A guide to tick-borne diseases

Quest Diagnostics®

What you need to know about tick-borne disease

Robert S. Jones, DO, MS, FIDSA, Medical Director, Infectious Diseases, Quest Diagnostics

Tick-borne diseases have become a growing problem in the US, increasing in prevalence and expanding in geographic range.[1] Approximately 30,000 to 35,000 cases of Lyme disease—the most common tick-borne illness—are reported each year.[2] Recent estimates suggest the number of Americans diagnosed and treated for Lyme disease are as high as 476,000.[2] This high number is likely an overestimation of actual infections due to patients being treated presumptively in medical practice.

The incidence of Lyme disease is on the rise, with a 320% increase in the number of northeastern US counties having a high incidence of the disease.[3]

In addition to Lyme disease, depending on where your practice is located, you may also see the following tick-borne illnesses:

- Rickettsial diseases, including Rocky Mountain spotted fever, anaplasmosis, and ehrlichiosis
- Non-rickettsial diseases, including Colorado tick fever, Q fever, tularemia, and babesiosis

Many tick-borne illnesses can have similar signs and symptoms, including skin rash, fever, and chills, presenting a diagnostic challenge. In the United States, the most frequent *Ixodes*-borne pathogens are *B burgdorferi* sensu stricto, *B microti* and *A phagocytophilum*, the causative agent of human granulocytic anaplasmosis (HGA).[4] Coinfections with various combinations of 2 or 3 of these pathogens have been described. Up to a fifth of Lyme disease patients experience concurrent babesiosis and approximately a tenth experience concurrent HGA or hard tick-relapsing fever (caused by *B miyamotoi*).[4] The incidence of coinfections that involve the *Ehrlichia muris*-like agent or deer tick virus (Powassan virus type II) is difficult to assess because case reports have been few.

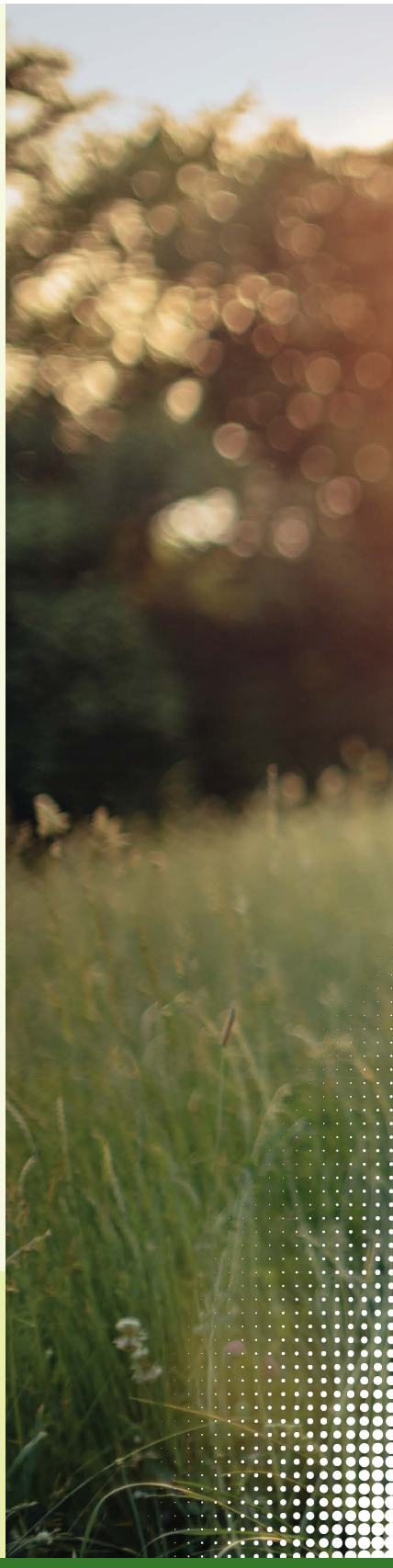
If left untreated, tick-borne infections can spread through the body, affecting the joints, heart, and central nervous system and requiring more intensive treatment. With the potential for overlapping symptoms and coinfection, identifying the right causative agent is essential to initiate effective treatment.

To help you gain a better understanding of tick-borne illnesses, we have authored a series of articles that provide important insights into: when to test and what tick-borne illnesses to test for; the importance of balancing an early diagnosis with appropriate test timing; the role of testing and test methodology in confirming a diagnosis; and a primer on Lyme disease, including helpful resources on tick-borne illnesses for healthcare professionals to share with patients.

I hope these articles help inform your understanding of the evolving nature of tick-borne illnesses and what to look for to make a timely, differential diagnosis for your patients.

References
1. CDC. Overview of tickborne diseases. Reviewed August 5, 2022. Accessed March 22, 2023. https://www.cdc.gov/ticks/tickbornediseases/overview.html
2. CDC. Data and surveillance: Lyme disease. Updated August 29, 2022. Accessed March 22, 2023. https://www.cdc.gov/lyme/datasurveillance/index.html
3. Kugeler KJ, Farley GM, Forrester JD, et al. Geographic distribution and expansion of human Lyme disease, United States. *Emerg Infect Dis*. 2015;21(8):1455-1457. doi:10.3201/eid2108.141878
4. Diuk-Wasser MA, Vannier E, Krause PJ. Coinfection by the tick-borne pathogens Babesia microti and Borrelia burgdorferi: ecological, epidemiological and clinical consequences. *Trends Parasitol*. 2016;32(1):30-42. doi:10.1016/j.pt.2015.09.008

Table of contents



Note:

This information is provided for informational purposes only and is not intended as medical advice. A physician’s test selection and interpretation, diagnosis, and patient management decisions should be based on their education, clinical expertise, and assessment of the patient.

A primer on Lyme disease

Robert S. Jones, DO, MS, FIDSA, Medical Director, Infectious Diseases, Quest Diagnostics

Lyme disease is the most common vector-borne infectious disease in the United States.[1] In most cases, treatment is straightforward and recovery is complete. Accurate, timely diagnosis is the key to effective treatment.

What Lyme Disease is

Lyme disease is due to an infection with the bacterium *Borrelia burgdorferi,* which is transmitted through the bite of an infected tick. Lyme disease can cause skin rash, joint pain, fever, and other symptoms. Untreated Lyme disease may lead to serious neurologic or cardiac symptoms.

Lyme disease is carried by the black-legged tick, *Ixodes scapularis*, also called the deer tick, in the East and upper Midwest. The western black-legged tick, *Ixodes pacificus*, carries the disease on the Pacific coast. Cases of Lyme disease are much rarer in the West than in the East and Upper Midwest.

Who gets Lyme disease

According to the CDC, approximately 30,000-35,000 cases of Lyme disease are reported every year in the United States.[2]

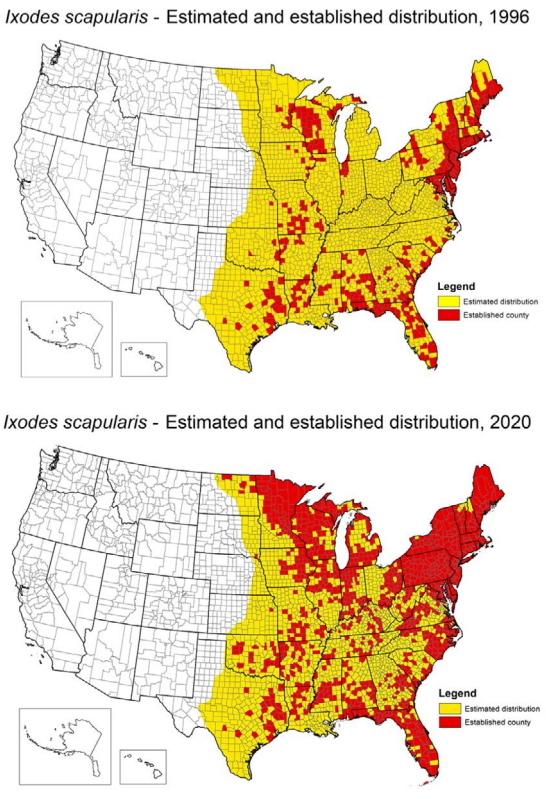


Fig. 1. Distribution of the *Ixodes scapularis* tick has tripled and expanded in geography since the late 1990s.[3]

The states with the highest incidence are in the Northeast, mid-Atlantic, and upper Midwest, but over the last few decades, the range of the tick that transmits Lyme disease has been expanding.[4] A number of factors may be contributing to the geographic expansion of Lyme disease, including: changes in land use patterns, including reforestation in the Northeast; suburban development; and changing climate patterns.[4]

Cases diagnosed in other states may be due to infected ticks in those states, or to individuals who were bitten in a state where the disease is endemic but who were diagnosed in another state.

Children between the ages of 5 and 9, especially boys, have the highest incidence of Lyme disease,[1] but it occurs in people of all ages.

How Lyme disease is contracted

Ticks live in wooded areas and grassy areas near woods. They wait for a host at the tips of low vegetation or grass and attach to a host when it passes by. They do not jump. The most common tick hosts are humans, white-tailed deer, field mice and other small mammals, and a variety of birds. The peak months for infection are May through August, but tick bites and infection can occur during any month of the year, including in winter.

While ticks can attach anywhere on the human body, they prefer certain areas more than others, especially the groin, beltline, armpits, and scalp. A tick that attaches to the skin will cause irritation or itching, but this may not be enough to lead to its discovery and removal. A tick usually must be attached for 36 to 48 hours to transmit the infection. During this time, it feeds on blood and will become engorged and swollen.

