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Developing and Refining New Candidate Criteria for SLE Classification: An International Collaboration

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Abstract

Objectives—We aimed to define candidate criteria within multi-phase development of SLE classification criteria, jointly supported by EULAR and ACR. Prior steps included item generation and reduction by Delphi exercise, further narrowed to 21 items in a Nominal Group Technique exercise. Our objectives were to apply an evidence-based approach to the 21 candidate criteria, and to develop hierarchical organization of criteria within domains.

Methods—A literature review identified the sensitivity and specificity of the 21 candidate criteria. Data on the performance of ANA as an entry criteria and operating characteristics of the candidate criteria in early SLE patients were evaluated. Candidate criteria were hierarchically

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organized into clinical and immunologic domains, and definitions were refined in an iterative process.

Results—Based on the data, consensus was reached on a positive ANA of ≥1:80 titer (HEp2 cells immunofluorescence) as an entry criterion; use of seven clinical and three immunologic domains, with hierarchical organization of criteria within domains; and definitions of the candidate criteria were specified.

Conclusion—Using a data-driven process, consensus was reached on new, refined criteria definitions and organization based on operating characteristics. This work will be followed by a multicriteria decision analysis exercise to weight criteria and to identify a threshold score for classification on a continuous probability scale.

Keywords

systemic lupus erythematosus; classification criteria; methodology

INTRODUCTION

The 1982 American College of Rheumatology (ACR) classification criteria for SLE and their 1997 revision have shaped our understanding of SLE and been used widely in lupus research for decades. However, novel information on the disease has emerged, such as the recognition of subacute cutaneous lupus erythematosus (SCLE) as an SLE manifestation, and the Systemic Lupus International Collaborating Clinics (SLICC) group showed that their sensitivity is suboptimal. On the other hand, while introducing important new concepts, the SLICC 2012 criteria have only partially succeeded in better performance, in that they had increased sensitivity at the price of reduced specificity. It appears likely that this decrease in specificity is due to maintaining the overall structure of the ACR criteria, which assigns equal weights to each criterion. While SLICC criteria require the presence of at least one clinical and one immunologic criterion, both the ACR and SLICC criteria classify SLE based a simple count of the number of criteria present. Due to the heterogeneity of SLE—ranging from mild to severe symptoms with a variety of organ manifestations—the overall performance of SLE classification criteria could be further increased by developing a weighted scoring system. This is particularly true for early phases of the disease, where both ACR and SLICC criteria perform worse than in established SLE.

Since 2014, a Steering Committee equally appointed by the European League Against Rheumatism (EULAR) and the ACR (n=12) has been working on developing new classification criteria for systemic lupus erythematosus (SLE) for clinical research purposes. This effort involves hundreds of SLE experts worldwide. The overarching goal is to develop a system to identify potential participants for clinical research studies, which requires some degree of homogeneity across subjects, while simultaneously dealing with the extreme heterogeneity of SLE. As with previously established classification criteria, the goal is to arrive at a system with the maximum combination of sensitivity and specificity for SLE, retaining face validity.[1]

In accordance with recommendations for rheumatic disease classification criteria development, a four phase, data-driven and expert-based methodologic approach is underway.[1–9] The item generation and reduction phases of this approach were completed by a Nominal Group Technique exercise[8] that produced 21 candidate criteria—two of which were proposed as candidate entry criteria—summarized in Table 1.

Three important issues were raised during the Nominal Group Technique exercise. First, it was important to understand the validity of each of the candidate criteria, particularly their sensitivity and specificity.[5] Second, a lack of precise definitions for the candidate criteria would result in inconsistent interpretation and application of the criteria, affecting the validity and reliability of the final classification system. Finally, clustering the criteria into 'buckets' or domains was recommended as a next step.

We report the process of refining the criteria for SLE classification. The goals were to apply an evidence-based approach to the 21 candidate criteria, and to develop hierarchical organization of criteria within domains.

METHODS

Literature review for test performance characteristics of candidate criteria

Two investigators (KHC, SKT) conducted a literature review on sensitivity and specificity of the candidate SLE criteria using PubMed. This step was foundational for subsequent steps, as sensitivity and specificity are among the most important aspects to consider when developing classification criteria.[3, 10] Several manuscripts have reported the prevalence of specific manifestations in SLE cohorts, but for the purposes of classification criteria development, it was important to evaluate both sensitivity and specificity in the same dataset. In the evaluative process, the following principles were considered:

- Sensitivity for SLE represents prevalence of a criterion in a given SLE population. Thus, the SLE population being studied affects the sensitivity.
- Specificity for SLE is contingent upon the comparator (non-SLE) population. For example, specificity of oral ulcers for SLE is the ratio of comparator patients *without* oral ulcers to the entire comparator population. Using a comparator population of Crohn's disease patients, who may develop oral ulcers as part of their disease, will produce different specificity than using a comparator population of rheumatoid arthritis patients among whom oral ulcers are uncommon.

