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Utilization of Biomarkers in Lupus Nephritis

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Abstract

Lupus nephritis (LN), occurs in up to 60% of SLE patients, and is a leading cause of disability and death. Current treatment of LN consists of a combination of high dose corticosteroids that non-specifically decrease inflammation and cytotoxic medications that reduce autoantibody production. That combination of therapy is associated with significant side effects while remission rates remain inadequate. Since the introduction of biologics into the pharmacological armamentarium, there has been hope for less toxic and more effective therapies for LN. Unfortunately, after multiple clinical trials, no biologic has improved efficacy over standard of care therapies for LN. This is likely, in part, due to disease heterogeneity. The utilization of biomarkers in LN may provide a way to stratify patients and guide therapeutic options. In this review we summarize traditional and novel LN biomarkers and discuss how they may be used to diagnose, stratify, and guide therapy in patients with LN, bringing precision medicine to the forefront of LN therapy.

Keywords

biomarkers; lupus nephritis; systemic lupus erythematosus; autoantibodies; precision medicine; genetic biomarkers

Background

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with genetic, environmental, immunoregulatory, hormonal, and epigenetic factors [1]. Kidney involvement, termed lupus nephritis (LN) occurs in 50-60% of patients with SLE [2]. After decades of research, non-specific immunosuppressive regimens remain the core of LN treatments. Current standard of care consists of corticosteroids combined with either cyclophosphamide or mycophenolate mofetil (MMF) [3]. Achieving complete clinical remission strongly correlates with long term kidney survival, but the rate of complete remission remains 40-60% at 2 years and is much lower at earlier time points [4, 5].

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While clinical outcomes have improved overall for LN, as many as 43% of patients with class IV LN and 20% with class V LN, will go on to develop End Stage Kidney Disease (ESKD) [6]. Outcomes are worse among certain ethnic groups, notably African Americans and Hispanics [7–10]. New therapies, with less toxicity and better efficacy, are needed. In recent years, several biologic agents have been tested, many of which target specific immune pathways. Unfortunately, after more than a decade of clinical trials, none have provided increased efficacy over standard of care [11]. This is, to an extent, because of the heterogeneity of the disease. For an individual patient, one immune pathway may contribute more to the disease process than another. Biomarkers identifying upregulated immune pathways in an individual patient may help stratify therapies for that patient, making precision medicine a reality in the treatment of LN. Additionally, novel activity biomarkers may identify early therapeutic failures so that treatment regimens can be altered sooner, reducing the risk of chronic injury. Biomarkers also potentially provide a non-invasive picture of what is happening at the tissue level, limiting the need for repeat kidney biopsies.

Defining Biomarkers

Biomarkers have been defined as biological characteristics that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or response to intervention [12]. Ideal LN biomarkers will identify those at risk for developing disease, determine risk of disease progression, distinguish between active and chronic disease, and help stratify choice and duration of therapy. A panel of genetic, serum, urine, and tissue biomarkers will need to be utilized since no individual biomarker can serve all of these functions.

Traditional LN Biomarkers

Clinical laboratory values such as elevated serum creatinine, proteinuria, and hematuria remain important biomarkers in LN and perturbations in these labs often lead to an initial or repeat diagnostic kidney biopsy. Of these labs, proteinuria appears to be the strongest predictor of long term renal outcome. Follow up of LN patients in two large European Trials demonstrated that proteinuria at one year was the best predictor of long term renal outcome [13, 14]. This finding was also observed in an ethnically diverse Brazilian Cohort [15]. One year proteinuria levels of less than 0.7-0.8 g/day were found to be the best predictor of long term renal survival [13–15]. Further studies are needed to evaluate whether proteinuria at one year may guide decisions on duration of immunosuppressive therapy.

Autoantibodies to double stranded DNA (dsDNA) and markers of complement activation are widely used in clinical practice in the diagnosis and surveillance of patients with LN. The predictability of anti-dsDNA in the development of nephritis is complicated by different testing methods (immunofluorescence, radioimmunoassay, enzyme linked immunosorbent assay), isotype, and variable cross reactivity of anti-dsDNA to glomerular antigens. Studies supporting the role of anti-dsDNA in LN include the observation that increased titers of anti-dsDNA precede LN flare and anti-dsDNA antibodies have been eluted from LN kidneys [16, 17]. Conversely, many patients with anti-dsDNA never develop LN and some patients with LN do not have anti-dsDNA [18–20].

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Serum C3 and C4 measurements are readily available as clinical tests and are frequently utilized in the clinical surveillance of LN patients. C3 is a component of the alternative pathway while C4 is a component of the classical pathway, which is triggered when C1q binds to immune complexes. C1q is critical for opsonization and clearance of apoptotic bodies and immune complexes[21]. Auto-antibodies to C1q (anti-C1q) are present in a significant number of SLE patients and correlate strongly with renal involvement [18, 22–24]. The role of anti-C1q in the pathogenesis of nephritis is not fully understood, but several potential mechanisms have been described. Anti-C1q may bind to C1q, and interfere with its clearance function, increasing exposure to nuclear antigens and enhancing anti-nuclear antibody formation [25]. Additionally, anti-C1q may activate complement through direct and indirect mechanisms. Anti-C1q isolated from SLE patients activated both classical and lectin complement pathways [26]. Anti-C1q bound to immobilized C1q increased C1q production by human monocyte-derived macrophages and subsequently, the secreted C1q activated the classical complement pathway [27]. Finally, anti-C1q led to enhanced complement activation in the setting of immune complex glomerulonephritis in mice [28].

While it is clear that complement activation is critical in the pathogenesis of LN, studies to determine how changes in complement levels can predict SLE or LN flare have yielded variable results [19, 29–31]. Esdaile et al. evaluated the sensitivity, specificity, and likelihood ratios of anti-dsDNA, C3, C4, and anti-C1q to predict future flares (renal and non-renal) in a cohort of 202 SLE patients [29]. They found sensitivity of approximately 50% for all tests and specificity of less than 75% [29]. Moroni et al. looked at these same variables to predict current flare and found that anti-dsDNA and C3/C4 were poor predictors of class V LN, but had sensitivities between 70-79% in proliferative LN [20]. Interestingly, anti-c1q was the only marker that predicted flares in both class V and proliferative LN and it out-performed all other markers, with a sensitivity of 80.5% and specificity of 71% in proliferative LN [20]. The timing of measurement may account for some discordance in the studies. Esdaile et al. evaluated samples 3-9 months preceding flare, while Moroni et al. evaluated samples at flare, suggesting that anti-C1q and C3/C4 are better at identifying current flares rather than predicting future flares[20, 29]. Birmingham et al. evaluated baseline, pre-flare (2 months), and at-flare C3/C4 levels in a longitudinal study. They found reduced C4 levels were predictive of a future flare, whereas reduced levels of C3 were seen at time of the flare [32]. The combination of anti-C1q with anti-dsDNA and/or complement levels improved diagnostic performance over individual tests [20, 22, 23, 33]. In a cross sectional study, the combination of anti-C1q, anti-dsDNA, and low complement levels was strongly associated with renal involvement (OR 14.9, $p < 0.01$) [22]. In a prospective longitudinal study, anti-C1q combined with C3 and C4 provided the best performance for predicting renal flares with multivariate analysis ($p<0.0005$, $p<0.0005$, $p<0.005$ respectively) [20]. Further, the combination of 4 negative tests had a high negative predictive value (NPV) [20]. In a prospective, nested case controlled study, the combination of anti-C1q with low C3 improved PPV of LN flare from 35 to 60% and NPV from 93 to 96% [33]. In a retrospective longitudinal study of LN patients, the presence of both anti-C1q and anti-dsDNA predicted higher activity and poorer prognosis [23].

