

Leveraging artificial intelligence and machine learning for unraveling pathogenesis and advancing precision medicine in autoimmune diseases

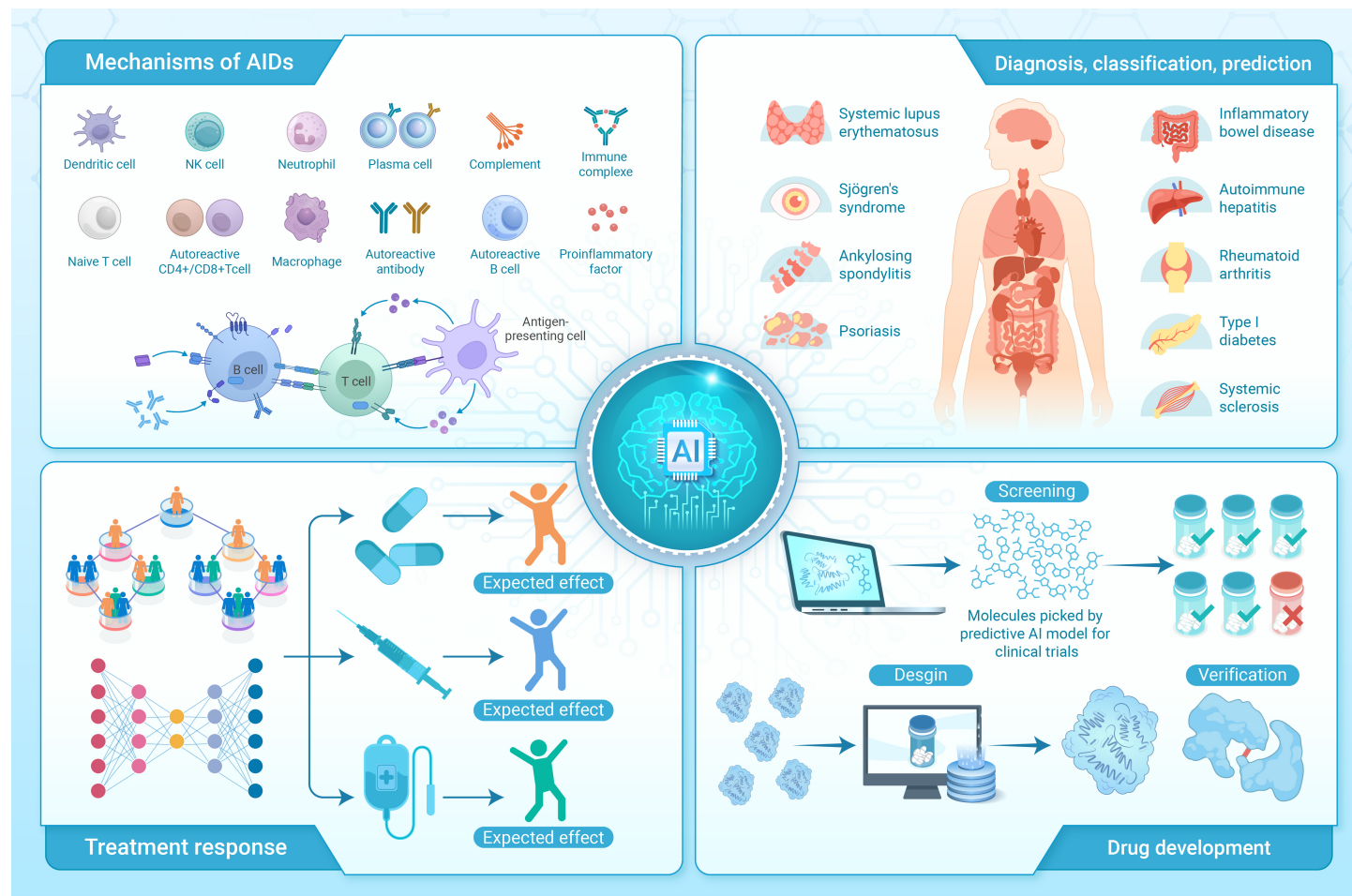
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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Artificial intelligence (AI) and machine learning (ML) accelerate understanding of the immune system.
- AI and ML provide new perspectives for diagnosing and treating autoimmune diseases.
- AI and ML assist in predicting treatment responses and contribute to drug development.

Leveraging artificial intelligence and machine learning for unraveling pathogenesis and advancing precision medicine in autoimmune diseases

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Autoimmune diseases (AIDs) are intricate disorders in which the immune system mistakenly attacks the body's own tissues. Recent advancements in omics technologies, as well as artificial intelligence (AI) and machine learning (ML), have significantly deepened our understanding of AIDs. AI, which mimics intelligent behavior to perform complex tasks, is transforming diagnostic approaches, risk assessments, and health management strategies. High-throughput technologies, including microarrays and single-cell RNA sequencing (scRNA-seq), now allow researchers to assess gene expression profiles, offering valuable insights into disease mechanisms. When combined, AI and ML facilitate the integration of multimodal omics data, aiding in the identification of key regulatory networks, disease subtypes, and potential biomarkers. In basic research, ML investigates immune cell functions, B cell receptor (BCR) and T cell receptor (TCR) interactions, and the major histocompatibility complex (MHC). Clinically, AI supports diagnosis, treatment response prediction, and outcome forecasting. It enables precise patient stratification in major AIDs, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc), through the integration of clinical, imaging, and multi-omics data. In drug development, AI is revolutionizing traditional research models by assisting in the design of small molecules, engineering antibodies, and developing innovative therapies. However, challenges regarding data quality, model interpretability, and ethical considerations persist. Despite these hurdles, the integration of AI and ML is anticipated to propel advances in precision medicine for AIDs. This review highlights the latest applications of AI and ML in AIDs, focusing on disease mechanisms, diagnostics, treatment prediction, and drug development.

INTRODUCTION

Autoimmune diseases (AID) are a group of highly complex and significantly heterogeneous disorders.^{1,2,3} Currently, nearly 100 types of AIDs are known, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc), multiple sclerosis (MS), type 1 diabetes (T1D), and inflammatory bowel disease (IBD).⁴ Due to the multifactorial etiology of these diseases, involving genetic, environmental, and immune regulatory factors,⁵ AIDs can affect multiple organ systems, including joints, skin, muscles, kidneys, lungs, liver, intestines, exocrine glands, and blood vessels. This leads to diverse clinical manifestations, with significant variations in disease severity, organ involvement, and systemic presentations among patients. Consequently, the diagnosis and treatment of AIDs remain challenging.⁶ The pathogenesis primarily involves multiple aspects of the immune system: abnormal activation of T and B lymphocytes, production of autoantibodies, secretion of various pro-inflammatory cytokines and chemokines, and often impaired function of regulatory immune cells. Although patient classification and personalized interventions are crucial for improving prognosis, traditional diagnosis and clinical classification of AIDs still largely rely on clinical features, serology, and histopathological characteristics. This

approach has limitations and often fails to fully reflect the complexity and individual variability of the diseases.²

In recent years, with the rapid development of high-throughput omics technologies, including proteomics, genomics, and metabolomics, it has become possible to conduct comprehensive molecular-level analyses of biological processes in patients' blood and target organs.^{7,8,9} These advancements have led to widespread clinical applications. For example, genome-wide association studies (GWAS) based on next-generation sequencing have identified hundreds of thousands of genetic variants associated with complex diseases or traits,¹⁰ providing strong support for the development of breakthrough therapies, such as targeted treatments for the IL23A gene in IBD.¹¹ Additionally, epigenomics and metabolomics can provide functional validation for variants identified in GWAS, supporting their disease associations and clinical translation.^{12,13,14} Furthermore, integrating multi-omics analyses (e.g., transcriptomics and proteomics) can identify pathogenic loci and key disease pathways affecting gene and protein levels, offering important insights into disease mechanisms.^{15,16,17} Compared to single-omics approaches, integrating multi-omics data provides a more comprehensive perspective in disease mechanism research, making it widely applicable for biomarker discovery, therapeutic target identification, treatment response, and patient outcome prediction.^{18,19,20} Moreover, the continuous improvement of multi-omics databases and the standardization of methodologies have significantly facilitated the integration of multimodal molecular data.²¹ In this context, Machine learning (ML) methods have shown great potential. Their applications have expanded from simple disease diagnosis to identifying disease-related biological pathways and subtypes. By integrating complex datasets across multiple omics layers, ML algorithms can discern disease subtypes and biomarker patterns that traditional methods might overlook.

Artificial intelligence (AI) can process and analyze large-scale, complex biomedical data, demonstrating powerful capabilities in interpreting high-throughput omics data.^{22,23} ML, a subfield of AI, uses statistical methods to train models on large datasets and optimize parameters without explicit programming.²⁴ Deep learning (DL), an important branch of ML, has significantly enhanced the analysis of medical imaging (radiomics, digital pathology), genomics (genomics, transcriptomics, epigenomics), immunology, and real-world multimodal data.²⁵ For example, in medical imaging, ML and DL are widely applied to CT and MRI images, offering significant advantages in saving time and reducing inter-observer variability.²⁶ They also improve diagnostic workflows, image standardization, quality enhancement, database mining, content-based indexing, report generation, and semantic labeling.²⁷ Overall, AI-based radiomics can reveal image details beyond the capabilities of the human eye.^{28,29}

In the clinical practice of AIDs, AI also holds great potential in disease diagnosis, treatment response prediction, and clinical outcome assessment. By integrating large-scale patient data, AI can identify early disease markers and predict the efficacy of specific treatments using multi-omics data. ML algorithms can extract disease features, build predictive models, and validate their

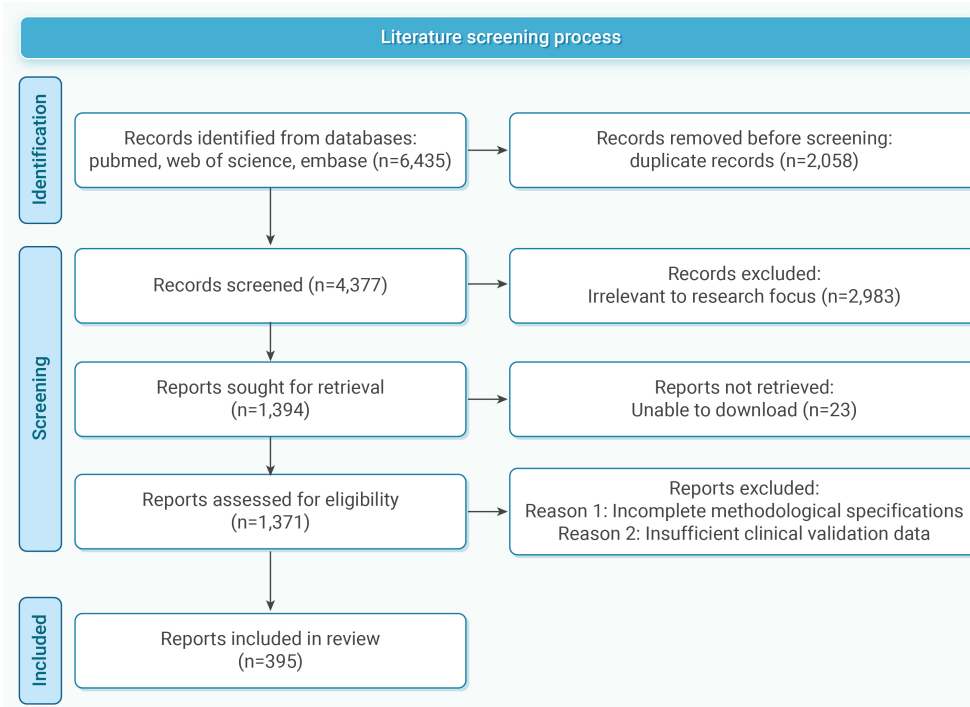


Figure 1. Literature screening workflow.

APPLICATION OF DIFFERENT ML ALGORITHMS IN AIDS

ML algorithms can be classified into five major categories: supervised learning, unsupervised learning, semi-supervised learning, reinforcement learning, and DL. Supervised learning trains models on labeled data to learn the mapping relationship between inputs and outputs and is primarily used for classification and regression tasks. Typical algorithms include decision trees and support vector machines (SVM).³³ Unsupervised learning, on the other hand, discovers inherent patterns and structures within unlabeled data and is commonly used for clustering analysis and dimensionality reduction, such as k-means clustering and principal component analysis (PCA). Semi-supervised learning combines the advantages of labeled and unlabeled data, using a small amount of labeled data to guide the model's learning, and then transferring the acquired knowledge to a large amount of unlabeled data.

performance on external datasets. DL techniques can further integrate massive multi-omics data to uncover potential key regulatory networks and therapeutic targets. Particularly in major AIDS such as RA, Sjögren's syndrome, and SSc, ML enables more precise patient stratification and individualized treatment plans by integrating clinical, imaging, and multi-omics data. For example, analyzing multidimensional data from genomics, transcriptomics, proteomics, metabolomics, and microbiomics can reveal the complex pathogenesis of autoimmune gastrointestinal diseases, predict drug responses, and support personalized treatments.³⁰ AI automates the extraction of complex data patterns and provides quantitative assessments, which, once integrated into clinical workflows, can make diagnosis and treatment more accurate and reproducible.³¹ In drug development, AI is reshaping traditional models, from small molecule drug design and antibody engineering to natural product screening, opening new perspectives for AIDS drug development through the integration of multimodal data (genomics, radiomics, pathology, and real-world data).³²

Despite its immense potential, AI faces challenges in autoimmune disease research, including data quality, model interpretability, and ethical regulation. The high heterogeneity and complexity of AIDS necessitate closer integration of AI technologies with traditional clinical methods to achieve true precision medicine. As AI technologies continue to evolve, they are expected to have a greater impact on the development of more accurate early diagnostic tools, novel therapeutic targets, optimized clinical trials, and personalized patient management strategies. This review aims to systematically summarize the latest advances in AI and ML technologies in AIDS research, with a focus on their applications in elucidating disease mechanisms, diagnostic classification, treatment prediction, and drug development. To ensure rigor and reproducibility, the literature selection process strictly followed the PRISMA 2020 guidelines, encompassing database search, duplicate removal, screening, and eligibility assessment. Figure 1 presents the PRISMA-compliant flow diagram that visualizes the entire screening process from initial retrieval to final study inclusion.

This PRISMA flowchart illustrates the literature screening process for AI and ML applications in autoimmune diseases. A comprehensive search of PubMed, Web of Science, and Embase from 2015 to 2025, using a combination of terms related to AI/ML, autoimmune diseases, pathogenesis, and precision medicine, initially identified 6,435 records. After removing 2,058 duplicates, 4,377 records were screened based on their titles and abstracts, resulting in the exclusion of 2,983 irrelevant studies. Full-text retrieval was attempted for 1,394 articles (with 23 unavailable), and ultimately, 395 studies were included based on criteria for technical rigor and clinical relevance.

Reinforcement learning optimizes decision-making strategies by interacting with the environment and receiving feedback, a method initially applied in games and robotics, such as Q-learning and deep reinforcement learning networks.³⁴ DL, as an important branch of ML, learns hierarchical representations of data by constructing multi-layer neural networks. These networks consist of a large number of interconnected nodes, which automatically learn complex feature representations, significantly improving the model's expressiveness and generalization ability.³⁵ Over the past two decades, thanks to significant advancements in computational power, ML models have made breakthrough progress in the medical field. In particular, in the field of autoimmune disease research, the number of published papers on disease diagnosis and subtype classification using ML has increased nearly tenfold from 2014 to October 2024, reflecting the growing importance of ML in autoimmune disease research.

The figure illustrates the entire workflow from raw genetic data to the final ML model. First, raw data (such as gene fragments) is processed through preprocessing steps to organize it into clean gene sequences, from which features are extracted. Subsequently, traditional ML models (such as RF, SVM, and PCA) can be used for regression or clustering analysis. In advanced ML models, DL models are introduced, where neural networks process gene features through input layers, hidden layers, and output layers. CNN extract local features through convolutional and pooling layers, while RNN handle sequence data through their recurrent structures. In recent years, Transformer models have been employed to calculate the relevance of each position in a sequence using self-attention mechanisms, capturing long-range dependencies. The embedding layer converts bases in the gene sequence into vectors, which are then processed through multiple Transformer blocks to produce more accurate predictions or classification results.

Supervised learning algorithms

Supervised learning is one of the important branches of ML and has broad applications in bioinformatics and medical research. These algorithms learn from labeled training data to predict the labels of new data, with the core task being to establish a mapping relationship between input features and output labels. Supervised learning algorithms can be widely applied to various tasks such as classification and regression, and they are suitable for different types of data. Moreover, there are clear evaluation metrics (such as accuracy, AUC, etc.) to assess model performance.³⁶ In bioinformatics and medical fields, commonly used supervised learning algorithms include support SVM, random forests (RF), and DL networks (such as CNN and RNN).³⁷ These algorithms have demonstrated strong application potential in various areas,

such as gene expression analysis (SVM is frequently used for classification and functional prediction of gene expression data),³⁸ protein structure prediction, sequence analysis (used for identifying coding regions in DNA sequences, like the GENSCAN tool),³⁹ and miRNA target gene prediction.⁴⁰ In AIDs research, supervised learning algorithms have multiple potential applications, such as disease diagnosis and classification (training models using clinical symptoms, laboratory test results, and gene expression data to diagnose different types of AIDs or identify disease pattern characteristics);⁴¹ prognostic prediction (analyzing longitudinal patient data to predict disease progression and long-term outcomes);⁴² drug response prediction (helping predict patient responses to specific treatments, facilitating personalized medicine);⁴³ biomarker identification (analyzing large-scale genomics, proteomics, or metabolomics data to identify novel biomarkers associated with diseases);⁴⁴ medical image analysis (such as analyzing imaging data from patients with RA or SSc to assist in diagnosis and disease progression evaluation).⁴⁵

Unsupervised learning algorithms

Unsupervised learning algorithms are an important branch of ML. Their basic principle is to discover hidden structures and patterns from unlabeled data. These algorithms do not rely on predefined labels or target variables; instead, they analyze the intrinsic features and relationships within the data to reveal underlying structures. Unsupervised learning algorithms are suitable for exploratory data analysis, where they can uncover hidden relationships and groupings within the data. They perform well in handling high-dimensional data, enabling effective dimensionality reduction and feature extraction.³⁷ However, unsupervised learning also has some limitations: first, due to the lack of predefined evaluation standards, there can be difficulties in reaching consensus on the interpretation of results; second, performance evaluation of the algorithms is challenging, mainly due to the absence of clear evaluation metrics; third, the algorithms may identify statistically significant but biologically irrelevant patterns, limiting their practical value; and finally, unsupervised learning is highly sensitive to initial conditions and parameter settings, which may lead to instability in the results.⁴⁶

Unsupervised learning-based algorithms include clustering algorithms (such as K-means and hierarchical clustering), dimensionality reduction techniques (such as principal component analysis [PCA] and t-SNE), self-organizing maps (SOM), and autoencoders, among others.⁴⁷ These algorithms have wide applications in bioinformatics, such as: K-means is commonly used for clustering gene expression data; PCA is used for visualizing and reducing dimensionality in high-dimensional transcriptomics or proteomics data;⁴⁸ t-SNE is used in single-cell RNA sequencing (scRNA-seq) data analysis for cell type identification and visualization.⁴⁹ Bioinformatics algorithms developed based on unsupervised learning also play a significant role in processing and analyzing complex biological data. For example: Gene expression clustering algorithms such as WGCNA, developed by Langfelder and Horvath, are used to identify gene co-expression network modules and are widely applied in gene function prediction and the discovery of disease-associated gene modules;⁵⁰ scRNA-seq data analysis algorithms such as Seurat's clustering and dimensionality reduction algorithms, developed by Satija et al., are used for visualizing single-cell data and identifying cell types;⁵¹ Protein-protein interaction network analysis algorithms such as MCODE (Molecular Complex Detection), developed by Bader and Hogue, are used to identify highly interconnected regions or complexes from protein interaction networks;⁵² Metabolic network reconstruction algorithms like ARACNE (Algorithm for the Reconstruction of Accurate Cellular Networks), developed by Margolin et al., are used to infer gene regulatory networks from gene expression data;⁵³ Drug repositioning algorithms like DRRS (Drug Repositioning Recommendation System), developed by Wang et al., use matrix factorization techniques to analyze drug-target interaction networks and predict new uses for drugs;⁵⁴ Protein function prediction algorithms like GeneMANIA, developed by Warde-Farley et al., use label propagation algorithms on gene functional networks to predict unknown gene functions.⁵⁵

