

# SLE: reconciling heterogeneity

Michael D Lockshin,<sup>1</sup> Medha Barbhayia,<sup>1</sup> Peter Izmirly,<sup>2</sup> Jill P Buyon,<sup>2</sup> Mary K Crow<sup>3</sup>

**To cite:** Lockshin MD, Barbhayia M, Izmirly P, *et al*. SLE: reconciling heterogeneity. *Lupus Science & Medicine* 2019;**6**:e000280. doi:10.1136/lupus-2018-000280

Received 3 June 2018  
Revised 14 November 2018  
Accepted 18 November 2018



© Author(s) (or their employer(s)) 2019. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

<sup>1</sup>Barbara Volcker Center, Hospital for Special Surgery, New York City, New York, USA

<sup>2</sup>Division of Rheumatology, Department of Medicine, New York University School of Medicine, New York City, New York, USA

<sup>3</sup>Mary Kirkland Center for Lupus Research, Hospital for Special Surgery, New York City, New York, USA

## Correspondence to

Professor Michael D Lockshin; lockshinm@hss.edu

Patients with SLE experience multiple, varied symptoms and laboratory abnormalities that occur in different combinations, at different points in time.<sup>1</sup> A result of the heterogeneity is that studies on SLE employ several, sometimes conflicting, definitions of the illness. Investigators disagree about when SLE begins; how SLE relates to similar and overlapping rheumatic illnesses; whether SLE-like illnesses of known genetic causes count as SLE; and whether the same diagnosis name should apply when investigators describe stratified populations, for instance, SLE with and without renal disease. Inconsistent definitions lead stakeholders—patients, practising physicians, administrators, epidemiologists and investigators—to count different patients and to develop different opinions about the mechanisms and treatment of SLE.

To advocate a consensus vocabulary and conceptual model, in this paper we deconstruct the process of making a diagnosis of SLE by examining its classification and diagnostic criteria, definitions and illness models. We discuss the ways by which stratification biases conclusions and how the purpose for which a stakeholder names a diagnosis determines whom they accept as having this disease.

## DEFINITIONS

### Classification and diagnostic criteria

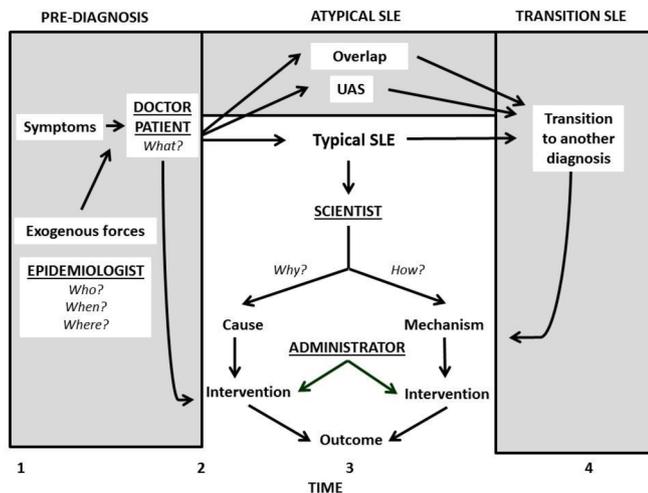
When in the mid-19th century Cazenave first used the name *lupus erythematosus*, SLE was a rare and life-threatening illness.<sup>2–3</sup> A century later, as new technologies identified more patients,<sup>4–10</sup> physicians found SLE to be more clinically diverse, and often less severe, than they once believed. To improve homogeneity of patient populations identified for clinical studies, investigators developed classification criteria that are specific, binary (SLE is present or not) and time limited (valid only for the extent of a study). The homogeneity of classification criteria is implied but not real. The American College of Rheumatology (ACR)

criteria allow 330 different combinations of symptoms and laboratory tests to affirm a diagnosis of SLE.<sup>11</sup> Classification criteria are insensitive; they exclude patients who, despite disabling and treatable symptoms, fall below criteria thresholds and those who have overlapping or changing forms of SLE, whom practising physicians treat according to rules established for typical SLE.<sup>12–21</sup> Diagnostic criteria, which would be more sensitive, if less specific, time independent and scalar rather than binary, do not exist for SLE. (An internet search (23 September 2018) for SLE diagnostic criteria identified references only to classification criteria. Many published papers fail to distinguish diagnostic from classification criteria.<sup>21</sup>)

### Exclusive and inclusive definitions

Many clinical and basic science investigators use an *exclusive* definition of SLE that accepts only classification criteria-defined patients and rejects (for ethical and practical reasons) patients with dementia, pregnancy, comorbid illness or specific forms of treatment.<sup>22–24</sup> Practising physicians use an *inclusive* definition that gathers under one name all patients with lupus spectrum illness, including those with *typical SLE* (criteria fulfilling), *overlap syndromes* (typical SLE associated with another definable autoimmune illness), *undifferentiated autoimmune syndrome (UAS)* (lupus-like illness that does not fulfil criteria),<sup>25–27</sup> *SLE-associated antibodies only* (diagnostic autoantibodies but no clinical illness)<sup>28</sup> and *cutaneous SLE* (skin disease without systemic manifestations).<sup>29</sup>

In rheumatology practice, only 35% of patients with lupus spectrum have typical SLE. Compared with patients with atypical forms of lupus spectrum disease, patients with typical SLE differ demographically, have different involved organ systems and receive different treatments.<sup>30–31</sup> Although differences between typical and atypical patients may result in different disease mechanisms and outcomes, many SLE studies include atypical patients with neither comment nor subanalysis.<sup>32</sup>



**Figure 1** A proposed model of SLE-lupus spectrum illness that considers stakeholders' definitions and the concept of time. Time 1 is first onset of clinical or laboratory abnormalities, time 2 first diagnosis, time 3 outcome measurement and time 4 transition to another illness. Practising doctors and their patients mostly ask what, epidemiologists who, when and where (to suggest answers to how and why) and investigators how and why. Most scientific research on SLE focuses on typical postdiagnosis SLE (clear area at the centre), but ignores prediagnosis (shaded area left), atypical illness (shaded area top) and transition illness (shaded area right). Practising physicians are more likely to consider SLE to be the entire spectrum (whole figure); epidemiologists, prediagnosis and typical SLE; investigators and administrators only postdiagnosis, typical SLE. UAS, undifferentiated autoimmune syndrome.

