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Emerging Biomarkers and Precision Immunology in Modern Clinical Immunology: Current Applications and Future Directions

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Abstract

Clinical immunology is undergoing a major transformation from traditional disease-centered approaches toward precision medicine based on a deeper understanding of immune pathogenesis and patient-specific biological characteristics. Conventional biomarkers, including autoantibodies, complement proteins, and acute-phase reactants, remain essential for diagnosis and disease monitoring. However, their ability to predict disease progression, explain inter-individual variability, and guide personalized treatment decisions is often limited. Recent advances in omics technologies, including genomics, transcriptomics, proteomics, metabolomics, epigenetics, and single-cell analysis, have significantly improved the understanding of immune-mediated diseases. These technologies enable the identification of molecular signatures, disease mechanisms, and biologically distinct patient subgroups. In parallel, growing research on the human microbiome and the emergence of artificial intelligence (AI) have expanded the analytical capabilities of clinical immunology by integrating molecular, environmental, and clinical data into comprehensive predictive models. This review examines the evolving role of traditional and emerging biomarkers in clinical practice and evaluates how multi-omics platforms, microbiome research, and AI-driven approaches can support personalized therapeutic decision-making in autoimmune diseases.

The synthesis identifies three consistent findings: conventional biomarkers remain indispensable for diagnosis and monitoring but have limited predictive precision; multi-omics and microbiome-derived signatures improve biological stratification but remain largely translational; and AI can integrate these data for risk and treatment-response prediction, although external validation, interpretability, and equitable implementation are still required before routine clinical adoption. Despite substantial progress, significant barriers remain to clinical implementation, including methodological heterogeneity, limited external validation, high costs, complex bioinformatics requirements, ethical concerns, and unequal access to advanced technologies. Precision immunology should therefore be viewed as an evolving clinical paradigm rather than an established standard. The integration of validated molecular biomarkers with clinical expertise offers considerable potential to advance predictive, preventive, and personalized healthcare in immunology.

Keywords: Clinical Immunology; Precision Immunology; Biomarkers; Autoimmune Diseases; Multi-omics; Artificial Intelligence.

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Introduction

Immunological diseases represent a broad spectrum of disorders in which dysregulated immune responses play a central role in causing tissue inflammation, organ damage, and subsequent chronic complications that affect patients' quality of life and clinical prognosis. Although many of these disorders are classified into specific diagnostic entities, individuals sharing the same clinical diagnosis may exhibit significant variation in genetic susceptibility, dominant immune pathways, clinical features, and responses to therapeutic interventions. This biological heterogeneity reflects the fact that a single diagnostic category may encompass several disease subtypes, each with distinct pathogenesis, diagnostic implications, and therapeutic considerations. Traditional practice in clinical immunology has long relied on clinical assessment supported by a well-established set of laboratory biomarkers. Autoantibodies, complement system indices, and systemic inflammatory markers have contributed to improved diagnostic accuracy and enhanced the ability to monitor disease activity, and they remain essential components of daily clinical practice. However, these tools were primarily developed for traditional diagnostic purposes and were not designed to accommodate the multidimensional molecular complexity that characterizes autoimmune diseases. Consequently, they may produce positive results in some clinically unaffected individuals, or negative results in the early stages of the disease or in seronegative individuals. Furthermore, they may lack the ability to accurately predict organ progression, estimate disease outcomes, or determine the likelihood of response to precisely targeted therapies (1,2).

The shortcomings of conventional biomarkers have been increasingly evident with the expansion of targeted therapies. The choice of treatment in diseases like RA, SLE, and IBD is usually based on trial and error. Consequently, there are chances of giving some patients useless treatments before controlling the disease, or they get unnecessary side effects. Precision immunology aims to minimize such variability by combining clinical data and patient-specific molecular information, which would help to make more specific and personalized treatment decisions. Highmthroughput technologies have helped in coming up with a new generation of biomarkers. Protein platforms can be used to quantitatively measure tissue damage markers and soluble media and genetic fingerprinting allows the detection of active immune pathways. The metabolic profiles indicate the functional impact of inflammation, and single-cell methods can indicate pathological cellular conditions that are not easily identified using the conventional comprehensive analysis (3-5). These methods are not only temporary laboratory discoveries, but they provide the description of how immune-mediated diseases are visualized.

