Challenge to Recommendation Requiring Diagnostic Test Confirmation of Lyme Disease

Raphael B. Stricker, MD
450 Sutter Street, Suite 1504
San Francisco, CA 94108

April 16, 2009

IDSA Guidelines (p. 1090): "Diagnostic testing performed in laboratories with excellent quality-control procedures is required for confirmation of extracutaneous Lyme disease…."

This recommendation should be withdrawn for the following reasons:

1. A study by Bakken et al. (1997) 🗐 comparing interlaboratory variation among 516 participants in the Wisconsin State Laboratory of Hygiene/College of American Pathologists Proficiency Testing Program reached the following conclusion: **"Our data indicated that the sensitivity and specificity of the currently used tests for Lyme disease are not adequate to meet the two-tier test approach being recommended."** Because of the poor performance of these tests, the study went on to say: **"In conclusion, our results suggest that stronger measures need to be taken by the Food and Drug Administration to control the quality of commercially available Lyme disease assay kits."**

2. A study by Hunfeld et al. (2002) 🗐 involving 337 microbiology laboratories in Europe reached the following conclusion: "Test results were found to be in part highly variable and clearly correlated with the manufacturers and the applied test methodology…. **Quantification of test results and reporting of specific immunoblot bands also showed high variability.** Moreover, for some assays a high number of false positive and false negative test results were reported by the participants….**In view of our results further standardisation of Lyme disease serology is not just desirable but is urgently needed. Moreover, stronger criteria for the validation of available test kits must be applied."** (G. Stanek, one of the guidelines authors, was a coauthor on this article).

3. A review by Stricker and Johnson (2007) 🗐 of North American case-control studies of commercial two-tier Lyme testing reached the following conclusion: "The two tier testing system endorsed by the Centers for Disease Control and Prevention (CDC) has a high specificity (99%) and yields few false positives. **But the tests have a uniformly miserable sensitivity (56%)—they miss 88 of every 200 patients with Lyme disease (table)."** An updated analysis including more recent studies found that the sensitivity of the two-tier test system was even worse (46%). This sensitivity is far

below the 95% cutoff required for an accurate diagnostic test, and much worse than the 99.5% sensitivity of commercial HIV testing.

4. In describing early neurologic and cardiac manifestations of Lyme disease, the guidelines state that the "vast majority" of patients will have positive serologic testing. This statement is not supported by the primary source material, which shows that only 40-65% of these patients are seropositive at the time of diagnosis. Many of these studies were performed prior to the use of commercial two-tier testing, yet the guidelines cite the studies as evidence that two-tier testing is accurate in these forms of Lyme disease.

5. In describing the high sensitivity of commercial two-tier testing for cardiac, rheumatologic and late neurologic manifestations of Lyme disease, the guidelines fail to recognize the circular reasoning involved in these diagnoses. The reasoning is flawed because these conditions are defined as clinical symptoms of arthritis or advanced neurologic disease **associated with a positive serologic test for B. burgdorferi**. The conclusion is then made that the sensitivity of serologic testing is 100% for these conditions. This circular reasoning is acknowledged by Bacon et al. 🗐 and best seen in the recent article by Steere et al. 🗐 Bacon et al. state: **"For late disease, the case definition requires at least 1 late manifestation and laboratory confirmation of infection [39], and therefore the possibility of selection bias toward reactive samples cannot be discounted."** After defining these conditions as stated above, Steere et al. appear to be oblivious to this flawed reasoning.

6. Finally, the very basis for two-tier Lyme testing is questionable. The guidelines rely on the CDC criteria for use and interpretation of Lyme testing. The CDC in turn cites two pivotal studies to support the current commercial test system, one by Dressler et al. 🗐 and the other by Engstrom et al. 🗐 However, Dressler et al. reach the following conclusion: **"In this study, the results obtained by ELISA and Westem blotting were concordant in patients with clearly positive or negative tests, and Western blotting was of *no additional value* in these patients."** Thus the utility of Western blotting was not substantiated by this study. The guidelines refer to the study by Engstrom et al. to support the current interpretation of the commercial IgG Western blot, which stipulates that at least 5 of 10 bands must be reactive to give a positive test result. However, the study by Engstrom et al. reached an entirely different conclusion: **"Recognition of just two of five proteins (20, 24, 35, 39, and 88 kDa) will satisfy the requirements for a positive IgG immunoblot**....**We found that the criterion we developed for the positive IgG immunoblot in early Lyme disease could also be applied to late Lyme disease."** Thus the Western blot interpretation used in all commercial test kits is not supported by the source material. Conversely, the interpretive criteria of Engstrom et al. are closest to those of specialty laboratories that are proficient in testing for tick-borne diseases using non-commercial test systems.

