In Case You Missed It: Dicey Path to Lyme Disease Diagnosis

Written by Mary Beth Pfeiffer

Go to a doctor with a red rash akin to a bull’s-eye, and you are likely to leave with a diagnosis of Lyme disease and a prescription for antibiotics.

Then, consider yourself lucky.

Tests in the early stages of the tick-borne illness pick up the disease just 40 percent of the time — and nearly a third of infected people get no blotchy flag that announces unequivocally: You have Lyme disease.

Diagnosing Lyme is of urgent concern in the mid-Hudson Valley, where rates are the highest in the nation and patients say falsely negative tests have led to damaging treatment delays.

Indeed, in the quest to find the elusive Lyme spirochete, that fleeting skin stain is a rare certainty. Without it, a test for the disease carried by the black-legged tick is, for all practical matters, anything but a choice between a positive and negative result.

It is, instead, a matter of counting smudges on test paper — but only if you have just enough of them and a lab has mastered the delicate task of running and reading the test. Diagnosis may turn on whether you’ve had the infection long enough to produce the requisite antibodies or if the bug has found ways to evade detection. It may hinge on whether you were infected with the one strain of spirochete that’s tested – among 25 identified; if you carried another tick-borne illness; and, maybe most important, whether your doctor was schooled in the perilous limits of Lyme testing.

Those shades of gray, gleaned from an exclusive Poughkeepsie Journal review of scientific studies, along with interviews with researchers, patients and Lyme-treating physicians, contrast sharply with advice that thousands of physicians nationwide see when they turn to the U.S. Centers for Disease Control for guidance.

“(P)atients who have had Lyme disease for longer than 4-6 weeks … will almost always test positive,” the agency’s web site declares. “Especially,” it says, in “later stages.”
“False,” said Dr. Daniel Cameron, a Westchester County epidemiologist and internist who believes, like other Lyme-treating physicians, that the CDC overstates the ease of diagnosing Lyme and creates false confidence among doctors in the so-called two-tier test.

The test’s early failures aside, key studies in 2003 and 2008 provided by the CDC found the test 85 to 100 percent correct in arthritis cases and patients with neurologic symptoms related to walking, speech, thinking and muscle control.

But those studies evaluated the test’s accuracy in later stages by retesting carefully chosen people who had already tested positive, which researchers acknowledge is “problematic” and potentially biased. The studies were also performed under ideal conditions, while results in the real world of patient testing have sometimes varied widely. And even if accepted as valid, the studies acknowledge that 1 in 7 patients with certain symptoms may be missed.

Beyond this, the tests didn’t perform nearly as well in previous studies, and little research has been done on the test’s performance on people with other common tick-borne infections that may inhibit immune response. Finally, the 18-year-old test technology was specifically designed to avoid diagnosing Lyme in people who do not have it — sometimes, researchers acknowledge, at the expense of people who do.

These qualifications and more, Lyme-treating physicians believe, should serve to temper the CDC’s wholesale endorsement of the test.

“Physicians take mental shortcuts because we have so much information we are processing,” said Dr. Elizabeth Maloney, a Minnesota physician who instructs doctors on Lyme diagnosis. The CDC advice tells doctors, she said, “‘You don’t need to do a long exam. If you are considering Lyme, just order the lab test because the negative test means they don’t have it.’ That’s not true.”

The agency’s “almost always” declaration on the test’s reliability has profound implications for people suffering from a disease characterized as much by scientific and political strife as by a tiny eight-legged arachnid. With at least five Lyme disease physicians under New York state investigation for the controversial use of long-term antibiotics — as reported by the Poughkeepsie Journal in August — front-line physicians are sometimes loath to diagnose without the black-and-white finding of a positive Lyme test, patients and Lyme physicians said. Hence, they may cede clinical judgment — even in the face of symptoms — to the comfort of a lab test.

Barbara Johnson, a Ph.D. microbiologist in the CDC’s vector-borne diseases division, said it was “inaccurate” that physicians are hesitant to treat Lyme disease, noting that a CDC survey found only 3 percent would withhold antibiotics pending tests. The 2009 survey, which the agency
declined to provide, referred specifically to early Lyme, however, whereas later-stage diagnosis is far trickier.

