as privacy protection and fairness, ensuring the sustainable development of AI technology in healthcare [34, 35].

Various deep learning neural network models

The following introduces several DL neural network models that can be used for multi-omics data integration, along with their advantages and applications (Fig. 1).

Multilayer perceptron

The multilayer perceptron (MLP) is a type of feedforward neural network, with a structure that includes an input layer, one or more hidden layers, and an output layer. Each layer consists of multiple nodes (or neurons), and the nodes between adjacent layers are connected by weights. The MLP utilizes nonlinear activation functions and a multi-layer structure to learn complex patterns in input data [38]. In the early stages of DL development, MLP was one of the first neural networks to be studied and applied. However, due to its relatively small number of layers (usually only a few), MLP has limitations when handling complex and high-dimensional data, such as images and speech. As DL has advanced, the number of layers in models has continually increased, resulting in the development of deep neural networks with dozens or even hundreds of layers, such as CNNs, RNNs, and their variants including LSTMs and Graph Neural Networks (GNNs). These models excel at handling complex tasks, which is why MLP is generally regarded as a more fundamental model in the modern DL field. In certain specific tasks, MLP can still perform excellently. For instance, in tasks that involve handling structured data, MLP can enhance the model's complexity and performance by increasing the number of layers and neurons. Additionally, MLP can also be combined with other DL models, such as in certain multimodal learning tasks where MLP acts as a module for processing structured data and integrates with other DL models that handle unstructured data, such as CNN or Transformer [39].

Convolutional Neural Network

The CNN is particularly widely used in image-based applications, such as medical image segmentation and disease classification [40–42]. It is an advanced data analysis method that performs excellently in processing high-dimensional datasets. The CNN excels at handling image data, with a strong ability to detect subtle local patterns. It performs convolution operations by sliding convolutional kernels over the input data to extract local and static features such as edges and textures, and constructs hierarchical models for accurate pattern recognition. The main components of a CNN are the convolutional layers, pooling layers, and fully connected layers. The convolutional layer applies local convolution operations on input data and outputs the results to the pooling layer; the pooling layer reduces the dimensionality of the data and lowers computational complexity; then, the fully connected layer integrates the previously extracted features for the final classification or regression tasks. Compared to traditional computer vision methods that require manual feature design and extraction, the CNN can automatically learn features, minimizing human intervention. In terms of flexibility, the CNN can be retrained on customized datasets to adapt to various use cases, whereas traditional computer vision algorithms are usually more domain-specific. The CNN also delivers much higher accuracy than conventional methods in tasks like image classification and object detection. In the medical field, The CNN is commonly used in medical image analysis, especially in cancer detection and diagnosis, where it has demonstrated great potential and advantages.

Recurrent Neural Network and Long Short-Term Memory Network

The RNN is an alternative neural network model to the CNN. Compared to CNNs, RNNs are unique in their ability to model dynamic temporal behaviors, capable of handling sequence data of any length and capturing temporal dependencies within the sequence, thus becoming an effective means for processing time-series data. An RNN is primarily composed of an input layer, hidden layers, and an output layer, with the hidden layers consisting of a series of recursive neurons, each processing a time step in the sequence, responsible for storing information in the sequence and enabling the network to remember previous states at each time step. Compared with traditional methods, RNNs can effectively capture temporal dependencies in sequence data and efficiently process dynamically changing sequence data, such as speech signals and stock prices [43]. The RNN finds extensive use in various domains, including medical image analysis, natural language processing (NLP), and time series prediction, among others. RNNs are particularly important for the analysis of complex medical images, thanks to their capacity to recognize long-range dependencies within the image data. For instance, they are used in lung lesion segmentation, cancer detection, and subtype classification [44, 45]. In oncology research, RNNs can also be used to analyze the RNA sequences of circulating tumor

cells (CTCs), thereby revealing the origins and migration paths of tumors [46].

Owing to the short-term memory limitations of RNN, which fail to process long sequence data, LSTM was introduced to overcome these challenges. LSTM, a specialized form of RNN, is optimized for preserving long-term information and capturing complex temporal dependencies [47]. LSTM introduces a complex gating structure and cell state based on RNN. It features three core gate mechanisms to protect and control cell states: the input gate, forget gate, and output gate. The input gate filters and accepts new information; the forget gate determines which old information to dispose of from cell states; the output gate controls the final output. With this gating mechanism, LSTM effectively controls the storage and updating of information, overcoming the common issues of gradient vanishing and exploding in traditional RNN [48]. In tasks requiring long-term dependencies, such as text generation and machine translation, LSTM shows remarkable improvement over traditional methods and standard RNN. For example, in traffic flow prediction, LSTM can effectively capture long-term trends in traffic data, such as the periodic changes during rush hours. LSTM aids in tumor detection and classification, disease progression and prognosis forecasting, and drug response prediction by integrating multi-omics data [49–52]. With ongoing developments in DL technologies, LSTM and its derived models will continually advance innovation and breakthroughs in the field of cancer medicine.

From a functional perspective, theoretically, an RNN can extract information from sequences of any length. However, in practical applications, due to issues like gradient vanishing and gradient explosion, their ability to learn long-term dependencies is limited, and they typically handle only shorter sequences [53]. LSTM can effectively solve the gradient vanishing problem in RNN through its unique gating mechanism and cell state, allowing it to better capture long-term dependencies, making it suitable for handling long sequence data [54]. In terms of application, RNN has a simple structure and can be faster to train and more computationally efficient when dealing with tasks that do not demand long-term dependencies, such as basic text generation and speech recognition. In contrast, LSTM excels in tasks that require handling long sequence data and high demands for long-term dependencies, such as machine translation, sentiment analysis, text classification in natural language processing, and time series prediction [55].

Autoencoder

AE, an unsupervised learning technique, consists of an encoder that compresses input data into a lower-dimensional latent representation, and a decoder that reconstructs the data from this compressed form. AE aims to learn compact representations of input data, seeking to discover effective low-dimensional feature extractors from unlabeled data. Traditional dimensionality reduction methods, such as PCA, are mostly based on linear transformations, while AE can learn low-dimensional representations of data through nonlinear transformations, making it suitable for reducing the dimensionality of complex data. AE can automatically extract important features from data for dimensionality reduction, feature extraction, data denoising, image generation, and restoration. It can learn compressed representations of data, helping to reveal the inherent structure of multi-omics data. AE is applicable for data dimensionality reduction and feature extraction, data denoising, image generation and recovery, etc., learning compressed data representations that help reveal the intrinsic structures of multi-omics data. AE can assist in the diagnosis, classification, prognosis analysis, and treatment response prediction of cancer. For example, VAEs can incorporate multi-omics data to identify cancer biomarkers, predict patient survival rates, and discern cancer subtypes [56, 57].

Graph Convolutional Network

Among the various types of GNN, Graph Convolutional Networks (GCNs) have received widespread attention for their efficacy in handling graph-structured data and capturing complex internode relationships. GCNs can effectively perform feature learning and prediction for nodes, edges, or the entire graph. A graph is composed of vertices and edges connecting these nodes, with node features typically represented by a feature matrix and the graph structure described by an adjacency matrix. The GCN combines the features of a vertex with those of its neighboring vertices through graph convolution operations and aggregates these features via the adjacency matrix. A notable strength of GCN is its capacity to capture local connectivity patterns within the graph structure, which can be optimized via end-to-end training, showcasing strong scalability and flexibility. Traditional methods for processing graph data, such as rule-based or simple statistical approaches, often require manual feature design or complex preprocessing, making it challenging to effectively utilize the structural information of the graph. The GNN, on the other hand, can learn directly on the graph structure, better exploring the relationships between nodes and the global structure, making it suitable for tasks such as social network analysis, traffic network prediction, and molecular graph prediction. GCNs have demonstrated significant potential in cancer research, encompassing areas such as cancer subtype classification, drug response prediction, and cancer survival prediction [58–60].

Transformer architecture

The Transformer architecture is a DL model introduced by Vaswani *et al.* [61] in 2017, primarily used for NLP and other sequence-to-sequence tasks. The Transformer architecture is composed of an encoder and a decoder. The encoder processes the input sequence, and the decoder generates the output sequence, making it suitable for sequence-to-sequence tasks. The encoder consists of multiple identical layers, each containing two sublayers: a self-attention mechanism and a feedforward neural network. The structure of the decoder is similar to that of the encoder but with an added encoder–decoder attention mechanism, which focuses on the output of the encoder when generating the target sequence. Each sublayer is followed by a residual connection and layer normalization. Residual connections are used for gradient propagation to prevent gradient vanishing or explosion, while layer normalization helps stabilize the training process and accelerate convergence.

The core of the Transformer architecture is the self-attention mechanism, which enables the model to simultaneously weight all elements in the sequence, dynamically attending to important features based on their relationships and capturing global dependencies and contextual information. This mechanism allows the model to process all elements of the sequence in parallel, significantly improving training and prediction efficiency compared to traditional RNN [62]. Since the self-attention mechanism itself does not take into account the order of elements in the sequence, Transformer adds positional information to each element through positional encoding, preserving the temporal characteristics of the data. Positional encoding is usually implemented using sine and cosine functions of different frequencies [63]. The Transformer architecture was initially applied in NLP, including tasks

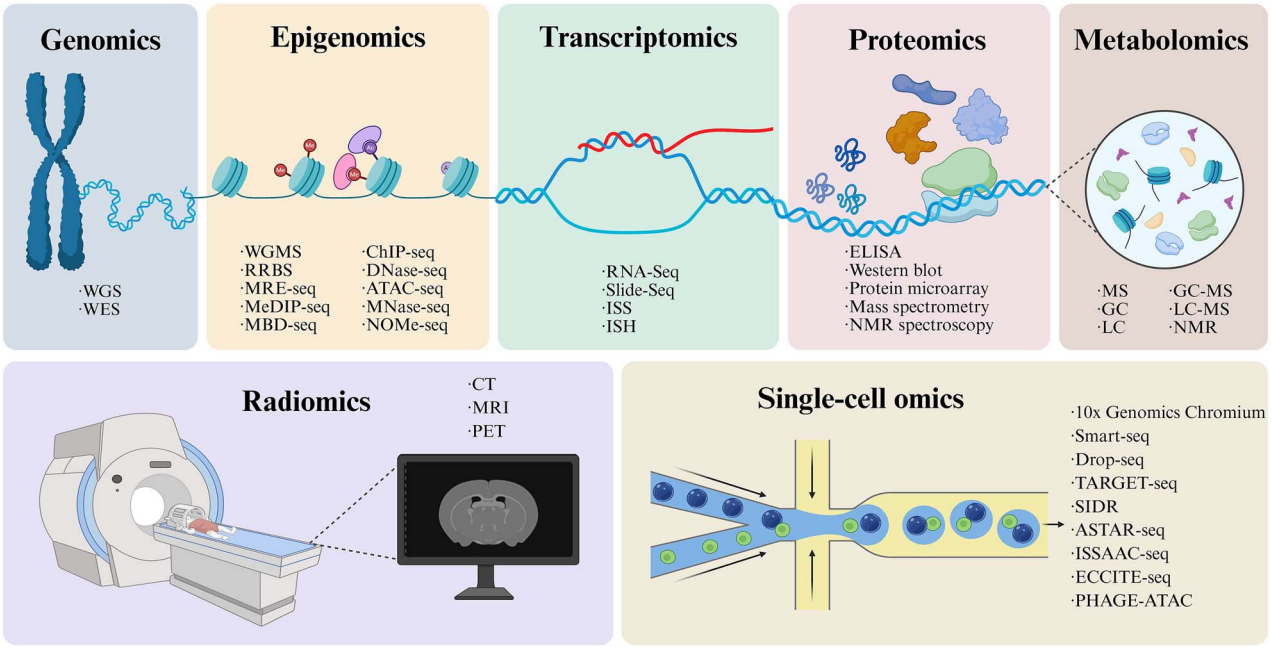

Figure 3. An illustration of multi-omics data encompasses various techniques such as genomics, epigenomics, transcriptomics, proteomics, metabolomics, radiomics, and single-cell omics, each contributing distinct layers of biological information for comprehensive analysis (by BioRender).

such as machine translation and text generation [64]. Due to its outstanding performance, it has also gained widespread application in the field of computer vision, such as image restoration, image enhancement, and image generation [65]. Furthermore, the Transformer architecture has demonstrated strong performance and potential in other domains, such as time series analysis and cybersecurity [64].

Multi-omics data and technologies

Multi-omics integrates data from genomics, transcriptomics, proteomics, radiomics, and single-cell omics, describing nearly all biomolecules from genes to metabolites, enabling a more comprehensive and systematic understanding of biological systems' complexity (Fig. 3).

Genomics

Originating from the Human Genome Project, genomics involves studying the structure, function, evolution, and environmental interactions of an organism's genome [66]. The primary data types in genomics include: DNA sequence data, obtainable via high-throughput sequencing technologies like Illumina, PacBio, and Nanopore [67]; variation data, such as single-nucleotide polymorphisms (SNPs), insertions/deletions (InDels), copy number variations (CNVs), and structural variations; gene annotation data, which provide details about gene locations, structures, and functions; genetic linkage data, related to familial genetic information associated with genomic structures, frequently used in the identification of disease-related genes; and genome assembly data, which involve genome splicing and assembly information from various sources [68].

Among different DL models, CNNs, AEs, and GNNs are appropriate for analyzing genomic data. The CNN is capable of extracting local features in genomic data, such as patterns and combinations of patterns within gene sequences. The AE can be used for dimensionality reduction and denoising of genomic data, thus helping to identify gene expression patterns. The GNN is applicable for analyzing gene interaction networks and uncovering the intricate relationships between genes [68]. When it comes to the application of models, DL models can integrate with genomic data for tasks like disease prediction, gene function prediction, and analyzing the impact of variants. For instance, DNA sequences can be converted into vectors, with common methods including One-Hot encoding, k-mer representations, and others, and these vectors can then be input into DL models [69]. CNN can be employed to detect local patterns in DNA sequences, where their convolutional layers identify gene features or regulatory elements in the sequence. In addition, variants like SNPs and InDels can be represented as numeric or binary codes and used as input features into the model, often processed by RNN or MLP for such data [70].

With advancements in technology, especially the introduction of next-generation sequencing (NGS), the speed and cost of genome sequencing have significantly improved [17], enabling doctors to complete high-quality genome sequencing in just a few hours [71]. With the continued development of ultra-fast genome sequencing technologies, the use of whole genome sequencing (WGS) and whole exome sequencing (WES) in clinical diagnostics is becoming increasingly widespread. WGS provides the most comprehensive genetic information [20], while WES focuses on variations in the coding regions [72]. As sequencing costs continue to decrease and data analysis capabilities improve, WGS is anticipated to be integrated as a standard configuration in clinical diagnostics, providing patients with more comprehensive and accurate genetic information. The incorporation of AI technology has significantly enhanced ultra-fast sequencing technologies in recent years, establishing a robust technical base for executing precision medicine and personalized treatment strategies [73].