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Novel Autoantibodies

Several glomerular antigens have been identified as potential targets of autoantibodies in LN. These include cell specific and glomerular basement membrane targets (table 1). Glomerular cell protein targets include alpha actinin, alpha enolase, annexin A1, and annexin A2 [34–40].

Glomerular basement membrane protein targets include heparan sulfate and laminin [41–44]. Cross-reactive anti-dsDNA targets glomerular alpha-actinin and multiple studies have identified antibodies to alpha-actinin in patients with LN [34–36, 45, 46]. Animal studies demonstrated that lupus prone (MRL/*lpr*) mice have high levels of circulating anti-alpha-actinin and that nonlupus prone (BALB/c) mice immunized with alpha actinin develop anti-alpha-actinin and immune complex glomerulonephritis[47, 48]. One group demonstrated that anti-alpha-actinin levels decrease with treatment, thus anti-alpha-actinin may be useful as both a diagnostic and disease activity biomarker [49]. However, other studies failed to demonstrate the association of anti-alpha-actinin with LN [50, 51].

Antibodies targeting Annexin A1 and A2 have been identified in human LN [38–40, 52]. Bruschi et al. identified IgG2 antibodies to annexin A1 in nephritic glomeruli and identified the same isoform in the sera of LN patients [37]. Anti-annexin A1 levels decreased after 12 months of therapy, suggesting a role as both a diagnostic and disease activity biomarker [52]. Annexin A1 is a ubiquitous protein, present in immune cells and resident glomerular cells. In immune cells, annexin A1 helps regulate innate and adaptive immune responses [53, 54]. Multiple groups have independently identified annexin A2 as a target for autoantibodies in LN [38–40]. Annexin A2 is expressed in glomerular mesangial cells, endothelial cells, and epithelial cells [38, 55]. Annexin A2 co-localizes with glomerular IgG and C3 deposits in LN [38]. Our group demonstrated that autoantibodies to annexin A2 are seen in LN class III and IV, but not class V LN [39]. Anti-annexin A2 decreased after disease remission [38]. Thus, anti-annexin A2 may be useful as a diagnostic and disease activity biomarker for proliferative LN.

Auto-antibodies targeting alpha-enolase have been identified in several immune mediated glomerular diseases including LN, mixed cryoglobulinemia, and primary membranous nephropathy [37, 56, 57]. In LN, antibodies to alpha-enolase were initially described as specific to IgG2 in an Italian cohort [52]. However, IgG1 and IgG3 isotypes were identified in a Japanese cohort [58]. The receiver operating characteristic curve (ROC) area under the curve (AUC) for anti-alpha-enolase IgG2 was 0.87 ($p<0.001$) in LN compared to normal controls and 0.70 ($p<0.001$) in LN compared to SLE controls[52]. Additionally, anti-alpha enolase levels decreased after 12 months of therapy, suggesting it may be useful as both a diagnostic and disease activity biomarker [52]. The role anti-alpha-enolase plays in the pathogenesis of LN is unclear. Alpha-enolase is a multifunctional protein and its function is determined by cellular location: intracellularly it serves as a glycolytic enzyme while it acts as a plasminogen receptor on the cell surface [59]. Antibodies to alpha-enolase may interfere with the plasminogen receptor function, leading to an increased risk of thrombosis. Li et al demonstrated that antibodies to alpha enolase positively correlated with proteinuria and negatively correlated with D-Dimer in an SLE cohort [60]. Additionally, alpha enolase may be

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released from neutrophil extracellular traps (NETs) during NETosis which may trigger auto-antibody formation [54].

Autoantibodies may bind to components of the glomerular basement membrane (GBM) directly or to nucleosomes which have become "planted antigens" bound to GBM [42, 43, 61, 62]. Nucleosomes have a high affinity for negatively charged GBM proteins including laminin, heparan sulfate, and collagen IV [43, 44, 63]. Autoantibodies binding heparan sulfate have been identified in animal models and human LN [41, 42].

While some glomerular antibodies appear to be nephritogenic, the pathogenic contribution of others remains elusive. Additionally, some SLE autoantibodies appear to protect against nephritis. Anti-pentraxin 3 reduces risk of LN in SLE patients [64–66]. This protective effect was recapitulated in an animal model of LN [67]. The exact mechanism is still under investigation, but anti-pentraxin 3 appears to decrease complement activation [67].

Multiple auto-antibodies targeting glomerular antigens have been proposed as biomarkers for LN, but no standardized approach has been utilized for identifying these auto-antibodies. Some centers have measured cross reactive anti-dsDNA while others have looked at reactivity alone. Isotype specificity may be critical for some autoantibodies [54]. The utilization of anti-glomerular antigens as LN biomarkers is limited further by lack of uniform assays and evaluation in multicenter cohorts. With improved standardization, an autoantibody panel of glomerular antigens might help in the diagnosis, surveillance, treatment of LN.

Urinary Biomarkers in LN

Urine is easily obtained and potentially provides a snapshot of what is going on in the kidney at the tissue level, making it an ideal source for biomarkers in LN. However, the development of urinary biomarkers in LN has been limited by inconsistent assays, processing differences, and lack of agreement regarding a normalization step. Several individual biomarkers have been identified (table 2), but more recent studies have moved away from individual markers to biomarker panels.

Neutrophil Gelatinase-Associated Lipicalin (NGAL)

NGAL is a 25 kDa glycosylated protein initially identified in neutrophils, but present in other tissues, including renal tubular cells. Urine and serum NGAL has been extensively studied as a biomarker in acute kidney injury (AKI) [68]. Urinary NGAL levels, with or without normalization for urine creatinine, correlated with LN activity in a pediatric SLE cohort [69]. Urine NGAL predicted LN flare better than anti-dsDNA in a cohort of adult SLE patients [70]. Further, urine NGAL at baseline predicted response to treatment in an Asian LN cohort [71].

Kidney injury molecule 1 (KIM-1)

KIM-1 is a transmembrane glycoprotein that is usually expressed in low levels in the kidney. It is highly upregulated in AKI and, similar to NGAL, has been studied extensively in AKI.

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Nozaki and colleagues demonstrated that urinary KIM-1 levels were elevated in patients with active LN [72]. They also showed KIM-1 levels correlated with proteinuria and tubular infiltration and injury [72].

Monocyte chemoattractant protein 1 (MCP-1)

MCP-1 is a leukocyte chemokine that mediates inflammatory responses [73]. In an animal model of LN, blockade of MCP-1 attenuated renal damage [74]. In multiple single center studies, urinary MCP-1 corresponded to LN activity and treatment non-responders had persistently elevated urinary MCP-1 [75–77]. A meta-analysis including 399 patients from 8 centers demonstrated that urine MCP-1 levels were significantly higher in patients with active LN than inactive LN and control subjects [78].

Tumor Necrosis Factor-Like Inducer of Apoptosis (TWEAK)

Tweak is a multifunctional cytokine that is involved in inflammatory, fibrotic, and apoptotic pathways [79, 80]. Tweak is thought to play a role in the pathogenesis of LN through increased burden of apoptotic materials and upregulation of inflammatory pathways [79, 80]. Urinary tweak levels correlated better with LN disease activity than anti-dsDNA and complement levels in multicenter cohort study [81]. Combining urinary TWEAK and urinary MCP levels to predict LN improved sensitivity and specificity over individual markers and improved the receiver operating characteristic curve (ROC) area under the curve (AUC) to 0.887 [82].

Urine Biomarker Panels

The renal activity index for lupus (RAIL) score combines 6 urinary biomarkers (NGAL, MCP-1, ceruloplasmin, adiponectin, hemopexin, and KIM-1) to predict LN activity in a pediatric cohort [83]. The combination of these 6 biomarkers (each normalized for urine creatinine and individually weighted to create a RAIL score) highly correlated with renal histology (NIH LN activity index) with an AUC of 0.92 [83]. When applying an identical algorithm to adult LN patients, the results were not as predictive and resulted in an AUC of 0.62 [84]. However, after adjusting the weight of individual biomarkers, the AUC improved to 0.88 [84] Both studies highlight the predictive potential of urinary biomarker panels in assessing LN activity, but require further optimization and validation in larger cohorts.

In addition to predicting LN activity, urine biomarker panels may also predict renal function decline. A prospective observational study found that a combination of 4 urinary biomarkers (liver-type fatty acid binding protein (LFABP), albumin, MCP-1, and transferrin) had good predictive accuracy of renal function decline in both pediatric (AUC=0.82) and adult (AUC= 0.79) cohorts [85]. All samples were normalized to urine creatinine levels and the combination of biomarkers performed better than any individual markers [85]. While promising, the study was carried out at a limited number of medical centers and needs to be further validated among larger cohorts.

The use of biomarker panels may help guide treatment decisions in LN. Current guidelines (KDIGO and ACR) recommend changing induction therapy if there is no response after 3-6 months, but there is no consensus on the definition of treatment failure [86, 87]. Wolf et al

utilized biomarker panels combined with machine learning to develop algorithms to stratify treatment responders and non-responders[88]. They assessed both traditional and novel biomarkers, including 46 urinary biomarkers. Univariate analyses by ROC were used to assess individual markers for response to therapy. The AUCs for individual biomarkers range from 0.42-0.67. AUC improved when they combined novel and traditional biomarkers (AUC= 0.79) rather than using traditional markers alone (AUC= 0.61) [88].

Genetic Biomarkers in LN

Genetic biomarkers in LN include genomic biomarkers and gene expression biomarkers. Genomic biomarkers include both rare mutations that follow Mendelian inheritance patterns and more common gene variants that confer increased genetic susceptibility. Gene expression biomarkers include molecular signatures found in the tissue, blood, and urine of patients and often correspond with disease activity. Both genomic and gene expression biomarkers may provide insights into key pathways to target and monitor in a personalized approach to therapy.

Genomic Biomarkers

Monogenic forms of SLE are extremely rare, but their identification has led to invaluable insights into the pathogenesis of disease. Many mutations are in pathways responsible for clearing immune complexes, removing cellular debris, or apoptosis[89]. Of the monogenic mutations, C1q mutations resulting in C1q deficiency are best described. C1q is crucial for opsonization and clearance of apoptotic bodies and immune complexes [21]. Genetic C1q deficiencies lead to SLE like autoimmunity and LN, highlighting the importance of this pathway in the development of disease [21, 90].

The investigation of genetic variants contributing to SLE goes back two decades, linking polymorphisms in major histocompatibility complex (MHC) to LN [91]. The completion of the human Genome Project in 2003 combined with more efficient technology for gene sequencing launched an era of genome-wide-association studies (GWAS) to identify genetic variants in specific disease cohorts. Munroe and James published a comprehensive review of the genetic risks for LN and possible clinical applications in 2015 and Iwamoto and Niewold more recently updated this topic in 2017 [92, 93]. The 2015 review lists over 50-candidate susceptibility genes associated with LN and grouped them into five regulatory systems (program cell death, immune complex clearance, intrarenal pathogenesis, innate immunity, and adaptive immunity). The 2017 review narrowed this list to 10 susceptibility loci with replicated, confirmed associated with LN (Table 2) [92, 93]. These genes include HLA-DR, ITGAM, FCGR3A, IRF5, TNIP1, STAT4, TNFSF4, APOL1, PDGFRA, and HAS2.

The majority of known LN susceptibility genes have functions that mediate inflammation via cytokine production and activation of leukocytes. The known cellular pathways mediated by these variant gene products also provide valuable mechanistic insight for development of personalized therapeutics. Defining genetic variants that reliably predict disease susceptibility, risk of progression, and response to treatment carries tremendous potential to improve and personalize patient care.

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Gene Expression Biomarkers

Interferon Signature—In recent years, activation of the type I interferon (IFN) pathway has been identified as key component of SLE [94]. IFNs are a family of cytokines that are part of the antiviral immune response and viral nucleic acids are potent inducers of type I IFN [95]. However, endogenous nucleic acids, which are increased in SLE patients, are also able to induce type I IFN [95]. Administration of IFN α (a type I IFN) exacerbated LN while IFN α blockade attenuated disease in animal models [96]. 50-75% of patients with SLE over express type I IFN regulated genes [97]. This over-expression can be objectively measured and quantified and is often termed the "IFN signature" [94]. Patients with increased expression of IFN genes are categorized as having a "high IFN signature," and those with normal expression are categorized as having "low IFN signature." The cutoffs have not been standardized, but some groups use the 95th percentile of healthy controls as the cutoff for high vs. low [98]. Cross sectional studies correlated high IFN signature in SLE with increased disease activity, including LN[99]. However, a longitudinal study failed to show that IFN signature predicted flare[100]. Over 100 genes have been identified as part of the type I IFN signature, but several groups have utilized more streamlined panels, consisting of 3 or 4 genes [98, 100, 101]. Yao and colleagues developed a 21 gene panel that was later simplified to a 4 gene (IFI27, IFI44, IFI44L, RSAD2) biomarker panel that has been used to stratify patients into "high" and "low" IFN signature groups in SLE clinical trials [101, 102].

Several drugs targeting type I IFN pathway are being studied in SLE and LN. These include anti-IFN monoclonal antibodies (sifalimumab, rontalizumab) and, anifrolumab, a monoclonal antibody targeting the type I IFN receptor [102–104]. Many clinical trials have incorporated measurements of the interferon signature into their studies [102–104]. Patients treated with anti-IFN agents have a decrease in IFN signature compared to those treated with placebo, supporting the validity of IFN signature [98]. In the phase II anifrolumab trial, that included mostly SLE patients without significant renal disease, a larger percentage of subjects with high IFN signature met the primary endpoint compared to patients with a low IFN signature, although both groups met the primary endpoint [102]. These results highlight how the use of gene expression biomarkers, might be utilized to tailor therapy, bringing precision medicine to the treatment of SLE and LN.

