Derivation and Validation of the Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus

Michelle Petri,[1] Ana-Maria Orbai,[1] Graciela S. Alarcón,[2] Caroline Gordon,[3] Joan T. Merrill,[4] Paul R. Fortin,[5] Ian N. Bruce,[6] David Isenberg,[7] Daniel J. Wallace,[8] Ola Nived,[9] Gunnar Sturfelt,[9] Rosalind Ramsey-Goldman,[10] Sang-Cheol Bae,[11] John G. Hanly,[12] Jorge Sánchez-Guerrero,[13] Ann Clarke,[14] Cynthia Aranow,[15] Susan Manzi,[16] Murray Urowitz,[17] Dafna Gladman,[17] Kenneth Kalunian,[18] Melissa Costner,[19] Victoria P. Werth,[20] Asad Zoma,[21] Sasha Bernatsky,[14] Guillermo Ruiz-Irastorza,[22] Munther A. Khamashta,[23] Soren Jacobsen,[24] Jill P. Buyon,[25] Peter Maddison,[26] Mary Anne Dooley,[27] Ronald F. van Vollenhoven,[28] Ellen Ginzler,[29] Thomas Stoll,[30] Christine Peschken,[31] Joseph L. Jorizzo,[32] Jeffrey P. Callen,[33] S. Sam Lim,[34] Barri J. Fessler,[2] Murat Inanc,[35] Diane L. Kamen,[36] Anisur Rahman,[7] Kristjan Steinsson,[37] Andrew G. Franks Jr.,[25] Lisa Sigler,[1] Suhail Hameed,[1] Hong Fang,[1] Ngoc Pham,[1] Robin Brey,[38] Michael H. Weisman,[39] Gerald McGwin Jr.,[2] and Laurence S. Magder[40]

Objective. The Systemic Lupus International Collaborating Clinics (SLICC) group revised and validated the American College of Rheumatology (ACR) systemic lupus erythematosus (SLE) classification criteria in order to improve clinical relevance, meet stringent methodology requirements, and incorporate new knowledge regarding the immunology of SLE.

Methods. The classification criteria were derived from a set of 702 expert-rated patient scenarios. Recursive partitioning was used to derive an initial rule that was simplified and refined based on SLICC physician consensus. The SLICC group validated the classification criteria in a new validation sample of 690 new expert-rated patient scenarios.

[1]Michelle Petri, MD, MPH, Ana-Maria Orbai, MD, Lisa Sigler, MA, Suhail Hameed, MD, Hong Fang, MD, MS, Ngoc Pham, BA: Johns Hopkins University, Baltimore, Maryland; [2]Graciela S. Alarcón MD, MPH, Barri J. Fessler, MD, MSPH, Gerald McGwin Jr., PhD, MS: University of Alabama at Birmingham; [3]Caroline Gordon, MD, FRCP: University of Birmingham, Birmingham, UK; [4]Joan T. Merrill, MD: Oklahoma Medical Research Foundation, Oklahoma City; [5]Paul R. Fortin, MD, MPH, FRCPC: Centre Hospitalier Universitaire de Québec, Université Laval, Quebec City, Quebec, Canada; [6]Ian N. Bruce, MD, FRCP: Manchester Academic Health Science Centre and University of Manchester, Manchester, UK; [7]David Isenberg, MD, Anisur Rahman, MD, FRCP, PhD: University College London, London, UK; [8]Daniel J. Wallace, MD: Cedars-Sinai Medical Center and University of California, Los Angeles; [9]Ola Nived, MD, PhD, Gunnar Sturfelt, MD, PhD: Lund University Hospital, Lund, Sweden; [10]Rosalind Ramsey-Goldman, MD, DrPH: Northwestern University, Chicago, Illinois; [11]Sang-Cheol Bae, MD, PhD, MPH: Hanyang University Hospital for Rheumatic Diseases, Seoul, South

Korea; [12]John G. Hanly, MD: Capital Health and Dalhousie University, Halifax, Nova Scotia, Canada; [13]Jorge Sánchez-Guerrero, MD: Mount Sinai Hospital and University Health Network, Toronto, Ontario, Canada; [14]Ann Clarke, MD, MSc, Sasha Bernatsky, MD, PhD: McGill University Health Centre, Montreal, Quebec, Canada; [15]Cynthia Aranow, MD: Feinstein Institute for Medical Research, Manhasset, New York; [16]Susan Manzi, MD, MPH: Allegheny Singer Research Institute and Allegheny General Hospital, Pittsburgh, Pennsylvania; [17]Murray Urowitz, MD, FRCPC, Dafna Gladman, MD, FRCPC: Toronto Western Hospital and University of Toronto, Toronto, Ontario, Canada; [18]Kenneth Kalunian, MD: University of California at San Diego, La Jolla; [19]Melissa Costner, MD: North Dallas Dermatology Associates, Dallas, Texas; [20]Victoria P. Werth, MD: Philadelphia VA Medical Center and University of Pennsylvania, Philadelphia; [21]Asad Zoma, MBChB, FRCP: Lanarkshire Centre for Rheumatology and Hairmyres Hospital, East Kilbride, UK; [22]Guillermo Ruiz-Irastorza, MD, PhD: Hospital Universitario Cruces and Universidad del Pais Vasco, Barakaldo, Spain; [23]Munther A. Khamashta, MD, FRCP, PhD: Rayne Institute and St. Thomas' Hospital, London, UK; [24]Soren Jacobsen, MD, DMSci: Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [25]Jill P. Buyon, MD, Andrew G. Franks Jr., MD, FACP: New York University, New York, New York; [26]Peter Maddison, MD: Ysbyty Gwynedd,