“CDC stands by its recommendation to perform two-tiered serologic (blood) testing for Lyme disease,” Johnson said in written answers to Journal questions. “After the (rash) stage of illness, the accuracy of two-tiered serologic testing is quite good.”

The definition of “quite good,” however, is a matter of interpretation and subject to a raft of pitfalls.

'Major problem'

The debate over testing, like that over the spirochete’s response to short-term antibiotics, is part of a furious struggle to define the scope and severity of Lyme disease in America. If the tests fail — and, in particular, if the definition of positive is narrowly drawn — the true count fails too.

“A major problem in assessing the magnitude of this serious public health issue,” Dr. Amiram Katz, a Lyme-treating neurologist who teaches at Yale University, testified at a recent hearing called by U.S. Sen. Richard Blumenthal, D-Conn., in Connecticut, “is the undiagnosed cases … It is clear that more accurate tests are needed.”

The CDC’s endorsement aside, the test is widely considered — even by supporters — to be an imperfect instrument.

“I think most everyone would acknowledge [the test] does not do a good job in the early stage of the disease,” said Joseph Breen, who administers $26 million in annual grants for Lyme research at the National Institutes of Health. Beyond this, “it’s not the most user-friendly test,” he said, with interpretation often “subjective” and dependent on how those smudges on paper, called “bands,” are read.

“NIH wouldn’t be funding millions of dollars if people thought the tests were as good as some people state,” said Brian A. Fallon, a psychiatry professor and director of the Lyme and Tick-borne Diseases Research Center at the Columbia University Medical Center in New York City.

The so-called “gold standard” would be a test that could grow the organism from a blood sample, now possible only for samples from the Lyme rash itself. In the absence of a culture test, the two-tier test looks for antibodies produced as the body fights infection, an indirect method that may signal an old infection and cannot tell if treatment is effective.

As significant for critics is the way the test is structured, allowing patients to get the second test only if they screen positive on the first. The first test — a measure of the quantity of antibodies
— helps to weed out people who may falsely test positive in the second, scientists say. But it was correct 33 to 49 percent of the time in early stages, 75 to 86 percent after a couple of weeks and 79 percent in neurologic patients, according to a 2005 review of studies in the journal of the American Society for Microbiology. This is an argument, some say, for going right to the second tier.

“We’re missing easily half the cases of Lyme disease,” said Holly Ahern, associate professor of microbiology at the State University of New York, Adirondack, a two-year state college in Queensbury, and an organizer of a Lyme disease conference at Skidmore College last May. “If you flipped a coin, it’s about as reliable.”

CDC officials and researchers refer often to “misconceptions” about the test’s early accuracy; it is, as one non-CDC scientist said, a “biological fact” related to bodily production of antibodies and not a test flaw.

Besides this, the early test’s performance, said Dr. Maria Aguero-Rosenfeld, a researcher and pathology chief at Bellevue Hospital Center in New York City, “is not a problem since the diagnosis in early disease is clinical, based on (the) skin lesion” — the Lyme disease rash that doctors use to confirm infection.

Never a rash

Lyme-treating physicians and activists believe that fewer patients may get the rash than the 69 percent of CDC-reported cases since the rash itself most often defines whether a case is reportable. Three to 12 times as many cases are not reported, according to published research.

Ahern, the SUNY professor, recently surveyed 600 people in three Adirondack counties, and found that only four of 12 doctor-diagnosed Lyme patients — or 33% — reported having the rash.

“I never had a rash, never saw the tick,” said Laurie Sweeney, 50, of LaGrange, a nurse hospitalized a year ago with a cerebral spinal fluid leak and intense head pain. Negative on the two-tier test, Sweeney sought new tests and came up positive for two tick-borne co-infections. She only tested positive for Lyme after using a California laboratory that includes alternative markers on the second-tier test.

Many people who believe they have suffered past or chronic Lyme disease, both locally and in a dozen states, told the Poughkeepsie Journal of torturous roads to diagnosis, littered by lab tests that were falsely negative or just shy of the CDC’s threshold of positive. Many said diagnosis delays allowed the disease to progress unchecked, the chief fear of test critics.
“I was misdiagnosed for four years as a child,” said Nicole Conti-Harris, 26, of East Fishkill, who was tested for ailments such as lupus and mononucleosis in the face of negative Lyme tests. Just 9 when she became ill, she lost a half year of school and was carried off a soccer field in fourth grade after collapsing. She now has a chronic case of Lyme disease — also diagnosed by an alternative laboratory — with painful periodic relapses, she said.

