Medical Policy

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Title: Intravenous Antibiotic Therapy and Associated Diagnostic Testing for Lyme Disease

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Populations	Interventions	Comparators	Outcomes
Individuals: • Who are suspected of having Lyme disease	Interventions of interest are: • Genotyping or phenotyping of *Borrelia burgdorferi* subspecies	Comparators of interest are: • Established, tiered diagnostic approach	Relevant outcomes include: • Change in disease status • Morbid events
Individuals: • Who are suspected of having Lyme disease	Interventions of interest are: • CXCL13 chemokine concentration testing	Comparators of interest are: • Established, tiered diagnostic approach	Relevant outcomes include: • Change in disease status • Morbid events
Individuals: • Who are suspected of having Lyme disease	Interventions of interest are: • Stand-alone C6 peptide assay testing	Comparators of interest are: • Established, tiered diagnostic approach	Relevant outcomes include: • Change in disease status • Morbid events

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Populations	Interventions	Comparators	Outcomes
Individuals: • Who are suspected of having Lyme disease	Interventions of interest are: • *Borrelia* Outer surface protein A testing	Comparators of interest are: • Established, tiered diagnostic approach	Relevant outcomes include: • Change in disease status • Morbid events
Individuals: • With confirmed Lyme disease	Interventions of interest are: • Prolonged or repeated courses of antibiotic therapy	Comparators of interest are: • Standard course of oral antibiotic therapy • Two- to 4-week course of intravenous antibiotic therapy	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Health status measures

DESCRIPTION

Lyme disease is a multisystem inflammatory disease caused by the spirochete *Borrelia burgdorferi* and transmitted by the bite of an infected *Ixodes scapularis* (northeastern U.S.) or *Ixodes pacificus* (Pacific coast, most common in Northern California) tick. The disease is characterized by stages, beginning with localized infection of the skin (erythema migrans), which may be followed by dissemination to many sites. Diagnostic testing for Lyme disease is challenging, and there is the potential for overdiagnosis and overtreatment.

OBJECTIVE

The objective of this evidence review is to evaluate whether the use of a specialized laboratory evaluation of individuals with suspected Lyme disease, and whether the use of repeated or prolonged courses of antibiotic therapy in individuals diagnosed with Lyme disease, improves the net health outcome.

BACKGROUND

Lyme Disease

Lyme disease is a multisystem inflammatory disease caused by the spirochete *Borrelia burgdorferi* and transmitted by the bite of an infected *Ixodes scapularis* (northeastern region) or *Ixodes pacificus* (Pacific coast, most often in Northern California) tick. The disease is characterized by stages, beginning with localized infection of the skin (erythema migrans), followed by acute dissemination, and then late dissemination to many sites. Manifestations of the early disseminated disease may include lymphocytic meningitis, facial palsy, painful radiculoneuritis, atrioventricular (AV) block, or migratory musculoskeletal pain. Months to years later, the disease may be manifested by intermittent oligoarthritis, particularly involving the knee joint; chronic encephalopathy; spinal pain; or distal paresthesias. While most manifestations of Lyme disease can be adequately treated with oral antibiotics, intravenous (IV) antibiotics are indicated in some patients with disseminated Lyme disease. The following paragraphs describe the various manifestations of Lyme disease, therapies, and the various laboratory tests used to support the diagnosis of Lyme disease.

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MANIFESTATIONS

Erythema migrans

Erythema migrans appears at the site of the tick bite and manifests generally between 7 to 14 days after the bite. The lesions typically expand slowly over the course of days or weeks, often with central clearing. If multiple lesions are present, it is considered a sign of early disseminated disease.

Neuroborreliosis

Lymphocytic meningitis, characterized by head and neck pain, may occur during the acute disseminated stage of the disease. In patients with meningitis, the cerebrospinal fluid (CSF) will typically show a lymphocytic pleocytosis (lymphocyte count greater than normal) with increased levels of protein and normal glucose levels. Intrathecal production of antibodies directed at spirochetal antigens is also typically present. Other manifestations of early disseminated disease can include cranial neuritis (including unilateral or bilateral facial palsy) and peripheral nervous system manifestations. Cranial neuritis, most frequently Bell palsy, may present early in the course of disseminated Lyme disease, occasionally before the development of antibodies. Peripheral nervous system manifestations of Lyme disease include paresthesias or radicular pain with only minimal sensory signs. Patients typically exhibit electromyographic or nerve conduction velocity abnormalities.

Neurological manifestations of late-stage dissemination can include mononeuropathy multiplex, encephalomyelitis, and subtle encephalopathy. A subacute encephalopathy is characterized by subtle disturbances in memory, mood, sleep, or cognition accompanied by fatigue. The symptoms are nonspecific and overlap with fibromyalgia and chronic fatigue syndrome. Much rarer, but of greater concern, is the development of encephalomyelitis, characterized by spastic paraparesis, ataxias, cognitive impairment, bladder dysfunction, and cranial neuropathy.

Lyme Carditis

Lyme carditis may appear during the early disseminated stage of the disease; symptoms include AV block, tachyarrhythmias, and myopericarditis. The most common abnormality is fluctuating degrees of AV block.

Lyme Arthritis

Lyme arthritis is a late manifestation of infection and is characterized by an elevated immunoglobulin G (IgG) response to *B. burgdorferi* and intermittent attacks of oligoarticular arthritis, primarily in the large joints such as the knee. However, both large and small joints may be affected.

DIAGNOSTIC TESTING

Overview

The optimum method of testing for Lyme disease depends on the stage of the disease. Diagnostic testing may not be necessary when a diagnosis can be made clinically in patients with a recent tick bite or exposure and the presence of the characteristic rash of erythema migrans, particularly in patients presenting early before the development of a detectable serum antibody

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response. While diagnosis of Lyme disease is generally based on the clinical picture and demonstration of specific antibodies (see below), polymerase chain reaction (PCR)-based technology can detect the spirochete in the central nervous system in cases of neuroborreliosis, in the synovial fluid of cases of Lyme arthritis, and rarely in skin biopsy specimens of those with atypical dermatologic manifestations.[1,2,] However, while PCR-based tests can identify organisms in skin biopsy specimens of patients with dermatologic manifestations (ie, erythema migrans), this diagnosis is typically made clinically, and antibiotic therapy is started empirically.

For Lyme neuroborreliosis, CSF examination may be useful in select patients.[3,] In patients with suspected neuroborreliosis, evaluation allows for exclusion of bacterial or viral meningitis and can provide a more definitive diagnosis. However, direct detection of *B. burgdorferi* in CSF, by PCR or culture, is usually not possible in patients with Lyme neuroborreliosis. Finally, intrathecal antibody production is considered a more sensitive test than PCR-based CSF detection in patients with suspected neuroborreliosis. PCR may be clinically useful as a second approach in patients with a short duration of neurologic symptoms (<14 days) during the window between exposure and the emergence of detectable levels of antibodies in the CSF.[4,] PCR-based detection is typically not performed with urine due to the variable presence of endogenous polymerase inhibitors that affect test sensitivity.

Similarly, the diagnosis of Lyme arthritis is based on clinical and serologic studies without the need for synovial tissue or fluid.

Fibromyalgia and chronic fatigue syndrome are the diseases most commonly confused with Lyme disease. Fibromyalgia is characterized by musculoskeletal complaints, multiple trigger points, difficulty in sleeping, generalized fatigue, headache, or neck pain. The joint pain associated with fibromyalgia is typically diffuse, in contrast to Lyme arthritis, which is characterized by marked joint swelling in one or more joints at a time, with few systemic symptoms. Chronic fatigue syndrome is characterized by multiple subjective complaints, such as overwhelming fatigue, difficulty in concentration, and diffuse muscle and joint pain. In contrast with Lyme disease, both of these conditions lack joint inflammation, have normal neurologic test results, or have test results suggesting anxiety or depression. Neither fibromyalgia nor chronic fatigue syndrome has been shown to respond to antibiotic therapy.