In autoimmune disease research, these algorithms have various potential applications, including: Discovery of disease subtypes: By performing clustering analysis on clinical, genomic, and proteomic data from patients, new subtypes or molecular phenotypes of diseases can be identified. For example,

Banchereau et al. used unsupervised learning methods to analyze transcriptomic data from RA patients and discovered new subtypes related to disease activity and treatment response;⁵⁶ Discovery of biomarkers: By reducing dimensions and extracting features from multi-omics data, novel biomarkers associated with diseases can be identified. For example, Tasaki et al. used PCA to analyze metabolomics data from SSc patients and identified metabolites linked to disease progression;⁵⁷ Identification of immune cell subsets: Through clustering analysis of flow cytometry or scRNA-seq data, new immune cell subsets and their roles in diseases can be uncovered. For example, Zhang et al. used t-SNE and clustering analysis on scRNA-seq data from RA patients to reveal the heterogeneity of T cells and macrophages in the synovium;⁵⁸ Development of disease progression prediction models: longitudinal clinical data were analyzed to identify patterns that predict the progression trajectories of disease comorbidities. In a study published in *Arthritis Research & Therapy*, Solomon et al. used unsupervised learning methods to analyze clinical data from patients with RA, identifying different progression patterns of comorbidities in RA patients.⁵⁹

Deep learning

DL is a subfield of ML that has shown exceptional performance in many practical applications. It is based on the concept of artificial neural networks and involves constructing models with multilayer architectures to learn complex patterns and representations in data. A key characteristic of DL models is their "depth," which refers to the multiple hidden layers in the network. This enables the models to automatically learn hierarchical representations of data, making them particularly effective in handling large-scale, high-dimensional datasets. DL has achieved breakthroughs in areas such as image recognition, natural language processing, and speech recognition. The main types of DL models include: Feedforward Neural Networks, the simplest DL models where information flows from the input layer through multiple hidden layers to the output layer, with full connections between layers; Convolutional Neural Network (CNN), especially suitable for grid-structured data like images, CNN use convolutional and pooling layers to extract local features and reduce parameter counts;²⁵ Recurrent Neural Network (RNN), designed for sequential data such as time series or natural language, RNN capture temporal dependencies;⁶⁰ Long Short-Term Memory Networks (LSTMs), a variant of RNN that handle long-term dependencies more effectively;⁶¹ Autoencoders, unsupervised models used for learning compressed representations of data, commonly for dimensionality reduction and feature learning;⁶² Generative Adversarial Networks (GANs), composed of a generator and a discriminator, GANs generate realistic samples through adversarial training;⁶³ Variational Autoencoders (VAEs), combining autoencoders and probabilistic graphical models, VAEs are used for generative modeling and representation learning;⁶⁴ Transformers, based on the self-attention mechanism, Transformers excel in natural language processing tasks. Examples include BERT and GPT models.⁶⁵ Transformers, initially introduced by Vaswani et al. in 2017 with the paper "Attention Is All You Need," have extended their applications beyond natural language processing (NLP) to bioinformatics. Applications include protein structure prediction (e.g., AlphaFold2),⁶⁶⁻⁶⁷ DNA sequence analysis (e.g., DNABERT),⁶⁸ drug-target interaction prediction (e.g., MolTrans),⁶⁹ protein function prediction (e.g., ProtTrans),⁷⁰ and gene expression prediction frameworks like Geneformer for modeling RNA sequencing data.⁷¹ The advantages of Transformers in bioinformatics include capturing long-range dependencies, flexible model architectures, and interpretability via attention mechanisms. However, they require substantial data and computational resources for training.

DL has significantly advanced the diagnosis and classification of AIDs: In rheumatic disease diagnosis, researchers combined Fourier-transform infrared spectroscopy (FTIR) with DL to rapidly screen ankylosing spondylitis (AS), RA, and osteoarthritis (OA). The MSResNet model achieved an accuracy of 87%.⁷² In RA, a CNN-based DL algorithm integrating transcriptomic data from the GEO database with clinical features achieved 99.6% diagnostic accuracy. The SBi-LSTM and ACNN single models reached 92% and 95% accuracy, respectively, providing technical support for precision medicine in SLE.⁷³ In central nervous system demyelinating diseases, Transformer-based models distinguished MS, neuromyelitis optica spectrum disorder (NMOSD), and myelin oligodendrocyte glycoprotein antibody-associated disease

(MOGAD) by integrating brain and spinal MRI images, achieving AUC values of 0.933, 0.942, and 0.803, comparable to neuroradiologists.⁷⁴ In autoimmune bullous diseases, a Swin Transformer-based model analyzed immunofluorescence images, achieving 98.5% accuracy on the validation set and 94.6% on the test set, with 95.3% sensitivity and 97.5% specificity.⁷⁵ In lupus subtype diagnosis, a multimodal DL system (MMDLS) integrated clinical images, multicolor immunohistochemistry images, and clinical data, achieving a sensitivity of 82.88%, specificity of 98.52%, and an AUC of 0.9844 in classifying 13 skin lesion types. This system improved dermatologists' diagnostic accuracy from 66.88% to 81.25%.⁷⁶ In autoimmune hepatitis (AIH) histological evaluation, the AI(H) model provided accurate, quantitative analysis of histological features such as tissue detection (99.4%), liver microanatomy (88.0%), necrotic inflammation (83.9%), and bile duct injury (81.7%).⁷⁷ In T1D retinopathy prediction, a Transformer-based model analyzing longitudinal glycated hemoglobin data achieved an AUC of 88.65%, showcasing deep learning's potential in predicting autoimmune disease complications.⁷⁸ These studies demonstrate the advantages of DL in autoimmune disease research, improving diagnostic accuracy and supporting clinical decision-making. Particularly, the integration of multimodal DL and Transformer architectures is driving autoimmune disease diagnostics toward greater precision and efficiency.

Other methods

In addition, ensemble learning and large language models (LLMs) are rapidly advancing in the field of bioinformatics, offering new possibilities for solving complex biological problems. Ensemble learning is a ML method based on the collaboration of multiple models, with the core idea being to combine the predictions from several base learners to construct a more accurate and robust prediction model, overcoming the limitations of individual models.⁷⁹ Common ensemble learning techniques include Bagging, Boosting, and Stacking. In bioinformatics, ensemble learning has shown excellent performance in disease diagnosis, gene expression analysis, drug-target interaction prediction, and more.⁸⁰ Specifically, in scRNA-seq data cell type annotation, ensemble learning methods like scClassify have improved annotation accuracy and generalizability by integrating the predictions from multiple classifiers.⁸¹ Large language models (LLMs), on the other hand, gain powerful language understanding and generation abilities by pre-training on large-scale text data. Their application range in bioinformatics is also growing, including areas such as biomedical literature mining, single-cell sequencing cell type annotation, biomedical question-answering systems, clinical decision support, and biomedical image analysis.⁸²⁻⁸³ Furthermore, LLMs assist in the rapid discovery of therapeutic targets through biomedical text mining. By pre-training on vast amounts of text data extracted from millions of publications, LLM-based chat functions, such as Microsoft's BioGPT⁸⁴ and Insilico Medicine's ChatPandaGPT,⁸⁵ can connect diseases, genes, and biological processes, quickly identifying the biological mechanisms involved in disease progression and uncovering potential drug targets and biomarkers. Ensemble learning effectively enhances prediction accuracy and model stability and reduces the risk of overfitting. LLMs have strong generalization capabilities, transfer learning abilities, the potential to handle unstructured data, and the capacity to integrate interdisciplinary knowledge.⁸⁶ However, they also face challenges such as increased computational complexity, reduced model interpretability, the specificity of biological data, and concerns over data privacy and security.⁸⁷ The future applications of ensemble learning and LLMs in bioinformatics are highly promising, and with improvements in model architectures, the development of biology-specific datasets, and stronger interdisciplinary collaboration, these methods are expected to bring more groundbreaking advances to biological research.⁸⁸

As shown in Figure 2, the workflow of machine learning in clinical disease research spans from raw genetic data to model construction. In the data preprocessing stage, raw DNA sequences undergo quality control and sequence alignment to generate standardized data. Supervised learning algorithms (e.g., Random Forest/SVM) then process labeled clinical phenotype data, while unsupervised methods (e.g., UMAP) perform nonlinear dimensionality reduction on single-cell transcriptomic data. During the feature extraction phase, CNN employ local convolutional kernels to capture spatial motif features in gene sequences. RNN model temporal dependencies in

TCR β chain CDR3 sequences through inter-layer recurrent connections. The Transformer architecture, leveraging its cross-scale analytical capabilities, quantifies correlation weights across nucleotide positions in DNA sequences, effectively identifying RNA regulatory elements. This enables the construction of gene regulatory networks to discover novel biomarkers.

HOW MACHINE LEARNING HELPS DECIPHER THE MECHANISMS OF AIDS

Immune cell function research

Research on immune cell function is crucial for understanding the pathogenesis of AIDs. In recent years, ML has made significant advancements in bioinformatics and immunology, particularly in processing and analyzing high-dimensional immune system data. This has not only improved prediction accuracy but also provided new perspectives for understanding complex biological processes. Against this backdrop, the AI Virtual Cell (AIVC) project has emerged, aiming to integrate multimodal and multiscale biological data to construct an AI model that comprehensively simulates cellular behavior.⁸⁹

In the innovative applications of ML, the Immune Elastic Network (iEN) has enhanced prediction performance and model interpretability by integrating prior immunological knowledge into elastic network algorithms.⁹⁰ In the field of antigen presentation prediction, ML-based web servers such as NetMHCpan-4.1 and NetMHCIIpan-4.0, using the NNAlign MA framework, have significantly improved prediction accuracy by integrating various data.⁹¹ In DL, the AI-TAC model has provided new insights into immune cell differentiation. This model can predict chromatin accessibility patterns in different immune cell types based solely on DNA sequence information, rediscovering known transcription factor binding motifs and constructing hierarchical transcription factor networks driving immune cell lineage differentiation.⁹² In single-cell analysis, InfinityFlow, a high-throughput protein expression analysis method combining flow cytometry and ML, allows for the analysis of over 200 proteins at the single-cell level. Using this technology, researchers comprehensively analyzed CD8⁺ T cells from multiple organs, revealing extensive heterogeneity within TCIRCM cells and further subdividing them into distinct subpopulations.⁹³ In spatial proteomics data analysis, MAPS, a novel ML method, is specifically designed to analyze highly multiplexed protein imaging data generated by techniques such as MIBI and CODEX. Its excellent performance has been validated on multiple disease datasets.⁹⁴

In the study of immune cell developmental trajectories, various algorithms and tools have been developed for trajectory reconstruction and analysis, including the Monocle algorithm,⁹⁵ SLICER algorithm,⁹⁶ and Wishbone algorithm.⁹⁷ These tools play an important role in cell development trajectory reconstruction, pseudotime analysis, and branching point prediction. For example, Chen et al.⁹⁸ used trajectory analysis to study the origin of macrophages in IgA nephropathy (IgAN), finding that these macrophages likely originate from monocytes in the blood, which undergo differentiation into tissue-specific macrophages. Wu et al., using single-cell sequencing technology, conducted pseudotime trajectory and functional enrichment analysis of brain and spleen tissues from a neuropsychiatric RA (NPSLE) mouse model, revealing a significant association between double-negative T cells (DNT) and cell senescence and dysfunction, clarifying DNT's role in T-cell developmental trajectories, and identifying DNT as a key point in the transition of T cells to an exhausted state during disease inflammation.⁹⁹ Zhao et al., through trajectory analysis, revealed the dynamic differentiation process and functional state changes of immune cells in Bullous Pemphigoid (BP) and Pemphigus Vulgaris (PV) lesions. The study found that there is a continuous differentiation trajectory between CD4⁺ and CD8⁺ T cell subpopulations in the skin and peripheral blood, suggesting that T cells infiltrating the skin mainly originate from peripheral blood. Furthermore, classical monocytes (cM-1) in peripheral blood differentiate into macrophages (such as Resident Mac and ISGs Mac) at the lesion site, while cDC2 cells in the skin partly originate from peripheral blood cDCs and show a trend of differentiating into migratory dendritic cells (migDC).¹⁰⁰ These studies demonstrate the significant role of trajectory analysis in revealing immune cell development and functional state changes, offering new perspectives and methods for understanding immunopathological mechanisms.

In T cell research, researchers have explored T cell activation responses to different antigens by combining experimental data, ML, and mathematical

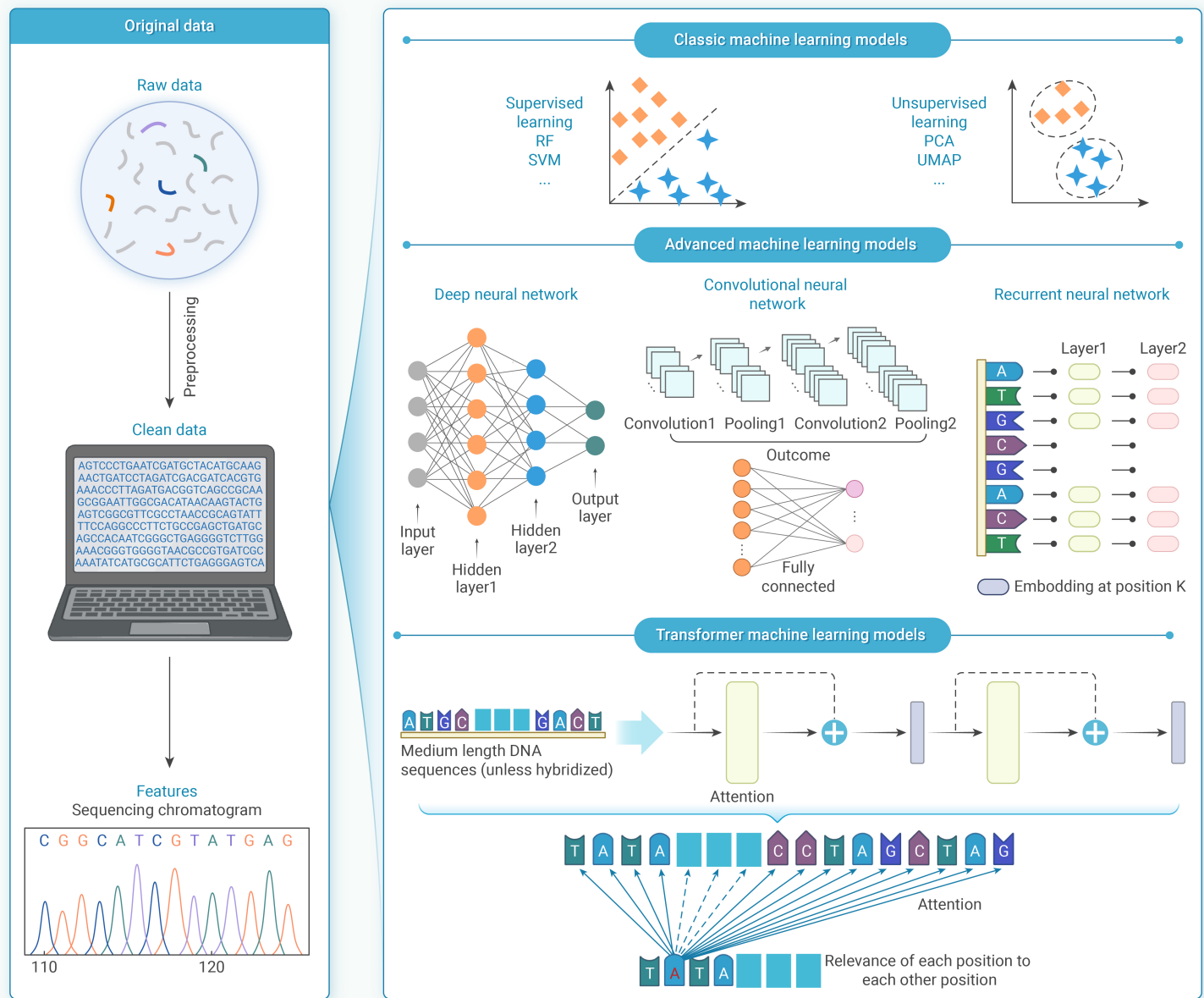


Figure 2. ML model architectures and data processing workflows.

modeling. When stimulated by antigens, T cells secrete various cytokines, forming complex high-dimensional data that traditional methods struggle to fully interpret. Using neural networks, researchers compressed this high-dimensional data into a 2D latent space, retaining antigen-specific information, and categorized T cell responses based on antigen sequences. Mathematical modeling showed that latent space trajectories could be fitted with a four-parameter ballistic equation, where the parameter v_0 correlates highly with antigen quality, offering a new metric for quantifying antigen quality. Based on this, researchers estimated that T cells could distinguish between six antigen categories, far exceeding the traditional three-class classification. This model has been validated in various immune environments, showcasing its broad application potential.¹⁰¹

In B cell research, researchers combined synthetic biology and DL to design and assemble 23,640 synthetic B cell-specific promoters, which exhibit a larger sequence space and B cell-specific expression. Through large-scale parallel reporter gene assays (MPRA), they decoded the sequence features that regulate promoter transcription and developed a DL model capable of directly predicting the transcriptional intensity of immunoglobulin V gene promoters from sequences.¹⁰² In the field of B cell epitope prediction, researchers developed a Python-based web tool, LBCEPred, which uses a RF classifier and statistical moment-based descriptors to predict B cell epitopes

from protein sequences. This tool outperformed existing sequence-based prediction models, achieving an accuracy of 0.868, an AUC of 0.934, and a 56.3% higher Matthews correlation coefficient on average.¹⁰³ These research achievements not only deepen our understanding of immune cell function and regulatory mechanisms but also provide new tools and methods for biomedical applications such as vaccine design and antibody production.

In CAR-T cell immunotherapy, research teams have optimized CAR-T cell design using protein language models (PLMs) in combination with high-throughput experimental platforms and preference optimization algorithms. Using the ProGen2 model, the team integrated greedy generation and exhaustive search strategies to significantly improve the activity of CAR sequences, with some optimized sequences showing more than a two-fold increase in activity. To enhance optimization efficiency, the team innovatively proposed the KTO loss function, balancing optimization efficiency with model generalization ability, and constructed a representative and effective preference dataset to ensure the learning effect. In experiments, the team used transfer learning and knowledge distillation methods to handle rare targets, demonstrating strong adaptability. These results show that this approach not only improves CAR-T cell design efficiency but also significantly reduces the cost of new drug development. In the future, combining single-cell sequencing and graph learning technologies, this approach is expected to extend to

other immune therapies, providing innovative ideas for the biomedical field and promoting the development of new treatment strategies.¹⁰⁴

Beyond T and B cells, in macrophage function research, researchers identified a feature pathway of 338 genes that accurately recognized the "reactive" and "tolerant" states of human macrophages under different conditions by analyzing over 12,500 datasets using ML algorithms.¹⁰⁵ This feature pathway successfully identified macrophage polarization states at a single-cell resolution and outperformed traditional features in disease state detection. The research team employed various ML techniques, including Boolean network models and logistic regression models, to construct and analyze macrophage gene expression networks. Boolean analysis using the StepMiner algorithm converted gene expression levels into binary values, providing a formal prediction framework for the precise diagnosis and treatment of macrophage-related conditions (<http://hegemon.ucsd.edu/SMaRT>).