Studies differ in how they define *onset* of SLE, which may be first appearance of ANA, anti-DNA antibody, symptoms, ACR criteria or diagnosis by a physician. In animal model studies, onset may be first appearance of glomerulonephritis, anti-DNA antibodies, biomarkers, gene expression profiles or disease-inducing intervention.<sup>33–35</sup> A study that defines SLE as first appearance of arthralgia or ANA may enrol patients more than a decade earlier than does one that defines SLE as first fulfilment of ACR criteria.<sup>36</sup> Although both studies will speak of SLE, their results cannot be compared.

Stakeholders who use different definitions describe different patients (figure 1). Clinical and basic science investigators usually use exclusive definitions (clear area, centre and bottom); by study design, they include only patients whom a practising physician has already diagnosed to have SLE, that is, after time 2. Patients, practising physicians and some investigators consider SLE to begin at time 1 (shaded area on the left). Symptoms and laboratory abnormalities first occur at the earlier date, when social, environmental and/or endogenous inducers may determine which patient will remain well, develop typical SLE or fall ill with a different lupus spectrum illness (shaded area at the top). Exogenous factors may also determine if, how, and when the clinical phenotype may change (time 4, shaded area at the right). Outcomes

are measurable after a diagnosis is assigned, throughout time 3.

Most administrators, patients, practising physicians and some clinical investigators ask the question *what*. The answer, for which the exclusive definition works best, is the diagnosis name. Most basic and some clinical science investigators ask *how*, the answer being disease mechanisms, for which the exclusive definition also functions best. Some epidemiological, clinical and basic science investigators, and practising physicians ask *why*—the aetiology. For this question the inclusive definition is preferred.

## ILLNESS MODELS

One can reduce the complexity of making a diagnosis of SLE by using conceptual models. There are two such models, one *separate illnesses*, the other *linear illness*; both cluster SLE's disparate elements. The separate illnesses model posits that typical, overlap, UAS and antibody-only SLE are separate but related illnesses. A strength of this model is that it assigns different, targetable biological mechanisms to each diagnosis. Another strength is that a diagnosis, once made, does not change.<sup>37–40</sup> Weaknesses of this model are that, in clinical practice, ambiguous diagnoses occur often, blurring the separating lines, and that diagnoses do sometimes change. Clinical protocols that rigidly adhere to sharp distinctions among diagnoses may remove options available to the treating physician. Another weakness is that insights suggested by evolving phenotypes may be unseen if an investigator believes that change of diagnosis cannot occur.<sup>30</sup>

The linear illness model posits that UAS, overlap, antibody-only and typical SLE reside within a continuum of a single pathogenic process. This model applies throughout a patient's lifetime, during which the diagnosis name may change.<sup>41–49</sup> The model's strengths are that it suggests common pathogenesis and flexible treatment protocols for all lupus spectrum illnesses; it highlights potential causes for phenotype changes. A weakness is that boundaries among diagnoses are vague, gathering under one name, like lupus spectrum, patients who have distinctly different phenotypes.

When the cause of a chronic illness is unknown, the separate illnesses model usually applies. Using this model, investigators mostly ask *how* of narrowly defined populations in order to discover mechanisms that will become the basis for targeted, ameliorative treatments. Investigators who ask *why* hope to find a single cause for a disease. When *why* is answered, syndromes will be seen to be different phases of a linear illness and treatment will be directed to prevention or cure.

For example, in the separate illness model, the syndrome consisting of an abnormal venereal disease research laboratory blood test, rash, aortic aneurysm and tabes dorsalis, lacking a known cause, consists of related different illnesses, mechanistically different, with mechanism-based ameliorative treatments. When the cause is

known—infection by *Treponema pallidum*—the separate symptoms are seen to be phases in a linear model of syphilis, amenable to aetiology-based cure. Similarly, anaemia, jaundice and neuropsychiatric symptoms are separate illnesses until deficiency of vitamin B<sub>12</sub> is recognised, at which time they become linear illness phases of pernicious anaemia; and pigment change, neuropathy, hepatitis and cytopenia are separate illnesses until arsenic poisoning is found.

The cause(s) of a chronic illness can be one or many things. Whether the cause is infection, deficiency, intoxication or autoimmunity, how one conceptualises the illness is important. The separate illness model favours mechanism-based management, the linear illness model aetiology-based cure. The choice depends mostly on whether the cause is or is not known.