The tick develops and grows from larva to nymph to adult stages, and can bite and infect at any stage. The majority of human infections are due to nymphs, which are about the size of a poppy seed.

Dog ticks (*Dermacentor variabilis*) do not spread Lyme disease. Dog ticks are larger than deer ticks, and have a characteristic white oval or a white pattern on their backs.

Symptoms of Lyme disease

Early symptoms

Erythema migrans rash: The earliest symptom of Lyme disease in most cases is a rash that develops from 3 to 30 days after the bite. The rash of Lyme disease is first seen at the site of the bite, and typically grows over time. It may clear in the center, leading to the classic "bulls-eye" rash that was once thought to be necessary for a Lyme disease

home → Does every patient with a tick bite need a test for Lyme disease? →

diagnosis. The rash occurs in 70% to 80% of patients with Lyme disease,[5] meaning many patients may not present with a rash despite being infected.[5]

Other symptoms: Fever, chills, aches, swollen lymph nodes.

Later symptoms

Arthritis: Known as Lyme arthritis, this occurs when bacteria enter joint tissue and cause inflammation. Lyme arthritis is reported in approximately 1 out of every 4 Lyme disease cases reported to the CDC.[6] It can be quite painful, and may particularly affect the knees.

Bell palsy: Facial palsy occurs in about 8% of patients.[7]

Other signs and clinical manifestations: multiple secondary annular rashes; flu-like symptoms; lymphadenopathy; migratory pain in tendons, bursae, muscle, and bones; lymphocytic meningitis; radiculoneuropahy.[5]

Diagnosis of Lyme disease

The diagnosis of Lyme disease is based on the presence of the signs and symptoms of the disease and exposure to infected ticks. The patient may not have any awareness of having been bitten.

When a patient presents with the classic erythema migrans rash and has had exposure to infected ticks, treatment may be given without additional testing. In less definitive cases, 2-stage laboratory testing may be appropriate.

The role of testing

Laboratory tests can be used to confirm a diagnosis of Lyme disease when the signs and symptoms are not definitive but there is suspicion of infection.

The CDC recommends a 2-step testing process for the serological diagnosis of Lyme disease. The **standard two-tier test (STTT)** includes an enzyme immunoassay (IFA) that detects antibodies against the *B burgdorferi* bacterium, followed by a second immunoblot used for confirmation.[8]

A modified two-tier test (MTTT) is part of an updated recommendation from the CDC for earlier detection and diagnosis of the disease. MTTT utilizes immunoassays rather than immunoblots in the second tier of the algorithm. During early-stage Lyme disease (first 30 days of infection), the MTTT has been shown to have improved sensitivity and detect more cases of Lyme disease compared to STTT.[9,10]

Treatment of Lyme disease[a]

Treatment depends on the stage of disease. Patients with early, or localized, Lyme disease (symptoms of rash, flu-like illness, and swollen lymph nodes) should receive 10-14 days of oral antibiotics.[5] For patients who have symptoms of pain, fatigue, or difficulty thinking that lasts for more than 6 months after they finish treatment, this condition is known as post-treatment Lyme disease syndrome (PTLDS).[11] Patients should consult their healthcare provider to discuss additional options for managing symptoms.[11]

[a] The treating healthcare professional should refer to the manufacturer's approved labeling for prescribing, warnings, side effects, and other important information. This information is provided for informational purposes only and is not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on their education, clinical expertise, and assessment of the patient.

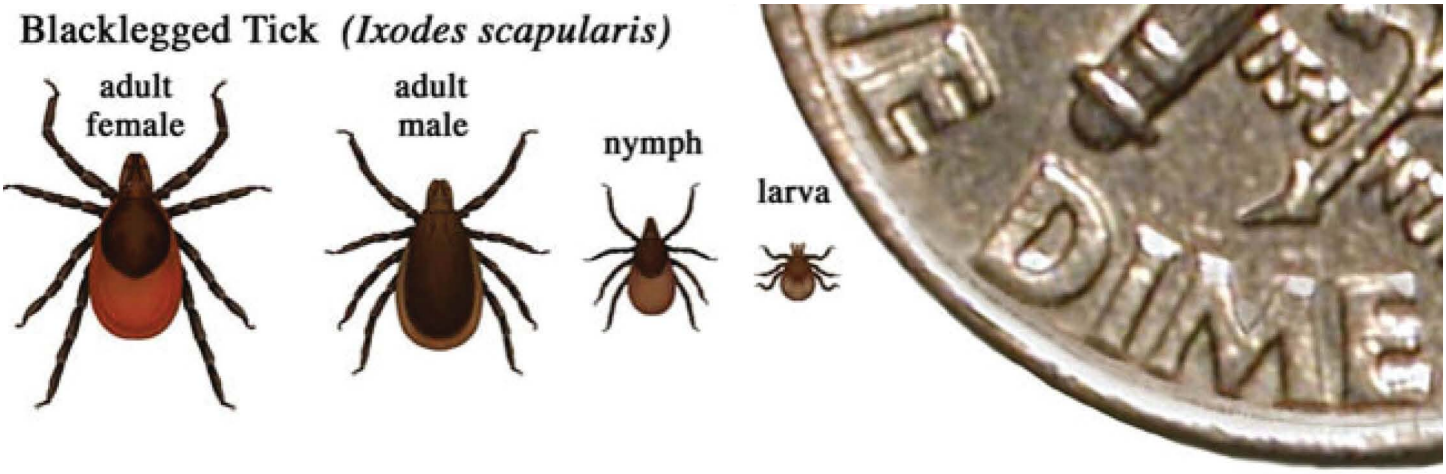


Fig. 2. In general, adult ticks are approximately the size of a sesame seed and nymphal ticks are approximately the size of a poppy seed.[12]

home
Does every patient with a tick bite need a test for Lyme disease?

References
1. Kugeler KJ, Mead PS, Schwartz AM, et al. Changing trends in age and sex distributions of Lyme disease-United States, 1992-2016. Public Health Rep. 2022;137(4):656-659. doi:10.1177/00333549211026777
2. CDC. Data and surveillance: Lyme disease. Updated August 29, 2022. Accessed March 22, 2023. https://www.cdc.gov/lyme/datasurveillance/index.html
3. CDC Tickborne disease geographic distribution. Reviewed August 11, 2022. Accessed March 29, 2023. https://www.cdc.gov/ticks/data-summary/geographic-distribution.html
4. CDC. Understanding Lyme and other tickborne diseases. Updated May 11, 2022. Accessed March 24, 2023. https://www.cdc.gov/ncezid/dvbd/media/lyme-tickborne-diseases-increasing.html
5. CDC. Lyme disease. Updated August 5, 2022. Accessed March 22, 2023. https://www.cdc.gov/ticks/tickbornediseases/lyme.html
6. CDC. Lyme arthritis. Updated October 7, 2021. Accessed March 22, 2023. https://www.cdc.gov/lyme/treatment/LymeArthritis.html
7. Huston, P. Canada communicable disease report highlights: new-onset Bell palsy and Lyme disease. *Can Fam Physician*. 2017;63(12):941. https://www.cfp.ca/content/63/12/941.long
8. Association of Public Health Laboratories. Suggested reporting language, interpretation and guidance regarding Lyme disease serologic test results. May 2021. Accessed March 22, 2023. https://www.aphl.org/aboutAPHL/publications/Documents/ID-2021-Lyme-Disease-Serologic-Testing-Reporting.pdf
9. Mead P, Petersen J, Hinckley A. Updated CDC recommendation for serologic diagnosis of Lyme disease. *MMWR Morb Mortal Wkly Rep*. 2019;68(32):703. doi:10.15585/mmwr.mm6832a4
10. Zeus ELISA Borrelia VlsE1/pepC10 IgG/IgM Test System. Package insert. Zeus Scientific Inc; 2019.
11. CDC. Post-treatment Lyme disease syndrome. Updated January 10, 2022. Accessed March 22, 2023. https://www.cdc.gov/lyme/postlds/index.html
12. CDC. Lyme disease transmission. Updated January 20, 2023. Accessed March 22, 2023. https://www.cdc.gov/lyme/transmission/index.html

home

Does every patient with a tick bite need a test for Lyme disease?

Does every patient with a tick bite need a test for Lyme disease?

Annual cases of Lyme disease reported to the CDC are approximately 30,000-35,000, all beginning with the bite of an infected tick.[1] But does every patient with a tick bite need a Lyme disease test? No, according to Robert Jones, DO, Medical Director for Infectious Diseases at Quest Diagnostics. Important considerations include tick identification, geography, symptoms and signs, and duration of tick attachment.

Lyme disease is caused by infection with *Borrelia burgdorferi*, carried by the deer tick. If the patient has removed the tick and is still in possession of it, the first question should be whether it is a deer tick (*Ixodes scapularis*) or a dog tick (*Dermacentor variabilis*). Deer ticks have a brown body with no white markings. Nymphs (juvenile deer ticks) are about the size of a pin head or poppy seed, while adults are 3-5 millimeters long. Dog ticks are larger than deer ticks, and have distinctive white markings on their backs. Dog ticks don't carry Lyme disease.

Often, though, the patient will not have the tick and may not even remember being bitten. When that's the case, the next consideration is geography, Dr Jones says. "Knowing the geography of the disease is helpful to determine whether your patient warrants testing. Lyme disease is an endemic disease. It is much more likely to be acquired in some areas than in others." Those living in the Northeast and Upper Midwest are most at risk, while those in the Mountain States and the Southwest are least at risk.