Discovery and analysis of TCR and BCR

The interaction between T cell receptors (TCR), antigen peptides, and the major histocompatibility complex (MHC)/HLA plays a central role in the immune system's recognition and response. This complex interaction network—often referred to as the "TCR-peptide-HLA synapse"—is fundamental not only to normal immune responses but also to the development of AIDs. When the TCR-peptide-HLA synapse is aberrantly activated, self-reactive T cells may mistakenly recognize normal tissues, breaking immune tolerance and triggering or exacerbating autoimmune responses. TCRs are generated through the V(D)J recombination process, a somatic recombination mechanism that produces a highly diverse repertoire of TCRs through the combination of different gene segments and the addition or removal of nucleotides.^{106,107} TCR sequencing (TCR-Seq), in combination with experimental techniques and ML, has been widely applied to autoimmune disease research. For example, to gain deeper insights into the pathological processes driving Th17 cell expansion, Jiang et al.¹⁰⁸ combined TCR-Seq with flow cytometry to analyze changes in the TCR repertoire in a cell-type-specific manner. Their research showed a significant reduction in the diversity of effector memory T cells and Th17 cells in RA patients. In recent years, as ML and DL technologies have advanced, their application in TCR research has focused on two main areas: 1) constructing the characterization, classification, and functional prediction of TCR repertoires; and 2) inferring and predicting the interactions between TCR peptide segments and HLA with high precision.

This figure illustrates the key processes involved in TCR-mediated immune responses, highlighting T cell co-stimulation, the TCR-CD3 complex, TCR repertoire sequencing, integrated assessment of TCR and cell phenotypes, multi-omics integration, and computational analysis. T cell co-stimulation is mediated by the interaction between CD28 on T cells and CD80/CD86 molecules on antigen-presenting cells (APCs), providing essential signals for T cell activation. The TCR interacts with CD3 molecules to recognize antigen peptides presented by MHC molecules. High-throughput sequencing technologies are employed to analyze TCR V(D)J rearrangement patterns, CDR3 length, and diversity, enabling comparative analysis of TCR repertoires between patients and healthy individuals. Depending on the strength of the TCR signal, T cells may be activated, enter an anergic state, or undergo clonal deletion to maintain immune tolerance. Integrating TCR sequencing with chromatin accessibility measurements helps pinpoint antigen epitopes driving T cell responses. Advanced computational methods, such as ML, are used to investigate T cell clonality, phenotypic diversity, and developmental trajectories, uncovering immune patterns associated with diseases. This figure underscores the value of integrating TCR sequencing and cell phenotype analysis at the single-cell level, providing crucial insights into T cell differentiation pathways and the role of TCR sequences and specificity in T cell selection, activation, and phenotype determination.

TCR repertoire characterization. TCR Repertoire Characterization¹⁰⁹ has represented a significant step forward. It uses a combination of CNN and VAE to classify, cluster, and mine latent sequence patterns from high-throughput TCR sequencing data. This framework has also been successfully applied to identify clonotype sequences related to immune therapy responses.¹¹⁰ Additionally, the model developed by Davidsen et al., based on VAE, successfully extracted key features that govern TCR generation and its population

frequency.¹¹¹

Figure 3 outlines a computational framework for dissecting TCR signaling pathways, integrating experimental biology and computational models to unravel multi-layered regulatory mechanisms of immune responses. At the antigen recognition level, dendritic cells present self-antigen peptides (Stimulating self-antigen) via MHC molecules, alongside co-stimulatory signals from CD80/CD86 (T cell Co-Stimulation), to activate naïve T cells and initiate TCR-CD3-CD28 complex signaling. TCR repertoire sequencing (TCR repertoire sequencing), leveraging V(D)J recombination patterns and comparative CDR3 length diversity analysis between patients and healthy individuals (Compare TCR diversity between patients vs. healthy), systematically deciphers heterogeneity in TCR clonal expansion and its molecular links to organ-specific autoimmune diseases (Organ-specific autoimmunity). For dynamic tracking, combining TCR sequencing with chromatin accessibility profiling (TCR sequencing combined with measuring chromatin) elucidates epigenetic regulatory dynamics during T cell differentiation. Pseudotime trajectory reconstruction (Developmental trajectories during T cell responses) pinpoints critical transitions in naïve T cell differentiation into effector subsets (e.g., Th17) and validates lineage-specific gene expression signatures. A machine learning framework (Machine learning MAPPING) further integrates T cell clonality, phenotype (T cell clonality and phenotype), chromatin accessibility dynamics (Chromatin accessibility), and clinical disease patterns (Disease patterns) to model antigen-driven clonal selection. This establishes a multi-dimensional analytical system bridging TCR signaling mechanisms to clinical phenotypes, offering systematic computational insights for understanding and targeting autoimmune diseases.

TCR peptide-HLA interaction prediction. In the domain of predicting TCR peptide-HLA interactions, research has mainly followed two paths: one focusing on the prediction of known TCR-antigen bindings, and the other exploring unknown antigens or neoantigen peptide interactions. TCRex¹¹² is a representative tool in the first category, using ML models like RF to predict TCR-peptide-HLA interactions based on training datasets of TCR-antigen epitope information. This approach has been extended by tools like MixTCRpred,¹¹³ which allows α/β TCR pair prediction. Predicting TCR interactions with unknown antigens/neoantigen peptides, however, remains more challenging due to the difficulty in obtaining large training datasets that include the complex three-way interaction information of TCR, peptide, and HLA. Furthermore, the high degeneracy of TCR-peptide-HLA complexes adds to the analytical complexity.¹¹⁴ Lu et al. proposed pMTnet,¹¹⁵ an innovative breakthrough in TCR-pMHC binding specificity prediction through a three-stage transfer learning framework: First, a stacked autoencoder encodes TCR CDR3 β sequences into 30-dimensional numerical vectors while preserving their physicochemical attributes and spatial conformational features. Second, an LSTM network jointly encodes antigen peptide sequences and full-length MHC protein sequences (rather than relying solely on HLA typing information) to decipher MHC molecular structural regulation on epitope anchoring conformations. Finally, a differential training strategy constructs a dual-channel contrastive neural network, compelling the model to learn TCR-pMHC interaction patterns through positive-negative sample comparisons. This model overcomes traditional limitations of HLA type or epitope length restrictions, achieving an AUC of 0.827 on independent validation sets (over 20% improvement versus existing tools), and demonstrates the first global prediction capability across 128 HLA types and arbitrary epitope lengths. It should be noted that although pMTnet significantly expands HLA and epitope coverage through transfer learning, developing a truly universal model applicable to all MHC-I subtypes and complex epitope variants still requires integration of more comprehensive training data and three-dimensional structural features; a global model that can accommodate multiple HLA proteins and various epitopes has yet to emerge. To address these challenges, the combination of DL and transfer learning has gained attention. For example, TAPIR (TCR and Peptide Interaction Recognizer), developed by Vcreate, uses deep CNN to process multiple representations of TCR and target sequences, applying multitask learning to predict interactions,¹¹⁶ Pep2TCR,¹¹⁷ developed by Diao et al., applies transfer learning to transfer knowledge from CD8 models to CD4 models, enhancing prediction accuracy by combining LSTM and CNN network structures. Although current advancements have partially addressed these challenges, future efforts will likely yield more robust and universally

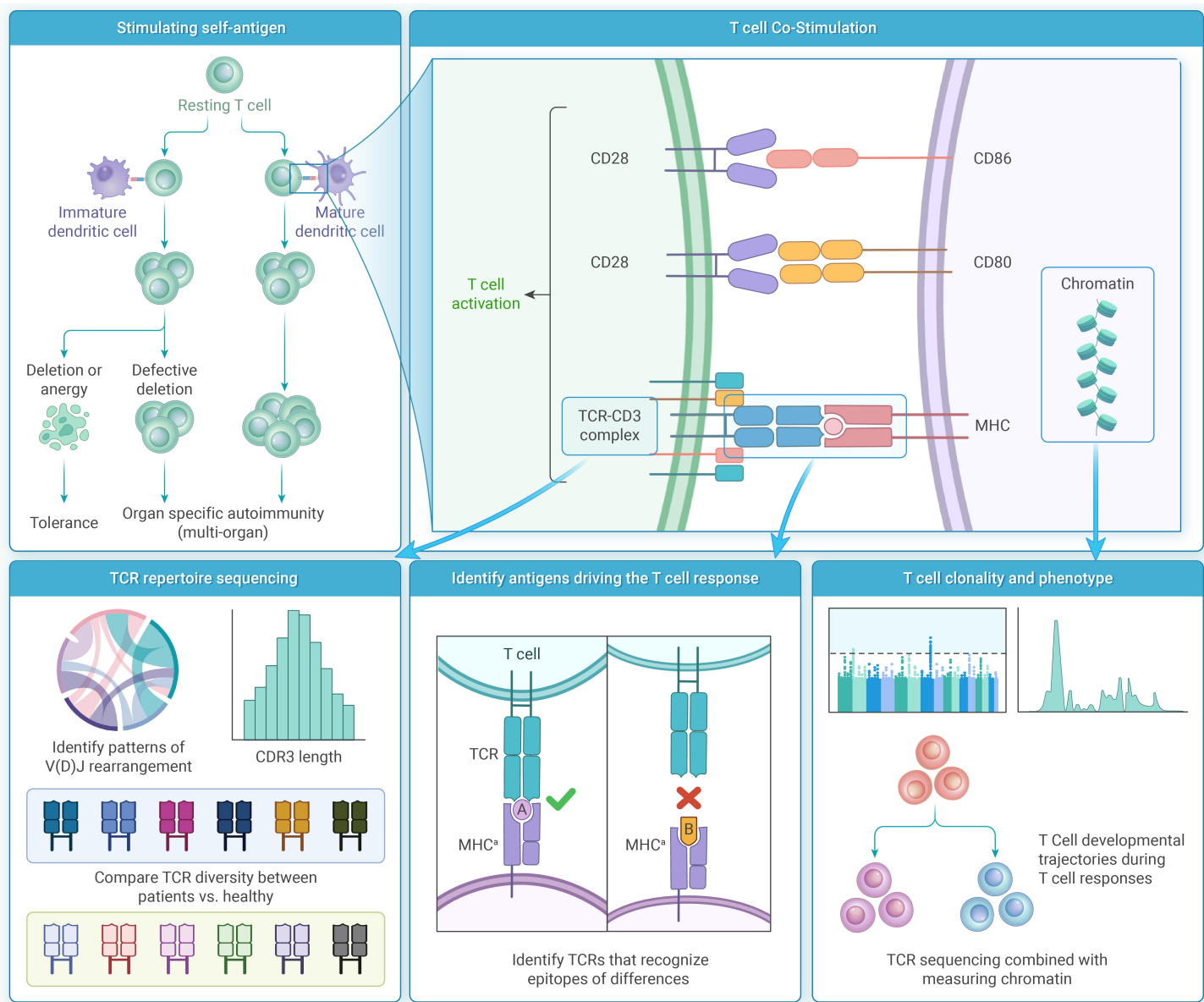


Figure 3. Schematic diagram of the mechanisms of TCR-mediated immune responses.

applicable models to fully unravel the intricacies of TCR-pMHC interactions.

DL for AIR-antigen binding prediction. DeepAIR, an innovative deep learning framework developed by Tencent AI Lab, achieves breakthrough performance through its core innovation of multimodal feature fusion. This framework integrates three critical data dimensions of adaptive immune receptors (AIRs, including TCRs and BCRs) - gene sequences, amino acid sequences, and AlphaFold2-predicted 3D structures - overcoming the limitations of conventional methods that rely solely on genetic sequences. The framework employs three specialized encoders: 1) A gene encoder deciphers V/D/J gene segment combinations to capture gene recombination patterns during receptor generation; 2) A Transformer-based sequence encoder extracts contextual semantics from amino acid sequences; 3) A novel structure encoder processes AlphaFold2-predicted 3D conformations, particularly converting spatial features of antigen-recognizing CDR3 loops (e.g., folding angles, surface charge distribution) into computable digital descriptors.

Two groundbreaking fusion technologies enable multidimensional integration: The gated attention mechanism dynamically weights sequence-structure feature contributions by identifying scenario-specific critical features, while the tensor fusion module mathematically combines gene, sequence, and structural features through higher-order interactions, precisely modeling the "sequence-structure-function" synergy during antigen binding. This

multidimensional integration empowers DeepAIR with unique capabilities - identifying conformation-sensitive binding sites missed by sequence-only methods and visualizing attention weights to pinpoint critical residues. Experimental validation demonstrates superior performance: Outperforming conventional sequence-based methods (DeepTCR, TCRAI, soNNia) in Pearson correlation coefficients for TCR/BCR binding affinity prediction, achieving higher AUCs in immune repertoire classification for nasopharyngeal carcinoma (NPC) and inflammatory bowel disease (IBD), and showing exceptional antigen-binding reactivity prediction accuracy.¹¹⁸

Widening applications in TCR and BCR sequence analysis. ML has demonstrated significant potential in broader TCR and BCR sequence analysis, enabling not only the assessment of receptor affinity to specific antigens but also the clustering of immune responses to identify "shared" receptor clonotypes, improving precision and scalability. To enhance the accuracy of TCR epitope predictions, researchers have evolved from simple amino acid pattern matching methods to modern DL-based systems. Platforms like IEDB (<https://www.iedb.org/>) and SysteMHC (<https://systemhc.sjtu.edu.cn/>) have developed multi-dimensional data resources and systematic benchmark evaluation systems. For example, the soNNia model uses deep generative selection models to characterize T and B cell receptor (BCR) repertoires, simulating nonlinear selection weights using a deep neural network. This

model categorizes sequence features into V/J gene usage, CDR3 length, and CDR3 amino acid composition, effectively reducing the number of parameters and balancing the contributions of each feature.¹¹⁹ On the other hand, the DeepImmuno framework combines CNN and GAN to predict peptide immunogenicity and generate immunogenic peptides, providing support for vaccine development and immunotherapy.¹²⁰

Latest advances in TCR epitope prediction and TCR-epitope interaction prediction. Recent breakthroughs in TCR epitope prediction have seen several DL models achieve remarkable results. TEINet, using transfer learning, predicts the specificity of TCR (CDR3 β) binding to antigen epitopes with high precision, requiring only the TCR and epitope sequences.¹²¹ The TRAP workflow, combining transfer learning and MHC binding information, accurately predicts CD8+ T cell epitopes.¹²² Moreover, the TCRmodel2 has been improved on the AlphaFold framework to model TCR-pMHC complexes at high resolution.¹²³

The AlphaEpi model, designed for B cell epitope prediction, has also emerged as an innovative solution to address the issues of sparse experimental validation and noisy structural data. AlphaEpi utilizes a dynamic selector module to adjust the priority between sequence and structural information, focusing on evolutionary information when structural prediction is uncertain. The model employs graph fusion to combine 3D protein structures with sequence evolutionary data, allowing for a precise match between structure and sequence data. AlphaEpi shows improved accuracy and robustness in complex environments, outperforming traditional methods and contributing breakthroughs to B cell epitope prediction and broader biomedical research.¹²⁴ In another major advancement, the TEIM-Res and TEIM-Seq models, developed by a research team at Tsinghua University, provide complementary solutions to predict TCR-epitope interactions and key binding sites at the amino acid level. The TEIM-Res model predicts the distances and contact points between residues, while the TEIM-Seq model uses sequence data to assess the likelihood of TCR-epitope binding. Combined, these models use high-throughput sequence data pretraining and residual network optimization to significantly enhance prediction accuracy and efficiency.¹²⁵

TEPCAM (TCR-Epitope recognition model), a deep learning framework developed by a research team at Shanghai Jiao Tong University, achieves precise prediction of TCR-antigen epitope binding specificity through synergistic integration of self-attention, cross-attention, and multi-channel convolutional mechanisms. Its core operation revolves around sequence interaction modeling and deep feature extraction. The model first standardizes TCR sequences using the IMGT numbering system, encoding the CDR3 β region of TCRs and epitope sequences (8-11 amino acids) into fixed-length embedding vectors with positional encoding to preserve sequential order information. These embedded sequences are then processed through self-attention layers, where multi-head mechanisms independently extract long-range residue-level dependencies within TCRs and epitopes, such as identifying critical conformational regions in CDR3 β (e.g., hypervariable segments in middle loops) or core anchoring residues in epitopes. Subsequently, the cross-attention layer dynamically aligns TCR and epitope sequences by constructing a bidirectional residue interaction matrix, using TCR as Query and epitope as Key-Value pairs. Through scaled dot-product attention calculations, this layer captures cross-sequence critical residue pairs (e.g., spatial proximity effects between TCR glycine and epitope tryptophan). The interaction matrix not only quantifies residue binding strengths but also enables local pattern mining through multi-channel convolutional layers. Different convolutional kernels extract multi-scale spatial features (e.g., hydrogen bonding or hydrophobic interaction patterns), with global and local features ultimately fused via fully connected layers to generate binding probabilities.

Three distinctive innovations define TEPCAM: 1) Cross-modal interaction modeling overcomes traditional single-sequence feature limitations by directly learning dynamic residue-level matching rules, achieving prediction AUCs of 0.677-0.952 on rigorously partitioned zero-shot TCR tasks and external datasets (ImmuneCODE), significantly outperforming models like TITAN and ATM-TCR. 2) Zero-shot generalization capability stems from cross-attention learning of universal residue interaction patterns rather than sequence similarity memorization. 3) Interpretability design quantifies residue contribution through attention matrices (e.g., in PDB 5EU6 case, the correla-

tion between epitope W5-TCR Y94/V95 attention weights and crystal structure distances), while adversarial pre-trained embedding analysis (random embeddings outperformed TCR-BERT) establishes a novel paradigm combining high accuracy with biological interpretability for immune mechanism elucidation and vaccine design.¹²⁶

These technological advancements have collectively propelled TCR and BCR research forward, providing a solid foundation for innovative and optimized immunotherapy strategies. By integrating AI and ML, from high-throughput sequencing analysis to precise epitope predictions, as well as the design of personalized immune therapies, these breakthroughs are reshaping the technological paradigms in vaccine development, immunotherapy, and autoimmune disease research.

The MHC/HLA system

The MHC encodes human leukocyte antigen (HLA) proteins, which are key molecules involved in antigen presentation within the immune system. The polymorphism of HLA genes is closely associated with the development of various AIDs, such as RA, AS, and type 1 diabetes (T1D).¹²⁷ Specifically, certain amino acid sequences within the HLA-DRB1 gene (such as "shared epitopes") are significantly correlated with RA susceptibility, with alleles like HLA-DRB104 and HLA-DRB101 being more common in RA patients. For SLE, alleles like HLA-DRB103 and HLA-DRB115 are linked to disease risk, while deletions in complement genes such as C4A and C4B play a significant role in the pathogenesis of SLE. In AS, the association with HLA-B27 is most pronounced, with individuals carrying HLA-B27 being 90 times more likely to develop AS than the general population. Additionally, specific haplotypes of HLA-DQ and HLA-DR genes, such as HLA-DQ2 and HLA-DQ8, are tightly associated with T1D susceptibility.¹²⁸ Due to the high polymorphism of HLA genes, individuals can express up to six different classical class I HLA alleles, each with a distinct peptide-binding preference. This complexity makes the analysis of immunopeptidomics data particularly challenging. However, the development of ML technologies provides new pathways to tackle this issue.

ML approaches in MHC/HLA analysis. MHCpLogics,¹²⁹ an ML-based interactive tool, integrates various analytical and visualization methods, including hierarchical clustering, k-means clustering, PCA, and t-SNE. It also introduces a novel sequence scoring function, LFSE, for visualizing and clustering immunopeptidomics data. In addition, seq2HLA, a DL-based HLA genotyping tool, can accurately predict HLA genotypes from RNA-Seq and other sequencing data, providing expression level information. The core process involves preparing labeled data (DNA/RNA sequences and corresponding HLA genotypes), extracting features (such as one-hot or k-mer encoding), transforming sequences into numerical features for learning by RNN, and training models using ML frameworks like TensorFlow or PyTorch. This tool can detect HLA classes with 100% specificity and 93.5% sensitivity, offering high accuracy, generalizability, and rich output information. It simplifies the HLA genotyping analysis workflow and supports research in AIDs, cancer immunotherapy, and other areas.¹³⁰

Technical innovations for MHC/HLA analysis. The Prosit DL model,¹³¹ which analyzes over 300,000 non-tryptic peptides (including MHC I and II ligands as well as products from proteases AspN and LysN), has significantly improved the identification of HLA peptides. MHCflurry,¹³² an open-source software, employs a novel neural network architecture and peptide encoding scheme to predict allele-specific binding and the binding affinity between MHC class I proteins and their peptide ligands. Other tools like NetMHCpan (NetMHCpan-3.0) have enhanced the prediction of peptide binding to MHC class I molecules by integrating information from multiple receptor and peptide length datasets, achieving high accuracy in predicting peptide sequences that bind to MHC molecules. By training large-scale datasets of known antigen-MHC binding interactions, ML algorithms (such as neural networks, SVM, and DL models) can quickly predict the affinity of specific antigen peptides to MHC molecules. For example, NetMHC¹³³ uses DL methods to predict the binding capacity of antigen peptides to MHC I or MHC II molecules, helping to identify potential self-antigens that could trigger autoimmune responses.