Serologic Tests

The antibody response to infection with *B. burgdorferi* follows a typical pattern. During the first few weeks after the initial onset of infection, there is no antibody production. The specific immunoglobulin M (IgM) response characteristic of acute infection peaks between the third and the sixth week. The specific IgG response develops only after months and includes antibodies to a variety of spirochetal antigens. Immunoglobulin G antibodies produced in response to Lyme disease may persist for months or years. Thus detection of IgG antibodies only indicates exposure, either past or present. In Lyme disease-endemic areas, underlying asymptomatic seropositivity may range up to 5% to 10%. Thus, as with any laboratory test, interpretation of serologic tests requires a close correlation with the patient's signs and symptoms. For example, patients with vague symptoms of Lyme disease, chronic fatigue syndrome, or fibromyalgia may undergo multiple serologic tests over many weeks to months to establish the diagnosis of Lyme disease. Inevitably, in this setting of repeat testing, one enzyme-linked immunosorbent assay (ELISA) or test, whether IgG or IgM, may be reported as weakly positive or indeterminate. These

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results most likely represent false-positive test results in the uninfected patient who has had long-standing symptoms from a different condition and previously negative test results.

Currently, the Centers for Disease Control and Prevention recommend a 2-tiered method for the serologic diagnosis of Lyme disease.[5,] This can be accomplished using the standard 2-tiered testing process, which uses a sensitive enzyme immunoassay (EIA) or immunofluorescence assay, followed by a western immunoblot assay for specimens yielding positive or equivocal results. Additionally, a modified 2-test methodology can be used, which uses a second EIA in place of the western immunoblot assay.

Enzyme-Linked Immunosorbent Assay for *Borrelia burgdorferi* Antibodies
This ELISA test is a screening serologic test for Lyme disease. ELISA tests are available to detect IgM or IgG antibodies or both antibody types together. More recently developed tests using recombinant or synthetic antigens have improved diagnostic sensitivity. For example, the U.S. Food and Drug Administration (FDA) approved C6 ELISA is highly sensitive to infection and is under study as an indicator of antibiotic therapy efficacy. A positive or indeterminate ELISA test result alone is inadequate serologic evidence of Lyme disease. All of these tests must be confirmed with a Western immunoblot or a second EIA. The overall predictive value is increased when correlated with the clinical picture.

Western Immunoblot
This immunoblot test is used to confirm the serologic diagnosis of Lyme disease in patients with positive or indeterminate ELISA tests. In contrast with the standard ELISA test, the immunoblot investigates the specific antibody response to the different antigens of *B. burgdorferi*. Typically, several clinically significant antigens are tested. According to Centers for Disease Control and Prevention criteria, the test result is considered positive if 2 of the 3 most common IgM antibody bands to spirochetal antigens are present, or 5 of the 10 most frequent IgG antibody bands are present. Because the Centers for Disease Control and Prevention criteria were developed for surveillance, they are conservative and may miss true Lyme disease cases. Some support the use of more liberal criteria for a positive result in clinical diagnosis; however, alternative criteria have not been well-validated. U.S. criteria for interpreting immunoblot results differ from those in Europe due to differences in the prevalence of different *Borrelia* species causing disease.

NONSEROLOGIC TESTS

Polymerase Chain Reaction
In contrast to the previously discussed serologic tests, which indirectly assess prior or present exposure to *B. burgdorferi*, PCR directly tests for the presence of *B. burgdorferi* DNA. Because PCR technology involves the amplification of DNA from a portion of *B. burgdorferi*, there is a high-risk of exogenous contamination, resulting in false-positive results. Positive results in the absence of clear clinical indicators or positive serology are not definitive for diagnosis. Also, the test cannot distinguish between live spirochetes or fragments of dead ones. The PCR technique has been studied using various specimens. PCR has the best detection rates for skin biopsies from patients with erythema migrans (but who may not be indicated with a recent history of tick bite or exposure) and for synovial tissue (and synovial fluid, to a lesser extent) from patients with Lyme arthritis. Cerebrospinal fluid may be positive by PCR during the first 2 weeks of infection but after that the detection rate is low. PCR is not recommended for urine or blood specimens.

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However, PCR-based direct detection of *B. burgdorferi* in the blood may be useful for documenting Lyme carditis when results of serologic studies are equivocal.

Borrelia PCR also provides information on which of the 3 major species pathogenic for humans has been found in the specimen tested (genotyping).

T-Cell Proliferative Assay
T-lymphocyte proliferation assays, which detect responses of human mononuclear cells to borrelial antigens, are not recommended as diagnostic tests because they are difficult to perform and standardize, and their sensitivity is not well characterized.

Chemoattractant CXCL13
CXCL13 is a B-lymphocyte chemoattractant that has been reported to be elevated in acute neuroborreliosis and other inflammatory disorders in the central nervous system. It is being investigated as an adjunct in identifying infections and as a potential marker for successful treatment. The Centers for Disease Control and Prevention notes that standardized interpretation criteria is required before this test can be recommended.[3,]

***Borrelia* outer surface protein A**
Antigen testing of urinary *Borrelia* outer surface protein A (OspA) C-terminus peptide has been investigated using the Nanotrap® Antigen Test.[6,] This test employs Nanotrap particles to concentrate urinary OspA and uses a highly specific anti-OspA monoclonal antibody as a detector of the C-terminus peptides. Consistent with recommendations from the Centers for Disease Control and Prevention, the manufacturer of the Nanotrap® Antigen Test recommends using the Nanotrap® Antigen Test in conjunction with 2-tiered testing (ELISA with reflex to Western blot) for confirmation of a Lyme disease.[7,]

Treatment of Lyme Disease
Recommended treatment regimens are based on the stage and manifestations of Lyme disease.[8,] Most patients can be treated with oral antibiotics, such as doxycycline, amoxicillin, or cefuroxime. Specific durations of therapy are dependent on the type of manifestations present. Treatment with IV antibiotics may be indicated in patients with central nervous system or peripheral neurologic involvement and in a small subset of patients with heart block or documented Lyme arthritis who have not responded to oral antibiotics. Typical IV therapy consists of a 2- to 4-week course of ceftriaxone. No data have suggested that prolonged or repeated courses of IV antibiotics are effective. Lack of effect should suggest an incorrect diagnosis or slow resolution of symptoms, which is commonly seen in Lyme disease. Also, some symptoms may persist after treatment, such as Lyme arthritis; this phenomenon may be related to various self-sustaining inflammatory mechanisms rather than persistent infection.

REGULATORY STATUS
The FDA has cleared multiple enzyme immunoassay, immunofluorescent assay, and Western Blot IgG and IgM tests through the 510(k) process. There are also commercially available laboratory-developed tests for serologic testing for Lyme disease. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA).

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POLICY

IV Antibiotic Therapy

Treatment of Lyme disease consists of oral antibiotics, except for the following indications:

A. **Neuroborreliosis**

1. A 2- to 4-week course of intravenous (IV) antibiotic therapy may be considered **medically necessary** in individuals with neuroborreliosis with objective neurologic complications of documented Lyme disease (see the following for methods of documentation). Objective neurologic findings include:
    a. Lymphocytic meningitis with documented cerebrospinal fluid (CSF) abnormalities
    b. Cranial neuropathy, other than uncomplicated cranial nerve palsy, with documented CSF abnormalities
    c. Encephalitis or encephalomyelitis with documented CSF abnormalities
    d. Radiculopathy
    e. Polyneuropathy

2. Lyme disease may be documented by serologic testing or by clinical findings of erythema migrans in early infection. Documentation of CSF abnormalities is required for suspected central nervous system infection, as indicated above.

3. Serologic documentation of infection requires:
    a. Positive or indeterminate enzyme-linked immunosorbent assay, **AND**
    b. Positive immunoblot blot by Centers for Disease Control and Prevention criteria

4. Documented CSF abnormalities include **ALL** of the following:
    a. Pleocytosis
    b. Evidence of intrathecal production of *Borrelia burgdorferi* antibodies in CSF; **AND**
    c. Increased protein levels

5. Polymerase chain reaction (PCR)-based direct detection of *B. burgdorferi* in CSF samples may be considered **medically necessary** and may replace serologic documentation of infection in individuals with a short duration of neurologic symptoms (<14 days) during the window between exposure and production of detectable antibodies.

