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# Diagnostic Challenges in SLE and the Promise of Emerging Immunological Biomarkers

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## ABSTRACT

Systemic Lupus Erythematosus (SLE) is a multifaceted systemic autoimmune disease, which presents with variable clinical features and big diagnostic problems. Diagnosis at an early stage has continued to be a challenge because of conflicting clinical manifestations with other autoimmune disorders, unstable clinical manifestations, and poor sensitivity and specificity of traditional biomarkers. Conventional diagnostic characteristics like antinuclear antibodies (ANA), anti-dsDNA, anti-Smith antibodies, and complement are still necessary, though inadequate, in the correct early diagnosis and monitoring of the disease. New biomarkers such as type I interferon signatures, neutrophil extracellular traps (NETs), and B-cell activating factor (BAFF) have been identified in recent developments in immunology and provide some hopeful insights into the pathogenesis of the disease and may help to diagnose it better. Moreover, omics technologies and artificial intelligence-driven methods of analysis are also driving biomarker discovery and precision medicine plans faster. Although these improvements have occurred, the majority of the new biomarkers are yet to undergo large multicenter studies to be validated before they can be used in routine clinical practice. This review pays attention to the diagnostic problems in SLE and explains how new immunological biomarkers may be used to enhance diagnostic quality in the early phase of the disease and its monitoring as well as tailored therapeutic interventions.

**Keywords:** Systemic Lupus Erythematosus; Antinuclear antibodies; Anti-dsDNA antibodies; Anti-Smith antibodies; Neutrophil extracellular traps; Lupus nephritis; Disease activity biomarkers; Transcriptomics; Proteomics; Biomarker discovery; Autoimmunity research.

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## INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a non-infectious, multifaceted, systemic autoimmune disorder that bothers millions of people both in the United States and globally and offers serious diagnostic difficulties leading to delayed treatment and further exacerbation of clinical manifestations. It is a multisystem disorder, which is marked by the abnormal response of the immune system where the immune system targets healthy organs and tissues, and the result is a broad range of clinical manifestations that include mild mucocutaneous symptoms like skin rashes and severe and potentially fatal organ involvement, including renal, neurological, and cardiovascular complications [1]. SLE has a significant gravity in the world, and the burden of this disease can be differentiated by geographical areas and ethnicity. In a study that was done by Tian et al., the data included in the analysis encompassed 112 epidemiological studies and estimated the global incidence of SLE to be about 5.14 cases in 100,000 person-years, with a much higher incidence seen in women (8.82/100,000) than in men

(1.53/100,000). The prevalence in the entire world was estimated to be 43.7 per 100,000 persons, which is almost 3.41 million individuals affected in the whole world. A substantial geographical difference in prevalence has been noted, with some of the highest levels of prevalence reported in the United Arab Emirates, Barbados, and Brazil [2]. Regardless of the advancements in the treatment plan, SLE still poses a tremendous health burden. The mortality rates of patients with SLE are still about 2-3 times greater than the population mortality rates, with infections and cardiovascular diseases being the major causes of deaths [3]. Moreover, chronic disease management and a high socioeconomic burden on chronic disease management are known to reduce health-related quality of life and functional limitations and add significantly to the socioeconomic burden of patients affected by chronic diseases [4]. The complexity of creating early and precise diagnoses is one of the greatest problems in SLE management. Clinical and serological variability of the disease is very high, and this makes the diagnosis assessments a tough task and can cause misdiagnosis or lead to ignorance of the disease [5]. Moreover, the community and primary care levels have a tendency to fail in their diagnosis early enough, and the symptoms can be non-specific and similar to other autoimmune or inflammatory conditions. These delays are one of the outstanding essential requirements in enhancing patient outcomes and avoiding organ damage that is irreversible [6].