Results. **Seventeen criteria were identified. In the derivation set, the SLICC classification criteria resulted in fewer misclassifications compared with the current ACR classification criteria (49 versus 70; *P* = 0.0082) and had greater sensitivity (94% versus 86%; *P* < 0.0001) and equal specificity (92% versus 93%; *P* = 0.39). In the validation set, the SLICC classification criteria resulted in fewer misclassifications compared with the current ACR classification criteria (62 versus 74; *P* = 0.24) and had greater sensitivity (97% versus 83%; *P* < 0.0001) but lower specificity (84% versus 96%; *P* < 0.0001).**

Conclusion. **The new SLICC classification criteria performed well in a large set of patient scenarios rated by experts. According to the SLICC rule for the classification of SLE, the patient must satisfy at least 4 criteria, including at least one clinical criterion and one immunologic criterion OR the patient must have biopsy-proven lupus nephritis in the presence of antinuclear antibodies or anti–double-stranded DNA antibodies.**

Systemic lupus erythematosus (SLE) is a proto-typic autoimmune disease that affects more than 300,000 people in the US (1) and millions of people worldwide.

Bangor, UK; [27]Mary Anne Dooley, MD, MPH: University of North Carolina, Chapel Hill; [28]Ronald F. van Vollenhoven, MD, PhD: Karolinska University Hospital, Stockholm, Sweden; [29]Ellen Ginzler, MD, MPH: State University of New York Downstate Medical Center, Brooklyn, New York; [30]Thomas Stoll, MD: Kantonsspital Schaff-hausen, Schaffhausen, Switzerland; [31]Christine Peschken, MD, MSc, FRCPC: University of Manitoba, Winnipeg, Manitoba, Canada; [32]Jo-seph L. Jorizzo, MD: Wake Forest University, Winston-Salem, North Carolina; [33]Jeffrey P. Callen, MD, FACP: University of Louisville, Louisville, Kentucky; [34]S. Sam Lim, MD, MPH: Emory University, Atlanta, Georgia; [35]Murat Inanc, MD: Istanbul University, Istanbul, Turkey; [36]Diane L. Kamen, MD, MSCR: Medical University of South Carolina, Charleston; [37]Kristjan Steinsson, MD, PhD: Landspitali University Hospital, Reykjavik, Iceland; [38]Robin Brey, MD, FAAN: University of Texas Health Science Center, San Antonio; [39]Michael H. Weisman, MD: Cedars-Sinai Medical Center, Los Angeles, California; [40]Laurence S. Magder, PhD, MPH: University of Maryland, Balti-more.

To ensure that there is a consistent definition of SLE for the purposes of research and surveillance, classification criteria for SLE are needed. The most widely used classification criteria for SLE are those developed by the American College of Rheumatology (ACR). These clas-sification criteria were published in 1982 (2) and were revised by a committee in 1997 (3); according to the revision, the item "positive LE preparation" was deleted, and the criteria for an immunologic disorder were changed to include anticardiolipin antibodies. The 1982 ACR criteria have been validated (4,5), but the 1997 revised criteria have not been validated.

Subsequently, multiple groups of investigators used new statistical methodology to refine the criteria for classification of SLE. Clough et al applied Bayes theorem to data from patient and control populations from the rheumatology department at the Cleveland Clinic to develop weighted criteria for the diagnosis of SLE (6). Costenbader et al formulated the Boston Weighted Criteria system for the classification of SLE, which was based on the Cleveland Clinic criteria but included antiphospholipid antibodies (aPL) and renal pathology (7). In addition, elements that might negate the diagnosis, such as negative antinuclear antibodies (ANAs), were subtracted from the criteria set. Some criteria definitions were revised, such as arthritis re-quiring an objective assessment of synovitis (7). The weighted criteria were applied by Sanchez et al and were shown to be more sensitive but less specific than the ACR criteria (8).

An alternative statistical methodology, recursive partitioning, was used by Edworthy et al (9). Recursive partitioning or classification and regression tree (CART) analysis is a computer-intensive method used to derive a classification rule based on multiple candidate pre-dictor variables (10). The CART software package di-chotomizes variables based on all possible cut points. The best discriminating cutoff is chosen for each vari-able. Edworthy et al used the same data set as that used for the 1982 ACR criteria but added 2 derived variables, a standardized ANA variable and a "composite" com-plement variable (9). In addition, analyses were per-formed with the criteria for immunologic disorder di-vided into components (anti–double-stranded DNA [anti-dsDNA], anti-Sm, false-positive serologic test re-sult for syphilis) and the hematologic disorder variable divided into hemolytic anemia, thrombocytopenia, and leukopenia. Using the best discriminating criteria, this method allowed correct classification of a majority of cases and controls.

In his 1987 methodology study (11), Fries re-

viewed the critical procedures for avoiding circularity when developing classification criteria for SLE, that is, avoiding use of criteria that are molded to the test data and are not necessarily generalizable. According to these critical procedures, a "gold standard" must be established by highly experienced clinicians, consecutively treated patients and multiple institutions need to be used to minimize selection bias, and control populations should be chosen to represent a realistic spectrum of related diseases that replicate the diagnostic problems that arise in real life. In addition, the variables must be defined with precision, because a small change in the definition of a criterion could lead to a large change in sensitivity and specificity. Finally, the proposed criteria need to be validated in a new population (because criteria always work well in the population from which they were developed).

The Systemic Lupus International Collaborating Clinics (SLICC) group is an international group of investigators dedicated to SLE clinical research. This group produced tools that form the basis of outcome studies in SLE today, such as the SLICC/ACR Damage Index (12). In the current study, the SLICC group undertook a revision of the SLE classification criteria to address multiple concerns that have arisen since development of the 1982 criteria. A formal assessment of the important clinical manifestations of SLE and the limitations of the 1982 ACR criteria, conducted by the SLICC group, was previously published (13).