Epigenomics

The main data types involved in epigenomics include: DNA methylation data, reflecting the distribution of methylation modifications on DNA (such as obtained via Bisulfite sequencing,

Methyl-seq) [74]; histone modification data, obtained through ChIP-Seq, relating to histone modifications (e.g. H3K27ac, H3K4me3); chromatin conformation data, such as Hi-C data, reflecting the 3D structure of chromosomes and the interactions within the genome; and chromatin accessibility data, such as ATAC-Seq and DNase-Seq, exploring the relationship between chromatin openness and gene regulation [75].

CNNs can identify local features in DNA sequences, which are used to predict chromatin effects, transcription factor binding, histone modifications, and others; LSTM is suitable for handling temporal dependencies in sequence data, and can be used to analyze the distribution patterns of epigenetic marks on the genome, as well as to predict gene expression; Transformer excels at handling long sequence data and capturing long-range dependencies and can be used to predict gene expression, and analyze the relationship between epigenetic modifications and gene expression. In terms of model applications, DL models can be combined with epigenomics data for tasks such as predicting gene expression and epigenomic regulation. For instance, methylation data can be converted into a matrix format (such as methylation measurements) and fed into CNNs or MLP for feature selection and prediction. At the same time, histone modification data can be processed in a manner similar to genomic data, or local patterns of modification sites can be captured using CNNs [76].

DNA methylation can be measured using various methods such as whole-genome bisulfite sequencing (WGMS) [77], reduced representation bisulfite sequencing (RRBS) [78], and techniques like methylation-sensitive restriction enzyme sequencing (MRE-seq), Methylated DNA Binding Domain-Sequencing (MBD-seq), and Methylated DNA Immunoprecipitation Sequencing (MeDIP-seq) [79]. Measurement of histone modifications can be performed using techniques like chromatin immunoprecipitation sequencing (ChIP-seq) [80]. Chromatin accessibility, an important manifestation of chromatin structural changes, refers to the degree to which macromolecular complexes can interact with DNA that is packaged into chromatin, influenced by nucleosome occupancy, topological organization, and other chromatin-binding factors. Methods for detecting chromatin accessibility include DNase I Hypersensitive Site Sequencing (DNase-seq) [81, 82], Assay for Transposase-Accessible Chromatin with high-throughput Sequencing (ATAC-seq) [83], Micrococcal Nuclease Sequencing (MNase-seq) [84, 85], Nucleosome Occupancy and Methylome Sequencing (NOMe-seq) [86], and so on.

Epigenetic factors regulate gene expression by modulating transcriptional activity without altering the DNA sequence, and disruptions in these factors can disrupt genomic regulation and lead to diseases such as cancer [87], autoimmune diseases [88], and cardiovascular diseases [89]. Epigenetic alterations are significant in the development and progression of human cancers; as high-throughput sequencing evolves, numerous mutations in epigenetic regulatory factors have been established as tumorigenic drivers. Emerging studies in epigenetics, such as the development of drugs targeting epigenetic changes [90] and exploration of molecular mechanisms [91, 92], aim to advance more accurate and specific diagnosis and treatment for individual cancer patients.

Transcriptomics

Transcriptomics involves the analysis of the entire set of RNA transcripts produced in an organism, capturing their expression profiles under specific conditions. Transcriptomics primarily focuses on the transcription products of genes, including coding RNA (such as messenger RNA, mRNA) and noncoding RNA (microRNA, long noncoding RNA, etc.), as well as their expression levels and regulatory networks in cells. The primary data types in transcriptomics consist of: mRNA expression data, which refer to gene expression profiles obtained by RNA-Seq and indicate the expression levels of various genes; small RNA data, including the expression of miRNAs, siRNAs, and other small RNAs; long noncoding RNA (lncRNA) data; transcript splicing data, involving variations in the transcripts of different genes, such as those produced by alternative splicing; and gene expression profiles, which can be obtained using technologies like microarrays or Quantitative Real-time polymerase chain reaction (qPCR) [93].

Different DL models, including RNN, LSTM, AE, and Transformer, are suitable for analyzing transcriptomics data. RNN and LSTM are effective in processing temporal features in transcriptomics data, such as the dynamic changes in gene expression; AE assists in dimensionality reduction and feature extraction, which helps identify essential genes in transcriptomics data; Transformer is outstanding in processing sequence information in transcriptomics data, capable of capturing intricate dependencies [94]. In the application of models, DL models can integrate with transcriptomics data for tasks such as gene expression prediction, disease classification, and transcript analysis [95]. For example, mRNA expression data can be represented as vectors or matrices and input into DL models, where RNNs or LSTM are used to process gene expression time series data.

Transcriptomics predominantly employs RNA-seq technology to deduce and quantify the transcriptome, facilitating a high-throughput and quantitative survey of the entire transcriptome. RNA-seq technology is a nonspatial transcriptomic approach that benefits from an exceptionally low background noise and is not restricted to detecting transcripts that correspond to known genomic sequences [96]. Spatial transcriptomics, a novel subdiscipline, merges the benefits of transcriptomics technologies with *in situ* hybridization, with its detection methods largely split into NGS-based and imaging-based approaches. Among the NGS-based spatial transcriptomics methods include 10x Visium [97], Slide-Seq [98], and Stereo-seq [99], while imaging-based techniques include *In Situ* Sequencing (ISS) [100] and *In Situ* Hybridization (ISH) methods [101]. In recent years, spatial transcriptomics technology has gained significant traction in oncology, offering insights across diverse areas of cancer research, such as tumor microenvironment description, cancer diagnosis, subtype classification, cancer prediction, and treatment, promoting personalized treatment for cancer patients.

Proteomics

Proteomics involves the comprehensive study of proteins, including their expression, structure, function, interactions, and modifications across various stages [102]. The data types include protein expression data, which are obtained from mass spectrometry (MS) or antibody detection [e.g. enzyme-linked immunosorbent assay (ELISA)], showing the relative abundance of different proteins across various samples; protein modification data, including phosphorylation, acetylation, methylation, and other post-translational modifications; protein interaction data, obtained through techniques such as yeast two-hybrid and co-immunoprecipitation (Co-IP); proteomic identification data, which identifies protein information through the mass-to-charge ratio (m/z) of peptide fragments; and protein structural data, derived from techniques like X-ray crystallography or cryo-electron microscopy, revealing the 3D structure of proteins.

CNNs, AEs, and GNNs are applicable for the analysis of proteomics. The CNN is used to analyze protein sequence and structural data to extract local features [103]; the AE can be applied to dimensionality reduction and feature extraction in proteomics, aiding in the identification of protein functional modules; and the GNN can analyze protein interaction networks and the interactions between proteins. DL models can integrate with proteomic data for protein function prediction, disease association analysis, drug target discovery, and more [104, 105]. For example, combining phosphorylation, acetylation, and other protein modification data with protein sequences and inputting them into DL models, using CNNs for feature extraction. Protein expression data can be quantified and used as input features in classification or regression tasks with models such as MLP or Support Vector Machine (SVM) [105].

The measurement of gene expression levels can be achieved through transcriptomic and proteomic techniques. However, since gene transcription is often influenced by post-transcriptional modifications and protein levels depend on the host's translation control and regulation, transcriptomics shows a low correlation with protein expression levels [106]. Proteomics, therefore, represents the data set most closely related to the biological phenotype [107]. Proteomics technologies are diverse, with traditional techniques including chromatography-based techniques [108, 109], ELISA [110], and Western blot [111]; advanced techniques such as protein microarray [112] and gel-based approaches [113]; and high-throughput techniques like mass spectrometry (MS) [102] and nuclear magnetic resonance (NMR) spectroscopy [114]. Proteomics plays a vital role in early diagnosis, treatment, and prognosis in diseases, including kidney disease [115], cardiovascular diseases [116], viral infections [117], and cancer [118]. With advancements in AI technologies, proteomics has merged with AI to utilize its significant computational power and ML algorithms for rapid and precise analysis of extensive proteomic data, which helps in identifying cancer biomarkers, developing cancer drugs, and supporting personalized treatment for cancer patients [104, 119, 120].

Metabolomics

Metabolomics examines all small molecular metabolites in an organism, encompassing primary metabolites like amino acids, short peptides, lipids, carbohydrates, and nucleic acids, as well as secondary metabolites such as alkaloids and terpenes, all participating in numerous cellular biological processes [121]. The primary data types in metabolomics include metabolite data, which measure metabolite abundance using techniques like MS or NMR [122]; metabolic pathway data, which are derived from metabolite data to infer relevant metabolic pathways and biological processes; metabolite biomarkers, where specific metabolites are used as biological markers to predict diseases or physiological states; and dynamic metabolite data, which reflect changes in metabolites under disease, drug interventions, or environmental changes.

Among various DL models, AEs, RNNs, and LSTM are suitable for analyzing metabolomics data. The AE is employed for dimensionality reduction and feature extraction in metabolomics, aiding in the identification of associations among metabolites; RNNs and LSTM are suitable for handling time-series information in metabolomics data, such as changes in metabolites over time [123]. In practical applications, DL models can be used for metabolite biomarker discovery, metabolic pathway analysis, etc. For instance, CNNs can analyze metabolite spectra to identify disease-related biomarkers.

Influenced by genomics, proteomics, and environmental factors, metabolomics can also modulate other omics levels, thereby impacting biological processes. Metabolomics technologies can capture rapid responses of organisms to environmental changes, disease states, or pharmacological interventions, thus serving as direct evidence and the most sensitive method for changes in gene and protein functions [124].

Metabolomics is categorized into targeted and untargeted types. Untargeted metabolomics, which does not preset metabolites, aims for a comprehensive coverage of the metabolome to discover new metabolites and pathways; targeted metabolomics conducts quantitative analyses on selected metabolites to confirm hypotheses [125]. The main research techniques in metabolomics include NMR, MS, gas chromatography (GC), liquid chromatography (LC), gas chromatography–mass spectrometry (GC–MS), and liquid chromatography–mass spectrometry (LC–MS) [114, 126]. The advantages of NMR primarily lie in its nondestructive and comprehensive nature, whereas MS is beneficial for its high sensitivity and high throughput [127].

Tumors impact metabolism in multiple ways, including altering the tumor microenvironment and the metabolism of normal tissues, thereby making metabolomics a fundamental element of cancer research. Metabolomics is applicable to early cancer detection, diagnosing cancer subtypes, and monitoring treatment targets [124]. As technology develops, the combination of metabolomics and AI is increasingly demonstrating significant potential in cancer therapy [128]. With the introduction of algorithms such as ML, not only can vast datasets be analyzed in a short time, but personalized treatments can also be realized through omics data analysis [129].

Radiomics

Radiomics is a high-throughput mining technology that extracts quantitative image features from standard medical imaging for analysis and modeling. Quantitative image features, or radiomic features, can provide rich information on tumor subtypes, locations, shapes, and sizes via imaging methods such as magnetic resonance imaging (MRI), computed tomography (CT), and positron emission tomography (PET) [130]. The types of data in radiomics include imaging data, such as CT, MRI, ultrasound, and other medical imaging data, which usually require image processing and analysis; quantitative image feature data, including texture, shape, size, and density features of images, are extracted using computer image analysis methods; radiomics data, extracted using ML and image analysis methods, derives high-dimensional features from images and correlates them with clinical or biological markers; imaging-genomic data, which combine imaging data and genomic data to study the correlation between imaging features and genetic information [131].

CNNs and GNNs are suitable for analyzing imaging data such as radiomics. The CNN excels in tasks like image classification, object detection, and segmentation in medical imaging. The GNN can be used to analyze structured information in images. For example, in classifying pathology samples using multiple-epitope-ligand cartography (MELC), the GNN combined with radiomic features significantly enhanced classification accuracy [132]. In model applications, DL combined with radiomics data can be used for tumor detection, disease prediction, imaging biomarker identification, and more. For instance, CNNs can directly analyze medical images (CT, MRI, etc.) to extract image features [133]. Computer vision techniques can also be employed to extract morphological and texture features from images,

which can then be input into GNNs for modeling. This combined approach, when dealing with complex medical image data, fully utilizes the CNN's image processing capabilities and the GNN's ability to analyze structured information, improving diagnostic accuracy and reliability [132].

The workflow of radiomics encompasses data selection, medical imaging, feature extraction, exploratory analysis, and modeling [134], with DL technology recently demonstrating significant potential in these areas.

During the feature extraction phase, traditional approaches necessitate manual extraction of radiologic features from regions of interest, which is tedious and does not accurately capture the underlying imaging details [135]. With the development of DL technologies such as CNN, DL's capability in feature extraction has been widely applied. Radiomics techniques, by integrating radiomic features and DL, can be used to detect and diagnose cancer, predict histopathology and tumor staging, and forecast treatment outcomes [135–137]. During the exploratory analysis phase, it's crucial to preprocess images prior to radiomic analysis to minimize noise impacts and enhance image quality, thereby ensuring reproducibility and comparability in radiomic studies. In the modeling stage, DL algorithms possess robust modeling capabilities, enabling the mining of abundant image data to uncover underlying biological mechanisms, thus facilitating personalized diagnosis and treatment of cancer [135].

Single-cell omics

Single-cell omics is a biomolecular analysis technique conducted at the individual cell level, encompassing fields such as genomics, transcriptomics, epigenomics, proteomics, and metabolomics. These techniques can reveal heterogeneity among cell populations, providing detailed information on cell functions and interactions. The data types in single-cell omics include single-cell DNA sequencing data, which are used to study the genomic characteristics of individual cells, such as gene variations, copy number changes, and more; single-cell epigenomic data, obtained using techniques such as ATAC-Seq, to acquire chromatin accessibility data at the single-cell level; single-cell RNA-seq data, which provide gene expression profiles at the single-cell level, reflecting the transcriptional activity of individual cells [138]; and single-cell metabolomics data, which reveal the metabolic characteristics of cells by measuring metabolites at the single-cell level.

Various DL models, such as AE, GNN, and Transformer, are extensively used in the analysis of single-cell omics data. AE is applied for dimensionality reduction and feature extraction in single-cell data, helping to identify cell types and states effectively; the GNN excels at analyzing intercellular interaction networks in single-cell data; Transformer performs excellently in single-cell transcriptomics data for cell type annotation and trajectory inference, handling complex sequence data and capturing long-range dependencies to improve the accuracy and reliability of analysis. In applications, single-cell omics data can be used for single-cell subgroup analysis, cell classification, and developmental trajectory analysis, among others. For example, the sparse matrix of single-cell RNA-seq data can be subjected to dimensionality reduction and clustering analysis using AE and then input into DL models such as CNN for cell classification or gene expression analysis [139]. This multi-model integration takes full advantage of the strengths of different models, improving the capacity to analyze single-cell data.

Single-cell omics technologies are crucial for cancer research, as they can reveal heterogeneity in tumor cells, tumor microenvironment composition, interactions between tumor cells and immune cells, and responses of tumor cells to treatment [140–143]. Such information is crucial for developing new therapeutic strategies and personalized medicine. For instance, single-cell omics applied to characterizing cancer stem cells opens avenues for identifying novel targeted molecular pathways, thus presenting unprecedented opportunities for developing new strategies to eradicate colorectal cancer (CRC) [144]. Single-cell technologies also enable the revelation of two response modes of tumor-infiltrating B cells and their effects on antitumor immunity, laying the groundwork for new immunotherapy strategies [145].