It is certainly possible to have Lyme disease in a state where it is not endemic, Dr Jones adds, but this is most often because it was acquired through travel to a state with a high infestation. If your patient is outside of the endemic zone and has not recently traveled there, another diagnosis may be more likely.

The duration of tick attachment is also an important consideration, he added. "In most cases a tick that carries Lyme disease needs to be attached for 36 to 48 hours before transmitting the disease. The *Borrelia* bacterium lives in the tick midgut, so the tick has to be attached, taking a blood meal, and the bacterium must migrate up to the salivary glands, and then enter the host. That takes time. If the tick is removed within 24 hours, some would say even longer, the risk of developing Lyme disease is little to none."

The next consideration is symptoms and signs. The most characteristic sign of Lyme disease is the rash. The Lyme rash is at least 4 centimeters in diameter, Dr Jones says, and may get larger. "It shouldn't be confused with a small area of redness at the tick bite site." The rash most commonly appears at the site of the bite, but may appear elsewhere. It may have a bulls-eye appearance, with resolution in the center surrounded by an area of redness. "The bulls-eye rash is diagnostic by itself," he says.

However, Dr Jones notes, up to 30% of patients infected with *Borrelia* never get a rash.[2] Infection occurs most commonly during the warm months when ticks are most active. Patients typically present with flu-like symptoms, including fatigue, headache, and low-grade fever, along with joint pain, especially asymmetric knee pain with effusion. Infection is more likely in those who spend more time outdoors, whether gardening, golfing, hunting, or just in the backyard.

"If you suspect it may be Lyme disease, but it's not quite clear that that's what it is, that's the time to get a Lyme disease test," Dr Jones says. Since there are other diseases also carried by the deer tick, which may be transmitted along with or instead of Lyme disease, it may be valuable to order these tests at the same time.

References
1. CDC. Tickborne disease surveillance data summary. Updated August 11, 2022. Accessed March 22, 2023. https://www.cdc.gov/ticks/data-summary/index.html
2. CDC. Lyme disease. Updated August 5, 2022. Accessed March 22, 2023. https://www.cdc.gov/ticks/tickbornediseases/lyme.html

Modified two-tier testing (MTTT) can identify early Lyme disease in the first 30 days

Tick-borne disease is a growing problem across the country: According to the CDC, approximately 30,000 to 35,000 cases of Lyme disease are reported each year.[1] Recent estimates suggest the number of Americans diagnosed and treated for Lyme disease is as high as 476,000.[1] This high number is likely an overestimation of actual infections due to patients being treated presumptively in medical practice.

While some patients show symptoms such as fever, rash, body aches, fatigue, headache, and chills, others may have a delay or absence of symptoms. In addition, coinfection with multiple tick-borne diseases is common, making timely selection of the appropriate test critical to proper treatment.

Diagnosing Lyme disease earlier is possible through an updated recommendation from the CDC for modified two-tier testing (MTTT),[2] which utilizes immunoassays rather than immunoblots in the second tier of the algorithm. The Quest MTTT may be able to identify Lyme disease within the first 30 days of infection.[2]

The MTTT follows a 2-step process:

1. Test serum in an immunoassay measuring combined IgG and IgM antibodies to specific borrelial proteins
2. Verify the results using a separate IgG and IgM immunoassay in place of a Western blot (immunoblot)

The CDC indicates clinicians and laboratories should consider serologic assays that utilize a second EIA in place of Western immunoblot assay as acceptable alternatives for serologic Lyme disease diagnosis,[2] and research studies have determined that MTTT is more sensitive than the standard two-tier test (STTT) in the early stages of the disease.[3,4]

For more information, visit Quest Diagnostics.

References

1. CDC. Data and surveillance: Lyme disease. Updated August 29, 2022. Accessed March 22, 2023. https://www.cdc.gov/lyme/datasurveillance/index.html
2. Mead P, Petersen J, Hinckley A. Updated CDC recommendation for serologic diagnosis of Lyme disease. *MMWR Morb Mortal Wkly Rep*. 2019;68(32):703. doi:10.15585/mmwr.mm6832a4
3. Porwancher RB, Hagerty CG, Fan J, et al. Multiplex immunoassay for Lyme disease using VlsE1-IgG and pepC10-IgM antibodies: improving test performance through bioinformatics. *Clin Vaccine Immunol*. 2011;18(5):851-859. doi:10.1128/CVI.00409-10
4. Branda JA, Linskey K, Kim YA, et al. Two-tiered antibody testing for Lyme disease with use of 2 enzyme immunoassays, a whole-cell sonicate enzyme immunoassay followed by a VlsE C6 peptide enzyme immunoassay. *Clin Infect Dis*. 2011;53(6):541-547. doi:10.1093/cid/cir464

← Does every patient with a tick bite need a test for Lyme disease? | home | If the Lyme disease test is negative, what then? →

If the Lyme disease test is negative, what then?

When the test for Lyme disease comes back negative, but your patient is still suffering, what might be the correct diagnosis? And if the result is positive, but treatment doesn't provide complete resolution, what else could they be infected with? These are among the challenges facing the physician with a patient with suspected Lyme disease.

Testing too soon can lead to negative test results

As with every diagnosis, the diagnosis of Lyme disease begins with a careful history. Patients with exposure to geographic areas where the deer tick is endemic, who present with symptoms consistent with Lyme disease, but don't recall a tick bite, may benefit from testing. But timing is crucial for a valid result. If the test is negative, one reason may be that the sample was taken too early. A patient who is infected by *Borrelia burgdorferi*, the bacterium that causes Lyme disease, may develop symptoms within days, but may not develop sufficient levels of antibodies to give unequivocal results on the screening test for several weeks. Samples taken before that may give a false negative, and may need to be repeated after 30 days unless an alternative diagnosis is determined. "It is important not to rush to take a sample in a newly infected patient," says Robert Jones, DO, Medical Director for Infectious Diseases at Quest Diagnostics.

A negative Lyme test, or an inadequate response to treatment, doesn't mean no tick-borne disease

A patient tested after the appropriate amount of time, who nonetheless receives a negative test result for Lyme disease, may be infected with another tick-borne organism. Similarly, when a patient tests positive but doesn't respond completely to antibiotic treatment, coinfection may be the cause.

← Modified two-tier testing (MTTT) can identify early Lyme disease in the first 30 days | home | → | Are longer-term antibiotics more effective than shorter-term treatment for Lyme disease? →

The deer tick may carry other pathogens in addition to *Borrelia*, which cause their own diseases. These include:

Anaplasmosis

Anaplasma phagocytophilum is a bacterium that causes flu-like symptoms without a rash, in most cases. According to the Centers for Disease Control and Prevention (CDC), treatment is most effective if it begins early, before lab testing can confirm the infection. Doxycycline, also effective against Lyme disease, is the recommended antibiotic treatment for anaplasmosis in adults and children.[1,a]

Babesiosis

Babesia microti is a protozoan parasite that infects red blood cells, causing flu-like symptoms and hemolytic anemia. Infected patients may be asymptomatic. Those most likely to be affected are the elderly, the immunocompromised, those with serious comorbidities, or those without a spleen.

Other ticks also carry diseases that may mimic Lyme disease in its early stages, and thus must be considered in the differential diagnosis before definitive testing is possible. These include:

Ehrlichiosis

Ehrlichia species are bacteria that cause flu-like symptoms with or without a rash. The bacterium is transmitted by the lone star tick (*Amblyomma americanum*). Early treatment can reduce the risk of developing severe illness.

Rocky Mountain spotted fever

This disease, due to infection by *Rickettsia* species, causes flu-like symptoms and, in most patients, a characteristic rash. It is transmitted by the American dog tick (*Dermacentor variabilis*), the Mountain wood tick (*Dermacentor andersoni*), and the brown dog tick (*Rhipicephalus sanguineus*). Unlike the rash in Lyme disease, the rash in Rocky Mountain spotted fever is an area of distinct spots or splotches, which develop several days after fever. Again, doxycycline is the treatment of choice, according to the CDC.[2,a] Cases occur throughout the United States, but are most common in states in the eastern and middle sections of the country, from Virginia to Kansas and from Mississippi to Illinois.[3] Despite the name, the incidence is relatively low in the Mountain states.

"Because of the possibility of coinfection or disease due to another tick-borne pathogen, most physicians won't just order the Lyme disease test," Dr Jones says. "Depending on the patient's geography of exposure, they will often order tests for other tick-borne diseases as well, to consider in the differential diagnosis." The Quest Diagnostics Tick-borne disease, Acute Molecular Panel combines testing for *Anaplasma, Babesia, Borrelia,* and *Ehrlichia*. A separate *Rickettsial Disease Panel* is also available.

[a] The treating healthcare professional should refer to the manufacturer's approved labeling for prescribing, warnings, side effects and other important information. This information is provided for informational purposes only and is not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on their education, clinical expertise, and assessment of the patient.

References
1. CDC. Anaplasmosis- treatment. Updated January 11, 2019. Accessed March 22, 2023. https://www.cdc.gov/anaplasmosis/treatment/index.html
2. CDC. Rocky mountain spotted fever- treatment. Updated October 26, 2018. Accessed March 22, 2023. https://www.cdc.gov/rmsf/treatment/index.html
3. CDC. Rocky mountain spotted fever- epidemiology and statistics. Updated August 15, 2022. Accessed March 22, 2023. https://www.cdc.gov/rmsf/stats/index.html

Are longer-term antibiotics more effective than shorter-term treatment for Lyme disease?