### STRATIFICATION

When studies stratify SLE populations, conclusions drawn from one subpopulation may differ from those drawn from another. Stratification by *clinical and serological phenotypes*, *demography* and *habits* is qualitative, on *disease activity measures* quantitative.<sup>50–57</sup> Stratification on sex, race, socioeconomic status,<sup>58–62</sup> access to medical care, medication choice and adherence,<sup>63</sup> willingness to participate in clinical trials, doctor–patient interactions,<sup>64</sup> patient preferences and perceptions,<sup>65</sup> lifestyle choices,<sup>66–67</sup> physician choices,<sup>68–71</sup> environmental triggers,<sup>72–76</sup> poverty,<sup>77</sup> social disparities,<sup>78</sup> and life events,<sup>79</sup> smoking<sup>80</sup> and the gut pathobiont<sup>81</sup> all affect manifestations and outcomes in ways that dictate who participates in a study on SLE and in ways that cannot be examined in animal models.<sup>82</sup> Stratification on *gene expression*, quantitative, predicts risk and possibly phenotype<sup>83–93</sup>; SLE-like illnesses

(the autoinflammatory diseases),<sup>94</sup> Aicardi-Goutières syndrome,<sup>95–96</sup> Canale-Smith syndrome<sup>97</sup> and SLE associated with immunodeficiency<sup>98</sup> suggest mechanisms for primary illness, and for phenotype diversity. Stratification by *molecular biomarkers* predicts fulfilment of classification criteria,<sup>99</sup> organ involvement and development of SLE in relatives of patients.<sup>100–104</sup> Stratifying by *time* will offer insight about how SLE diagnoses change.<sup>105</sup> *New computational techniques*, like multidimensional models, cluster analyses, machine learning, the word cloud, personalised immunomonitoring and transancestral mapping, are modern ways to stratify.<sup>106–114</sup> Many of today's mechanistic studies compare one dependent against one independent variable. *Three-dimensional* stratification can quantify combinations of biomarkers, severity indices, phenotypes, microscopic pathology, immunopathology, gene patterns, epidemiological variables, microbiomes or gradations of biological sex. *Four-dimensional* studies can compare non-calendric variables at different points in time.

Studies on stratified populations of patients with SLE that demonstrate different mechanisms among the groups validate the separate illness model of SLE; studies that identify common mechanisms validate the linear illness model. Although stratification by itself cannot explain the origins of SLE, its ability to show population differences enhances understanding and treatment of the disease.

### STAKEHOLDERS' PURPOSES

How different stakeholders use the name SLE and which definition they use depends on the purpose for which they assign the name (table 1).

**Table 1** Types and purposes of SLE definitions used by different stakeholders. The types of definitions, illness models, modes of diagnosis and time considerations are described in the text

Stakeholder	Purpose of naming a diagnosis	Definition	Illness model	Mode	Time limited?
Payer	Determine reimbursement.	Exclusive	Separate	Binary	Yes
Administrator	Count affected persons.	Exclusive	Separate	Binary	Yes
Epidemiologist	Count affected persons.	Inclusive or exclusive	Separate >linear	Binary	Yes
Clinical researcher	Identify homogeneous populations to identify risk, measure outcomes, study mechanisms, develop and test treatments.	Exclusive	Separate	Binary	Yes
Basic/translational researcher	Identify affected persons to study mechanisms and/or causes.	Inclusive or exclusive	Separate or linear	Binary or scalar	Yes or no
Editor	Classify published articles.	Inclusive or exclusive	Separate or linear	Not considered	Not considered
Physician	Identify cause of symptoms, prognosticate and treat.	Inclusive	Linear	Scalar	No
Patient	Know prognosis, choose among diagnostic and treatment options.	Inclusive	Linear	Scalar	No

The purpose for which *payers* and *administrators* use the name SLE is to guide reimbursement and regulatory policy. *Epidemiologists* do so to identify disparities among populations that may identify the exogenous and endogenous factors that drive the illness and that demarcate boundaries by which *clinical and basic science researchers* can study mechanisms, causes, treatments and outcomes. *Office physicians* use the name SLE to anchor prognoses, justify interventions and enhance patients' confidence (and their own). *Patients* use it to understand their options and their futures. *Editors* of medical journals use it to flag articles for readers' attention.

Payers, administrators, clinical researchers and some basic science researchers mostly select the separate illness model and the exclusive, binary and time-limited definition of SLE.<sup>115–124</sup> Physicians, patients and other basic researchers choose the inclusive, scalar and time-variable definition and linear illness model. Journal editors consider the definition and disease models irrelevant if the published report can be indexed and identified by a keyword. A result of this choice is that literature and internet searches on SLE yield studies of patients and animals defined in many different ways, with little attention to distinctions among the definitions.

Until recently American physicians used common language diagnosis names in medical charts, biasing recorded diagnoses towards the exclusive definition. Quality monitors did not challenge common language diagnoses, payers reimbursed expenses and patients with ambiguous diagnoses usually did not participate in studies of SLE. New administrative rules require American physicians to use International Classification of Diseases (ICD) code numbers that disregard the uncertainty of lupus spectrum illness.<sup>125 126</sup> Because when diagnoses are ambiguous payers often refuse to reimburse costs of SLE-relevant tests and medications, American physicians now assign the ICD code for typical SLE to patients they previously diagnosed with UCTD, overlap or other lupus spectrum disease, and these patients may now participate in studies that select patients by ICD code.

## A CONSENSUS DEFINITION

Although many investigators suggest improvements to the available SLE criteria,<sup>22 39 121 127–132</sup> the argument for more precise and more exclusive criteria is circular. Studies that exclude patients who do not fulfil criteria cannot prospectively examine phenomena that antedate diagnosis or that cause patients to develop non-criteria variants within lupus spectrum. Deconstructing the process of diagnosis—its definitions, models, stratifications and purposes—can help solve this problem. A consensus vocabulary is the first step to an agreed concept of SLE, including consensus answers to these questions:

1. When does SLE begin?
2. Do persons with autoantibodies only, UAS or overlap illness have 'SLE'?

3. Do persons with predisposing genetic abnormalities have 'SLE'?
4. Do patients with mild and severe 'SLE' have the same illness?
5. When 'SLE' changes course or changes to a different illness, does the change represent alteration of a continuous process or introduction of a new process?