In summary, the application of AI and ML technologies has shown great potential in the field of immunotherapy and in the prediction of peptide-MHC binding.¹³⁴ ML-based algorithms, by integrating multiple immune-related

Table 1. High-quality immune-related algorithms.

Application area	method	Purpose	GitHub address/ web servers	References
Immune cell function research	immune elastic network (IEN)	enhanced prediction performance and model interpretability by integrating prior immunological knowledge into elastic network algorithms.	https://github.com/Teculos/immunological-EN	90
	T cell activation research	used neural networks to compress high-dimensional cytokine data into a 2D latent space, enabling antigen-specific categorization of T cell responses.	NA	101
TCR and BCR discovery and analysis	B cell-specific promoter design	combined synthetic biology and DL to design 23,640 synthetic B cell-specific promoters, improving transcriptional intensity prediction.	NA	102
	TCR repertoire characterization	used CNN and VAE to classify and cluster TCR sequences, identifying clonotypes related to immune therapy responses.	https://github.com/sidhomj/DeepTCR https://github.com/sidhomj/DeepTCR_Cancer	109 110
	MixTCRpred	enabled α/β TCR pair prediction for TCR-peptide-HLA interactions.	https://github.com/GfellerLab/MixTCRpred	113
	pMTnet	Predicted binding of unknown peptides with TCRs in different HLA environments.	https://github.com/tianshilu/pMTnet	114
	DeepAIR	integrated sequence and structural features of adaptive immune receptors (AIR) for precise antigen-binding prediction, outperforming traditional methods.	https://github.com/TencentAILabHealthcare/DeepAIR ¹¹⁸	
	TRAP workflow	Combined transfer learning and MHC binding information to accurately predict CD8+ T cell epitopes.	https://github.com/ChloeHJ/TRAP	122
	TCRmodel2	improved TCR-pMHC complex modeling on the AlphaFold framework.	https://github.com/piercelab/tcrmodel2	123
	TEIM-Res and TEIM-Seq models	Provided complementary solutions for predicting TCR-epitope interactions and key binding sites at the amino acid level.	https://github.com/pengxingang/TEIM	125
MHC/HLA System Analysis	MHCflurry	used neural networks to predict allele-specific binding and peptide-MHC class I affinity.	https://github.com/openvax/mhcflurry	132

features, can enhance the accuracy of immunogenic peptide predictions. These technological advances are driving forward the development of new therapeutic strategies for AIDs, cancer, and other immune-related disorders. As AI continues to advance, it is expected to play a key role in the personalized treatment and design of vaccines, further revolutionizing the landscape of immunotherapy. ML has revolutionized our understanding of AIDs through advanced analysis of immune cell functions, TCR/BCR interactions, and MHC/HLA systems, enabling more accurate predictions and deeper insights into disease mechanisms (Table 1). These technological advances have led to breakthrough developments in immunotherapy, from improved prediction models to personalized treatment strategies, marking a new era in autoimmune disease research and treatment.

ML-ASSISTED DIAGNOSIS, CLASSIFICATION, AND PREDICTION OF CLINICAL OUTCOMES IN AIDs

In clinical practice for AIDs, the lack of clear disease-specific markers, along with the nonspecific clinical symptoms and the absence of definitive laboratory biomarkers or histological features, often makes diagnosis challenging.^{135,136} Furthermore, due to the long-term suffering that patients endure, the need for effective monitoring and management of chronic diseases, as well as predicting clinical outcomes, has become a growing concern among healthcare professionals. However, certain challenges arise due to the variation in standards across healthcare institutions, differences in patient involvement in their care, and significant variation in adherence to treatment regimens. As a result, some disease classification and outcome prediction methods have encountered difficulties. ML offers a flexible, trainable approach, aiming to understand the intricate interactions among various variables, minimize errors, and gradually generate more accurate results by continually refining models with new data. With its strengths in extracting and analyzing patients' statistical features, disease onset patterns, and integrating laboratory test and imaging results, ML has provided critical support in improving diagnostic accuracy for AIDs.¹³⁷

RA

RA is a systemic autoimmune disease associated with chronic inflammation that can lead to joint and extra-articular organ damage.¹ Although genetic, autoimmune, and environmental factors all play crucial roles in the pathogenesis of RA, the exact mechanisms are not fully understood.¹³⁸ The advancement of ML techniques offers new insights into the diagnosis, classification, and prediction of RA, providing innovative solutions to longstanding challenges.

ML in RA diagnosis and classification. Early studies in RA diagnosis demonstrated that ML methods could identify key variables by comparing the disease/non-disease relative frequency for secondary care diagnoses and use ML for prediction.¹³⁹ ML was validated in large database studies. For example, Chin et al. used data from 1,007 RA patients and 921,192 controls, demonstrating its potential in disease risk assessment.¹⁴⁰ Maarseveen et al. applied various ML algorithms to extract RA patient records from electronic health records (EHRs) with high accuracy, achieving a positive predictive value of 0.94.¹⁴¹⁻¹⁴²

Key serological indicators for RA diagnosis, according to the 2010 ACR (American College of Rheumatology) and EULAR (European League Against Rheumatism) diagnostic criteria, include anti-citrullinated protein antibodies (ACPAs), rheumatoid factor, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).^{143,144} Several studies have used ML techniques to identify novel RA biomarkers. For instance, Hu et al. successfully identified 24 biomarkers through mass spectrometry analysis, particularly noting that ORM1 showed significant differences in the sera of RA patients.¹⁴⁵ Yeo et al. used ML to analyze cytokine expression in synovial biopsies, identifying CXCL4 and CXCL7 as early disease markers.¹⁴⁶ Liu et al. utilized a RF model to determine 9 mRNAs as potential RA predictors.¹⁴⁷ Additionally, Rychkov and Sirota identified 6 RA gene biomarkers through gene expression data from whole blood and synovial tissue.¹⁴⁸ Yu et al. identified LSP1, GNLY, and MEOX2 as diagnostic biomarkers.¹⁴⁹ Chen et al. identified FADD, CXCL2, and CXCL8 through LASSO regression and SVM analysis.¹⁵⁰

Genetic factors also play a critical role in RA, with high disease prevalence observed in family members, particularly in first-degree relatives, indicating a strong genetic contribution to RA development.¹⁵¹ Dana E Orange et al. improved histological scoring of RA synovial tissue by training on gene expression data and using ML. Their clustering revealed three distinct synovial subtypes: a high-inflammation subtype characterized by extensive leukocyte infiltration, a low-inflammation subtype enriched with pathways such as transforming growth factor- β , glycoproteins, and neuronal genes, and a mixed subtype. Different synovial subtypes may have different mechanisms of pain in RA patients.¹⁵² Ashley J W Lim et al. utilized a ML-optimized polygenic risk score to enhance genetic prediction models, identifying features of 9 single nucleotide polymorphisms (SNPs). These features not only predicted RA in the training dataset but also demonstrated excellent predictive performance (average AUC > 0.99; average sensitivity > 0.96, average specificity > 0.95, average accuracy > 0.96, and average precision > 0.96).¹⁵³

Imaging diagnostics. In imaging diagnostics, X-ray has traditionally been used to study bone lesions, while MRI shows greater sensitivity in detecting synovitis, tenosynovitis, osteitis, and cartilage damage.^{154,155} Miyama et al. developed a deep neural network-based system for automatic bone damage assessment using hand X-ray images.¹⁵⁶ Ahalya et al.'s CNN model achieved 95% sensitivity and 94% specificity in detecting RA joint damage.¹⁵⁷ Kemal Üreten used CNN to analyze hand X-rays for RA detection, demonstrating excellent performance in terms of accuracy, error rate, sensitivity, specificity, and precision.¹⁵⁸ Hongyang Li et al. used ML to analyze joint images, accurately quantifying joint damage levels. In the recent DREAM RA Challenge, their model ranked first in joint space narrowing scoring.¹⁵⁹ Young Bin Joo and colleagues conducted a genome-wide association study (GWAS) using SNP data from 374 Korean RA patients, identifying genetic markers associated with severe imaging outcomes.¹⁶⁰ Notably, the successful application of explainable model techniques (GradCAM) in medical imaging,¹⁶¹ as demonstrated by frameworks like DGXINet for brain tumor diagnosis, underscores their potential in autoimmune disease imaging analysis. For example, heatmap visualization of joint inflammation regions could enhance the credibility of clinical decision-making.

Disease activity monitoring. ML plays an essential role in monitoring disease activity. For instance, the ActConnect study used ML to analyze physical activity data, achieving 96% average sensitivity and 97% average specificity in predicting disease flares.¹⁶² Norgeot et al. and Kalweit et al. developed longitudinal DL models using structured EHR data from 820 RA patients to predict disease activity. The results showed that accurate models could be constructed using EHR data to predict complex disease outcomes, and such models could be generalized across different patient populations in hospitals.^{163,164} Alison K. Spencer and colleagues developed a ML framework to assess the clinical disease activity index (CDAI) score, achieving a positive predictive value (PPV) of 0.80, a negative predictive value (NPV) of 0.84, and an area under the curve (AUC) of 0.88.¹⁶⁵ Additionally, a study involving 210 RA patients used ultrasound and blood tests to predict disease flares with significant success, achieving an AUC of 0.747.¹⁶⁶

Extra-articular manifestations and comorbidities. ML also plays a vital role in recognizing extra-articular manifestations of RA, such as cardiovascular risk, joint damage, fatigue, and interstitial lung disease (ILD). Ceccarelli et al. used ML to identify anti-dsDNA antibodies, complement C4, and disease activity indices as important predictors of early erosive arthritis.¹⁶⁷ Other studies by England et al.,¹⁶⁸ Konstantonis et al.,¹⁶⁹ Liu et al.,¹⁷⁰ Goñi et al.,¹⁷¹ and Qin et al.¹⁷² have also made significant advancements in this area. Daniel H. Solomon analyzed patient data from the CorEvitas registry and assessed the presence of 24 comorbidities using ML, clustering patients with similar comorbid conditions, and revealing similar clinical outcomes across these clusters.⁵⁹

ML has significantly advanced the diagnosis, monitoring, and prediction of RA, providing tools for better early detection, risk prediction, and personalized treatment. From identifying new biomarkers and genetic markers to optimizing imaging analysis and disease activity monitoring, ML techniques are reshaping the landscape of RA care and offering new possibilities for improved patient outcomes (Table 2).

SLE

SLE is a complex systemic autoimmune disease characterized by the abnormal activation of the immune system and loss of tolerance to self-antigens.¹⁷³ The diagnosis of SLE primarily relies on the 2019 EULAR/ACR classification criteria, which require a positive antinuclear antibody (ANA) as a necessary condition, along with evidence of systemic, hematologic, neuropsychiatric, and skin/mucosal involvement.¹⁷⁴ In recent years, ML techniques have shown significant potential in the diagnosis, organ damage assessment, and prediction of clinical outcomes for SLE patients (Table 3).

ML in SLE diagnosis. Several ML approaches have been employed to improve SLE diagnosis and classification. For example, Wu et al. developed a CNN-based mobile application that can accurately identify cutaneous lupus erythematosus (CLE), with sensitivity and specificity of 92.1% and 93.8%, respectively.¹⁷⁵ Furthermore, Turner et al. developed a text analysis model based on Word2Vec to automatically identify SLE phenotypes from clinical notes in electronic health records, achieving an F1 score of 0.943.¹⁷⁶ Murray et al. used "noise labeling" technology to create a flexible SLE identification model with 95% sensitivity and 90% specificity on a validation set.¹⁷⁷

Huang et al. used decision tree models to analyze serum proteomics and created a diagnostic model that included seven protein biomarkers, achieving an accuracy of 89.2%.¹⁷⁸ Sasaki et al. used mass spectrometry and multiplex plate assays to analyze frozen peripheral blood mononuclear cells from early and diagnosed SLE patients, using ML to identify unique cellular populations.¹⁷⁹

Chunjiang Liu et al. performed bioinformatics analysis and ML to identify five key genes (SPI1, MMP9, C1QA, CX3CR1, and MND4), establishing an efficient prognostic model for SLE.¹⁸⁰ Li et al. integrated proteomics with scRNA-seq technology to identify critical biomarkers, such as CD38, GZMB, and TNFSF13B, which could not only accurately diagnose SLE but also predict disease flares.¹⁸¹ Additionally, a longitudinal study based on the SLICC cohort of 805 SLE patients identified specific clusters associated with disease activity, organ involvement, treatment needs, and mortality risk.¹⁸²

ML in assessing lupus-associated risks. ML techniques have also shown tremendous potential in assessing organ-specific damage in SLE, particularly lupus nephritis, which affects over 50% of SLE patients.¹⁸³ About 20-40% of SLE patients may develop renal involvement.¹⁸⁴ Isabelle Ayoub et al. developed a ML model combining 13 novel urinary protein biomarkers with traditional clinical data to assess glomerular filtration rate (GFR) in lupus nephritis.¹⁸⁵ Another study using quantitative protein microarray screening found V-set immunoglobulin domain-containing protein 4 (VSI4G) to be a promising diagnostic marker for lupus nephritis, with its serum levels correlating positively with SLE Disease Activity Index (SLEDAI) scores and other clinical parameters.¹⁸⁶

Chen et al. used the XGBoost model to successfully predict the risk of renal flare, achieving an AUC of 0.83.¹⁸⁷ Tang et al. developed a DL model to predict the WHO classification of lupus nephritis based on clinical indicators, with an accuracy of 88.79%.¹⁸⁸ Yang et al. created a glomerular detection model that demonstrated excellent performance in histopathological assessments with an accuracy of 96.7%.¹⁸⁹ In neuropsychiatric lupus (NPSLE), Gu et al. used natural language processing and ML to identify significant associations between CD4+ T cell subsets and anxiety symptoms in NPSLE patients.¹⁹⁰ Rumetshofer et al. developed an unsupervised learning model based on MRI imaging to successfully identify white matter hyperintensity patterns associated with NPSLE.¹⁹¹

For lupus patients who are pregnant, Fazzari et al. developed a model based on data from the PROMISSE study, showing that antihypertensive drug use, thrombocytopenia, and disease activity are important predictors of adverse pregnancy outcomes.¹⁹²

Additionally, autoimmunity is a key factor in accelerating atherosclerosis in SLE patients.¹⁹³ Recent research using unsupervised hierarchical clustering methods has identified three distinct groups of adolescent SLE patients with different atherosclerosis progression trajectories based on baseline carotid intima-media thickness.¹⁹⁴ In the context of SLE-associated antiphospholipid syndrome, Nikolopoulos et al. highlighted the distinct immune features of venous and arterial thrombotic events.¹⁹⁵

ML in hospitalization risk and disease activity prediction. About 10% of SLE patients are hospitalized annually due to infection or disease reactivation.

Table 2. ML in RA diagnosis and classification.

Application area	Method	Key findings	references
Diagnosis and classification	RF	identified 8 predictors related to diagnostic codes for RA	139
	SVM	data from 1,007 RA patients validated the potential of ML in disease risk assessment.	140
	8 different ML methods	high accuracy in extracting RA patient records, achieving a positive predictive value.	141 142
	RF	ORM1 significantly altered in RA sera	145
	Generalized Matrix Relevance Learning Vector Quantization	identified CXCL4 and CXCL7 as early disease markers.	146
	RF	9 mRNAs were identified as potential predictors of RA.	147
	RF	identified 6 RA gene biomarkers from whole blood and synovial tissue.	148
	LASSO & SVM & RF	LSP1, GNLY, and MEOX2 were identified as diagnostic biomarkers for RA.	149
Imaging diagnostics	LASSO & SVM	FADD, CXCL2, and CXCL8 were identified as RA biomarkers.	150
	a deep neural network-based system	used hand X-ray images for automatic bone damage assessment.	156
	CNN	achieved 95% sensitivity and 94% specificity in detecting RA joint damage.	157
	CNN	demonstrated excellent performance in accuracy, error rate, sensitivity, specificity, and precision.	158
	CNN	an AI approach for automatic scoring joint space narrowing and bone erosion.	159
	SVM	identified genetic markers associated with severe imaging outcomes using SNP data from 374 RA patients.	160
	multiclass Bayesian methods	achieved 96% average sensitivity and 97% average specificity in predicting disease flares.	162
	longitudinal DL models	EHR-derived models predict disease outcomes with cross-population generalizability.	163 164
Disease activity monitoring	a ML framework to assess CDAI scores	achieved a PPV of 0.80, NPV of 0.84, and AUC of 0.88.	165
	RF & XGBoost	achieved an AUC of 0.747 in predicting disease flares.	166
	Decision Trees	identified anti-dsDNA antibodies, complement C4, and disease activity indices as important predictors of early erosive arthritis.	167
	5 different ML methods	Patient clusters based on comorbidities demonstrated similar clinical outcomes.	59
Extra-Articular manifestations and comorbidities			

tion.¹⁹⁶ Reddy et al. developed a RNN-long short-term memory (RNN-LSTM) model, which showed the best performance with an AUC of 0.70 in predicting hospitalization risk.¹⁹⁷ Zhao et al. further validated this result and recommended setting a monitoring period between 6 to 24 months.¹⁹⁸

Jorge et al. used RF analysis to identify key predictors for hospitalization, such as positive anti-dsDNA antibodies, C3 levels, blood cell counts, and albumin.¹⁹⁹ Additionally, ML models developed by Leuchten et al. integrated clinical symptoms, laboratory results, and treatment information to accurately predict short-term disease activity changes in SLE patients.²⁰⁰ Ceccarelli et al. created a neural network model for predicting chronic damage in SLE patients.²⁰¹ Kegerreis et al. used gene expression data to build a predictive ML model for the SLEDAI.²⁰² Alves et al. also developed a regression-based tool for quickly estimating SLEDAI categories.²⁰³

Sjögren's syndrome

Primary Sjögren's syndrome (pSS) is a chronic autoimmune disease primarily characterized by impaired function of exocrine glands, particularly the salivary and lacrimal glands, leading to symptoms such as xerostomia (dry mouth) and keratoconjunctivitis sicca (dry eyes). In recent years, AI and ML technologies have made significant progress in the diagnosis, classification, and personalized treatment of pSS (Table 4).

ML in pSS diagnosis. One of the challenges in diagnosing pSS is the absence of specific antibodies, such as Ro/SS-A and La/SS-B, in a subset of patients. Sherri Longobardi and colleagues conducted a study based on plasma proteomics array and ML techniques to identify 30 new biomarkers for pSS. The study demonstrated that these biomarkers had an area under the receiver operating characteristic curve (ROC) of 0.79 (95% CI: 0.64–0.93), significantly improving the identification of Ro-seronegative pSS patients.

This discovery holds promise for the precise diagnosis of nearly half of Ro-seronegative pSS patients.²⁰⁴

ML in imaging diagnosis. Salivary gland ultrasound (SGUS) is a non-invasive diagnostic tool widely used for repeated screening and longitudinal monitoring of pSS patients. However, its reliability and standardized diagnostic patterns still need improvement.²⁰⁵ To address this issue, Vukicevic et al. employed a DL framework based on FCN-DenseNet to enhance the reliability of SGUS in pSS diagnosis. Their model showed superior performance in salivary gland segmentation compared to human observers.²⁰⁶

Molecular classification of pSS. Perrine Soret proposed an innovative molecular classification framework involving comprehensive analysis of over 300 patients' whole blood samples, incorporating a large cohort of age- and sex-matched healthy controls. Using multi-dimensional molecular data, including transcriptomics, genomics, epigenetics, cytokine expression profiles, and flow cytometry, the researchers applied ML algorithms to classify patients into four distinct groups with different immune dysregulation patterns. This detailed classification approach facilitates prospective patient stratification and aids in accurately assessing treatment responses in clinical trials.²⁰⁷ Further research has differentiated three major patient clusters based on different mechanisms, including type I IFN, IFN + B cell activation, or widespread inflammatory mechanisms, as well as a subgroup with normal biological features. This refined molecular classification approach is expected to provide clearer guidance for personalized therapies. Meanwhile, Wenjie Zen and colleagues developed the "Florida Scoring System," a ML-based algorithm framework from the University of Florida, aimed at classifying and longitudinally monitoring pediatric patients with suspected Sjögren's syndrome. This system cleverly categorizes patients into three distinct classes: Class I, Class II, and Class III. This precise patient stratification

Table 3. ML in SLE diagnosis and classification.