Identification of domains

After reviewing the literature, the candidate criteria were clustered into independent domains. This was an iterative process, with input from the Steering Committee. Based on the development of published criteria sets[11–14] and consultation with an expert in additive point systems for disease classification (RPN), the following principles for domain development were proposed:

- Classification criteria should be organized into 8–10 domains, each containing 2–3 criteria;
- Domains should be independent from one another, and therefore additive;
- Within a domain, criteria should be ordered from least to most influential (i.e. least specific to most specific) regarding their importance when considering the likelihood of a patient being classified as having the disease;
- Only the one most influential criterion in each domain will be scored;
- Scores from all domains will be summed to produce a final SLE classification score.

In-person meeting at the EULAR 2016 Congress

During a one-day meeting, the literature review and a draft hierarchical organization of criteria within domains were presented to the Steering Committee and two patient representatives from Lupus Europe for feedback and comment. Challenges with drawing generalizable conclusions from the literature review, such as the use of different comparator populations for sensitivity and specificity calculations, and definitions used in past criteria were discussed. Definitions and the order within domains were further refined. The reliability (i.e. reproducibility between clinicians and within individual clinicians) of the candidate clinical criteria was discussed. The precision and availability of candidate immunologic assays were discussed.

Assessment of face and content validity of domains and criteria

Following the in-person meeting, the domains and criteria were further refined through an iterative process. Changes to the number and content of domains, and criteria within domains, were made in response to feedback given during the discussions. The guiding principles were that criteria should be sensitive for SLE (i.e. prevalent in SLE cohorts), criteria should be arranged in order of increasing specificity for SLE, and domains must be independent. Additionally, candidate criteria were assessed for creditability (face validity) and comprehensiveness (content validity) to reflect all aspects of SLE.[3, 5]

RESULTS

Literature review and performance characteristics of candidate criteria

The sources of sensitivity and specificity data were: American Rheumatism Association (ARA) 1971 preliminary SLE classification criteria,[15] ACR 1982 revised criteria for the classification of SLE and the 1997 update of these criteria,[16, 17] Systemic Lupus International Collaborating Clinics (SLICC) 2012 classification criteria for SLE,[18] data from a recent, early SLE (diagnosed in the preceding 12 months) cohort study,[19] and a recent, large study of test characteristics of low complements in new-onset SLE.[20] These study populations are summarized in Table 2. Sensitivity and specificity data for the candidate criteria are summarized in Table 3. When present, published definitions were reviewed.

Definitions for candidate criteria

While the complete list of candidate criteria is shown in Table 1, and previous classification criteria definitions are detailed in Table 3, discussions on several items were critical and are therefore presented here in more detail.

Fever—Fever was not included in previous classification criteria. In the early SLE cohort, fever was present in 34% of SLE patients vs. 14% of patients with conditions only mimicking SLE (mimickers).[19] Fever of unknown origin is defined as >38.3 Celsius for >3 weeks with no source identified after one week of investigation.[21] This definition had not been studied in SLE.

Alopecia with associated scalp inflammation—The ACR 1982 classification criteria omitted alopecia as "it did not perform well in distinguishing SLE from scleroderma and dermato/polymyositis [data not shown]."[16] The ARA 1971 SLE classification criteria and SLICC 2012 SLE classification criteria both defined alopecia as *non-scarring*.

Acute cutaneous lupus—The ACR 1982 criteria included two independent acute cutaneous lupus criteria: malar rash and photosensitivity, while the SLICC 2012 definition included malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, and photosensitive lupus rash in the absence of dermatomyositis.

Subacute cutaneous lupus was observed in 4.6% of a large European cohort,[22] and a 1981 dermatology report estimated 10–15% prevalence in SLE.[23] We did not find specificity data for subacute cutaneous lupus.

We reviewed skin biopsy histopathology definitions developed through an international Delphi consensus process of relevant stakeholders at the 2013 International Meeting on Cutaneous Lupus Erythematosus.[24] Interface vacuolar dermatitis was common to acute cutaneous, subacute cutaneous, and discoid lupus. Immunofluorescence findings were not specifically mentioned.

Chronic cutaneous lupus—The Gilliam 1981 classification of chronic cutaneous lupus erythematosus included discoid lupus, and excluded lupus profundus/panniculitis, chilblain lupus, and lupus tumidus.[23] The ACR 1982 criteria included only discoid lupus, whereas the expanded SLICC criteria included: classic discoid rash (localized above the neck, or generalized), hypertrophic (verrucous) lupus, lupus panniculitis (profundus), mucosal lupus, lupus erythematosus tumidus, chilblains lupus, and discoid lupus/lichen planus overlap. Test characteristics of these single entities were not reported.