B. **Lyme Carditis**

1. A single 2- to 4-week course of IV antibiotics may be considered **medically necessary** in individuals with Lyme carditis, as evidenced by positive serologic findings (defined above) and associated with high degree atrioventricular block or a PR interval more than 0.3 second. Documentation of Lyme carditis may include PCR-based direct detection of *B. burgdorferi* in the blood when results of serologic studies are equivocal.

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C. **Lyme Arthritis**

1. A single 2- to 4-week course of IV antibiotic therapy may be considered **medically necessary** in the small subset of individuals with well-documented Lyme arthritis who have such severe arthritis that it requires the rapid response associated with IV antibiotics. Documentation of Lyme arthritis may include PCR-based direct detection of *B. burgdorferi* in the synovial tissue or fluid when results of serologic studies are equivocal.

D. **Antibiotic Therapy**

1. Intravenous antibiotic therapy is considered **experimental / investigational** in the following situations:
    a. Individuals with symptoms consistent with chronic fatigue syndrome or fibromyalgia, in the absence of objective clinical or laboratory evidence of Lyme disease
    b. Individuals with seronegative Lyme disease in the absence of CSF antibodies
    c. Initial therapy in individuals with Lyme arthritis without coexisting neurologic symptoms
    d. Cranial nerve palsy (e.g., Bell palsy) without clinical evidence of meningitis
    e. Post-antibiotic Lyme arthritis (unresponsive to 2 courses of oral antibiotics or to 1 course of oral and 1 course of intravenous antibiotic therapy)
    f. Individuals with vague systemic symptoms without supporting serologic or CSF studies
    g. Individuals with a positive enzyme-linked immunosorbent assay test, unconfirmed by an immunoblot or Western blot test (see definition above)
    h. Individuals with an isolated positive serologic test in the setting of multiple negative serologic studies
    i. Individuals with chronic (≥6 months) subjective symptoms ("post-Lyme syndrome") after receiving recommended treatment regimens for documented Lyme disease

2. Repeat or prolonged courses (e.g., >4 weeks) of IV antibiotic therapy are considered **experimental / investagional.**

E. **Diagnostic Testing**

1. PCR-based detection of *B. burgdorferi* is considered **experimental/ investigational** when the above criteria is not met.

2. Repeat PCR-based direct detection of *B. burgdorferi* is considered **experimental / investigational** in the following situations:
    a. As a justification for the continuation of IV antibiotics beyond 1 month in individuals with persistent symptoms
    b. As a technique to follow therapeutic response

3. Genotyping or phenotyping of *B. burgdorferi* is considered **experimental / investigational**.

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4. Other diagnostic testing is considered **experimental / investigational** including but not limited to "stand-alone" C6 peptide enzyme-linked immunosorbent assay determination of levels of the B-lymphocyte chemoattractant CXCL13, or outer surface protein A (OspA) antigen testing for diagnosis or monitoring treatment.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review was created using searches of the PubMed database. The most recent literature update was performed through August 20, 2025.

Suspected Lyme Disease

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

ANALYSIS OF *BORRELIA BURGDORFERI* GENOTYPE OR PHENOTYPE

Clinical Context and Test Purpose

The purpose of genotyping or phenotyping of *Borrelia burgdorferi* subspecies testing in individuals suspected of having Lyme disease is to inform an accurate diagnosis and, if positive, to initiate a treatment regimen.

Polymerase chain reaction (PCR)-based technology has been used in the genotypic analysis of *B. burgdorferi. Borrelia burgdorferi* was originally characterized as a single species (*B. burgdorferisensulato*) but genotypic analysis has revealed that this group represents 4 distinct species and genomic groups. Of these, the following have been isolated from individuals with Lyme disease: *B. burgdorferisensustricto*, *B. garinii*, *B. afzelii*, and *B. bavariensis*. The prevalence of these genospecies may vary among populations and may be associated with different clinical manifestations.[9,]

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is individuals with suspected Lyme disease.

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Interventions
The tests being considered are genotyping or phenotyping of *B. burgdorferi* subspecies.

Comparators
The following practice is currently being used to diagnose Lyme disease: established, 2-tiered diagnostic approach using either the standard methodology (enzyme immunoassay [EIA] or immunofluorescence assay, followed by a confirmatory western immunoblot assay) or the modified methodology (use of a second EIA in place of the western immunoblot assay).

Outcomes
The general outcome of interest is the diagnostic accuracy of the test to identify those with or without Lyme disease.

Follow-up over several weeks to months would be needed to confirm test findings and conduct further testing. Long-term follow-up may be necessary to monitor for residual symptoms (eg, joint inflammation, encephalopathy) after the active infection has been eliminated.

Study Selection Criteria
For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described
- Included a validation cohort separate from development cohort.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
Nigrovic et al (2020) evaluated the test characteristics of Lyme PCR-based testing compared to a standard 2-tier serology approach in 124 children of whom 54 (43.5%) had Lyme disease.[10,] The authors found PCR-based testing had a sensitivity of 41.8% (95% confidence interval [CI], 29.7% to 55.0%) and a specificity of 100% (95% CI, 94.2% to 100%), which did not reflect an improvement in diagnosis over the 2-tier approach.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

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Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No data were found in the published literature regarding whether or how knowledge of the genotype or phenotype of *B. burgdorferi* could be used to improve patient management and outcomes. In the U.S., *B. burgdorferisensustricto* and *B. mayonii*[11,] are the only human pathogenic species, but in Europe, 3 species cause infection. A study by Wilske et al (2007) reported that *B. spielmanii* was found in a small number of European patients; accordingly, criteria for interpreting immunoblot results differ between Europe and the U.S.[12,]

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility. Because the clinical validity of genotyping or phenotyping of *B. burgdorferi* subspecies has not been established, a chain of evidence cannot be established.

Section Summary: Analysis of *Borrelia Burgdorferi* Genotype or Phenotype
A prospective cohort study reported that use of PCR-based testing in Lyme disease evaluation did not improve the diagnosis compared to standard 2-tiered testing. No data were found in the published literature regarding whether or how knowledge of the genotype or phenotype of *B. burgdorferi* could be used to improve patient management and outcomes.

CXCL13 CHEMOKINE CONCENTRATION TESTING

Clinical Context and Test Purpose
The purpose of CXCL13 concentration testing in individuals suspected of having Lyme disease is to inform an accurate diagnosis and, if positive, to initiate a treatment regimen.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with suspected Lyme disease.

Interventions
The test being considered is testing for CXCL13 chemokine concentration.

Comparators
The following practice is currently being used to diagnose Lyme disease: established, 2-tiered diagnostic approach using either the standard methodology (EIA or immunofluorescence assay, followed by a confirmatory western immunoblot assay) or the modified methodology (use of a second EIA in place of the western immunoblot assay).

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Outcomes
The general outcome of interest is the diagnostic accuracy of the test to identify those with or without Lyme disease.

Follow-up over several weeks to months would be needed to confirm test findings and conduct further testing. Long-term follow-up may be necessary to monitor for residual symptoms (eg, joint inflammation, encephalopathy) after the active infection has been eliminated.

Study Selection Criteria
For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
The clinically validity of CXCL13 for diagnosis of acute Lyme neuroborreliosis has been primarily evaluated in European cohorts. Rupprecht et al (2018) performed a meta-analysis on studies investigating cerebrospinal fluid (CSF) CXCL13 concentration as a diagnostic marker for Lyme neuroborreliosis.[13,] A total of 18 studies (N=2944) were identified; all of which were conducted in Europe. According to the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) criteria, only 7 of 18 studies were classified as high quality.

Waib et al (2023) prospectively evaluated CSF CXCL13 concentrations in 440 adults in Austria, of whom 42 have been diagnosed as having acute and untreated definite Lyme neuroborreliosis.[14,] The median intrathecal CXCL13 concentration was 2384 pg/mL for patients with neuroborreliosis and 0 pg/mL in patients without disease ($p \leq .001$). Eckman et al (2021) retrospectively evaluated CSF CXCL13 concentrations in 132 patients with a broad spectrum of neuroinflammatory disorders to determine the relationship between CXCL13 and intrathecal *Borrelia*-specific antibodies in an US-based cohort.[15,] The study reported a moderate correlation between CSF CXCL13 concentrations and intrathecal antibodies (CSF:serum antibody index: $r=0.54$; $p=.016$) in patients with possible or definite Lyme neuroborreliosis. Tables 1 and 2 describe the study characteristics and results, respectively. Jung et al (2025) reported the results of a retrospective analysis of CSF CXCL13 concentrations in hospitalized children who were tested for Lyme neuroborreliosis with intrathecal antibody testing.[16,] There was a significant difference in CXCL13 concentrations among patients with definite neuroborreliosis (according to the European Federation of Neurological Societies definition; 56% had CXCL13 >500 pg/mL and 44% had median CXCL13 ranging from 37.9 to 325.0 pg/mL) and patients without neuroborreliosis (91.9% had CXCL13 <7.8 pg/mL).