Neutrophil Phenotype and Expression Signature—Neutrophils are the most abundant leukocyte in human circulation and are critical for innate immune responses. Neutrophils have long been observed in LN kidney biopsies and the presence of neutrophils corresponds to disease activity [105, 106]. In recent years, the identification of neutrophil extracellular traps (NETs) and a subset of low–density granulocytes (LDG) has expanded our understanding of the role of neutrophils in LN [107]. NET formation occurs following a unique form of cell death, termed NETosis, in which the nuclear content decondenses into the cytoplasm, and the plasma membrane ruptures releasing strands of chromatin decorated with granular proteins [108]. Neutrophils isolated from SLE patients are more likely to form NETs which contain antigens (dsDNA, histones) recognized by lupus autoantibodies [109–112]. NETs also stimulate dendritic cells to release type I IFN and enhance T cell activation [110–113]. SLE patients with impaired degradation of NETs were significantly more likely to have LN [114]. A subpopulation of neutrophils, LDGs, are found in patients with SLE

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and are more likely to form NETs, damage endothelial cells, and increase type I IFN production [112]. Low density granulocytes are primarily described under inflammatory conditions, but may be present in low quantities under normal conditions [115, 116]. They have a unique gene expression profile compared with normal density neutrophils [112]. The top upregulated genes in lupus LDGs included genes for bactericidal molecules and enzymes found in neutrophil granules [112]. Additionally, patients with increased LDG were found to have increased IFN signature [116].

The upregulation of neutrophil related transcripts, termed the blood neutrophil signature, is observed in SLE and associated with LN [117–119]. Banchereau et al. conducted a longitudinal study of 158 patients and examined clinical and transcriptional profiling to identify immune correlates of disease activity and found neutrophil expression signatures were associated with progression to LN [119]. A modular neutrophil signature was strongly associated with LN and LN flares (88 vs. 17%) in another study [117]. Neutrophil related gene expression was increased in the transcriptomic profile of active SLE patients with LN compared to those without renal involvement [118].

Conclusions

Over the last decade, there has been hope that biologic agents will lead to more effective and less toxic treatments for LN. Unfortunately, no biologic to date has provided added efficacy when added to standard of care regimens. The use of biomarkers in LN is needed to better stratify patients and guide therapeutics. Several novel biomarkers for LN have been proposed, yet none have become incorporated into clinical use [120]. Reevaluation of the role of current clinical biomarkers, such as proteinuria and complement markers, to inform intensity and duration of immunosuppression is needed. Novel biomarkers such as urine biomarkers and autoantibodies to glomerular antigens, require further validation and standardization, but have the potential to improve diagnosis, disease surveillance, and treatment. Finally, genomic and gene expression biomarkers, offer crucial insight into which immune pathways are upregulated in individual patients. The combination of these biomarkers has the potential to herald a new era of precision medicine in LN.

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Abbreviations:

SLE	systemic lupus erythematosus
LN	lupus nephritis
Anti-dsDNA	anti-double stranded DNA antibodies

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ESKD	End Stage Kidney Disease
GBM	glomerular basement membrane
IFN	Interferon
NETs	neutrophil extracellular traps
LDG	low–density granulocytes
PPV	positive predictive value
NPV	negative predictive value

Literature Cited

1. Tsokos GC. Systemic lupus erythematosus. N Engl J Med. 2011;365(22): 2110–2121. [PubMed: 22129255]
2. Bomback AS, Appel GB. Updates on the treatment of lupus nephritis. Journal of the American Society of Nephrology: JASN. 2010;21(12): 2028–2035. [PubMed: 21051743]
3. Rovin BH, Caster DJ, Cattran DC, et al. Management and treatment of glomerular diseases (part 2): conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney international. 2019;95(2): 281–295. [PubMed: 30665569]
4. Davidson JE, Fu Q, Ji B, et al. Renal Remission Status and Longterm Renal Survival in Patients with Lupus Nephritis: A Retrospective Cohort Analysis. The Journal of rheumatology. 2018;45(5): 671–677. [PubMed: 29496892]
5. Almaani S, Meara A, Rovin BH. Update on Lupus Nephritis. Clin J Am Soc Nephrol. 2017;12(5): 825–835. [PubMed: 27821390]
6. Tektonidou MG, Dasgupta A, Ward MM. Risk of End-Stage Renal Disease in Patients With Lupus Nephritis, 1971–2015: A Systematic Review and Bayesian Meta-Analysis. Arthritis & rheumatology (Hoboken, N.J.). 2016;68(6): 1432–1441.
7. Barr RG, Seliger S, Appel GB, et al. Prognosis in proliferative lupus nephritis: the role of socioeconomic status and race/ethnicity. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2003;18(10): 2039–2046.
8. Costenbader KH, Desai A, Alarcon GS, et al. Trends in the incidence, demographics, and outcomes of end-stage renal disease due to lupus nephritis in the US from 1995 to 2006. Arthritis Rheum. 2011;63(6): 1681–1688. [PubMed: 21445962]
9. Feldman CH, Hiraki LT, Liu J, et al. Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000–2004. Arthritis Rheum. 2013;65(3): 753–763. [PubMed: 23203603]
10. Sexton DJ, Reule S, Solid C, Chen SC, Collins AJ, Foley RN. ESRD from lupus nephritis in the United States, 1995–2010. Clin J Am Soc Nephrol. 2015;10(2): 251–259. [PubMed: 25534208]
11. Parikh SV, Rovin BH. Current and Emerging Therapies for Lupus Nephritis. Journal of the American Society of Nephrology : JASN. 2016;27(10): 2929–2939. [PubMed: 27283496]
12. Biomarkers Definitions Working G. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001;69(3): 89–95. [PubMed: 11240971]
13. Dall'Era M, Cisternas MG, Smilek DE, et al. Predictors of long-term renal outcome in lupus nephritis trials: lessons learned from the Euro-Lupus Nephritis cohort. Arthritis Rheumatol. 2015;67(5): 1305–1313. [PubMed: 25605554]
14. Tamirou F, D'Cruz D, Sangle S, et al. Long-term follow-up of the MAINTAIN Nephritis Trial, comparing azathioprine and mycophenolate mofetil as maintenance therapy of lupus nephritis. Ann Rheum Dis. 2016;75(3): 526–531. [PubMed: 25757867]