🗐 *Article included in ILADS binder*

7. The guidelines also caution that Lyme testing has poor positive predictive value when such testing is done on patients "who do not reside in or travel to a geographic area where Lyme disease is endemic." Reed 🗐 states that "patients with vague subjective complaints such as headache, fatigue, and myalgia are considered to have a low pretest probability of LD (<=0.20). A positive ELISA result in this setting very likely represents a false-positive result and can lead to misdiagnosis as well as unnecessary and inappropriate use of antimicrobial therapy." However, Reed also cautions that "**because LD incidence rates and vector abundance vary widely between different geographic areas, it can be difficult for physicians to have sufficient information to allow accurate assessment of pretest probability of LD for individual patients.**" The risk of false-positive testing is also based on an assumption of high background seropositivity in an endemic region. However, Nadelman et al. 4 found that…**in Westchester County**…t**he prevalence in healthy blood donors from this area were reported to be 0.7%.**" Thus the likelihood of a true-positive test in a patient with Lyme symptoms in this setting is significant. Finally, the extent of endemic Lyme locales appears to be changing with global warming. Brownstein et al. 🗐 have shown that most of the eastern United States and Canada will be suitable for tick infestation in the 21st century. This fact makes the definition of Lyme endemicity even more nebulous for physicians, who will have to maintain a high index of suspicion when confronted by Lyme symptoms in an individual patient regardless of serologic test results.

In conclusion, the recommendation that clinical findings in Lyme disease must be supported by positive serologic testing is unacceptable due to commercial test insensitivity, variable test performance, lack of test standardization, misinterpretation of positive test criteria and circular reasoning surrounding application of test results. In addition, the epidemiologic risk of exposure to Lyme disease is often too vague to help with diagnosis in an individual patient. Until better commercial testing is developed, Lyme disease should remain a clinical diagnosis, and commercial testing should only support, but NEVER RULE OUT, the diagnosis of Lyme disease.

Appendix

Subheading 1

🗐 Bakken LL, Callister SM, Wand PJ, Schell RF. Interlaboratory comparison of test results for detection of Lyme disease by 516 participants in the Wisconsin State Laboratory of Hygiene/College of American Pathologists Proficiency Testing Program. *J Clin Microbiol.* 1997 Mar;35(3):537-43.

"In 1991, we reported that 55% of laboratories participating in the Wisconsin Proficiency Testing Program could not accurately identify serum samples from Lyme disease patients containing antibody against *Borrelia burgdorferi*….From 1992 through 1994, 50 serum samples were sent to participants of the survey. Each laboratory received 28 serum samples from individuals with Lyme disease according to the case definition of the Centers for Disease Control and Prevention and 22 serum samples from healthy individuals. Unfortunately, the serodiagnosis of Lyme disease by participants had not improved….These results suggest that stronger criteria must be applied for approving and continuing to approve commercially available kits for the serodiagnosis of Lyme disease."

"Recently, CDC along with the Association of State and Territorial Public Health Laboratory Directors have recommended that sera submitted for serology be tested by an enzyme immunoassay or indirect fluorescent-antibody assay and that borderline or positive samples be tested by Western blotting (immunoblotting) (5, 8). **Our data indicated that the sensitivity and specificity of the currently used tests for Lyme disease are not adequate to meet the two-tier test approach being recommended.** Ideally, a screening test should have a high degree of sensitivity (.95%). The current methodologies need to be improved to adequately screen serum samples for confirmatory testing."