Application area	Method	Key findings	References
SLE diagnosis	CNN	accurately identified cutaneous lupus erythematosus with 92.1% sensitivity and 93.8% specificity.	¹⁷⁵
	a machine learning algorithm called decision boosting	created a diagnostic model with seven protein biomarkers, achieving 89.2% accuracy.	¹⁷⁸
	SVM	established an efficient prognostic model for SLE.	¹⁸⁰
	RF	identified critical biomarkers (CD38, GZMB, TNFSF13B) for accurate SLE diagnosis and flare prediction.	¹⁸¹
	PCA & K-means	identified clusters linked to disease activity, organ involvement, treatment needs, and mortality.	¹⁸²
	tSNE	revealed distinct cellular populations in early vs. diagnosed SLE.	¹⁷⁹
	Word2Vec-based text analysis model	automatically identified SLE phenotypes from clinical notes in EHRs with an F1 score of 0.943.	¹⁷⁶
	Ensemble Learning model	noise-labeling achieved 95% sensitivity/90% specificity for SLE identification.	¹⁷⁷
Lupus-Associated Risk Assessment	SVM & RF & ANN	assessed glomerular filtration rate in lupus nephritis patients.	¹⁸⁵
	RF	protein microarray identified VSIG4 as a novel LN biomarker, with serum levels correlating to SLEDAI and clinical activity	¹⁸⁶
	XGBoost	predicted renal flare risk (AUC 0.83).	¹⁸⁷
	RF & Multiple Linear Regression	ML model to predict WHO classification of LN achieved 88.79% accuracy.	¹⁸⁸
	a CNN glomerular detection model	demonstrated excellent performance in histopathological assessments with 96.7% accuracy.	¹⁸⁹
	NLP and 4 different ML models	CD4+ T cell subset analysis in NPSLE revealed significant associations with anxiety symptoms.	¹⁹⁰
	an unsupervised learning model based on MRI imaging	identified white matter hyperintensity patterns associated with NPSLE.	¹⁹¹
	7 different ML models	identified antihypertensive drug use, thrombocytopenia, and disease activity as important predictors of adverse pregnancy outcomes.	¹⁹²
Hospitalization risk and disease activity prediction	Unsupervised hierarchical clustering analysis	3 distinct atherosclerosis progression trajectories were identified using baseline carotid intima-media thickness.	¹⁹⁴
	an RNN-LSTM model	achieved good performance in predicting hospitalization risk with an AUC of 0.70.	¹⁹⁷
	an RNN-LSTM model	recommended a monitoring period of 6 to 24 months.	¹⁹⁸
	RF	identified predictors such as positive anti-dsDNA antibodies, C3 levels, blood cell counts, and albumin.	¹⁹⁹
	Meta-regression analysis	accurately predicted short-term disease activity changes in SLE patients.	²⁰⁰
	a neural network model	predicted chronic damage in SLE patients.	²⁰¹
	RF & KNN	successfully predicted SLEDAI scores.	²⁰²
	a regression-based tool	provided rapid estimation of SLEDAI categories.	²⁰³

Table 4. ML in pSS diagnosis and classification.

Application area	Method	Key findings	References
pSS Diagnosis	RF	identified 30 new biomarkers for pSS with an AUC of 0.79.	²⁰⁴
Imaging diagnostics	a DL framework based on fully convolutional "DenseNets" network	improved the reliability of salivary gland ultrasound for pSS diagnosis.	²⁰⁶
Molecular classification	k-means	classified patients into four groups with distinct immune dysregulation.	²⁰⁷
	7 different ML methods	classified pediatric patients with suspected Sjögren's syndrome into three classes.	²⁰⁸
	developed a model to predict lymphoma risk in Sjögren's syndrome patients	provided a tool for early identification of high-risk patients.	²⁰⁹

method has profound implications for improving clinical management strategies, optimizing trial designs, and advancing pathobiological research.²⁰⁸

Additionally, Bunya and colleagues developed a model for predicting the risk of lymphoma development in Sjögren's syndrome patients. This model considers factors such as salivary gland enlargement, low complement levels, and monoclonal gammopathy, providing a tool for the early identification of high-risk patients.²⁰⁹

In summary, AI and ML technologies are significantly advancing research

in Sjögren's syndrome. From the discovery of new biomarkers and the optimization of imaging diagnostics to molecular classification and personalized treatment strategies, these innovations provide reliable tools and precise strategies for the future of pSS diagnosis and management.

SSc

SSc, also known as scleroderma, is a complex autoimmune disease with an unclear etiology. It is characterized by vascular abnormalities, immune

Table 5. ML in SSc diagnosis and classification.

Application area	Method	Key findings	References
Genomic and transcriptomic advances	Supervised and unsupervised ML	classified SSc patients into intrinsic subgroups based on gene expression patterns.	213
	SVM & RF	identified three patient subgroups (inflammation, fibroproliferation, normal patterns).	214
	Supervised and unsupervised ML	identified two major transcriptomic features (keratin and fibroinflammation).	215
	LASSO	identified predictive biomarkers and linked KRT6A and S100A8 expression to skin disease severity.	216
ML for classification and prognosis	a DL-based method for chest CT analysis	outperformed traditional visual scoring in assessing ILD morphological and functional deterioration.	217
	SVM & RF & LASSO	identified three distinct gene clusters, with Cluster B showing B-cell enrichment and Cluster C showing monocyte enrichment.	218
Advanced multi-omics and ML	CIBERSORTx	identified pro-fibrotic and pro-inflammatory fibroblast characteristics and classified SSc patients into progressive and stable subgroups.	219
	RF	identified eight proteins for early detection of PAH risk in SSc patients.	220
	10 ML classifiers	identified metabolites associated with skin fibrosis and ILD, highlighting the importance of targeted metabolic dysregulation in SSc diagnosis and treatment.	221
	SVM	identified disrupted metabolites and pathways linked to disease progression and histological markers, providing insights into disease mechanisms.	222

system activation, and fibroblast overproliferation leading to tissue fibrosis. SSc can affect the skin and multiple internal organs, such as the lungs, gastrointestinal tract, heart, and kidneys.²¹⁰ Common manifestations include skin thickening and hardening, Raynaud's phenomenon, pulmonary arterial hypertension (PAH), and ILD.²¹¹

Due to the disease's high heterogeneity and multi-organ involvement, early diagnosis and treatment are challenging. With the increasing use of omics technologies and AI in clinical research and practice, there has been a significant advancement in SSc research, particularly in genomics, transcriptomics, metabolomics, proteomics, and imaging (Table 5). These technologies, combined with ML algorithms such as DL, SVM, RF, and logistic regression, are enabling more accurate classification and disease progression predictions.²¹²

Genomic and transcriptomic advances in SSc. Recent studies have shown that SSc patients exhibit significant changes in gene expression compared to healthy controls, particularly in skin tissues and peripheral blood cells. The objective analysis of SSc molecular patterns has become a powerful tool for classifying patients with similar clinical phenotypes and predicting treatment responses. Milano et al. first used DNA microarrays and unsupervised ML to classify SSc patients into intrinsic subgroups.²¹³ Franks et al. assessed three differentially expressed gene (DEG) research cohorts, identifying three distinct patient subgroups with typical features of inflammation, fibroproliferation, and normal patterns. The study showed that GLMnet outperformed other ML algorithms in terms of accuracy and sensitivity.²¹⁴ Assassi et al. and Swindell WR's teams analyzed skin biopsies, revealing 2,754 differentially expressed transcripts and linking higher keratin scores to shorter disease duration and elevated fibro-inflammation scores to diffuse skin involvement. Significant heterogeneity was observed in transcriptomic profiles, suggesting that keratin activation plays a crucial role in SSc pathogenesis.²¹⁵ Further scRNA-seq research identified predictive biomarkers of disease severity based on fibroblast and myeloid cell subgroups, such as SFRP2+ fibroblasts and monocytes. These findings were corroborated by gene expression and protein levels of KRT6A and S100A8 in keratinocytes, showing a close relationship to skin disease severity, laying the groundwork for more precise treatment approaches.²¹⁶

ML for classification and prognosis in SSc. ML has also been applied to imaging and molecular classification in SSc. Guillaume Chassagnon et al. developed a DL-based method to analyze chest CT scans for ILD in SSc patients. Their model outperformed traditional visual scoring in assessing morphological and functional deterioration of ILD.²¹⁷ Qi Wang et al. used ML algorithms to identify three distinct gene clusters (gene_ClusterA-C) in SSc. Cluster B was marked by significant B-cell enrichment and moderate activation of various immune cells, while Cluster C showed monocyte enrichment, helping to create a diagnostic model with clinical applications.²¹⁸

Advanced multi-omics and ML in systemic sclerosis. Research by Zhu et al. utilized scRNA-seq and multi-omics data to identify various pro-fibrotic and pro-inflammatory fibroblast characteristics, such as COMP+, COL11A1+, and CCL19+ fibroblasts. These fibroblasts were associated with the clinical severity of skin fibrosis, allowing for the classification of SSc patients into progressive and stable subgroups based on skin fibrosis.²¹⁹ In the realm of proteomics and metabolomics, Yasmina Bauer et al. identified eight key proteins, including collagen IV, endostatin, IGFBP-2, and RAGE, that can be used for early detection of PAH risk in SSc patients, based on the DETECT study, which assessed the levels of 313 proteins.²²⁰ ML has been employed to analyze the serum metabolomic profiles of 326 human subjects and 33 murine models of SSc. This analysis identified disrupted metabolites and pathways associated with disease progression, specifically medicagenic acid 3-O-b-D-glucuronide, a metabolite with potential prognostic value for skin fibrosis. Additionally, histological and gene expression profiles have been linked to histological markers, such as alpha-smooth muscle actin (aSMA), CD34, and collagen, providing new insights into disease mechanisms and improving clinical outcomes.²²¹⁻²²²

ML and omics technologies are significantly enhancing the understanding of SSc. From genomic profiling and transcriptomic classification to proteomics and metabolomics, these tools are facilitating early diagnosis, identifying biomarkers for disease progression, and optimizing personalized treatment strategies for SSc. With continuous advancements in these areas, especially in computational approaches, the future holds promise for better patient stratification, prognosis, and treatment in SSc.

Other autoimmune and inflammatory diseases

ML has demonstrated significant potential in a variety of autoimmune and inflammatory diseases, including atopic dermatitis (AD), psoriasis (PsA), inflammatory myopathies (IIM), IgA nephropathy, primary immunodeficiencies (PIDD), antiphospholipid syndrome (APS), IgG4-related diseases, and AS. Below are some of the latest advances and their clinical implications.

Atopic dermatitis. An innovative study combined unsupervised clustering with the CIBERSORT algorithm to analyze gene expression data from skin samples of AD and psoriasis patients. This study identified three major keratinocyte transcriptional programs (KC1, KC2, and KC17), revealing the complex interactions of different inflammatory pathways in skin diseases. It also suggested that single-pathway treatments may be insufficient to fully correct the keratinocyte abnormalities in AD. Another Croatian study on AD patients (100 AD patients and 50 healthy controls) utilized multiplex immune assays of 21 cytokines and ML methods such as stability selection and elastic net to classify the data. The model achieved a 99% accuracy rate using just three cytokines from lesional skin and 76% accuracy using five cytokines from non-lesional skin. These findings underline the potential of ML in skin

disease biomarker research.²²³⁻²²⁴

Psoriatic arthritis. Patrick MT et al. developed a computational pipeline to predict the risk of psoriasis patients developing PsA, a chronic musculoskeletal disease occurring in approximately 30% of psoriasis cases. This study, based on data from over 7,000 patients across six cohorts, identified nine new genetic loci associated with psoriasis and its subtypes. A ML model integrating 200 genetic markers achieved an AUC of 0.82 for distinguishing PsA from psoriasis alone. This model demonstrated over 90% accuracy in the highest-risk 5% of patients, underscoring the genetic differences between psoriasis subtypes for personalized risk assessment.²²⁵

Inflammatory myopathies. In IIM, ML has been particularly effective in phenotype classification and prognosis prediction. A study involving 1,669 IIM patients (421 with anti-MDA5 positive dermatomyositis) found that peripheral lymphocyte count was a significant predictor of clinical features, such as skin ulcers and rapidly progressive interstitial lung disease (RP-ILD), and mortality. In patients with ILD and non-myopathic dermatomyositis (ADM), multi-color flow cytometry and ML methods identified two distinct immune phenotypes, with one associated with poor prognosis. Additionally, gene expression profiling and ML algorithms, such as SVM, achieved over 90% accuracy in classifying patients with inclusion body myositis or myositis-specific antibodies.²²⁶⁻²²⁸ Another study involving 103 IIM patients evaluated the effectiveness of various ML algorithms in predicting disease prognosis, with results indicating that the CART regression tree performed best in predicting MMT8 scores during follow-up.²²⁹ Overlap myositis (OM) is often associated with other connective tissue diseases (such as SSc, SLE, RA, SS, or MCTDs). Troyanov et al. developed a new classification system that incorporates these overlapping features, significantly improving the diagnostic rate and sensitivity for OM,²³⁰ further highlighting the importance of combining multiple factors and methods. These findings suggest that ML has unique advantages in the classification, prognosis, and personalized treatment of inflammatory myopathies.

Ankylosing spondylitis. Joo YB and colleagues used unsupervised ML to classify 412 axial spondyloarthritis (axSpA) patients, identifying three subgroups with distinct clinical features, including gender, smoking history, HLA-B27 status, and baseline mSASSS scores. These subgroups showed significant differences in radiological progression rates. In a separate study, Koo BS et al. used ML models to analyze 1,123 AS patients' clinical data, achieving a 73.7% accuracy in predicting radiographic progression, with baseline mSASSS scores, age, and alkaline phosphatase being key predictors.²³¹⁻²³²

Antiphospholipid syndrome. ML has been used to identify novel diagnostic biomarkers in APS. A study analyzing whole-blood RNA sequencing data from 62 APS patients identified 34 differentially expressed genes, with interferon regulatory genes showing significant upregulation and an accuracy of 82% in distinguishing APS patients from healthy controls.²³³ Zhang et al. used ML methods to study antiphospholipid syndrome (APS) combined with recurrent implantation failure (RIF). By analyzing differentially expressed genes (DEGs) and immune infiltration, they identified four candidate diagnostic genes: MARK2, CCDC71, GATA2, and KLRC3, and established a diagnostic nomogram.²³⁴ Verrou et al. applied ML to analyze whole blood transcriptome data and found that interferon-regulated genes (IRGs) were significantly upregulated in thrombotic primary APS patients. The model achieved 79% accuracy in distinguishing APS patients from healthy controls, and the accuracy improved to 82% when analyzing only the most informative IRGs.²³⁵

IgG4-related disease (IgG4-RD). IgG4-related disease, often known as a "mimicker" due to its symptom overlap with other conditions, has been another focus of ML research. In a study by Songxin Yan et al., a RF model was used to analyze plasma metabolomic data from healthy controls, pancreatic cancer (PC) patients, Sjogren's syndrome (SS), and IgG4-RD patients. The model successfully constructed a diagnostic tool based on five differential metabolites, providing a valuable approach for early diagnosis and prognosis.²³⁵⁻²³⁶

Others. Researchers utilized genome-wide DNA methylation data from 554 participants of the Osteoarthritis Biomarkers Consortium (OABC) to develop a ML prediction model based on peripheral blood DNA methylation for predicting the progression of knee OA.²³⁷ The study employed an elastic net regularized generalized logistic regression model as the core algorithm to

construct prediction models for future knee pain progression, radiographic progression, combined (pain + radiographic) progression, and any (pain, radiographic, or combined) progression. The research team first trained the models on the complete DNA methylation dataset and then used feature selection techniques to identify 13 CpG sites with the highest predictive value, creating a simplified model. These models demonstrated excellent performance in the OABC cohort, with accuracy ranging from 72% to 89% and an AUC between 0.79 and 0.97.

ML has also shown great potential in broader autoimmune disease diagnosis and screening. Iain S. Forrest and colleagues developed a model using longitudinal electronic health records to identify more patients requiring autoimmune antibody testing, uncovering a higher proportion of autoimmune antibody carriers compared to existing clinical standards. Other studies have focused on non-invasive predictive models for IgA nephropathy based on key indicators like serum albumin, IgA/C3 ratios, and urinary red blood cells, improving patient management.²³⁸⁻²³⁹ In a study on the early diagnosis of primary immunodeficiency diseases (PIDD), researchers analyzed the electronic health records of 247 PIDD patients and 6,175 asthma patients. They constructed an ML model incorporating pre-diagnosis comorbidities and laboratory test information. The model's c-statistic improved from 0.62 to 0.70, demonstrating the feasibility of early identification of PIDD.²⁴⁰

These studies collectively demonstrate the powerful role of ML in autoimmune and inflammatory diseases. By integrating molecular markers, immune cell features, and electronic health records, ML offers precise disease classification, early prediction, and identification of potential diagnostic and therapeutic targets. These advancements lay a strong foundation for personalized and precision medicine in the treatment and management of AIDs.

ML IN PREDICTING TREATMENT RESPONSE AND ASSISTING CLINICAL MEDICATION DECISIONS FOR AIDs

With the explosive growth of medical data and the rapid development of AI technology, ML is playing an increasingly important role in clinical decision support. Predicting patients' responses to drug treatments and assisting in clinical medication decisions is a key application of ML in healthcare. By analyzing large-scale clinical data, including patients' genomics, clinical phenotypes, and treatment outcomes, ML algorithms can help doctors more accurately predict an individual patient's drug response, thereby enabling more precise and personalized treatment plans. This not only improves treatment efficacy but also reduces the risk of adverse reactions and optimizes the use of medical resources.

RA

The response to MTX treatment. According to the latest EULAR recommendations, rheumatologists should initiate treatment for RA immediately after diagnosis, with methotrexate (MTX) as the primary treatment option, which can be combined with other medications.²⁴¹ Several studies have used ML to develop models predicting treatment responses. For example, Lim et al. integrated genetic and clinical data using ML to identify a feature set consisting of 56 pfsnPs and 5 non-genetic factors. Most of these pfsnPs are located in pathways related to the pathogenesis of RA or MTX's mechanism of action, and this feature set can robustly predict the response to MTX in RA.²⁴² In studies of juvenile idiopathic arthritis (JIA), ML techniques identified six distinct groups based on MTX response and achieved an accuracy of approximately 90% in distinguishing JIA patients from healthy controls using deep flow cytometry analysis.²⁴³ Artacho et al.²⁴⁴ constructed a microbiome-based model that confirmed the direct impact of the gut microbiota on MTX metabolism and treatment outcomes in newly diagnosed RA patients, which can independently predict the response to MTX treatment.