CNS manifestations—The ACR 1982 classification criteria included a neurologic criterion with two possible manifestations: seizures or psychosis, in the absence of other causes. SLICC included both central nervous system (CNS) and peripheral nervous system (PNS) manifestations. CNS manifestations were: seizures, psychosis, cranial neuropathy, and acute confusional state in the absence of other causes.

Among 1,206 early SLE patients with mean disease duration of 5.4 (standard deviation [SD] 4.2) months at enrollment and mean 1.9 (SD 1.2) years of follow-up, 486 (40.3%) had a neuropsychiatric event, most commonly headache and mood disorder.[25] Among these 486 patients, 13–24% of neuropsychiatric events were attributable to SLE depending on the decision rule applied. Another study reported that most SLE CNS manifestations occur in patients with lupus anticoagulant, anti-cardiolipin, or anti-dsDNA antibodies.[26] This raised questions about the etiology of CNS events and whether they are predominantly consequences of antiphospholipid syndrome (APS).

In the early SLE cohort, seizures were among the presenting manifestations in 2.8%, psychosis in 1%, and stroke in 1%.[19] The definition for each of these diagnoses was not specified. Definitions of neurologic criteria from the ACR 1999 Ad Hoc Committee on Neuropyschiatric Lupus were reviewed and are presented in Table 1 (Neurologic domain).[27] Stroke was omitted as it is most commonly a manifestation of long-standing SLE in the context of cerebrovascular risk factors and/or APS. The ACR 1999 publication indicated that "acute confusional state" was synonymous with "delirium"; the latter term was adopted due to clinical familiarity.

Serositis—In ACR 1982 criteria, serositis included "pleuritis," characterized by a convincing history of pleuritic pain or a pleuritic rub heard by a physician or evidence of pleural effusion, or "pericarditis" documented by EKG or rub or evidence of pericardial effusion.[16] SLICC defined serositis as "typical pleurisy for >1 day or pleural effusions or pleural rub", or "typical pericardial pain (pain with recumbency improved by sitting forward) or pericardial effusion or pericardial rub or pericarditis by electrocardiography [EKG]" in the absence of other causes.[18] We did not find data on sensitivity or specificity of abdominal serositis in SLE.

The European Society of Cardiology 2015 Guidelines for diagnosis and management of pericardial diseases defined acute pericarditis as an inflammatory syndrome with ≥2 of the following: (1) pericarditic chest pain ("typically sharp and pleuritic, improved by sitting up and leaning forward"), (2) pericardial friction rub, (3) new widespread ST-elevation or PR depression on EKG, (4) pericardial effusion (new or worsening).[28] This definition has not been evaluated in SLE to our knowledge.

Lupus nephritis—The ACR 1982 criteria did not include renal biopsy. Biopsy-proven lupus nephritis in the setting of positive ANA or anti-dsDNA antibodies is considered sufficient for classification as SLE using the SLICC classification criteria. The SLICC publication did not present sensitivity or specificity data for renal biopsy, however. We reviewed lupus nephritis renal histopathology definitions from the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 Classification system.[29] These definitions include characteristic findings by both light microscopy and immunofluorescence.

Active urine sediment was defined as "cellular casts – may be red cell, hemoglobin, granular, tubular, or mixed" in the ACR 1982 criteria.[16] SLICC criteria include urinary red blood cell (RBC) casts as the sole indicator of an active urine sediment. ACR 2006 criteria

for response in SLE clinical trials defined active urine sediment as >5 RBC/high power field (hpf) and >5 WBCs/hpf and/or ≥1 cellular cast.[30] However, urinary RBC ≤5/hpf had low sensitivity and specificity in predicting improved renal function at 12 months in the Euro-Lupus Nephritis cohort.[31]

Antiphospholipid antibodies—The 1997 update to ACR 1982 criteria included antiphospholipid antibodies as follows: "abnormal" ACL IgG or IgM, or positive lupus anticoagulant, or false-positive serologic test for syphilis for at least six months and confirmed by a second test.[17] SLICC criteria assign points for the presence of ≥1 of the following: positive lupus anticoagulant; false-positive rapid plasma reagin; medium- or high-titer anti-cardiolipin (ACL) IgA, IgG, or IgM (titers not defined); positive anti-β2-glycoprotein I (anti-β2GP1) IgA, IgG, or IgM. The need for repeat testing was not specified.

A 2006 international consensus statement updating the Sapporo Criteria stated that APS requires one of the following: ACL IgG >40 GPL units or IgM >40 MPL units; anti-β2GP1 IgG or IgM >99th percentile; and/or positive lupus anticoagulant.[32] Per email discussion with an international expert on antiphospholipid antibodies, most clinical laboratories do not report the percentile for anti-β2GP1 IgG or IgM (D. Erkan, personal communication).