"**In conclusion, our results suggest that stronger measures need to be taken by the Food and Drug Administration to control the quality of commercially available Lyme disease assay kits.** One solution is to force all currently used or approved assay systems through an evaluation with sera obtained from culture-positive patients. An arbitrary sensitivity of 90% could be selected. The specificity could also be set at 95%. Commercially available tests that did not reach these performance levels would be removed from the market. Although this is a drastic solution, its time has come. This measure would lessen the overdiagnosis of Lyme disease (19) and prevent the use of costly laboratory solutions, like Western immunoblotting, to make a serodiagnosis of Lyme disease."

Subheading 2

🗐 Hunfeld KP, **Stanek G**, Straube E, Hagedorn HJ, Schörner C, Mühlschlegel F, Brade V. Quality of Lyme disease serology. Lessons from the German Proficiency Testing Program 1999-2001. A preliminary report. *Wien Klin Wochenschr*. 2002 Jul 31;114(13-14):591-600.

"From 1999 to 2001, between 226 and 337 microbiological laboratories participated in each of the four surveys that have been held so far…. Test results were found to be in part highly variable and

clearly correlated with the manufacturers and the applied test methodology….Quantification of test results and reporting of specific immunoblot bands also showed high variability. Moreover, for some assays a high number of false positive and false negative test results were reported by the participants. CONCLUSION: **In view of our results further standardisation of Lyme disease serology is not just desirable but is urgently needed.** Moreover, stronger criteria for the validation of available test kits must be applied.

Subheading 3

Stricker RB, Johnson L. Lyme wars: let's tackle the testing. *BMJ*. 2007 Nov 17;335(7628):1008.

"The two tier testing system endorsed by the Centers for Disease Control and Prevention (CDC) has a high specificity (99%) and yields few false positives. **But the tests have a uniformly miserable sensitivity (56%)—they miss 88 of every 200 patients with Lyme disease (table).**

Sensitivity/Specificity of Commercial Two-Tier Testing for Convalescent/Late Stage Lyme Disease*

Study/Year	Location	Patients/Controls	Sensitivity	Specificity
Schmitz et al., 1993	USA	25/28	66%	100%
Engstrom et al., 1995	USA	55/159†	55%	96%
Ledue et al., 1996	USA	41/53	44%	100%
Tilton et al., 1997	USA	23/23	45%	100%
Trevejo et al., 1999	USA	74/38	29%	100%
Bacon et al., 2003	USA	106/559	67%	99%
Binnicker et al., 2008	USA	35/5	49%	100%
Steere et al., 2008	USA	76/86††	18%	99%
TOTALS	**USA 8**	**435/951**	**46%**	**99%**

* Limited to studies from USA that included negative controls
† Non-commercial ELISA and Western blot
†† Non-commercial ELISA

1. Schmitz et al. *Eur J Clin Microbiol Infect Dis*. 1993;12:419-24;
2. Engstrom et al. *J Clin Microbiol*. 1995;33:419-27;
3. Ledue et al. *J Clin Microbiol*. 1996;34:2343-50;
4. Tilton et al. *Clin Infect Dis*. 1997;25(Suppl 1):S31-4;
5. Trevejo et al. *J Infect Dis*. 1999;179:931-8;
6. Bacon et al. *J Infect Dis*. 2003;187:1187-99;
7. Binnicker et al. *J Clin Microbiol*. 2008;46:2216-21;
8. Steere et al. *Clin Infect Dis*. 2008;47:188-95.

Article included in ILADS binder

Positive Predictive Value, Negative Predictive Value and Likelihood Ratios of Two-Tier Test System

Lyme Diagnosis ("Gold Standard")

Tests	Yes	No	
Positive	198 (TP)	10 (FP)	PPV = 95% (198/208)
Negative	237 (FN)	941 (TN)	NPV = 80% (941/1178)
	Sensitivity = 46% (198/435)	Specificity = 99% (941/951)	

Pretest probability = 435/1386 = 31%

Positive LR = 0.46/0.01 = 46
Negative LR = 0.54/0.99 = 0.55

Likelihood Ratio	**Interpretation**
> 10	**Large and often conclusive increase in the likelihood of disease**
5 – 10	Moderate increase in the likelihood of disease
2 – 5	Small increase in the likelihood of disease
1 – 2	Minimal increase in the likelihood of disease
1	No change in the likelihood of disease
0.5 - 1.0	**Minimal decrease in the likelihood of disease**
0.2 - 0.5	Small decrease in the likelihood of disease
0.1 - 0.2	Moderate decrease in the likelihood of disease
< 0.1	Large and often conclusive decrease in the likelihood of disease