Concerns about the clinical criteria used in the current ACR classification system include possible duplication of highly correlated terms relating to cutaneous lupus (such as malar rash and photosensitivity) and the lack of inclusion of many other cutaneous manifestations of lupus, the omission of many neurologic manifestations of SLE, and the need to use new standards in the quantification of urine protein. Concerns about the immunologic criteria included the omission of low complement levels and the need to include new information regarding aPL. Most of all, there were concerns that patients who did not satisfy any of the criteria for immunologic disorder were being classified as having SLE, which is an autoantibody-mediated disease. Indeed, clinical trials have had to add the requirement for the presence of an SLE-related autoantibody when recruiting patients, in order to optimize the likelihood of response to immunosuppressive therapy (14). It was thought that important control groups, including patients with chronic cutaneous lupus, needed to be included in a validation exercise. Therefore, we included several dermatology practices. Finally, it was thought

that biopsy-confirmed nephritis compatible with SLE (in the presence of lupus autoantibodies) was so indisputably representative of the disease that it should be considered sufficient as a "stand alone" clinical criterion. The revision exercise was conducted in accordance with the methodology requirements summarized by Fries (11).

PATIENTS AND METHODS

Derivation step. *Choosing a set of relevant variables.* An initial set of precisely defined variables to be abstracted from the medical records of each patient was determined at an SLICC meeting in Lund, Sweden, April 25–27, 2003. At this meeting, experts in each organ system affected by SLE gave a formal presentation, reviewing the current (1997) ACR classification criteria and other classification approaches to that organ system. The list of variables was further refined at an SLICC meeting in Orlando, Florida in October 2003 and has been published previously (13,15–23).

Obtaining the example patient scenarios. Each participating center was asked to submit data on 10–12 consecutive patients with a clinical diagnosis of SLE and 12–15 consecutive control subjects with one of the following diagnoses: rheumatoid arthritis (RA), myositis, chronic cutaneous lupus erythematosus, undifferentiated connective tissue disease, vasculitis, primary antiphospholipid syndrome (APS), scleroderma, fibromyalgia, Sjögren's syndrome, rosacea, psoriasis, sarcoidosis, and juvenile idiopathic arthritis (JIA). Because it was recognized that important control groups that had not necessarily been a part of previous efforts (including patients with chronic cutaneous lupus) needed to be represented, cases were also contributed by several dermatologists.

Arriving at a consensus diagnosis for each patient scenario. The information regarding each patient was summarized in a standardized short narrative, and these were sent to 32 rheumatologists from the SLICC group. The SLICC experts who classified patients were unaware of the diagnoses made by the submitting physicians. The SLICC experts then classified each patient as having SLE or not having SLE. If 80% of the rheumatologists agreed on the classification, that diagnosis was considered the "consensus" diagnosis. Those scenarios that did not reach consensus in this way were later discussed by a panel of 5 physicians, and if 4 of the 5 physicians agreed on a classification, that diagnosis was also considered the "consensus" diagnosis.

Identifying a reduced set of variables to consider for the classification rule. An SLICC subcommittee (GSA, PF, CG, JM, and GM) examined dozens of variables. The subcommittee reviewed extensive logistic regression analyses and decision tree analyses in order to use a data-driven approach to the selection and combination of items, examining ~40 different combinations of >20 items. Although a few clinically important items were kept in the final criteria because of their clinical importance (such as low complement level), both the selection and elimination of many items were strongly influenced by logistic regression analyses. Thus, the final selection of items was data driven but was refined by consensus view.

These variables were then considered the candidate predictor variables for the recursive partitioning analyses.

Using recursive partitioning to derive a relatively simple classification rule. Recursive partitioning (using the CART software package) was performed to categorize patients into 2 groups based on all candidate variables, and the resulting partitions were evaluated. The partition that resulted in the best separation of SLE cases from non-cases was chosen for the first split of the tree. At subsequent steps, the procedure was repeated within the subgroups created by previous splits. The algorithm identified subgroups of patients defined by predictor variables that were relatively homogeneous with respect to a diagnosis of SLE. The resulting subgroups could then be identified using a relatively simple rule. This approach was applied by the SLICC subcommittee (chaired by Graciela S. Alarcón, MD, MPH), using the candidate set of variables to result in a preliminary data-driven classification rule, with the requirement that patients must satisfy at least one clinical criterion and at least one immunologic criterion.

Refining the rule. The preliminary classification rule was discussed at 3 meetings of SLICC members in 2008. These small group meetings, which were organized with the help of Drs. Ian Bruce and David Isenberg, allowed intense discussions of the criteria deficiencies. Cases that were misclassified by the rule were used to stimulate discussions regarding how the rule or definitions of the variables could be changed to improve the classification rule. At the final SLICC meeting, a discussion, followed by a vote, was used to ratify remaining items for which agreement was not unanimous. As a result of this step, 1) anti-C1q was excluded from the immunologic criteria, 2) a "constitutional" clinical criterion of fever and lymphadenopathy was excluded, and 3) joint line tenderness with morning stiffness was included in the "arthritis" criteria.

Validation step. *Obtaining the validation patient scenarios.* To assess the performance of the new classification rule, we obtained detailed data for a new set of 690 additional patients. Participating centers were again asked to submit information for patients in whom SLE was diagnosed and for an approximately equal number of control subjects with the following diagnoses: RA, undifferentiated connective tissue disease, primary APS, vasculitis, chronic cutaneous lupus erythematosus, scleroderma, Sjögren's syndrome, myositis, psoriasis, fibromyalgia, alopecia areata, and sarcoidosis. These data were collected on standardized case report forms and were sent to the coordinating site. Information included a demographics summary, a clinical scenario, specification of ACR criteria that were or were not met, specification of SLICC criteria that were or were not met, autoantibody titers, and complement titers.