Complement proteins—ACR 1982 criteria do not include complements because, "we were unable to improve accuracy by using any combination of serum complement determinations, either as a separate criterion or by adding these determinations into one of the other combined variables."[16] SLICC criteria include low C3, low C4, or low CH50. In a large study of newly-diagnosed SLE and non-SLE patients, complement assays were performed by immunization rate scattering turbidimetry; low C3 was <0.79 g/L and low C4 was <0.16 g/L.[20]

Presence of multiple autoantibodies—In the early SLE cohort, anti-Ro antibody was present in 25% of SLE patients vs. 23% of mimickers; anti-La antibody was found in 11% of SLE vs. 9% of mimickers. Anti-U1-RNP was detected more frequently in SLE (22%) vs. mimickers (5%).[19]

Identification of domains

Clinical and immunologic domains identified before the EULAR 2016 Congress meeting included:

- Clinical domains
  - Constitutional
  - Cutaneous
  - Arthritis
  - Serositis
  - Hematologic
  - Renal

- Neurologic was not included as a domain prior to this meeting; however, during phone calls and emails in the months after the meeting, consensus was reached about including a Neurologic domain as defined in Table 1

- Immunologic domains
  - Other serologies
  - Complement proteins
  - Highly specific autoantibodies

In-person meeting at the EULAR 2016 Congress

Data from the literature review, the proposed clinical and immunologic domains, and proposed clustering of criteria within domains, were reviewed. In applying the criteria, consensus was achieved for: (Table 1)

- "For each criterion, do not score if a cause *more likely* than SLE exists (such as infection, malignancy, medication, rosacea, endocrine disorder, other autoimmune disease)." This statement was proposed to avoid redundancy in stating "in the absence of [insert specific causes]" after each criterion. This statement may be bolded on the final version of the scoring form to emphasize its great importance in scoring each criterion, and it underscores the clinical judgment and experience of the clinician scoring the patient.
- "Occurrence of a criterion on at least one occasion is sufficient." This is an important change compared to the ACR 1982 hematologic criteria, and is grounded in more recent data.
- "Criteria need not occur simultaneously." This statement reflects that SLE can evolve over time, with new manifestations appearing years after diagnosis.
- "At least one clinical criterion must be present." The group agreed that for the purposes of clinical research, the new classification criteria should not classify an asymptomatic patient as having SLE based on positive serologies only.
- "Within each domain, only the highest weighted criterion is counted toward the total score." This is based on the fact that symptoms in one category, such as leukopenia and thrombocytopenia, could stem from a non-SLE (e.g. bone marrow) disease.

It was also decided that the new criteria should avoid classifying patients with positive ANA and only cutaneous manifestations as SLE. It was agreed that ANA ≥1:80 by HEp2 immunofluorescence would be an entry criterion (e.g. must be present to be considered for classification as SLE), with the addition of the phrase "history of," as patients with SLE may have a positive ANA that later normalizes.[9] Because of the relatively low sensitivity of low complement levels identified through literature review, it was agreed that this should not be an entry criterion and it was re-assigned as an Immunologic domain.

Discussions about candidate criteria are summarized in Supplemental File 1.

DISCUSSION

In this phase of SLE classification criteria development, we applied a data-driven, consensus-based approach to categorize candidate criteria into independent domains. Through literature review, we synthesized the test performance characteristics of candidate criteria under consideration for classification of SLE. We then refined definitions for the candidate criteria, thereby improving the validity and reliability of the final classification system. Additionally, we adhered to the recommendation of SLE experts to cluster criteria into domains, creating hierarchical organization of criteria within domains.[8]

Our literature review revealed knowledge gaps about the sensitivity and specificity of some of the newly proposed criteria, thus expert consensus and patient input was critical for decision making. This was evident, for example, in the discussion regarding neurologic manifestations of SLE. Individual CNS and PNS manifestations have a low prevalence and consequently poor operating characteristics in SLE. In addition, it has been recognized that the attribution of neurologic events to SLE is difficult, and these events can occur up to 20 years before SLE diagnosis.[33] However, both SLE experts and patients felt it was important to retain this domain into the next phase, for further testing.

Similarly, the concept of "*presence of multiple autoantibodies"* was an appealing criterion to many experts. However, it was evident that antibodies already part of candidate items by themselves could not be included, and antibodies that were not testable worldwide should not be included. This would preclude the feasibility of the final criteria system. Anti-Ro, anti-La, and anti-RNP antibodies remained for consideration. However, whether the presence of these antibodies increases or decreases the likelihood of SLE is highly dependent on the clinical context. For example, a patient with ANA 1:160 by Hep2 immunofluorescence, positive anti-Ro and anti-La antibodies, sicca syndrome, and no other signs or symptoms likely has primary Sjögren's syndrome; in this case, anti-Ro and anti-La antibodies should carry negative weight for likelihood of SLE. Another patient with the same autoantibody profile, inflammatory arthritis, and pericarditis would be more properly classified as SLE; in this scenario, anti-Ro and anti-La antibodies should not detract from the likelihood of SLE, but whether they add to it is unclear.