## Pathophysiology of SLE

SLE pathophysiology is complex and multifactorial, comprising genetic susceptibility, environmental stimuli, and dysregulation of immune system balance, which eventually results in the formation of autoantibodies and the deposition of tissue-damaging immune complexes in different body organs. The combination of these mechanisms leads to the non-homogenous clinical manifestation of the disease. The immunological loss of immune tolerance to self-antigens is a crucial characteristic of SLE pathogenesis caused by autoreactive B and T lymphocytes that are activated. This dysregulation of the immune system facilitates the generation of pathogenic autoantibodies that are aimed at nuclear constituents including DNA and histones and ribonucleoproteins. In the development of SLE, genetic predisposition is also important because of the formation of circulating immune complexes that deposit in the tissues and organs leading to the activation of complement and inflammatory reactions that eventually cause tissue damage and organ dysfunction [6,7]. The disease has been identified to be polygenic meaning that it has many susceptibility genes that by themselves have a minor effect but together they add to the prevalence of the disease due to gene-gene and gene-environment interaction. Environmental factors also play a role in predisposing people with genetic susceptibilities to the disease and enhancing the control process as well as disease progression [8]. Immune activation of the type I interferon pathway through external stimulation (ultraviolet radiation, infections, and some drugs) and internal (hormonal influences, female gender) have been reported to play a critical role in the pathogenesis of SLE [9]. Recent immunology progress has demonstrated that the innate immune system plays an important role in SLE pathogenesis. Plasmacytoid dendritic cells and immune cells including plasmacytoid dendritic cells release high levels of interferon in response to immune complexes that contain nucleic acid. Also, the neutrophil extracellular traps (NETs) formation leads to the leaking of nuclear antigens and enhancement of autoimmune reactions. The other significant pathogenic phenomenon is the malfunction of apoptotic cells and immune complexes clearance, resulting in the formation of cellular debris with nuclear antigens [10]. Continued presence of antigenic stimulation also stimulates autoantibody formation and formation of immune complex, which in turn perpetuates the inflammatory response and leads to the disease process [8].

## Current Diagnostic Criteria for SLE

SLE classification and diagnosis has also changed significantly within the last few decades, and a number of criteria have been designed to enhance diagnostic accuracy and ease research. The most developed framework according to which the classification of SLE is carried out at the present moment is the 2019 criteria that were developed by the European League Against Rheumatism and the American College of Rheumatology. These criteria have high diagnostic performance, with a sensitivity of about 96.1% and a specificity of about 93.4 percent, and include a domain-based strategy involving a weighted system with a combination of clinical and serological observations to form the basis of standardization of SLE classification [14]. Prior attempts to standardise SLE classification started with the ACR criteria released in 1982 and updated later in 1997 and incorporated a domain-based strategy which embodies a weighted system based on the combination of clinical and serological observations. The criteria in such a system were that there has to be at least four out of eleven criteria to be classified. Despite the long years of use, these criteria did use an unweighted structure and occasionally had limitations in the ability to detect early or unusual manifestations of the disease [12]. To overcome the limitations, the Systemic Lupus International Collaborating Clinics (SLICC) criteria was introduced in 2012 and enlarged the number of clinical and immunological characteristics incorporated in the classification system. The new criterion of 2019 EULAR/ACR classification was the first step in enhancing the diagnostic sensitivity of SLE by enabling its earlier diagnosis but at the cost of slightly decreased specificity, which caused false

diagnoses in certain patients [13]. A positive test on Antinuclear Antibody (ANA) in this system is a mandatory entry criterion. As soon as this requirement is fulfilled, patients are assessed based on a set of weighted clinical and immunological criteria ordered into hierarchical domains and each of the items allocated is assigned a score between 2 and 10 points. A total of 10 points and above is needed to qualify as SLE. Other important laboratory tests that are involved in this system are also the Anti-double stranded DNA antibodies, Anti-Smith antibodies, Antiphospholipid antibodies and low levels of complement such as the C3 and C4 which are used to reflect on the activity of the immune complexes [12,13]. There are also comparative studies that have been done to check the performance of these classification systems. The meta-analysis of 29 studies (18 studies of adult-onset SLE and 11 studies of childhood-onset SLE) showed that the 2019 EULAR /ACR criteria show the highest diagnostic accuracy in adults with SLE, and the 2012 SLICC criteria are more effective in the context of childhood-onset SLE, which is why age factor should be considered when classifying a disease [15].