Most patients who have been infected with the Lyme disease bacterium, *Borrelia burgdorferi*, recover quickly after a short course of oral antibiotics. For some patients, symptoms may persist for months or even longer. This has led to the question of whether such patients have "chronic Lyme disease," a posited persistent infection despite standard antibiotic treatment, and the related question of whether longer-term antibiotic therapy can improve symptoms in such patients.

Recently, a major double-blind trial of long-term antibiotics was reported in the *New England Journal of Medicine*, showing an absence of benefit compared to placebo.[1] The same researchers published a related study looking at the cost-effectiveness of such treatment, finding that a short course of antibiotics was as cost-effective as a longer course.[2]

Randomized trial of longer-term therapy for symptoms attributed to Lyme disease[1]

Berende et al enrolled 281 patients in the Persistent Lyme Empiric Antibiotic Study Europe (PLEASE) study. Eligible patients had persistent symptoms related to a prior Lyme disease diagnosis, confirmed either by the presence of a rash, a tick bite in a Lyme-endemic area, or a positive IgM or IgG test. Patients received 2 weeks of open-label intravenous ceftriaxone, and were then randomized to 1 of 3 treatment arms: 12 weeks oral doxycycline, 12 weeks oral clarithromycin-hydroxychloroquine, or 12 weeks placebo. Adherence was verified by pill counts and electronic monitoring of pill bottle opening.

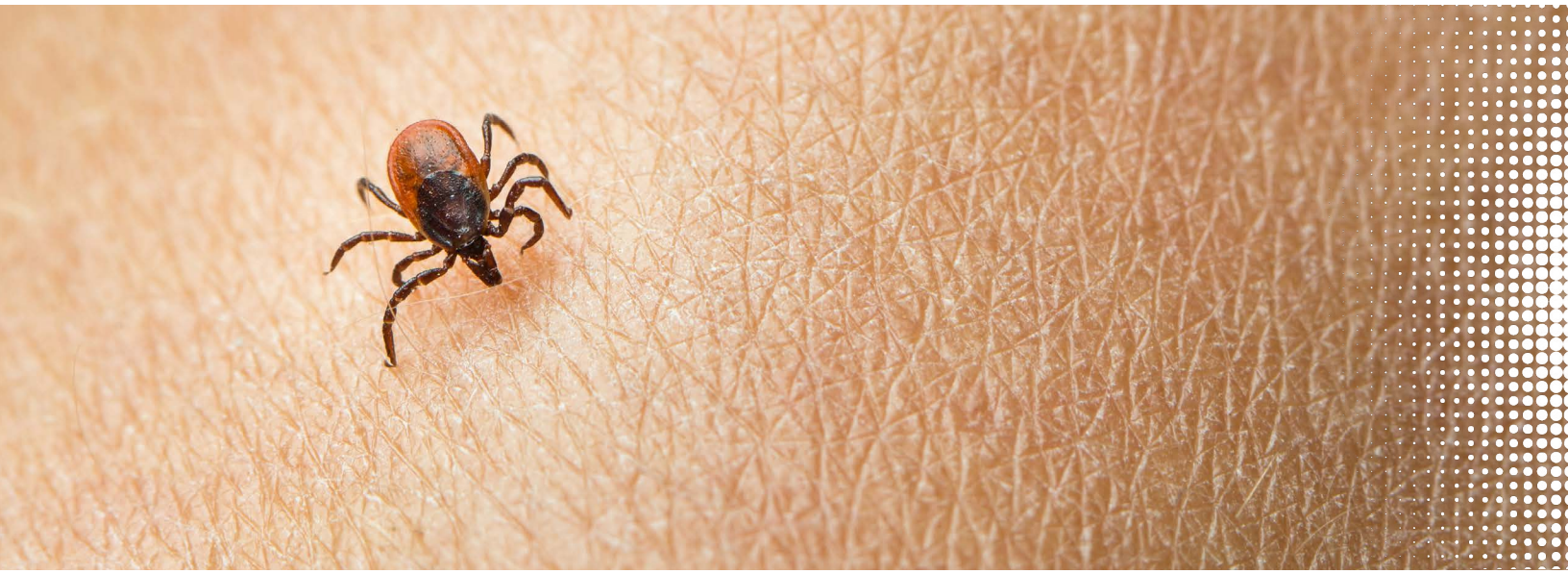
The authors explained the decision to include a short course of open-label ceftriaxone, rather than a placebo-only arm, was made on ethical grounds, "because it was judged to be unethical to withhold treatment from patients who might have an infection at baseline that had not yet been treated."

Patients in the study were about half female, were almost all White, had an average age of about 48 years, and had experienced symptoms for about 2.5 years. The most common symptoms, experienced by at least 70% of patients, included arthralgia, musculoskeletal pain, fatigue, sensory disturbances, and neurocognitive symptoms. Neuralgia was much less common, reported by less than 20% of patients.

About 90% of patients had received previous antibiotics, with a median of 2 courses, most for at least a month, with about 15% of patients receiving intravenous treatment.

The primary outcome measure of the study was health-related quality of life as measured by the physical component summary score on the SF-36 health survey. At baseline, the average patient score was about 31, and was well-balanced among the 3 treatment arms. This score is considered low, the authors pointed out, reflecting "the poor quality of life in these patients."

About 90% of patients in each group completed the 12 weeks of treatment, with no differences among groups for adherence. While all groups improved significantly on the SF-36, there was no difference in the magnitude of improvement among the three arms (P= .69) either after 12 weeks of therapy, or over the course of an additional



40 weeks of follow-up. Fatigue severity, a secondary outcome, was also not different among the groups.

Treatment-related adverse events were common on open-label ceftriaxone, reported by 45% of patients. Treatment-related adverse events during the oral therapy phase were reported by 49% of those on doxycycline, 44% of those on clarithromycin-hydroxychloroquine, and 35% of those on placebo.

"In this randomized, double-blind trial involving patients with persistent symptoms attributed to Lyme disease, prolonged antibiotic treatment (ceftriaxone followed by 12 weeks of either doxycycline or clarithromycin–hydroxychloroquine) did not lead to a better health-related quality of life than that with shorter-term treatment (ceftriaxone followed by placebo)," the authors concluded.

As to whether treatment was long enough, they noted that while there are diseases for which long-term antibiotic therapy is the standard, "the purpose of prolonged therapy for such diseases is for the prevention of microbiologic relapse rather than for a delayed onset of clinical alleviation of signs or symptoms. We are not aware of any infectious disease in which the initial effect on signs, symptoms, and laboratory findings is delayed beyond the first 3 months of effective therapy."

Cost-effectiveness of longer-term versus shorter-term provision of antibiotics in patients with persistent symptoms attributed to Lyme disease[2]

The same group of researchers, again led by Berende, evaluated the cost-effectiveness of longer-term treatment with antibiotics in the PLEASE study. "Regardless of clinical effect, it is important to assess the economic impact of the comparative antibiotic strategies," they stated. "This is essential for policy makers, in order to prioritize and make complex decisions about healthcare interventions."

Outcome measures in this study were cost and quality-adjusted life-years (QALYs), as determined by the EQ-5D. The EQ-5D is a health status assessment tool that comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Patient-reported and -weighted scores are combined with time to generate QALYs. Costs included direct medical costs and productivity losses.

Average QALYs yielded during the 1-year follow-up was about 0.81 for all 3 treatment groups, with no significant differences among them (P= .96). Total costs were also not different among the groups, ranging from 12,000 to 15,000 Euros per patient for the year-long study. The authors note that the study drug contributed relatively little to the total costs.

"Because the PLEASE study did not show any additional clinical benefit of longer-term compared to shorter-term treatment on health-related quality of life, we did not expect to find any large differences in costs and cost-effectiveness as the oral antibiotic treatment is low-priced," they noted. However, "Costs of potential antibiotic resistance among both the patients' intestinal flora and the environment were not included in our evaluation. If these costs could have been taken into account, the longer-term treatment regimens likely would have been less favorable in terms of costs and cost-effectiveness compared to the shorter-term treatment. Considering the growing concern to antibiotic resistance because of unnecessary use, the shorter-term provision of antibiotics should be preferred."

References
1. Berende A, ter Hofstede HJM, Vos FJ, et al. Randomized trial of longer-term therapy for symptoms attributed to Lyme disease. *N Engl J Med*. 2016;374(13):1209-1220. doi:10.1056/NEJMoa1505425
2. Berende A, Nieuwenhuis L, ter Hofstede HJM, et al. Cost-effectiveness of longer-term versus shorter-term provision of antibiotics in patients with persistent symptoms attributed to Lyme disease. *PLoS One*. 2018;13(4):e0195260. doi:10.1371/journal.pone.0195260

Post-treatment Lyme disease

Post-treatment Lyme disease syndrome may occur, but is not "chronic Lyme disease"

Most patients who are diagnosed and treated for Lyme disease recover quickly without sequelae. Some patients, though, especially those who remained infected for long periods before treatment, may have symptoms that persist after the prescribed course of antibiotics is completed.

This is known as post-treatment Lyme disease syndrome (PTLDS), which should be distinguished from "chronic Lyme disease," according to Dr Robert Jones, Medical Director for Infectious Diseases at Quest Diagnostics. "Chronic Lyme disease" has been proposed to be a persistent infection after standard antibiotic therapy. "There is no evidence that chronic Lyme disease exists," Dr Jones says, and no evidence that prolonged use of antibiotics is better than placebo at relieving the symptoms of PTLDS.