With clarity on the definitions of the candidate criteria, their operating characteristics, and the hierarchical organization of criteria within domains,[8] we are able to embark on the next phase of criteria development. In Phase III, ascertainment of criteria weights, possible further refinement of criteria and identification of a threshold for classification will be achieved using multicriteria decision analysis. It is anticipated that this will result in a numeric additive point system that will assign a probability that an individual with a combination of particular signs and symptoms can be classified as SLE. This scoring system will undergo validation and comparison against pre-existing classification systems. Certainly, our understanding of the immunologic basis of SLE is rapidly evolving and molecular diagnostic testing is being developed to more accurately distinguish SLE from non-SLE, and to allow sub-phenotyping of patients.[34–37] These assays are not yet universally accepted or commercially available, and thus not ready for incorporation in disease classification criteria. However, as attempts at the cellular and molecular

characterization of SLE are underway, it will be interesting to see whether they will support this clinically-derived set of SLE classification criteria and the underlying concepts—or radically change our ways of thinking about SLE classification.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance and Innovations

- We conducted a literature review to understand the performance characteristics of candidate classification criteria for SLE.
- Organization of criteria into independent additive domains will facilitate, in the next phase of this international EULAR/ACR joint project, the development of an additive scoring system, with identification of a threshold score above which a patient will be classified as SLE for the purpose of clinical research studies.

Table 1

Evolution of candidate SLE classification criteria in a multi-phase development process

Nominal Group Technique (2015)	Literature Review and Iterative Revisions (through October 2016)
Entry criteria	
ANA by HEp 2 immunofluorescence ≥1:80	History of a positive ANA by HEp 2 immunofluorescence ≥1:80
Low C3 and/or low C4	[Not an entry criterion, but included as a domain]
Criteria	
Candidate additive criteria, listed in no particular order	Criteria were grouped into domains. Items within domains were listed in order of increasing importance. The following **Opening Statements** were agreed upon: • For each criterion, do not score if a cause *more likely* than SLE exists (such as infection, malignancy, medication, rosacea, endocrine disorder, other autoimmune disease). • Occurrence of a criterion on at least one occasion is sufficient. • Criteria need not occur simultaneously. • At least one clinical criterion must be present. • Within each domain, only the highest weighted criterion is counted toward the total score.
	Clinical Domains and Criteria
Fever (definition to be determined)	*Constitutional domain:* **Fever:** >38.3 Celsius with no other source identified
Rash with dermoepidermal interface changes and immunoglobulin and/or complement deposition on immunofluorescence Alopecia with associated scalp inflammation Oral mucosal lesions on the hard palate Acute cutaneous lupus: SLICC definition Chronic cutaneous: SLICC definition	*Cutaneous domain:* • **Oral ulcers**, not necessarily observed by a physician [eliminated “on the hard palate”] • **Non-scarring alopecia**, not necessarily observed by a physician [eliminated “scalp inflammation”] • **Subacute cutaneous lupus**: Annular or papulosquamous (psoriasiform) cutaneous eruption, usually photodistributed. If skin biopsy is performed, typical changes[a] must be present. • **Acute cutaneous lupus**: Malar rash (localized) or maculopapular rash (generalized), with or without photosensitivity. If skin biopsy is performed, typical changes[a] must be present • **Discoid lupus**: Erythematous-violaceous cutaneous lesions with secondary changes of atrophic scarring, dyspigmentation, often follicular hyperkeratosis/plugging (scalp) leading to scarring alopecia on the scalp. Lesions have a preference for the head and neck, especially the conchal bowl, but may be found in nearly any location. If skin biopsy is performed, typical changes[a] must be present.
Arthritis: inflammatory arthritis with tenderness or swelling	*Arthritis domain:* • **Synovitis in ≥2 joints**: characterized by joint swelling and tenderness. If x-rays are obtained and erosions are present, or if anti-CCP assay is obtained and is ≥3× upper limit of normal, then do not score this item.
CNS manifestations (seizures, psychosis, chorea, myelitis, optic	*Neurologic domain:*