Selecting biologic therapies. In autoimmune disease treatment, selecting biologic therapies is a complex clinical decision-making process. In predicting treatment responses, van der Helm-van Mil's study¹⁴² demonstrated the efficacy of combining clinical and genetic features, achieving an AUC of 0.85 in independent validation. The R4RA clinical trial further showcased the practical utility of ML in predicting responses to rituximab (AUC = 0.74) and tocilizumab (AUC = 0.68). Regarding biological therapy, South Korean researchers used explainable AI (XAI) to create a model that could predict biological therapy responses and identify clinical features associated with a

high likelihood of remission. This study, involving 1,204 patients treated with various biologics (etanercept, adalimumab, golimumab, infliximab, abatacept, and tocilizumab), employed several ML models (LASSO, ridge, SVM, RF, and XGBoost), with accuracies ranging from 52.8% to 72.9%. Additionally, the authors were able to determine the most important features for predicting treatment responses: age for adalimumab, rheumatoid factor for etanercept, ESR for infliximab and golimumab, disease duration for abatacept, and CRP for tocilizumab.²⁴⁵ Venerito et al.²⁴⁶ applied various ML algorithms to predict disease activity scores in 367 RA patients, with XGBoost performing the best (accuracy 72.7%). In predicting TNF inhibitor treatment responses, multiple studies have shown promising results. For example, Miyoshi et al.²⁴⁷ developed a neural network model that achieved 92% accuracy, while Bouget et al.²⁴⁸ created a model predicting TNF inhibitor response based on clinical and biomolecular data. This model used DAS28 (Disease Activity Score 28), lymphocyte and neutrophil counts, ALT (aspartate aminotransferase), age, weight, and smoking as input data. The CatBoost model showed the best performance (AUROC = 0.72), with an average prediction error of 1.1 points for DAS28 variation. In the same year, Kim et al.²⁴⁹ developed an elastic net model with excellent performance. Furthermore, they found that four different polymorphisms of the resistin gene (rs1862513, rs3219178, rs3219177, and rs3745369) were associated with higher remission rates after TNF inhibitor treatment.

In a prospective multicenter integrated molecular and clinical longitudinal study, the serological changes of RA patients receiving TNF inhibitors were evaluated, and an algorithm was developed to estimate the response to biological therapy.²⁵⁰ The Luque-Tévar research group considered parameters such as inflammatory markers, oxidative stress biomarkers, and biological products derived from NETosis and miRNomas, combined with clinical and molecular parameters induced by biologic therapy. Through ML and integrating clinical and molecular profiles, new feature combinations were identified as potential predictors of TNF inhibitor treatment response. Prasad's TNF inhibitor response prediction model proved effective (accuracy 81%, sensitivity 75%, and specificity 86%), helping clinicians guide treatment by identifying non-responders and saving costs.²⁵¹ Tao et al. also used ML to predict treatment responses by studying gene expression and DNA methylation profiles of monocytes and CD4+ T cells in RA patients. The authors identified transcriptional and epigenetic features related to treatment responses, according to the EULAR standard²⁵² and built a random forest-based ML model to predict responses to TNF inhibitors (adalimumab and etanercept). These models had prediction accuracies of 85.9% for adalimumab and 79% for etanercept. Yoosuf et al., through multi-omics integration analysis, found that responders to TNF inhibitors had significantly higher EPPK1 gene expression, while the expression of T-cell suppressor CHI3L1 and its protein YKL-40 was suppressed post-treatment. Using ML, they developed a multi-omics-based predictive model.²⁵³

Given the evidence supporting the role of Toll-like receptors (TLR)-4 and TLR9 in RA development and TNF- α regulation,²⁵⁴⁻²⁵⁵ Kim and his team²⁵⁶ studied the association between TLR4 or TLR9 gene polymorphisms and disease remission in RA patients receiving TNF inhibitor treatment. They evaluated six single nucleotide polymorphisms and assessed their association with treatment responses using logistic regression analysis. The study confirmed that TLR9 polymorphism (rs352139) was associated with the response to TNF inhibitor treatment in RA patients. Johansson et al.²⁵⁷ used ML to analyze tocilizumab treatment outcomes from randomized controlled trials and applied this to real-world research, successfully developing a predictive score for monotherapy disease remission. The study also included patients receiving other biologic disease-modifying antirheumatic drug (bDMARDm) monotherapy to enhance predictions. In a recent study, Kalweit et al.²⁵⁸ used ML to identify RA patient subgroups with different responses to first-line biologics/tsDMARDs (targeted synthetic DMARDs), obtaining promising results. Male patients with low disease activity who received two or more conventional synthetic DMARDs (csDMARDs) and prednisone responded better to tocilizumab.

SLE

In the treatment of RA, the therapies used are often only partially effective. These challenges are primarily due to the molecular heterogeneity of the

disease. In this context, ML methods have provided groundbreaking solutions for the individualized treatment of SLE by analyzing complex patterns in patient data to predict treatment outcomes. Toro-Domínguez et al. developed the MyPROSLE tool, which quantifies the specific dysfunction of each patient through an M score and predicts impending disease activity or response to Tabalumab treatment.²⁵⁹ or Belimumab, a study collected blood samples from SLE patients receiving Belimumab treatment for 6 months, performed RNA sequencing, and used ML to build a predictive model for Belimumab response.²⁶⁰

Hong Kan et al.²⁶¹ used cluster analysis to systematically identify four-year treatment patterns and estimate the outcomes associated with the identified treatment patterns. The results indicated that the minimal treatment approach was the most common for newly diagnosed SLE patients. Clinical and economic outcomes were poorest for corticosteroid monotherapy but adding hydroxychloroquine and/or immunosuppressants could improve these outcomes. In an exploratory analysis by Muhammad Shipa et al., ML was used to investigate laboratory and clinical biomarkers associated with major clinical responses to B-cell targeted therapies, constructing molecular networks related to responses to B-cell targeted treatment.²⁶²

In summary, ML algorithms have provided essential tools for the personalized and precise treatment of SLE.

Sjögren's syndrome

RA and pSS share similarities in immune cell characteristics and clinical manifestations, which has led researchers to explore similar biological treatment strategies. However, approved biologics are currently limited to treatment for refractory SLE, while SS still lacks FDA-approved medications. To improve treatment outcomes, researchers²⁶³ conducted phenotypic analysis of 29 immune cell subpopulations in peripheral blood from 45 primary SS patients, 29 SLE patients, and 14 SLE/SS patients (SLE with comorbid SS), comparing these results with those from 31 healthy controls. Using various ML methods (balanced random forests, sparse partial least squares discriminant analysis, logistic regression, multiple t-tests), along with K-means clustering, the study found that although SLE and SS differ in clinical presentation and prognosis, they still share similar immunological features. These features could be further divided into two distinct immunophenotypes, which could be highly differentiated by a combination of 8 T cell subpopulations (AUC=0.9979). Clinical trajectory analysis also showed distinct changes in damage scores and disease activity levels over five years between the two patient groups. These findings highlight the value of ML in immunophenotypic analysis and offer new insights for precision treatment in both SLE and SS. Perrine Soret et al. developed a new molecular classification that identified four groups of patients with different immune dysregulation patterns. The results strongly support the use of type I interferon (IFN) response inhibitors, either alone or in combination, for treating different patients, and have implications for trials involving B cell depletion antibodies.²⁰⁷ In the current drug treatment research for SSc, gene expression analysis and ML methods play a crucial role in predicting treatment responses and patient stratification.

Mycophenolate mofetil and cyclophosphamide. During mycophenolate mofetil (MMF) treatment, 321 DEGs were identified between skin responders and non-responders in SSc patients (FDR<5%), with all skin responders being classified into the inflammatory subgroup.²⁶⁴ In a study comparing the effects of MMF and cyclophosphamide (CYC) in SSc-related ILD, RNA sequencing showed that CYC upregulated erythropoiesis, inflammation, and myeloid-related modules while downregulating lymphoid-related modules. MMF had a milder impact, primarily downregulating plasmablast modules. Despite MMF's comparable effect to CYC in improving lung function, it was found to have better safety and tolerability profiles.²⁶⁵⁻²⁶⁶

Dasatinib. In a study on dasatinib, 12 patients with diffuse cutaneous systemic sclerosis (dcSSc) and ILD who completed baseline and follow-up biopsies exhibited 1,062 differentially expressed genes (DEGs). The responders at baseline showed an enrichment of genes associated with the cell cycle, while non-responders showed an increase in genes related to inflammatory pathways.²⁶⁷ Moreover, dasatinib demonstrated anti-aging effects, with 80.3% of senescence-associated secretory phenotype (SASP) genes showing reduced expression in the responder group.²⁶⁸

Biologic therapies. In a study on Abatacept, responders showed increased expression of inflammatory genes at baseline, followed by upregulation of genes related to cell growth and cell cycle, while genes associated with immune activation were downregulated after treatment.²⁶⁹ Subsequent phase 2 RCTs categorized patients into three intrinsic subgroups, with early-stage disease patients more likely to belong to the inflammatory or normal-like subgroups.²⁷⁰ In a study on Belimumab for early diffuse SSc, ML analysis showed that 60% of patients switched from the inflammatory or fibrotic subgroups to the normal-like subgroup, with significant reductions in B-cell signaling, pro-fibrotic genes, and pathways in the treatment group, which was not observed in the placebo group.²⁷¹ In a Rituximab study, hierarchical clustering identified three intrinsic subgroups, with minimal changes in gene expression and intrinsic subgroup affiliation for most patients.²⁷² Lenabasum, a CB2 agonist used in the treatment of dcSSc, was shown through gene expression analysis to have 1,937 DEGs after 12 weeks of treatment. The lenabasum group demonstrated significant improvements in inflammation ($P = 0.006$) and fibrosis ($P = 0.05$), significantly modifying the expression of inflammation and fibrosis-related genes, improving tissue histological features in dcSSc patients, showcasing its potential therapeutic effects.²⁷³

Hematopoietic stem cell transplantation. In studies of hematopoietic stem cell transplantation (HSCT) for SSc treatment, gene expression analysis indicated that, compared to monthly CYC treatment, HSCT resulted in significant decreases in interferon (IFN) and neutrophil modules, while cytotoxic/NK modules increased significantly. No significant changes were observed in the CYC group.²⁷⁴ Long-term follow-up demonstrated that, compared to healthy controls, the HSCT group showed upregulation of B-cell and plasmablast modules and downregulation of myeloid and inflammatory modules in samples taken after 38 months, suggesting immune reconstitution. After 54 months, samples from the HSCT group showed no difference from healthy controls, indicating completion of immune reset. The CYC group showed persistent SSc transcriptional features at both time points, suggesting that HSCT can normalize the molecular features of SSc and achieve long-term immune resetting after transplantation.²⁷⁵ Moreover, participants in the fibrotic subgroup in the HSCT group had significantly better event-free survival (EFS) than those in the fibrotic subgroup of the CYC group ($p=0.0091$), while participants in the normal-like ($p=0.77$) and inflammatory ($p=0.1$) subgroups showed no significant differences between the two groups. More DEGs were observed in the HSCT group at each time point, with significant changes in immune response pathways, suggesting that participants in the fibrotic subgroup derive long-term benefit from HSCT. Intrinsic subgroup-based patient stratification may be used to identify SSc patients who benefit most from HSCT.²⁷⁶ Recent studies further support these findings, showing that patients in the fibrotic subgroup have better improvement in the modified Rodnan skin score (mRSS).²⁷⁷

Others

In the precision medicine research of immune-mediated inflammatory diseases (IMiDs), ML methods are playing an increasingly important role. The SDTC-CPMed team developed the scDrugPrio computational framework,²⁷⁸ which constructs a detailed inflammatory disease network model by analyzing scRNA-seq data. It integrates cell-type-specific expression changes, cell crosstalk, and pharmacological characteristics for drug screening and ranking. This framework has been validated in a mouse antigen-induced arthritis model and successfully applied to research on MS, Crohn's disease, and psoriatic arthritis, demonstrating its potential in personalized drug screening.

In the study of IgA nephropathy,²⁷⁹ a model-based recursive partitioning ML method successfully identified three patient subgroups that could benefit from immunosuppressive therapy. These studies highlight the enormous potential of ML methods in molecular subtyping of complex immune diseases, predicting treatment responses, and individualizing treatment decisions, providing new research ideas for improving IMiD treatment outcomes.

Additionally, Daniel Schaffert and colleagues utilized automated ML (AutoML) technology²⁸⁰ to develop high-accuracy predictive models aimed at addressing key clinical issues in patients with plaque psoriasis (PsV) and psoriatic arthritis (PsA), including predicting treatment changes and identifying the causes of treatment changes. By analyzing clinical data from 309 patients, the study successfully constructed models to predict changes in

treatment, psoriasis area and severity index (PASI) scores. These models were able to effectively predict PASI score changes ($AUC=0.9241$). Key influencing factors included the initial treatment drugs (such as MTX or specific biologics), baseline PsA classification scores, changes in quality of life, initial PASI scores, changes in itching levels, and psychological status scores (such as the Hospital Anxiety and Depression Scale scores). Lower initial PASI scores and sustained lower itching levels were associated with better treatment outcomes, while increased pain, disease activity, and psychological distress typically led to higher BASDAI scores. These findings provide important support for clinical decision-making in PsV and PsA and help optimize treatment plans and improve patient prognosis.

These research advances demonstrate the powerful application potential of ML in bioinformatics and immunology research, particularly in integrating and utilizing large-scale heterogeneous data. By combining expert knowledge with data-driven methods, these technologies provide crucial support for understanding immune system functions, developing new vaccines and immunotherapies, and offer new insights and tools for solving complex biological problems.

APPLICATION OF MACHINE LEARNING IN AUTOIMMUNE DISEASE-RELATED DRUG DEVELOPMENT

AI technology has permeated the entire drug development pipeline, significantly enhancing efficiency across all stages: identifying disease targets, constructing disease-drug network maps, pinpointing specific antigenic epitopes, predicting antibody 3D structures and generating optimized sequences, training graph neural network (GNN) models, and reducing virtual screening time (Figure 4).

Over the past century, the academic and pharmaceutical industries have been committed to developing new treatments for autoimmune disease patients due to the multiple challenges faced in autoimmune drug development and application. Firstly, the high heterogeneity of diseases makes a single treatment plan difficult to meet the needs of all patients, and personalized treatment has become an inevitable trend. However, precise subtyping and biomarker screening are still in the exploration phase. Secondly, drug development has long cycles, high costs, and high failure rates. Some drugs (such as TNF- α inhibitors) show significant efficacy in certain patients but may be ineffective or cause severe adverse reactions in others.²⁸¹ Additionally, the widespread use of immunosuppressive drugs may increase the risk of infections. For instance, anti-CD20 monoclonal antibodies, while clearing B cells, weaken the body's immune response to pathogens. Long-term drug use may also lead to drug tolerance or decreased efficacy, such as the emergence of antibody neutralization in some patients after using TNF- α inhibitors.²⁸² Emerging therapies, such as CAR-T cell therapy, show potential but are limited by high costs and potential adverse effects (e.g., cytokine release syndrome).²⁸³

AI has made significant progress in drug design and development, especially in areas such as protein structure prediction, molecular virtual screening, molecular design, and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) prediction. On one hand, breakthroughs in AI, such as AlphaFold in protein structure prediction, are crucial for studying key molecules in the immune system (e.g., MHC-peptide complexes), offering new ideas for the development of AID antibodies and novel immune modulators. On the other hand, AI technologies can significantly reduce the workload in drug development and enhance the efficiency of early drug discovery. For example, through deep generative models, researchers can extract molecular features, explore chemical space, and optimize molecular structures to develop innovative molecules with ideal drug characteristics. The conditional diffusion deep generative model guided by the International Union of Pure and Applied Chemistry (IUPAC) can convert IUPAC names to SMILES strings and generate similar compounds with diverse scaffolds under specific constraints.²⁸⁴ Large language models (LLMs) have shown great potential in the fields of chemistry and drug science, particularly in understanding and generating human-like text. By interpreting scientific literature, automating compound design, and predicting molecular properties, LLMs have greatly enhanced the efficiency of drug discovery.

Furthermore, DL has shown immense potential in drug target identification. The deepDTnet model developed by Zeng et al., which integrates 15 types of

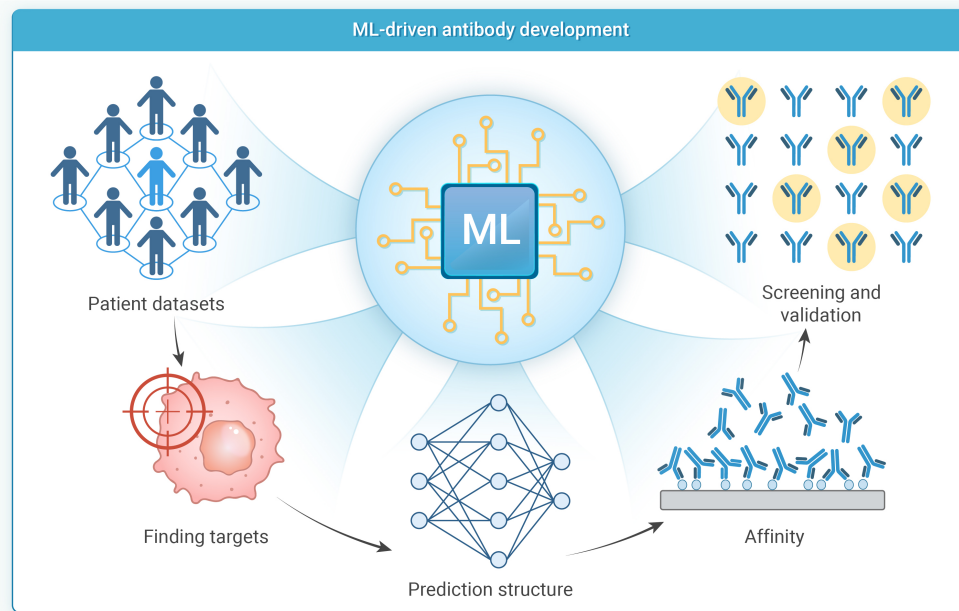


Figure 4. Schematic diagram of ML-driven antibody development process.

development, including drug property prediction, drug design, drug discovery, and natural product discovery. Below is a summary of the applications of ML in the drug development of various AIDs.

Antibody development

Antibodies (immunoglobulins, Ig) are glycoproteins produced by differentiated B lymphocytes and constitute the humoral components of the adaptive immune system's response to pathogens. Antibodies consist of two larger heavy chains (H) (Igh) and two light chains (L) (Iglk or Iglg) linked by covalent disulfide bonds to form a tetrameric structure. Due to their high specificity and affinity, as well as their remarkable efficiency in clinical diagnostics and therapy, antibodies have become a key focus of research. Antibody derivatives, including

recombinant monoclonal antibodies (mAbs), antibody-drug conjugates (ADCs), bispecific antibodies (BsAbs), antibody fragments, and Fc fusion proteins, have become important therapeutic agents for AIDs.

In recent years, AI and ML technologies have played an increasingly significant role in antibody development, particularly in the field of AIDs, transforming traditional development models. In antibody structure prediction, DL tools like AlphaFold and RoseTTAFold, by analyzing large-scale antibody sequence databases, can predict with high accuracy the three-dimensional structures of antibodies bound to self-antigens related to AIDs.⁶⁶ This provides essential support for understanding the molecular mechanisms of autoimmune responses and developing targeted therapeutic strategies.

This figure shows how ML is used in antibody development, including analyzing patient data, finding targets, predicting antibody structures, optimizing binding affinity, and screening and validating antibodies. ML helps identify targets, predict structures, and improve antibody effectiveness, speeding up the development of antibody drugs.