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15. Ugolini-Lopes MR, Seguro LPC, Castro MXF, et al. Early proteinuria response: a valid real-life situation predictor of long-term lupus renal outcome in an ethnically diverse group with severe biopsy-proven nephritis? Lupus science & medicine. 2017;4(1): e000213. [PubMed: 29238603]
16. Olson SW, Lee JJ, Prince LK, et al. Elevated subclinical double-stranded DNA antibodies and future proliferative lupus nephritis. Clin J Am Soc Nephrol. 2013;8(10): 1702–1708. [PubMed: 23833315]
17. Mannik M, Merrill CE, Stamps LD, Wener MH. Multiple autoantibodies form the glomerular immune deposits in patients with systemic lupus erythematosus. The Journal of rheumatology. 2003;30(7): 1495–1504. [PubMed: 12858447]
18. Matrat A, Veysseyre-Balter C, Trolliet P, et al. Simultaneous detection of anti-C1q and anti-double stranded DNA autoantibodies in lupus nephritis: predictive value for renal flares. Lupus. 2011;20(1): 28–34. [PubMed: 20943718]
19. Julkunen H, Ekblom-Kullberg S, Miettinen A. Nonrenal and renal activity of systemic lupus erythematosus: a comparison of two anti-C1q and five anti-dsDNA assays and complement C3 and C4. Rheumatology international. 2012;32(8): 2445–2451. [PubMed: 21706294]
20. Moroni G, Radice A, Giammarresi G, et al. Are laboratory tests useful for monitoring the activity of lupus nephritis? A 6-year prospective study in a cohort of 228 patients with lupus nephritis. Ann Rheum Dis. 2009;68(2): 234–237. [PubMed: 18718989]
21. Thielens NM, Tedesco F, Bohlson SS, Gaboriaud C, Tenner AJ. C1q: A fresh look upon an old molecule. Molecular immunology. 2017;89: 73–83. [PubMed: 28601358]
22. Orbai AM, Truedsson L, Sturfelt G, et al. Anti-C1q antibodies in systemic lupus erythematosus. Lupus. 2015;24(1): 42–49. [PubMed: 25124676]
23. Yang XW, Tan Y, Yu F, Zhao MH. Combination of anti-C1q and anti-dsDNA antibodies is associated with higher renal disease activity and predicts renal prognosis of patients with lupus nephritis. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2012;27(9): 3552–3559.
24. Bock M, Heijnen I, Trendelenburg M. Anti-C1q antibodies as a follow-up marker in SLE patients. PLoS One. 2015;10(4): e0123572. [PubMed: 25881125]
25. Holers VM. Anti-C1q autoantibodies amplify pathogenic complement activation in systemic lupus erythematosus. The Journal of clinical investigation. 2004;114(5): 616–619. [PubMed: 15343378]
26. Thanei S, Vanhecke D, Trendelenburg M. Anti-C1q autoantibodies from systemic lupus erythematosus patients activate the complement system via both the classical and lectin pathways. Clin Immunol. 2015;160(2): 180–187. [PubMed: 26148903]
27. Thanei S, Trendelenburg M. Anti-C1q autoantibodies from patients with systemic lupus erythematosus induce C1q production by macrophages. Journal of leukocyte biology. 2017;101(2): 481–491. [PubMed: 27630215]
28. Trouw LA, Groeneveld TW, Seelen MA, et al. Anti-C1q autoantibodies deposit in glomeruli but are only pathogenic in combination with glomerular C1q-containing immune complexes. The Journal of clinical investigation. 2004;114(5): 679–688. [PubMed: 15343386]
29. Esdaile JM, Joseph L, Abrahamowicz M, Li Y, Danoff D, Clarke AE. Routine immunologic tests in systemic lupus erythematosus: is there a need for more studies? J Rheumatol. 1996;23(11): 1891–1896. [PubMed: 8923362]
30. Ricker DM, Hebert LA, Rohde R, Sedmak DD, Lewis EJ, Clough JD. Serum C3 levels are diagnostically more sensitive and specific for systemic lupus erythematosus activity than are serum C4 levels. The Lupus Nephritis Collaborative Study Group. Am J Kidney Dis. 1991;18(6): 678–685. [PubMed: 1962653]
31. Ho A, Barr SG, Magder LS, Petri M. A decrease in complement is associated with increased renal and hematologic activity in patients with systemic lupus erythematosus. Arthritis Rheum. 2001;44(10): 2350–2357. [PubMed: 11665976]
32. Birmingham DJ, Irshaid F, Nagaraja HN, et al. The complex nature of serum C3 and C4 as biomarkers of lupus renal flare. Lupus. 2010;19(11): 1272–1280. [PubMed: 20605879]
33. Fatemi A, Samadi G, Sayedbonakdar Z, Smiley A. Anti-C1q antibody in patients with lupus nephritic flare: 18-month follow-up and a nested case-control study. Mod Rheumatol. 2016;26(2): 233–239. [PubMed: 26357965]

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34. Seret G, Canas F, Pougnet-Di Costanzo L, et al. Anti-alpha-actinin antibodies are part of the anti-cell membrane antibody spectrum that characterize patients with lupus nephritis. Journal of autoimmunity. 2015;61: 54–61. [PubMed: 26071203]
35. Zhang WH, Pan HF, Zhao XF, Ye DQ, Li XP, Xu JH. Anti-alpha-actinin antibodies in relation to new-onset systemic lupus erythematosus and lupus nephritis. Molecular biology reports. 2010;37(3): 1341–1345. [PubMed: 19319662]
36. Becker-Merok A, Kalaaji M, Haugbro K, et al. Alpha-actinin-binding antibodies in relation to systemic lupus erythematosus and lupus nephritis. Arthritis Res Ther. 2006;8(6): R162. [PubMed: 17062137]
37. Bruschi M, Sinico RA, Moroni G, et al. Glomerular Autoimmune Multicomponents of Human Lupus Nephritis In Vivo: alpha-Enolase and Annexin AI. Journal of the American Society of Nephrology: JASN. 2014.
38. Yung S, Cheung KF, Zhang Q, Chan TM. Anti-dsDNA antibodies bind to mesangial annexin II in lupus nephritis. Journal of the American Society of Nephrology: JASN. 2010;21(11): 1912–1927. [PubMed: 20847146]
39. Caster DJ, Korte EA, Merchant ML, et al. Autoantibodies targeting glomerular annexin A2 identify patients with proliferative lupus nephritis. Proteomics. Clinical applications. 2015.
40. Cheung KF, Yung S, Chau MK, et al. Annexin II-binding immunoglobulins in patients with lupus nephritis and their correlation with disease manifestations. Clinical science (London, England: 1979). 2017;131(8): 653–671.
41. Kim HJ, Hong YH, Kim YJ, et al. Anti-heparan sulfate antibody and functional loss of glomerular heparan sulfate proteoglycans in lupus nephritis. Lupus. 2017;26(8): 815–824. [PubMed: 28420046]
42. Krishnan MR, Wang C, Marion TN. Anti-DNA autoantibodies initiate experimental lupus nephritis by binding directly to the glomerular basement membrane in mice. Kidney international. 2012;82(2): 184–192. [PubMed: 22297676]
43. Olin AI, Morgelin M, Truedsson L, Sturfelt G, Bengtsson AA. Pathogenic mechanisms in lupus nephritis: Nucleosomes bind aberrant laminin beta1 with high affinity and colocalize in the electron-dense deposits. Arthritis & rheumatology (Hoboken, N.J.). 2014;66(2): 397–406.
44. Mjelle JE, Rekvig OP, Fenton KA. Nucleosomes possess a high affinity for glomerular laminin and collagen IV and bind nephritogenic antibodies in murine lupus-like nephritis. Ann Rheum Dis. 2007;66(12): 1661–1668. [PubMed: 17504842]
45. Mostoslavsky G, Fischel R, Yachimovich N, et al. Lupus anti-DNA autoantibodies cross-react with a glomerular structural protein: a case for tissue injury by molecular mimicry. European journal of immunology. 2001;31(4): 1221–1227. [PubMed: 11298348]
46. Zou X, Cheng H, Zhang Y, Fang C, Xia Y. The antigen-binding fragment of anti-double-stranded DNA IgG enhances F-actin formation in mesangial cells by binding to alpha-actinin-4. Experimental biology and medicine (Maywood, N.J.). 2012;237(9): 1023–1031.
47. Zhao Z, Deocharan B, Scherer PE, Ozelius LJ, Putterman C. Differential binding of cross-reactive anti-DNA antibodies to mesangial cells: the role of alpha-actinin. J Immunol. 2006;176(12): 7704–7714. [PubMed: 16751418]
48. Deocharan B, Zhou Z, Antar K, et al. Alpha-actinin immunization elicits anti-chromatin autoimmunity in nonautoimmune mice. J Immunol. 2007;179(2): 1313–1321. [PubMed: 17617624]
49. Renaudineau Y, Deocharan B, Jousse S, Renaudineau E, Putterman C, Youinou P. Anti-alpha-actinin antibodies: a new marker of lupus nephritis. Autoimmunity reviews. 2007;6(7): 464–468. [PubMed: 17643934]
50. Manson JJ, Ma A, Rogers P, et al. Relationship between anti-dsDNA, anti-nucleosome and anti-alpha-actinin antibodies and markers of renal disease in patients with lupus nephritis: a prospective longitudinal study. Arthritis Res Ther. 2009;11(5): R154. [PubMed: 19828047]
51. Babaei M, Rezaieyazdi Z, Saadati N, et al. Serum alpha-actinin antibody status in systemic lupus erythematosus and its potential in the diagnosis of lupus nephritis. Caspian journal of internal medicine. 2016;7(4): 272–277. [PubMed: 27999645]