In addition, serum samples obtained from each patient were sent to the coordinating site and analyzed at the Rheumatology Diagnostic Laboratory (Los Angeles, CA) for anti-dsDNA by enzyme-linked immunosorbent assay (ELISA), *Crithidia* assay, and Farr assay, and for anti-Sm antibody and complement C3 and C4 levels. A second set of blood samples were tested for aPL (lupus anticoagulant, and ELISA for IgG, IgM, and IgA isotypes of anticardiolipin antibodies and anti–β_2-glycoprotein I [anti-β_2GPI] antibodies) at the laboratory of Joan Merrill, MD (Oklahoma Medical Research Foundation). Direct Coombs' tests were performed at the laboratory of each center or at Quest Diagnostics. A short description of each patient ("patient scenario") was generated, containing the submitted information and the updated autoantibody and complement profiles.

Arriving at a consensus diagnosis for each patient. The patient scenarios were submitted to participating SLICC experts for rating as either SLE or not SLE. Twelve SLICC experts rated all 690 scenarios, and 3 SLICC experts rated some but not all scenarios. Those scenarios for which 80% consensus was not reached in the initial rating process were edited for clarity and re-rated by the larger group of 33 SLICC experts. The SLICC experts who were classifying patients were unaware of the diagnoses made by the submitting physicians. More than 80% consensus was achieved on 615 cases, while 75 cases remained without a consensus diagnosis of SLE or not SLE. After this second round of ratings, the 75 non-consensus scenarios were classified as either SLE or not SLE based on the majority opinion.

Statistical analysis. The kappa statistic was used to quantify the chance-adjusted degree of agreement between the classification rules and the gold standard rating based on the majority opinions of the raters. McNemar's test was used to assess significant differences between the current ACR revised classification criteria and the SLICC classification criteria with respect to accuracy.

The study was approved by institutional review boards at all institutions involved, and all patients provided written informed consent.

RESULTS

In the derivation step, abstracted data for 716 patients were submitted from 25 different sites. Although most sites submitted data for >20 patients, 2 sites submitted data for <10 patients, and one site (Johns Hopkins) submitted data for 171 patients. Among the 716 cases that were contributed, the diagnoses assigned at the various sites were as follows: SLE (n = 293), RA (n = 119), myositis (n = 55), chronic cutaneous lupus (n = 50), undifferentiated connective tissue disease (n = 44), vasculitis (n = 37), primary APS (n = 33), scleroderma (n = 28), fibromyalgia (n = 25), Sjögren's syndrome (n = 15), rosacea (n = 8), psoriasis (n = 7), sarcoidosis (n = 1), and JIA (n = 1).

Data for each case submitted were reviewed by 26–32 clinicians. The results of the initial classification are summarized in Table 1. For 262 (36.6%) of the 716 scenarios, ≥80% of the physicians classified the patient as having SLE. For 354 (49.4%) of the scenarios, ≥80% of the physicians classified the patient as not having SLE. Thus, there was ≥80% agreement for 616 (86%) of the scenarios with respect to SLE status. For 561 of these 616 scenarios (91%), the classifications were consistent with the submitted diagnoses.

For the remaining 100 scenarios (14%), agreement regarding classification as having SLE or not having SLE was <80% (Table 1). These 100 scenarios then underwent further review and discussion by

Table 1. Number of patient scenarios from the derivation sample in subgroups defined by the percentage of experts who initially classified the scenarios as SLE (n = 716 scenarios)*

Percentage of experts initially classifying the scenario as SLE	Number (%) of patient scenarios
0†	250 (34.9)
1–20	104 (14.5)
20–49	47 (6.6)
50–79	53 (7.4)
80–99	138 (19.3)
100‡	124 (17.3)

* The initial ratings were assigned by 26–32 Systemic Lupus International Collaborating Clinics (SLICC) clinicians. For 616 (86%) of the 716 scenarios, there was ≥80% agreement with respect to systemic lupus erythematosus (SLE) status.
† None of the physicians classified these scenarios as SLE.
‡ All of the physicians classified these scenarios as SLE.

5-member panels, and 80% consensus was reached for 86 cases. Thus, ultimately, a consensus diagnosis was achieved for 702 (98%) of the 716 patient scenarios submitted to the study. The consensus diagnosis agreed with the diagnosis of the submitting physician 95% of the time. The analyses described below are based on these 702 patients.

Eighteen criteria that were associated with a diagnosis of SLE were identified and were initially considered. These criteria were divided into the categories of "clinical" and "immunologic," based on the judgment of the SLICC subcommittee. The sensitivity and specificity of each criterion are shown in Table 2. Recursive partitioning was applied to this set of variables to arrive at the initial working rule. After discussion and examination of misclassified cases, some definitions were refined, and leukopenia and lymphopenia were combined.

Table 3 shows the final list of criteria and provides details regarding how each criterion was ultimately defined. The criteria do not need to be present concurrently. The proposed classification rule is as follows: *classify a patient as having SLE if he or she satisfies 4 of the clinical and immunologic criteria used in the SLICC classification criteria, including at least one clinical criterion and one immunologic criterion, OR if he or she has biopsy-proven nephritis compatible with SLE in the presence of ANAs or anti-dsDNA antibodies.*

Table 4 shows the performance of the proposed classification rule in the derivation set of patients. In the derivation set, the proposed rule had greater sensitivity than the 1997 ACR criteria (94% versus 86%; $P < 0.0001$) and equal specificity (92% versus 93%; $P = 0.39$). Using McNemar's test, we observed that appli-

cation of the proposed classification rule resulted in significantly fewer misclassifications than did use of the current ACR classification rule ($P = 0.0082$).