**Conventional Biomarkers Used in SLE Diagnosis**

Traditional immunological biomarkers still are the basic means of SLE diagnosis and follow-up. These include Antinuclear Antibody (ANA), Anti-double stranded DNA antibodies (anti-dsDNA), Anti-Smith antibodies, and complement proteins C3 and C4 that are commonly used in routine clinical practice. These biomarkers are included in the existing classification systems and play a major role as they are used as major indicators of autoimmune processes in patients with SLE suspicions [16]. Among the traditional markers, the presence of anti-dsDNA antibodies is of particular importance due to their correlation with disease activity and organ involvement. The diagnostic efficacy of the traditional biomarkers also shows a significant variation, even though they are all clinically useful, with anti-dsDNA antibodies being the most common laboratory presentation at presentation in a clinical study of 35 healthy controls versus 35 SLE patients [17]. A more recent multicenter validation study on 105 SLE patients, 173 other autoimmune disease patients, and 83 healthy controls tested the diagnostic accuracy of some of the established markers. Anti-dsDNA antibodies in this analysis produced an area under the receiver operating characteristic curve (AUC) of 0.72 which represents a moderate diagnostic performance. Conversely, anti-Smith antibodies had a reduced diagnostic value with an AUC of 0.61 and complement levels had equal modesty with C3 with an AUC of 0.69 and C4 with an AUC of 0.66 [18]. Besides diagnostic use, some traditional biomarkers do give information on the disease activity and the organ involvement with C3 having an AUC of 0.69 and C4 having an AUC of 0.66. Research has shown that the analysis of anti-dsDNA antibody levels, low serum C3 levels, and proteinuria have a moderate predictive capacity of the disease activity and renal involvement especially in patients with lupus nephritis [19]. However, the main weakness of these traditional biomarkers is that none of them has high sensitivity and specificity in the diagnosis of SLE. Consequently, clinicians in most cases use both clinical observations and various laboratory markers to make a proper diagnosis and follow the course of the disease [17]. The mentioned restrictions have stimulated a growing research interest in identifying new immunological biomarkers that could enhance the diagnostic accuracy and allow detecting the disease earlier.

**Diagnostic Challenges in SLE**

SLE diagnosis is of significant clinical concern because of the heterogeneity of the disease and due to the similarity between the manifestations of the disease and other autoimmune and inflammatory diseases, the diagnostic quality of biomarkers that are currently available is low. All this leads to delays in diagnosis and can potentially lead to complications in the provision of appropriate treatment on time since the disease may touch upon many organ systems and a large number of symptoms. There is also significant clinical heterogeneity of SLE, which can be one of the obstacles on the way to the timely introduction of appropriate treatment. These are similar to other similar autoimmune diseases like rheumatoid arthritis, Sjogren syndrome, or mixed connective tissue disease, which complicate the process of differentiation. Research has highlighted the complexity of the diagnosis of SLE and the fact that despite the importance of serological tests in diagnosing the disease, they are not always conclusive to diagnose the disease [20]. The other critical limitation is the time sensitivity and specificity of diagnostic tests. Most of the laboratory markers that are being used in the diagnosis of SLE might not be specific at the early stages of the disease. On the other hand, some biomarkers with higher diagnostic certainty tend to be detected only at the time of a later disease advancement or when the organ damage is already done. It generates a diagnostic gap at the initial stages of the disease when timely diagnosis would be most useful to avoid irreversible complications [21]. The mentioned diagnostic difficulties often result in a significant delay between the onset of the symptoms and their definite diagnosis. The recent researches point to the scale of this issue. As an example, one study has indicated a median time of about 47 months between the onset of the first symptoms and the actual diagnosis, whereas other studies have estimated a median of about two years in which the disease is actually diagnosed [22,23]. Prolonged length of diagnostic interval has severe clinical consequences. Delayed diagnosis has been linked to higher risk of organ damage, worse overall health outcomes and increased morbidity and mortality rates. Moreover to

the physical impact, diagnostic uncertainty and persistent disease being can also have a deleterious impact on the psychological well-being of patients, being a major contributor to diseases including depression, anxiety and poor quality of life [23].Notably, the SLE can be classified as a clinical diagnosis as there is no single pathogenic element that can establish the disease conclusively, in spite of the improved laboratory test and classification criteria. Doctors should thus use a holistic diagnosis that incorporates clinical presentation, laboratory results and immunological markers to make the right diagnosis [24]. These diagnostic shortcomings are consistent, thus the pressing necessity of more sensitive and specific biomarkers, which would enable earlier diagnosis and better patient outcome.