The rapidly evolving single-cell multi-modal omics (scMulti-omics) technologies integrate different single-mode omics such as omics data with clinical information, for comprehensive analysis to gain a broader biological understanding [146]. Single-cell omics includes many widely adopted representative technologies, such as 10x Genomics Chromium [147], Smart-seq [148], Drop-seq, and DR-seq [149], which serve as the foundation of current single-cell research. Single-cell multi-omics technologies also cover numerous representative techniques, such as TARGET-seq [150], simultaneous isolation of genomic DNA and total RNA (SIDR) [151], and G&T-seq [152], which are employed to integrate the genome and transcriptome; for integrating the transcriptome and epigenome, there are techniques like ASTAR-seq [153], ISSAAC-seq [154], and Paired-Tag [152]; for combining the transcriptome and proteome, methods such as ECCITE-seq [155], PHAGE-ATAC [156], and REAP-seq [152] are used; and there are also various other multi-omics modalities. Furthermore, single-cell multi-omics technologies positively influence various applications, including cell lineage tracing, development of tissue and cell-specific atlases, tumor immunology, and cancer genetics, offering detailed insights at the cellular level [143].

Application of deep learning–based multi-omics analysis in cancer diagnosis and treatment

Multi-omics analysis based on DL is becoming more significant in cancer diagnosis and treatment, as it integrates genomic, transcriptomic, and other multi-omics data to deliver accurate diagnostic and therapeutic solutions [157]. Benchmark testing is critical for evaluating DL models, ensuring their effectiveness in practical applications. Benchmark testing generally consists of three key steps: dataset selection, model training, and performance assessment. Selecting the appropriate dataset is crucial, with common cancer databases including The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO). During data preprocessing, it is essential to handle missing values, noise, and other issues while standardizing the data to ensure training stability and precision. Furthermore, choosing the right DL model (e.g. CNN, LSTM, or GNN) and using techniques such as cross-validation to avoid overfitting is crucial for ensuring optimal model performance. Performance metrics in benchmark testing include accuracy, sensitivity, specificity, precision, F1 score, and Area Under Curve (AUC)–receiver operating characteristic (ROC) curve, which help comprehensively assess model performance. Accuracy and sensitivity are particularly critical in cancer diagnosis and treatment, as they directly affect the risks of misdiagnosis and missed diagnoses. The F1 score balances precision and recall, making it particularly suitable for addressing the issue of imbalanced data in cancer diagnosis. The performance of different models varies in benchmark testing. The CNN performs exceptionally well in image data analysis, often achieving accuracy above 90% and high F1 scores. LSTM achieves high sensitivity

and F1 scores when processing gene expression time-series data. The GNN can effectively capture the relationships between genes. Practical case studies demonstrate that DL models, backed by multi-omics data, offer highly accurate diagnoses and provide a basis for personalized treatment. Consequently, benchmark testing is essential to ensure the validity and reliability of DL-based multi-omics analysis, and attention should be paid to the results when selecting models and evaluating their application.

Early cancer detection and screening

Early detection is a key step in controlling and curing cancer, and detecting and treating cancer as early as possible can effectively reduce mortality and increase long-term survival rates [158, 159]. Screening methods based on DL have enhanced the efficiency and accuracy of early cancer detection, also enabling large-scale screening. DL methods integrated with various omics, like genomics and imaging omics, are crucial in the early detection of various cancers (Table 1). For the early prediction of chronic non-communicable diseases (NCDs), Dong *et al.* [160] developed a DL model called Omicsformer based on Transformer, which analyzes and categorizes routine blood samples to detect the risk of nine diseases (including cancer, cardiovascular diseases, and mental disorders). Omicsformer outperformed other methods (such as SVM and MOGONET) in accuracy (ACC), F1 score, and purity, with average accuracy improving by 8.3%, F1 score by 6.0%, and purity by 8.3%. These findings show that the Omicsformer model performs well and consistently in multi-omics data classification and disease risk prediction. For predicting pan-cancer types, Osseni *et al.* [161] developed the Multi-Omics Transformer (MOT) model, which uses five omics datasets to perform multi-class classification for 33 different cancer types. The results showed that the MOT model achieved an F1 score of 98.37% on the test set without missing omics views and an F1 score of 96.74% on the test set with missing omics views. This indicates that the model has high accuracy and robustness when handling multi-omics data. The MOT model can also identify the most influential omics data types for predicting each tumor type, a feature that helps allocate resources more rationally during clinical decision-making. In recent years, several emerging technologies have been developed for predicting individual cancers. Cao *et al.* [162] developed PANDA, an AI-based pancreatic cancer detection tool, which can accurately detect and classify pancreatic lesions using noncontrast-enhanced CT. PANDA demonstrated an AUC of 99.6%, 94.9% sensitivity, and 100% specificity in the internal testing cohort; in the external multi-center testing cohort, it achieved an AUC of 98.4%, 93.3% sensitivity, and 98.8% specificity; in multi-scenario validation, it achieved 92.9% sensitivity and 99.9% specificity; PANDA outperformed the average performance of radiologists. In summary, PANDA has the potential to serve as a new tool for large-scale pancreatic cancer screening. These studies highlight the potential of DL in advancing cancer screening and risk prediction, especially in improving detection accuracy, minimizing false positives and false negatives, and facilitating personalized risk assessment for patients.

Liquid biopsy is another crucial method for early cancer detection that involves identifying biomarkers in blood or other bodily fluids, such as CTCs, circulating tumor DNA (ctDNA), cell-free DNA (cfDNA), and extracellular vesicles (EVs), to gather information related to the cancer. Despite the relatively low content of biomarkers in the blood limiting their clinical application, DL-based multi-omics analysis methods are able to integrate and analyze various data types, significantly boosting the sensitivity and accuracy of liquid biopsies. CancerSEEK, developed by Cohen *et al.* [163], is a more traditional method of blood testing that determines the origin tissue of cancer and the anatomical location of the primary tumor by analyzing both genetic alterations and protein biomarkers. CancerSEEK has a median sensitivity of 70% and a specificity >99% across eight cancer types. For five cancer types—ovarian cancer, liver cancer, gastric cancer (GC), pancreatic cancer, and esophageal cancer—that currently lack screening methods, the sensitivity ranges from 69% to 98%. The sensitivity for breast cancer (BC) is as low as 33%. For the most common stage II cancers, CancerSEEK demonstrated a median sensitivity of 73%, 78% for stage III cancers, and 43% for stage I cancers. The sensitivity for stage I cancers is highest in liver cancer (100%) and lowest in esophageal cancer (20%). With recent technological advancements, liquid biopsy techniques have expanded beyond traditional ML approaches. Li *et al.* [164] developed a new DL-based method named DISMIR, which predicts the location and tumor burden of cancer by integrating DNA sequences and methylation status. DISMIR showed high precision in detecting hepatocellular carcinoma with low-depth sequencing data, with an ROC AUC of 0.9932 ± 0.0038. Even with ultra-low sequencing depths (0.01× to 0.03×), it still achieved an AUC of 0.9033 ± 0.0396. These results indicate that this method can accurately predict cancer even with very low sequencing depths. At the same time, Albaradei *et al.* [165] developed a DL framework based on raw CTC mRNA data called DNNraw, which excels in detecting subtypes of various cancers with an average precision of 0.9652 and an overall accuracy of 0.9640, more precise than many traditional ML methods. Besides detecting common biomarkers like CTC and cfDNA in the blood, early detection of cancer can also be achieved by capturing immune signals. Cai *et al.* [166] developed the DL framework iCanTCR, which precisely identifies individuals with early-stage cancer by monitoring changes in the TCR repertoire in peripheral blood. The overall AUC of iCanTCR for early cancer detection reached 0.86; in simulations with a real cancer prevalence of 5.02%, the positive predictive value (PPV) was 0.442, and the negative predictive value (NPV) was 0.956; the F1 scores were high when differentiating between various cancer types, with an overall accuracy of 0.81, showing excellent detection and classification performance. Moreover, DL-based multi-omics analysis is also applicable for predicting lymph node metastasis in cancer [193–195]. In summary, as AI and multi-omics technologies continue to advance, the field of early cancer detection is set to achieve greater sensitivity and accuracy, potentially playing a role in broader applications and supporting early intervention and treatment in cancer patients.

Cancer diagnosis

DL algorithms can facilitate the integration and analysis of extensive data from multiple omics, as well as clinical and laboratory data, extracting valuable insights to aid clinicians in diagnosing cancer [196, 197]. The XAI used in DL-based medical image analysis, by integrating applications from various fields such as histopathology, radiology (including CT and MRI), and endoscopic imaging (such as esophagogastroduodenoscopy and colonoscopy), has demonstrated accuracy and sensitivity close to that of professionals [198].

DL can correlate histopathological images with cancer genetic mutations and epigenomic data (Table 1). In the application of combining cancer gene data, Fu *et al.* [167] developed PC-CHiP using the TCGA data, which can identify patterns related to specific gene mutations from images, helping to predict tumor purity, tumor-infiltrating lymphocyte (TIL) levels, and tumor proliferation rates. When distinguishing 42 different tissue types,

Table 1. Summary of applications of multi-omics analysis based on different DL models in cancer diagnosis and treatment

Application	DL model	Omics technology	Description	Reference
Early cancer detection and screening	PANDA	Noncontrast CT images, pathology images	Detecting and classifying pancreatic lesions with high accuracy via noncontrast CT.	Cao *et al.* [162]
	Omicsformer	Transcriptomic, proteomic, metabolomics data	Identifying potential risks of nine chronic noncommunicable diseases (NCDs), including cancer, cardiovascular disease, and mental illness	Dong *et al.* [160]
	MOT	Genomic, epigenomic, transcriptomic, proteomic data	Predicting across 33 distinct cancer types.	Osseni *et al.* [161]
	CancerSEEK	Genomic (cfDNA), proteomic data	Detection and localization of multiple cancer types, including ovary, liver, stomach, pancreas, esophagus, colorectum, lung, and breast cancer.	Cohen *et al.* [163]
	DISMIR	Genomic (cfDNA), epigenomic data	Predicting the risk that the plasma donor is suffering from cancer.	Li *et al.* [164]
	DNNraw	Genomics, transcriptomic (mRNA), proteomic data	Predicting the presence of multiple cancer types by using raw CTC mRNA data.	Albaradei *et al.* [165]
	iCanTCR	Genomic, proteomic (TCR, BCR) data	Capturing immune signals from peripheral blood for noninvasive cancer diagnosis.	Cai *et al.* [166]
Cancer diagnosis	PC-CHiP	Genomic, transcriptomic data,pathology images	Classifying cancer types and providing spatially resolved tumor and normal tissue distinction.	Fu *et al.* [167]
	ShuffleNet	Genomic data,pathology images	Predict a wide range of molecular alterations of pan-cancer.	Kather *et al.* [168]
	DenseNet121	Genomic data,pathology images	Accurately diagnosing frequent subtypes.	Foersch *et al.* [169]
	DEPLOY	Epigenomic data, pathology images	Diagnosing CNS tumors within a clinically relevant short time frame.	Hoang *et al.* [170]
	HEPNET	Genomic, transcriptomic data, pathology images	Distinguishing between intrahepatic cholangiocarcinoma (iCCA) and colorectal cancer liver metastasis (CRM).	Albrecht *et al.* [171]
	DenseNet-121,DenseNet-169	Radiomic data, pathology images	Detection and grading of invasive dual carcinoma (IDC) breast cancer.	Barsha *et al.* [172]
Molecular subtype classification and biomarker discovery	DILCR	Epigenomic, transcriptomic (mRNA, miRNA) data	Capturing the consistent representations in omics data of cancer subtypes.	Cai *et al.* [173]
	ProgCAE	Genomic (CNV), epigenomic, transcriptomic data	Identifying cancer subtypes and estimating patient prognosis.	Liu *et al.* [174]
	MODEC	Epigenomic, transcriptomic data	Identifying cancer subtypes and essential clinical markers.	Zhang *et al.* [175]
	Subtype-DCC	Genomic, epigenomic, transcriptomic, proteomic data	Cancer subtype identification and discovery of new biomarkers.	Zhao *et al.* [176]
	imCMS	Genomic data,pathology images	Classifying colorectal cancer without RNA analysis.	Sirinukunwattana *et al.* [177]
	CNN	Radiomic data, pathology images	Developing a prognostic biomarker to guide adjuvant treatment.	Skrede *et al.* [178]
	DeepKEGG	Genomic (SNV), transcriptomic data	Predicting cancer recurrence and discovering biomarkers.	Lan *et al.* [179]
	DeeProM	Genomic, epigenomic, transcriptomic, proteomic data	Revealing thousands of protein biomarkers of cancer vulnerabilities.	Gonçalves *et al.* [180]
Cancer prognosis prediction	MMF	Genomic, transcriptomic data,pathology images	Predicting patient prognosis and identifying features associated with good and poor outcomes.	Chen *et al.* [181]
	CNN	Radiomic data, pathology images, immunoscore	Predicting postoperative outcome of colorectal cancer lung metastasis patients.	Wang *et al.* [182]
	Autoencoder	Genomic (CNV), epigenomic, transcriptomic data	Predicting relapse in prostate cancer.	Wei *et al.* [183]
	MesoNet	Genomic, proteomic data, pathology images	Accurately predicting the overall survival of mesothelioma patients.	Courtiol *et al.* [184]
	GGNN	Genomic, epigenomic, transcriptomic, proteomic data	Predicting cancer survival outcomes.	Zhu *et al.* [185]
	AUTOSurv	Genomic, transcriptomic data, clinical data	Prognosis prediction for breast cancer and ovarian cancer patients.	Jiang *et al.* [186]
Treatment response prediction	CCIM-Net	Transcriptomic, proteomic data	Establishing a spatial interaction map and predicting chemotherapy response.	Bao *et al.* [187]
	CNN	Genomic, radiomic data, pathology images	Prediction of pCR and chemosensitivity for breast cancer patients.	Jiang *et al.* [188]
	SimTA	CT images, clinical data	Predicting the response of advanced NSCLC patients to PD-1/PD-L1 monotherapy.	Yang *et al.* [189]
	Image deep learning	Genomic, transcriptomic, proteomic, single-cell omics data, pathology images	Predicting the response of gastric cancer patients to chemotherapy and immunotherapy.	Che *et al.* [190]
	ADNN	Genomic, transcriptomic, radiomics data	Joint prediction of radiation therapy outcomes in NSCLC patients.	Cui *et al.* [191]
	CNN	Radiomic, dosiomic data	Radiation pneumonitis prediction in lung cancer patients.	Su *et al.* [192]

PC-CHiP achieved an average AUC of 0.98; for differentiating tumor and normal tissue, the average AUC was 0.99. Transcriptomic association testing found that 25% of gene–cancer pairs were linked to histopathological characteristics; 193 pathways were significantly enriched in at least 1 cancer type; and 14 cancer types showed detectable associations with proliferation scores. Similarly, in pan-cancer research, Kather *et al.* [168] refined a DL process that directly deduces a series of genetic mutations, gene expression traits, and biomarkers from hematoxylin and eosin (H&E)-stained tissue sections, clarifying and quantifying the genotype–phenotype connections in cancer. In terms of combining with epigenomics, Hoang *et al.* [170] created DEPLOY, a DL model that predicts whole-genome scale DNA methylation β-values from images of H&E-stained tissue sections, and then classifies different types of tumors by using a classifier based on DNA methylation. The DEPLOY model integrates three different components: a direct model, an indirect model, and a demographic model. This research achieved 95% overall accuracy and 91% balanced accuracy on three independent external datasets; the AUPRC for the combined three models reached 0.92; and in cases where the initial diagnosis disagreed with the pathologist, DEPLOY's high-confidence predictions matched methylation classification results 84% of the time. The results indicate that this model helps pathologists diagnose central nervous system tumors within clinically relevant short timeframes. Numerous studies demonstrate that DL technology not only significantly reduces the workload of pathologists in the diagnosis of malignant tumors but also exhibits outstanding efficiency, accuracy, and sensitivity [41, 167, 169, 170].