The study of the microbiome introduces a new facet into this developing paradigm; the gut microbiome also plays a role in the control of the mucosal immunity, metabolite production, and the integrity of the intestinal barrier. It has been found that an imbalance in the microbiome is an additional risk factor of autoimmune and inflammatory diseases (6,7).

Microbiome analysis is not a standard diagnostic test in the majority of clinical immunology practices; however, it is a promising element in the translational precision medicine application. The technologies of AI and machine learning can be promising for study complex biomedical data.

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Computer models can be used to support in diagnosis, risk prediction, and choice of treatment by incorporating clinical data, biomarker profiles, imaging results, genomic and proteomic data. Nevertheless, when applied clinically, it is necessary for ensuring external validation, transparency, and reducing possible biases (8,9).

This narrative review will focus on the importance of traditional and emerging biomarkers in clinical immunology, and will discuss the potential of precision immunology to enhance the diagnostic process, make outcome predictions, and guide treatment decisions.

Review Methodology:

This paper was written as a narrative review and not as a systematic review or meta-analysis, and was meant to introduce and integrate ideas of clinical significance in fast-paced areas, such as the traditional biomarkers, multigenomics, microbiome studies, AI, and precision medicine in immunology. Preference was also made to those studies published in the period between 2015 and 2026, but preference was given to those which are published after 2020. Reference studies that were old were also in use where necessary to elaborate on important concepts. The sources of evidence were clinical practice guidelines, narrative and systematic reviews, translational studies, cohort analysis and systematic studies pertaining to the discovery and use of biomarkers**.**

Representative diseases were chosen due to their significance in clinical immunology and the role in the use of biomarker-guided care. SLE, RA, and IBD were the reviewed diseases, since they are the models that help understand the typical challenges of autoimmune diseases, such as clinical variability, the response to treatment, and the necessity to improve patient classification. Seeing that this review was narrative in nature, no formal risk assessment of bias was done. Rather, they were rated according to the clinical relevance, quality of methods, reproducibility, practical applicability and their conformity with international guidelines. This method concurs with the conceptual purpose of the review, but it should be noted that such extensive clinical usage will need more solid evidence based on prospective, multicentric validation research (10).

This narrative review was prepared in accordance with the principles of the Scale for the Assessment of Narrative Review Articles (SANRA) to improve methodological transparency and reporting quality (11).

Traditional biomarkers in clinical immunology

The conventional biomarkers are still cornerstone to clinical immunology because they are readily available, cheap, quick to obtain, and they can be used with the usual diagnosis guidelines. They are applied in everyday practice in screening, classifying, evaluating the inflammatory activity, and monitoring the manifestations of certain diseases. Autoantibodies are some of the most common biomarkers used in the clinical immunology. The antinuclear antibodies (ANA) are very sensitive to systemic autoimmune diseases, but they lack specificity due to its presence in healthy people, and in non-immune conditions. In some patients, the presence of anti-double-stranded DNA (dsDNA) antibodies is more specific to SLE, and could be linked to disease activity or lupus nephritis. Rheumatoid factor (RF) has been found to be useful in RA; however, its positive result is less desirable since it is found in other diseases, including chronic infections, some autoimmune disorders, and in the elderly.

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On the contrary, citrullinated proteins (CIs) antibodies are very specific to RA and could occur earlier than the clinical manifestations thereby increasing their diagnostic and prognostic value. Several longitudinal studies have demonstrated that anti-citrullinated protein antibodies (ACPAs) may be detected years before the clinical onset of rheumatoid arthritis (1,12,13).

In SLE, the presence of a low level of complement components (especially C3 and C4) is important as a marker of complement activation in the presence of immune complexes. But they depend on various aspects, including synthesis, consumption, and genetics and have to be interpreted in the framework of clinical data. Serum C3 and C4 concentrations may also be influenced by hepatic synthesis rates, inherited complement deficiencies, and complement gene copy-number variation, which should be considered during clinical interpretation (14-16).