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Overall, the quality of the data are varied. In particular, lower quality studies were limited by small populations of patients with acute Lyme neuroborreliosis, lack of blinding to reference standard tests, and use of populations that are not representative of those who would receive the test in clinical practice.

Table 1. Study Characteristics of Clinical Validity of CXCL13 Concentration Testing

Study	Study Population	Design	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests
Jung et al (2025)[16],	N=232 hospitalized children (3 months to 17 years) who underwent testing for suspected LNB	Retrospective evaluation of stored CSF samples that had previously undergone *Borrelia*-specific antibody testing	CSF *Borrelia*-specific antibody index	55 pg/mL	Reference was assayed at time of collection; index test was assayed retrospectively
Waib et al (2023)[14],	N=440 adults in Austria, of whom 42 had acute and untreated definite neuroborreliosis	Prospective evaluation of CSF CXCL13 concentrations as a diagnostic marker for LNB	Control group consisted of patients scheduled for a spinal tap but not clinically diagnosed with LNB	CXCL13 results; normal range: <20 pg/mL; borderline range: ≥20 to <30 pg/mL; increased: ≥30 to ≤100 pg/mL; strongly increased: >100 pg/mL	Not reported
Eckman et al (2021)[15],	N=132 patients with CSF and serum collected from lumbar punctures for suspected neuroinflammatory disease in Lyme-endemic areas of the northeast US	Retrospective evaluation of consecutive stored samples with a WBC count with >5/µL, regardless of diagnosis	ELISA and Western immunoblot to detect antibodies	Calculated as the concentration at which the Youden index (sensitivity + specificity - 1) was greatest	Reference was assayed at time of collection; index test was assayed retrospectively
Rupprecht et al (2018) [13],	N=2944 patients enrolled in studies investigating the CSF CXCL13 concentration as a diagnostic marker for LNB (non-LNB population varied across studies)	Meta-analysis of 18 studies (4 prospective designs; 10 case-control designs; rest unspecified)	Based on individual study (no further details)	Calculated as the concentration at which the Youden index (sensitivity + specificity - 1) was greatest	Based on individual study (no further details)

CSF: cerebrospinal fluid; ELISA: enzyme-linked immunoabsorbent assay; LNB: Lyme neuroborreliosis; WBC: white blood cell.

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Table 2. Clinical Validity of CXCL13 Concentration Testing

Study	Comparison	Optimal cut-off	Clinical Validity (95% CI)	
Meta-analyses			***Sensitivity***	***Specificity***
Rupprecht et al (2018)[13,]	LNB (n=618) vs. non-LNB (n=2326)	162 pg/mL	89% (85% to 93%)	96% (92% to 98%)
Prospective studies				
Waib et al (2023)[14,]	LNB (n=44) vs. control (n=398)	271 pg/mL	95.2%	97.2%
Retrospective studies				
Jung et al (2025)[16,]	Definite LNB (n=25) vs. non-LNB (n=174); an additional 33 patients had probable LNB	55 pg/mL	100% (86.3% to 100%)	98.9% (97.4% to 100%)
Eckman et al (2021)[15,]	Definite LNB (n=8) vs. all non-Lyme conditions with CSF pleocytosis (n=77)	1726 pg/mL	97% (91% to 100%)	75% (35% to 97%)
	Definite LNB (n=8) vs. all non-Lyme conditions with or without CSF pleocytosis (n=113)	1726 pg/mL	NR	99% (95% to 100%)

CI: confidence interval; CSF: cerebrospinal fluid; LNB: Lyme neuroborreliosis; NR: not reported.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of CXCL13 chemokine concentration levels were identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

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Because the clinical validity of CXCL13 concentration testing has not been established, a chain of evidence cannot be established.

Section Summary: CXCL13 Chemokine Concentration Testing
The diagnostic utility of CXCL13 in patients with suspected neuroborreliosis has been evaluated in a meta-analysis of 18 studies (N=2944) conducted in Europe, 2 retrospective studies (one US-based and one European), and a European-based prospective study. The results have demonstrated a high specificity and strong correlation with *B. burgdorferi*-specific antibody responses in patients with acute Lyme neuroborreliosis. However, there is wide variability in studies in defining a threshold for a significantly elevated CXCL13 value, which makes clinical performance characteristics unclear. Additionally, the generalizability of findings in European studies to the US population is unknown as the causative *Borrelia* strains are often different.

STAND-ALONE C6 PEPTIDE TESTING

Clinical Context and Test Purpose
The purpose of stand-alone C6 peptide assay testing in individuals suspected of having Lyme disease is to inform an accurate diagnosis and, if positive, to initiate a treatment regimen.

Traditional enzyme-linked immunosorbent assays (ELISA) used in the diagnosis of Lyme disease are whole cell-based. Newer ELISA, such as the C6 peptide test, use purified antigens rather than whole-cell bacterial lysates, which are more specific for *B. burgdorferi.*

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with suspected Lyme disease.

Interventions
The test being considered is stand-alone C6 peptide assay testing, which involves a single EIA using the C6 peptide of a *B. burgdorferi* lipoprotein.

Comparators
The following practice is currently being used to diagnose Lyme disease: established, 2-tiered diagnostic approach using either the standard methodology (EIA or immunofluorescence assay, followed by a confirmatory western immunoblot assay) or the modified methodology (use of a second EIA in place of the western immunoblot assay).

Outcomes
The general outcome of interest is the diagnostic accuracy of the test to identify those with or without Lyme disease.

Follow-up over several weeks to months would be needed to confirm test findings and conduct further testing. Long-term follow-up may be necessary to monitor for residual symptoms (eg, joint inflammation, encephalopathy) after the active infection has been eliminated.

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Study Selection Criteria
For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

REVIEW OF EVIDENCE

Systematic Reviews
A systematic review by Sanchez et al (2016), which assessed the diagnosis and treatment of Lyme disease, concluded that "stand-alone" C6 testing is not recommended over the 2-tiered approach due to slightly lower specificity.[17,]

Cohort Studies
Lipsett et al (2016) evaluated C6 EIA in 944 children of whom 114 (12%) had Lyme disease.[18,] The authors found stand-alone C6 EIA testing had lower specificity than standard 2-tiered testing (94.2% vs. 98.8%); specificity was increased to 98.6% with a supplemental immunoblot.

Zannoli et al (2020) reported on a multicenter evaluation of the C6 Lyme ELISA Kit in 804 samples collected from January to October 2019 across 3 laboratories in Italy.[19,] A total of 173 samples (21.5%) tested positive for Lyme disease. Compared with the standard 2-step algorithm, concordance was good overall with the C6 testing (Cohen's k=0.619). But, concordance varied by lab (Cohen's k range, 0.423 to 0.742). Overall, there were 67 false positive findings, resulting in a specificity of 89.4%. Study authors noted that this pattern of results was indicative of a lower specificity than the 2-tier workflow.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of stand-alone C6 peptide assay testing were identified.

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Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of stand-alone C6 peptide assay testing has not been established, a chain of evidence cannot be established.

Section Summary: Stand-Alone C6 Peptide Testing
Limited data have shown specificity is slightly lower with stand-alone C6 peptide testing compared to 2-tiered approaches. Additional research is necessary to determine diagnostic and treatment utility.

BORRELIA OUTER SURFACE PROTEIN A TESTING

Clinical Context and Test Purpose
The purpose of *Borrelia* Outer surface protein A (OspA) testing in individuals suspected of having Lyme disease is to inform an accurate diagnosis and, if positive, to initiate a treatment regimen.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is individuals with suspected Lyme disease.