Nominal Group Technique (2015)	Literature Review and Iterative Revisions (through October 2016)
neuritis, stroke or acute confusional state)	• **Delirium**: characterized by (1) change in consciousness or level of arousal with reduced ability to focus, and (2) symptom development over hours to <2 days, and (3) symptom fluctuation throughout the day, and (4) either (4a) acute/subacute change in cognition (e.g. memory deficit or disorientation), or (4b) change in behavior, mood, or affect (e.g. restlessness, reversal of sleep/wake cycle, etc.) • **Psychosis**: characterized by (1) delusions and/or hallucinations without insight and (2) absence of delirium • **Seizure**: primary generalized seizures or partial/focal seizures, with independent description by a reliable witness. If EEG is performed, abnormalities must be present • **Mononeuropathy (single or multiplex) or cranial neuropathy**: – **Mononeuropathy**: either motor or sensory disturbance in distribution of one or more peripheral nerves on physical examination, or abnormalities on nerve conduction study or EMG – **Cranial neuropathy**: disorder of sensory and/or motor function of one or more cranial nerves, including optic neuritis [Eliminated chorea, myelitis, stroke; added mononeuropathy; broadened optic neuritis to cranial neuropathy; term “acute confusional state” changed to “delirium” per ACR 1999 nomenclature[27]]
Serositis (*pleural or pericardial effusion*) pleurisy, pericarditis, abdominal serositis	*Serositis domain:* • **Pleural or pericardial effusion**: imaging evidence (such as ultrasound, x-ray, CT scan, MRI) of pleural or pericardial effusion, or both, not meeting the definition of acute pericarditis below • **Acute pericarditis**: ≥2 of: (1) pericardial chest pain (sharp, worse with inspiration, improved by leaning forward), (2) pericardial rub, (3) EKG with new widespread ST-elevation or PR depression, (4) new or worsened pericardial effusion on imaging (such as ultrasound, x-ray, CT scan, MRI) [Eliminated pleurisy, abdominal serositis]
Leukopenia (<4000/mm3 on 2 or more occasions) Thrombocytopenia < 100,000 on 2 or more occasions Autoimmune hemolytic anemia	*Hematologic domain:* • **Leukopenia**: WBC <4,000/mm^3 • **Thrombocytopenia**: Platelets <100,000/mm^3 • **Autoimmune hemolysis** with (1) evidence of hemolysis, such as reticulocytosis, low haptoglobin, elevated indirect bilirubin, elevated LDH and (2) positive Coomb’s (direct antiglobulin test) [Only need to occur once]
Lupus nephritis by renal biopsy with immune deposits Persistent proteinuria (>0.5g/day) Active urine sediment (without UTI)	*Renal domain:* • **Proteinuria>0.5g/24h**: on 24 hour urine collection or spot urine protein-to-creatinine ratio representing >0.5g protein/24h • **Renal biopsy**: International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification findings[b] – **Class II or V lupus nephritis** – **Class III, IV, or VI lupus nephritis** [Eliminated active urine sediment]
	Immunologic Domains and Criteria
Antiphospholipid antibodies (LA, anticardiolipin, anti-B2GPI, or prolonged RVVT)	*Antiphospholipid antibodies domain:* • **AnticardiolipinIgG (>40 GPL units)** *or* **anti-β2GP1 IgG (>40 units)** *or* **lupus anticoagulant positive**

Nominal Group Technique (2015)	Literature Review and Iterative Revisions (through October 2016)
	[Eliminated DRVVT]
[See Entry Criteria above]	*Complement protein domain:* • **Low C3 or low C4** • **Low C3 and low C4**
Anti-dsDNA antibody Anti-Smith antibody	*Highly specific antibodies domain:* • **Anti-dsDNA antibody** • **Anti-Smith antibody**
Presence of multiple autoantibodies	[Eliminated]
Significant changes between the two phases are summarized in brackets	

[a] *Typical skin biopsy histopathology*[24]
acute cutaneous lupus: interface vaculolar dermatitis consisting of a peri-vascular lymphohistiocytic infiltrate, often with dermal mucin noted. Peri-vascular neutrophilic infiltrate may be present early in the course.
subacute cutaneous lupus: interface vaculolar dermatitis consisting of a peri-vascular lymphohistiocytic infiltrate, often with dermal mucin noted
discoid lupus: interface vacuolar dermatitis consisting of a peri-vascular and/or peri-appendageal lymphohistiocytic infiltrate. In the scalp, follicular keratin plugs may be seen. In longstanding lesions, mucin deposition and basement membrane thickening may be noted.

[b] *ISN/RPS definitions*[29]
***Class II*: Mesangial proliferative lupus nephritis**: Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposit. A few isolated subepithelial or subendothelial deposits may be visible by immunofluorescence or electron microscopy, but not by light microscopy.
***Class III*: Focal lupus nephritis**: Active or inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations.
***Class IV*: Diffuse lupus nephritis**: Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation.
***Class V*: Membranous lupus nephritis**: Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations
***Class VI*: Advanced sclerotic lupus nephritis**: ≥90% of glomeruli globally sclerosed without residual activity

Table 2

Patient populations in studies reporting sensitivity and specificity of candidate SLE classification criteria

Study	Patient populations		
	SLE (n)	Non-SLE (n)	Medical conditions (n) in non-SLE group
ARA 1971 preliminary SLE classification criteria[15]	245	451	RA (234), non-rheumatic diseases (217)
ACR 1982 revised criteria for the classification of SLE[16] *	177	162	RA (95), scleroderma (16), juvenile onset arthritis (7), dermatomyositis (6); <5 of each of the following: ankylosing spondylitis, psoriatic arthritis, Reiter's syndrome, osteoarthritis, mixed connective tissue disease, diagnosis not specified, Sjögren'ssyndrome, polyarthritis, Behcet's syndrome, hyperlipidemia, reflex sympathetic dystrophy, Wegener's granulomatosus, vasculitis, regional enteritis, discoid lupus, undifferentiated connective tissue disease, chronic active hepatitis, multicentric reticulohistiocytosis
SLICC 2012 criteria for classification of SLE[18]	310 +	392 +	RA (119), myositis (55), chronic cutaneous lupus (50), undifferentiated connective tissue disease (44), vasculitis (37), primary antiphospholipid syndrome (33), scleroderma (28), fibromyalgia (25), Sjögren'ssyndrome (15), rosacea (8), psoriasis (7), sarcoidosis (1), juvenile idiopathic arthritis (1)
Early SLE cohort study[19]	389	227	Undifferentiated connective tissue disease (136), Sjögren's syndrome (22), RA (13), scleroderma (10), fibromyalgia (10), primary Raynaud's (10), mixed connective tissue disease (9), thyroiditis (8), hematologic disease (5), infection (4), autoimmune hepatitis (1), other (20)
Study of low complements in new-onset SLE[20]	158 #	2,294	"Other" diseases including malignancy, infection, cardiovascular disease, neuropathy (1,048), non-SLE rheumatic disease including connective tissue disease, primary vasculitis, spondyloarthritis, metabolic joint disease (622), hematologic disease including leukemia, myelodysplastic syndromes, lymphoma, chronic myeloproliferative disorders, non-autoimmune anemia, thrombocytopenia, leukopenia (366), nephropathy including proteinuria, hematuria, renal insufficiency (258)

Abbreviations: ARA, American Rheumatism Association. ACR, American College of Rheumatology. SLICC, Systemic Lupus International Collaborating Clinics. RA, rheumatoid arthritis.

* The 1997 update did not publish sensitivity/specificity data

+ Among 716 cases contributed by the investigators, consensus on SLE present vs. absent was reached on 702; among these, SLE was considered present in 310. The distribution of non-SLE diseases presented in this table reflects what was reported among the initial 716 cases.

New-onset SLE with biopsy-proven lupus nephritis with positive ANA or positive anti-dsDNA, or fulfilling ≥4 of 16 SLICC SLE classification criteria excluding low complement

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Table 3

Sensitivity and specificity of candidate SLE classification criteria from a literature review *

Candidate criteria	Sensitivity (%)*			Specificity (%)*		
	ACR 1982[16]	SLICC 2012[18]	Other	ACR 1982[16]	SLICC 2012[18]	Other
Fever	Not reported	Not reported	Early SLE cohort[19]: 34	Not reported	Not reported	86
Rash with dermoepidermal interface changes and immunoglobulin and/or complement deposition on immunofluorescence	Not reported	Not reported		Not reported	Not reported	
Alopecia with associated scalp inflammation	56[a]	32[b]	ARA 1971[15]: 43[c]	88[a]	96[b]	97[c]
Oral mucosal lesions on the hard palate	27[d]	44[e]		96[d]	92[e]	
Acute cutaneous lupus	57[f], 43[g]	65[h]		96[f], 96[g]	80[h]	
Chronic cutaneous lupus	18[i]	20[j]		99[i]	94[j]	
Inflammatory arthritis with tenderness or swelling	86[k]	79[l]		37[k]	44[l]	
CNS manifestations, including seizures, psychosis, chorea, myelitis, optic neuritis, stroke, or acute confusional state	12[m], 13[n]	5.5[o]	Early SLE cohort[19]: seizure 2.8, psychosis 1, stroke 1 Early SLE cohort[25] chorea 0.4, myelopathy 0.8, cranial neuropathy 0.9[p] (optic neuritis not reported separately) and 1.8[38,q], acute confusional state 1.4, mononeuropathy (not a candidate criterion) 1.5	99[m], 99[n]	99[o]	seizure: 100, psychosis 99, stroke 100
Serositis, including pleural or pericardial effusion, pleurisy, pericarditis, and abdominal serositis	52[r],18[s]	35[t]		89[r], 96[s]	97[t]	
Leukopenia (<4000/mm3 on ≥2 occasions)	46[u]	46[v]		89[u]	95[v]	
Thrombocytopenia (<100,000/mm3 on ≥2 occasions)	21[w]	13.5[x]		99[w]	98.0[x]	
Autoimmune hemolytic anemia	18[y]	7[z]		99[y]	99.5[z]	