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52. Bruschi M, Sinico RA, Moroni G, et al. Glomerular autoimmune multicomponents of human lupus nephritis in vivo: alpha-enolase and annexin AI. Journal of the American Society of Nephrology: JASN. 2014;25(11): 2483–2498. [PubMed: 24790181]
53. Iaccarino L, Ghirardello A, Canova M, et al. Anti-annexins autoantibodies: their role as biomarkers of autoimmune diseases. Autoimmunity reviews. 2011;10(9): 553–558. [PubMed: 21527362]
54. Bonanni A, Vaglio A, Bruschi M, et al. Multi-antibody composition in lupus nephritis: isotype and antigen specificity make the difference. Autoimmunity reviews. 2015;14(8): 692–702. [PubMed: 25888464]
55. Bharadwaj A, Bydoun M, Holloway R, Waisman D. Annexin A2 heterotetramer: structure and function. International journal of molecular sciences. 2013;14(3): 6259–6305. [PubMed: 23519104]
56. Pratesi F, Moscato S, Sabbatini A, Chimenti D, Bombardieri S, Migliorini P. Autoantibodies specific for alpha-enolase in systemic autoimmune disorders. The Journal of rheumatology. 2000;27(1): 109–115. [PubMed: 10648026]
57. Bruschi M, Carnevali ML, Murtas C, et al. Direct characterization of target podocyte antigens and auto-antibodies in human membranous glomerulonephritis: Alfa-enolase and borderline antigens. Journal of proteomics. 2011;74(10): 2008–2017. [PubMed: 21640210]
58. Kimura Y, Miura N, Debiec H, et al. Circulating antibodies to alpha-enolase and phospholipase A2 receptor and composition of glomerular deposits in Japanese patients with primary or secondary membranous nephropathy. Clin Exp Nephrol. 2017;21(1): 117–126. [PubMed: 26830547]
59. Diaz-Ramos A, Roig-Borrellas A, Garcia-Melero A, Lopez-Alemany R. alpha-Enolase, a multifunctional protein: its role on pathophysiological situations. Journal of biomedicine & biotechnology. 2012;2012: 156795. [PubMed: 23118496]
60. Li M, Li J, Wang J, Li Y, Yang P. Serum level of anti-alpha-enolase antibody in untreated systemic lupus erythematosus patients correlates with 24-hour urine protein and D-dimer. Lupus. 2018;27(1): 139–142. [PubMed: 28728510]
61. Jones B Lupus nephritis: Nucleosomes trapped by aberrantly expressed laminin-beta1. Nature reviews. Nephrology. 2014;10(1): 4.
62. Hanrotel-Saliou C, Segalen I, Le Meur Y, Youinou P, Renaudineau Y. Glomerular antibodies in lupus nephritis. Clinical reviews in allergy & immunology. 2011;40(3): 151–158. [PubMed: 20414746]
63. van Bavel CC, van der Vlag J, Berden JH. Glomerular binding of anti-dsDNA autoantibodies: the dispute resolved? Kidney international. 2007;71(7): 600–601. [PubMed: 17387307]
64. Yuan M, Tan Y, Pang Y, et al. Anti-pentraxin 3 auto-antibodies might be protective in lupus nephritis: a large cohort study. Ren Fail. 2017;39(1): 465–473. [PubMed: 28393653]
65. Doria A, Gatto M. Nephritogenic-antinephritogenic antibody network in lupus glomerulonephritis. Lupus. 2012;21(14): 1492–1496. [PubMed: 23042821]
66. Gatto M, Iaccarino L, Ghirardello A, Punzi L, Doria A. Clinical and pathologic considerations of the qualitative and quantitative aspects of lupus nephritogenic autoantibodies: A comprehensive review. Journal of autoimmunity. 2016;69: 1–11. [PubMed: 26879422]
67. Gatto M, Ghirardello A, Luisetto R, et al. Immunization with pentraxin 3 (PTX3) leads to anti-PTX3 antibody production and delayed lupus-like nephritis in NZB/NZW F1 mice. Journal of autoimmunity. 2016;74: 208–216. [PubMed: 27405845]
68. Singer E, Marko L, Paragas N, et al. Neutrophil gelatinase-associated lipocalin: pathophysiology and clinical applications. Acta physiologica (Oxford, England). 2013;207(4): 663–672.
69. Suzuki M, Wiers KM, Klein-Gitelman MS, et al. Neutrophil gelatinase-associated lipocalin as a biomarker of disease activity in pediatric lupus nephritis. Pediatric nephrology (Berlin, Germany). 2008;23(3): 403–412.
70. Rubinstein T, Pitashny M, Levine B, et al. Urinary neutrophil gelatinase-associated lipocalin as a novel biomarker for disease activity in lupus nephritis. Rheumatology (Oxford). 2010;49(5): 960–971. [PubMed: 20144927]
71. Satirapoj B, Kitiyakara C, Leelahavanichkul A, Avihingsanon Y, Supasyndh O. Urine neutrophil gelatinase-associated lipocalin to predict renal response after induction therapy in active lupus nephritis. BMC nephrology. 2017;18(1): 263. [PubMed: 28778196]