According to the CDC, the term "chronic Lyme disease" (CLD) has been used to describe a wide variety of different conditions and can be confusing. Because of the confusion over how the term CLD is employed, experts do not support its use.[1]

Neither does prolonged treatment with antibiotics improve most symptoms in people with prolonged symptoms, according to multiple placebo-controlled trials, Dr Jones notes. In 2 randomized trials published in the *New England Journal of Medicine*, 1 for seropositive patients and 1 for seronegative patients, both with a documented history of Lyme disease, patients received a combination of intravenous and oral antibiotics for 90 days, or placebo.[2] There was no evidence for persistent infection at baseline in either group of patients, as measured by a variety of microbiological tests.[2]

Health-related quality of life was significantly impacted at baseline, similar to that caused by congestive heart failure or osteoarthritis, the authors noted.[2] But treatment did not produce an improvement versus placebo.[2] About equal numbers of patients receiving active treatment and receiving placebo treatment improved and worsened during the study, in both seropositive and seronegative patients, a result that the authors noted mimicked changes seen in placebo treatment of patients "with other rheumatologic diseases that do not appear to be related to persistent infection."[2]

"There is considerable impairment of health-related quality of life among patients with persistent symptoms despite previous antibiotic treatment for acute Lyme disease," the authors concluded.[2] "However, in these 2 trials, treatment with intravenous and oral antibiotics for 90 days did not improve symptoms more than placebo."[2]

Post-treatment Lyme disease syndrome

While CLD is not a recognized entity, PTLDS is, and it is one for which there are not good treatments, Dr Jones says. "The underlying causes of the syndrome have not been identified, and that has hindered development of therapies."

When a patient presents with persistent symptoms after a course of antibiotics for Lyme disease or another tick-borne illness, "You first want to make sure there is not another, untreated infection, such as babesiosis," he said. Other diagnoses, such as fibromyalgia or chronic fatigue syndrome, should also be considered. "A very thorough physical and history is important" to uncover clues. "Referral to a rheumatologist or an infectious disease specialist may also be in order to complete the evaluation."

It is also important to reassure the patient that a post-treatment syndrome is sometimes seen, that it does not mean they are going to get worse, and that further antibiotic treatment is not going to help and may cause harm. "It is important to help the patient understand that more antibiotics are not the answer."[a]

[a] The treating healthcare professional should refer to the manufacturer's approved labeling for prescribing, warnings, side effects and other important information. This information is provided for informational purposes only and is not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on their education, clinical expertise, and assessment of the patient.

References
1. CDC. Lyme disease frequently asked questions. Updated June 13, 2022. Accessed March 22, 2023. https://www.cdc.gov/lyme/faq/index.html
2. Klemper MS, Hu LT, Evans J, et al. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med*. 2001; 345(2):85-92. doi:10.1056/NEJM200107123450202

← Are longer-term antibiotics more effective than shorter-term treatment for Lyme disease? | home | Making sense of "chronic" Lyme disease diagnoses →

Making sense of "chronic" Lyme disease diagnoses

For most patients who contract Lyme disease, oral antibiotics will successfully treat the symptoms. However, some patients who get the infection caused by the bacterium *Borrelia burgdorferi* report lingering symptoms such as fatigue, pain, and joint and muscle aches long after the antibiotics are finished. Sometimes referred to as "chronic" Lyme disease (CLD), the Centers for Disease Control and Prevention (CDC) refers to the condition as post-treatment Lyme disease syndrome (PTLDS).[1]

The cause for PTLDS is not only unknown but the term "chronic" Lyme disease is mired in controversy. The National Institute of Allergy and Infectious Diseases reports that CLD "has been used to describe people with different illnesses. While the term is sometimes used to describe illness in patients with Lyme disease, it has also been used to describe symptoms in people who have no clinical or diagnostic evidence of a current or past infection with *B. burgdorferi*."[2]

A 2015 report published in the Infectious Disease Clinics of North America points out that "chronic" Lyme disease "has no clinical definition and is not characterized by any objective clinical findings."[3] In 7 studies conducted in areas where Lyme disease is common, 50% to 88% of 1,902 patients referred for suspected infection had no evidence of ever having contracted the disease.[3]

"Most of these patients had either alternative medical diagnoses or had medically unexplained symptoms, such as chronic fatigue syndrome or fibromyalgia," the study said.[3] "Lyme disease was in many cases diagnosed simply for lack of an alternative diagnosis—referred to in 1 paper as a 'diagnosis of Lyme disease by exclusion.'"[4]

Robert S. Jones, DO, MS, FIDSA
Medical Director, Infectious Diseases,
Quest Diagnostics

If it is possible that over half of patients suspected of PTLDS were never exposed,[3] then how do doctors evaluate patients who report symptoms of the disease? Quest Diagnostics Medical Director of Infectious Diseases Robert S. Jones, DO, MS, FIDSA, helps answer that question. He offered the following recommendations for doctors treating PTLDS patients.

Start from scratch

"PTLDS can be a frustrating disease," said Dr Jones. "The first thing I do is make sure I keep an open mind when patients come to me."

He mentioned the many factors that need to be considered when evaluating patients. These include the patient's health history, length of symptoms, type of symptoms, where they suspect they contracted Lyme disease, and the possibility of other tick-borne illnesses.

Patient history

Symptoms of Lyme disease may vary depending on the length of time the patient has been infected. While one of the most commonly known symptoms is a rash, Dr Jones recommends physicians consider the patient's health history.

A 2010 Clinics in Laboratory Medicine article went in depth about the possibility that symptoms may be related to other conditions and reiterated the need to examine all possibilities.[5] "The diagnosis of Lyme disease, especially in the absence of the characteristic rash, may be difficult, since the other clinical manifestations of Lyme disease are not specific. Even the diagnosis of erythema migrans sometimes may be difficult, since the rash initially may be confused with nummular eczema, granuloma annulare, an insect bite, ringworm, or cellulitis."[5]

Symptoms associated with PTLDS can be even more difficult to attribute. In the Lantos report referenced earlier, more than half of the patients who lacked evidence of Lyme disease "had alternative medical diagnoses or medically unexplained symptoms, such as chronic fatigue or fibromyalgia."[3]

Length of symptoms

Another critical factor when diagnosing PTLDS is to examine the length of time a patient has been experiencing symptoms. The medical community is well aware that some patients experience prolonged symptoms while being treated for Lyme disease. These symptoms can lead to a "subset of significant functional impairment" including joint and muscle pain, headache, fatigue, neck and back ache, irritability, and difficulty with memory and concentration.

The International Lyme and Associated Diseases Society recommends the following criteria in their proposed definition of post-Lyme disease syndromes[3]:

- An adult or child with a documented episode of early or late Lyme disease fulfilling the case definition of the Centers for Disease Control and Prevention. If based on erythema migrans, the diagnosis must be made and documented by an experienced healthcare practitioner
- After treatment of the episode of Lyme disease with a generally accepted treatment regimen, there is resolution or stabilization of the objective manifestation(s) of Lyme disease
- Onset of any of the following subjective symptoms within 6 months of the diagnosis of Lyme disease and persistence of continuous or relapsing symptoms for at least a 6-month period after completion of antibiotic therapy:
    - Fatigue
    - Widespread musculoskeletal pain
    - Complaints of cognitive difficulties
- Subjective symptoms are of such severity that, when present, they result in substantial reduction in previous levels of occupational, educational, social, or personal activities

Fig. 1. Centers for Disease Control and Prevention[7]

Location of suspected exposure

Where a person lives and travels is another consideration when diagnosing PTLDS. While Lyme disease is a recognized public health concern, most cases occur in the upper midwestern, northeastern, and mid-Atlantic states.[6]

"It is important to remember there are different species of ticks across the United States," Dr Jones explained. Deer ticks, or black-legged ticks, are found across the eastern United States and are the ones that may transmit the bacteria that cause Lyme disease.

Other tick-borne illnesses

As Dr Jones pointed out, the location of the suspected infection matters. That information can help doctors eliminate or consider other tick-borne illnesses.

"Different ticks carry different diseases," Jones said. "Sometimes a single tick can carry more than one disease."

The CDC reports that Lyme disease is the most commonly reported tick-borne illness.[8] Others include anaplasmosis, spotted fever rickettsiosis, and ehrlichiosis.[8]

Taking the next step

PTLDS or "chronic" Lyme disease diagnosis involves a lengthy process of elimination. Besides understanding a patient's history, one of the first steps to reach a diagnosis and start treatment is to get the right testing done. For more information on how to get started, click here.

References
1. CDC. Post-treatment Lyme disease syndrome. Updated January 10, 2022. Accessed March 22, 2023. https://www.cdc.gov/lyme/postlds/index.html
2. NIH. Chronic Lyme disease. Updated November 21, 2018. Accessed March 22, 2023. https://www.niaid.nih.gov/diseases-conditions/chronic-lyme-disease
3. Lantos PM. Chronic Lyme disease. *Infect Dis Clin North Am*. 2015; 29(2): 325–340. doi:10.1016/j.idc.2015.02.006
4. Rose CD, Fawcett PT, Gibney KM, et al. The overdiagnosis of Lyme disease in children residing in an endemic area. *Clin Pediatr (Phila)*. 1994;33(11):663-668. doi:10.1177/000992289403301105
5. Murray TS, Shapiro ED. Lyme disease. *Clin Lab Med*. 2010;30(1):311-328. doi:10.1016/j.cll.2010.01.003
6. CDC. Lyme disease. August 5, 2022. Updated August 5, 2022. https://www.cdc.gov/ticks/tickbornediseases/lyme.html
7. CDC. Regions where ticks live. Updated December 5, 2022. Accessed March 22, 2023. https://www.cdc.gov/ticks/geographic_distribution.html
8. CDC. Tickborne disease surveillance data summary. Updated August 11, 2022. Accessed March 22, 2023. https://www.cdc.gov/ticks/data-summary/index.html

Resources for Lyme disease for healthcare professionals and patients

Below are some important web resources that can help the healthcare professional stay informed and educate patients in turn.