In the field of antibody engineering, ML algorithms can predict the affinity and specificity of antibodies with self-antigens by analyzing the features and structural information of CDR sequences.²⁹⁷ This capability is particularly important in AIDs like RA and RA, helping develop more precise therapeutic antibodies. Additionally, methods based on graph neural networks (GNN) simulate the amino acid interactions at the antibody-self-antigen interface, offering molecular-level guidance for antibody optimization.²⁹⁸ During high-throughput screening, ML models can rapidly identify potential therapeutic antibody candidates from vast datasets. For example, AbCellera, through its AI platform, has successfully developed several autoimmune disease antibody drugs (<https://abcellera.com/>). AI also predicts the physicochemical properties and immunogenicity of antibodies, which is crucial for more cost-effective screening of lead candidates and the development of safe and effective therapeutic antibodies.²⁹⁷ In process optimization, ML methods can analyze the relationship between process parameters and yield to optimize the expression and purification conditions for therapeutic antibodies used in AIDs.²⁹⁹ Despite the immense potential of AI/ML technologies in autoimmune disease antibody development, challenges remain, such as insufficient training data and poor model interpretability. As technology advances and clinical data accumulates, AI/ML will play an increasingly important role in the development of personalized antibody therapies. The application of AI or DL in antibody development can be summarized in three main areas:

(1) Sequence-to-Structure Prediction: Especially in the prediction of CDR-H3 structures, DL methods have resolved bottlenecks that traditional methods could not overcome. Recent studies show that DL approaches are more accurate than traditional methods in antibody structure prediction. For instance, Jeffrey A. Ruffolo and colleagues developed the DeepAb method,

heterogeneous network data (including chemical, genomic, phenotypic, and cellular networks), significantly improves the ability to identify known drug targets. This method successfully identified a drug targeting ROR- γ t and demonstrated significant therapeutic effects in a MS mouse model.²⁸⁵ Recently, a research team at Pennsylvania State University developed the EXPRESSO algorithm, which integrates single-cell expression quantitative trait locus (eQTL) data, 3D genomic structures, and epigenetic information to significantly improve disease prediction accuracy. EXPRESSO has been successfully applied to the genome-wide association study (GWAS) datasets of 14 AIDs, revealing 26% more novel genes and feature associations. These findings not only shed light on cell-type-specific gene expression regulatory mechanisms but also offer new ideas for drug repositioning, such as the potential therapeutic applications of Vitamin K and Metformin in AIDs.²⁸⁶

In drug development, drug repositioning is also an important strategy. Although AIDs share some common clinical manifestations and immune dysregulation features, significant differences in pathogenesis and phenotypic characteristics between different diseases pose challenges for drug repositioning. However, ML provides practical solutions to these difficulties. For example, the PREDICT algorithm²⁸⁷ predicts new indications for drugs by constructing similarity measures between drug-drug and disease-disease pairs. Another ML-based tool, deepDR,²⁸⁸ integrates ten networks, including drug side effects, targets, and disease associations, and uses autoencoders to learn drug features. It has successfully predicted therapeutic drugs for neurodegenerative diseases.

In recent decades, high-throughput screening (HTS) has become the standard method for evaluating compound targets and discovering potential leads. Although experimental facilities can assess hundreds of thousands of compounds for bioactivity each week,²⁸⁹ the large scale of compound libraries still limits discovery efficiency.²⁹⁰ Advances in computer technology have promoted the development of computer-aided drug design (CADD), accelerating the process of new drug development and reducing associated costs. Structure-based virtual screening (SBVS) and ligand-based virtual screening (LBVS) are common CADD methods. SBVS retrieves small molecules from compound libraries based on the structural features of the target protein binding site. To improve the performance of virtual screening scoring functions, ML techniques such as SVM and RF have been applied.²⁹¹⁻²⁹² In recent years, a large number of DL-based scoring functions have been introduced, demonstrating superior performance over traditional scoring functions in predicting protein-ligand binding affinity. DL-based scoring functions, such as AtomNet, DeepVS, KDEEP, and TB-IECS, have also been proposed and have shown superior performance in predicting protein-ligand binding affinity.²⁹³⁻²⁹⁶

Overall, advancements in AI are driving progress in all aspects of drug

Table 6. Selected AI-designed drugs in or entering clinical trials.

Drug code	Organization	Description	Phase	Disease
TAK-279	Nimbus	tyrosine Kinase 2 (TYK2) Inhibitor	Phase 1/2	moderate to Severe Plaque Psoriasis
ISM5411	Insilico Medicine	Hypoxia-inducible factor Prolyl Hydroxylase Inhibitor	Phase 1	IBD
ISM012-042	Insilico Medicine	prolyl hydroxylase-2(PHD2) small molecule inhibitor	Phase 1	IBD
BEN-2293	BenevolentAI	topical Pan-tyrosine Kinase Inhibitor	Phase 2a	AD
EXS-4318	Excientia	PKC- θ Inhibitor	Phase 1/2	inflammatory and autoimmune conditions
BEN-8744	BenevolentAI	small molecule RRElg inhibitor phase	Phase 1	ulcerative colitis

which combines the Rosetta protocol and deep neural networks to successfully predict the distances and orientations between antibody residues;³⁰⁰

(2) Antigen-Antibody Docking, Interaction Prediction, and Affinity Maturation: For example, Constantin Schneider and colleagues developed the DL-based structure prediction tool DLAB, which can predict the binding of an unknown antibody to its target antigen.³⁰¹ Brennan Abanades and colleagues proposed ABlooper, which uses an end-to-end DL model based on CDR loop structures, offering higher precision predictions and confidence estimates.³⁰² For antigen epitope prediction, Rahmad Akbar and colleagues, by analyzing a large number of antigen-antibody interactions, identified key interaction motifs that provide new insights for predicting epitope binding.³⁰³ Additionally, generative ML techniques have been applied to antibody sequence design and humanization, such as David Prihoda's BioPhi platform, which supports antibody design, humanization, and evaluation based on natural antibody libraries and DL.³⁰⁴ With continuous advancements in AI technology, new tools like RFdiffusion, which fine-tunes the RoseTTAFold structure prediction network using GANs, have made significant breakthroughs in antibody design. Research by Wang et al. showed that RFdiffusion effectively addresses multiple challenges, such as designing novel binders and high-order symmetric structures.³⁰⁵ Furthermore, given that protein sequences can be considered a language, researchers have started applying large-scale pre-trained models from NLP to protein characterization, further improving the efficiency and accuracy of antibody design.³⁰⁶

(3) Predicting Functional Characteristics of Antibodies: Currently, predicting the functional characteristics of antibodies based on their amino acid sequences and structure, including target binding affinity, specificity, and agonist activity, has become a key focus of various DL methods. This not only improves the developability of antibodies but also effectively reduces their immunogenicity.^{297,307-308}

These advancements demonstrate the powerful role that AI and ML can play in the development of therapeutic antibodies, particularly in AIDs, and underscore their potential to revolutionize the way antibody-based therapies are developed and optimized.

Small molecule drugs / virtual screening

AI is demonstrating distinct advantages in the development of small-molecule drugs for AIDs (Table 6). In a project by Insilico Medicine, the team focused on developing innovative therapies to reduce intestinal inflammation and promote mucosal repair. Using the commercialized AI bio-research engine PandaOmics for target screening and prioritization, they identified HIF-PHD as a therapeutic target for IBD. The team then utilized the generative AI platform Chemistry42 and its submodules (including Generative Chemistry, Alchemy, and ADMET analysis) to design PHD inhibitors with ideal properties.³⁰⁹ Specifically, the team used the Generative Chemistry module within Chemistry42 to build preferred fragments based on reported PHD complex structures, specifying six key pharmacological points to initiate fragment growth. At the same time, they enhanced novelty and synthetic feasibility screening, resulting in a series of promising compounds with good activity. Subsequently, the potential candidate molecule was optimized using structure-activity relationship (SAR) analysis and Alchemy to estimate the binding free energy of the PHD2-ligand complex, evaluating the drug efficacy of the generated compounds. Additionally, the ADMET module was employed to predict critical properties such as solubility and permeability, ultimately identifying a candidate molecule with the least systemic exposure. This led to

the development of the potent PHD-specific inhibitor ISM012-042. Following the validation of molecular generation conditions and biological mechanisms in multiple preclinical models, ISM012-042 received regulatory approval to start a phase 1 clinical trial (NCT06012578), with the first human volunteers dosed before December 7, 2023.³¹⁰ Meanwhile, two phase 1 clinical trials for ISM5411 in the treatment of IBD are concurrently being conducted in Australia and China, aimed at evaluating the safety, tolerability, pharmacokinetics, and food effects of oral ISM5411 in healthy volunteers. The final subject in both studies has completed the trial, with preliminary data expected to be released in early 2025.

Several companies have also made significant progress in AI-assisted drug development: Excientia developed the AI drug candidate EXS4, a selective PKC- θ inhibitor, which targets inflammation and AIDs. This candidate was acquired by Bristol Myers Squibb for \$1.2 billion. BenevolentAI developed BEN-8744 (a PDE10 inhibitor) for ulcerative colitis and submitted a clinical trial application to the UK MHRA in December 2022; their BEN-2293 (for atopic dermatitis) Phase IIa trial confirmed safety but failed to meet secondary endpoints related to reducing itching and inflammation. Nimbus Therapeutics' TYK2 inhibitor, NDI-034858/TAK-279,³¹¹ performed outstandingly in clinical trials for moderate to severe plaque psoriasis. In Phase II trials, patients receiving TAK-279 (5 mg, 15 mg, and 30 mg) showed significantly higher psoriasis area and severity index (PASI) response rates compared to placebo.

Different companies employ varied AI application strategies: Recursion uniquely uses cell images as the primary dataset, capturing pathological cell images and applying ML to assess drug efficacy. Relay Therapeutics focuses on developing highly selective therapeutic drugs, such as their FGFR2 inhibitor RLY-4008. Notably, Insilico Medicine's announcement in January 2023 that ISM001-055 was the first AI-driven project from target discovery to Phase I clinical trial demonstrates the potential of AI in fully integrating the drug development process. Furthermore, the Drugs for Neglected Diseases Institute (DNDi)³¹² in Geneva, Switzerland, is leveraging ML to develop better drugs for major diseases affecting the world's poor (such as Chagas disease and dengue fever), transitioning toward AI strategies to guide its drug repurposing pipeline. These advances fully demonstrate that AI can not only accelerate the drug development process but also help discover innovative treatment solutions that may be overlooked by traditional methods.³¹³

Many biotech companies are integrating diverse chemical libraries and advanced screening techniques to advance the development of new therapies for AIDs (Table 1). Nimble Therapeutics (<https://nimbletherapeutics.com/>) focuses on developing oral peptide drugs, one of which is an oral peptide inhibitor targeting IL-23R (preclinical phase), mainly used for psoriasis and IBD. Seismic Therapeutics (<https://seismictx.com/>) combines ML with structural biology, protein engineering, and translational immunology through its IMPACT™ platform, developing several candidate drugs with innovative mechanisms. One of these, S-4321, is a bifunctional antibody that binds PD-1 with low affinity in the Fab region for sustained activation, while the Fc region selectively binds the FcγRIIb receptor, jointly inhibiting T cells (PD-1 mediated) and B cells/APCs (FcγRIIb mediated). Another project, IgSc Enzyme, focuses on S-1117, a "single drug, multiple mechanisms" solution based on a new type of pan-IgG protease. It fuses with the human IgG1 Fc region and, through a ML platform, achieves low immunogenicity and high productivity. This protease degrades all human IgG subclasses and IgG BCRs on memory B cells, thus directly clearing soluble and cell-surface IgG and

inhibiting their reconstitution. In an ITP prevention and treatment model, it exhibited faster and more sustained IgG clearance than FcRn inhibitors, and pharmacokinetics predictions show that low-dose, intermittent dosing can achieve up to a 90% reduction in IgG.³¹⁴ These results suggest that the bifunctional antibody S-4321 and the pan-IgG protease S-1117 hold broad prospects for the treatment of various AIDs, while Nimble Therapeutics' oral IL-23R inhibitor offers new options for inflammatory diseases like psoriasis and IBD.

In small molecule drug development, researchers widely use AI for small molecule generation. For instance, Yang et al. trained an LSTM neural network model using around 200,000 compounds from the ChEMBL database and fine-tuned it with a published p300 inhibitor dataset. This led to the successful generation of a molecular library containing 672 valid chemical structures.³¹⁵

Natural product drugs

The application of DL in drug discovery and natural product research is expanding rapidly, with key advantages in molecular generation, property prediction, virtual screening, and biosynthetic pathway inference. The success of AlphaFold in protein structure prediction has demonstrated the transformative potential of DL, now increasingly applied to natural product research and drug design. For instance, Meller et al. used AlphaFold to predict the 3D structure of the Mg^{2+}/Mn^{2+} -dependent protein phosphatase 1D (PPM1D). Molecular dynamics simulations revealed a cryptic binding pocket, providing a theoretical basis for the design of allosteric inhibitors for this enzyme.³¹⁶

In natural product studies, multi-omics data analysis has become critical for uncovering biosynthetic potential. Metabolomics analysis directly reveals the chemical composition of natural products and has identified metabolic abnormalities in autoimmune disease research.³¹⁷ Using mass spectrometry data, ML can infer molecular structures through techniques like spectral similarity matching, molecular formula annotation, and molecular class annotation. These capabilities are vital for identifying natural products and discovering metabolic biomarkers for AIDs.³¹⁸

For predicting the biosynthetic pathways of natural products, algorithms like BioNavi-NP leverage DL to analyze chemical structures and infer biosynthetic routes. This method supports gene cluster matching and bridges the gap between genomics and metabolomics.³¹⁹ However, the uneven distribution of data resources in the natural product domain and the lack of interoperability pose challenges. Integrating global data resources requires addressing standards and ontology compatibility. By integrating DL with multi-omics data analysis, AI technologies are unlocking the potential of natural products for autoimmune disease research.

Other emerging therapeutics

Novel drug delivery systems. Novel drug delivery systems aim to enhance drug targeting, stability, and bioavailability, improving efficacy while reducing side effects. ML plays a crucial role in designing and optimizing these systems.

For instance, GenEdit developed the NanoGalaxy platform, employing hydrophilic nanoparticles (HNPs) for nucleic acid delivery in AIDs. ML was utilized to analyze the relationships between nanoparticles' physicochemical properties (e.g., size, surface charge, and stability) and their *in vivo* distribution, optimizing delivery system design. GenEdit has partnered with Roche's Genentech to develop HNPs for autoimmune indications, with Genentech overseeing preclinical, clinical, and regulatory development as well as commercialization.³²⁰

Nucleic acid aptamers. Nucleic acid aptamers are single-stranded DNA or RNA molecules obtained through *in vitro* selection techniques that bind to target molecules with high specificity. DL technology has made significant progress in the field of nucleic acid aptamer research, particularly in the prediction of aptamer-protein interactions (API) and aptamer generation. Aptanet³²¹ is a novel deep neural network designed to predict interactions between aptamers and proteins by integrating features of both aptamers and target proteins. Specifically, aptamers are encoded using k-mer and reverse complementary k-mer frequencies, while proteins are represented by amino acid composition (AAC) and pseudo-amino acid composition (PseAAC)

combined with 24 physicochemical and conformational properties. To address data imbalance issues, Aptanet employs a neighborhood cleaning algorithm and constructs a predictor based on deep neural networks, while using a random forest algorithm to select optimal features. This provides an efficient and accurate computational method for predicting aptamer-protein interactions. Aptatrans³²¹ is another DL-based tool focused on predicting aptamer-protein interactions. Although the traditional SELEX (Systematic Evolution of Ligands by Exponential Enrichment) method is widely used for aptamer screening, it is time-consuming and has limited accuracy. Aptatrans addresses this issue by leveraging DL technology, particularly Transformer-based encoders. It uses Transformer encoders to process monomer sequences of aptamers and proteins, combined with pre-trained encoders to represent structural information. After validation on benchmark datasets, Aptatrans outperforms existing prediction models, significantly improving the efficiency of aptamer screening. Additionally, a research team from Waseda University in Japan developed a variational autoencoder (VAE) model named RaptGen³²² for generating nucleic acid aptamers. Aptamers are short single-stranded oligonucleotides that can bind to specific targets through their three-dimensional folded structures. Although traditional aptamer screening methods such as SELEX are effective, they are time-consuming and costly. RaptGen integrates a profile hidden Markov model (HMM) decoder to embed simulated sequence data into a low-dimensional latent space and generate new aptamer sequences. It can even generate truncated aptamer sequences shorter than the original ones, thereby reducing manufacturing costs. Furthermore, RaptGen uses a Bayesian optimization algorithm to generate candidate aptamer sequences with high binding activity, significantly enhancing the efficiency and practicality of aptamer screening. Aptanet and Aptatrans improve the accuracy and efficiency of aptamer-protein interaction prediction from the perspectives of feature encoding and pre-trained encoders, respectively, while RaptGen provides a novel approach to aptamer discovery and optimization by generating new aptamer sequences.

In autoimmune disease treatment, researchers have developed a cell-specific and cytotoxic SELEX system (CSCT-SELEX) that identifies therapeutic aptamers without prior knowledge of target cell surface characteristics. For example, the SAPT8 aptamer targets nucleolin (NCL), selectively eliminating RA-derived fibroblast-like synoviocytes (RA-FLSs) and modulating the NCL-p53/Bcl-2 signaling pathway. This represents a potential alternative or complementary therapy for RA.³²³

Protein degradation technologies. Proteolysis targeting chimeras (PROTACs) are bifunctional molecules that induce targeted protein degradation via the ubiquitin-proteasome system (UPS). These molecules can target previously "undruggable" proteins, overcome acquired drug resistance, and require low affinity for target proteins. In AIDs, PROTACs show significant promise. For example, researchers at Tsinghua University developed a next-generation BTK-PROTAC degrader, L181, for treating RA and diffuse alveolar hemorrhage (DAH). L181 effectively degrades BTK protein, inhibits TLR signaling pathways, and significantly reduces inflammation and autoantibody production, outperforming traditional BTK inhibitors like Ibrutinib.³²⁴

AI is instrumental in PROTAC design and optimization. The DeepPROTACs model, developed by ShanghaiTech University, uses graph neural networks to predict the degradation efficiency of PROTACs. By analyzing structural features of target proteins, E3 ligases, and linkers, this DL-based model improves PROTAC design efficiency and accuracy, providing a powerful tool for autoimmune disease therapy.³²⁵

The integration of AI with innovative technologies like PROTACs, nucleic acid aptamers, and novel delivery systems holds immense potential for autoimmune disease treatment. As more data is accumulated and algorithms are refined, AI is expected to play a greater role in drug design, target discovery, and clinical trials, advancing the development of precision medicine. These cutting-edge approaches promise more effective and personalized therapies, offering new hope for patients with AIDs.

CHALLENGES AND PROSPECTS

Although ML algorithms demonstrate tremendous potential in bioinformatics and medical research, their application faces numerous challenges and limitations, primarily related to data quality and availability, model inter-

pretability, and ethical concerns.

Data quality and availability

Supervised learning models heavily depend on high-quality labeled data, which remains a major bottleneck in their application. In the medical domain, obtaining large volumes of accurately labeled training data is often costly and challenging. Moreover, limited training data can lead to model overfitting, reducing generalizability and making it difficult for models to handle patterns not present in the training set. If training data labels are biased, models may learn and amplify these biases, undermining the reliability of the results.³²⁶⁻³³¹ The accuracy and applicability of AI models largely depend on the quality and quantity of training and testing data.³³

For example, in transcriptomics research, reference genomes may lack complete annotations for certain genes or regions, leading to the omission of critical transcripts. Quantification challenges, such as accurately measuring low-abundance transcripts and dealing with noise sensitivity, further exacerbate these issues. Transparent data collection methods with detailed methodological descriptions are essential for ensuring reproducibility and generalizability, as variations in sequencing platforms and bioinformatics pipelines can introduce biases. While ML holds promise for biomarker discovery, careful consideration of inherent model limitations and biases is crucial. Another significant challenge is the lack of standardization in ML modeling for biomarker discovery. Variability in feature selection, model training, and evaluation metrics often results in inconsistent or conflicting outcomes. Additionally, different ML algorithms may perform variably depending on the dataset and specific research questions, complicating the selection of the optimal approach. Efforts are underway to address these issues, including developing standardized protocols for data sharing and analysis and establishing benchmark datasets for evaluating ML algorithm performance.³³² Researchers must remain mindful of data quality, model interpretability, and potential biases to ensure the reliability and clinical translatability of their findings. Incorporating alternative ML approaches, such as unsupervised and semi-supervised learning, could help overcome some limitations of supervised learning and improve the effectiveness of ML applications in bioinformatics and medical research.

In high-throughput omics studies, batch effects from clinical samples (e.g., arising from sampling time, processing procedures, or equipment differences) often significantly interfere with data quality. Their impact is widespread and critical, potentially masking true biological signals or introducing spurious associations (Tackling the widespread and critical impact of batch effects in high-throughput data). This challenge is particularly prominent in the rapidly growing field of single-cell datasets, as researchers need to integrate multiple samples from diverse biological and technical backgrounds (such as different experiments, reagent batches, or sequencing technologies) and compile them into large atlases. While these atlas resources are invaluable for advancing single-cell-based research, integrating such vast datasets necessitates overcoming confounding effects (i.e., batch effects) that can obscure genuine biological differences, potentially impacting downstream analyses like differential expression.³³³

Traditional batch effect correction methods, such as the linear model-based ComBat (implemented in the *sva* R package), although widely used,³³⁴ rely on the accurate definition of batch variables. They struggle to effectively handle complex scenarios common in multi-center studies, such as confounding equipment differences or non-linear interactions between batch and biological factors, leading to limited correction efficacy. To address these challenges, emerging algorithms are enhancing robustness through multi-dimensional data integration and more flexible modeling. For instance, the MOFA+ framework utilizes batch-based gradient descent algorithms to synchronously resolve latent factors across data modalities (e.g., genomics, transcriptomics, proteomics) and sample groups (e.g., different experimental conditions, disease subtypes) in multi-omics clustering analyses, thereby reducing batch interference. Meanwhile, joint matrix factorization techniques like iNMF and Mowgli³³⁵ combine Non-negative Matrix Factorization (NMF) with Optimal Transport (OT) theory, aiming to balance biological interpretability and clustering performance optimization during single-cell multi-omics data integration.