Subheading 4

Background and Diagnosis of Early Neurologic Lyme Disease

Guidelines (p. 1107): "The **vast majority** of patients with early neurologic Lyme disease are seropositive [157, 162–164]"

Halperin [157]: "Between July and September 1989, LB serologies were performed on all patients with new-onset Bell's palsy. **Seven of 32 had serologic evidence of LB at onset.** One, initially seronegative, was highly seropositive 5 weeks later. In the five in whom we examined CSF, there was no evidence of intrathecal synthesis of specific antibody."

"Immunologic testing. Serum: Total anti-*B. burgdorferi* antibody activity (**total IgG, A and M**) was measured by standard ELISA, as previously described." (NOT TWO-TIER TESTING, INCLUDES NON-STANDARD IgA ELISA)

Bacon [162]: Table 1, Two-tier testing

Condition/Stage	N	Positive	Negative	%Positive
Early neurologic	**15**	**13**	**2**	**87**
Early neurologic convalescent	**11**	**9**	**2**	**82**
Late neurologic	11	11	0	100

BUT…

"Lyme disease samples (n=280) were from patients who met the CDC surveillance case definition for national reporting of Lyme disease [39]…. Twenty additional samples were from 20 patients with early neuroborreliosis, of which **15** were from persons with acute
early neurologic disease and were obtained before antibiotic treatment. Of these 15 patients, 10 had meningitis, 8 had facial palsy, and 3 had radiculoneuropathy. The remaining **5** samples were obtained from treated patients during convalescence. The presenting signs in these patients before treatment were meningitis (4 of 5), facial palsy (1 of 5), and radiculoneuropathy (2 of 5). Most patients with early neuroborreliosis (18 of 20) had a history of EM….**For late disease, the case definition requires at least 1 late manifestation and laboratory confirmation of infection [39], and therefore the possibility of selection bias toward reactive samples cannot be discounted."**

Stiernstedt [163]: "Antibodies to *Borrelia* were measured by an ELISA assay using sonicated whole cell antigen. Antibody titers were determined in both CSF and serum in all 75 patients studied. Twelve out of 75 (48%) patients were positive in both CSF and serum serology. Eighteen out of 75 (24%) were positive only in CSF serology and 12 out of 75 (16%) were positive only in serum serology….**The total sensitivity of the serum assay was 64%."**

Peltomaa [164]: "Serum samples from 47 Lyme patients with facial paralysis and 86 control subjects were analyzed for IgG antibodies to VlsE peptide of Borrelia burgdorferi and for immunoglobulin M (IgM) and IgG antibodies to sonicate antigens of B. burgdorferi using the two-tier approach….**In the two-tier test, 41 (87%) patients had positive IgM, 31 (66%) had positive IgG, and all 47**

patients had positive IgM or IgG responses. Of the 86 control subjects, 2 (2%) had positive results with the two-tier test. Thus, the sensitivities of the VlsE and the two-tier tests were 100%; the specificity of the VlsE ELISA was 95% and the specificity of the two-tier test was 98%."

Background and Diagnosis of Cardiac Manifestations of Lyme Disease

Guidelines (p. 1108): "The **vast majority** of patients with cardiac manifestations of Lyme disease are seropositive at the time of presentation [183, 192].

Sigal [183]: "Lyme carditis should be considered in the proper clinical setting with appropriate use of diagnostic tests, **recalling that patients with carditis early in Lyme disease may be seronegative** and that all patients who are seropositive do not necessarily have Lyme disease."

Pinto [187]: "Serologic testing may support the diagnosis of Lyme carditis but cannot make a diagnosis independently. **Serologic tests can be negative in the first 6-8 weeks of disease, so a negative test does not rule out the diagnosis** [45]."

BUT…

van der Linde & Ballmer [192]: "As Lyme carditis may be the only expression of Lyme borreliosis, a recent history of the infection cannot unconditionally be a necessary criterion for diagnosis. Resolution of the (cardiac) manifestations with antibiotic therapy supports the diagnosis of Lyme carditis, especially if a Jarisch-Herxheimer reaction occurs. **Although seronegative Lyme borreliosis has been reported, we currently think that positive serology is still required for the diagnosis of Lyme carditis**."

<u>Subheading 5</u>

Background and Diagnosis of Rheumatologic Manifestations of Lyme Disease

Guidelines (p. 1110): "In the **vast majority** of patients, the clinical manifestations are too nonspecific to warrant a purely clinical diagnosis of Lyme arthritis. Confirmation of the diagnosis requires serologic testing. All patients should be determined to be seropositive by 2-tier testing that includes an ELISA and IgG immunoblot [162, 206]"

Steere [206]: "The diagnosis of Lyme arthritis is usually based on the presence of a characteristic clinical picture, exposure in an endemic area for the disease, and an elevated IgG antibody response to B. burgdorferi (Table 2) . [20] Because serologic testing for Lyme disease has a marked risk of false-positive results, it is now recommended that all equivocal or positive results by enzyme-linked immunosorbent assay (ELISA) be confirmed by Western blotting. [22] For a positive IgG blot, patients are required to have reactivity with at least 5 of the 10 most common IgG bands (18, 23 [OspC], 28, 30, 39, 41 [fla], 45, 58 [not GroEL], 66, and 93-kDa), [29] and patients with Lyme arthritis usually have responses to all of these spirochetal proteins. The limitation of serologic testing is that it does not distinguish active from inactive disease. Because patients with Lyme arthritis remain seropositive for many years after antibiotic treatment, a positive test for Lyme

disease may cause diagnostic confusion if the patient subsequently develops another illness, particularly another illness with joint symptoms."

Bacon [162]: Table 1, Two-tier testing

Condition/Stage	N	Positive	Negative	Sensitivity
Arthritis	33	32	1	97%
Arthritis convalescent	24	23	1	96%

BUT…

"Lyme disease samples (*n*=280) were from patients who met the CDC surveillance case definition for national reporting of Lyme disease [39]….Forty-nine samples were from patients with Lyme arthritis, all of whom had intermittent objective swelling of 1 joint (**28** samples were obtained before antibiotic treatment, **5** were obtained from patients who had joint inflammation despite prior antibiotic treatment, and **16** were obtained during convalescence)….For late disease, the case definition requires at least 1 late manifestation and laboratory confirmation of infection [39], and **therefore the possibility of selection bias toward reactive samples cannot be discounted**."

AND…

Stricker RB, Johnson LB. Serologic tests for Lyme disease: More smoke and mirrors. *Clin Infect Dis* 2008;47:1111-2.

"Steere et al. [1] classified 44 patients as having disseminated (stage 2) or persistent (stage 3) infection due to *Borrelia burgdorferi,* the spirochetal agent of Lyme disease. The mandatory inclusion criteria for these categories were neurologic, cardiac, or joint involvement and a serologic result positive for *B. burgdorferi* by ELISA and Western blot [2]. Thus, by definition, all patients with disseminated or persistent Lyme disease were required to have a positive serologic test result. **It is disingenuous to define a condition by a positive test result and then state that the test has 100% sensitivity**."

Background and Diagnosis of Late Neurologic Lyme Disease

Guidelines (p. 1110): "Two-tier (ELISA and IgG immunoblot) seropositivity with serum samples and evidence of intrathecal antibody production to *B. burgdorferi* **are expected** [149, 162, 213]"

Bacon [162]: Table 1, Two-tier testing

Condition/Stage	N	Positive	Negative	%Positive
Early neurologic	15	13	2	87
Early neurologic convalescent	11	9	2	82
Late neurologic	**11**	**11**	**0**	**100**

BUT…

"Lyme disease samples (*n*=280) were from patients who met the CDC surveillance case definition for

national reporting of Lyme disease [39]….**Eight** samples were from individuals with late-stage neurologic disease (7 of the 8 patients had encephalopathy, 3 had polyneuropathy, and **7** had received antibiotic therapy for EM and/or Lyme arthritis previously). **For late disease, the case definition requires at least 1 late manifestation and laboratory confirmation of infection [39], and therefore the possibility of selection bias toward reactive samples cannot be discounted."**

Chronic meningitis (CM): Stiernstedt et al, *J Clin Microbiol* 1985;21:819-25

"Influence of duration of disease and antibiotic treatment on titer levels. Levels of (serum) ELISA titer to spirochete in relation to duration of disease and antibiotic treatment are shown in Fig. 5. **Of 39 pretreatment samples, 21 (54%) were seropositive for IgG, 8 (21%) were positive for IgM, and 23 (59%) were positive for IgG or IgM or both**. With increasing duration of disease before the start of treatment with antibiotics, the percentage of positive CM patients and their IgG titers increased and their IgM titers decreased."

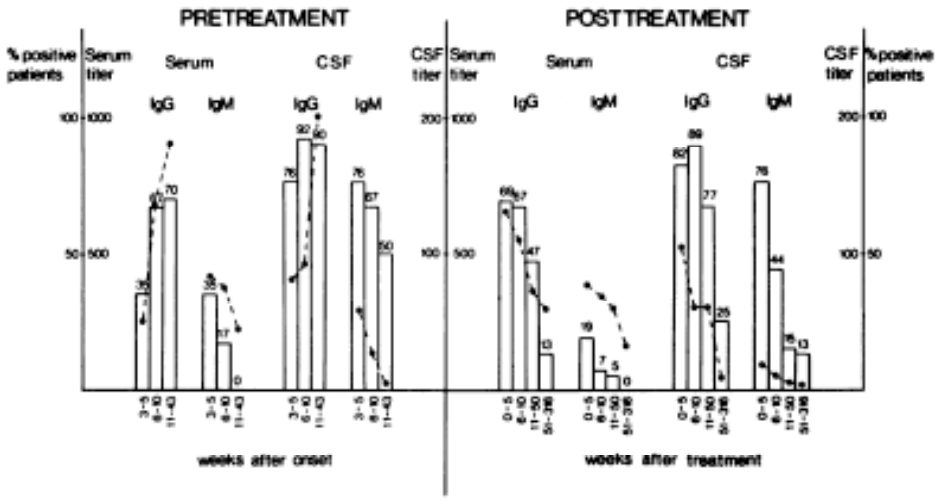

FIG. 5. Kinetics of the antibody response, measured by ELISA, in relation to onset of disease and antibiotic treatment. Columns represent the percentage of positive patients; ●, median titer levels. Seventeen, 12, and 10 paired CSF and serum pretreatment samples from 39 patients with 3 to 5, 6 to 10, and 11 to 43 weeks duration of disease, respectively, were tested, as were 48 CSF and 67 serum posttreatment samples from 36 patients.

Subheading 6

🗐 Dressler: "In this study. the results obtained by ELISA and Westem blotting were concordant in patients with clearly positive or negative tests, and Western blotting was of **no additional value** in these patients."

🗐 Engstrom: "The most sensitive and specific interpretation criterion for IgG immunoblot in early Lyme disease was found to be the recognition of two of the following five proteins: **88, 39, 35, 24 (.19 intensity units), and 20 kDa**. According to this criterion, 43.6% (24 of 55) of Lyme disease patients were positive by immunoblot at V1 versus 23.6% (13 of 55) positive by ELISA IgG (*P* 5 0.026). At V2, 80.0% (44 of 55) of early Lyme disease patients were IgG immunoblot positive compared with 41.8% (23 of 55) positive by IgG ELISA (*P* , 0.001). Few healthy blood donors or persons with other illnesses

tested IgG immunoblot positive with this IgG interpretation criterion (4.0 and 7.1%, respectively)."

"Our study of the use of the immunoblot for the serodiagnosis of early Lyme disease demonstrated that relatively simple criteria can be used for the interpretation of IgM and IgG immunoblots. Only two of three proteins (24 [OspC], 39, and 41 kDa) need be recognized for a positive IgM immunoblot. **Recognition of just two of five proteins (20, 24 [.19 intensity units], 35, 39, and 88 kDa) will satisfy the requirements for a positive IgG immunoblot**... **On the basis of the analysis of a limited number of serum specimens, we found that the criterion we developed for the positive IgG immunoblot in early Lyme disease could also be applied to late Lyme disease.** Although antibodies to the 31-kDa (OspA) and 34-kDa (OspB) proteins occur relatively infrequently, these proteins can be included among the significant proteins reactive in late disease because of their high levels of specificity, especially when they occur in tandem."

Subheading 7

Guidelines (p. 1117): "If serologic testing for Lyme disease is done for chronically ill patients who only have fatigue or musculoskeletal complaints without any objective manifestation of Lyme disease, the test results have a **poor positive predictive value** [98, 99, 101, 102, 104, 270]. Regardless of the nature of the symptom(s), **a low positive predictive value can also be anticipated if serologic testing is done for patients who do not reside in or travel to a geographic area where Lyme disease is endemic.** Under these circumstances, the majority of patients with a positive test result will not have active *B. burgdorferi* infection and, accordingly, would be unlikely to obtain a durable response from antibiotic treatment directed at this infection."

🗐 Reed KD. Laboratory testing for Lyme disease: Possibilities and practicalities. J Clin Microbiol 2002;40:319-3
"The American College of Physicians (ACP) recommends serologic testing for patients with objective clinical signs that have a pretest probability of LD in the range of 0.20 to 0.80 (3). Patients with vague subjective complaints such as headache, fatigue, and myalgia are considered to have a low pretest probability of LD (<=0.20). A positive ELISA result in this setting very likely represents a false-positive result and can lead to misdiagnosis as well as unnecessary and inappropriate use of antimicrobial therapy. **Because LD incidence rates and vector abundance vary widely between different geographic areas, it can be difficult for physicians to have sufficient information to allow accurate assessment of pretest probability of LD for individual patients**. Exaggerated perceptions of risk by patients and health care providers can result in significant amounts of unnecessary testing and associated expense (5).

🗐 Nadelman RB, Herman E, Wormser GP. Screening for Lyme disease in hospitalized psychiatric patients: prospective serosurvey in an endemic area. *Mt Sinai J Med*. 1997 Nov;64(6):409-12.
BACKGROUND: Nervous system involvement in Lyme disease may mimic certain psychiatric disorders. We studied whether it is worthwhile to conduct routine screening of psychiatric inpatients for serologic evidence of Lyme disease. METHODS: Between March 1988 and June 1989, we prospectively screened sera for Lyme disease from adults admitted to an acute care psychiatric hospital in Westchester County. New York, an area in which this infection is endemic. **Of all cases of Lyme disease reported to the U.S. Public Health Service in 1988, 16% originated in**

Westchester County. **The prevalence in healthy blood donors from this area were reported to be 0.7%.** Sera were tested by fluorescent immunoassay alone (90%) or fluorescent immunoassay plus enzyme-linked immunosorbent assay (10%). RESULTS: Sera from only 1 of 517 patients demonstrated antibodies to Borrelia burgdorferi, the etiologic agent of Lyme disease (0.2% [95% CI, 0.0% to 1.1%]). This patient had a nonreactive Western blot, which suggested a false-positive antibody test. CONCLUSIONS: We cannot presently recommend routine serologic screening for Lyme disease for adult psychiatric inpatients, even in areas of the United States where this illness is endemic.

Bunikis J, Barbour AG. Laboratory testing for suspected Lyme disease. Med Clin North Am. 2002 Mar;86(2):311-40.

Laboratory testing for B. burgdorferi infection is intended to substantiate a physician's clinical judgment of whether a patient has Lyme disease or not. Cultivation of B. burgdorferi from a patient's skin or blood is the gold standard for demonstration of active infection, but it is expensive and lacks clinical sensitivity. Detection of spirochetal DNA in clinical samples by PCR has better sensitivity, but PCR for B. burgdorferi has not yet been standardized for more routine diagnostic testing. Detection of antibodies to B. burgdorferi is the most practical and common approach for laboratory work-up of a case of suspected Lyme disease. Serologic assays fall short of 100% sensitivity and specificity, however, and examination of a single specimen in time does not discriminate between previous and ongoing infection. **Because of a background false positivity even among healthy populations of nonendemic regions, serologic testing is recommended only when there is at least a one in five chance, in the physician's estimation, that the patient has active Lyme disease.** The pretest likelihood of the disease is determined by the physician in the context of epidemiologic and clinical facts of the case. This estimate can serve to reassure patients who are at low risk of B. burgdorferi infection but are seeking a Lyme test for complaints of a more nonspecific nature. Although new subunit serologic assays based on recombinant proteins are becoming available commercially, the longstanding two-test approach, in which a positive or indeterminate result with a standardized, sensitive ELISA test is followed by verification with a more specific Western blot assay, still provides the physician with a reasonably accurate and reliable assessment of the presence of antibodies to B. burgdorferi. More recent challenges for serologic testing are seropositivity in the population as the result of immunization with the Lyme disease vaccine and the emergence of new Borrelia species that cause Lyme disease-like illnesses.

Brownstein JS, Holford TR, Fish D. Effect of Climate Change on Lyme Disease Risk in North America. Ecohealth. 2005 Mar;2(1):38-46.

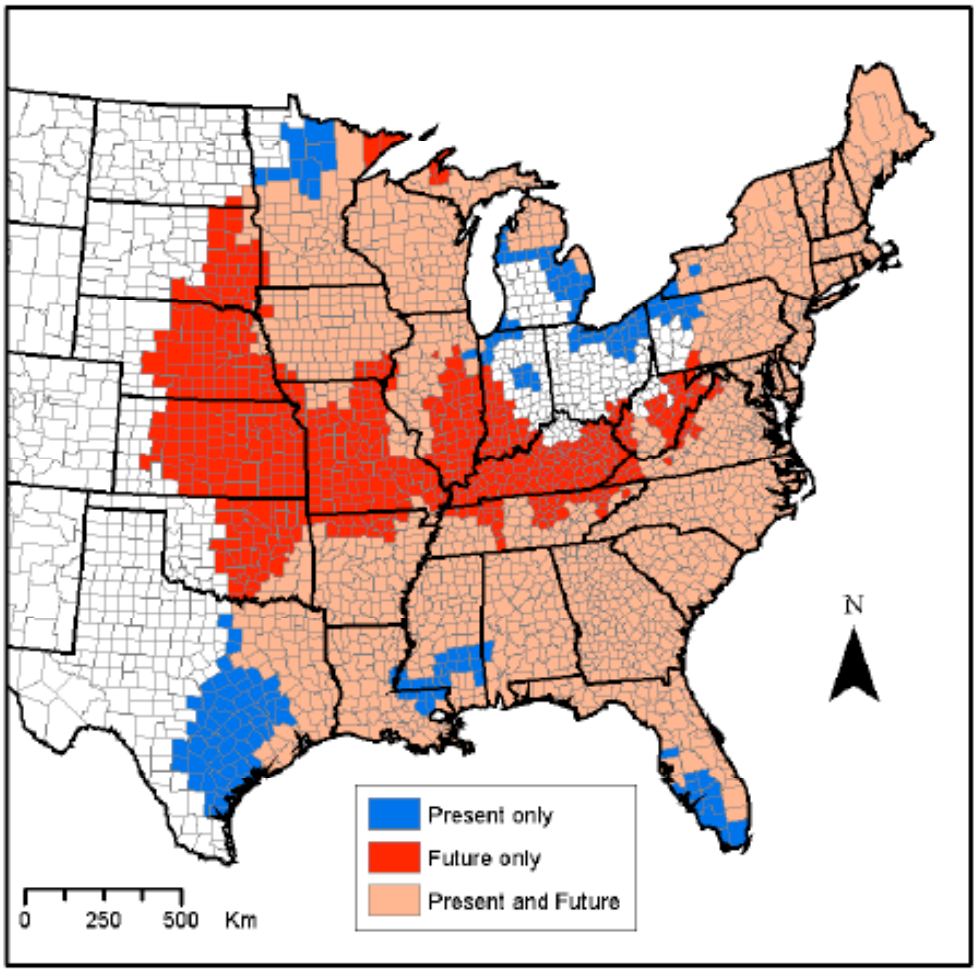

Figure 3.
Change in county-based distribution of *I. scapularis* from present to the 2080s. The future distribution based on climate change data, which considers the effects of both greenhouse ga and sulfate aerosols, was overlaid on the current predicted distribution. The map reveals future suitable (in red) and unsuitable (in blue) counties. Counties that remain suitable over time (i pink) are also displayed.

Article included in ILADS binder