The application of DL technology in combination with multi-omics data has also made notable progress in the diagnosis of individual cancers, with ongoing reports of successful cases [199–203]. For example, Albrecht *et al.* [171] developed HEPNET to differentiate intrahepatic cholangiocarcinoma (iCCA) from CRC liver metastasis (CRM), the most common primary and secondary forms of hepatic adenocarcinoma. On the internal test set, HEPNET achieved an AUROC of 0.994 and an accuracy of 96.522%, on the external test set, it reached an AUROC of 0.997 and an accuracy of 98.113%, and in external tests on biopsy samples, it showed an AUROC of 0.994 and an accuracy of 96.203%. Furthermore, HEPNET outperformed six pathologists with varying levels of experience ($P = .0005$) and was able to elevate the performance of hospital pathologists to the level of senior pathologists. Regarding BC diagnosis, Barsha *et al.* [172] used DenseNet-121 and DenseNet-169 models along with test-time augmentation techniques to automatically detect and grade invasive ductal carcinoma (IDC). The integrated model achieved a balanced accuracy of 92.70% and an F1 score of 95.70% in IDC detection, surpassing current state-of-the-art technologies; on the Databiox dataset, the model achieved accuracies of 62.44%, 79.14%, 76.62%, and 71.05% for images at various magnifications. On the Agios Pavlos dataset, the model achieved an accuracy of 90.07%. This study indicates that DL models can effectively assist pathologists in detecting and grading IDC BC while improving detection accuracy and reducing pathologists' workload. Other studies have also employed DL algorithms based on radiological images for detecting distant cancer metastasis [204] and predicting occult metastasis of cancer [205, 206].

Discovery of molecular subtype and biomarker

The classification of cancer subtypes is essential for precise cancer diagnosis and personalized treatment, and DL-based multi-omics analysis is indeed becoming increasingly pivotal in the classification of cancer subtypes. Various DL algorithms can integrate multiple bioinformatics data types such as TCGA, gene expression, CNV, methylation status, and protein expression to reveal the heterogeneity of cancer and identify molecular subtypes associated with prognosis and treatment response [52, 177] (Table 1). For instance, Cai *et al.* [173] developed a VAE-based DL model, Deeply Integrating Latent Consistent Representations (DILCR), capable of capturing latent consistent representations from high-noise multi-omics data, which facilitates accurate cancer classification and improves the integration of information against noisy backgrounds. This experiment compared DILCR with 14 state-of-the-art integration methods, and the results showed that DILCR obtained more clinical parameters and higher −log10P values for survival analysis in nine datasets compared to other methods. This suggests that the cancer subtypes identified by DILCR have higher biological relevance, and there are more significant survival differences between the cancer subtypes. The application of DILCR in the classification of cancers such as breast-invasive carcinoma (BRCA) and colon adenocarcinoma (COAD) also has significant biological significance and interpretability [173]. In further research into various cancer subtype classifications, Liu *et al.* [174] developed ProgCAE, based on convolutional autoencoders (CAEs), to handle multi-omics data. The study found that ProgCAE outperformed traditional statistical methods in 12 TCGA datasets; additionally, the SVM classifier built from clustering labels obtained by ProgCAE performed well in the ACC, BRCA, LUAD, and SARC datasets, with significant survival differences in test samples ($P < .05$). This suggests that ProgCAE can accurately predict the survival prognosis of most cancer patients. In another study, Zhang *et al.* [175] used six TCGA data cohorts to compare the performance of MODEC (An unsupervised clustering method integrating omics data for identifying cancer subtypes), a fully unsupervised clustering method, with eight widely used existing technique. The results showed that MODEC outperformed or was equivalent to eight competing methods in four clustering-related metrics (accuracy, F-value, normalized mutual information, and adjusted Rand index) in six cancer datasets. Zhao *et al.* [176] also developed Subtype-DCC to identify cancer subtypes, and this method performed excellently across multiple cancer datasets. Compared with ten existing advanced multi-omics data clustering methods, Subtype-DCC achieved better results on six datasets. Notably, in the Kidney Renal Clear Cell Carcinoma (KIRC) dataset, the survival −log10 *P*-value was as high as 8.79, suggesting that this method can efficiently identify cancer subtypes with differing prognoses. In addition to these studies, there are also subtype identification methods tailored to specific cancers. Sirinukunwattana *et al.* [177] developed an image-based consensus molecular subtype (imCMS) classification method to predict CRC's CMS by analyzing standard H&E-stained tissue sections, without the need for RNA expression analysis. The findings indicated that imCMS achieved an AUC of 0.84 in the TCGA dataset ($n = 431$ slides) and an AUC of 0.85 in the rectal cancer biopsy dataset ($n = 265$ slides). The emergence of imCMS offers a new, cost-effective method for molecular subtyping of CRC. The potential of these DL-based multi-omics integration analysis approaches in cancer subtype classification is immense, offering the prospect of more precise molecular typing for personalized cancer treatment.

In addition to subtype classification, multi-omics data are also used for the discovery of cancer biomarkers, which has significant clinical implications in cancer diagnosis, prognosis assessment, and personalized treatment [119]. By detecting specific molecules, gene mutations, or protein expressions in blood, urine, or tissue

samples, early cancer diagnosis can be made, even identifying tumors before symptoms emerge, thus improving cure rates [207]. For example, a liquid biopsy of lung cancer (LC) can identify tumors early by detecting circulating tumor DNA [208]. Biomarkers can also evaluate cancer prognosis, aid in predicting tumor aggressiveness and metastatic potential, and offer personalized prognostic information to guide treatment choices. For instance, Ki-67 in BC and KRAS mutations in CRC are typical prognostic biomarkers [209]. Furthermore, biomarkers play a key role in personalized therapy, helping to select the optimal treatment approach, such as targeting drugs based on EGFR mutations or immunotherapy based on PD-L1 expression [210]. Liquid biopsy can also monitor the dynamic changes of cancer in real-time, detecting treatment failure or recurrence early, and aiding in adjusting treatment strategies. As research advances, biomarkers will play a more significant role in cancer diagnosis and treatment, enhancing the precision of therapy and the quality of life for patients [211].

Among various cancer biomarkers, prognostic biomarkers deliver information about patient diagnosis and overall outcomes, while predictive biomarkers offer insights into treatment decisions and responses [212]. Integrating multi-omics data to discover genes associated with cancer aids in deeply understanding the molecular mechanisms of cancer and offers fresh perspectives for clinical diagnosis and treatment [213]. For example, Skrede *et al.* [178] trained multiple CNNs to analyze H&E-stained tissue slice images and developed a new prognostic biomarker to forecast the prognosis of patients after CRC resection. In the validation cohort, in the unadjusted analysis, the biomarker showed a hazard ratio (HR) of 3.84 (95% CI 2.72–5.43; $P < .0001$) for poor versus good prognosis. When adjusted for other known prognostic biomarkers, the HR still remained at 3.04 (2.07–4.47; $P < .0001$), illustrating the biomarker's independent predictive value. Recently, numerous DL-based frameworks for integrating multi-omics data have emerged, aimed at revealing new biomarkers or therapeutic targets. At the same time, Lan *et al.* [179] introduced the DeepKEGG method for predicting cancer recurrence and identifying biomarkers. This method enhances the model's predictive performance by constructing biological hierarchy modules and path self-attention modules to explore correlations between different samples. However, the scarcity of large omics datasets constrains the identification of new biomarkers. To tackle this issue, Gonçalves *et al.* [180] presented a pan-cancer proteomic map (ProCanDepMapSanger) that encompasses over 40 types of cancer and 949 cancer cell lines, quantifying 8498 proteins across 28 tissue types through mass spectrometry, capturing data on cell types and post-transcriptional modifications. Based on this, a DL-based computational pipeline, DeepProM, was developed to identify protein biomarkers associated with cancer vulnerability. This pipeline is capable of identifying biomarkers that are not detectable solely by gene expression measurements. For instance, a study discovered the protein biomarker BSG, linked to FOXAI gene knockout, whose expression in BC cells was correlated with dependence on FOXAI gene knockout. This resource is crucial for uncovering cancer biomarkers and delving into the proteomic regulatory mechanisms of cancer, which are essential for advancing our understanding of the disease and developing targeted therapies. Looking ahead, we anticipate more extensive and comprehensive omics datasets being made publicly available to further the study of cancer biomarkers.

Cancer prognosis and treatment response prediction

DL constructs predictive models by integrating multi-omics data, including genomics, transcriptomics, and radiomics, precisely forecasting cancer prognosis and treatment responses, thereby guiding the selection of treatment modalities [182, 214–216]. This approach provides a more comprehensive perspective for model analysis by integrating multiple types of omics data, which not only helps reduce biases caused by the singularity of data types but also enhances the predictive accuracy of the models [217, 218]. In recent years, several new DL frameworks have emerged for forecasting cancer prognosis and the risk of recurrence [183, 219] (Table 1). In pan-cancer prognosis and recurrence predictions, Chen *et al.* used multimodal DL techniques to perform integrated analyses of histopathological and genomic data across 14 types of cancer [181]. The Attention-based Multiple Instance Learning (AMIL) model, using only whole slide images (WSIs), and the self-normalizing network (SNN) model, using only molecular features, had average c-Indices of 0.585 and 0.607, respectively. Meanwhile, multimodal fusion deep learning model (MMF) exhibited a higher average c-Index of 0.645 across 12 cancer types, demonstrating better performance than the unimodal models. Concurrently, predictive frameworks for specific types of cancer continue to be proposed, such as for CRC [182], prostate cancer (PCa) [183], malignant mesothelioma (MM) [184], and so on. In cancer prognosis prediction, besides assessing the risk of recurrence, it also includes evaluations of patient survival, as well as predictions of their quality of life and potential complications. In the field of survival analysis [220], researchers can use various methods such as the Cox proportional hazards regression model, random survival forests [221], and support vector machines for survival to explore factors affecting survival time. For instance, Zhu *et al.* [185] introduced the Geometric Graph Neural Network (GGNN), which integrates geometric features into GNN to boost both prediction accuracy and interpretability. In most experiments, GGNN demonstrated better predictive performance than other alternative methods, such as Cox-EN, Cox-AE, DCAP, and DCAP-XGB. For example, in low-grade glioma, the C-index of GGNN reached 0.817, significantly higher than that of other methods. In this approach, a multivariate Cox proportional hazards regression model is employed in the network's final layer to produce risk scores for each sample. However, time-related factors and other complexities can cause nonlinear relationships between predictive factors and survival outcomes in cancer [222], and existing models assuming linear relationships (like the Cox proportional hazards model) may yield inaccurate results; thus, new methods for survival analysis have emerged [186, 223]. Similar studies include AUTOSurv developed by Jiang *et al.* [186], which uses dimensionality reduction techniques and VAE to extract low-dimensional features, and employs an MLP network (LFSurv) to calculate personalized prognostic indices (PIs) to distinguish between patient groups of different risks, thereby predicting patients' survival risks. Autosurv performed optimally when integrating gene expression, miRNA expression, and clinical data. Its "entangle" integration strategy, combined with Kullback-Leibler (KL)-annealing learning, achieved median C-indexes of 0.749 and 0.629 in the TCGA-BRCA and TCGA-OV datasets, significantly outperforming other methods. These studies demonstrate that DL technologies are significantly advantageous in integrating multi-omics data to predict cancer prognoses, offering more accurate predictions and aiding in the discovery of potential mechanisms underlying cancer progression.

DL algorithms demonstrate higher clinical relevance in predicting drug sensitivity and treatment responses, which helps doctors make more precise treatment recommendations. For example, Song *et al.* [224] proposed a drug sensitivity prediction model based on multi-stage multi-modal drug representation (ModDRDSP), which simulates the interaction between cells and drugs to comprehensively reflect the properties of drug. Khan *et al.* [225] also built the CytomegaloVirusDb database to obtain detailed information about specific cytomegalovirus (CMV), which helps in understanding the immune mechanisms and pathological processes of CMV and aids in the development of new anti-CMV strategies.

Numerous studies indicate that DL algorithms integrating multi-omics data can accurately predict drug responses for various malignancies including CRC [187], GC [190], BC [188], and LC [226]. Among various cancer treatments, immunotherapy has become one of the widespread and effective methods, thus predicting the response to immunotherapy is a crucial part of forecasting drug reactions [141, 227, 228]. To predict immunotherapy responses, Yang *et al.* [189] created a temporal attention module named SimTA, which analyzes asynchronous time series imaging and laboratory data to differentiate the response of nonsmall cell lung cancer (NSCLC) patients to PD-1/PD-L1 immunotherapy. The study revealed that the median progression-free survival (PFS) for the low-risk and high-risk groups were 8.4 and 1.5 months, respectively, while the median overall survival (OS) was 26.7 and 8.6 months, respectively, demonstrating that the PFS and OS in the low-risk group were significantly longer than those in the high-risk group. Likewise, Che *et al.* [190] devised an image DL model integrating multiplex immunohistochemistry staining, feature extraction, and ML to reveal complex cellular interactions of potential drug resistance, successfully forecasting GC patients' clinical responses to chemotherapy and anti-PD1 treatments. Additionally, there are studies focused on predicting complications in cancer patients after radiotherapy [191, 192]. For instance, Cui *et al.* [191] proposed three ADNN models: ADNN-DVH, ADNN-com, and ADNN-com-joint, which combine the CNN and VAE to extract features and use Surv-Net to predict event occurrence probabilities. The research found that the cross-validation c-indices for RP2 prediction were 0.660 (95% CI: 0.630–0.690), 0.691 (95% CI: 0.661–0.722), and 0.705 (95% CI: 0.676–0.734) for ADNN-DVH, ADNN-com, and ADNN-com-joint, respectively, while the c-indices for LC prediction were 0.727 (95% CI: 0.700–0.753), 0.735 (95% CI: 0.710–0.761), and 0.740 (95% CI: 0.715–0.765). These results indicate that the three models outperform the traditional TCP/NTCP models in predicting radiation pneumonitis and local control. With ongoing technological advancements, it is expected that more DL models will be developed in the future to enhance the accuracy and clinical value of cancer treatment response predictions.

Conclusion and prospect

In this review, we first delve into the basic concepts, workflows, and common strategies of DL data integration, and list several common DL models. Secondly, we discuss in detail the classification of multi-omics, the main data types involved in each omic, and the analysis techniques associated with them. Finally, we present the applications of DL-based multi-omics analysis in the field of cancer, covering areas such as early detection and screening of cancer, diagnosis, subtype classification, and prediction of cancer prognosis and treatment responses. While citing relevant studies, we also provide specific performance metrics such as accuracy, AUC, and sensitivity, which present the characteristics of each model more intuitively, offering readers clear references. In general, DL demonstrates vast potential for application in cancer diagnosis and treatment. It is capable of integrating heterogeneous, high-dimensional multi-omics data, improving the precision and efficiency of early cancer detection, diagnosis, and treatment, thereby promoting personalized therapies for cancer patients. Looking forward, it is anticipated that more new DL models will be developed, contributing significantly to the progress of cancer medicine.

Despite its significant advantages in multi-omics cancer research, such as automatic feature extraction and strong predictive abilities, DL's limitations should still not be ignored. Firstly, DL models have limited generalization ability when applied to external datasets. Multi-omics data have heterogeneity across different studies, such as differences in data sources, collection methods, experimental design, etc., which may lead to performance degradation when models are applied to different datasets [229]. Additionally, DL models are susceptible to overfitting, especially when the sample size is small, which may cause the model to capture noise and incidental patterns in the data while overlooking clinically significant features [3, 25]. Secondly, the differences in molecular mechanisms and phenotypic characteristics across various types of cancer may lead to instability in the performance of DL models when applied across different cancer types. Despite DL's ability to identify patterns from vast datasets, the cross-cancer application of current models is limited due to differences in genetic mutations, microenvironments, and other factors across cancers. This usually necessitates specialized training and tuning for each cancer type, significantly increasing the workload and hindering the broader application of DL in precision therapy. The noise and missing data issues in multi-omics data also present a significant challenge. Cancer data often come from different experimental platforms and technologies, with considerable variation in quality, accuracy, and missing values across omics data. This can impact the training and predictive accuracy of DL models, especially when integrating data, making noise and missing data handling crucial [230]. Furthermore, the "black-box" nature of DL limits its clinical application. While DL provides efficient predictive outcomes, its internal mechanisms and decision-making processes lack interpretability, making it challenging for DL to gain broad acceptance and trust in some situations [231]. Hence, there is a need for a more transparent clinical decision-making process. Finally, the high computational resource requirements of DL also limit its widespread application. The high-dimensional characteristics of multi-omics data require DL models to possess powerful computational capabilities, particularly when handling large-scale datasets. In resource-constrained research and clinical settings, the high computational requirements may limit the application of DL. In conclusion, while DL holds great potential in multi-omics cancer research, its limitations still persist. Enhancing the model's generalization ability, addressing data heterogeneity and noise issues, improving model interpretability, and reducing computational resource demands are key areas of focus for future research. We look forward to further research in the future that can resolve these challenges and accelerate the application of DL in cancer research and precision therapy.

Key Points

- With the advancement of various multi-omics technologies, the volume of omics data derived from cancer

samples has increased dramatically, posing a significant challenge for data processing.
- Deep learning (DL) enables the integration of high-dimensional and heterogeneous multi-omics data by providing models that can learn from complex and massive feature sets, thus becoming a potent approach for biomedical data analysis.
- DL is capable of learning nonlinear and hierarchical features from multimodal data, fitting heterogeneous and high-dimensional inputs to identify relevant granular features and generate meaningful insights.
- We present the basic concepts, workflow, and widely adopted strategies for integrating data using deep learning, alongside examples of commonly used DL models. Furthermore, we provide a detailed discussion on the classification of multi-omics, associated data types, and their analytical methodologies.
- Subsequently, we explore the practical applications of deep learning in oncology, covering early detection and screening, diagnosis, classification of cancer subtypes, and identification of biomarkers, as well as prediction of prognosis and treatment response.

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Author contributions

Jiayang Zhang (Writing—original draft, Writing—review & editing, Software, Visualization, Investigation, Validation, Formal analysis, Conceptualization), Yilin Che (Software, Project administration, Visualization, Methodology), Rongrong Liu (Writing—review & editing, Supervision), Zhicheng Wang (Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization), and Weiwu Liu (Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization)

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Data availability

No new data were generated or analyzed in this review.

References

1. McCarthy J, Minsky ML, Rochester N. *et al.* A proposal for the Dartmouth summer research project on artificial intelligence, august 31, 1955. *AI Mag* 2006;**27**:12–2.
2. Alom MZ, Taha TM, Yakopcic C. *et al. The History Began from Alexnet: A Comprehensive Survey on Deep Learning Approaches*. arXiv preprint arXiv:1803.01164, 2018.
3. LeCun Y, Bengio Y, Hinton G. Deep learning. *Nature* 2015;**521**:436–44. https://doi.org/10.1038/nature14539.
4. O'Mahony N, Campbell S, Carvalho A. *et al. Deep Learning vs. Traditional Computer Vision*. in *Advances in Computer Vision*. 2020. Cham: Springer International Publishing. https://doi.org/10.1007/978-3-030-17795-9_10.
5. Angelov P, Soares E. Towards explainable deep neural networks (xDNN). *Neural Netw* 2020;**130**:185–94. https://doi.org/10.1016/j.neunet.2020.07.010.
6. Ahmed SF, Alam MSB, Hassan M. *et al.* Deep learning modelling techniques: Current progress, applications, advantages, and challenges. *Artif Intell Rev* 2023;**56**:13521–617. https://doi.org/10.1007/s10462-023-10466-8.
7. Krittanawong C, Johnson KW, Rosenson RS. *et al.* Deep learning for cardiovascular medicine: A practical primer. *Eur Heart J* 2019;**40**:2058–73. https://doi.org/10.1093/eurheartj/ehz056.
8. Xu Z, Sun J. Model-driven deep-learning. *Natl Sci Rev* 2018;**5**:22–4. https://doi.org/10.1093/nsr/nwx099.
9. Mait JN, Euliss GW, Athale RA. Computational imaging. *Adv Opt Photon* 2018;**10**:409–83. https://doi.org/10.1364/AOP.10.000409.
10. Ramachandram D, Taylor GW. Deep multimodal learning: A survey on recent advances and trends. *IEEE Signal Process Mag* 2017;**34**:96–108. https://doi.org/10.1109/MSP.2017.2738401.
11. Selmy HA, Mohamed HK, Medhat W. Big data analytics deep learning techniques and applications: A survey. *Inf Syst* 2023;**120**:102318. https://doi.org/10.1016/j.is.2023.102318.
12. Tran KA, Kondrashova O, Bradley A. *et al.* Deep learning in cancer diagnosis, prognosis and treatment selection. *Genome Med* 2021;**13**:152. https://doi.org/10.1186/s13073-021-00968-x.
13. Collins C, Dennehy D, Conboy K. *et al.* Artificial intelligence in information systems research: A systematic literature review and research agenda. *Int J Inf Manag* 2021;**60**:102383. https://doi.org/10.1016/j.ijinfomgt.2021.102383.
14. Wainberg M, Merico D, Delong A. *et al.* Deep learning in biomedicine. *Nat Biotechnol* 2018;**36**:829–38. https://doi.org/10.1038/nbt.4233.
15. Zhang C, Yuan G, Niu W. *et al. ClickTrain: An Efficient End-to-End Deep Learning Training Framework via Fine-Grained Pattern-Based Pruning*. ArXiv, 2020. abs/2011.10170.
16. Rigden DJ, Fernández XM. The 2024 nucleic acids research database issue and the online molecular biology database collection. *Nucleic Acids Res* 2024;**52**:D1–d9. https://doi.org/10.1093/nar/gkad1173.
17. McCombie WR, McPherson JD, Mardis ER. Next-generation sequencing technologies. *Cold Spring Harb Perspect Med* 2019;**9**(11). https://doi.org/10.1101/cshperspect.a036798.
18. Yohe S, Thyagarajan B. Review of clinical next-generation sequencing. *Arch Pathol Lab Med* 2017;**141**:1544–57. https://doi.org/10.5858/arpa.2016-0501-RA.
19. Xu J, Liao K, Yang X. *et al.* Using single-cell sequencing technology to detect circulating tumor cells in solid tumors. *Mol Cancer* 2021;**20**:104. https://doi.org/10.1186/s12943-021-01392-w.
20. Meienberg J, Bruggmann R, Oexle K. *et al.* Clinical sequencing: Is WGS the better WES? *Hum Genet* 2016;**135**:359–62. https://doi.org/10.1007/s00439-015-1631-9.
21. Stahlschmidt SR, Ulfenborg B, Synnergren J. Multimodal deep learning for biomedical data fusion: A review. *Brief Bioinform* 2022;**23**:bbab569. https://doi.org/10.1093/bib/bbab569.

22. Peng J, Khuat TT, Musial K. *et al. Machine Learning Methods for Small Data and Upstream Bioprocessing Applications: A Comprehensive Review*. arxiv:2506.12322, 2025.
23. Waqas A, Tripathi A, Ramachandran RP. *et al.* Multimodal data integration for oncology in the era of deep neural networks: A review. *Front Artif Intell* 2024;**7**:1408843. https://doi.org/10.3389/frai.2024.1408843.
24. Shi Y, Han L, Zhang X. *et al. Deep Learning Meets Process-Based Models: A Hybrid Approach to Agricultural Challenges*. arxiv:2504.16141, 2025.
25. Waqas A, Tripathi A, Ahmed S. *et al. Self-Normalizing Foundation Model for Enhanced Multi-Omics Data Analys Is in Oncology*. arxiv:2405.08226, 2025.
26. Leng D, Zheng L, Wen Y. *et al.* A benchmark study of deep learning-based multi-omics data fusion methods for cancer. *Genome Biol* 2022;**23**:171. https://doi.org/10.1186/s13059-022-02739-2.
27. Lepe-Soltero D, Artières T, Baudot A. *et al. MODIS: Multi-Omics Data Integration for Small and Unpaired Datasets*. arXiv preprint arXiv:2503.18856, 2025.
28. Xin L, Huang C, Li H. *et al. Artificial Intelligence for Central Dogma-Centric Multi-Omics: Challenges and Breakthroughs*. arXiv preprint arXiv:2412.12668, 2024.
29. Baião AR, Cai Z, Poulos RC. *et al. A technical review of multi-omics data integration methods: from classical statistical to deep generative approaches*. Brief Bioinform, 2025. 26(4).
30. Ribeiro MT, Singh S, Guestrin C. "Why should I trust you?": Explaining the predictions of any classifier. In: *Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining*, p. 1135–44. San Francisco, California, USA: Association for Computing Machinery, 2016.
31. Lundberg SM, Lee S-I. *A unified approach to interpreting model predictions*, in *Proceedings of the 31st International Conference on Neural Information Processing Systems*. 2017, Curran Associates Inc.: Long Beach, California, USA. p. 4768–4777.
32. Zafar MR, Khan N. Deterministic local interpretable model-agnostic explanations for stable explainability. *Mach Learn Knowl Extr* 2021;**3**:525–41. https://doi.org/10.3390/make3030027.
33. Rezaeian O, Asan O, Bayrak AE. *The impact of AI explanations on clinicians' trust and diagnostic accuracy in breast cancer*. Applied Ergonomics, 2025. 129: p. 104577.
34. Chaddad A, Hu Y, Wu Y. *et al.* Generalizable and explainable deep learning for medical image computing: An overview. *Curr Opin Biomed Eng* 2024;**33**:100567. https://doi.org/10.1016/j.cobme.2024.100567.
35. Khandaker MAA, Raha ZS, Iqbal SB. *et al. From images to insights: Transforming brain cancer diagnosis with explainable AI* in: *2024 27th International Conference on Computer and Information Technology (ICCIT)*. IEEE, 2024.
36. Talaat FM, Gamel SA, el-Balka RM. *et al.* Grad-CAM enabled breast cancer classification with a 3D inception-ResNet V2: Empowering radiologists with explainable insights. *Cancers (Basel)* 2024;**16**:3668. https://doi.org/10.3390/cancers16213668.
37. Nalela P, Rao D, Rao P. *Predicting Survivability of Cancer Patients with Metastatic Patterns Using Explainable AI*. arXiv preprint arXiv:2504.06306, 2025.
38. Mersha M, Bitewa M, Abay T. *et al. Explainability in Neural Networks for Natural Language Processing Tasks*. arXiv preprint arXiv:2412.18036, 2024.
39. Oo HYN, Lee MH, Lim JH. *A Multimodal Fusion Model Leveraging MLP Mixer and Handcrafted Features-Based Deep Learning Networks for Facial Palsy Detection*. in *Data Science: Foundations and Applications*. 2025. Singapore: Springer Nature Singapore. https://doi.org/10.1007/978-981-96-8298-0_16.
40. Sarvamangala DR, Kulkarni RV. Convolutional neural networks in medical image understanding: A survey. *Evol Intell* 2022;**15**:1–22. https://doi.org/10.1007/s12065-020-00540-3.
41. Gehrung M, Crispin-Ortuzar M, Berman AG. *et al.* Triage-driven diagnosis of Barrett's esophagus for early detection of esophageal adenocarcinoma using deep learning. *Nat Med* 2021;**27**:833–41. https://doi.org/10.1038/s41591-021-01287-9.
42. Sunny SP, Khan AI, Rangarajan M. *et al.* Oral epithelial cell segmentation from fluorescent multichannel cytology images using deep learning. *Comput Methods Prog Biomed* 2022;**227**:107205. https://doi.org/10.1016/j.cmpb.2022.107205.
43. Hou H, Yu FR. *Rwkv-Ts: Beyond Traditional Recurrent Neural Network for Time Series Tasks*. arXiv preprint arXiv:2401.09093, 2024.
44. Messay T, Hardie RC, Tuinstra TR. Segmentation of pulmonary nodules in computed tomography using a regression neural network approach and its application to the lung image database consortium and image database resource initiative dataset. *Med Image Anal* 2015;**22**:48–62. https://doi.org/10.1016/j.media.2015.02.002.
45. Nasser M, Yusof UK. Deep learning based methods for breast cancer diagnosis: A systematic review and future direction. *Diagnostics (Basel)* 2023;**13**:161. https://doi.org/10.3390/diagnostics13010161.
46. Yan F, Jiang L, Ye F. *et al.* Deep neural network based tissue deconvolution of circulating tumor cell RNA. *J Transl Med* 2023;**21**:783. https://doi.org/10.1186/s12967-023-04663-w.
47. Yu Y, Si X, Hu C. *et al.* A review of recurrent neural networks: LSTM cells and network architectures. *Neural Comput* 2019;**31**:1235–70. https://doi.org/10.1162/neco_a_01199.
48. Van Houdt G, Mosquera C, Nápoles G. A review on the long short-term memory model. *Artif Intell Rev* 2020;**53**:5929–55. https://doi.org/10.1007/s10462-020-09838-1.
49. Srikantamurthy MM, Rallabandi VPS, Dudekula DB. *et al.* Classification of benign and malignant subtypes of breast cancer histopathology imaging using hybrid CNN-LSTM based transfer learning. *BMC Med Imaging* 2023;**23**:19. https://doi.org/10.1186/s12880-023-00964-0.
50. Salem SB, Ali SZ, Leo AJ. *et al.* Early breast cancer detection and differentiation tool based on tissue impedance characteristics and machine learning. *Front Artif Intell* 2023;**6**:1248977. https://doi.org/10.3389/frai.2023.1248977.
51. Hou J, Deng J, Li C. *et al.* Tracing and forecasting metabolic indices of cancer patients using patient-specific deep learning models. *J Pers Med* 2022;**12**:742. https://doi.org/10.3390/jpm12050742.
52. Wang T, Shao W, Huang Z. *et al.* MOGONET integrates multi-omics data using graph convolutional networks allowing patient classification and biomarker identification. *Nat Commun* 2021;**12**:3445. https://doi.org/10.1038/s41467-021-23774-w.
53. Deligiannidis S, Bogris A, Mesaritakis C. *et al.* Compensation of fiber nonlinearities in digital coherent systems leveraging long short-term memory neural networks. *J Lightwave Technol* 2020;**38**:5991–9. https://doi.org/10.1109/JLT.2020.3007919.
54. Mohammadi M, al-Fuqaha A, Sorour S. *et al.* Deep learning for IoT big data and streaming analytics: A survey. *IEEE Commun Surv Tutor* 2018;**20**:2923–60. https://doi.org/10.1109/COMST.2018.2844341.

55. Qin Z, Wei B, Gao C. *Innovative LSGTime Model for Crime Spatiotemporal Prediction Based on MindSpore Framework*. arXiv preprint arXiv:2503.20136, 2025.
56. Madhumita, Paul S. Capturing the latent space of an autoencoder for multi-omics integration and cancer subtyping. *Comput Biol Med* 2022;**148**:105832. https://doi.org/10.1016/j.compbiomed.2022.105832.
57. Simidjievski N, Bodnar C, Tariq I. *et al.* Variational autoencoders for cancer data integration: Design principles and computational practice. *Front Genet* 2019;**10**:1205. https://doi.org/10.3389/fgene.2019.01205.
58. Ramirez R, Chiu YC, Hererra A. *et al.* Classification of cancer types using graph convolutional neural networks. *Front Phys* 2020;**8**:203. https://doi.org/10.3389/fphy.2020.00203.
59. Liu Q, Hu Z, Jiang R. *et al.* DeepCDR: A hybrid graph convolutional network for predicting cancer drug response. *Bioinformatics* 2020;**36**:i911–8. https://doi.org/10.1093/bioinformatics/btaa822.
60. Wang C, Guo J, Zhao N. *et al.* A cancer survival prediction method based on graph convolutional network. *IEEE Trans Nanobioscience* 2019;**19**:117–26. https://doi.org/10.1109/TNB.2019.2936398.
61. Vaswani A, Shazeer N, Parmar N. *et al. Attention is all you need*, in *Proceedings of the 31st International Conference on Neural Information Processing Systems*. 2017, Curran Associates Inc.: Long Beach, California, USA. p. 6000–6010.
62. Huang T, Xu Z, Yu P. *et al. A Hybrid Transformer-Based Model for Optimizing Fake News Detection*. IEEE Access, 2024. 12: p. 160822-160834.
63. Chua J, Li Y, Yang S. *et al. AI Safety in Generative ai Large Language Models: A Survey*. arXiv preprint arXiv:2407.18369, 2024.
64. Dilek E, Dener M. An overview of transformers for video anomaly detection. *Neural Comput & Applic* 2025;**37**:17825–57. https://doi.org/10.1007/s00521-025-11218-1.
65. Gholami S, Gholami S, Lim JI. *et al. Multi-OCT-SelfNet: Integrating Self-Supervised Learning with Multi-Source Data Fusion for Enhanced Multi-Class Retinal Disease Classification*. arXiv preprint arXiv:2409.11375, 2024.
66. Collins FS, Morgan M, Patrinos A. The human genome project: Lessons from large-scale biology. *Science* 2003;**300**:286–90. https://doi.org/10.1126/science.1084564.
67. Yang J, Liu Y, Shang J. *et al.* The quartet data portal: Integration of community-wide resources for multiomics quality control. *Genome Biol* 2023;**24**:245. https://doi.org/10.1186/s13059-023-03091-9.
68. Alharbi WS, Rashid M. A review of deep learning applications in human genomics using next-generation sequencing data. *Hum Genomics* 2022;**16**:26. https://doi.org/10.1186/s40246-022-00396-x.
69. Sherkatghanad Z, Abdar M, Charlier J. *et al.* Using traditional machine learning and deep learning methods for on- and off-target prediction in CRISPR/Cas9: A review. *Brief Bioinform* 2023;**24**:bbad131. https://doi.org/10.1093/bib/bbad131.
70. Yue T, Wang Y, Zhang L. *et al.* Deep learning for genomics: From early neural nets to modern large language models. *Int J Mol Sci* 2023;**24**:15858. https://doi.org/10.3390/ijms242115858.
71. Goenka SD, Gorzynski JE, Shafin K. *et al.* Accelerated identification of disease-causing variants with ultra-rapid nanopore genome sequencing. *Nat Biotechnol* 2022;**40**:1035–41. https://doi.org/10.1038/s41587-022-01221-5.
72. LaDuca H, Farwell KD, Vuong H. *et al.* Exome sequencing covers >98% of mutations identified on targeted next generation sequencing panels. *PLoS One* 2017;**12**:e0170843. https://doi.org/10.1371/journal.pone.0170843.
73. Caskey T. Precision medicine: Functional advancements. *Annu Rev Med* 2018;**69**:1–18. https://doi.org/10.1146/annurev-med-041316-090905.
74. Tahir M, Norouzi M, Khan SS. *et al.* Artificial intelligence and deep learning algorithms for epigenetic sequence analysis: A review for epigeneticists and AI experts. *Comput Biol Med* 2024;**183**:109302. https://doi.org/10.1016/j.compbiomed.2024.109302.
75. Huang L, Song M, Shen H. *et al.* Deep learning methods for omics data imputation. *Biology (Basel)* 2023;**12**:1313. https://doi.org/10.3390/biology12101313.
76. Tsimenidis S, Vrochidou E, Papakostas GA. Omics data and data representations for deep learning-based predictive modeling. *Int J Mol Sci* 2022;**23**:12272. https://doi.org/10.3390/ijms232012272.
77. Gong T, Borgard H, Zhang Z. *et al.* Analysis and performance assessment of the whole genome bisulfite sequencing data workflow: Currently available tools and a practical guide to advance DNA methylation studies. *Small Methods* 2022;**6**:e2101251. https://doi.org/10.1002/smtd.202101251.
78. Paun O, Verhoeven KJF, Richards CL. Opportunities and limitations of reduced representation bisulfite sequencing in plant ecological epigenomics. *New Phytol* 2019;**221**:738–42. https://doi.org/10.1111/nph.15388.
79. Li S, Tollefsbol TO. DNA methylation methods: Global DNA methylation and methylomic analyses. *Methods* 2021;**187**:28–43. https://doi.org/10.1016/j.ymeth.2020.10.002.
80. Nakato R, Sakata T. Methods for ChIP-seq analysis: A practical workflow and advanced applications. *Methods* 2021;**187**:44–53. https://doi.org/10.1016/j.ymeth.2020.03.005.
81. Boyle AP, Davis S, Shulha HP. *et al.* High-resolution mapping and characterization of open chromatin across the genome. *Cell* 2008;**132**:311–22. https://doi.org/10.1016/j.cell.2007.12.014.
82. Hesselberth JR, Chen X, Zhang Z. *et al.* Global mapping of protein-DNA interactions in vivo by digital genomic footprinting. *Nat Methods* 2009;**6**:283–9. https://doi.org/10.1038/nmeth.1313.
83. Grandi FC, Modi H, Kampman L. *et al.* Chromatin accessibility profiling by ATAC-seq. *Nat Protoc* 2022;**17**:1518–52. https://doi.org/10.1038/s41596-022-00692-9.
84. Mieczkowski J, Cook A, Bowman SK. *et al.* MNase titration reveals differences between nucleosome occupancy and chromatin accessibility. *Nat Commun* 2016;**7**:11485. https://doi.org/10.1038/ncomms11485.
85. Mueller B, Mieczkowski J, Kundu S. *et al.* Widespread changes in nucleosome accessibility without changes in nucleosome occupancy during a rapid transcriptional induction. *Genes Dev* 2017;**31**:451–62. https://doi.org/10.1101/gad.293118.116.
86. Pott S. Simultaneous measurement of chromatin accessibility, DNA methylation, and nucleosome phasing in single cells. *elife* 2017;**6**:e23203. https://doi.org/10.7554/eLife.23203.
87. Hogg SJ, Beavis PA, Dawson MA. *et al.* Targeting the epigenetic regulation of antitumour immunity. *Nat Rev Drug Discov* 2020;**19**:776–800. https://doi.org/10.1038/s41573-020-0077-5.
88. Gupta B, Hawkins RD. Epigenomics of autoimmune diseases. *Immunol Cell Biol* 2015;**93**:271–6. https://doi.org/10.1038/icb.2015.18.

89. Fischer MA, Vondriska TM. Clinical epigenomics for cardiovascular disease: Diagnostics and therapies. *J Mol Cell Cardiol* 2021;**154**:97–105. https://doi.org/10.1016/j.yjmcc.2021.01.011.
90. Zhang Y, Sun Z, Jia J. *et al.* Overview of histone modification. *Adv Exp Med Biol* 2021;**1283**:1–16. https://doi.org/10.1007/978-981-15-8104-5_1.
91. Sidhu H, Capalash N. UHRF1: The key regulator of epigenetics and molecular target for cancer therapeutics. *Tumour Biol* 2017;**39**:1010428317692205. https://doi.org/10.1177/1010428317692205.
92. Fattahi S, Amjadi-Moheb F, Tabaripour R. *et al.* PI3K/AKT/mTOR signaling in gastric cancer: Epigenetics and beyond. *Life Sci* 2020;**262**:118513. https://doi.org/10.1016/j.lfs.2020.118513.
93. Edelman LB, Toia G, Geman D. *et al.* Two-transcript gene expression classifiers in the diagnosis and prognosis of human diseases. *BMC Genomics* 2009;**10**:583. https://doi.org/10.1186/1471-2164-10-583.
94. Zahedi R, Ghamsari R, Argha A. *et al.* Deep learning in spatially resolved transcriptfomics: A comprehensive technical view. *Brief Bioinform* 2024;**25**:bbae082. https://doi.org/10.1093/bib/bbae082.
95. Rajdeo P, Aronow B, Surya Prasath VB. Deep learning-based multimodal spatial transcriptomics analysis for cancer. *Adv Cancer Res* 2024;**163**:1–38. https://doi.org/10.1016/bs.acr.2024.08.001.
96. Wang Z, Gerstein M, Snyder M. RNA-seq: A revolutionary tool for transcriptomics. *Nat Rev Genet* 2009;**10**:57–63. https://doi.org/10.1038/nrg2484.
97. Galeano Niño JL, Wu H, LaCourse KD. *et al.* Effect of the intratumoral microbiota on spatial and cellular heterogeneity in cancer. *Nature* 2022;**611**:810–7. https://doi.org/10.1038/s41586-022-05435-0.
98. Rodriques SG, Stickels RR, Goeva A. *et al.* Slide-seq: A scalable technology for measuring genome-wide expression at high spatial resolution. *Science* 2019;**363**:1463–7. https://doi.org/10.1126/science.aaw1219.
99. Wu L, Yan J, Bai Y. *et al.* An invasive zone in human liver cancer identified by stereo-seq promotes hepatocyte-tumor cell crosstalk, local immunosuppression and tumor progression. *Cell Res* 2023;**33**:585–603. https://doi.org/10.1038/s41422-023-00831-1.
100. Ke R, Mignardi M, Pacureanu A. *et al.* In situ sequencing for RNA analysis in preserved tissue and cells. *Nat Methods* 2013;**10**:857–60. https://doi.org/10.1038/nmeth.2563.
101. Gozzetti A, Le Beau MM. Fluorescence in situ hybridization: Uses and limitations. *Semin Hematol* 2000;**37**:320–33. https://doi.org/10.1016/S0037-1963(00)90013-1.
102. Domon B, Aebersold R. Mass spectrometry and protein analysis. *Science* 2006;**312**:212–7. https://doi.org/10.1126/science.1124619.
103. Boadu F, Lee A, Cheng J. Deep learning methods for protein function prediction. *Proteomics* 2025;**25**:e2300471. https://doi.org/10.1002/pmic.202300471.
104. Mann M, Kumar C, Zeng WF. *et al.* Artificial intelligence for proteomics and biomarker discovery. *Cell Syst* 2021;**12**:759–70. https://doi.org/10.1016/j.cels.2021.06.006.
105. Chen C, Hou J, Tanner JJ. *et al.* Bioinformatics methods for mass spectrometry-based proteomics data analysis. *Int J Mol Sci* 2020;**21**:2873. https://doi.org/10.3390/ijms21082873.
106. Rogers S, Girolami M, Kolch W. *et al.* Investigating the correspondence between transcriptomic and proteomic expression profiles using coupled cluster models. *Bioinformatics* 2008;**24**:2894–900. https://doi.org/10.1093/bioinformatics/btn553.
107. Fagerberg L, Hallström BM, Oksvold P. *et al.* Analysis of the human tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. *Mol Cell Proteomics* 2014;**13**:397–406. https://doi.org/10.1074/mcp.M113.035600.
108. Cummins PM, Rochfort KD, O'Connor BF. Ion-exchange chromatography: Basic principles and application. *Methods Mol Biol* 2017;**1485**:209–23. https://doi.org/10.1007/978-1-4939-6412-3_11.
109. Hage DS, Anguizola JA, Bi C. *et al.* Pharmaceutical and biomedical applications of affinity chromatography: Recent trends and developments. *J Pharm Biomed Anal* 2012;**69**:93–105. https://doi.org/10.1016/j.jpba.2012.01.004.
110. Lequin RM. Enzyme immunoassay (EIA)/enzyme-linked immunosorbent assay (ELISA). *Clin Chem* 2005;**51**:2415–8. https://doi.org/10.1373/clinchem.2005.051532.
111. Kurien BT, Scofield RH. Western blotting. *Methods* 2006;**38**:283–93. https://doi.org/10.1016/j.ymeth.2005.11.007.
112. MacBeath G. Protein microarrays and proteomics. *Nat Genet* 2002;**32**:526–32. https://doi.org/10.1038/ng1037.
113. Görg A, Weiss W, Dunn MJ. Current two-dimensional electrophoresis technology for proteomics. *Proteomics* 2004;**4**:3665–85. https://doi.org/10.1002/pmic.200401031.
114. Emwas AH. The strengths and weaknesses of NMR spectroscopy and mass spectrometry with particular focus on metabolomics research. *Methods Mol Biol* 2015;**1277**:161–93. https://doi.org/10.1007/978-1-4939-2377-9_13.
115. Dubin RF, Rhee EP. Proteomics and metabolomics in kidney disease, including insights into etiology, treatment, and prevention. *Clin J Am Soc Nephrol* 2020;**15**:404–11. https://doi.org/10.2215/CJN.07420619.
116. Nayor M, Brown KJ, Vasan RS. The molecular basis of predicting atherosclerotic cardiovascular disease risk. *Circ Res* 2021;**128**:287–303. https://doi.org/10.1161/CIRCRESAHA.120.315890.
117. Battaglini D, Lopes-Pacheco M, Castro-Faria-Neto HC. *et al.* Laboratory biomarkers for diagnosis and prognosis in COVID-19. *Front Immunol* 2022;**13**:857573. https://doi.org/10.3389/fimmu.2022.857573.
118. Li Y, Dou Y, da Veiga Leprevost F. *et al.* Proteogenomic data and resources for pan-cancer analysis. *Cancer Cell* 2023;**41**:1397–406. https://doi.org/10.1016/j.ccell.2023.06.009.
119. Li K, du Y, Li L. *et al.* Bioinformatics approaches for anticancer drug discovery. *Curr Drug Targets* 2020;**21**:3–17. https://doi.org/10.2174/1389450120666190923162203.
120. Duo L, Liu Y, Ren J. *et al.* Artificial intelligence for small molecule anticancer drug discovery. *Expert Opin Drug Discov* 2024;**19**:933–48. https://doi.org/10.1080/17460441.2024.2367014.
121. Erb M, Kliebenstein DJ. Plant secondary metabolites as defenses, regulators, and primary metabolites: The blurred functional trichotomy. *Plant Physiol* 2020;**184**:39–52. https://doi.org/10.1104/pp.20.00433.
122. Huang Z, Wang C. A review on differential abundance analysis methods for mass spectrometry-based metabolomic data. *Metabolites* 2022;**12**:305. https://doi.org/10.3390/metabo12040305.
123. Johnson H, Tipirneni-Sajja A. Towards optimizing neural network-based quantification for NMR metabolomics. *Metabolites* 2025;**15**:249. https://doi.org/10.3390/metabo15040249.
124. Schmidt DR, Patel R, Kirsch DG. *et al.* Metabolomics in cancer research and emerging applications in clinical oncology. *CA Cancer J Clin* 2021;**71**:333–58. https://doi.org/10.3322/caac.21670.

