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## Intravenous Antibiotic Therapy and Associated Diagnostic Testing for Lyme Disease

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<b>Related Policies (if applicable)</b>
None

### Disclaimer

*Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.*

### Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

### Legislative Mandates

**EXCEPTION:** Illinois legislation requires coverage for long-term antibiotic therapy, including necessary office visits and ongoing testing, for a person with a tick-borne disease when determined to be medically necessary and ordered by a physician licensed to practice medicine in all its branches after making a thorough evaluation of the person's symptoms, diagnostic test results, or response to treatment. An experimental drug shall be covered as a long-term antibiotic therapy if it is approved for an indication by the United States Food and Drug Administration. A drug, including an experimental drug, shall be covered for an off-label use in the treatment of a tick-borne disease if the drug has been approved by the United States Food and Drug Administration.

## Coverage

### Lyme Disease

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

#### Neuroborreliosis

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:

- Lymphocytic meningitis with documented cerebrospinal fluid (CSF) abnormalities;
- Cranial neuropathy, other than uncomplicated cranial nerve palsy, with documented CSF abnormalities;
- Encephalitis or encephalomyelitis with documented CSF abnormalities;
- Radiculopathy; or
- Polyneuropathy.

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

Serologic documentation of infection requires:

- Positive or indeterminate enzyme-linked immunosorbent assay (ELISA), AND
- Positive immunoblot blot by Centers for Disease Control and Prevention criteria.

Documented CSF abnormalities include ALL of the following:

- Pleocytosis; AND
- Evidence of intrathecal production of *Borrelia (B) burgdorferi* antibodies in CSF; AND
- Increased protein levels.

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.

#### Lyme Carditis

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 (AV) block or a PR interval more than 0.3 seconds. Documentation of Lyme carditis may include PCR-based direct detection of *B. burgdorferi* in the blood when results of serologic studies are equivocal.

### Lyme Arthritis

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.

### Antibiotic Therapy

Intravenous antibiotic therapy **is considered not medically necessary** in the following situations:

- Individuals with symptoms consistent with chronic fatigue syndrome or fibromyalgia, in the absence of objective clinical or laboratory evidence for Lyme disease;
- Individuals with seronegative Lyme disease in the absence of CSF antibodies;
- Initial therapy in individuals with Lyme arthritis without coexisting neurologic symptoms;
- Cranial nerve palsy (e.g., Bell palsy) without clinical evidence of meningitis;
- Post-antibiotic Lyme arthritis (unresponsive to 2 courses of oral antibiotics or to 1 course of oral and 1 course of intravenous antibiotic therapy);
- Individuals with vague systemic symptoms without supporting serologic or CSF studies;
- Individuals with a positive enzyme-linked immunosorbent assay test (ELISA), unconfirmed by an immunoblot or Western blot test (see definition above);
- Individuals with an isolated positive serologic test in the setting of multiple negative, serologic studies; and
- Individuals with chronic ( $\geq 6$  months) subjective symptoms (“post-Lyme syndrome”) after receiving recommended treatment regimens for documented Lyme disease.

Repeat or prolonged courses (e.g., >4 weeks) of IV antibiotic therapy **are considered not medically necessary**.

### Diagnostic Testing

Repeat PCR-based direct detection of *B. burgdorferi* **is considered experimental, investigational and/or unproven** in the following situations:

- As a justification for the continuation of IV antibiotics beyond 1 month in individuals with persistent symptoms;
- As a technique to follow therapeutic response.

PCR-based direct detection of *B. burgdorferi* in urine samples **is considered experimental, investigational and/or unproven** in all clinical situations.

Genotyping or phenotyping of *B. burgdorferi* **is considered experimental, investigational and/or unproven**.

Other diagnostic testing **is considered experimental, investigational and/or unproven**, 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.

## Policy Guidelines

None.

## Description

### 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.

### 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 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 (i.e., 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 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. 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).

#### **Rationale**

## **SUSPECTED LYME DISEASE**

Medical policies 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. Medical policies assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these policies, 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 policy.

#### *Populations*

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

#### *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 (e.g., 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).

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.

### *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. burgdorferi sensu stricto* 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 policy.

#### *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).

#### *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 (e.g., 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).

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 ( $p \leq 0.001$ ). 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).

Overall, the quality of the data is 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 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	CSF <i>Borrelia</i> -specific antibody index	55 pg/mL	Reference was assayed at time of collection; index test was

		undergone <i>Borrelia</i> -specific antibody testing			assayed retrospectively
Waiß 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 U.S.	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 immunosorbent assay; LNB: Lyme neuroborreliosis; U.S.: United States; WBC: white blood cell.

**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%)
<b><i>Prospective studies</i></b>				
Waiß et al. (2023) (14)	LNB (n=44) vs control (n=398)	271 pg/ml	95.2%	97.2%
<b><i>Retrospective studies</i></b>				
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.

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 U.S.-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 policy.

#### *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 (e.g., 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).

### 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.

### *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 policy.

#### *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 (e.g., 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).

#### 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 (e.g., 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.

### *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 (e.g., 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**

Medical policies 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 policy.

### *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 (e.g., 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.

### 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.

**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 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 weeks	Doxycycline or clarithromycin/hydroxylchloroquine for 12 weeks	Placebo
Fallon et al. (2008) (25)	37 patients with documented objective memory impairment	IV ceftriaxone daily for 70 days	IV placebo daily for 70 days
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 months (34 assigned, 17 evaluable)	Oral placebo daily for 3 months
Oksi et al. (2007) (27)	152 consecutive patients treated with standard antibiotic regimen for 21 days	Amoxicillin twice daily for 100 days starting immediately after standard regimen	Placebo twice daily for 100 days starting immediately after 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 $\geq 6$ months	IV ceftriaxone daily for 28 days	IV placebo
Klempner et al. (2001) (29)	<ul style="list-style-type: none"> <li>• 78 positive for IgG to <i>B. burgdorferi</i>; persistent symptoms interfered with patient functioning</li> <li>• 51 patients negative for IgG to <i>B. burgdorferi</i>; else, as above</li> </ul>	<ul style="list-style-type: none"> <li>• IV ceftriaxone daily for 30 days</li> <li>• Oral doxycycline for 60 days</li> </ul>	IV and oral placebo

IgG: immunoglobulin G; IV: intravenous.

**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)	<ul style="list-style-type: none"> <li>• SF-36 PCS did not differ across 3 study groups.</li> <li>• Adverse event rates similar across 3 study groups.</li> <li>• 4 serious ceftriaxone-related adverse events.</li> </ul>
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)	<ul style="list-style-type: none"> <li>• 44% of enrolled patients inevaluable at 6 mo; 17 had poorer baseline QOL and were lost due to treatment failure.</li> <li>• SF-36 improvements for antibiotic vs placebo arm were significant (46% vs 18%, p=0.007), but unclear whether analysis included all or only evaluable patients.</li> <li>• SF-36 PCS improvement did not differ significantly between treatment arms for evaluable patients (8.5 vs 7).</li> <li>• SF-36 MCS significantly improved in antibiotic arm for evaluable patients (14.4 vs 6.2, p=0.04).</li> </ul>
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. <i>B. burgdorferi</i> -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; mo: month; PCS: Physical Component Summary; QOL: quality of life; SF-36: 36- Item Short-Form Health Survey; VAS: visual analog scale.

### 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.

### **Summary of Evidence**

For individuals who are suspected of having Lyme disease who receive genotyping or phenotyping of *B. burgdorferi* subspecies, the evidence is limited. Relevant outcomes are a change in disease status and morbid events. Polymerase chain reaction (PCR)-based testing for *B. burgdorferi* genospecies is feasible. However, no evidence was identified that knowledge of the *B. burgdorferi* genotype or phenotype could be used to improve patient management and outcomes. Additionally, 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are suspected of having Lyme disease who receive CXCL13 chemokine concentration testing, the evidence includes a meta-analysis of 18 studies of European cohorts, 2 retrospective studies (one U.S.-based and one European), and a European-based prospective study. Relevant outcomes are a change in disease status and morbid events. Study 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. Additional research is needed to determine the diagnostic utility of CXCL13 levels. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are suspected of having Lyme disease who receive stand-alone C6 peptide assay testing, the evidence includes cohort studies. Relevant outcomes are a change in disease status and morbid events. Limited data have shown specificity is slightly lower with stand-alone C6 peptide testing compared to 2-tiered approaches. Additional research is needed to determine the diagnostic utility of stand-alone C6 testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who are suspected of having Lyme disease who receive *Borrelia* OspA testing, the evidence includes 2 cohort studies. Relevant outcomes are a change in disease status and morbid events. Limited data have shown that the presence of *Borrelia* OspA in the urine is linked to concurrent active symptoms (e.g., erythema migrans rash and arthritis), while resolution of these symptoms after therapy is correlated with urinary conversion to OspA negative. Additional research is needed to determine the diagnostic utility of *Borrelia* OspA testing. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with confirmed Lyme disease who receive prolonged or repeated courses of antibiotic therapy, the evidence includes randomized controlled trials (RCTs). Relevant

outcomes are symptoms, change in disease status, morbid events, and health status measures. Oral antibiotics usually are adequate for treatment of Lyme disease, though, in some persistent cases, a 2- to 4-week course of intravenous (IV) antibiotics may be appropriate. Evidence from RCTs has not shown a benefit in prolonged (>4 weeks) or repeat courses of oral or IV antibiotics. The evidence is sufficient to determine that the technology is unlikely to improve the net health outcome.

### **Practice Guidelines and Position Statements**

#### 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 led 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 approaches is not clear, in part due to the lack of an 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
<b>Erythema migrans</b>		
"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
<b>Lyme neuroborreliosis</b>		
"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
<b>Lyme carditis</b>		
"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
<b>Lyme arthritis</b>		
"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 <i>Borrelia</i> 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
<b>Persistent symptoms following standard treatment of Lyme disease</b>		
"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	Strong	Moderate quality

objective signs of disease activity, such as arthritis, meningitis, or neuropathy."		
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#### 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."

#### National Institute for Health and Care Excellence (NICE)

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.

#### **Ongoing and Unpublished Clinical Trials**

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

**Table 6. Summary of Key Trials**

NCT Number	Trial Name	Enrollment	Completion Date
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NCT04422314 <sup>a</sup>	ImmuneSense Lyme Study	893	Dec 2021
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NCT: national clinical trial.

<sup>a</sup>Industry sponsored or partially sponsored.

## Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	84181, 86617, 86618, 86619, 87475, 87476, 96374, 0041U, 0042U, 0043U, 0044U, 0316U
HCPCS Codes	None

\*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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## **Centers for Medicare and Medicaid Services (CMS)**

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <<https://www.cms.hhs.gov>>.

## **Policy History/Revision**

<b>Date</b>	<b>Description of Change</b>
12/15/2025	Document updated. Coverage unchanged. Added references 16 and 20.
12/15/2024	Document updated with literature review. Coverage unchanged. Added/updated the following references: 8, 14, and 29.
01/01/2024	Document updated with literature review. The following change was made to Coverage: Added "Outer surface protein A (OspA) antigen testing" to list of "other diagnostic testing" that is considered to be experimental, investigational, and/or unproven. Added references 6, 7, and 20; other(s) updated.
09/15/2022	Document updated with literature review. The following change was made to Coverage: Updated statement on Lyme arthritis to change "antibiotic-refractory" to preferred terminology of "post-antibiotic"; intent unchanged. Added references 3, 5, 6, 11, 12 and 25.
02/01/2022	Reviewed. No changes.
03/15/2021	Document updated with literature review. Coverage unchanged. Added references 5 and 12.
08/15/2020	Reviewed. No changes.
02/15/2019	Document updated with literature review. Coverage unchanged. Added references 21 and 26.
04/15/2018	Reviewed. No changes.
07/15/2017	Document updated with literature review. The following editorial change was made to Coverage: "Stand alone" was added to bullet regarding C6 peptide ELISA for clarification.
02/15/2016	Reviewed. No changes.
07/01/2015	Document updated with literature review. The following was removed from the coverage section as the vaccine is no longer marketed: "Administration of the Lyme disease vaccine, recombinant OspA, may be considered medically necessary if the patient is between 15 to 70 years of age and lives or works in a grassy or wooded area where ticks may be present that may be harboring the bacterium <i>Borrelia burgdorferi</i> (B. burgdorferi)." Otherwise coverage unchanged. