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

**Joseph M. Ahearn, MD**
Director, Autoimmunity Institute, Director, Lupus Center of Excellence, Allegheny Health Network

Dr Ahearn is a consultant for Exagen Diagnostics.*

The author would like to thank Global Academy for Medical Education and Charles Bankhead for assistance with the preparation of this supplement.

**Recent advances in cellular and molecular biology have provided new insights into the etiology and pathogenesis of diseases. This progress has catalyzed a new era of biomarker discovery that will likely play a major role in the diagnosis and clinical management of many diseases that continue to challenge even the most astute physicians. There is no greater need for improved diagnostic biomarkers than in the field of systemic lupus erythematosus (SLE), which continues to be frequently misdiagnosed, even by expert rheumatologists.**

**Improved accuracy of lupus diagnosis is essential to optimize therapeutic intervention and ensure treatment of the right patient with the right drug at the right time. Correct diagnosis of lupus versus lupuslike mimics is also critical for enrollment of subjects into lupus clinical trials that might be tainted even by a small number of misdiagnosed patients.**

**Historical “Gold Standards”**

Assays for antinuclear antibody (ANA) and anti-double-stranded DNA antibody (anti-dsDNA) have been the basis of diagnostic laboratory testing for SLE for decades, with little improvement in diagnostic tests for decades, with little utility of the assays, and advances in our understanding of the complement system have led to investigation of cell-bound complement activation products (CB-CAPs) as potential biomarkers for a lupus diagnosis.

CB-CAPs were recognized as a potential source of lupus biomarkers for several reasons, one of which was the observation that these products might be rapidly hydrolyzed in the circulation or absorbed by cells and/or tissues, making them short lived. In addition, multiple types of hematopoietic cells express receptors for complement activation (split) products. In this regard, C4d has been identified on surfaces of normal erythrocytes, T and B lymphocytes, and reticulocytes. In addition to potential as diagnostic biomarkers, the capacity of C4d to bind covalently to cell surfaces suggested that CB-CAPs might be a fertile source of biomarkers for disease stratification based on the biology of distinct circulating cell types. Over the past decade, a series of investigations has demonstrated that patients with SLE have substantially higher levels of erythrocyte-bound, lymphocyte-bound, platelet-bound, and reticulocyte-bound C4d than do healthy individuals or patients with other inflammatory, autoimmune, and rheumatologic diseases.† 9

**Diagnostic Panel**

Given the complexity of SLE, a single test is unlikely to provide results that a clinician can use with confidence for a definitive diagnosis. As such, CB-CAP assays have been shown to add significant value to accurate lupus diagnosis when combined with other tests such as ANA and anti-dsDNA. The current panel, which will likely evolve with future study, includes ANA, anti-dsDNA, anti-mutated citrullinated vimentin (anti-MCV) antibody, and the CB-CAPs erythrocite-bound C4d (E-C4d) and B-cell C4d (B-C4d). In a multicenter clinical trial conducted at 16 sites by investigators with expertise in lupus diagnosis, this panel demonstrated 80% sensitivity and greater than 80% specificity for a lupus diagnosis.‡

From the most practical perspective, the CB-CAPs can prove especially useful to accurately rule in or rule out a diagnosis of lupus in patients who are ANA positive and anti-dsDNA negative, assays that are included in this panel. Moreover, a second-generation test panel has incorporated additional autoantibody tests for connective-tissue diseases, which can help distinguish patients with SLE from lupuslike conditions such as scleroderma and polymyositis.

**CB-CAPs Beyond Lupus Diagnosis**

**Monitoring:** The chronicity of SLE requires regular follow-up and adjustment of management strategies to control disease activity. In this regard, there is an urgent need to identify and validate lupus biomarkers for monitoring and predicting increasing disease activity and flares. Preliminary investigations of the reticulocyte-bound RC4d and RC3d have demonstrated good correlation with disease activity and superior performance compared with the use of measurements of serum C3 and C4. A multicenter validation study was launched earlier this year to confirm the potential of CB-CAPs in monitoring SLE disease activity.

**Stratification:** Preliminary studies have identified platelets bearing C4d (PC4d) as a potential biomarker to identify patients with SLE who have an increased likelihood of remission or exacerbation of disease activity.

**Precision Medicine:** Clinical care of patients with lupus is rapidly moving toward improved precision (personalized) medicine. It is generally held that not all patients benefit from the same therapeutic agents and not all biomarkers will be useful in all subsets of patients. Current efforts are underway to determine which CB-CAPs are useful in lupus to assess potential response to specific treatments such as those that interfere with complement activation during disease pathogenesis.

**Summary**

CB-CAP assays have demonstrated potential for improving the diagnosis of SLE, as a complementatory test to anti-dsDNA, ANA, and the MCV assay.**

**Supported by an educational grant from**

**Exagen Diagnostics**

To get instant CME credit online, go to http://bit.ly/lupus2013

**References:**

**Provider Contact Information:** For questions about the CME activity content, please contact University of Louisville at cmep@louisville.edu

**Privacy Policy:** All information provided by course participants is confidential and will not be shared with any other parties for any reason without permission.

**Original Release Date:** November 2013

**Most Recent Review Date:** November 2013

**Expiration Date:** October 31, 2014

**Estimated Complete Activity:** 0.5 hour

**Medium or Combination of Media Used:** Written Supplement

**Method of Physician Participation:** Journal Supplement

**Hardware/Software Requirements:** Windows operating system and high-speed Internet connection

*For additional disclosure information, go to the Web posting at globalacademy.com/rheumatology.

**Accreditation:** This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Louisville School of Medicine and Global Academy for Medical Education, LLC. The University of Louisville School of Medicine is accredited by the ACCME to provide continuing education for physicians.

**Designation Statement:** The University of Louisville Continuing Medical Education designates this enduring educational material supplement for a maximum of 0.5 AMA PRA Category 1 Credit(s)™. Each individual must claim only the credit commensurate with the extent of their participation in the activity.

**Target Audience:** This course 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 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 CB-CAPs are currently available only as a research tool. A CB-CAPs 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:

- Identify conventional and emerging assays and biomarkers used to diagnose systemic lupus erythematosus (SLE)
- Understand limitations of conventional diagnostic tests for SLE
- Describe the principles underlying the use of cell-bound complement activation products in the diagnosis of SLE
- Appreciate the need for multiple biomarkers and assays to obtain information necessary to make an accurate diagnosis of SLE.

This supplement was produced by Global Academy for Medical Education, LLC. Neither the editors of this supplement, the Academic Sponsor, nor the reviewers made any editorial changes to the content. The opinions expressed in this supplement are those of the Faculty and not necessarily reflected those of the Joint Sponsor, the University of Louisville, or the Publisher. Copyright © 2013 Global Academy for Medical Education, LLC and Frontline Medical Communications, Inc. All rights reserved. The information contained herein is for informational purposes only and is not intended to replace the advice of a licensed professional. Reprints of any part of this publication are available, with prior written permission of the Publisher. The Publisher will not authorize reprints for any purpose other than those explicitly stated in this publication, including any claims related to the products, drugs, or services mentioned herein.
Diagnosis of Lupus in the New Age of Biomarkers
New and Emerging Biomarker Technology in the Diagnosis of Lupus
CME Post-Test Answer Sheet and Evaluation Form

Release Date of Activity: November 2013  •  Expiration Date of Activity for AMA PRA Credit: October 31, 2014

Estimated Time to Complete This Activity: 0.5 hour

To get instant CME credits online, go to http://bit.ly/lupus2013. Upon successful completion of the online test and evaluation form, you will be directed to a Web page that will allow you to receive your certificate of credit via e-mail. Please add cmepd@louisville.edu to your e-mail “safe” list. If you have any questions or difficulties, please contact the University of Louisville School of Medicine Continuing Medical Education (CME & PD) office at cmepd@louisville.edu.

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

1. Complete the statement.
   Advances in cellular and molecular biology have:
   A. Eliminated most problems associated with misdiagnosis of SLE
   B. Eliminated underdiagnosis of SLE
   C. Eliminated underdiagnosis of SLE
   D. Failed to produce a biomarker or assay that permits diagnosis of SLE with reasonable certainty

2. The historical laboratory standard for diagnosis of SLE has been
   A. Antinuclear antibodies (ANA)
   B. Anti-dsDNA
   C. ANA and anti-dsDNA
   D. Cell-bound complement-activation products

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  DO  PharmD  RPh  NP  RN  BS  PA  Other ________________________________
Affiliation: ________________________________
Address: ________________________________
City: __________________ State: ____________ ZIP: ____________
Telephone: __________________ Fax: __________________
E-mail: __________________________________

Signature: ________________________________

CME CREDIT VERIFICATION
I verify that I have spent _____ hour(s)/_____ minutes of actual time working on this CME activity. No more than 2.0 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:
• Utilizing new treatment targets being researched for systemic lupus erythematosus (SLE).
• Using updated diagnostic testing methods for SLE.
• Utilizing adequate tools to diagnose SLE.

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

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Somewhat Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Please elaborate on your answer. __________________________________________________________

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

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Somewhat Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

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?

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Somewhat Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Please elaborate on your answer. __________________________________________________________

How certain are you that you will implement this change?

<table>
<thead>
<tr>
<th>Strongly Agree</th>
<th>Agree</th>
<th>Somewhat Agree</th>
<th>Disagree</th>
<th>Strongly Disagree</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

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 articles were without commercial bias?  Yes  No

If no, please list the article(s) that was (were) biased. __________________________________________________________

The University of Louisville thanks you for your participation in this CME activity. All information provided improves the scope and purpose of our programs and your patients’ care.

© 2013 Global Academy for Medical Education, LLC. All Rights Reserved.