To validate the proposed new rule, we used data for 690 additional patients, which had not been used to derive this rule. Data for these patients were submitted from 15 different sites. All sites submitted data for >20 patients, and one site (Johns Hopkins) submitted data for 180 patients. Among the 690 validation scenarios that were submitted, the following diagnoses were made at the contributing site: SLE (n = 337), RA (n = 118), undifferentiated connective tissue disease (n = 89), primary APS (n = 30), vasculitis (n = 29), chronic cutaneous lupus (n = 24), scleroderma (n = 20), Sjögren's syndrome (n = 15), myositis (n = 14), psoriasis (n = 8), fibromyalgia (n = 4), alopecia areata (n = 1), and sarcoidosis (n = 1).

Eighty percent agreement was achieved for 590 (86%) of the patient scenarios during the first round of rating. The 100 scenarios for which 80% agreement was not achieved during the first round of ratings were then sent to a larger group of SLICC members for the second round of rating. Table 5 shows the degree of agreement achieved for all 690 scenarios based on both rounds of rating. Note that ≥80% agreement was achieved on whether the case was SLE or not SLE for all but 75 (11%) of the scenarios. In 93% of cases, the majority

Table 2. Sensitivity and specificity of each criterion for SLE in the derivation sample

Criterion	Sensitivity, %*	Specificity, %†
Malar rash/photosensitive rash/ acute cutaneous lupus	65.2	80.1
Discoid rash	19.7	93.6
Oral ulcers	44.2	92.1
Nonscarring alopecia	31.9	95.7
Arthritis	79.0	43.6
Serositis	35.2	97.2
Renal	32.9	96.4
Neurologic	5.5	99.0
Hemolytic anemia	7.1	99.5
Leukopenia	46.4	94.8
Lymphopenia, <1,500/mm^3	49.0	81.6
Lymphopenia, <1,000/mm^3	17.0	94.7
Thrombocytopenia	13.5	98.0
Antinuclear antibody	96.5	45.2
Anti–double-stranded DNA	57.1	95.9
Anti-Sm	26.1	98.7
Antiphospholipid antibody	53.6	86.0
Low complement	59.0	92.6

* Among the 310 scenarios that were classified as systemic lupus erythematosus (SLE) by ≥80% of the clinicians.
† Among the 392 scenarios that were classified as not SLE by ≥80% of the clinicians.

Table 3. Clinical and immunologic criteria used in the SLICC classification system*

Clinical criteria
  1. Acute cutaneous lupus, including:
     Lupus malar rash (do not count if malar discoid)
     Bullous lupus
     Toxic epidermal necrolysis variant of SLE
     Maculopapular lupus rash
     Photosensitive lupus rash
     in the absence of dermatomyositis
        OR subacute cutaneous lupus (nonindurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although
           occasionally with postinflammatory dyspigmentation or telangiectasias)
  2. Chronic cutaneous lupus, including:
     Classic discoid rash
        Localized (above the neck)
        Generalized (above and below the neck)
     Hypertrophic (verrucous) lupus
     Lupus panniculitis (profundus)
     Mucosal lupus
     Lupus erythematosus tumidus
     Chillblains lupus
     Discoid lupus/lichen planus overlap
  3. Oral ulcers
     Palate
        Buccal
        Tongue
     OR nasal ulcers
        *in the absence of other causes, such as vasculitis, Behçet's disease, infection (herpesvirus), inflammatory bowel disease, reactive arthritis,
           and acidic foods*
  4. Nonscarring alopecia (diffuse thinning or hair fragility with visible broken hairs)
     in the absence of other causes such as alopecia areata, drugs, iron deficiency, and androgenic alopecia
  5. 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
  6. Serositis
     Typical pleurisy for more than 1 day
        OR pleural effusions
        OR pleural rub
     Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day
        OR pericardial effusion
        OR pericardial rub
        OR pericarditis by electrocardiography
           in the absence of other causes, such as infection, uremia, and Dressler's pericarditis
  7. Renal
     Urine protein–to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours
        OR red blood cell casts
  8. Neurologic
     Seizures
     Psychosis
     Mononeuritis multiplex
        in the absence of other known causes such as primary vasculitis
     Myelitis
     Peripheral or cranial neuropathy
        in the absence of other known causes such as primary vasculitis, infection, and diabetes mellitus
     Acute confusional state
        in the absence of other causes, including toxic/metabolic, uremia, drugs
  9. Hemolytic anemia
 10. Leukopenia ($<$4,000/mm^3 at least once)
     in the absence of other known causes such as Felty's syndrome, drugs, and portal hypertension
        OR
     Lymphopenia ($<$1,000/mm^3 at least once)
        in the absence of other known causes such as corticosteroids, drugs, and infection
 11. Thrombocytopenia ($<$100,000/mm^3) at least once
     in the absence of other known causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura
Immunologic criteria
  1. ANA level above laboratory reference range
  2. Anti-dsDNA antibody level above laboratory reference range (or $>$2-fold the reference range if tested by ELISA)
  3. Anti-Sm: presence of antibody to Sm nuclear antigen
  4. Antiphospholipid antibody positivity as determined by any of the following:
     Positive test result for lupus anticoagulant
     False-positive test result for rapid plasma reagin
     Medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM)
     Positive test result for anti–β_2-glycoprotein I (IgA, IgG, or IgM)
  5. Low complement
     Low C3
     Low C4
     Low CH50
  6. Direct Coombs' test *in the absence of hemolytic anemia*

* Criteria are cumulative and need not be present concurrently. SLICC = Systemic Lupus International Collaborating Clinics; SLE = systemic lupus erythematosus;
ANA = antinuclear antibody; anti-dsDNA = anti–double-stranded DNA; ELISA = enzyme-linked immunosorbent assay.