**Emerging Immunological Biomarkers in SLE**

Over the last few years, developments in the field of immunology have brought in the discovery of a number of new biomarkers that could contribute to the diagnosis and monitoring of SLE. Among them, the most well-characterized and studied biomarkers include the interferon (IFN) signature and neutrophil extracellular traps (NETs), and increasing evidence indicates them to be relevant to the clinics. Others like the B-cell activating factor (BAFF) and some cytokines have also been explored but the diagnostic utility of these molecules is relatively little known. The finding of an interferon signature, which is the upregulation of type I interferon-controllable genes in immune cells is one of the most important findings in SLE research. Early transcriptomic papers showed an unusual gene expression signature of SLE. Indicatively, a landmark study by Bennett et al. found 15 of the most significant genes upregulated in patients with active SLE of which 14 were interferon-inducible genes, illustrating that interferon signaling has a strong role in the pathogenesis of the disease. Other potential biomarkers include the development of Neutrophil Extracellular Traps (NETs), which are web like structures of DNA, histone and antimicrobial proteins that are released by activated neutrophils and they are associated with disease activity and clinical severity [25,26]. The contribution of NET formation to SLE autoimmune responses is that nuclear antigens are exposed, and hence, autoimmune responses take place. Clinical trials have shown that there are large quantities of NET-related biomarkers, such as cell-free DNA (cfDNA) released into the blood, activity of myeloperoxidase (MPO), and anti-MPO antibodies, in individuals with SLE over healthy controls. These markers have been demonstrated to be associated with anti-dsDNA antibody level and total disease activity, which implies they can be used in diagnosis and monitoring of the disease. Also, growing focus has been placed on the B-cell Activating Factor (BAFF), which is a cytokine that is essential in preserving the survival of B-cells, their development, as well as the production of autoantibodies [27,28]. High levels of BAFF have been detected in patients with SLE and especially those who have not been put on immunosuppressive therapy yet. There has been a report of correlations between high concentrations of BAFF and NET-related markers and anti-dsDNA antibodies, indicating that BAFF could be involved in the intensification of autoimmune activities. Nevertheless, in comparison with interferon signatures and NETs, there is still a relative lack of evidence to support BAFF as a diagnostic biomarker [27]. Generally, the existing body of literature on such immunological markers demonstrates that they can enhance the early detection of the disease, monitoring, and therapeutic decision-making in SLE. However, further larger-scale research is needed to confirm their clinical use and to establish whether these biomarkers can be used as an adjunct or even as a supplement to existing diagnostic approaches. The major diagnostic challenges of SLE and the role of emerging immunological biomarkers in improving diagnostic accuracy are summarized in **Figure 1**. Key emerging immunological biomarkers and their clinical significance are summarized in Table 1.

**Role of Omics Technologies in Biomarker Discovery**

The emergence of high-throughput molecular technologies in recent years has enhanced the rate at which the novel biomarkers of complex diseases like SLE are discovered. Omics technology, such as genomics, transcriptomics, proteomics, and metabolomics, offers new formidable platforms of biological analysis on large scales and has become a crucial tool in the current biomedical studies. Omics technologies allow exploring changes in the state of the molecules related to the disease processes in a comprehensive way and help identify possible diagnostic and prognostic biomarkers [29]. The platforms of these omics studies molecular changes in relation to the disease processes at a different level of cell organization. Genomics concentrates on the study of the sequence of DNA material and genetic variation that could be a cause of diseases. Transcriptomics assesses the expression pattern of genes based on the measurement of RNA transcripts and it gives us an idea of genes that are actively regulated during disease progression. Proteomics examines the expression of proteins, post-translational modification of proteins that influence cellular behavior. Lastly, metabolomics is used to measure the small-molecule metabolites that are generated in cellular metabolism, which indicate downstream functional state of biological pathways. Combined with other complementary technologies, these technologies allow producing extensive molecular profiles that could assist with the diagnosis and prognosis of a disease, its staging, and therapeutic choices [30,31]. Nevertheless, the translation of the biomarkers, which are derived in omics, into clinical practice is rather difficult. Despite the identification of thousands of candidate