The accepted medical wisdom is that a few weeks of antibiotics kills the Lyme spirochete and negative tests indicate something else. “Lyme disease tests typically become positive within several weeks after onset of infection. If you’re sick six months or six years and you don’t have a positive test,” said Dr. Gary Wormser, a prominent Lyme researcher at New York Medical College in Westchester County, “those symptoms are not due to Lyme disease.”

Over-diagnosis of Lyme disease is clearly a CDC concern, in particular since a 1993 study found that 43 percent of diagnosed patients did not have it — a figure critics dispute as a reflection of poor tests and other factors. The CDC website page for Lyme testing cautions doctors that positive results are likely wrong if a patient “has not been in an area where Lyme disease is common” or has atypical symptoms — an indicator, perhaps, of the test’s imprecision. The web page expresses no concern for false negatives — namely failing to diagnose someone who does have the disease.

Many Lyme physicians believe the emphasis is misplaced. In a 2011 letter to the CDC, Dr. Kenneth B. Liegner, a Pawling physician who treats late-stage Lyme, said the tests guarantee “frequent false negative results, consigning patients to needless suffering.”

Bar set high

As it stands, the two-tier Lyme test finds that more than half the people who do have early Lyme disease test negative; that means it’s incorrect in more than 1 out of 2 cases. But it is wrong the opposite way — diagnosing people as positive when they aren’t — in just 1 out of 100 cases.

That’s because the bar is set high to test positive on the first screening test; if the false positive rate went up just 1 percentage point, to 2 in 100, the test would yield 27,000 false positives among 2.7 million Lyme tests performed annually, according to the 2005 Microbiology Reviews article. That year, 23,000 Lyme cases were reported nationwide.

But the high screening threshold invariably means some people with Lyme will not be diagnosed. As a 2008 study of testing in a journal called Clinical Infectious Diseases acknowledged: “A higher cutoff value” that avoids falsely diagnosing Lyme comes “at the expense of sensitivity” — namely not diagnosing it.
“The test is inherently bad,” said Dr. Raphael Stricker, vice president of the International Lyme & Associated Diseases Society, a group of Lyme physicians and advocates. “If you have a sick patient in front of you, you want something sensitive enough to make a diagnosis.”

Indeed, when the regimen was adopted in 1994 at a conference in Dearborn, Mich., judgments were made on the line between positive and negative. New York State health officials even wrote to the CDC in 1996 to say that the guidelines effectively eliminated 31 percent of the state’s 1995 reported cases. These were 1,237 people who had been diagnosed with Lyme disease.

The CDC’s Lyme definition — aligned closely to the rash and the test — was intended as a way to count the surest cases and hence monitor progression of the disease. Instead, it has become, said Lorraine Johnson, CEO of Lymedisease.org, an advocacy group, “a de facto diagnostic standard. ... Patients who do not meet the narrow surveillance definition of Lyme disease are not diagnosed or treated.”

Many Lyme physicians say the guidelines are flawed because they exclude late-stage patients who register abnormal on highly specific indicators of the Lyme bacteria — but often just short of the 5 of 10 markers, or bands, needed on the second tier test. Some patients will always test negative, they believe, because their immune systems are beaten down by illness, they have other tick-borne infections or are being treated with immune-suppressing medications.

Martin Eisenhardt, a Greene County resident, suffered through unrelenting headaches, low-grade fever and progressive neurologic decline that left him, in later years, in little more than a vegetative state. In seven years, Eisenhardt never tested positive for Lyme disease though his wife, Mary Lou, had long suspected it. Her husband was an active outdoorsman in a Lyme-prone area and had had a groin rash.

After Eisenhardt’s death at 68 in 1993, autopsy tissue tests found what his wife had suspected: evidence of the Lyme spirochete was spread widely throughout his central nervous system. His case and three others were reported in a 1997 article in the Journal of Spirochetal and Tick-Borne Diseases by Dr. Liegner, the Pawling physician.

Eisenhardt’s wife, 75, said many doctors, until Liegner, refused treatment, a common complaint among advanced Lyme patients. “The attitude of how I was treated amazed me,” she said. “They just didn’t want to know about it.”

Testing accuracy

A recent study by Tulane University researchers found support for the notion of repeated, and incorrect, negative tests. Seven of 12 intentionally infected and untreated monkeys – 60 percent — tested negative in late stages of Lyme as the spirochete itself changed and evaded detection.
Several studies, mostly in Europe, have also found evidence of so-called “seronegativity” — negative tests on positive subjects — while a 2001 study of chronic Lyme disease tested antibiotics on a group that some scientists say does not exist: 25 Lyme patients who did not test positive.

Fallon, the Columbia University researcher and physician, said he sees patients who test negative on the two-tier test but positive on tests of spinal fluid. His particular worry is for neurologic cases; one 1999 study of patients with Lyme encephalopathy, or brain impairment, found tests incorrect for 3 of 18 patients who had the infection. “That’s a concern,” he said. Similarly, the 2008 study showed an 87 percent accuracy in such cases.

“If it’s 87 percent, that’s 13 percent missed,” said Dr. Maloney, noting these are people who may go on to develop problems of balance, thinking and bodily control. “The consequences can be quite profound.”

Critics like Maloney say the late disease studies rely on a curious and questionable paradox: To study the accuracy of the test, researchers only test patients who have already tested positive, which Dr. Stricker calls “ridiculous circular logic.”

Agreed Fallon: “If the test development is based on patients previously diagnosed in a way that required seroposivity” — namely positive tests — “that would be a significant flaw as a result of circular reasoning.”

The 2003 study, which appeared in the Journal of Infectious Diseases, acknowledged this quandary, saying, “the possibility of selection bias… cannot be discounted.” So did the 2008 study in the journal Clinical Infectious Diseases: “It is problematic to determine the frequency” of positive tests in later stage cases, because a positive test is “a part of the case definition.” That study rejected 75 “possible Lyme disease” patients who “did not meet clinical criteria,” including some with other illnesses.

Lyme physicians say other tick-borne infections, common with Lyme disease, likely reduce test accuracy.

Additionally, researchers test the test in high-quality research labs that employ different methods and tools from standard labs. The 2008 study that the CDC points to used “noncommercial, in-house tests” for the first portion of the test not available to standard labs. At least three studies, including two in Europe, found wide variation in results among Lyme-test laboratories; Jill Auerbach of the Town of LaGrange told of having the same blood sample tested by two university laboratories, each time coming up with different sets of markers that only when combined signaled a positive result.
“(T)he inconsistencies of the test results between different laboratories and even in the same laboratory are so frequent,” Dr. Katz, the Connecticut neurologist, testified, “that it is difficult to trust their reports.”

Johnson, the CDC official, has acknowledged in public presentations that the test is “complex, technically demanding (and) … difficult to interpret.” Reading it “requires judgment and experience,” she told a 2006 conference in Canada. In response to Journal questions about her statements, Johnson said that, since 2006, “substantial progress in addressing the limitations” of the test has been made.

Beyond this, at least 25 strains of the Lyme bacteria have been identified in the U.S. so far, while the test is based on just one strain. Said Alan Barbour, a widely published microbiologist at the University of California at Irvine, “I think we may be missing some because the strain that someone was infected with is different enough from the one that’s in the test.” CDC’s Johnson does not believe is a problem because the strain tested is the only one “demonstrated to cause Lyme disease in North America,” she said.

Many Lyme physicians believe the test has been oversold as the ultimate arbiter of a Lyme diagnosis. Yet even ardent supporters, like Jorge Benach, chairman of microbiology at SUNY Stony Brook, urge caution. A doctor who relies solely on the test “is doing a huge disservice to his patients,” he said, and should instead use judgment in close Lyme calls — something test critics say many are unwilling to do.

Kimberly Collins, 50, of Shokan, Ulster County, had the rash in 2008 and was treated with antibiotics. The test failed her then, as is common, and it failed her a year later when she suffered brain lesions, trouble walking and swollen joints. Some would say antibiotics blunted the second test; others that the spirochete survived the antibiotics.

Dr. Eva Sapi, a University of New Haven researcher who is working on a new diagnostic method, said the disagreement could be settled, “the minute we have a better test.”