CDC

The CDC provides extensive information for both professionals and patients. Here you will find discussion of epidemiology, signs and symptoms, testing, treatment, and prevention. Highlights of CDC resources include:

- Educational materials, brochures, and fact sheets designed for patients, including children's resources. Fact sheets are available in English, Spanish, Brazilian, Portuguese, and Tagalog. Do you maintain a website for your practice? The CDC provides a code for a free Flash widget you can post to your site
- Extensive discussions for healthcare professionals on treatment and testing, as well as a 52-page manual on tick-borne diseases of the United States. There are also expert-commentary videos on Lyme carditis, southern tick-associated rash illness, and PCR testing
- A page of statistics, graphs, and maps provides a fascinating look at the spread of Lyme disease over the past decades

Clinical trials

Clinical trials for people with Lyme disease can be searched on clinicaltrials.gov using the search term "Lyme."

Free major research and review articles

- Shapiro ED. Lyme disease. *N Engl J Med*. 2014;370(18): 1724-1731.doi:10.1056/NEJMcp1314325
- Steere AC, Strle F, Wormser GP, et al. Lyme borreliosis. *Nat Rev Dis Primers*. 2016;2:16090. doi:10.1038/nrdp.2016.90
- Eickhoff C, Blaylock J. Tickborne diseases other than Lyme in the United States. *Cleve Clin J Med*. 2017;84:555-567. doi:10.3949/ccjm.84a.16110
- Berende A, ter Hofstede HJ, Vos FJ, et al. Randomized trial of longer-term therapy for symptoms attributed to Lyme disease. *New Engl J Med*. 2016;31:1209-1220. doi:10.1056/NEJMoa1505425

Quest Diagnostics Health Trends®

An in-depth Health Trends report reveals the spread of Lyme disease by geography

- Disease by geography; available at Quest Diagnostics Lyme Disease Health Trends Report reveals the spread of Lyme disease by geography.

The Infectious Disease Society of America

The Infectious Disease Society of America (IDSA) presents materials on Lyme disease for patients, professionals, policy officials, and the press. Highlights include:

- Clinical practice guidelines by the IDSA, American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 guidelines for the prevention, diagnosis, and treatment of Lyme disease

- Video series that reviews what Lyme disease is, IDSA Lyme disease guidelines, and what is "chronic Lyme disease"

A guide to lesser known tick-borne illnesses

Getting bitten by a tick may be the start of complex medical conditions in patients. Ticks that transmit the bacteria that causes Lyme disease often carry other disease-causing microbes that can cause multiple tick-borne illnesses in humans.

These tick-borne diseases complicate a person's health, leading to more symptoms and longer recovery periods. As with Lyme disease, early detection of these other illnesses can lead to more effective treatment and reduce the chances of suffering more serious, long-term medical conditions.

Understanding coinfections

Tick-borne illnesses are animal diseases that can be transmitted to humans. Ticks get diseases from animals, like squirrels, mice, and deer; infections get passed to humans through the tick's bite.

Ticks that acquire more than one bacteria, virus, or protozoan at once can pass on multiple diseases or coinfections to humans with a single bite. *Ixodes* ticks that transmit *Borrelia burgdorferi*, the bacterium that causes Lyme disease, can also carry bacteria and viruses that may lead to coinfections, such as:

- Anaplasmosis
- Babesiosis
- Ehrlichiosis
- Rocky Mountain spotted fever
- Tularemia

Numbers of patients with Lyme disease coinfections

Coinfections with various combinations of 2 or 3 pathogens can occur. Epidemiological and clinical studies of acute tick-borne illnesses in residents in the northeastern United States have shown that the frequency of Lyme disease patients experiencing concurrent babesiosis ranges from 2% to 19%, and the percentage of babesiosis patients experiencing concurrent Lyme disease varies between 6% and 23%.[1]

Factors that may contribute to the variation in coinfection frequency include:[1]

- Geographic and temporal differences in tick density
- Prevalence of infected ticks
- Risk of human exposure to ticks
- Susceptibility to disease in humans
- Testing methodology that identifies concurrent or sequential infection
- Case definitions

According to the CDC, ticks may carry some species of *Bartonella* bacteria, but there is "no causal evidence" that ticks can transmit the infection to humans through their bites.[2]

A deeper look at each coinfection

Babesiosis

Babesia is a malaria-like parasite that causes the disease babesiosis, which is an infection of the red blood cells. Pregnant women who are bitten by infected ticks can pass this disease onto their children. Though it shares similar symptoms to Lyme disease, babesiosis more often starts with a high fever and chills. As the infection progresses, patients may develop

- Headaches
- Fatigue
- Muscle aches
- Loss of appetite
- Nausea
- Sweats

While the symptoms can be so mild that they are overlooked, they can be life-threatening to those with compromised immune systems and the elderly. Delayed detection and treatment can lead to more severe medical complications, including:

- Low blood pressure
- Liver problems
- Severe hemolytic anemia
- Kidney failure

With babesiosis, early detection is critical. Blood tests can detect the disease, but they are most reliable within the first 2 weeks of infection. Often, babesiosis can be treated with a combination of antimalarial drugs and antibiotics.[a] Some patients experience relapses, requiring additional retreatment.[a]

Ehrlichiosis

Ehrlichiosis is a term used to describe several diseases caused by the bacteria *Ehrlichia chaffeensis, E ewingii,* or *E muris eauclairensis.* Up to 1 in 3 patients infected develops a rash that can look like red splotches or pinpoints.[3]

The rash often comes about 5 days after having a fever. Other symptoms include headaches, muscle aches, and upset stomach. The disease is detected with blood tests and treated with antibiotics. Early detection can reduce the risk

of more serious complications, including

- Meningoencephalitis
- Respiratory failure
- Severe bleeding
- Death

Those with weakened immune systems, the very young, and the elderly are at greater risk of severe illnesses. Like other tick-borne illnesses, ehrlichiosis can easily be missed by physicians.

Anaplasmosis

Formerly known as human granulocytic ehrlichiosis, anaplasmosis is often considered less severe than other rickettsial diseases.[4] However, factors such as age, suppressed immunities, and delayed detection and treatment can lead to more serious conditions.

Those with this disease may experience fever, severe headaches, chills, malaise, and gastrointestinal symptoms. Less than 10% of those with anaplasmosis get a rash.[4] The disease is commonly treated with antibiotics.[a]

Rocky Mountain spotted fever

Rocky Mountain spotted fever shares similar symptoms to other tick-borne illnesses, such as headache and fever. However, this disease can progress quickly to a serious and life-threatening illness.[5]

A rash, which appears within 4 days after a fever begins, is the most common sign among patients. While not all patients will get a rash, Rocky Mountain spotted fever can be difficult to diagnose because the rash may not appear early in the illness.[5]

Once the disease is treated with antibiotics, patients do not suffer from chronic infections later. Those treated for severe Rocky Mountain spotted fever may still suffer from long-term conditions, including paralysis, hearing loss, and mental disabilities.[5]

Tularemia

Caused by the bacterium *Francisella tularensis*, tularemia causes headaches, sudden fever, dry cough, progressive weakness, and upset stomach. Tularemia can be fatal, so it needs to be treated with antibiotics.[a]

Prevention of tick-borne diseases

As the number of cases of Lyme disease and coinfections continues to rise, patients should be informed of the best ways to prevent these illnesses. Some of the best ways to prevent these diseases are:

- Use insect repellent
- Remove ticks promptly
- Reduce tick habitat in yards

Information about tick-borne illness testing

Since tick-borne illnesses share many of the same signs and symptoms, the right diagnostic tests can help doctors make the most accurate diagnoses. More information about laboratory testing is available here.

[a] The treating healthcare professional should refer to the manufacturer's approved labeling for prescribing, warnings, side effects, and other important information. This information is provided for informational purposes only and is not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on their education, clinical expertise, and assessment of the patient.

References
1. Diuk-Wasser MA, Vannier E, Krause PJ. Coinfection by the tick-borne pathogens Babesia microti and Borrelia burgdorferi: ecological, epidemiological and clinical consequences. *Trends Parasitol.* 2016;32(1):30-42. doi:10.1016/j.pt.2015.09.008
2. CDC. Bartonella infection: transmission. Updated March 22, 2023. Accessed February 23, 2022. https://www.cdc.gov/bartonella/transmission/index.html
3. CDC. Ehrlichiosis: signs and symptoms. Updated January 17, 2019. Accessed March 22, 2023. https://www.cdc.gov/ehrlichiosis/symptoms/index.html
4. CDC. Anaplasmosis. Updated August 5, 2022. Accessed March 22, 2023. https://www.cdc.gov/ticks/tickbornediseases/anaplasmosis.html
5. CDC. Rocky mountain spotted fever: signs and symptoms. Updated February 19, 2019. Accessed February 25, 2022. https://www.cdc.gov/rmsf/symptoms/index.html

Tick-borne illnesses: the risks of a missed diagnosis

For a patient with a tick-borne illness, early diagnosis matters. Luckily, according to Robert Jones, DO, medical director for Infectious Diseases at Quest Diagnostics, physicians are much more aware of Lyme disease and other tick-borne infections than in the early days of the epidemic. "It's a much more 'Lyme-literate' population these days," he says.