Acute-phase reactants, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are also applicable in measuring the systemic inflammation, although not specific and may be influenced by infection, anemia, age, pregnancy and comorbidities. Although these biomarkers are clinically important, they are not as reflective of the disease's biological complexity.

They seldom determine the particular immune pathways in each individual patient and their prediction of the most effective biological or targeted therapies is not well developed. Such limitations are even more eminent when the treatment options increase and the clinical and economic cost of ineffective treatments are increased (17). The issue thus is not in the substitution of the traditional biomarkers, but rather in the combination with molecular and computational tools to improve the clinical care accuracy. These biomarkers are summarized in Table 1, the most significant ones, their frequent clinical use, and their major limitations.

Table 1: Conventional biomarkers in clinical immunology.

Biomarker	Common clinical use	Main limitations
ANA	Screening for systemic autoimmune disease	High sensitivity but limited specificity; positive results may occur in healthy individuals
Anti-dsDNA	Diagnosis and activity assessment in SLE, especially nephritis	Variable sensitivity and imperfect correlation with activity
RF	Supportive marker for rheumatoid arthritis	Limited specificity; positive in infections and other autoimmune diseases
ACPA	Diagnosis and prognosis in rheumatoid arthritis	Not present in all patients; does not reliably select therapy alone
C3/C4	Monitoring complement activation in SLE	Influenced by synthesis, consumption, and genetic variation
ESR/CRP	Assessment of systemic inflammation	Nonspecific and variably informative across immune-mediated diseases

Emerging biomarkers

The focus of precision immunology relies on biomarkers that can reflect disease mechanisms more directly than traditional tests. Emerging platforms offer diverse biological insights and

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are increasingly being used in applied research to improve the characterization of disease phenotypes.

Gene transcriptomics studies gene expression of RNA to identify active immune pathways. In SLE, interferon-associated gene signatures have helped identify molecular subsets and support the development of targeted therapies. In RA, synovial transcriptomic analysis has revealed different phenotypes that may influence response to biological therapy (3,4).

Proteomics measures protein molecules that play functional roles in inflammation. Multiple analytical platforms allow for the measurement of cytokines, chemokines, complement fragments, and markers of tissue damage. Proteomic data can reflect active immune pathways at the time of sampling more accurately than gene expression alone. Therefore, protein fingerprinting is studied to assess disease activity, predict flares, and guide the selection of appropriate treatment.

Metabolomics focuses on the study of small molecules produced by metabolic processes in the body and microbes. Given the close relationship between immune cell function and metabolic pathways, metabolic alterations can reveal disorders related to oxidative stress, lipid and amino acid metabolism, and energy production. Metabolic signatures are important in distinguishing between active inflammation and tissue damage or other pathological processes in autoimmune diseases (18). Epigenetic biomarkers, like DNA methylation, histone modifications and the expression of microRNA give a better insight into the effects of environmental factors on the regulation of immune genes. Their dynamic and reversible nature is especially significant, but low reproducibility and the absence of a standardization is a significant limitation to clinical implementation. The single-cell methods have transformed immunology because now it is possible to study the immune cells down to the individual cell level in a very detailed manner. The methods enable the detection of infrequent pathological cell groups and functional states that could not be evident in aggregate analyses. They have helped in a clearer understanding of immune and stromal cells in the synovial membrane in RA and has been used in the discovery of new therapeutic targets (5).

New biomarkers remain a long way off the routine use in the majority of clinical practice since use must be supported by evidence of their capacity to enhance treatment decisions over conventional clinical assessment. Table 2 is a summary list of the most notable of these biomarkers and their readiness level for clinical use (19-22).