Candidate criteria	Sensitivity (%)*			Specificity (%)*		
	ACR 1982[16]	SLICC 2012[18]	Other	ACR 1982[16]	SLICC 2012[18]	Other
Lupus nephritis by renal biopsy with immune deposits	83[aa]	Not reported		100[aa]	Not reported	
Persistent proteinuria (>0.5 g/day)	50[bb]	33[cc]		94[bb]	96[cc]	
Active urine sediment (without urinary tract infection)	36[dd]	33[ee]		97[dd]	96[ee]	
Antiphospholipid antibodies (lupus anticoagulant, anticardiolipin, anti-B2GP1, or prolonged RVVT)	Not reported[ff]	54[gg]		Not reported[ff]	86[gg]	
Complement protein	64[hh], 64[ii], 70[jj]	59[kk]	Newly diagnosed SLE[20]: 6[ll], 11[mm], 90.5[nn], 73[oo]	91[hh], 65[ii], 70[jj]	93[kk]	90[ll], 88.5[mm], 69[nn], 90[oo]
Anti-dsDNA antibody	67[pp]	57[qq]		92[pp]	96[qq]	
Anti-Smith antibody	31[rr]	26[ss]		95[rr]	98.7[ss]	
Presence of multiple autoantibodies	Not reported	Not reported	Early SLE cohort[19]: anti-Ro 25, anti-La 11, anti-RNP 22	Not reported	Not reported	anti-Ro 77, anti-La 91, anti-RNP 95

*Definitions of each criterion are specified in footnotes. It is important to note that the definitions used to determine sensitivity and specificity in past studies often differed from the candidate criteria resulting from the Nominal Group Technique exercise.

Abbreviations: SLICC, Systemic Lupus International Collaborating Clinics. ACR, American College of Rheumatology. ARA, American Rheumatism Association.

[a]Non-scarring alopecia

[b]Non-scarring with “diffuse thinning or hair fragility with visible broken hairs” in the absence of other causes

[c]Non-scarring alopecia

[d]Location of oral ulcers was not specified; nasopharyngeal ulcers were included; observation by a physician was required

[e]Oral ulcers occurring on the palate, buccal mucosa, or tongue in the absence of other causes, or nasal ulcers

[f]Malar rash

[g]Photosensitivity

[h] Data reported for "malar rash/photosensitive rash/acute cutaneous lupus", although the SLICC definition of acute cutaneous lupus was more comprehensive than those three entities and included: malar rash, bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, and photosensitive lupus rash in the absence of dermatomyositis. Subacute cutaneous lupus was included in this category.

[i] Discoid lupus

[j] Discoid lupus; the SLICC definition of chronic cutaneous lupus was more comprehensive, but sensitivity and specificity were only reported for discoid lupus.

[k] Non-erosive joint disease affecting 2 or more peripheral joints, characterized by tenderness, swelling, or effusion

[l] "Synovitis involving 2 or more joints, characterized by swelling or effusion, or tenderness in 2 or more joints and at least 30 minutes of morning stiffness"

[m] Seizure, in the absence of other causes

[n] Psychosis, in the absence of other causes

[o] "Neurologic" criterion, without distinction between central and peripheral nervous system

[p] After mean follow-up 1.9 years

[q] After mean follow-up 10 years

[r] "Pleurisy"

[s] Pericarditis

[t] "Typical pleurisy for >1 day or pleural effusions or pleural rub", *or* "typical pericardial pain (pain with recumbency improved by sitting forward) or pericardial effusion or pericardial rub or pericarditis by electrocardiography" in the absence of other causes

[u] WBC <4000/mm^3 on ≥2 occasions

[v] WBC <4000/mm^3 at least once, or lymphopenia (<1,000/mm^3) at least once in the absence of other known causes

[w] Platelet count <100,000/mm^3

[x] Platelet count <100,000/mm^3

[y] "Hemolytic anemia – with reticulocytosis"

[z] "Hemolytic anemia"

[aa] "Renal biopsy", without a description of renal histopathology

[bb] "Persistent proteinuria greater than 0.5 grams per day, or greater than 3+ if quantitation not performed"

[cc] Test characteristics of proteinuria were reported together with the presence of urinary red blood cell casts

[dd] "Cellular casts – may be red cell, hemoglobin, granular, tubular, or mixed"

[ee] Test characteristics of proteinuria were reported together with the presence of urinary red blood cell casts

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[ff] Not reported in the 1997 update to the 1982 criteria

[gg] Any one of the following: positive lupus anticoagulant; false-positive rapid plasma reagin; medium- or high-titer anticardiolipin (ACL) IgA, IgG, or IgM (titers not defined); positive anti-β2-glycoprotein I (anti-β2GP1) IgA, IgG, or IgM

[hh] C3

[ii] C4

[jj] CH50

[kk] Low C3, low C4, or low CH50

[ll] Low C3 alone

[mm] Low C4 alone

[nn] Low C3 or low C4

[oo] Both low C3 and low C4

[pp] Abnormal titer of “antibody to native DNA”

[qq] Above laboratory reference range, or >2-fold the reference range if tested by ELISA

[rr] “Presence of antibody to Smith nuclear antigen”

[ss] “Presence of antibody to Smith nuclear antigen”