Table 4. Performance of the proposed SLICC criteria compared with the current ACR criteria in the derivation sample (n = 702 scenarios)*

	Rule	
	1997 ACR criteria	SLICC criteria
Sensitivity†	267/310 (86)	292/310 (94)
Specificity‡	365/392 (93)	361/392 (92)
Misclassified cases	70	49

* The American College of Rheumatology (ACR) rule is based on satisfying 4 of 11 criteria. Values are the proportion (%). SLICC = Systemic Lupus International Collaborating Clinics.
† Among the 310 scenarios that were classified as systemic lupus erythematosus (SLE) by ≥80% of the experts.
‡ Among the 392 scenarios that were classified as not SLE by ≥80% of the experts.

rule rating was in agreement with the submitted diagnosis with respect to SLE status.

Table 6 shows the sensitivity and specificity of each classification rule relative to the classification made by the majority of raters in the validation set of patients. The SLICC rule was more sensitive (97% versus 83%; $P < 0.0001$) than the current (1997) ACR rule but was less specific (84% versus 96%; $P < 0.0001$). Overall, the SLICC rule performed better than the ACR rule, and use of the SLICC classification rule resulted in the misclassification of 12 fewer patients and a higher kappa value. The difference between the rules, however, was not statistically significant ($P = 0.24$).

When the analysis was restricted to those 615 scenarios for which at least 80% agreement was achieved after the second round of rating, the sensitivity and specificity of the SLICC criteria were 98% and 91%, respectively. In contrast, in this subset of scenarios, the sensitivity and specificity of the ACR criteria were 88% and 98%, respectively, and use of the ACR classification rule resulted in 9 more misclassifications.

Table 5. Number of patient scenarios from the validation sample in subgroups defined by the percentage of experts who ultimately classified the scenario as SLE (n = 690 scenarios)*

Percentage of experts ultimately classifying the patient scenario as SLE	Number (%) of scenarios
0†	227 (33)
1–20	75 (10.8)
20–49	38 (5.5)
50–79	37 (5.4)
80–99	95 (13.7)
100‡	218 (31.6)

* For 615 (89%) of the 690 scenarios, there was ≥80% agreement with respect to systemic lupus erythematosus (SLE) status.
† None of the physicians classified these scenarios as SLE.
‡ All of the physicians classified these scenarios as SLE.

Table 6. Performance of the proposed SLICC criteria compared with the current ACR criteria in the validation sample (n = 690 scenarios)*

	Rule	
	1997 ACR criteria	SLICC criteria
Sensitivity†	290/349 (83)	340/349 (97)
Specificity‡	326/341 (96)	288/341 (84)
κ	0.79	0.82
Misclassified cases§	74	62

* The American College of Rheumatology (ACR) rule is based on satisfying 4 of 11 criteria. Values are the proportion (%). SLICC = Systemic Lupus International Collaborating Clinics.
† Among the 349 scenarios that were classified as systemic lupus erythematosus (SLE) by the majority of the experts.
‡ Among the 341 scenarios that were classified as not SLE by the majority of the experts.
§ The difference between rules was not statistically significant ($P = 0.24$).

DISCUSSION

The SLICC classification criteria for SLE represent an 8-year effort of clinical review, consensus, and statistical analyses. The final criteria were derived using recursive partitioning ("tree-based" approach) but were simplified to a simple rule: the patient must satisfy at least 4 criteria, including at least one clinical criterion and one immunologic criterion OR the patient must have biopsy-proven lupus nephritis in the presence of antinuclear antibodies or anti-dsDNA antibodies. The requirement for at least one clinical and one immunologic criterion reflects the opinion of SLICC that neither clinical criterion alone nor positive serologic test results alone should be considered as diagnostic of SLE, because SLE is ultimately an autoantibody-driven clinical disease.

The new clinical criteria improve on the revised ACR classification criteria in several important ways. Malar rash and photosensitivity are not separate items, because they are largely overlapping. One criterion for cutaneous lupus includes both acute and subacute cutaneous lupus, whereas a separate criterion now includes discoid rash and the many different types of chronic cutaneous lupus not included in the current ACR classification criteria. For optimal use of these criteria, it is anticipated that some patients with suspected SLE will require a dermatologic consultation and sometimes a skin biopsy. Nonscarring alopecia is included in the new criteria, as it was in the original (1971) preliminary criteria for the classification of SLE (24); although nonscarring alopecia is not specific for SLE, it performed well in the univariate and recursive partitioning analyses and met the bar for clinical consensus.

The arthritis criterion has been substantially re-

defined. First, it does not require a radiograph: some SLE-related arthritis is, in fact, erosive (25). Second, the presence of joint line tenderness with 30 minutes of morning stiffness now qualifies as arthritis. Because of the overlap of fibromyalgia and SLE in some patients, it will be necessary to confirm that there is specifically joint line tenderness rather than diffuse allodynia. It is also essential to underscore that for all of the SLICC criteria, the clinician must be able to determine that the cause is likely attributable to SLE and not to another disease process or condition.

The renal criterion now includes measurement of proteinuria by the urine protein–to-creatinine ratio without the requirement of a time frame for collection. This reflects acceptance that the "spot" or random urine protein–to-creatinine ratio is easier to obtain than a 24-hour urine protein value (26), and that a qualitative estimate of proteinuria using a dipstick is insufficient for clinical judgment, because it is an unreliable quantitative measure. The gold standard, however, remains the urine protein–to-creatinine ratio obtained for a 24-hour urine collection (27).

The neurologic criterion has been substantially rewritten to include a greater number of neurologic manifestations of SLE than were included in the original ACR definition of seizures or psychosis. It does not include all of the ACR neuropsychiatric case definitions (28) due to the absence of specificity of most of these for SLE (29).

The hematologic criteria have been split into 3 parts: hemolytic anemia, leukopenia/lymphopenia, and thrombocytopenia. Statistical modeling showed that it made no difference whether "once" or "more than once" was required. Therefore, to simplify assessment, the SLICC criteria require only one abnormal assessment (of course, the result must be due to SLE and not other factors, such as prednisone [for lymphopenia], immunosuppressive drug use, infection, or other causes). We accept that the cutoff range for leukopenia may need to be amended for patients of certain ethnicities (30).

The immunologic criterion reflects new knowledge about serologic tests in SLE and also the concern of the SLICC group about the wider use of ELISAs and multiplex assays (31). The ANA criterion remains unchanged. In the previous immunologic criterion, anti-dsDNA antibodies, anti-Sm antibodies, lupus anticoagulant, false-positive test results for syphilis, and anticardiolipin antibodies were combined. The new SLICC classification system has split these features into separate criteria, so that each may contribute to classification. The new anti-dsDNA antibody criterion, how-

ever, requires a stricter cutoff for ELISAs. Anti-Sm antibody is now an individual criterion. The new aPL criterion now includes anti-β_2GPI antibodies. The anticardiolipin antibody definition excludes nonspecific "low" levels (which were included in the revised ACR criteria) (3). IgG, IgM, or IgA isotypes are allowed for anti-β_2GPI and anticardiolipin antibodies, reflecting new knowledge that IgA isotypes are important in SLE (32).

Upon consensus of the SLICC members, low complement (defined by C3, C4, or total hemolytic complement, reflecting the contribution of complement to disease pathogenesis) was included, even though this addition did not improve statistical modeling. The direct Coombs' (antiglobulin) test was also included and improved statistical modeling. To avoid "double counting," however, this test is not counted if the patient has met the clinical criterion for hemolytic anemia.

The final important aspect of the new SLICC classification criteria is that biopsy-confirmed nephritis compatible with SLE according to the International Society of Nephrology/Renal Pathology Society 2003 classification of lupus nephritis (33), in the presence of ANAs or anti-dsDNA antibodies, is now sufficient for a classification of SLE. The SLICC committee thought this was important in both clinical practice and for enrollment in clinical trials. It is acknowledged that the presence of anti-dsDNA antibodies in the absence of ANAs is a rare phenomenon and may be attributable to laboratory error.

The SLICC classification criteria perform better than the revised ACR criteria in terms of sensitivity but not specificity. The SLICC criteria are meant to be clinically more relevant, allowing the inclusion of more patients with clinically defined lupus than are included using the current ACR criteria. Use of the new criteria will be important in clinical trials and in longitudinal observational studies.

The SLICC classification criteria were subjected to rigorous testing. The new patient sample used for validation consisted of 690 patients and included patients from multiple centers with multiple diagnoses that have clinical features that overlap with the clinical features of lupus. In the validation sample, the SLICC classification criteria misclassified fewer cases and had higher sensitivity but lower specificity compared with the ACR criteria. The difference between the performance of the ACR classification criteria and the SLICC classification criteria was not statistically significant. The SLICC classification criteria have better face and content validity, because they overcome many concerns associated with the current ACR criteria. In particular,

the new classification system requires the presence of both clinical and serologic criteria, so that patients without autoantibodies or with low complement levels, the hallmark of SLE, cannot be classified as having SLE. In order to overcome this deficiency, clinical trials of lupus have had to add the requirement for lupus auto-antibodies to their inclusion criteria (14).

This SLICC exercise serves as the first validation of the SLICC classification criteria (and validation of the revised ACR criteria as well) in studies involving the largest multicenter population sample since the initial conception of the ACR classification criteria for SLE. It is important to emphasize that the 1997 revision of the ACR criteria was never validated. The ACR criteria continue to perform well compared with the current gold standard of physician diagnosis but do not include the updated and more inclusive definitions of variables of the SLICC criteria. The SLICC classification criteria provide alternative classification criteria for use in SLE clinical care and research. The validated SLICC classification criteria have gained in face validity compared with the revised ACR criteria and are more consistent with advancing concepts of SLE pathogenesis. It should be noted that, as with the original revised ACR criteria, the SLICC criteria have not been tested for purposes of diagnosis. The SLICC group concludes that the new criteria retain the goal of simplicity of use yet reflect current knowledge of SLE obtained in the 29 years since the initial ACR criteria were proposed.

ACKNOWLEDGMENTS

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Petri had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Petri, Alarcón, Gordon, Merrill, Fortin, Bruce, Isenberg, Wallace, Nived, Ramsey-Goldman, Hanly, Sánchez-Guerrero, Clarke, Aranow, Manzi, Urowitz, Gladman, Kalunian, Zoma, Khamashta, Jacobsen, Buyon, Maddison, Dooley, van Vollen-hoven, Stoll, Peschken, Callen, Kamen, Steinsson, Hameed, Magder.
Acquisition of data. Petri, Orbai, Alarcón, Gordon, Merrill, Fortin, Bruce, Isenberg, Wallace, Nived, Sturfelt, Ramsey-Goldman, Bae, Hanly, Sánchez-Guerrero, Clarke, Aranow, Manzi, Urowitz, Gladman, Kalunian, Costner, Werth, Zoma, Bernatsky, Ruiz-Irastorza, Khamashta, Jacobsen, Buyon, Maddison, Dooley, van Vollenhoven, Ginzler, Stoll, Peschken, Jorizzo, Lim, Fessler, Inanc, Kamen, Steinsson, Franks, Sigler, Hameed, Brey, Weisman.
Analysis and interpretation of data. Petri, Orbai, Alarcón, Gordon, Merrill, Fortin, Bruce, Wallace, Nived, Sturfelt, Hanly, Sánchez-Guerrero, Aranow, Manzi, Gladman, Werth, Zoma, Bernatsky, Khamashta, Buyon, Maddison, Dooley, van Vollenhoven, Stoll, Inanc, Rahman, Franks, Fang, Pham, McGwin, Magder.