Is SLE a clinical syndrome, having doctor-defined symptoms and specific organ system abnormalities? An abnormal biologic state, defined by laboratory phenomena that may or may not accompany clinical illness? A state of susceptibility, determined by genes and environment? Can it fully subside? What exogenous and/or endogenous factors trigger its onset or its change?

There are no definitive answers to these questions, but they will be better addressed when stakeholders agree on consensus definitions. Which definition, illness model or stratification we choose is less important than is consensus about the vocabulary that describes which patients we study, and to whom the results of our inquiries apply.

**Contributors** All authors contributed to, reviewed and approved this document.

**Funding** This study was funded by Barbara Volcker Center for Women and Rheumatic Diseases, Rheumatology Research Foundation.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Provenance and peer review** Commissioned; externally peer reviewed.

**Data sharing statement** No additional data are available.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0>

## REFERENCES

1. Fritzler MJ, Mahler M. Redefining systemic lupus erythematosus - SMAARTT proteomics. *Nat Rev Rheumatol* 2018;14:451–2.
2. Pierre Louis Alphée Cazenave. 2018. Available from: <https://www.revolvy.com/main/index.php?s=Pierre%20Louis%20Alph%20C3%A9%20Cazenave>
3. Wallace DJ, Lyon I. Pierre Cazenave and the first detailed modern description of lupus erythematosus. *Semin Arthritis Rheum* 1999;28:305–13.
4. Hargraves MM, Richmond H, Morton R. Presentation of two bone marrow elements; the tart cell and the L.E. cell. *Proc Staff Meet Mayo Clin* 1948;23:25–8.
5. Holborow EJ, Weir DM, Johnson GD. A serum factor in lupus erythematosus with affinity for tissue nuclei. *Br Med J* 1957;2:732–4.
6. Robbins WC, Holman HR, Deicher H, et al. Complement fixation with cell nuclei and DNA in lupus erythematosus. *Exp Biol Med* 1957;96:575–9.
7. Tan EM, Kunkel HG. Characteristics of a soluble nuclear antigen precipitating with sera of patients with systemic lupus erythematosus. *J Immunol* 1966;96:464.
8. Keil H. Dermatomyositis and systemic lupus erythematosus. II. A comparative study of the essential clinicopathologic features. *Arch Intern Med* 1940;66:339–83.
9. Bowie EJ, THOMPSON JH, Pascuzzi CA, et al. Thrombosis in systemic lupus erythematosus despite circulating anticoagulants. *J Lab Clin Med* 1963;62:416–30.
10. Nilsson IM, Åstedt B, Hedner U, et al. Intrauterine death and circulating anticoagulant ("antithromboplastin"). *Acta Med Scand* 1975;197:153–9.

