

SLE: reconciling heterogeneity

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Patients with SLE experience multiple, varied symptoms and laboratory abnormalities that occur in different combinations, at different points in time.¹ 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.

criteria allow 330 different combinations of symptoms and laboratory tests to affirm a diagnosis of SLE.¹¹ 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.^{12–21} 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.²¹)

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.^{22–24} 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),^{25–27} *SLE-associated antibodies only* (diagnostic autoantibodies but no clinical illness)²⁸ and *cutaneous SLE* (skin disease without systemic manifestations).²⁹

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.^{30 31} 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.³²

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.^{2 3} A century later, as new technologies identified more patients,^{4–10} 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)



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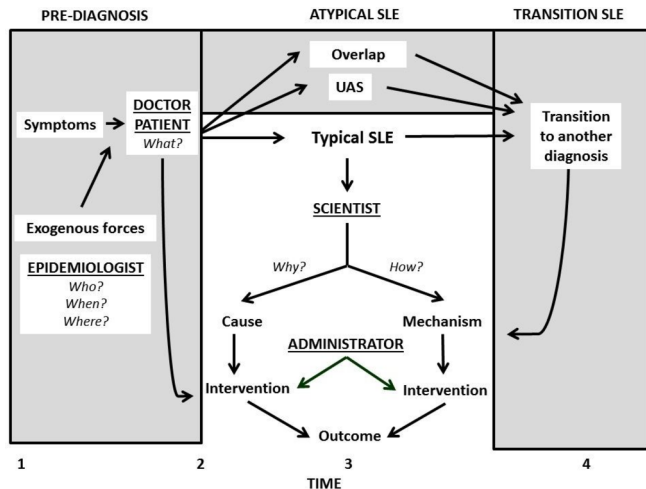


Figure 1 A proposed model of SLE-lupus spectrum illness that considers stakeholders' definitions and the concept of time. Time 1 is first onset of clinical or laboratory abnormalities, time 2 first diagnosis, time 3 outcome measurement and time 4 transition to another illness. Practising doctors and 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.^{33–35} 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.³⁶ 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.^{37–40} 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.³⁰

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.^{41–49} 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 B₁₂ 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.^{50–57} Stratification on sex, race, socioeconomic status,^{58–62} access to medical care, medication choice and adherence,⁶³ willingness to participate in clinical trials, doctor–patient interactions,⁶⁴ patient preferences and perceptions,⁶⁵ lifestyle choices,^{66–67} physician choices,^{68–71} environmental triggers,^{72–76} poverty,⁷⁷ social disparities,⁷⁸ and life events,⁷⁹ smoking⁸⁰ and the gut pathobiont⁸¹ 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.⁸² Stratification on *gene expression*, quantitative, predicts risk and possibly phenotype^{83–93}; SLE-like illnesses

(the autoinflammatory diseases),⁹⁴ Aicardi-Goutières syndrome,^{95–96} Canale-Smith syndrome⁹⁷ and SLE associated with immunodeficiency⁹⁸ suggest mechanisms for primary illness, and for phenotype diversity. Stratification by *molecular biomarkers* predicts fulfilment of classification criteria,⁹⁹ organ involvement and development of SLE in relatives of patients.^{100–104} Stratifying by *time* will offer insight about how SLE diagnoses change.¹⁰⁵ *New computational techniques*, like multidimensional models, cluster analyses, machine learning, the word cloud, personalised immunomonitoring and transancestral mapping, are modern ways to stratify.^{106–114} 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.^{115–124} 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.^{125 126} 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,^{22 39 121 127–132} 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.

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