Interventions
The test being considered is testing for *Borrelia* OspA.

Comparators
The following practice is currently being used to diagnose Lyme disease: established, 2-tiered diagnostic approach using either the standard methodology (EIA or immunofluorescence assay, followed by a confirmatory western immunoblot assay) or the modified methodology (use of a second EIA in place of the western immunoblot assay).

Outcomes
The general outcome of interest is the diagnostic accuracy of the test to identify those with or without Lyme disease.

Follow-up over several weeks to months would be needed to confirm test findings and conduct further testing. Long-term follow-up may be necessary to monitor for residual symptoms (eg, joint inflammation, encephalopathy) after the active infection has been eliminated.

Study Selection Criteria
For the evaluation of the clinical validity of the tests, studies that meet the following eligibility criteria were considered:
- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard

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- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

REVIEW OF EVIDENCE

Cohort Studies
Cantero et al (2025) published a prospective cohort of 57 patients with erythema migrans (n=46 with Lyme borreliosis, n=11 controls) who underwent PCR and mass spectrometry-based proteomics on skin biopsy samples.[20,] The positive rate of PCR testing was 61%. A total of 28 patients (61%) had positive proteomic screens. Of these, OspA was detected in 22 patients. Eight of the patients with detectable OspA had negative PCR results.

Magni et al (2015) published a cohort study evaluating antigen testing of urinary *Borrelia* OspA C-terminus peptide in early-stage Lyme borreliosis before and after treatment.[6,] A total of 268 urine samples from 168 patients were collected in a Lyme borreliosis endemic area. Results demonstrated that presence of OspA in the urine was linked to concurrent active symptoms (eg, erythema migrans rash and arthritis), while resolution of these symptoms after therapy correlated with urinary conversion to OspA negative. Pre-treatment, 100% (n=24) of newly diagnosed patients with an erythema migrans rash were positive for urinary OspA and no asymptomatic patients had false-positive results. Among these 24 patients, serology results were positive in 12 patients, negative in 5 patients, equivocal in 3 patients, and non-determinate in 4 patients. Urinary OspA was positive in all patients who, during the course of antibiotic therapy, exhibited persistence of erythema migrans rash (n=10) or arthritis (n=6). Post-treatment, urinary OspA switched from detectable to undetectable following symptom resolution in 100% of patients (n=8). The lowest limit of detection for urinary OspA was 1.7 pg/mL (range, 1.7 to 30). Furthermore, when evaluating the correlation of urinary OspA to Centers for Disease Control serology criteria for early-stage Lyme borreliosis, the specificity of the test was 87.5 % (21 urinary OspA positive/24 serology positive).

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

No RCTs assessing the clinical utility of *Borrelia* OspA testing were identified.

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Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Because the clinical validity of *Borrelia* OspA testing has not been established, a chain of evidence cannot be established.

Section Summary: *Borrelia* Outer surface protein A testing

A single cohort study evaluated antigen testing of urinary *Borrelia* OspA C-terminus peptide in early-stage Lyme borreliosis before and after treatment. Results demonstrated that the presence of OspA in the urine was linked to concurrent active symptoms (eg, erythema migrans rash and arthritis), while resolution of these symptoms after therapy correlated with urinary conversion to OspA negative. A second cohort study found that some patients with negative Lyme PCR screening tests had detectable OspA on proteomic screening tests.

Confirmed Lyme Disease

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The RCT is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

PROLONGED OR REPEATED COURSES OF ANTIBIOTIC THERAPY

Clinical Context and Therapy Purpose

The purpose of prolonged or repeated courses of antibiotic therapy in individuals with confirmed Lyme disease is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

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Populations
The relevant population of interest is individuals with confirmed Lyme disease.

Interventions
The therapy being considered is prolonged or repeated courses of antibiotic therapy.

Comparators
The following therapies are currently being used to treat confirmed Lyme disease: a standard course of oral antibiotic therapy and a 2- to 4-week course of intravenous (IV) antibiotic therapy.

Outcomes
The general outcomes of interest are disease remission and symptom reduction.

Follow-up over the long-term may be necessary to monitor for residual symptoms (eg, joint inflammation, encephalopathy).

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

REVIEW OF EVIDENCE

Randomized Controlled Trials
The evidence does not support the use of antibiotic therapy to treat patients with persistent *B. burgdorferi* infection and well-documented Lyme disease.[21,] See Tables 3 and 4, which summarize the characteristics and results of blinded, RCTs of extended antibiotic therapy versus placebo in such patients. Overall, the evidence has provided inconsistent results.

While morphologic variants of *B. burgdorferi* are thought to be related to persistent Lyme disease symptoms, a systematic review by Lantos et al (2014) found no evidence to support this thinking.[22,] Reviewers found no pathogenic relation between morphologic variants of *B. burgdorferi* and persistent symptoms of Lyme disease. Additionally, no literature was identified that would support a role for treatment of *B. burgdorferi* morphologic variants.

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Table 3. Summary of Randomized Controlled Trial Characteristics: Prolonged Antibiotic Therapy

Study	Participants	Interventions	
		Active	Comparator
Solheim et al (2022)[23,]	121 patients with European Lyme neuroborreliosis	Doxycycline daily for 6 weeks	Doxycycline daily for 2 weeks followed by 4 weeks of placebo
Berende et al (2016)[24,]	280 patients with persistent Lyme disease symptoms given IV ceftriaxone for 2 wk	Doxycycline or clarithromycin/hydroxyl-chloroquine for 12 wk	Placebo
Fallon et al (2008)[25,]	37 patients with documented objective memory impairment	IV ceftriaxone daily for 70 d	IV placebo daily for 70 d
Cameron (2008)[26,]	86 patients with symptoms of arthralgia, cardiac, or neurologic involvement with or without fatigue after previous successful antibiotic treatment of Lyme disease; study conducted in a primary care internal medicine practice (52 assigned, 31 evaluable)	Oral amoxicillin 3 g daily for 3 mo (34 assigned, 17 evaluable)	Oral placebo daily for 3 mo
Oksi et al (2007)[27,]	152 consecutive patients treated with a standard antibiotic regimen for 21 d	Amoxicillin twice daily for 100 d starting immediately after a standard regimen	Placebo twice daily for 100 d starting immediately after a standard regimen
Kaplan et al (2003)[28,]	129 patients (same trial as Klempner et al [2001])[29,]		
Krupp et al (2003)[30,]	Patients with persistent severe fatigue ≥6 mo	IV ceftriaxone daily for 28 d	IV placebo
Klempner et al (2001)[29,]	• 78 positive for IgG to *B. burgdorferi*; persistent symptoms interfered with patient functioning • 51 patients negative for IgG to *B. burgdorferi*; else, as above	• IV ceftriaxone daily for 30 d • oral doxycycline for 60 d	IV and oral placebo

IgG: immunoglobulin G; IV: intravenous.

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Table 4. Summary of Randomized Controlled Trial Results: Prolonged Antibiotic Therapy