But the risks of missing the diagnosis are still there, especially when a patient has a nonstandard presentation, such as lack of a rash for Lyme disease. The rash occurs in 70% to 80% of patients with Lyme disease,[1] meaning up to 30% of patients may not present with a rash despite being infected.[1]

"As with most diseases, the earlier you catch it the better," Dr Jones says. Early treatment requires a short course of antibiotics, usually oral doxycycline, which is not only effective against infection by the *Borrelia burgdorferi* bacterium that causes Lyme disease, but also *Anaplasma* and *Ehrlichia*, 2 other tick-borne bacteria that can cause infection instead of or along with *Borrelia*.[a]

Untreated, the infection can spread to the joints, heart, and central nervous system days to months after the initial infection. "Acutely, the symptoms are tied to site of infection—fluid in the joints, inflammation of the heart, or invasion into the meninges," notes Dr Jones. In the joints, the infection can cause arthritis, severe joint pain, and swelling, especially in the knees. In the heart (called Lyme carditis), it can cause palpitations, shortness of breath, and chest pain. In the central nervous system, it can cause severe neck pain, headache, neuropathy, Bell palsy, and cognitive symptoms. "Not everyone follows the same course, and there is no linear progression of symptom development," he says.

Disseminated Lyme disease manifestations could include arthritis, facial palsy, carditis, and meningitis.[2]

When the infection has progressed, more invasive treatment may be required. "If there is a concern for central nervous system Lyme disease, we will typically use intravenous antibiotics, usually a third-generation cephalosporin such as ceftriaxone,"[a] says Dr Jones. Mild heart block can be treated with oral antibiotics, but more significant heart block may also require IV antibiotics.[a] "Generally speaking, doxycycline will treat *Ehrlichia, Anaplasma*, and Lyme disease," but not babesiosis.[a] Amoxicillin can treat Lyme disease, but not the others, so that if doxycycline is contraindicated, it may be valuable to rule out their presence through testing.[a]

Treatment is still effective after a delayed diagnosis, Dr Jones adds, "although the symptoms may take longer to dissipate," even after successful eradication of the infection. The persistence of symptoms after treatment, called post-treatment Lyme disease syndrome (PTLDS), is not the same as "chronic Lyme disease," defined as a persistent infection after antibiotic treatment, he emphasizes. There is no clinical evidence that the latter condition exists, he says, as the Infectious Disease Society of America has emphasized in their guidelines.[3]

While not every patient with a suspected tick-borne illness needs to be tested, it can provide important information. "From an epidemiological standpoint, it is always nice to know what is in your community," Dr Jones says. "If I recognize babesiosis is in my community, for example, then I know to look for it, and to test for it." It may help guide the choice of treatment as well, especially if the patient is not responding to an initial round of oral doxycycline, which is often the first agent given. "And it is useful to be able to tell the patient exactly what they have," he added.

[a] The treating healthcare professional should refer to the manufacturer's approved labeling for prescribing, warnings, side effects and other important information. This information is provided for informational purposes only and is not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on their education, clinical expertise, and assessment of the patient.

References
1. CDC. Lyme disease. Updated August 5, 2022. Accessed March 22, 2023. https://www.cdc.gov/ticks/tickbornediseases/lyme.html
2. Kwit NA, Nelson CA, Max R, et al. Risk factors for clinician-diagnosed Lyme arthritis, facial palsy, carditis, and meningitis in patients from high-incidence states. *Open Forum Infect Dis*. 2017; 5(1):ofx254. doi:10.1093/ofid/ofx254
3. Lantos PM, Rumbaugh J, Bockenstedt LK, et al. Clinical practice guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 guidelines for the prevention, diagnosis and treatment of Lyme disease. *Clin Infect Dis*. 2021; 72(1): e1-e48. doi:10.1093/cid/ciaa1215

← A guide to lesser known tick-borne illnesses | home | Comprehensive tick-borne illness testing leads to better patient outcomes →

Comprehensive tick-borne illness testing leads to better patient outcomes

Ticks are expanding their habitat across the United States, leading to an increase in the prevalence of tick-borne illness. Since there are multiple types which vary regionally[1] and coinfection with similar symptoms can occur, it can be challenging to determine which illness—or combination of illnesses—afflicts the infected person.

In addition, patients are often unfamiliar with the symptoms of tick-borne illness, which can delay treatment. To help diagnose and treat tick-borne illness earlier, proper identification is key. The CDC recommends healthcare providers consider lab testing, depending on the symptoms and the geographic region where the bite occured.[2]

Depending on the patient's initial exposure, onset, and symptoms, there are molecular and serological tests available. In fact, Quest Diagnostics has expanded its portfolio of tick-borne illness testing:

Tick-Borne Disease Testing Panels

There are 2 tick-borne disease testing panels that can help provide the insight you need for diagnosis. The acute molecular panel is most helpful 1-2 weeks after disease onset to differentiate pathogens and possible coinfection, while the antibody panel is ideal when symptoms or infection are unclear.

Two-Step Testing for Lyme Disease

Quest offers both of the CDC-recommended 2-step testing processes for the serological diagnosis of Lyme disease, including the standard two-tier test (STTT) and the modified two-tier test (MTTT), which may be able to assist in the early identification of Lyme disease within the first 30 days of infection.[3,4]

Borrelia PCR Test

The addition of the *Borrelia* PCR test to the Quest portfolio provides a more comprehensive and differentiating test for *Borrelia* diagnosis.

For more information on different types of tick-borne testing, visit Quest Diagnostics.

References
1. CDC. Overview of tickborne diseases. Updated August 5, 2022. Accessed March 22, 2023. https://www.cdc.gov/ticks/tickbornediseases/overview.html
2. CDC. Symptoms of tickborne illness. Updated August 5, 2021. Accessed March 22, 2023. https://www.cdc.gov/ticks/symptoms.html
3. Association of Public Health Laboratories. Suggested reporting language, interpretation and guidance regarding Lyme disease serologic test results. May 2021. Accessed March 22, 2023. https://www.aphl.org/aboutAPHL/publications/Documents/ID-2021-Lyme-Disease-Serologic-Testing-Reporting.pdf
4. Mead P, Petersen J, Hinckley A. Updated CDC recommendation for serologic diagnosis of Lyme disease. *MMWR Morb Mortal Wkly Rep*. 2019;68(32):703. doi:10.15585/mmwr.mm6832a4

← Tick-borne illnesses: the risks of a missed diagnosis | home | Test list for tick-borne diseases →

Make timely, differential tick-borne disease diagnoses with comprehensive testing from Quest

Test name	Test code	CPT code(s)
Tick-borne Disease, Acute Molecular Panel[a] Includes: *Borrelia* Species DNA, Qualitative Real-Time PCR, Miscellaneous (15777); *Anaplasma phagocytophilum* DNA, Qualitative Real-Time PCR[b] (17320); *Babesia microti* DNA, Real-Time PCR[b] (37314); *Borrelia miyamotoi* DNA, Real-Time PCR, Miscellaneous[b] (93795); *Ehrlichia chaffeensis* DNA, Real-Time PCR[b] (11353)	94322	87801, 87468, 87469, 87478, 87484
Tick-borne Disease, Acute Molecular Panel, Non-Lyme[a] Includes: *Anaplasma phagocytophilum* DNA, Qualitative Real-Time PCR[b] (17320); *Babesia microti* DNA, Real-Time PCR[b] (37314); *Borrelia miyamotoi* DNA, Real-Time PCR, Miscellaneous[b] (93795); *Ehrlichia chaffeensis* DNA, Real-Time PCR[b] (11353)	32338	87468, 87469, 87478, 87484
***Borrelia miyamotoi* DNA, Real-Time PCR, Tick**[b]	93794	87478
***Francisella tularensis* Antibody, Direct Agglutination (DA)**[b]	35176	86000
Tick ID with Reflex to Lyme Disease DNA, Real-Time PCR, Tick When applicable, Lyme Disease (*Borrelia spp*) DNA, Qualitative, Real-Time PCR, Tick will be performed at an additional charge (15510), (CPT code(s): 87801).	90558	87168
***Borrelia* Species DNA, Qualitative Real-Time PCR, Tick**[b]	15510	87801
Malaria/*Babesia*/Other Blood Parasites	831	87207
***Rickettsia* Species DNA, Real-Time PCR**[b]	70191	87798
Tick (and Other Arthropods) Identification	3946	87168
Tick-borne Disease, Antibody Panel with Reflex to Blot (IgG, IgM)[a] Includes: Lyme Disease Ab with Reflex to Blot (IgG, IgM) (6646). If Lyme Disease Antibody Screen is ≥0.90, then Lyme Disease Antibodies (IgG, IgM), Immunoblot will be performed at an additional charge (8593), (CPT code(s): 86617 x2); *Anaplasma phagocytophilum* Antibodies (IgG, IgM)[b] (34464); *Babesia microti* Antibodies (IgG, IgM), IFA[b] (34300); *Babesia duncani* (WA1) Antibody (IgG), IFA[b] (17231); *Ehrlichia chaffeensis* (IgG, IgM)[b] (34271)	36942	86666 (x2), 86753 (x3), 86618, 86666 (x2)
***Anaplasma phagocytophilum* and *Ehrlichia chaffeensis* Antibody Panel**[a,b] Includes: *Anaplasma phagocytophilum* (IgG, IgM)[b] (34464) and *Ehrlichia chaffeensis* (IgG, IgM) (34271)	10611	86666 (x4)
***Borrelia miyamotoi* Antibodies (IgG, IgM)**[b]	39684	86619 (x2)
Colorado Tick Fever Antibody Panel, IFA Includes: Colorado Tick Fever IgG and Colorado Tick Fever IgM	34986	86790 (x2)