REFERENCES

1. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, et al, for the National Arthritis Data Workgroup. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: part I. Arthritis Rheum 2008;58: 15–25.
2. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfeld NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.
3. Hochberg MC, for the Diagnostic and Therapeutic Criteria Committee of the American College of Rheumatology. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997;40:1725.
4. Levin RE, Weinstein A, Peterson M, Testa MA, Rothfield NF. A comparison of the sensitivity of the 1971 and 1982 American Rheumatism Association criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1984;27:530–8.
5. Passas CM, Wong RL, Peterson M, Testa MA, Rothfield NF. A comparison of the specificity of the 1971 and 1982 American Rheumatism Association criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1985;28:620–3.
6. Clough JD, Elrazak M, Calabrese LH, Valenzuela R, Braun WB, Williams GW. Weighted criteria for the diagnosis of systemic lupus erythematosus. Arch Intern Med 1984;144:281–5.
7. Costenbader KH, Karlson EW, Mandl LA. Defining lupus cases for clinical studies: the Boston weighted criteria for the classifi-cation of systemic lupus erythematosus. J Rheumatol 2002;29: 2545–50.
8. Sanchez ML, Alarcon GS, McGwin G Jr, Fessler BJ, Kimberly RP. Can the weighted criteria improve our ability to capture a larger number of lupus patients into observational and interventional studies? A comparison with the American College of Rheumatol-ogy criteria. Lupus 2003;12:468–70.
9. Edworthy SM, Zatarain E, McShane DJ, Bloch DA. Analysis of the 1982 ARA lupus criteria data set by recursive partitioning methodology: new insights to the relative merit of individual criteria. J Rheumatol 1988;15:1493–8.
10. Breiman L, Friedman JH, Olshen RA, Stone CG. Classification and regression trees. Belmont: Wadsworth International Group; 1984.
11. Fries JF. Methodology of validation of criteria for SLE. Scand J Rheumatol Suppl 1987;65:25–30.
12. Gladman D, Ginzler E, Goldsmith C, Fortin P, Liang M, Urowitz M, et al. The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. Arthritis Rheum 1996;39:363–9.
13. Petri M, Magder L. Classification criteria for systemic lupus erythematosus: a review. Lupus 2004;13:829–37.
14. Navarra SV, Guzman RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet 2011;377:721–31.
15. Albrecht J, Berlin JA, Braverman IM, Callen JP, Costner MI, Dutz J, et al. Dermatology position paper on the revision of the 1982 ACR criteria for systemic lupus erythematosus. Lupus 2004;13: 839–49.
16. Zoma A. Musculoskeletal involvement in systemic lupus erythem-atosus. Lupus 2004;13:851–3.
17. Clarke A. Proposed modifications to 1982 ACR classification criteria for systemic lupus erythematosus: serositis criterion. Lupus 2004;13:855–6.

18. Dooley MA, Aranow C, Ginzler EM. Review of ACR renal criteria in systemic lupus erythematosus. Lupus 2004;13:857–60.
19. Hanly JG. ACR classification criteria for systemic lupus erythematosus: limitations and revisions to neuropsychiatric variables. Lupus 2004;13:861–4.
20. Kao AH, Manzi S, Ramsey-Goldman R. Review of ACR hematologic criteria in systemic lupus erythematosus. Lupus 2004;13:865–8.
21. Merrill JT. Antibodies and clinical features of the antiphospholipid syndrome as criteria for systemic lupus erythematosus. Lupus 2004;13:869–76.
22. Nived O, Sturfelt G. ACR classification criteria for systemic lupus erythematosus: complement components. Lupus 2004;13:877–9.
23. Isenberg D. Anti-dsDNA antibodies: still a useful criterion for patients with systemic lupus erythematosus? Lupus 2004;13:881–5.
24. Cohen AS, Reynolds WE, Franklin EC, Kulka JP, Ropes MW, Shulman LE, et al. Preliminary criteria for the classification of systemic lupus erythematosus. Bull Rheum Dis 1971;21:643–8.
25. Wright S, Filippucci E, Grassi W, Grey A, Bell A. Hand arthritis in systemic lupus erythematosus: an ultrasound pictorial essay. Lupus 2006;15:501–6.
26. Christopher-Stine L, Petri M, Astor BC, Fine D. Urine protein-to-creatinine ratio is a reliable measure of proteinuria in lupus nephritis. J Rheumatol 2004;31:1557–9.
27. Fine DM, Ziegenbein M, Petri M, Han EC, McKinley AM, Chellini JW, et al. A prospective study of protein excretion using short-interval timed urine collections in patients with lupus nephritis. Kidney Int 2009;76:1284–8.
28. ACR Ad Hoc Committee on Neuropsychiatric Lupus Nomenclature. The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 1999;42:599–608.
29. Ainiala H, Hietaharju A, Loukkola J, Peltola J, Korpela M, Metsanoja R, et al. Validity of the new American College of Rheumatology criteria for neuropsychiatric lupus syndromes: a population-based evaluation. Arthritis Rheum 2001;45:419–23.
30. Reed WW, Diehl LF. Leukopenia, neutropenia, and reduced hemoglobin levels in healthy American blacks. Arch Intern Med 1991;151:501–30.
31. American College of Rheumatology position statement on methodology of testing for antinuclear antibodies. 2009. URL: http://www.rheumatology.org/practice/clinical/position/ana_position_stmt.pdf.
32. Mehrani T, Petri M. Association of IgA anti-β2 glycoprotein I with clinical and laboratory manifestations of systemic lupus erythematosus. J Rheumatol 2011;38:64–8.
33. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, et al. The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int 2004;65:521–30.