Study	Results
Solheim et al (2022)[23,]	At 6 months, the between-group difference in the primary outcome (Composite Clinical Score [0-64 points]) from baseline was 0.06 (95% CI, -1.2 to 1.2; p=.99) in the intention-to-treat population and -0.4 (95% CI, -1.4 to 0.7; p=.51) in the per-protocol population. Noninferiority of the treatment regimens was not established using the predetermined margin of 0.5 points.
Berende et al (2016)[24,]	• SF-36 PCS did not differ across 3 study groups • Adverse event rates were similar across 3 study groups • 4 serious ceftriaxone-related adverse events
Fallon et al (2008)[25,]	Primary outcome (cognitive function across 6 domains) similarly improved in both groups at week 24 and did not differ significantly between groups; improvement between groups differed marginally at week 12 (p=.05). Exploratory subgroup analyses suggested significantly better improvement in ceftriaxone-treated patients with more severe baseline pain and physical functioning.
Cameron (2008)[26,]	• 44% of enrolled patients inevaluable at 6 mo; 17 had poorer baseline QOL and were lost due to treatment failure • SF-36 improvements for antibiotic vs. placebo arm were significant (46% vs. 18% ; p=.007), but unclear whether analysis included all or only evaluable patients • SF-36 PCS improvement did not differ significantly between treatment arms for evaluable patients (8.5 vs. 7) • SF-36 MCS significantly improved in antibiotic arm for evaluable patients (14.4 vs. 6.2 ; p=.04)
Oksi et al (2007)[27,]	Both treatment and control arms showed similar and not significantly different decreases in patient- and investigator-reported VAS outcomes (VAS range, 0-100; 0=no symptoms) at 12 mo. *B. burgdorferi*-specific antibodies declined similarly in both groups over 12 mo.
Kaplan et al (2003)[28,]	Both treatment and control arms showed similar and not significantly different decreases in SF-36 cognitive, pain, and role functioning scales, and improved mood as assessed with BDI and MMPI
Krupp et al (2003)[30,]	Ceftriaxone treatment arm showed no significant improvement in the primary outcome (laboratory measure of persistent infection). Significant improvement in secondary outcome (disabling fatigue); no significant treatment effect on cognitive function; no difference in change in SF-36 scores. Patients in the ceftriaxone group were significantly more likely to correctly identify their treatment assignment.
Klempner et al (2001)[29,]	No significant difference in QOL outcomes for either patient group. Studies terminated after interim analyses indicated it was highly unlikely that a significant difference in treatment efficacy would be observed.

BDI: Beck Depression Inventory; CI: confidence interval; MCS: Mental Component Summary; MMPI: Minnesota Multiphasic Personality Inventory; PCS: Physical Component Summary; QOL: quality of life; SF-36: 36-Item Short-Form Health Survey; VAS: visual analog scale.

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Section Summary: Prolonged or Repeated Courses of Antibiotic Therapy
Oral antibiotics usually are adequate for treatment of Lyme disease, though in some persistent cases, a 2- to 4-week course of IV antibiotics may be appropriate. Evidence from RCTs has not shown a benefit to prolonged (>4 weeks) or repeat courses of oral or IV antibiotics.

SUPPLEMENTAL INFORMATION
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

Centers for Disease Control and Prevention
In 2019, the Centers for Disease Control and Prevention (CDC) updated its recommendations for the serological diagnosis of Lyme disease.[5,] In addition to the standard 2-tiered testing process (sensitive enzyme immunoassay [EIA] or immunofluorescence assay, followed by a western immunoblot assay for specimens yielding positive or equivocal results), a modified 2-test methodology can be used, which uses a second EIA in place of the western immunoblot assay. Specifically, the CDC noted that "[w]hen cleared by FDA [Food and Drug Administration] for this purpose, serologic assays that utilize EIA rather than western immunoblot assay in a two-test format are acceptable alternatives for the laboratory diagnosis of Lyme disease."

Regarding treatment of Lyme disease, appropriate, oral antibiotics in the early stages of Lyme disease typically lead to rapid and complete recovery.[8,] In those with disseminated, non-cutaneous manifestations of Lyme disease, longer courses of antibiotics or intravenous treatment with antibiotics such as ceftriaxone may be required.

Infectious Diseases Society of America et al
The Infectious Diseases Society of America, American Academy of Neurology, and American College of Rheumatology published guidelines on the prevention, diagnosis, and treatment of Lyme disease in 2020.[3,] Table 5 lists their recommendations regarding diagnosis and treatment for Lyme disease and its various manifestations. Overall, antibody tests are considered first-line for diagnosis due to their performance characteristics and availability of accessible, clinically validated assays. Serum antibody tests are recommended to be used in a standard 2-tiered testing protocol, in which an EIA or indirect fluorescent antibody test is followed by immunoglobulin M (IgM) and IgG immunoblots. A modified 2-tiered testing protocol, in which 2 different EIAs are performed sequentially or concurrently without the use of immunoblots can also be used. The overall predictive value of these tests are increased when correlated with specific signs and symptoms, patient history, and risk factors. Antibody testing is limited by false negatives, especially in patients who present with cutaneous symptoms only within 2 weeks after the development of the skin lesion. The guidance notes that nonserological methods have been developed, such as polymerase chain reaction (PCR) assays, but the clinically validity of these

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approaches is not clear, in part due to the lack of a FDA-cleared test for Lyme disease diagnosis. Additionally, the guidance states that "[m]easurement of CXCL13 has not been sufficiently studied or standardized to recommend at present."

Table 5. Selected Recommendations for Lyme Diagnosis and Treatment

Recommendation	Strength of Recommendation	Level of Evidence
Erythema migrans		
"In patients with potential tick exposure in a Lyme disease endemic area who have 1 or more skin lesions compatible with erythema migrans, we recommend clinical diagnosis rather than laboratory testing."	strong	moderate quality
"In patients with 1 or more skin lesions suggestive of, but atypical for erythema migrans, we suggest antibody testing performed on an acute-phase serum sample (followed by a convalescent-phase serum sample if the initial result is negative) rather than currently available direct detection methods such as polymerase chain reaction (PCR) or culture performed on blood or skin samples."	weak	low quality
"For patients with erythema migrans, we recommend using oral antibiotic therapy with doxycycline, amoxicillin, or cefuroxime axetil."	strong	moderate quality
"We recommend that patients with erythema migrans be treated with either a 10-day course of doxycycline or a 14-day course of amoxicillin or cefuroxime axetil rather than longer treatment courses."	strong	moderate quality
Lyme neuroborreliosis		
"When assessing patients for possible Lyme neuroborreliosis involving either the peripheral nervous system (PNS) or central nervous system (CNS), we recommend serum antibody testing rather than PCR or culture of either cerebrospinal fluid (CSF) or serum."	strong	moderate quality
"In patients with Lyme disease-associated meningitis, cranial neuropathy, radiculoneuropathy or with other PNS manifestations, we recommend using intravenous (IV) ceftriaxone, cefotaxime, penicillin G, or oral doxycycline over other antimicrobials."	strong	moderate quality
"In patients with Lyme disease-associated parenchymal involvement of the brain or spinal cord, we recommend using IV over oral antibiotics."	strong	moderate quality
Lyme carditis		
"In outpatients with Lyme carditis, we suggest oral antibiotics over IV antibiotics."	weak	very low quality
"In the hospitalized patient with Lyme carditis, we suggest initially using IV ceftriaxone over oral antibiotics until there is evidence of clinical improvement, then switching to oral antibiotics to complete treatment."	weak	very low quality
"For the treatment of Lyme carditis, we suggest 14–21 days of total antibiotic therapy over longer durations of treatment."	weak	very low quality
Lyme arthritis		

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Recommendation	Strength of Recommendation	Level of Evidence
"When assessing possible Lyme arthritis, we recommend serum antibody testing over PCR or culture of blood or synovial fluid/tissue."	strong	moderate quality
"In seropositive patients for whom the diagnosis of Lyme arthritis is being considered but treatment decisions require more definitive information, we recommend PCR applied to synovial fluid or tissue rather than *Borrelia* culture of those samples."	strong	moderate quality
"For patients with Lyme arthritis, we recommend using oral antibiotic therapy for 28 days."	strong	moderate quality
"In patients with Lyme arthritis with partial response (mild residual joint swelling) after a first course of oral antibiotic, we make no recommendation for a second course of antibiotic versus observation."	no recommendation	knowledge gap
"In patients with Lyme arthritis with no or minimal response (moderate to severe joint swelling with minimal reduction of the joint effusion) to an initial course of oral antibiotic, we suggest a 2- to 4-week course of IV ceftriaxone over a second course of oral antibiotics."	weak	low quality
"In patients who have failed one course of oral antibiotics and one course of IV antibiotics, we suggest a referral to a rheumatologist or other trained specialist for consideration of the use of disease modifying anti-rheumatic drugs (DMARDs), biologic agents, intraarticular steroids, or arthroscopic synovectomy. **Comment:** Antibiotic therapy for longer than 8 weeks is not expected to provide additional benefit to patients with persistent arthritis if that treatment has included 1 course of IV therapy."	weak	very low quality
Persistent symptoms following standard treatment of Lyme disease		
"For patients who have persistent or recurring nonspecific symptoms such as fatigue, pain, or cognitive impairment following recommended treatment for Lyme disease, but who lack objective evidence of reinfection or treatment failure, we recommend against additional antibiotic therapy. **Comment:** Evidence of persistent infection or treatment failure would include objective signs of disease activity, such as arthritis, meningitis, or neuropathy."	strong	moderate quality

Association of Public Health Laboratories

In April 2024, the Association of Public Health Laboratories published updated guidance on the suggested reporting language, interpretation, and guidance for serologic test results for Lyme disease.[31,] The standard 2-tiered testing and modified 2-tiered testing methods are recommended for diagnosis of Lyme disease. In disseminated Lyme disease, standard 2-tiered testing has a high sensitivity (>87%) and specificity (99%) and can provide strong support for a diagnosis. The guidance also notes that "[s]ome laboratories offer tests that have not been cleared by FDA (e.g., molecular tests, antibody tests on samples other than serum). Use of these tests is generally not recommended, as their accuracy and clinical usefulness have not been adequately established."