Test name	Test code	CPT code(s)
Febrile Antibodies Panel[a] Includes: *Rickettsia* (RMSF) Antibodies (IgG, IgM) with Reflex to Titers (6419). If Rickettsia (RMSF) screen is detected, IgG or IgM, the appropriate Titer will be performed at an additional charge (CPT code(s) 86757 per titer performed); *Rickettsia* (Typhus Fever) Antibodies (IgG, IgM) with Reflex to Titers (37503). If Rickettsia (Typhus Fever) screen is detected, IgG or IgM, the appropriate Titer will be performed at an additional charge (CPT code(s) 86757 per titer performed); *Salmonella*, Total Antibody, EIA (10582). Includes (*Salmonella* H Type A, *Salmonella* H Type B, *Salmonella* H Type D, *Salmonella* O Type D, *Salmonella* O Type Vi); *Brucella* Antibodies (IgG, IgM), EIA with Reflex to Agglutination (91068).[b] If *Brucella* IgM is ≥1.10, then *Brucella* Antibody, Agglutination will be performed at an additional charge (982), (CPT code(s): 86622).[b]	91121	86757 (x4), 86622 (x2), 86768 (x5)
Febrile Antibodies and *Francisella* Panel[a] Includes: *Rickettsia* (RMSF) Antibodies (IgG, IgM) with Reflex to Titers (6419). If Rickettsia (RMSF) screen is detected, IgG or IgM, the appropriate Titer will be performed at an additional charge (CPT code(s) 86757 per titer performed); *Rickettsia* (Typhus Fever) Antibodies (IgG, IgM) with Reflex to Titers (37503). If Rickettsia (Typhus Fever) screen is detected, IgG or IgM, the appropriate Titer will be performed at an additional charge (CPT code(s) 86757 per titer performed); *Salmonella*, Total Antibody, EIA (10582). Includes (*Salmonella* H Type A, *Salmonella* H Type B, *Salmonella* H Type D, *Salmonella* O Type D, *Salmonella* O Type Vi); *Brucella* Antibodies (IgG, IgM), EIA with Reflex to Agglutination (91068).[b] If *Brucella* IgM is ≥1.10, then *Brucella* Antibody, Agglutination will be performed at an additional charge (982), (CPT code(s): 86622).[b] *Francisella tularensis* Antibody, Direct Agglutination (DA)[b] (35176).	91122	86757 (x4), 86622 (x2), 86768 (x5), 86000
Lyme Disease Antibodies (IgG, IgM), Immunoblot	8593	86617 (x2)
Lyme Disease Antibody (IgG), Immunoblot	29477	86617
Lyme Disease Antibodies (IgG, IgM), Immunoblot, CSF	70028	86617 (x2)
Lyme Disease Antibody with Reflex to Immunoassay (IgG, IgM) Includes: If Lyme Disease Antibody is Positive or Equivocal (≥0.91), then Lyme Disease Supplemental Antibodies (IgG, IgM), Immunoassay will be performed at an additional charge (CPT code(s): 86617(x2))	39733	86618
Lyme Disease Antibody Index for CNS Infection	34194	82040, 82042, 82784 (x2), 86618 (x4)
Q Fever (*Coxiella burnetii*) Antibodies (IgG, IgM), with Reflex to Titers Includes: If Q Fever screen is positive, IgG or IgM Phase I or Phase II, the appropriate Titer will be performed at an additional charge (CPT code(s): 86638 per titer performed).	37071	86638 (x4)
***Rickettsia* (RMSF) Antibodies (IgG, IgM) with Reflex to Titers** Includes: If *Rickettsia* (RMSF) Antibodies (IgG, IgM) is Detected, the appropriate Titer will be performed at an additional charge (CPT code(s): 86757 per titer performed).	6419	86757 (x2)

[a] Components of panels can be ordered separately.

[b] This test was developed, and its analytical performance characteristics have been determined by Quest Diagnostics. It has not been cleared or approved by FDA. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

← Comprehensive tick-borne illness testing leads to better patient outcomes | home →

Test name	Test code	CPT code(s)
***Rickettsia* Antibody Panel with Reflex to Titers**[a] Includes: *Rickettsia* (RMSF) Antibodies (IgG, IgM) with Reflex to Titers (6419); *Rickettsia* (Typhus Fever) Antibodies (IgG, IgM) with Reflex to Titers (37503). If *Rickettsia* (RMSF) screen is Detected, IgG or IgM, the appropriate Titer will be performed at an additional charge (CPT code(s) 86757 per titer performed). If *Rickettsia* (Typhus Fever) screen is Detected, IgG or IgM, the appropriate Titer will be performed at an additional charge (CPT code(s) 86757 per titer performed).	37507	86757 (x4)
***Rickettsia conorii* Antibody Panel, IFA**[b,c] Includes: *Rickettsia conorii* (IgG) and *Rickettsia conorii* (IgM)	15332	86757(x2)
***Rickettsia* (Typhus Fever) Antibodies (IgG, IgM) with Reflex to Titers**[a] Includes: If *Rickettsia* (Typhus Fever) screen is Detected, IgG or IgM, the appropriate Titer will be performed at an additional charge (37503), (CPT code(s) 86757 per titer performed).	37503	86757 (x2)
Rickettsial Disease Panel[a] *Rickettsia* (RMSF) Antibodies (IgG, IgM) with Reflex to Titers (6419). If *Rickettsia* (RMSF) screen is detected, IgG or IgM, the appropriate Titer will be performed at an additional charge (CPT code(s) 86757 per titer performed); *Rickettsia* (Typhus Fever) Antibodies (IgG, IgM) with Reflex to Titers (37503). If *Rickettsia* (Typhus Fever) screen is detected, IgG or IgM, the appropriate Titer will be performed at an additional charge (CPT code(s) 86757 per titer performed); Q Fever (*Coxiella burnetii*) Antibodies (IgG, IgM), with Reflex to Titers (37071). If Q Fever screen is positive, IgG or IgM Phase I or Phase II, the appropriate Titer will be performed at an additional charge (CPT code(s): 86638 per titer performed).	37478	86638 (x4), 86757 (x4)

Test name	Description	Test code	CPT code(s)
***Borrelia* Species DNA, Real-Time PCR, with Reflexes, Blood**[a,b]	In the first stage, a PCR assay detects the potential presence of *Borrelia* species DNA. If *Borrelia* species DNA is detected, then an additional species-specific PCR assay is performed to identify and differentiate between *B burgdorferi* (Lyme disease) and *B miyamotoi* (tick-borne relapsing fever). A positive result for *Borrelia* species but negative result for *Borrelia burgdorferi* and *Borrelia miyamotoi*, may indicate that infection is caused by other *Borrelia* species. When appropriate, *Borrelia burgdorferi* DNA, Qualitative Real-Time PCR, Miscellaneous (39209) and *Borrelia miyamotoi* DNA, Real-Time PCR, Miscellaneous (93795) will be performed at an additional charge (CPT Code(s): 87476, 87798).	39219[d]	87801
***Borrelia* Species DNA, Real-Time PCR, with Reflexes, Synovial Fluid/CSF**[a,b]	In the first stage, a PCR assay detects the potential presence of *Borrelia* species DNA. If *Borrelia* species DNA is detected, then an additional species-specific PCR assay is performed to identify and differentiate between *B burgdorferi* (Lyme disease) and *B miyamotoi* (tick-borne relapsing fever). A positive result for *Borrelia* species but negative result for *Borrelia burgdorferi* and *Borrelia miyamotoi*, may indicate that infection is caused by other *Borrelia* species. When appropriate, *Borrelia burgdorferi* DNA, Qualitative Real-Time PCR, Miscellaneous (39209) and *Borrelia miyamotoi* DNA, Real-Time PCR, Miscellaneous (93795) will be performed at an additional charge (CPT Code(s): 87476, 87798).	39218[d]	87801
***Borrelia miyamotoi* Antibodies (IgG, IgM), Immunoassay**[b]	Positive antibody results suggest *B miyamotoi* infection; however, other tick-borne organisms may induce cross-reactive antibodies. Negative IgG and IgM results do not exclude the possibility of *B miyamotoi* infection.	39684	86619 (x2)

[a] Components of panels can be ordered separately.

[b] This test was developed, and its analytical performance characteristics have been determined by Quest Diagnostics. It has not been cleared or approved by FDA. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

[c] Available from Quest Diagnostics Nichols Institute, Chantilly, VA.

[d] Please refer to the Quest Test Directory for your service area for test availability.

Please contact your Quest Diagnostics sales representative at **1.866.MYQUEST** (1.866.697.8378) for more information about our tick-borne disease testing or visit **QuestDiagnostics.com.**

← Comprehensive tick-borne illness testing leads to better patient outcomes | ← home

Test codes may vary by location. Please contact your local laboratory for more information.

The CPT® codes provided are based on American Medical Association guidelines and are for informational purposed only. CPT coding is the sole responsibility of the billing party. Please direct any questions regarding coding to the payer being billed.

This communication is intended for healthcare professionals in the USA.

This information is provided for informational purposes only and is not intended as medical advice. A physician's test selection and interpretation, diagnosis, and patient management decisions should be based on his/her education, clinical expertise, and assessment of the patient.

The treating healthcare professional should refer to the manufacturer's approved labeling for prescribing, warnings, side effects, and other important information.

Image content features models and is intended for illustrative purposes only.

QuestDiagnostics.com