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72. Nozaki Y, Kinoshita K, Yano T, et al. Estimation of kidney injury molecule-1 (Kim-1) in patients with lupus nephritis. Lupus. 2014;23(8): 769–777. [PubMed: 24598218]
73. Lv W, Booz GW, Wang Y, Fan F, Roman RJ. Inflammation and renal fibrosis: Recent developments on key signaling molecules as potential therapeutic targets. Eur J Pharmacol. 2018;820: 65–76. [PubMed: 29229532]
74. Kulkarni O, Pawar RD, Purschke W, et al. Spiegelmer inhibition of CCL2/MCP-1 ameliorates lupus nephritis in MRL-(Fas)lpr mice. Journal of the American Society of Nephrology : JASN. 2007;18(8): 2350–2358. [PubMed: 17625118]
75. Gupta R, Yadav A, Aggarwal A. Longitudinal assessment of monocyte chemoattractant protein-1 in lupus nephritis as a biomarker of disease activity. Clinical rheumatology. 2016;35(11): 2707–2714. [PubMed: 27624649]
76. Rovin BH, Song H, Birmingham DJ, Hebert LA, Yu CY, Nagaraja HN. Urine chemokines as biomarkers of human systemic lupus erythematosus activity. Journal of the American Society of Nephrology: JASN. 2005;16(2): 467–473. [PubMed: 15601744]
77. Singh RG, Usha, Rathore SS, Behura SK, Singh NK. Urinary MCP-1 as diagnostic and prognostic marker in patients with lupus nephritis flare. Lupus. 2012;21(11): 1214–1218. [PubMed: 22759858]
78. Lee YH, Song GG. Urinary MCP-1 as a biomarker for lupus nephritis: a meta-analysis. Zeitschrift fur Rheumatologie. 2017;76(4): 357–363. [PubMed: 27278779]
79. Kaplan MJ, Lewis EE, Shelden EA, et al. The apoptotic ligands TRAIL, TWEAK, and Fas ligand mediate monocyte death induced by autologous lupus T cells. J Immunol. 2002;169(10): 6020–6029. [PubMed: 12421989]
80. Michaelson JS, Wisniacki N, Burkly LC, Putterman C. Role of TWEAK in lupus nephritis: a bench-to-bedside review. Journal of autoimmunity. 2012;39(3): 130–142. [PubMed: 22727560]
81. Schwartz N, Rubinstein T, Burkly LC, et al. Urinary TWEAK as a biomarker of lupus nephritis: a multicenter cohort study. Arthritis Res Ther. 2009;11(5): R143. [PubMed: 19785730]
82. Dong XW, Zheng ZH, Ding J, et al. Combined detection of uMCP-1 and uTWEAK for rapid discrimination of severe lupus nephritis. Lupus. 2018;27(6): 971–981. [PubMed: 29451067]
83. Brunner HI, Bennett MR, Abulaban K, et al. Development of a Novel Renal Activity Index of Lupus Nephritis in Children and Young Adults. Arthritis care & research. 2016;68(7): 1003–1011. [PubMed: 26473509]
84. Gulati G, Bennett MR, Abulaban K, et al. Prospective validation of a novel renal activity index of lupus nephritis. Lupus. 2017;26(9): 927–936. [PubMed: 28361601]
85. Abulaban KM, Song H, Zhang X, et al. Predicting decline of kidney function in lupus nephritis using urine biomarkers. Lupus. 2016;25(9): 1012–1018. [PubMed: 26873651]
86. Chapter 12: Lupus nephritis. Kidney international supplements. 2012;2(2): 221–232. [PubMed: 25018937]
87. Hahn BH, McMahon MA, Wilkinson A, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis care & research. 2012;64(6): 797–808. [PubMed: 22556106]
88. Wolf BJ, Spainhour JC, Arthur JM, Janech MG, Petri M, Oates JC. Development of Biomarker Models to Predict Outcomes in Lupus Nephritis. Arthritis & rheumatology (Hoboken, N.J.). 2016;68(8): 1955–1963.
89. Alperin JM, Ortiz-Fernandez L, Sawalha AH. Monogenic Lupus: A Developing Paradigm of Disease. Frontiers in immunology. 2018;9: 2496. [PubMed: 30459768]
90. Macedo AC, Isaac L. Systemic Lupus Erythematosus and Deficiencies of Early Components of the Complement Classical Pathway. Frontiers in immunology. 2016;7: 55. [PubMed: 26941740]
91. Lindqvist AK, Alarcon-Riquelme ME. The genetics of systemic lupus erythematosus. Scand J Immunol. 1999;50(6): 562–571. [PubMed: 10607304]
92. Munroe ME, James JA. Genetics of Lupus Nephritis: Clinical Implications. Semin Nephrol. 2015;35(5): 396–409. [PubMed: 26573543]
93. Iwamoto T, Niewold TB. Genetics of human lupus nephritis. Clin Immunol. 2017;185: 32–39. [PubMed: 27693588]

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94. Bengtsson AA, Ronnblom L. Role of interferons in SLE. Best practice & research. Clinical rheumatology. 2017;31(3): 415–428. [PubMed: 29224681]
95. Lorenz G, Anders HJ. Neutrophils, Dendritic Cells, Toll-Like Receptors, and Interferon-alpha in Lupus Nephritis. Seminars in nephrology. 2015;35(5): 410–426. [PubMed: 26573544]
96. Lorenz G, Desai J, Anders HJ. Lupus nephritis: update on mechanisms of systemic autoimmunity and kidney immunopathology. Curr Opin Nephrol Hypertens. 2014;23(3): 211–217. [PubMed: 24662982]
97. Felten R, Scher F, Sagez F, Chasset F, Arnaud L. Spotlight on anifrolumab and its potential for the treatment of moderate-to-severe systemic lupus erythematosus: evidence to date. Drug design, development and therapy. 2019;13: 1535–1543.
98. Kennedy WP, Maciuca R, Wolslegel K, et al. Association of the interferon signature metric with serological disease manifestations but not global activity scores in multiple cohorts of patients with SLE. Lupus science & medicine. 2015;2(1): e000080. [PubMed: 25861459]
99. Baechler EC, Batliwalla FM, Karypis G, et al. Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. Proc Natl Acad Sci U S A. 2003;100(5): 2610–2615. [PubMed: 12604793]
100. Petri M, Singh S, Tesfasyone H, et al. Longitudinal expression of type I interferon responsive genes in systemic lupus erythematosus. Lupus. 2009;18(11): 980–989. [PubMed: 19762399]
101. Yao Y, Higgs BW, Richman L, White B, Jallal B. Use of type I interferon-inducible mRNAs as pharmacodynamic markers and potential diagnostic markers in trials with sifalimumab, an anti-IFNα antibody, in systemic lupus erythematosus. Arthritis research & therapy. 2010;12 Suppl 1(Suppl 1): S6–S6. [PubMed: 20392292]
102. Furie R, Khamashta M, Merrill JT, et al. Anifrolumab, an Anti-Interferon-alpha Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. Arthritis & rheumatology (Hoboken, N.J.). 2017;69(2): 376–386.
103. Khamashta M, Merrill JT, Werth VP, et al. Sifalimumab, an anti-interferon-alpha monoclonal antibody, in moderate to severe systemic lupus erythematosus: a randomised, double-blind, placebo-controlled study. Ann Rheum Dis. 2016;75(11): 1909–1916. [PubMed: 27009916]
104. Kalunian KC, Merrill JT, Maciuca R, et al. A Phase II study of the efficacy and safety of rontalizumab (rhuMAb interferon-alpha) in patients with systemic lupus erythematosus (ROSE). Ann Rheum Dis. 2016;75(1): 196–202. [PubMed: 26038091]
105. Austin HA 3rd, Muenz LR, Joyce KM, Antonovych TT, Balow JE. Diffuse proliferative lupus nephritis: identification of specific pathologic features affecting renal outcome. Kidney international. 1984;25(4): 689–695. [PubMed: 6482173]
106. Bajema IM, Wilhelmus S, Alpers CE, et al. Revision of the International Society of Nephrology/ Renal Pathology Society classification for lupus nephritis: clarification of definitions, and modified National Institutes of Health activity and chronicity indices. Kidney international. 2018;93(4): 789–796. [PubMed: 29459092]
107. Nishi H, Mayadas TN. Neutrophils in lupus nephritis. Curr Opin Rheumatol. 2019;31(2): 193–200. [PubMed: 30540580]
108. Papayannopoulos V, Zychlinsky A. NETs: a new strategy for using old weapons. Trends in immunology. 2009;30(11): 513–521. [PubMed: 19699684]
109. Craft JE. Dissecting the immune cell mayhem that drives lupus pathogenesis. Sci Transl Med. 2011;3(73): 73ps79.
110. Garcia-Romo GS, Caielli S, Vega B, et al. Netting neutrophils are major inducers of type I IFN production in pediatric systemic lupus erythematosus. Sci Transl Med. 2011;3(73): 73ra20.
111. Lande R, Ganguly D, Facchinetti V, et al. Neutrophils activate plasmacytoid dendritic cells by releasing self-DNA-peptide complexes in systemic lupus erythematosus. Sci Transl Med. 2011;3(73): 73ra19.
112. Villanueva E, Yalavarthi S, Berthier CC, et al. Netting neutrophils induce endothelial damage, infiltrate tissues, and expose immunostimulatory molecules in systemic lupus erythematosus. J Immunol. 2011;187(1): 538–552. [PubMed: 21613614]