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National Institute for Health and Care Excellence

Guidance on Lyme disease from NICE was published in 2018.[32,] The NICE recommended that if "there is clinical suspicion of Lyme disease in people without erythema migrans," an "enzyme-linked immunosorbent assay (ELISA) test for Lyme disease" should be offered. If the ELISA is "positive or equivocal," an "immunoblot test" for Lyme disease should be performed. The NICE recommended oral antibiotics for the treatment of erythema migrans and/or nonfocal symptoms, and a 21-day course of IV antibiotics for Lyme disease affecting the central nervous system or for Lyme carditis when the patients are hemodynamically unstable.

International Lyme and Associated Diseases Society

In 2014, the International Lyme and Associated Diseases Society published guidelines to address 3 clinical issues: the usefulness of antibiotic prophylaxis of tick bites, the effectiveness of erythema migrans treatment, and antibiotic retreatment in patients with persistent symptoms.[33,] The Society noted that the evidence on treatment of tick bites, erythema migrans rashes, and persistent manifestations is limited. Regarding the treatment of patients with persistent symptoms, the Society concluded that the evidence for retreatment is adequate to support retreatment, but is not strong enough to mandate treatment. The Society determined that there was no compelling evidence supporting withholding antibiotics from symptomatic patients, especially since there is a lack of alternative treatment options. Due to the number of clinical variables and the heterogeneity of the patient population, clinical judgment and patients' values and goals should be considered when planning a treatment strategy.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently ongoing or unpublished trials that might influence this review are listed in Table 6.

Table 6. Summary of Key Trials

NCT No.	Trial Name	Enrollment	Completion Date
Unpublished			
NCT04422314[a]	ImmuneSense Lyme Study	893	Dec 2021

NCT: national clinical trial.
[a] Industry sponsored or partially sponsored.

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CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
86617	Antibody; *Borrelia burgdorferi* (Lyme disease) confirmatory test (e.g., Western blot or immunoblot)
86618	Antibody; Borrelia burgdorferi (Lyme disease)
86619	Antibody; Borrelia (relapsing fever)
87475	Infectious agent detection by nucleic acid (DNA or RNA); *Borrelia burgdorferi*, direct probe technique
87476	Infectious agent detection by nucleic acid (DNA or RNA); *Borrelia burgdorferi,* amplified probe technique
96374	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug
0041U	Borrelia burgdorferi, antibody detection of 5 recombinant protein groups, by immunoblot, IgM [Lyme ImmunoBlot IgM Manufacturer- IGeneX Inc, ID-FISH Technology Inc.]
0042U	Borrelia burgdorferi, antibody detection of 12 recombinant protein groups, by immunoblot, IgG [Lyme ImmunoBlot IgG Manufacturer- IGeneX Inc, ID-FISH Technology Inc.]
0043U	Tick-borne relapsing fever Borrelia group, antibody detection to 4 recombinant protein groups, by immunoblot, IgM [Tick-Borne Relapsing Fever (TBRF) Borrelia ImmunoBlots IgM Test Manufacturer- IGeneX Inc, ID-FISH Technology Inc.]
0044U	Tick-borne relapsing fever Borrelia group, antibody detection to 4 recombinant protein groups, by immunoblot, IgG [Tick-Borne Relapsing Fever (TBRF) Borrelia ImmunoBlots IgG Test Manufacturer- IGeneX Inc, ID-FISH Technology Inc.]
0316U	Borrelia burgdorferi (Lyme disease), OspA protein evaluation, urine

REVISIONS	
04-04-2011	Policy added to the bcbsks.com web site.
04-12-2012	Description section updated
	In Policy section: ▪ Added to C 1 "in the absence of objective clinical or laboratory evidence for Lyme disease" to read "Patients with symptoms consistent with chronic fatigue syndrome or fibromyalgia, in the absence of objective clinical or laboratory evidence for Lyme disease;"

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REVISIONS	
	▪ Revised in C 9 ">" to "≥" to read, "Patients with chronic (≥6 months) subjective symptoms…" ▪ Revised in H "Determination of levels of the B lymphocyte chemoattractant CXCL13 for diagnosis or monitoring treatment is considered experimental / investigational." to "Other diagnostic testing is considered experimental / investigational including but not limited to C6 peptide ELISA or determination of levels of the B lymphocyte chemoattractant CXCL13 for diagnosis or monitoring treatment."
	Rationale section updated
	In Coding section: ▪ Updated nomenclature for CPT codes: 86617, 87475, 87476, 87477, 96367
	References updated
12-07-2012	Description section updated
	Rationale section updated
	References updated
02-28-2014	In Coding Section: ▪ ICD-10 Diagnoses codes added
02-01-2017	Description section updated
	In Policy section: ▪ Added the sub-heading "IV Antibiotic Therapy" ahead of the policy statements I through VI. ▪ Added the sub-heading "Diagnostic Testing" and renumbered the remaining policy statements to I through IV. ▪ The following updates were made with no change to policy intent: ▪ In Item I replaced "IV" with "intravenous" ▪ In Item I 2 replaced "CNS" with "central nervous system" ▪ In Item I 3 replaced "CDC" with "Centers for Disease Control and Prevention" ▪ In Item II replaced "greater" with "more" ▪ In Item V replaced "greater than" with ">" ▪ In Item IX added "stand-alone" to read "…"stand-alone" C6 peptide ELISA"…
	Rationale section updated
	In Coding section: ▪ Coding notation removed
	References updated
04-11-2018	In Coding section: ▪ Added CPT Codes: 0041U, 0042U, 0043U, 0044U (Effective 04-01-2018)
11-20-2018	Description section updated
	In Policy section: ▪ Added the following headers to define each section: Neuroborreliosis, Lyme Carditis, Lyme Arthritis, Antibiotic Therapy ▪ In Item I 2 replaced "by" with "on the basis of" to read "Lyme disease may be documented on the basis of serologic testing…"
	Rationale section updated
	In Coding section: ▪ Deleted termed CPT code: 87477 ▪ Updated CPT nomenclature: 87476, 0041U, 0042U, 0043U, 0044U
	Rationale updated
02-25-2021	Updated Description section
	Updated Rationale section
	In the coding section: • Added CPT codes 86618 and 86619

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REVISIONS	
	• Removed CPT codes 96365, 96366, 96367, 96368, 96375, 96376
	Updated Reference section
12-2-2021	Updated Description Section
	Updated Policy Section • Section D.1.e.Changed "Antibiotic-refractory" to "Post-antibiotic"
	Updated Rationale Section
	Updated Coding Section • Added CPT code 96374
	Updated References Section
Posted 1-24-2023 Effective 2-23-2023	Updated Description Section
	Updated Policy Section ▪ Section E Diagnostic Testing ▪ Added: "PCR-based detection of B. burgdorferi is considered experimental / investigational when the above criteria is not met." ▪ Removed: "PCR-based direct detection of B. burgdorferi in urine samples is considered experimental / investigational in all clinical situations." ▪ Section E6 Added: "or Outer surface protein A (OspA) antigen testing"
	Updated Rationale Section
	Updated Coding Section ▪ Added 0316U
	Updated References Section
11-17-2023	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Removed the ICD-10 codes
	Updated References Section
12-03-2024	Updated Description Section
	Updated Rationale Section
	Updated References Section
Posted 11-26-2025 Effective 12-26-2025	Updated Description Section
	Updated Policy Section ▪ In Section D1 and D2 changed from not medically necessary to experimental/investigational.
	Updated Rationale Section
	Updated Reference Section