11. Combinations and Permutations Calculator. 2018. Available from: <http://stattrek.com/online-calculator/combinations-permutations.aspx>
12. Aggarwal R, Ringold S, Khanna D, *et al.* Distinctions between diagnostic and classification criteria? *Arthritis Care Res* 2015;67:891–7.
13. Aringer M, Dörner T, Leuchten N, *et al.* Toward new criteria for systemic lupus erythematosus—a standpoint. *Lupus* 2016;25:805–11.
14. Cohen AS, Reynolds WE, Franklin EC. Preliminary criteria for the classification of systemic lupus erythematosus. *Bull Rheum Dis* 1971;21:643–8.
15. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997;40:1725.
16. Petri M, Orbai AM, Alarcón GS, *et al.* Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. *Arthritis Rheum* 2012;64:2677–86.
17. Clough JD, Elrazak M, Calabrese LH. Weighted criteria for the diagnosis of systemic lupus erythematosus. *Arch Intern Med* 1984;144:281–5.
18. Costenbader KH, Karlson EW, Mandl LA. Defining lupus cases for clinical studies: the Boston weighted criteria for the classification of systemic lupus erythematosus. *J Rheumatol* 2002;29:2545–50.
19. Aringer M, Costenbader KH, Brinks R. Validation of new systemic lupus erythematosus classification criteria. *Ann Rheum Dis* 2018;77(suppl 2).
20. Izmirly PM, Buyon JP, Wan I. The incidence and prevalence of adult primary Sjögren's syndrome in New York County. *Arthritis Care Res*;2018.
21. Yu C, Gershwin ME, Chang C. Diagnostic criteria for systemic lupus erythematosus: a critical review. *J Autoimmun* 2014;48:49:10–13.
22. Dall'Era M, Cisternas MG, Snipes K, *et al.* The incidence and prevalence of systemic lupus erythematosus in San Francisco County, California: The California lupus surveillance project. *Arthritis Rheumatol* 2017;69:1996–2005.
23. Aberle T, Bourn RL, Chen H, *et al.* Use of SLICC criteria in a large, diverse lupus registry enables SLE classification of a subset of ACR-designated subjects with incomplete lupus. *Lupus Sci Med* 2017;4:e000176.
24. Izmirly P, Wan I, Sahl S. The incidence and prevalence of systemic lupus erythematosus in New York County (Manhattan), New York. *Arthritis Rheumatol* 2017;69:2006–17.
25. Ferreira S, D'Cruz DP, Hughes GRV. Multiple sclerosis, neuropsychiatric lupus and antiphospholipid syndrome: where do we stand? *Rheumatology* 2005;44:434–42.
26. Sharp GC. MCTD: a concept which stood the test of time. *Lupus* 2002;11:333–9.
27. Ungprasert P, Crowson CS, Chowdhary VR, *et al.* Epidemiology of Mixed Connective Tissue Disease, 1985–2014: A Population-Based Study. *Arthritis Care Res* 2016;68:1843–8.
28. Wu Z, Casciola-Rosen L, Shah AA, *et al.* Estimating autoantibody signatures to detect autoimmune disease patient subsets. *Biostatistics* 2017.
29. Drenkard C, Parker S, Aspey LD, *et al.* Racial disparities in the incidence of primary chronic cutaneous lupus erythematosus in the Southeastern United States: the georgia lupus registry. *Arthritis Care Res* 2018.
30. Lockshin MD, Levine AB, Erkan D. Patients with overlap autoimmune disease differ from those with 'pure' disease. *Lupus Sci Med* 2015;2:e000084.
31. Jia L, Levine AB, Lockshin MD. American College of Rheumatology criteria for systemic lupus erythematosus exclude half of all systemic lupus erythematosus patients. *Arthritis Rheumatol* 2017;69:1502–3.
32. Jia L, Sevim E, Barbhaya M. What do we mean when we say SLE? *Lupus Science & Medicine* 2018;5(Suppl 2):A37.
33. McCormick N, Marra CA, Sadatsafavi M, *et al.* Incremental direct medical costs of systemic lupus erythematosus patients in the years preceding diagnosis: A general population-based study. *Lupus* 2018;27:1247–58.
34. Li W, Titov AA, Morel L. An update on lupus animal models. *Curr Opin Rheumatol* 2017;29:434–41.
35. Richard ML, Gilkeson G. Mouse models of lupus: what they tell us and what they don't. *Lupus Sci Med* 2018;5:e000199.
36. Arbuckle MR, McClain MT, Rubertone MV, *et al.* Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *N Engl J Med Overseas Ed* 2003;349:1526–33.
37. Doria A, Mosca M, Gambari PF, *et al.* Defining unclassifiable connective tissue diseases: incomplete, undifferentiated, or both? *J Rheumatol* 2005;32:213–5.
38. Mosca M, Tani C, Bombardieri S. Defining undifferentiated connective tissue diseases: a challenge for rheumatologists. *Lupus* 2008;17:278–80.
39. Ugarte-Gil MF, Alarcón GS. Incomplete Systemic Lupus Erythematosus: Early Diagnosis or Overdiagnosis? *Arthritis Care Res* 2016;68:285–7.
40. Daikh DI, Costenbader KH. How Do We Classify "Incomplete Lupus?". *Arthritis Care Res* 2017;69:1777–9.
41. Rees F, Doherty M, Lanyon P, *et al.* Early clinical features in systemic lupus erythematosus: can they be used to achieve earlier diagnosis? A risk prediction model. *Arthritis Care Res* 2017;69:833–41.
42. Bortoluzzi A, Furini F, Campanaro F, *et al.* Application of SLICC classification criteria in undifferentiated connective tissue disease and evolution in systemic lupus erythematosus: analysis of a large monocentric cohort with a long-term follow-up. *Lupus* 2017;26:616–22.
43. Slight-Webb S, Lu R, Ritterhouse LL, *et al.* Autoantibody-positive healthy individuals display unique immune profiles that may regulate autoimmunity. *Arthritis Rheumatol* 2016;68:2492–502.
44. Costenbader KH, Schur PH. We Need Better Classification and Terminology for "People at High Risk of or in the Process of Developing Lupus". *Arthritis Care Res* 2015;67:593–6.
45. Berens-Norman HM, Boackle SA. Editorial: Subduing Lupus: Can Preclinical Autoimmune Disease Be Arrested? *Arthritis Rheumatol* 2016;68:2357–60.
46. García-González M, Rodríguez-Lozano B, Bustabad S, *et al.* Undifferentiated connective tissue disease: predictors of evolution into definite disease. *Clin Exp Rheumatol* 2017;35:739–45.
47. Munroe ME, Young KA, Kamen DL, *et al.* Discerning risk of disease transition in relatives of systemic lupus erythematosus patients utilizing soluble mediators and clinical features. *Arthritis Rheumatol* 2017;69:630–42.
48. van Vollenhoven RF. Editorial: Who Gets Lupus? Clues to a Tantalizing Syndrome. *Arthritis Rheumatol* 2017;69:483–6.
49. van Steenberg HW, da Silva JAP, Huizinga TWJ, *et al.* Preventing progression from arthralgia to arthritis: targeting the right patients. *Nat Rev Rheumatol* 2018;14:32–41.
50. Muangchan C, van Vollenhoven RF, Bernatsky SR, *et al.* Treatment Algorithms in Systemic Lupus Erythematosus. *Arthritis Care Res* 2015;67:1237–45.
51. Romero-Diaz J, Isenberg D, Ramsey-Goldman R. Measures of adult systemic lupus erythematosus. *Arthritis Care & Research* 2011;63(S11):S37–S46.
52. Isenberg D, Sturgess J, Allen E, *et al.* Study of flare assessment in systemic lupus erythematosus based on paper patients. *Arthritis Care Res* 2018;70:98–103.
53. Wallace DJ. Editorial: Epratuzumab: Reveille or Requiem? Teachable Moments for Lupus and Sjögren's Syndrome Clinical Trials. *Arthritis Rheumatol* 2018;70:633–6.
54. Pisetsky DS, Spencer DM, Lipsky PE, *et al.* Assay variation in the detection of antinuclear antibodies in the sera of patients with established SLE. *Ann Rheum Dis* 2018;77:annrheumdis-2017-212599.
55. Lewis MJ, McAndrew MB, Wheeler C, *et al.* Autoantibodies targeting TLR and SMAD pathways define new subgroups in systemic lupus erythematosus. *J Autoimmun* 2018;91:1–12.
56. Bombardier C, Gladman DD, Urowitz MB, *et al.* Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. *Arthritis Rheum* 1992;35:630–40.
57. Isenberg DA, Rahman A, Allen E, *et al.* BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. *Rheumatology* 2005;44:902–6.
58. Vashisht P, Sayles H, Cannella AC, *et al.* Generalizability of patients with rheumatoid arthritis in biologic agent clinical trials. *Arthritis Care Res* 2016;68:1478–88.
59. Merrill JT, Immermann F, Whitley M, *et al.* The Biomarkers of Lupus Disease Study: A Bold Approach May Mitigate Interference of Background Immunosuppressants in Clinical Trials. *Arthritis Rheumatol* 2017;69:1257–66.
60. Barbhaya M, Feldman CH, Guan H, *et al.* Race/ethnicity and cardiovascular events among patients with systemic lupus erythematosus. *Arthritis Rheumatol* 2017;69:1823–31.
61. Pope JE, Weisman MH, Sjöwall C. Editorial: The Effect of Ethnicity on Cardiovascular Outcomes in Systemic Lupus Erythematosus Is Perhaps Not a Paradox. *Arthritis Rheumatol* 2017;69:1707–9.

62. Falasinnu T, Chaichian Y, Bass MB, *et al.* The representation of gender and race/ethnic groups in randomized clinical trials of individuals with systemic lupus erythematosus. *Curr Rheumatol Rep* 2018;20:20:20.
63. Feldman CH, Broder A, Guan H, *et al.* Sex Differences in Health Care Utilization, End-Stage Renal Disease, and Mortality Among Medicaid Beneficiaries With Incident Lupus Nephritis. *Arthritis Rheumatol* 2018;70:417–26.
64. Yelin E, Yazdany J, Trupin L. Relationship between process of care and a subsequent increase in damage in systemic lupus erythematosus. *Arthritis Care Res* 2017;69:927–32.
65. Qu H, Shewchuk RM, Alarcón G, *et al.* Mapping perceptions of lupus medication decision-making facilitators: the importance of patient context. *Arthritis Care Res* 2016;68:1787–94.
66. Arat S, Lenaerts JL, De Langhe E, *et al.* Illness representations of systemic lupus erythematosus and systemic sclerosis: a comparison of patients, their rheumatologists and their general practitioners. *Lupus Sci Med* 2017;4:e000232.
67. Barbhaiya M, Lu B, Sparks JA, *et al.* Influence of alcohol consumption on the risk of systemic lupus erythematosus among women in the Nurses' Health Study Cohorts. *Arthritis Care Res* 2017;69:384–92.
68. Golder V, Morand EF, Hoi AY. Quality of care for systemic lupus erythematosus: mind the knowledge gap. *J Rheumatol* 2017;44:271–8.
69. Ryu J, Lee TH. The Waiting Game — Why providers may fail to reduce wait times. *N Engl J Med Overseas Ed* 2017;376:2309–11.
70. Kim M, Merrill J, Kalunian K, *et al.* Brief Report: Longitudinal Patterns of Response to Standard of Care Therapy for Systemic Lupus Erythematosus: Implications for Clinical Trial Design. *Arthritis Rheumatol* 2017;69:785–90.
71. Walunas TL, Jackson KL, Chung AH, *et al.* Disease outcomes and care fragmentation among patients with systemic lupus erythematosus. *Arthritis Care Res* 2017;69:1369–76.
72. Rider L, Miller FW, 2017. Environmental factors in pediatric systemic autoimmune diseases. The Rheumatologist. Available from: [www.the-rheumatologist.org/article/environmental-factors-pediatric-systemic-autoimmune-diseases/](http://www.the-rheumatologist.org/article/environmental-factors-pediatric-systemic-autoimmune-diseases/)
73. Bouziat R, Hinterleitner R, Brown JJ, *et al.* Reovirus infection triggers inflammatory responses to dietary antigens and development of celiac disease. *Science* 2017;356:44–50.
74. Fotis L, Shaikh N, Baszis KW, *et al.* Serologic Evidence of Gut-driven Systemic Inflammation in Juvenile Idiopathic Arthritis. *J Rheumatol* 2017;44:1624–31.
75. Zeng P, Chen Z, Klareskog L, *et al.* Amount of smoking, duration of smoking cessation and their interaction with silica exposure in the risk of rheumatoid arthritis among males: results from the Swedish Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study. *Ann Rheum Dis* 2018;77:annrheumdis-2017-212145.
76. Barbhaiya M, Hart J, Malspeis S, 2017. Association of Ultraviolet-B Radiation and Risk of SLE Among Women in the Nurses' Health Studies. *Arthritis Rheum*. Available from: <https://www.rheumatology.org/Learning-Center/Publications-Communications/Abstract-Archives>
77. Yelin E, Trupin L, Yazdany J. A prospective study of the impact of current poverty, history of poverty, and exiting poverty on accumulation of disease damage in systemic lupus erythematosus. *Arthritis Rheumatol* 2017;69:1612–22.
78. West KM, Blacksher E, Burke W. Genomics, health disparities, and missed opportunities for the Nation's research agenda. *JAMA* 2017;317:1831–2.
79. Roberts AL, Malspeis S, Kubzansky LD, *et al.* Association of trauma and posttraumatic stress disorder with incident systemic lupus erythematosus in a longitudinal cohort of women. *Arthritis Rheumatol* 2017;69:2162–9.
80. Barbhaiya M, Tedeschi SK, Lu B, *et al.* Cigarette smoking and the risk of systemic lupus erythematosus, overall and by anti-double stranded DNA antibody subtype, in the Nurses' Health Study cohorts. *Ann Rheum Dis* 2018;77:196–202.
81. Manfredo Vieira S, Hiltensperger M, Kumar V, *et al.* Translocation of a gut pathobiont drives autoimmunity in mice and humans. *Science* 2018;359:1156–61.
82. Reardon S. A mouse's house may ruin studies. *Nature* 2016;530:264.
83. Cho JH, Gregersen PK. Genomics and the multifactorial nature of human autoimmune disease. *N Engl J Med Overseas Ed* 2011;365:1612–23.
84. YR L, Li J, Zhao SD, *et al.* Meta-analysis of shared genetic architecture across ten pediatric autoimmune diseases. *Nat Med* 2015;21:1018–27.
85. Nigrovic PA, Raychaudhuri S, Thompson SD. Review: genetics and the classification of arthritis in adults and children. *Arthritis Rheumatol* 2018;70:7–17.
86. Blegvad C, Egeberg A, Nielsen T, Tind Nielsen TE, *et al.* Autoimmune disease in children and adolescents with psoriasis: a cross-sectional study in Denmark. *Acta Derm Venereol* 2017;97:1225–9.
87. International Consortium for Systemic Lupus Erythematosus Genetics (SLEGEN), Harley JB, Alarcón-Riquelme ME, *et al.* Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PTK, KIAA1542 and other loci. *Nat Genet* 2008;40:204–10.
88. Guerra SG, Vyse TJ, Cunninghame Graham DS. The genetics of lupus: a functional perspective. *Arthritis Res Ther* 2012;14:211.
89. Blair DR, Lytle CS, Mortensen JM, *et al.* A nondegenerate code of deleterious variants in Mendelian loci contributes to complex disease risk. *Cell* 2013;155:70–80.
90. Phillips D, 2015. Multiple autoimmune diseases share same genetic risk factors. Medscape. Available from: <http://www.medscape.com/viewarticle/850543>
91. Boycott KM, Innes AM. When One Diagnosis Is Not Enough. *N Engl J Med Overseas Ed* 2017;376:83–5.
92. Posey JE, Harel T, Liu P, *et al.* Resolution of disease phenotypes resulting from multilocus genomic variation. *N Engl J Med Overseas Ed* 2017;376:21–31.
93. Raj P, Pichilingue-Reto P, Dozmorov I. Immune repertoire and genetic risk alleles in healthy pediatric populations with autoimmune indicators. *Lupus Sci & Med* 2018;5(Suppl 2):A58.
94. Yao Q, Shen B. A systematic analysis of treatment and outcomes of NOD2-associated autoinflammatory disease. *Am J Med* 2017;130:365.e13–365.e18.
95. Gao D, Li T, Li XD, *et al.* Activation of cyclic GMP-AMP synthase by self-DNA causes autoimmune diseases. *Proc Natl Acad Sci U S A* 2015;112:E5699–E5705.
96. Kim H, Sanchez GA, Goldbach-Mansky R. Insights from Mendelian Interferonopathies: Comparison of CANDLER, SAVI with AGS, Monogenic Lupus. *J Mol Med* 2016;94:1111–27.
97. Drappa J, Vaishnav AK, Sullivan KE, *et al.* Fas gene mutations in the canale-Smith syndrome, an inherited lymphoproliferative disorder associated with autoimmunity. *N Engl J Med Overseas Ed* 1996;335:1643–9.
98. Demirkaya E, Zhou Q, Smith CK, *et al.* Brief report: deficiency of complement 1r subcomponent in early-onset systemic lupus erythematosus: the role of disease-modifying alleles in a monogenic disease. *Arthritis & Rheumatology* 2017;69:1832–9.
99. Kottyan LC, Zoller EE, Bene J, *et al.* The IRF5-TNPO3 association with systemic lupus erythematosus has two components that other autoimmune disorders variably share. *Hum Mol Genet* 2015;24:582–96.
100. Salaman MR, Isenberg DA. The immunological personality of close relatives of SLE patients. *Lupus* 2017;26:1513–6.
101. Md YMY, Psarras A, El-Sherbiny YM. Prediction of autoimmune connective tissue disease in an at-risk cohort: prognostic value of a novel two-score system for interferon status. *Ann Rheum Dis*.
102. Obermoser G, Pascual V. The interferon- $\alpha$  signature of systemic lupus erythematosus. *Lupus* 2010;19:1012–9.
103. Monteith AJ, Kang S, Scott E, *et al.* Defects in lysosomal maturation facilitate the activation of innate sensors in systemic lupus erythematosus. *Proc Natl Acad Sci U S A* 2016;113:E2142–E2151.
104. Kubo S, Nakayamada S, Yoshikawa M, *et al.* Peripheral immunophenotyping identifies three subgroups based on T cell heterogeneity in lupus patients. *Arthritis Rheumatol* 2017;69:2029–37.
105. Hanly JG, Li Q, Su L, *et al.* Psychosis in systemic lupus erythematosus. *Arthritis Rheumatol*. In Press;2019.
106. Mina-Osorio P. *Progress in Inflammation Research: Next-Generation Therapies and Technologies for Immune-Mediated Inflammatory Diseases*. Switzerland: Springer, 2017.
107. Cepika AM, Bancheureau R, Segura E, *et al.* A multidimensional blood stimulation assay reveals immune alterations underlying systemic juvenile idiopathic arthritis. *J Exp Med* 2017;214:3449–66.
108. Char DS, Shah NH, Magnus D. Implementing Machine Learning in Health Care - Addressing Ethical Challenges. *N Engl J Med* 2018;378:981–3.
109. Tag cloud. 2018. Available from: [https://en.wikipedia.org/wiki/Tag\\_cloud](https://en.wikipedia.org/wiki/Tag_cloud)
110. Mok CC. Systemic lupus erythematosus: Withdrawing standard of care therapies in SLE trials? *Nat Rev Rheumatol* 2017;13(6):328–330.

