# CLINICAL UPDATE Diagnosis of Lupus in the New Age of Biomarkers Meeting Diagnostic Challenges in Lupus With Cell-Bound Complement Activation Products



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### **Persistent Misdiagnosis**

Despite advances that have led to improved survival in systemic lupus erythematosus (SLE), disease management remains suboptimal, in part, because of misdiagnosis, including overdiagnosis and underdiagnosis.

Results of one frequently cited study emphasized the clinical obstacles created by misdiagnosis. Investigators compared initial and final diagnoses for 476 patients referred to an autoimmune disease clinic over a 13-month period.1 Overall, the data showed less than 50% agreement between the diagnosis of the referring physician and the final diagnosis of the rheumatologist. Of 263 patients referred with a presumptive diagnosis of SLE, 125 had diagnoses other than SLE at final disposition. Of note, 76 patients with presumptive SLE diagnoses tested antinuclear-antibody (ANA) positive but did not have an autoimmune disease.

### **Epidemiology of SLE**

A recent review by the Centers for Disease Control and Prevention (CDC) yielded estimates of SLE prevalence in the United States ranging from 161,000 definite and 322,000 definite or probable cases<sup>2</sup> to as many as 1.5 million cases.<sup>3</sup> The CDC found incidence estimates of 1.8 to 7.6 cases per 100,000 persons per year, depending on the geographic area.<sup>4</sup> A study of a predominantly white population in the vicinity of Rochester, Minnesota, showed that SLE incidence more than tripled from 1.5 cases per 100,000 persons in a cohort followed from 1950 to 1979 to 5.6 cases per 100,000 persons in a second cohort followed from 1980 to 1992.5

Diagnosis by a rheumatologist is the current standard for SLE. The American College of Rheumatology (ACR) has developed a classification system to guide diagnosis. A patient who meets four of the 11 criteria fulfills requirements for a diagnosis of SLE.<sup>6</sup> However, the ACR classification system was developed as an aid to clinical research but over the years became the de facto diagnostic criteria for clinical rheumatology practice. Exclusive reliance on the ACR criteria can lead to underdiagnosis of SLE in early disease, or sometimes to overdiagnosis in patients with nonspecific signs and symptoms.

### **Differential Diagnosis**

The ACR diagnostic criteria for SLE provide a starting point for the differential diagnosis. The criteria comprise a broad spectrum of signs and symptoms involving multiple organ systems (Table). One classic presentation that has often prompted careful investigation of SLE is the combination of fever, joint pain, and rash in a woman of childbearing age.<sup>7,8</sup> Developed in the 1950s and 1960s, the symptom triad was one of several early approaches to diagnosis of SLE, each of which characterized only a subgroup of patients. The ACR criteria have broader applicability but remain imperfect.

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Recently, the Systemic Lupus International Collaborating Clinics (SLICC), a consortium of SLE centers worldwide, performed a validation study of the ACR criteria and revised recommendations for diagnosis.9 Participants in SLICC have defined SLE diagnosis in two ways: a combination of biopsy-proven lupus nephritis and presence of ANAs or anti-double-stranded (ds) DNA antibodies or fulfillment of four ACR diagnostic criteria, including at least one clinical criterion and one immunologic criterion.

Collectively, the evidence suggests that consideration of SLE in the differential diagnosis is the first step toward better diagnosis of the condition.

### The Role of Laboratory Tests

Carefully selected laboratory tests can augment diagnostic accuracy of clinical signs and symptoms associated with SLE. ANA testing has proven useful as a general screen for SLE. Use of ANA testing inherently involves a tradeoff between sensitivity and specificity. More than 90% of patients with SLE test positive for ANAs. Unfortunately, 5–15% or more of healthy individuals also have positive ANA tests, albeit usually with lower titers. Consequently, an ANA test cannot be viewed as anything more than an initial screen for SLE.

More than 40 years ago, researchers found that kidney tissue from patients with lupus nephritis had autoantibodies to native dsDNA.<sup>10</sup> Subsequent studies confirmed that anti-dsDNA antibodies played a key role in the pathogenesis of SLE.11 Moreover, studies showed that anti-dsDNA antibodies occur in as many as 70% of patients with lupus but rarely in healthy individuals. From these observations, testing for anti-dsDNA antibodies has become a goldstandard confirmatory test for SLE.

Despite offering improved accuracy over ANA testing, anti-dsDNA antibodies still require a trade-off between sensitivity and specificity. A substantial number of patients with SLE, approaching 50% in some studies, do not test positive for anti-dsDNA antibodies. This significant limitation has provided the impetus for continued investigation of potentially more accurate biomarker assays for SLE. The search led to a test for cell-bound complement activation products (CB-CAPs).<sup>12</sup>

Investigators in a multicenter randomized trial evaluated CB-CAPs in combination with ANAs, antidsDNA antibodies, and anti-mutated citrullinated vimentin (MCV) antibodies for diagnosis of SLE.<sup>13</sup> The study involved 210 patients with SLE, 178 patients with other rheumatic diseases, and 205 healthy individuals. The results showed that anti-dsDNA antibodies had a low sensitivity (30%) and a high specificity (>95%). Among 523 participants who were anti-dsDNA antibody negative, multivariate logistic regression analysis showed that SLE was associated with ANA positivity, anti-MCV negativity, and elevated levels of the CB-CAPs EC4d and BC4d (P<0.001). A weighted index comprising the four markers correctly identified 72% of patients with SLE. The combination of anti-dsDNA antibodies and the index yielded a sensitivity of 80% for SLE and a specificity of 87% against other rheumatic conditions.

### **Summary**

SLE remains a diagnostic challenge. Nonspecific signs and symptoms and limitations of available laboratory tests contribute to the challenge. Misdiagnosis occurs in a not insignificant proportion of cases, including underdiagnosis



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and overdiagnosis. Considering the diagnosis of SLE, which can be overlooked, especially by nonrheumatologists, is a critical step toward improved diagnostic accuracy. Recent developments in laboratory tests have shown promise for improving the diagnosis of this disease and directing patients toward effective treatment as soon as practical.

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Target Audience: This educational activity is designed for rheumatologists, internists, primary care physicians, physician assistants, nurse practitioners, and other healthcare providers who treat patients with SLE and other connective tissue diseases. Educational Needs: Systemic lupus erythematosus (SLE) affects 1.5 million Americans, according to the Lupus Foundation of America. These patients have a substantially increased risk of morbidity and mortality as compared with the general population. Advances in diagnosis and treatment of SLE have led to a dramatic increase in 5-year survival, from about 50% during the 1950s to more than 90% today. However, much work remains to reduce the morbidity burden imposed by SLE. A great paed exits for earlier and more accurate diagnosis. Studies suggest a SLE. A great need exists for earlier and more accurate diagnosis. Studies suggest a misdiagnosis rate as high as 50%. In particular, clinicians and their patients could benefit greatly from more accurate biomarker-based laboratory tests for SLE. Tests for antinuclear antibodies represent only a general screen, and the widely used assay for anti-double stranded DNA antibodies fails to provide definitive diagnoses for a substantial proportion of patients.

Learning Objectives: Upon completing this educational activity, participants should be able to:

- Describe diagnostic challenges in SLE Identify limitations of widely used laboratory tests for SLE
- Discuss diagnostic information provided by measurement of cell-bound complement activation products
- Develop strategies to optimize use of available diagnostic tests for SLE

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### **Diagnosis of Lupus in the New Age of Biomarkers**

Meeting Diagnostic Challenges in Lupus With Cell-Bound Complement Activation Products

**CME Post-Test Answer Sheet and Evaluation Form** 

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### **CME** Questions

Instructions: For each question or incomplete statement, choose the answer or completion that is correct. Circle the most appropriate response.

- 1. According to the data cited, misdiagnosis of SLE may occur in as many as of cases.
  - A. 25%
  - **B.** 50%
  - **C.** 75%
  - **D** Nono of the
  - **D.** None of the above
- 2. The role of antinuclear antibody testing in SLE is:
  - A. As a definitive laboratory test
  - **B.** As a general screening test
  - C. For identifying SLE subtypes
  - **D.** As a confirmatory test

### **EVALUATION FORM**

We would appreciate your answering the following questions in order to help us plan for other activities of this type. All information is confidential. *Please print*.

Name:	 			 	
Specialty:	 			 	
Degree: 🗖 MD					
□ Other	 			 	
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### CME CREDIT VERIFICATION

I verify that I have spent \_\_\_\_\_hour(s)/\_\_\_\_ minutes of actual time working on this CME activity. No more than 0.5 CME credit(s) will be issued for this activity.

### COURSE EVALUATION: GAPS

This activity was created to address the professional practice gaps listed below. Please respond regarding how much you agree or disagree that the following gaps were met:

- Using new treatment targets being researched for systemic lupus erythematosus (SLE)
- Using updated diagnostic testing methods for SLE
- Using adequate tools to diagnose SLE

## Did participating in this educational activity change your KNOWLEDGE in the professional practice gaps that are listed above?

Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
1	2	3	4	5

Please elaborate on your answer.\_\_\_\_\_

- 3. What percentage of patients with SLE have anti-double-stranded DNA antibodies?
  - **A.** 10%
  - **B.** 25%
  - **C.** 55%
  - **D.** 70%
- Results of a randomized trial showed that using cell-bound complement activation products with two other diagnostic tests accurately identified what proportion of patients with SLE?
   A. >95%
  - **A.** >95% **B.** >70%
  - **C.** ~60%
  - **C.**  $\sim 00\%$
  - **D.** 50%

Did participating in this educational activity change your COMPETENCE in the professional practice gaps that are listed on the left?

Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
1	2	3	4	5

Please elaborate on your answer.\_\_\_\_

Did participating in this educational activity change your PERFORMANCE in the professional practice gaps that are listed on the left?

Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
1	2	3	4	5

Please elaborate on your answer.\_\_\_\_\_

Please identify a change that you will implement into practice as a result of participating in this educational activity (eg, new protocols, different medications).

How certain are you that you will implement this change?

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Strongly Agree	Agree	Somewhat Agree	Disagree	Strongly Disagree
1	2	3	4	5

What topics do you want to hear more about, and what issue(s) in your practice will they address?\_\_\_\_\_

Were the patient recommendations based on acceptable practices in medicine? • Yes • No

If no, please explain which recommendation(s) was (were) not based on acceptable practices in medicine.

Do you think the article was without commercial bias? O Yes O No

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