REFERENCES

1. Steere AC. Lyme disease. N Engl J Med. Jul 12 2001; 345(2): 115-25. PMID 11450660
2. Institute of Medicine (IOM). Critical Needs and Gaps in Understanding: Prevention, Amelioration, and Resolution of Lyme and Other Tick-Borne Diseases: The Short-Term and Long-Term Outcomes: Workshop Report. Washington, DC: National Academies Press; 2011.
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. Jan 23 2021; 72(1): e1-e48. PMID 33417672

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Contains Public Information

4. Situm M, Poje G, Grahovac B, et al. Diagnosis of Lyme borreliosis by polymerase chain reaction. Clin Dermatol. 2002; 20(2): 147-55. PMID 11973049
5. Mead P, Petersen J, Hinckley A. Updated CDC Recommendation for Serologic Diagnosis of Lyme Disease. MMWR Morb Mortal Wkly Rep. Aug 16 2019; 68(32): 703. PMID 31415492
6. Magni R, Espina BH, Shah K, et al. Application of Nanotrap technology for high sensitivity measurement of urinary outer surface protein A carboxyl-terminus domain in early stage Lyme borreliosis. J Transl Med. Nov 04 2015; 13: 346. PMID 26537892
7. Galaxy Advanced Microbial Diagnostics. Lyme Borrelia Nanotrap Antigen Test. https://www.galaxydx.com/nanotrap-urine-test-for-lyme-disease/. Accessed August 18, 2025.
8. Centers for Disease Control and Prevention. Lyme Disease: Treatment. Updated May 15, 2024; https://www.cdc.gov/lyme/treatment/index.html. Accessed August 18, 2025.
9. Oksi J, Marjamäki M, Nikoskelainen J, et al. Borrelia burgdorferi detected by culture and PCR in clinical relapse of disseminated Lyme borreliosis. Ann Med. Jun 1999; 31(3): 225-32. PMID 10442678
10. Nigrovic LE, Lewander DP, Balamuth F, et al. The Lyme Disease Polymerase Chain Reaction Test Has Low Sensitivity. Vector Borne Zoonotic Dis. Apr 2020; 20(4): 310-313. PMID 31821110
11. Pritt BS, Mead PS, Johnson DKH, et al. Identification of a novel pathogenic Borrelia species causing Lyme borreliosis with unusually high spirochaetaemia: a descriptive study. Lancet Infect Dis. May 2016; 16(5): 556-564. PMID 26856777
12. Wilske B, Fingerle V, Schulte-Spechtel U. Microbiological and serological diagnosis of Lyme borreliosis. FEMS Immunol Med Microbiol. Feb 2007; 49(1): 13-21. PMID 17266710
13. Rupprecht TA, Manz KM, Fingerle V, et al. Diagnostic value of cerebrospinal fluid CXCL13 for acute Lyme neuroborreliosis. A systematic review and meta-analysis. Clin Microbiol Infect. Dec 2018; 24(12): 1234-1240. PMID 29674128
14. Waiß C, Ströbele B, Graichen U, et al. CXCL13 as a biomarker in the diagnostics of European lyme Neuroborreliosis - A prospective multicentre study in Austria. J Cent Nerv Syst Dis. 2024; 16: 11795735241247026. PMID 38706882
15. Eckman EA, Clausen DM, Herdt AR, et al. Specificity and Diagnostic Utility of Cerebrospinal Fluid CXCL13 in Lyme Neuroborreliosis. Clin Infect Dis. May 18 2021; 72(10): 1719-1726. PMID 32221538
16. Jung L, Lâm TT, Streng A, et al. Elevated Cerebrospinal Fluid CXCL13 Is a Helpful Marker for the Early Diagnosis of Neuroborreliosis in Children. Pediatr Infect Dis J. Jun 01 2025; 44(6): 577-581. PMID 39898650
17. Sanchez E, Vannier E, Wormser GP, et al. Diagnosis, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: A Review. JAMA. Apr 26 2016; 315(16): 1767-77. PMID 27115378
18. Lipsett SC, Branda JA, McAdam AJ, et al. Evaluation of the C6 Lyme Enzyme Immunoassay for the Diagnosis of Lyme Disease in Children and Adolescents. Clin Infect Dis. Oct 01 2016; 63(7): 922-8. PMID 27358358
19. Zannoli S, Fantini M, Semprini S, et al. Multicenter Evaluation of the C6 Lyme ELISA Kit for the Diagnosis of Lyme Disease. Microorganisms. Mar 24 2020; 8(3). PMID 32213811
20. Cantero P, Ehret-Sabatier L, Lenormand C, et al. Detection of Borrelia burgdorferi sensu lato by proteomics: a complementary diagnosis tool on erythema migrans biopsies. Clin Microbiol Infect. Jan 2025; 31(1): 78-86. PMID 39454756

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Contains Public Information

21. Halperin JJ, Shapiro ED, Logigian E, et al. Practice parameter: treatment of nervous system Lyme disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology [RETIRED]. Neurology. Jul 03 2007; 69(1): 91-102. PMID 17522387
22. Lantos PM, Auwaerter PG, Wormser GP. A systematic review of Borrelia burgdorferi morphologic variants does not support a role in chronic Lyme disease. Clin Infect Dis. Mar 2014; 58(5): 663-71. PMID 24336823
23. Solheim AM, Lorentzen ÅR, Dahlberg AO, et al. Six versus 2 weeks treatment with doxycycline in European Lyme neuroborreliosis: a multicentre, non-inferiority, double-blinded, randomised and placebo-controlled trial. J Neurol Neurosurg Psychiatry. Jul 27 2022; 93(11): 1222-8. PMID 35896378
24. Berende A, ter Hofstede HJ, Vos FJ, et al. Randomized Trial of Longer-Term Therapy for Symptoms Attributed to Lyme Disease. N Engl J Med. Mar 31 2016; 374(13): 1209-20. PMID 27028911
25. Fallon BA, Keilp JG, Corbera KM, et al. A randomized, placebo-controlled trial of repeated IV antibiotic therapy for Lyme encephalopathy. Neurology. Mar 25 2008; 70(13): 992-1003. PMID 17928580
26. Cameron D. Severity of Lyme disease with persistent symptoms. Insights from a double-blind placebo-controlled clinical trial. Minerva Med. Oct 2008; 99(5): 489-96. PMID 18971914
27. Oksi J, Nikoskelainen J, Hiekkanen H, et al. Duration of antibiotic treatment in disseminated Lyme borreliosis: a double-blind, randomized, placebo-controlled, multicenter clinical study. Eur J Clin Microbiol Infect Dis. Aug 2007; 26(8): 571-81. PMID 17587070
28. Kaplan RF, Trevino RP, Johnson GM, et al. Cognitive function in post-treatment Lyme disease: do additional antibiotics help?. Neurology. Jun 24 2003; 60(12): 1916-22. PMID 12821733
29. Klempner 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. Jul 12 2001; 345(2): 85-92. PMID 11450676
30. Krupp LB, Hyman LG, Grimson R, et al. Study and treatment of post Lyme disease (STOP-LD): a randomized double masked clinical trial. Neurology. Jun 24 2003; 60(12): 1923-30. PMID 12821734
31. Association of Public Health Laboratories. Suggested Reporting Language, Interpretation and Guidance Regarding Lyme Disease Serologic Test Results. April 2024; https://www.aphl.org/aboutAPHL/publications/Documents/ID-2024-Lyme-Disease-Serologic-Testing-Reporting.pdf. Accessed August 18, 2025.
32. National Institute for Health and Care Excellence (NICE). Lyme disease [NG95]. 2018; https://www.nice.org.uk/guidance/NG95. Accessed August 18, 2025.
33. Cameron DJ, Johnson LB, Maloney EL. Evidence assessments and guideline recommendations in Lyme disease: the clinical management of known tick bites, erythema migrans rashes and persistent disease. Expert Rev Anti Infect Ther. Sep 2014; 12(9): 1103-35. PMID 25077519

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