111. Barturen G, Beretta L, Cervera R, *et al.* Moving towards a molecular taxonomy of autoimmune rheumatic diseases. *Nat Rev Rheumatol* 2018;14:75–93.
112. Weckerle CE, Franek BS, Kelly JA, *et al.* Network analysis of associations between serum interferon- $\alpha$  activity, autoantibodies, and clinical features in systemic lupus erythematosus. *Arthritis Rheum* 2011;63:1044–53.
113. Langefeld CD, Ainsworth HC, Cunninghame Graham DS, *et al.* Transancestral mapping and genetic load in systemic lupus erythematosus. *Nat Commun* 2017;8:16021.
114. Bernstein S, 2018. Experts discuss the latest precision medicine research. The Rheumatologist. Available from: <http://www.the-rheumatologist.org/article/experts-discuss-latest-precision-medicine-research-2/?singlepage=1&theme=print-friendly>
115. Castrejón I, Tani C, Jolly M. Indices to assess patients with systemic lupus erythematosus in clinical trials, long-term observational studies, and clinical care. *Clin Exp Rheumatol* 2014;32(Suppl. 85):S85–S95.
116. Amezcua-Guerra LM, Higuera-Ortiz V, Arteaga-García U, *et al.* Performance of the 2012 systemic lupus International collaborating clinics and the 1997 American college of rheumatology classification criteria for systemic lupus erythematosus in a real-life scenario. *Arthritis Care Res* 2015;67:437–41.
117. Inês L, Silva C, Galindo M. Classification of systemic lupus erythematosus. *Arthritis Care & Research* 2015;67:437–41.
118. Inês L, Silva C, Galindo M, *et al.* Classification of systemic lupus erythematosus: Systemic lupus international collaborating clinics versus american college of rheumatology criteria. A comparative study of 2,055 patients from a real-Life, international systemic lupus erythematosus cohort. *Arthritis Care Res* 2015;67:1180–5.
119. Isenberg D, Sturgess J, Allen E, *et al.* Study of flare Assessment in systemic lupus erythematosus based on paper patients. *Arthritis Care Res* 2018;70:98–103.
120. Sanz I. New perspectives in rheumatology: may you live in interesting times: challenges and opportunities in lupus research. *Arthritis Rheumatol* 2017;69:1552–9.
121. Aberle T, Bourn RL, Munroe ME, *et al.* Clinical and serologic features in patients with incomplete lupus classification versus systemic lupus erythematosus patients and controls. *Arthritis Care Res* 2017;69:1780–8.
122. Raymond SC, Hanrahan LM, Merrill J. *Lupus classification criteria effort is going in the wrong direction.* Dermatology News, 2017.
123. Merrill JT, Manzi S, Aranow C, *et al.* Lupus community panel proposals for optimising clinical trials: 2018. *Lupus Sci Med* 2018;5:e000258.
124. International Statistical Classification of Diseases and Related Health Problems. 2018. Available from: [https://en.wikipedia.org/wiki/International\\_Statistical\\_Classification\\_of\\_Diseases\\_and\\_Related\\_Health\\_Problems](https://en.wikipedia.org/wiki/International_Statistical_Classification_of_Diseases_and_Related_Health_Problems)
125. Systemic lupus erythematosus, unspecified. 2018. Available from: <http://www.icd10data.com/ICD10CM/Codes/M00-M99/M30-M36/M32-/M32.9>
126. Leuchten N, Milke B, Winkler-Rohlfing B. on behalf of the SLE Classification Criteria Steering Committee. Early symptoms of systemic lupus erythematosus (SLE) recalled by 339 SLE patients. *Lupus* 2018;27:1431–6.
127. Lu R, Munroe ME, Guthridge JM, *et al.* Dysregulation of innate and adaptive serum mediators precedes systemic lupus erythematosus classification and improves prognostic accuracy of autoantibodies. *J Autoimmun* 2016;74:182–93.
128. Mosca M, Costenbader KH, Johnson SR. New SLE classification criteria for clinical research are being developed, sponsored by EULAR and ACR. How Do Patients with Newly Diagnosed Systemic Lupus Erythematosus Present? A Multicenter Cohort of Early Systemic Lupus Erythematosus to Inform the Development of New Classification Criteria. *Arthritis Rheumatol* 2018. Epub ahead of print 23 Jul 2018.
129. Munroe ME, Lu R, Zhao YD, *et al.* Altered type II interferon precedes autoantibody accrual and elevated type I interferon activity prior to systemic lupus erythematosus classification. *Ann Rheum Dis* 2016;75:2014–21.
130. Olsen NJ, McAloose C, Carter J, *et al.* Clinical and immunologic profiles in incomplete lupus erythematosus and improvement with hydroxychloroquine treatment. *Autoimmune Dis* 2016;2016:1–9.
131. Schmajuk G, Hoyer BF, Aringer M, *et al.* multicenter Delphi exercise to identify important key items for classifying systemic lupus erythematosus. *Arthritis Care Res* 2018;70:1488–94.
132. Tedeschi SK, Johnson SR, Boumpas D, *et al.* Developing and refining new candidate criteria for systemic lupus erythematosus classification: An international collaboration. *Arthritis Care Res* 2018;70:571–81.