125. Schrimpe-Rutledge AC, Codreanu SG, Sherrod SD. *et al.* Untargeted metabolomics strategies-challenges and emerging directions. *J Am Soc Mass Spectrom* 2016;**27**:1897–905. https://doi.org/10.1007/s13361-016-1469-y.
126. Alseekh S, Aharoni A, Brotman Y. *et al.* Mass spectrometry-based metabolomics: A guide for annotation, quantification and best reporting practices. *Nat Methods* 2021;**18**:747–56. https://doi.org/10.1038/s41592-021-01197-1.
127. Amberg A, Riefke B, Schlotterbeck G. *et al.* NMR and MS methods for metabolomics. *Methods Mol Biol* 2017;**1641**:229–58. https://doi.org/10.1007/978-1-4939-7172-5_13.
128. Giera M, Yanes O, Siuzdak G. Metabolite discovery: Biochemistry's scientific driver. *Cell Metab* 2022;**34**:21–34. https://doi.org/10.1016/j.cmet.2021.11.005.
129. Barberis E, Khoso S, Sica A. *et al.* Precision medicine approaches with metabolomics and artificial intelligence. *Int J Mol Sci* 2022;**23**:11269. https://doi.org/10.3390/ijms231911269.
130. Lambin P, Rios-Velazquez E, Leijenaar R. *et al.* Radiomics: Extracting more information from medical images using advanced feature analysis. *Eur J Cancer* 2012;**48**:441–6. https://doi.org/10.1016/j.ejca.2011.11.036.
131. Wang F, Zou Z, Sakla N. *et al.* TopoTxR: A topology-guided deep convolutional network for breast parenchyma learning on DCE-MRIs. *Med Image Anal* 2025;**99**:103373. https://doi.org/10.1016/j.media.2024.103373.
132. Rivera Monroy LC, Rist L, Ostalecki C. *et al.* Graph neural networks in multi-stained pathological imaging: Extended comparative analysis of radiomic features. *Int J Comput Assist Radiol Surg* 2025;**20**:497–505. https://doi.org/10.1007/s11548-024-03277-x.
133. He Z, McMillan AB. *Comparative Evaluation of Radiomics and Deep Learning Models for Disease Detection in Chest Radiography*. arXiv preprint arXiv:2504.12249, 2025.
134. Lambin P, Leijenaar RTH, Deist TM. *et al.* Radiomics: The bridge between medical imaging and personalized medicine. *Nat Rev Clin Oncol* 2017;**14**:749–62. https://doi.org/10.1038/nrclinonc.2017.141.
135. Avanzo M, Wei L, Stancanello J. *et al.* Machine and deep learning methods for radiomics. *Med Phys* 2020;**47**:e185–202. https://doi.org/10.1002/mp.13678.
136. Bera K, Braman N, Gupta A. *et al.* Predicting cancer outcomes with radiomics and artificial intelligence in radiology. *Nat Rev Clin Oncol* 2022;**19**:132–46. https://doi.org/10.1038/s41571-021-00560-7.
137. Bo Z, Song J, He Q. *et al.* Application of artificial intelligence radiomics in the diagnosis, treatment, and prognosis of hepatocellular carcinoma. *Comput Biol Med* 2024;**173**:108337. https://doi.org/10.1016/j.compbiomed.2024.108337.
138. Ge S, Sun S, Xu H. *et al.* Deep learning in single-cell and spatial transcriptomics data analysis: Advances and challenges from a data science perspective. *Brief Bioinform* 2025;**26**:bbaf136. https://doi.org/10.1093/bib/bbaf136.
139. Wani SA, Khan SA, Quadri SMK. Application of deep learning for single cell multi-omics: A state-of-the-art review. *Arch Comput Methods Eng* 2025;**32**:2987–3029. https://doi.org/10.1007/s11831-025-10230-x.
140. Nam AS, Chaligne R, Landau DA. Integrating genetic and non-genetic determinants of cancer evolution by single-cell multi-omics. *Nat Rev Genet* 2021;**22**:3–18. https://doi.org/10.1038/s41576-020-0265-5.
141. Xu Y, Su GH, Ma D. *et al.* Technological advances in cancer immunity: From immunogenomics to single-cell analysis and artificial intelligence. *Signal Transduct Target Ther* 2021;**6**:312. https://doi.org/10.1038/s41392-021-00729-7.
142. Zeng Q, Mousa M, Nadukkandy AS. *et al.* Understanding tumour endothelial cell heterogeneity and function from single-cell omics. *Nat Rev Cancer* 2023;**23**:544–64. https://doi.org/10.1038/s41568-023-00591-5.
143. Baysoy A, Bai Z, Satija R. *et al.* The technological landscape and applications of single-cell multi-omics. *Nat Rev Mol Cell Biol* 2023;**24**:695–713. https://doi.org/10.1038/s41580-023-00615-w.
144. Frank MH, Wilson BJ, Gold JS. *et al.* Clinical implications of colorectal cancer stem cells in the age of single-cell omics and targeted therapies. *Gastroenterology* 2021;**160**:1947–60. https://doi.org/10.1053/j.gastro.2020.12.080.
145. Ma J, Wu Y, Ma L. *et al.* A blueprint for tumor-infiltrating B cells across human cancers. *Science* 2024;**384**:eadj4857. https://doi.org/10.1126/science.adj4857.
146. Ma A, McDermaid A, Xu J. *et al.* Integrative methods and practical challenges for single-cell multi-omics. *Trends Biotechnol* 2020;**38**:1007–22. https://doi.org/10.1016/j.tibtech.2020.02.013.
147. Wang X, He Y, Zhang Q. *et al.* Direct comparative analyses of 10X genomics chromium and smart-seq2. *Genomics Proteomics Bioinformatics* 2021;**19**:253–66. https://doi.org/10.1016/j.gpb.2020.02.005.
148. Picelli S, Faridani OR, Björklund ÅK. *et al.* Full-length RNA-seq from single cells using smart-seq2. *Nat Protoc* 2014;**9**:171–81. https://doi.org/10.1038/nprot.2014.006.
149. Ziegenhain C, Vieth B, Parekh S. *et al.* Comparative analysis of single-cell RNA sequencing methods. *Mol Cell* 2017;**65**:631–643.e4. https://doi.org/10.1016/j.molcel.2017.01.023.
150. Rodriguez-Meira A, O'Sullivan J, Rahman H. *et al.* TARGET-seq: A protocol for high-sensitivity single-cell mutational analysis and parallel RNA sequencing. *STAR Protoc* 2020;**1**:100125. https://doi.org/10.1016/j.xpro.2020.100125.
151. Han KY, Kim KT, Joung JG. *et al.* SIDR: Simultaneous isolation and parallel sequencing of genomic DNA and total RNA from single cells. *Genome Res* 2018;**28**:75–87. https://doi.org/10.1101/gr.223263.117.
152. Flynn E, Almonte-Loya A, Fragiadakis GK. Single-cell multi-omics. *Annu Rev Biomed Data Sci* 2023;**6**:313–37. https://doi.org/10.1146/annurev-biodatasci-020422-050645.
153. Xing QR, Farran CAE, Zeng YY. *et al.* Parallel bimodal single-cell sequencing of transcriptome and chromatin accessibility. *Genome Res* 2020;**30**:1027–39. https://doi.org/10.1101/gr.257840.119.
154. Xu W, Yang W, Zhang Y. *et al.* ISSAAC-seq enables sensitive and flexible multimodal profiling of chromatin accessibility and gene expression in single cells. *Nat Methods* 2022;**19**:1243–9. https://doi.org/10.1038/s41592-022-01601-4.
155. Collora JA, Liu R, Pinto-Santini D. *et al.* Single-cell multi-omics reveals persistence of HIV-1 in expanded cytotoxic T cell clones. *Immunity* 2022;**55**:1013–1031.e7. https://doi.org/10.1016/j.immuni.2022.03.004.
156. Fiskin E, Lareau CA, Ludwig LS. *et al.* Single-cell profiling of proteins and chromatin accessibility using PHAGE-ATAC. *Nat Biotechnol* 2022;**40**:374–81. https://doi.org/10.1038/s41587-021-01065-5.
157. Sartori F, Codicè F, Caranzano I. *et al.* A comprehensive review of deep learning applications with multi-omics data in cancer research. *Genes* 2025;**16**:648. https://doi.org/10.3390/genes16060648.
158. Crosby D, Bhatia S, Brindle KM. *et al.* Early detection of cancer. *Science* 2022;**375**:eaay9040. https://doi.org/10.1126/science.aay9040.