In practice, the most widely used single-cell data analysis tools, such as

the R-based Seurat v5 (<https://github.com/satijalab/seurat>) and the Python-based Scanpy (<https://github.com/scverse/scanpy>), offer comprehensive functionalities including visualization, clustering, and trajectory analysis. They notably support batch effect correction and data integration, essential steps for harmonizing datasets from diverse origins. However, the specific methods they provide differ: Seurat primarily employs an "anchor"-based integration strategy based on mutual nearest neighbors (MNN), and version V5 added native support for Harmony and scVI. Scanpy, on the other hand, integrates multiple methods, including BBKNN, Combat, Scanorama, Harmony, and several deep learning algorithms, offering greater flexibility in handling batch effects and aligning datasets. The effectiveness of these methods depends on the complexity of the data (such as the number of samples, diversity of cell types, and technical differences). Nevertheless, despite the availability of various methods and tools, existing approaches still face challenges in generalization, particularly when batch effects are highly coupled with true biological signals, and especially in scenarios with high clinical heterogeneity and limited sample sizes. Therefore, developing advanced algorithms capable of dynamically identifying confounding factors and adaptively adjusting for non-linear relationships remains a critical area requiring breakthroughs.

Model interpretability

In medical applications, the interpretability of AI models is critical for supporting medical decision-making, meeting regulatory requirements, gaining patient trust, and providing scientific insights. As AI technology becomes more prevalent in healthcare, improving model interpretability has become an indispensable research focus. Current efforts include using inherently interpretable models, developing post-hoc explanation techniques, and designing DL architectures with built-in interpretability. Certain ML models are considered highly interpretable due to their simplicity and transparent decision-making processes. For example, linear regression models directly reflect feature importance through coefficients, while decision trees present decision rules in a tree-like structure. These models are particularly popular in medical applications because they provide intuitive explanations that help clinicians understand the decision-making process. However, these models may lack the predictive performance of more complex models, such as deep neural networks.³³⁶⁻³³⁹

DL models, including convolutional and RNN, often excel in performance but are criticized for their "black-box" nature. To enhance the interpretability of DL models, researchers are exploring methods such as attention mechanisms and interpretable neural networks. Attention mechanisms highlight the most critical input parts during decision-making, while interpretable neural networks are specifically designed to offer insights into the decision process.³⁴⁰

Interpretability of machine learning models - SHAP analysis

For large modern datasets, the highest accuracy is often achieved through complex models that are difficult for even experts to interpret, such as ensemble models or deep learning models,³⁴¹ which creates a tension between accuracy and interpretability. Machine learning models (like the widely used XGBoost) often outperform traditional scorecard models, but compared to methods like logistic regression where explicit weights can be assigned to each input variable, the training and deployment of machine learning are more like a "black box," where we input variables and directly obtain predicted probability values, making it difficult to understand which variables inside the model play key roles and how they affect the prediction results. Therefore, there is an urgent need for a method that can provide interpretability while retaining the superior performance of machine learning, seeking a balance point.

In response, various methods have emerged in recent years to explain complex model predictions, among which SHAP (SHapley Additive exPlanations) proposes a unified framework.³⁴¹ SHAP is based on the Shapley value theory from game theory, with its core idea originating from the principle of fair allocation in cooperative game theory: just as Shapley values quantify the marginal contribution of each participant in a cooperative task to determine a fair payoff (Explainable artificial intelligence model to predict acute critical illness from electronic health records), SHAP applies this idea to machine

learning, assigning an importance value (i.e., SHAP value) to the contribution of each feature towards a specific prediction. It decomposes the model's prediction output into a sum of a baseline prediction (usually the average prediction over the entire dataset) and the contribution values of individual features, satisfying the additive formula: Prediction Value = Baseline Value + Feature 1 Contribution Value + Feature 2 Contribution Value + ... + Feature n Contribution Value. A positive SHAP value for a feature indicates it pushes the prediction higher, while a negative value indicates it pushes the prediction lower. This allows SHAP not only to quantify the global importance of features but also to intuitively demonstrate the specific direction and magnitude of each feature's impact on the prediction at the individual sample level.

Key innovations of the SHAP framework include identifying a class of additive feature importance measures and proving that there is a unique solution within this class that satisfies desirable properties such as local accuracy, consistency, and missingness, thereby unifying six existing explanation methods, including LIME and DeepLIFT, and pointing out that some of these methods lack these desired properties. Furthermore, SHAP proposes more computationally efficient polynomial-time algorithms specifically for tree-based models, and makes explanation results more aligned with human intuition through the quantification and visualization of feature interaction effects (e.g., using force plots, summary plots), effectively addressing the interpretability challenges posed by the "black box" nature of machine learning models.

In practice, especially in the field of medical artificial intelligence (AI), explainability (XAI) is one of the core challenges for model deployment. Tools like SHAP and LIME (Local Interpretable Model-agnostic Explanations) quantify the impact of each input (such as laboratory indicators, imaging features) on the prediction, making the model's decision logic transparent, helping doctors understand the AI's reasoning process, reducing "black box" concerns, and enhancing patient trust in AI technology. For example, in a study on Myasthenia Gravis (MG), a random forest model combined with SHAP value analysis found that Lachnospiraceae in the gut microbiota and the metabolite inosine had the highest contributions to MG diagnosis (SHAP values reaching 0.42 and 0.38, respectively), with the model achieving an AUC of 0.99.³⁴² Clinicians can intuitively understand the basis for individualized predictions through SHAP waterfall plots. Similarly, in the prediction of Autoimmune Encephalitis (AE), SHAP analysis revealed the key roles of CSF monocyte percentage and prealbumin levels, with the model achieving an AUC of 0.906.³⁴³ Furthermore, in gene regulatory network research, introducing SHAP values to quantify gene interaction contributions revealed a regulatory role for the IRF1 gene that was previously overlooked in traditional experiments; subsequent experiments validated its ability to regulate Th17 cell differentiation.³⁴⁴ Therefore, SHAP is not only used in fields like credit scoring to identify globally important features and explain individual cases (e.g., an applicant's score decreasing due to "short work tenure"), but also demonstrates significant value in high-risk areas such as medical diagnosis for balancing model predictive performance with decision transparency, becoming an important tool for model auditing and ensuring regulatory compliance.

Ethical issues

The application of AI in healthcare brings significant advancements but also raises a range of complex ethical issues, including privacy protection, fairness, accountability, informed consent, human-AI interaction, and data ownership, which require attention from researchers and policymakers alongside technological development.³⁴⁵⁻³⁴⁹ Algorithmic bias and fairness are critical concerns, as AI systems rely on training data that may contain biases or imbalances, leading to unfair outcomes, such as poor performance in specific racial, gender, or age groups, resulting in unequal healthcare resource allocation or diagnostic errors, often stemming from data-driven biases, subjective biases in algorithm design, or uneven data distribution.³⁵⁰ Privacy and data security are also major issues, as AI systems require large volumes of patient data for training and optimization, increasing the risk of privacy breaches, misuse, illegal trading, or commercial exploitation, exacerbated by security vulnerabilities during data collection, storage, and transmission, and the lack of robust privacy protection regulations. The erosion of physician authority is another concern, as the widespread use of AI in medical decision-making may lead patients to overly rely on AI recommendations, potentially

undermining physicians' professional judgment, disrupting the balance in doctor-patient relationships, weakening physicians' authority, and impacting decision quality and patient trust. Accountability and legal issues further complicate the landscape, as determining responsibility becomes complex when AI errors or medical incidents occur, with unclear accountability among developers, medical institutions, or physicians, exacerbated by the absence of clear legal frameworks, leading to disputes and challenges in protecting patient rights.³⁵¹ Overdiagnosis and resource waste are additional ethical challenges, as AI's efficiency in areas like image recognition may lead to overdiagnosis, identifying conditions that do not require intervention, resulting in unnecessary treatments, increased healthcare costs, and unnecessary physical and financial burdens on patients. Finally, the lack of ethical oversight and regulation poses significant risks, as many AI products are deployed without sufficient validation, and the absence of unified ethical review standards and robust regulatory systems compounds these issues.³⁵²

To address these ethical challenges, several strategies can be implemented: enhancing data privacy protection through stringent regulations; optimizing algorithm design to reduce biases and improve transparency and fairness; establishing clear legal frameworks to define accountability for AI-related medical incidents; strengthening ethical oversight with standardized review processes to ensure the safety and efficacy of AI products; and educating physicians and patients to improve AI literacy.

Researchers are also developing new methods to tackle technical challenges, such as interpretable AI, transfer learning, and few-shot learning. Combining DL with domain expertise to create hybrid models is another promising direction. Additionally, developing model architectures tailored to the characteristics of biological data and integrating domain knowledge into models can enhance performance and reliability in bioinformatics applications.

By implementing these measures, the ethical and technical challenges of AI in healthcare can be effectively addressed, ensuring the responsible and sustainable development of AI technologies in the medical field.⁸⁸

Prospects

The application of AI and ML technologies in healthcare holds immense potential, particularly in improving clinical workflow efficiency. For example, AI/ML-powered medical transcription applications can automate documentation, enhance accuracy, and alleviate the workload on physicians. These technologies can also streamline complex administrative tasks, support predictive analytics, enable personalized medicine, and provide valuable insights in areas like genetic testing and precision medicine. By analyzing medical records, imaging data, and genomic sequences, AI can automatically identify abnormalities, significantly improving diagnostic accuracy and efficiency. Additionally, neural networks can analyze individualized patient data to recommend optimal treatment plans, thereby enhancing therapeutic outcomes.³⁵³

Large language models (LLMs), such as those driving chatbots and mobile applications, have the potential to improve patient engagement and adherence to treatment plans,³⁴⁸ making it easier for patients to access health information. Research shows that ChatGPT performs comparably to human experts in addressing clinical genetics questions but demonstrates weaker performance in scenarios requiring critical thinking.³⁵⁴ LLMs also exhibit strong capabilities in summarizing information, such as generating discharge summaries³⁵⁵ and contributing to multi-omics research in medicine,³⁵⁶ though their usage must undergo rigorous validation.³⁵⁷

Deep neural networks (DNNs) also show substantial promise in reducing healthcare costs, particularly in managing adverse drug reactions.³⁵⁸ AI/ML methods are being developed as tools for pharmacovigilance³⁵⁹ and adverse event prediction systems,³⁶⁰ potentially minimizing healthcare expenditures associated with drug side effects. However, the application of clinical risk stratification models still faces challenges, including the clinical relevance of predictions, integration into workflows, and training requirements for healthcare professionals.³⁶¹⁻³⁶⁴ Key metrics like care quality and patient outcomes should remain the focus when evaluating these models.³⁶⁵

Digital pathology presents a vast opportunity for AI/ML applications.³⁶⁶ Traditional ML often requires high-quality labeled data, but advances in AI technologies have mitigated this dependency, reducing reliance on expensive

datasets. DL and computer vision technologies are poised to revolutionize disease diagnosis and monitoring. For instance, CNN can analyze endoscopic images or pathology slides to improve the diagnostic accuracy of IBD.³⁶⁷ NLP demonstrates significant potential in analyzing medical records, mining scientific literature, and interpreting patient-reported outcomes, enabling early symptom detection and disease progression prediction.³⁶⁸

Integrating multi-omics data with advanced ML algorithms holds promise for uncovering complex molecular mechanisms and identifying novel biomarkers and therapeutic targets.³⁶⁹ The rapid advancement of multimodal single-cell technologies now enables the integration of multilayered cellular information (epigenetic, transcriptomic, proteomic) at unprecedented resolution, overcoming limitations of traditional bulk tissue analysis. A pioneering example is the SCENT method developed by Harvard Medical School, which integrates scATAC-seq and scRNA-seq data to construct cell type-specific enhancer-gene regulatory maps across 120,000+ cells. By combining Poisson regression with nonparametric bootstrap testing, SCENT precisely captures chromatin accessibility-gene expression relationships while controlling technical noise and batch effects. Validated across nine tissue datasets, SCENT-predicted enhancers show evolutionary conservation and experimental validation through CRISPR-Flow FISH and HiChIP. This approach has revealed hierarchical enrichment of GWAS risk variants in cell type-specific enhancers, identified autoimmune disease hubs like the rs72928038-BACH2 regulatory axis in T cells, and uncovered novel RA synovial fibroblast mechanisms through NOTCH signaling pathway analysis.³⁷⁰

In clinical applications of multimodal single-cell analysis, a landmark study by Brigham and Women's Hospital analyzed synovial tissue from 79 RA patients through integrated scRNA-seq, bulk RNA-seq, and surface protein detection (CITE-seq/flow cytometry) across 314,000+ cells. The developed Cell Type Abundance Phenotype (CTAP) classification system identified six distinct synovial inflammation subtypes (e.g., T/B cell-dominant CTAP-TB, fibroblast-driven CTAP-F). This multimodal approach revealed that 35% of cases exhibited non-immune stromal cell-driven inflammation mediated by TGF- β 1/CCL5-secreting ITGA5+ fibroblasts and endothelial cells, while also demonstrating subtype-specific treatment responses - CTAP-TB showing JAK inhibitor sensitivity versus CTAP-F resistance to TNF inhibitors.³⁷¹

Federated learning allows different institutions to collaboratively train AI models while preserving data privacy,³⁷² offering new solutions for medical data sharing and utilization. Reinforcement learning can optimize treatment strategies, advancing personalized medicine.

The combination of AI with wearable devices and Internet of Things (IoT) technologies provides powerful tools for personalized healthcare. Applications include disease stratification and subtype identification,³⁶ predictive modeling,³⁷³ precision dosing,³⁷⁴ virtual clinical trials,³⁷⁵ creating digital twins,³⁷⁶ and personalized lifestyle interventions.³⁷⁷ However, to fully realize these technologies' potential, challenges in technical development, ethics, and regulation must be addressed.

Rieke et al.³⁷² highlight that implementing digital healthcare can leverage advancements in federated learning to address some of these challenges. Federated learning enables the sharing of DNN model updates and parameters to develop consensus models that outperform individually trained models. This approach has also been applied in biomedical science, as described by Kaissis et al.³⁷⁸ However, federated learning alone cannot entirely resolve privacy and security concerns. Biomedical data often faces challenges such as inconsistent variable definitions, mismatched distributions, missing data, and class imbalances.³⁷⁹ AI/ML methods can assist in data cleaning, quality assurance (QA), and quality control (QC) by detecting anomalies and facilitating data integration and transformation. For example, an automatic concept-mapping method uses DNNs to align datasets from different institutions with unified healthcare data models.³⁸⁰

While data volume is critical, issues of bias and fairness emphasize the importance of high-quality data generation. This has driven the development of tools supporting prospective data collection, such as the NIH Common Fund's Bridge2AI initiative,³⁸¹ which aims to create ethically sourced, meticulously curated, and accessible flagship biomedical datasets.

AI's application in medicine, particularly in addressing problems akin to those handled by resident physicians, has been widely adopted across multi-

ple medical specialties, including pathology and radiology. In some cases, AI has achieved performance comparable to human experts.³⁸² For instance, integrating AI into pathology not only generates advanced diagnostics but also improves workflows, enabling clinicians to quickly view and share images while leveraging computational algorithms to derive valuable insights.³⁸³⁻³⁸⁴ These algorithms extract data from medical images that are difficult to discern through human analysis, providing crucial information for diagnostics, treatment sensitivity, and prognosis. Furthermore, neural networks can analyze genetic sequences to predict patients' hereditary disease risks.³⁸⁵

In image recognition, AI has demonstrated remarkable success, particularly in analyzing radiographic images and pathology slides. Digital radiographic images reduce information loss and facilitate fully digital workflows.³⁸⁶ However, the sheer volume of pathology slides, coupled with artifacts like bubbles and tissue folds, increases costs and storage challenges. Whether AI can surpass human experts in diagnostic accuracy and treatment efficacy remains a topic of debate among pathologists.³⁸⁷⁻³⁸⁸ When addressing these issues, it is essential to recognize the inherent uncertainties in technological predictions and account for biases and subjectivity in expert opinions.³⁸⁹

With the rapid advancement of AI/ML technologies and a deeper understanding of AIDs, the future of AI in medicine looks promising. Emerging technologies and methodologies are opening new avenues for research and management in AIDs, driving the development of personalized medicine. Generative AI is expected to continue leading discussions and innovations in the healthcare IT sector. This technology has the potential to find broader applications in clinical decision support, personalized medicine, and medical education, while progressively integrating into existing healthcare systems to enhance services and improve patient outcomes.

CONCLUSION

This study identified several critical issues in the application of machine learning to clinical research: Open dissemination of complete source code is essential for verifying the reproducibility of results through testing on external datasets. However, among the studies reviewed here, only a few provided open-access code, and even fewer offered fully reproducible and clearly documented code, though many high-quality journals now mandate authors to share original code. Additionally, external validation is crucial in AI research as it assesses real-world model performance, yet nearly half of the studies included in this review lacked independent external datasets for model validation. Since the quality of AI models depends on the data used for training, future investigations must prioritize large-scale, high-quality datasets, achievable by creating multimodal repositories integrating patient demographic, clinical, laboratory, genomic, imaging, and lifestyle features.³⁹⁰ Concurrently, future studies should address potential algorithmic biases during model development by including sufficient data points representing minority populations to mitigate bias risks. Notably, while most current studies compare AI algorithm performance against human experts, evaluating AI-human collaborative performance relative to human experts alone would yield more realistic and applicable outcomes.³⁹¹ Furthermore, AI algorithm designs may introduce profit-driven biases by preferentially recommending specific drugs, tests, or devices that benefit developers or purchasers, a concern often unrecognized by clinicians using these tools.³⁴⁵

ABBREVIATION

AI: artificial intelligence; ML: machine learning; DL: deep learning; AIDs: autoimmune diseases; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; MS: multiple sclerosis; IBD: inflammatory bowel disease; TCR: T cell receptor; MHC: major histocompatibility complex; HLA: human leukocyte antigen; LN: lupus nephritis; pSS: primary Sjögren's syndrome; SSc: systemic sclerosis; PAH: pulmonary arterial hypertension; ILD: interstitial lung disease; AD: atopic dermatitis; PsA: psoriatic arthritis; APS: antiphospholipid syndrome; AS: ankylosing spondylitis; OA: osteoarthritis; EULAR: European League Against Rheumatism; ACR: American College of Rheumatology; SLEDAL: Systemic Lupus Erythematosus Disease Activity Index; DAS28: Disease Activity Score 28; MTX: methotrexate; CAR-T: chimeric antigen receptor T-cell; ADMET: absorption, distribution, metabolism, excretion, and

toxicity; GANs: generative adversarial networks; VAEs: variational autoencoders; RNN: recurrent neural network; CNN: convolutional neural network; LSTM: long short-term memory; SVM: support vector machine; RF: random forest; LASSO: Least Absolute Shrinkage and Selection Operator; AUC: area under the curve; ROC: receiver operating characteristic; scRNA-seq: single-cell RNA sequencing; NLP: Natural language processing.

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C.L. and A.L. supervised and revised the manuscript. C.C. and J.G. wrote and edited the manuscript. W.Z. and Z.W. drew the figures. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

Aiping Lu is an Editorial Board member of The Innovation Medicine. He was blinded from reviewing or making final decisions on the manuscript. The article was subject to the journal's standard procedures, with peer review handled independently of this Editorial Board member and their research groups. The other authors declare no conflict of interest.

DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study.

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