**Table 1: Emerging Immunological Biomarkers in Systemic Lupus Erythematosus and Their Clinical Significance**

| *Biomarker* | *Biological Role* | *Diagnostic/Clinical Significance* | *Key References* |
|---|---|---|---|
| *Type I Interferon (IFN) Signature* | Upregulation of interferon-stimulated genes in immune cells | Associated with disease activity; useful for early diagnosis and monitoring | [25,26] |
| *Neutrophil Extracellular Traps (NETs)* | Web-like DNA-histone structures released by neutrophils | Promote autoantigen exposure; correlate with disease severity and organ damage | [27,28] |
| *B-cell Activating Factor (BAFF)* | Regulates B-cell survival and autoantibody production | Elevated in untreated SLE; potential marker for immune activation | [27] |
| *Cell-free DNA (cfDNA)* | Released during apoptosis and NET formation | Reflects systemic inflammation and disease activity | [27] |
| *Monocyte Chemoattractant Protein-1 (MCP-1)* | Chemokine for monocyte recruitment | Associated with lupus nephritis and renal inflammation | [36] |
| *TNF-like Weak Inducer of Apoptosis (TWEAK)* | Inflammatory cytokine involved in tissue injury | Potential marker for renal involvement and disease progression | [36] |
| *Neutrophil Gelatinase-Associated Lipocalin (NGAL)* | Protein released during kidney injury | Early biomarker for lupus nephritis | [36] |
| *Cytokines (IL-10, IL-17, IP-10)* | Immune signaling mediators | Correlate with disease activity and flare prediction | [35,36] |

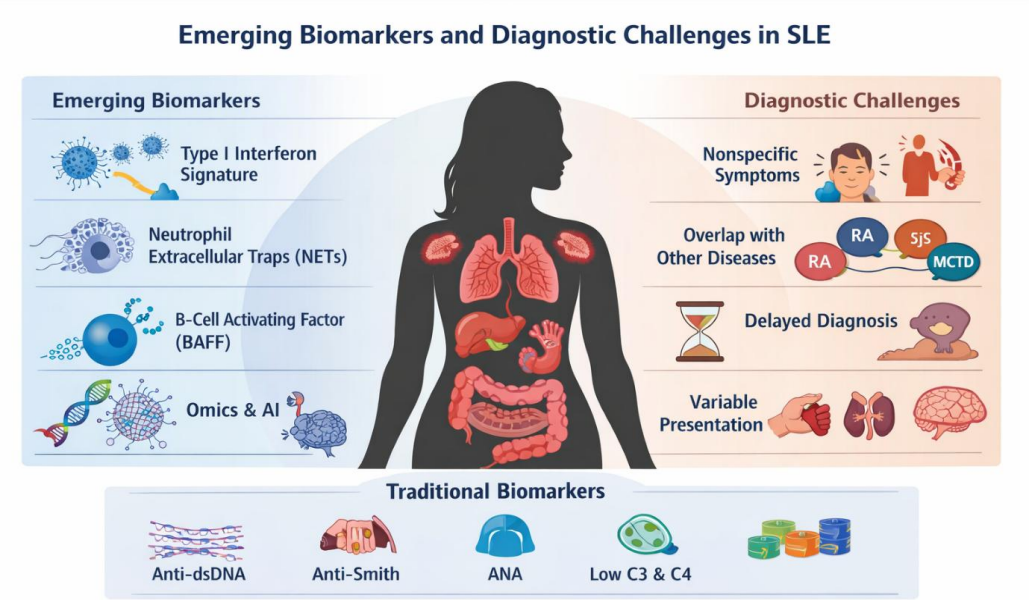


**Figure 1: Emerging biomarkers and diagnostic challenges in systemic lupus erythematosus**

biomarkers through omics technologies, a very small fraction has been able to go on to clinical validation and clinical diagnostic utilization. Limited reproducibility, lack of uniformity in experimental protocols, and lack of large-scale validation studies have been some of the factors that have hampered the clinical implementation of some of the proposed biomarkers [32]. Technological developments have however enhanced the performances of some of the omics methods. Specifically, recent advances in mass spectrometry-related methods of analysis have allowed improving the sensitivity and accuracy of the proteomic and metabolomic analyses, thereby promoting more credible identification and confirmation of disease-related molecular signatures [33]. Nonetheless, current studies indicate that there is limited progress in integrating multi-omics (combining genomics, transcriptomics, proteomics, and metabolomics) technologies, although this could be a more definitive way to understand the pathophysiology of disease and enhance the validity of biomarker discovery [34]. Nevertheless, there are still some challenges to overcome before omics technologies can fully utilize their clinical potential. The problem of data standardization, reproducibility, and the incorporation of extensively large and complicated datasets remain obstacles in

the application of the omics results as a diagnostic technique. In its turn, this will require the creation of effective analytical frameworks and knowledge-based methods to allow the effective clinical implementation of omics-derived biomarkers in diseases like SLE.

**Clinical Utility of Emerging Biomarkers**

There has been a lot of attention to the emerging biomarkers in their potential to enhance clinical treatment of SLE. Such biomarkers could be used to aid in the early diagnosis, disease activity monitoring, and prediction of flares of the disease or organ involvement. Even though a lot of candidate biomarkers have been discovered due to the recent studies, the majority of them are still in the investigation phase and have not yet found their application in clinical practice on a regular basis. Early diagnosis is one of the essential directions of application. Research into biomarkers has also helped in improving the classification criteria of many autoimmune and rheumatic diseases, which has helped the clinicians to have the opportunity of identifying the patients in the earlier stages of disease progression. Indicatively, various molecular and immunology markers have been integrated into new classification systems to enhance diagnostic or detection sensitivity of autoimmune disorders at an earlier or even earlier time [35]. Some of the biomarkers that have shown potential to aid in monitoring disease activity in the context of lupus nephritis, a severe renal complication of SLE, include monocyte chemoattractant protein-1 (MCP-1), TNF-like weak inducer of apoptosis (TWEAK), and neutrophil gelatinase-associated lipocalin (NGAL) [36]. A number of cytokines and chemokines have been examined as the indicators of the inflammatory activity in SLE. Interleukin-10 (IL-10), interleukin-17 (IL-17), MCP-1 and interferon-g-induced protein-10 (IP-10) are biomolecules linked with the variation in the disease activity and could provide valuable data to evaluate the extent of the inflammation and immune response [36]. Moreover, biomarkers are also being investigated in detecting organ specifics of autoimmune diseases. As an example, the predictive ability of biomarkers to avert disease flare and prognosis has been shown to be useful in identifying the active gastrointestinal involvement in inflammatory vasculitis and other autoimmune diseases [37]. Biomarkers can be used to define specific subgroups of patients, and can be useful to clinicians in forecasting the course of disease progression and therapeutic toleration. Some of the initial studies have indicated that patient stratification in terms of disease severity and clinical outcomes can be carried out with the help of biomarker profiling [38]. However, with encouraging results, the application of new biomarkers to everyday clinical practice is still wanting [36]. Even though decades of research have been able to identify a great number of potential biomarkers, exceptionally few of them have been sufficiently validated to be included in a regular diagnostic or monitoring regimen [39]. Various factors would limit this, such as small sample sizes, non-reproducibility between studies, and inconsistency in analytical methodologies. Future studies would need to look at large multicenter validation studies and creation of multiplex biomarker panels, which are biomarkers combined to enhance diagnostic accuracy and clinical applicability. These combined measures can increase the quality of biomarker-based diagnostics and eventually drive precision medicine tactics in addressing the SLE at the end [40].

**Future Perspectives and Personalized Medicine in SLE**

Integrated biomarker panels, artificial intelligence (AI)-aided diagnostics, and precision medicine are becoming more oriented in the future of SLE diagnosis and management. These new strategies are to break the constraints of the conventional diagnostic techniques and to enhance the detection and monitoring of the diseases and customized therapy decision-making. Even though these aspects have been widely developed, a large-scale clinical adoption still awaits further confirmation, but one of the brightest developments is the use of biomarker panels, a combination of various immunological and molecular markers to increase diagnostic accuracy and disease monitoring. Combined autoantibody, complement, and type I interferon signature-based panels have been suggested to serve as a unanimous approach to measuring disease activity and therapeutics in SLE. Combinations of biomarkers can further refine our comprehension of immune dysregulation than single biomarkers and can assist clinicians to define patient subpopulations sharing common disease features at cellular and molecular scales [41].Improved capabilities to profile immune dysregulation on a cellular and molecular scale have been brought about by advances in immune profiling technologies, such as flow cytometry and transcriptome analysis, which can help clinicians identify patient subgroups with specific disease features [41]. The application of machine learning and artificial intelligence in SLE research is another area of rapidly developing knowledge, as it enables researchers to determine differences in the populations of immune cells and patterns of gene expression of patients with SLE and use them as valuable insights into the mechanisms of the disease and possible therapeutic targets [42]. Predictive models that are developed based on AI-based analytical models are increasingly employed in the early diagnosis, disease progression, and treatment response. With the large datasets, machine learning algorithms can be used to detect the new biomarkers and patterns that can not be detected by traditional statistical approaches [43]. Nonetheless, there are a number of challenges in the path of these innovations being adopted in the near future, even though

medical imaging, multi-omics, and wearable-generated digital health data are now being read automatically using AI-assisted system tools with potentially beneficial outcomes [44]. Most of the predictive models that have been trained using machine learning methods have not gone through external validation on a sample of patients, and this is needed to make it reliable and applicable in the natural clinical environments [43]. In addition, concerns about data standardization, reproducibility, and regulatory approval still reduce the translation of these technologies into clinical practice, where genetic, epigenetic, and molecular pathway data can be combined into informed targeted therapeutic interventions and individual patient care. Altogether, the data standardization, reproducibility, and regulatory approval remain the challenges that limit the translation of these technologies into clinical practice. All in all, the sphere of SLE research is gradually shifting toward the framework of precision medicine, where genetic, epigenetic, and pathway data can be combined to inform targeted therapeutic interventions These methods can change the way SLE is treated because they can allow earlier diagnosis, better disease monitoring, and more effective individual treatment can be offered [45].

## CONCLUSION

Systemic Lupus Erythematosus is one of the most difficult autoimmune diseases to diagnose autoimmune disease with its clinical heterogeneity, similarity in symptoms with other autoimmune diseases, as well as the inability of current biomarkers. Patients manifest over a broad range of symptoms which may include various organ systems and therefore it is difficult to recognize them at an early stage. Even though the classification criteria and the traditional biomarkers including Antinuclear Antibody, Anti-double stranded DNA antibodies, Anti-Smith antibodies, and complement levels (C3 and C4) are important in the diagnosis of the disease, none of them would be sensitive and specific enough to detect the disease positively. Consequently, diagnostic delays are still prevalent and are linked to a greater risk of organ damage, diminished quality of life, and higher morbidity and mortality.Recent breakthroughs in immunology and molecular biology have marked the potential of the emerging immunological biomarkers such as interferon signatures, Neutrophil Extracellular Traps, and B-cell-related marker, to enhance diagnostic accuracy and disease surveillance. Also, the combination of multi-omics technologies and biomarker panels with artificial intelligence-based analysis tools provides new opportunities to detect diseases earlier and manage them individually.Even though all these promising results are available, the majority of emerging biomarkers still need to be validated and standardized at large scale to implement them into regular clinical practice. Future studies must thus aim at validating multiplex biomarker panels and incorporating sophisticated computational methods to enable earlier diagnosis, better monitoring of the disease and precision medicine-based intervention plans in SLE.

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