Table 2. Emerging biomarkers and translational potential

Technology	Information provided	Potential clinical application	Current status
Transcriptomics	Gene expression and immune pathway activity	Disease endotyping and response prediction	Translational
Proteomics	Soluble mediators and tissue injury proteins	Activity assessment and target discovery	Emerging
Metabolomics	Functional metabolic state	Response prediction and mechanism discovery	Investigational
Epigenetics	Regulation of immune gene expression	Environmental and disease-memory signatures	Early translational

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Microbiome and immune regulation

The human microbiome is playing an increasingly important role in maintaining immune homeostasis, as it has been shown to affect the functionality of the epithelial barrier, antigen exposure and metabolite production as well as the differentiation of immune cells. Special focus has been placed on the gut microbiome, as the intestinal mucosa is an important immune interface that needs exquisite balance between immune tolerance and protective response. Several autoimmune diseases such as RA, SLE, IBD, and multiple sclerosis have been reported to have microbial imbalance. Research in RA has shown that it can increase Prevotella species during the early phases of the disease, but has been inconsistent across populations. Associations have been reported in new-onset untreated RA and in some European and Asian cohorts, whereas other population-based studies have shown weaker or inconsistent enrichment, indicating that geography, diet, disease stage, treatment exposure, and strain-level differences may influence the findings (23-29).

A reduction in microbial diversity and changed bacterial composition has been linked to impaired immune control in SLE. Microbiome imbalance is an important aspect of IBD that is closely associated with mucosal inflammation and the pathophysiology of the disease (6,7). Mechanistically, the microbiome can impact immunity by stimulating regulatory T cells, generating short-chain fatty acids, controlling epithelial barrier permeability, and molecular mimicry. These processes emphasize the potential of the microbiome as a biomarkers source and a potential therapy. Dietary change, probiotics and prebiotics, and fecal microbiota transplantation are the proposed interventions, but their systematic use in autoimmune diseases remains under-evidenced.

Precision immunology

Precision immunology uses the principles of precision medicine to autoimmune diseases to go beyond a standardized treatment method, through detecting biological characteristics linked to individual risk, disease progression and anticipated response to therapy. The purpose of it is not to substitute clinical assessment, but to supplement with molecular and computational data. Biological classification, individual treatment selection, dynamic monitoring of the disease and incorporation of clinical and molecular data are the core pillars of precision immunology. As an illustration, it is conceivable that the pathogenesis of RA varies between patients of same diagnosis and that other patterns, including interferon activity or complement-associated activation, are the outstanding ones in patients with SLE.

These differences can be identified, and more specific and logical treatment choices can be made (3,4,17).

Adoption of the biomarkers needs to prove that they are able to enhance the clinical outcomes through ensuring that they have analytical and clinical validity and practicability. A biomarker alone is not sufficient based on its biological importance unless it helps to guide case management or enhance patient outcomes. The conceptual model of precision immunology depicted in figure (1) highlights the fact that precision care is founded on the incorporation and refinement, rather than substitution of the already existing clinical practices.

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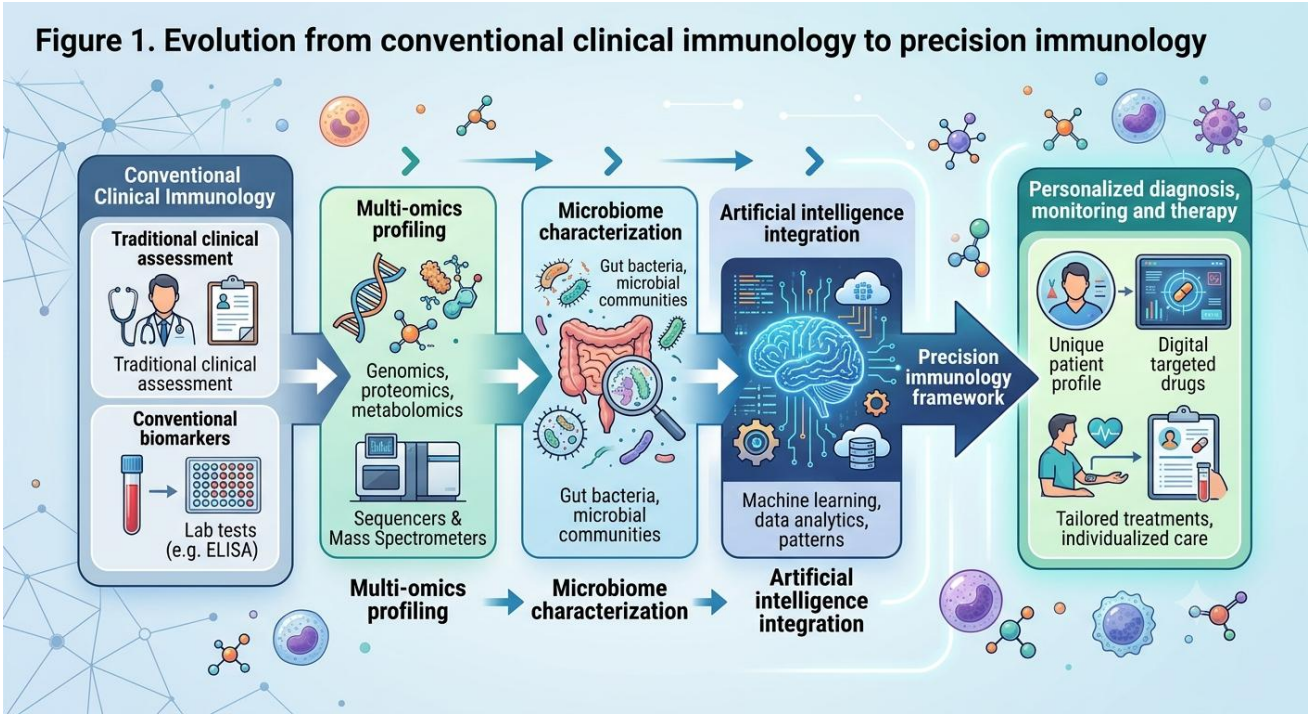

Artificial intelligence in clinical immunology

The increase in biomedical data has prompted the need to develop methods of analysis that can help identify complex patterns with a wide range of data. Machine learning especially AI can be used to aid in the classification, prediction, and detection of biomarkers in immune diseases. Treatment response, risk of disease progression, or organ involvement can be predicted with the use of supervised learning models. Conversely, unsupervised learning techniques can identify clusters of diseases without any prior classification and would possibly be useful in identifying disease phenotypes. Deep learning is also finding more and more applications for the analysis of imaging data, data with high dimensions in omics, and electronic health records. The significance of AI can be further illustrated by the combination with multi-layered data, since integrating clinical data with gene transcription, proteomics, metabolites, and microbiome can provide even some patterns that cannot be identified through the use of traditional analysis methods. Nevertheless, over-allocation issues, bias in the dataset, and lack of interpretability of the model should be taken into consideration carefully. Prediction models frequently show reduced performance when evaluated in independent cohorts because of overfitting, dataset shift, and methodological bias; therefore, external multicenter validation and transparent reporting are required before clinical implementation (8,9,30-34). A safe clinical implementation requires interpretable AI; without this, clinicians would need to be aware of the principles behind the model suggestions, especially when making immunosuppression or biological treatment decisions, or risk of severe adverse effects. As such, AI must complement clinical expertise, rather than take its place.

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Current clinical applications

Although precision immunology is at the clinical development stage, its applications are slowly coming into the picture. Interferon markers, complement activation markers, and protein markers are under investigation in SLE to enhance the classification of the patient and predict the organ involvement. In the meantime, European League Against Rheumatism (EULAR) guidelines highlight the significance of personalized management, risk minimization, and specific therapy, but still, they use the conventional biomarkers in clinical follow-ups (17,35). Antibodies to cyclic citrullinated peptide (ACPA) and the rheumatoid factor (RF) are still valuable classification and prognosis markers in RA.

However, molecular analysis of blood and synovial tissue may contribute to guiding the selection of biological therapies in the future. The challenging nature of RA also highlights the need for more precise biomarkers, given the likelihood that patients may switch between multiple treatment options without achieving sustained disease control (1,17).In IBDs, precision medicine seeks to improve the biological classification of patients, identifying those most likely to respond to treatments targeting tumor necrosis factor (TNF), interleukin-12/23, or interleukin-23 pathways, as well as employing molecular and microbial indicators to predict disease course (36). These examples demonstrate that precision immunology is most beneficial when clinical need is integrated with a variety of treatment options and advancements in biomarker research. Table 3 summarizes the key clinical applications of this approach.

Table 3. Current clinical applications of precision immunology

Disease area	Precision approach	Potential benefit	Clinical readiness
Systemic lupus erythematosus	Interferon signatures, complement, and protein biomarkers	Improved stratification and monitoring	Moderate
Rheumatoid arthritis	Autoantibodies plus synovial/blood molecular profiling	Treatment selection and prognosis	Moderate
Inflammatory bowel disease	Transcriptomic, proteomic, and microbiome markers	Biologic response prediction	Emerging
Multiple sclerosis	Immune and microbiome profiling	Disease characterization	Investigational
Psoriatic arthritis	Integrated biomarker assessment	Personalized treatment pathways	Early translational

Challenges and limitations

Transition from biomarker discovery to the clinical setting is a major challenge for most candidate biomarkers being discovered in small studies that have not been independently validated. Moreover, sample processing variations, bioinformatics tools, analytical platforms, and statistical approaches reduce the reproducibility of results. Cost is another significant issue to the use of precision immunology since single-cell methods, proteomics, and multi-nuclear analyses demand a high level of infrastructure, which might be unavailable in most healthcare

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systems. As such, a lack of equitable and well-planned implementation might increase the inequalities in health instead of decreasing them. The ethics and regulations are core to the world of precision immunology, with molecular data potentially being sensitive, and AI systems being reflective of biases of training data. Hence, transparent governance, informed consent, and equitable usage of technologies are necessary to have responsible usage. The principal implementation barriers and corresponding mitigation strategies are summarized in Table 4.

Table 4. Challenges and future directions

Challenge	Implication	Potential solution
Methodological heterogeneity	Poor reproducibility across studies	Consensus protocols and harmonized reporting
Limited external validation	Uncertain generalizability	Large multicenter prospective cohorts
High cost	Restricted access	Cost-effectiveness studies and scalable platforms
Bioinformatic complexity	Implementation barriers	Interdisciplinary clinical-bioinformatics teams
Algorithmic bias	Unequal performance across populations	Diverse training datasets and explainable AI
Ethical concerns	Privacy and governance risks	Transparent regulatory frameworks

Future perspectives

Clinical immunology is set to shift towards a new paradigm of integrated models to incorporate conventional biomarkers, molecular analyses, and computational decision support. Longitudinal immunological surveillance could also acquire more and more importance compared to individual tests due to its capability to predict the course of the disease, failure of treatment, or toxic side effects. Interpretable AI can be used to transform complex data into understandable and clear clinical guidelines. Nonetheless, the most successful ones will be models that are supported by robust clinical evidence, externally validated, and provide an orientation towards patient outcome improvement rather than a better prediction accuracy. One of the encouraging trends in immunology is precise prevention because it is possible to identify high-risk individuals before irreversible tissue damage can occur, and, by doing so, change the current care towards reactive method to proactive interventions.

Conclusions

Clinical immunology is going through a tremendous transformation process. Classical biomarkers still retain an important place, but alone they do not give a full picture of biological complexity of immune disorders. Biomarker research, microbiome analysis, multilayer data integration and artificial intelligence are promising approaches to discover the reasons for disease variability and improve decision-making process. Precision medicine is regarded as one of the emerging models in clinical practice, whose efficiency depends on scientific validation, cost-effectiveness, ethical approach and collaboration of all the parties involved. When used wisely, it can make clinical immunology predictive, preventive, and personalized. In

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clinical immunology, the immediate priority is therefore not to replace ANA, anti-dsDNA, ACPA, complement, ESR, or CRP, but to validate whether molecular, microbial, and computational biomarkers add reproducible value to disease stratification, flare prediction, organ-risk assessment, and treatment selection in SLE, RA, and IBD. Prospective multicenter studies using standardized assays and clinically meaningful outcomes are required before these tools can support routine immunology practice.

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