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113. Tillack K, Breiden P, Martin R, Sospedra M. T lymphocyte priming by neutrophil extracellular traps links innate and adaptive immune responses. J Immunol. 2012;188(7): 3150–3159. [PubMed: 22351936]
114. Hakkim A, Furnrohr BG, Amann K, et al. Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis. Proc Natl Acad Sci U S A. 2010;107(21): 9813–9818. [PubMed: 20439745]
115. Carmona-Rivera C, Kaplan MJ. Low-density granulocytes: a distinct class of neutrophils in systemic autoimmunity. Seminars in immunopathology. 2013;35(4): 455–463. [PubMed: 23553215]
116. Rahman S, Sagar D, Hanna RN, et al. Low-density granulocytes activate T cells and demonstrate a non-suppressive role in systemic lupus erythematosus. Ann Rheum Dis. 2019;78(7): 957–966. [PubMed: 31040119]
117. Jourde-Chiche N, Whalen E, Gondouin B, et al. Modular transcriptional repertoire analyses identify a blood neutrophil signature as a candidate biomarker for lupus nephritis. Rheumatology (Oxford). 2017;56(3): 477–487. [PubMed: 28031441]
118. Wither JE, Prokopec SD, Noamani B, et al. Identification of a neutrophil-related gene expression signature that is enriched in adult systemic lupus erythematosus patients with active nephritis: Clinical/pathologic associations and etiologic mechanisms. PLoS One. 2018;13(5): e0196117. [PubMed: 29742110]
119. Banchereau R, Hong S, Cantarel B, et al. Personalized Immunomonitoring Uncovers Molecular Networks that Stratify Lupus Patients. Cell. 2016;165(3): 551–565. [PubMed: 27040498]
120. Birmingham DJ, Merchant M, Waikar SS, Nagaraja H, Klein JB, Rovin BH. Biomarkers of lupus nephritis histology and flare: deciphering the relevant amidst the noise. Nephrol Dial Transplant. 2017;32(suppl_1): i71–i79. [PubMed: 28391335]
121. Brunner HI, Mueller M, Rutherford C, et al. Urinary neutrophil gelatinase-associated lipocalin as a biomarker of nephritis in childhood-onset systemic lupus erythematosus. Arthritis Rheum. 2006;54(8): 2577–2584. [PubMed: 16868980]
122. Rubinstein T, Pitashny M, Putterman C. The novel role of neutrophil gelatinase-B associated lipocalin (NGAL)/Lipocalin-2 as a biomarker for lupus nephritis. Autoimmunity reviews. 2008;7(3): 229–234. [PubMed: 18190883]
123. Ding Y, Nie LM, Pang Y, et al. Composite urinary biomarkers to predict pathological tubulointerstitial lesions in lupus nephritis. Lupus. 2018;27(11): 1778–1789. [PubMed: 30020021]

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Summary

- Standard of care treatment for lupus nephritis has significant toxicity and inadequate response rates.
- Identification of novel LN treatments has been difficult due to disease heterogeneity.
- Better utilization of biomarkers may help stratify patients and guide therapy.

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Table 1.

Native Glomerular Antigens

Glomerular Antigen	Location
Alpha Actinin [34–36]	mesangial cells, podocytes
Alpha-enolase [37]	mesangial cell, podocytes
Annexin A1 [37]	podocytes
Annexin A2 [38–40]	mesangial cells, podocytes, matrix
Heparan sulfate [41, 42]	glomerular basement membrane
Laminin [43, 44]	glomerular basement membrane

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Table 2.

Urine Biomarkers in Lupus Nephritis

Urine Biomarker	Predicts Flare	Correlates with Activity
NGAL	+[70]	+[69, 70, 121, 122]
KIM-1		+[72, 123]
MCP-1	+[76, 77]	+[78]
TWEAK	+[81]	+[81]

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Table 3.

Gene Variants Associated with LN [92, 93]

Gene Name	Variant in LN	Function
ITGAM	rs1143679	Integral membrane protein important in neutrophil and monocyte - endothelial cell transmigration and compliment phagocytosis.
IRF5	rs2004640, rs10954213	Transcription factor that regulates virus-mediated activation of interferon, and modulation of cell growth, differentiation, apoptosis, and immune system activity.
TNIP1	rs4958881, rs7708392	A polyubiquitin binding protein that is a physiological inhibitor of NF-κB and MAPK-mediated inflammatory activity.
STAT4	rs7574865	Regulates transcription in response cytokines and other inflammatory mediators.
TNFSF4	rs1234315	A TNF family cytokine that functions in T cell antigen-presenting cell (APC) interactions and mediates adhesion of activated T cells to endothelial cells.
APOL1	rs73885319, rs60910145	A secreted high-density lipoprotein which binds to apolipoprotein A-I and promotes efflux of cholesterol from cells.
PDGFRA	rs1364989	A cell surface tyrosine kinase receptor for members of the platelet-derived growth factor family that plays a role in organ development, wound healing, and tumor progression.
HAS2	rs7834765	Mediates synthesis of hyaluronic acid (HA), a polysaccharide that is actively produced during wound healing and tissue repair to provide a framework for ingrowth of blood vessels and fibroblasts. The interaction of HA with the leukocyte receptor CD44 is important in tissue-specific homing by leukocytes and changes in the serum concentration of HA are associated with rheumatoid arthritis.
FCGR3A	rs396991	A receptor for the Fc portion of immunoglobulin G, that is involved in the removal of antigen-antibody complexes from the circulation, as well as other antibody-dependent responses.
HLA-DR		The primary function of HLA-DR is to present peptide antigens to the immune system that lead to the production of antibodies against the same peptide antigen.
PLA2R1	rs4664308	Receptor for secretory phospholipase A2 (sPLA2)-1B. Binding of sPLA2-IB induces various effects depending on the cell type, such as activation of the mitogen-activated protein kinase (MAPK) cascade to induce cell proliferation, the production of lipid mediators. In neutrophils, binding of sPLA2-iB can activate p38 MAPK to stimulate elastase release and cell adhesion and may be involved in responses in proinflammatory cytokine production.