159. Fitzgerald RC, Antoniou AC, Fruk L. *et al.* The future of early cancer detection. *Nat Med* 2022;**28**:666–77. https://doi.org/10.1038/s41591-022-01746-x.
160. Dong Z, Li P, Jiang Y. *et al.* Integrative multi-omics and routine blood analysis using deep learning: Cost-effective early prediction of chronic disease risks. *Adv Sci (Weinh)* 2025;**12**:e2412775. https://doi.org/10.1002/advs.202412775.
161. Osseni MA, Tossou P, Laviolette F. *et al.* MOT: A multi-omics transformer for multiclass classification tumour types predictions. *bioRxiv* 2022;2022.11.14.516459.
162. Cao K, Xia Y, Yao J. *et al.* Large-scale pancreatic cancer detection via non-contrast CT and deep learning. *Nat Med* 2023;**29**:3033–43. https://doi.org/10.1038/s41591-023-02640-w.
163. Cohen JD, Li L, Wang Y. *et al.* Detection and localization of surgically resectable cancers with a multi-analyte blood test. *Science* 2018;**359**:926–30. https://doi.org/10.1126/science.aar3247.
164. Li J, Wei L, Zhang X. *et al.* DISMIR: Deep learning-based noninvasive cancer detection by integrating DNA sequence and methylation information of individual cell-free DNA reads. *Brief Bioinform* 2021;**22**:bbab250. https://doi.org/10.1093/bib/bbab250.
165. Albaradei S, Alganmi N, Albaradie A. *et al.* A deep learning model predicts the presence of diverse cancer types using circulating tumor cells. *Sci Rep* 2023;**13**:21114. https://doi.org/10.1038/s41598-023-47805-2.
166. Cai Y, Luo M, Yang W. *et al.* The deep learning framework iCanTCR enables early cancer detection using the T-cell receptor repertoire in peripheral blood. *Cancer Res* 2024;**84**:1915–28. https://doi.org/10.1158/0008-5472.CAN-23-0860.
167. Fu Y, Jung AW, Torne RV. *et al.* Pan-cancer computational histopathology reveals mutations, tumor composition and prognosis. *Nat Cancer* 2020;**1**:800–10. https://doi.org/10.1038/s43018-020-0085-8.
168. Kather JN, Heij LR, Grabsch HI. *et al.* Pan-cancer image-based detection of clinically actionable genetic alterations. *Nat Cancer* 2020;**1**:789–99. https://doi.org/10.1038/s43018-020-0087-6.
169. Foersch S, Eckstein M, Wagner DC. *et al.* Deep learning for diagnosis and survival prediction in soft tissue sarcoma. *Ann Oncol* 2021;**32**:1178–87. https://doi.org/10.1016/j.annonc.2021.06.007.
170. Hoang DT, Shulman ED, Turakulov R. *et al.* Prediction of DNA methylation-based tumor types from histopathology in central nervous system tumors with deep learning. *Nat Med* 2024;**30**:1952–61. https://doi.org/10.1038/s41591-024-02995-8.
171. Albrecht T, Rossberg A, Albrecht JD. *et al.* Deep learning-enabled diagnosis of liver adenocarcinoma. *Gastroenterology* 2023;**165**:1262–75. https://doi.org/10.1053/j.gastro.2023.07.026.
172. Barsha NA, Rahman A, Mahdy MRC. Automated detection and grading of invasive ductal carcinoma breast cancer using ensemble of deep learning models. *Comput Biol Med* 2021;**139**:104931. https://doi.org/10.1016/j.compbiomed.2021.104931.
173. Cai Y, Wang S. Deeply integrating latent consistent representations in high-noise multi-omics data for cancer subtyping. *Brief Bioinform* 2024;**25**:bbae061. https://doi.org/10.1093/bib/bbae061.
174. Liu Q, Song K. ProgCAE: A deep learning-based method that integrates multi-omics data to predict cancer subtypes. *Brief Bioinform* 2023;**24**:bbad196. https://doi.org/10.1093/bib/bbad196.
175. Zhang Y, Kiryu H. MODEC: An unsupervised clustering method integrating omics data for identifying cancer subtypes. *Brief Bioinform* 2022;**23**:bbac372. https://doi.org/10.1093/bib/bbac372.
176. Zhao J, Zhao B, Song X. *et al.* Subtype-DCC: Decoupled contrastive clustering method for cancer subtype identification based on multi-omics data. *Brief Bioinform* 2023;**24**:bbad025. https://doi.org/10.1093/bib/bbad025.
177. Sirinukunwattana K, Domingo E, Richman SD. *et al.* Image-based consensus molecular subtype (imCMS) classification of colorectal cancer using deep learning. *Gut* 2021;**70**:544–54. https://doi.org/10.1136/gutjnl-2019-319866.
178. Skrede OJ, de Raedt S, Kleppe A. *et al.* Deep learning for prediction of colorectal cancer outcome: A discovery and validation study. *Lancet* 2020;**395**:350–60. https://doi.org/10.1016/S0140-6736(19)32998-8.
179. Lan W, Liao H, Chen Q. *et al.* DeepKEGG: A multi-omics data integration framework with biological insights for cancer recurrence prediction and biomarker discovery. *Brief Bioinform* 2024;**25**:bbae185. https://doi.org/10.1093/bib/bbae185.
180. Gonçalves E, Poulos RC, Cai Z. *et al.* Pan-cancer proteomic map of 949 human cell lines. *Cancer Cell* 2022;**40**:835–849.e8. https://doi.org/10.1016/j.ccell.2022.06.010.
181. Chen RJ, Lu MY, Williamson DFK. *et al.* Pan-cancer integrative histology-genomic analysis via multimodal deep learning. *Cancer Cell* 2022;**40**:865–878.e6. https://doi.org/10.1016/j.ccell.2022.07.004.
182. Wang R, Dai W, Gong J. *et al.* Development of a novel combined nomogram model integrating deep learning-pathomics, radiomics and immunoscore to predict postoperative outcome of colorectal cancer lung metastasis patients. *J Hematol Oncol* 2022;**15**:11. https://doi.org/10.1186/s13045-022-01225-3.
183. Wei Z, Han D, Zhang C. *et al.* Deep learning-based multi-omics integration robustly predicts relapse in prostate cancer. *Front Oncol* 2022;**12**:893424. https://doi.org/10.3389/fonc.2022.893424.
184. Courtiol P, Maussion C, Moarii M. *et al.* Deep learning-based classification of mesothelioma improves prediction of patient outcome. *Nat Med* 2019;**25**:1519–25. https://doi.org/10.1038/s41591-019-0583-3.
185. Zhu J, Oh JH, Simhal AK. *et al.* Geometric graph neural networks on multi-omics data to predict cancer survival outcomes. *Comput Biol Med* 2023;**163**:107117. https://doi.org/10.1016/j.compbiomed.2023.107117.
186. Jiang L, Xu C, Bai Y. *et al.* Autosurv: Interpretable deep learning framework for cancer survival analysis incorporating clinical and multi-omics data. *NPJ Precis Oncol* 2024;**8**:4. https://doi.org/10.1038/s41698-023-00494-6.
187. Bao X, Li Q, Chen D. *et al.* A multiomics analysis-assisted deep learning model identifies a macrophage-oriented module as a potential therapeutic target in colorectal cancer. *Cell Rep Med* 2024;**5**:101399. https://doi.org/10.1016/j.xcrm.2024.101399.
188. Jiang C, Zhang XF, Qu T. *et al.* The prediction of pCR and chemosensitivity for breast cancer patients using DLG3, RADL and Pathomics signatures based on machine learning and deep learning. *Transl Oncol* 2024;**46**:101985. https://doi.org/10.1016/j.tranon.2024.101985.
189. Yang Y, Yang J, Shen L. *et al.* A multi-omics-based serial deep learning approach to predict clinical outcomes of single-agent anti-PD-1/PD-L1 immunotherapy in advanced stage non-small-cell lung cancer. *Am J Transl Res* 2021;**13**:743–56.
190. Che G, Yin J, Wang W. *et al.* Circumventing drug resistance in gastric cancer: A spatial multi-omics exploration of chemo and immuno-therapeutic response dynamics. *Drug Resist Updat* 2024;**74**:101080. https://doi.org/10.1016/j.drup.2024.101080.

191. Cui S, Ten Haken RK, El Naqa I. Integrating multiomics information in deep learning architectures for joint actuarial outcome prediction in non-small cell lung cancer patients after radiation therapy. *Int J Radiat Oncol Biol Phys* 2021;**110**:893–904. https://doi.org/10.1016/j.ijrobp.2021.01.042.
192. Su W, Cheng D, Ni W. *et al.* Multi-omics deep learning for radiation pneumonitis prediction in lung cancer patients underwent volumetric modulated arc therapy. *Comput Methods Prog Biomed* 2024;**254**:108295. https://doi.org/10.1016/j.cmpb.2024.108295.
193. Fu N, Fu W, Chen H. *et al.* A deep-learning radiomics-based lymph node metastasis predictive model for pancreatic cancer: A diagnostic study. *Int J Surg* 2023;**109**:2196–203. https://doi.org/10.1097/JS9.0000000000000469.
194. Li X, Yang L, Jiao X. Deep learning-based multiomics integration model for predicting axillary lymph node metastasis in breast cancer. *Future Oncol* 2023;**19**:1429–38. https://doi.org/10.2217/fon-2023-0070.
195. Han W, Wang Y, Li T. *et al.* A CT-based integrated model for preoperative prediction of occult lymph node metastasis in early tongue cancer. *PeerJ* 2024;**12**:e17254. https://doi.org/10.7717/peerj.17254.
196. Danishuddin SK, Kim JJ. From cancer big data to treatment: Artificial intelligence in cancer research. *J Gene Med* 2024;**26**:e3629. https://doi.org/10.1002/jgm.3629.
197. Ozaki Y, Broughton P, Abdollahi H. *et al.* Integrating omics data and AI for cancer diagnosis and prognosis. *Cancers (Basel)* 2024;**16**:2448. https://doi.org/10.3390/cancers16132448.
198. Anaya-Isaza A, Mera-Jiménez L, Zequera-Diaz M. An overview of deep learning in medical imaging. *Inform Med Unlocked* 2021;**26**:100723. https://doi.org/10.1016/j.imu.2021.100723.
199. Gao R, Zhao S, Aishanjiang K. *et al.* Deep learning for differential diagnosis of malignant hepatic tumors based on multiphase contrast-enhanced CT and clinical data. *J Hematol Oncol* 2021;**14**:154. https://doi.org/10.1186/s13045-021-01167-2.
200. Ibrahim DM, Elshennawy NM, Sarhan AM. Deep-chest: Multi-classification deep learning model for diagnosing COVID-19, pneumonia, and lung cancer chest diseases. *Comput Biol Med* 2021;**132**:104348. https://doi.org/10.1016/j.compbiomed.2021.104348.
201. Peng S, Liu Y, Lv W. *et al.* Deep learning-based artificial intelligence model to assist thyroid nodule diagnosis and management: A multicentre diagnostic study. *Lancet Digit Health* 2021;**3**:e250–9. https://doi.org/10.1016/S2589-7500(21)00041-8.
202. Lotter W, Diab AR, Haslam B. *et al.* Robust breast cancer detection in mammography and digital breast tomosynthesis using an annotation-efficient deep learning approach. *Nat Med* 2021;**27**:244–9. https://doi.org/10.1038/s41591-020-01174-9.
203. Liu KL, Wu T, Chen PT. *et al.* Deep learning to distinguish pancreatic cancer tissue from non-cancerous pancreatic tissue: A retrospective study with cross-racial external validation. *Lancet Digit Health* 2020;**2**:e303–13. https://doi.org/10.1016/S2589-7500(20)30078-9.
204. Song X, Duan X, He X. *et al.* Computer-aided diagnosis of distal metastasis in non-small cell lung cancer by low-dose CT based radiomics and deep learning signatures. *Radiol Med* 2024;**129**:239–51. https://doi.org/10.1007/s11547-024-01770-6.
205. Jiang Y, Zhang Z, Yuan Q. *et al.* Predicting peritoneal recurrence and disease-free survival from CT images in gastric cancer with multitask deep learning: A retrospective study. *Lancet Digit Health* 2022;**4**:e340–50. https://doi.org/10.1016/S2589-7500(22)00040-1.
206. Yuan Z, Xu T, Cai J. *et al.* Development and validation of an image-based deep learning algorithm for detection of synchronous peritoneal carcinomatosis in colorectal cancer. *Ann Surg* 2022;**275**:e645–51. https://doi.org/10.1097/SLA.0000000000004229.
207. Alharbi F, Budhiraja N, Vakanski A. *et al. Graph Kolmogorov-Arnold Networks for Multi-Cancer Classification and Biomarker Identification, An Interpretable Multi-Omics Approach*. arXiv preprint arXiv:2503.22939, 2025.
208. Wan JCM, Sasieni P, Rosenfeld N. Promises and pitfalls of multi-cancer early detection using liquid biopsy tests. *Nat Rev Clin Oncol* 2025;**22**:566–80. https://doi.org/10.1038/s41571-025-01033-x.
209. Massa C, Seliger B. Combination of multiple omics techniques for a personalized therapy or treatment selection. *Front Immunol* 2023;**14**:1258013. https://doi.org/10.3389/fimmu.2023.1258013.
210. Liu L, Li F, Zhao J. *et al.* The real-world therapeutic analysis of first-line immunotherapy in Chinese patients with drive gene positive for advanced non-small cell lung cancer. *J Cancer* 2023;**14**:952–65. https://doi.org/10.7150/jca.77199.
211. Nilsson A, Meimetis N, Lauffenburger DA. Towards an interpretable deep learning model of cancer. *NPJ Precis Oncol* 2025;**9**:46. https://doi.org/10.1038/s41698-025-00822-y.
212. Mathema VB, Sen P, Lamichhane S. *et al.* Deep learning facilitates multi-data type analysis and predictive biomarker discovery in cancer precision medicine. *Comput Struct Biotechnol J* 2023;**21**:1372–82. https://doi.org/10.1016/j.csbj.2023.01.043.
213. Wang S, Wang S, Wang Z. A survey on multi-omics-based cancer diagnosis using machine learning with the potential application in gastrointestinal cancer. *Front Med (Lausanne)* 2022;**9**:1109365.
214. Kang W, Qiu X, Luo Y. *et al.* Application of radiomics-based multiomics combinations in the tumor microenvironment and cancer prognosis. *J Transl Med* 2023;**21**:598. https://doi.org/10.1186/s12967-023-04437-4.
215. Chai H, Zhou X, Zhang Z. *et al.* Integrating multi-omics data through deep learning for accurate cancer prognosis prediction. *Comput Biol Med* 2021;**134**:104481. https://doi.org/10.1016/j.compbiomed.2021.104481.
216. Hoang DT, Dinstag G, Shulman ED. *et al.* A deep-learning framework to predict cancer treatment response from histopathology images through imputed transcriptomics. *Nat Cancer* 2024;**5**:1305–17. https://doi.org/10.1038/s43018-024-00793-2.
217. Tommasi T, Patricia N, Caputo B. *et al.* A deeper look at dataset bias. In: Csurka G (ed.), *Domain Adaptation in Computer Vision Applications*. Cham: Springer International Publishing, 2017, 37–55. https://doi.org/10.1007/978-3-319-58347-1_2.
218. Zhu W, Xie L, Han J. *et al.* The application of deep learning in cancer prognosis prediction. *Cancers (Basel)* 2020;**12**:603. https://doi.org/10.3390/cancers12030603.
219. Chaudhary K, Poirion OB, Lu L. *et al.* Deep learning-based multi-omics integration robustly predicts survival in liver cancer. *Clin Cancer Res* 2018;**24**:1248–59. https://doi.org/10.1158/1078-0432.CCR-17-0853.
220. Lánczky A, Győrffy B. Web-based survival analysis tool tailored for medical research (KMplot): Development and implementation. *J Med Internet Res* 2021;**23**:e27633. https://doi.org/10.2196/27633.
221. Rahman SA, Walker RC, Maynard N. *et al.* The AUGIS survival predictor: Prediction of long-term and conditional survival after esophagectomy using random survival forests. *Ann Surg* 2023;**277**:267–74. https://doi.org/10.1097/SLA.0000000000004794.

222. Jiang N, Wu Y, Li C. Limitations of using COX proportional hazards model in cardiovascular research. *Cardiovasc Diabetol* 2024;**23**:219. https://doi.org/10.1186/s12933-024-02302-2.
223. Poirion OB, Jing Z, Chaudhary K. *et al.* DeepProg: An ensemble of deep-learning and machine-learning models for prognosis prediction using multi-omics data. *Genome Med* 2021;**13**:112. https://doi.org/10.1186/s13073-021-00930-x.
224. Song J, Wei M, Zhao S. *et al.* Drug sensitivity prediction based on multi-stage multi-modal drug representation learning. *Interdiscip Sci: Comput Life Sci* 2025;**17**:231–43. https://doi.org/10.1007/s12539-024-00668-1.
225. Khan T, Khan A, Nasir SN. *et al.* CytomegaloVirusDb: Multi-omics knowledge database for cytomegaloviruses. *Comput Biol Med* 2021;**135**:104563. https://doi.org/10.1016/j.compbiomed.2021.104563.
226. Tanaka I, Furukawa T, Morise M. The current issues and future perspective of artificial intelligence for developing new treatment strategy in non-small cell lung cancer: Harmonization of molecular cancer biology and artificial intelligence. *Cancer Cell Int* 2021;**21**:454. https://doi.org/10.1186/s12935-021-02165-7.
227. Yu J, Wu X, Song J. *et al.* Loss of MHC-I antigen presentation correlated with immune checkpoint blockade tolerance in MAPK inhibitor-resistant melanoma. *Front Pharmacol* 2022;**13**:928226. https://doi.org/10.3389/fphar.2022.928226.
228. Jiang Y, Zhang Z, Wang W. *et al.* Biology-guided deep learning predicts prognosis and cancer immunotherapy response. *Nat Commun* 2023;**14**:5135. https://doi.org/10.1038/s41467-023-40890-x.
229. Jendoubi T. Approaches to integrating metabolomics and multi-omics data: A primer. *Metabolites* 2021;**11**:184. https://doi.org/10.3390/metabo11030184.
230. Tabakhi S, Suvon MN, Ahadian P. *et al. Multimodal Learning for Multi-Omics: A Survey.* World Sci. Annu. Rev. Artif. Intell., 2022. 1: p. 2250004:1-2250004:39.
231. Ching T, Himmelstein DS, Beaulieu-Jones BK. *et al.* Opportunities and obstacles for deep learning in biology and medicine. *J R Soc Interface* 2018;**15**(141). https://doi.org/10.1098/rsif.2017.0387.

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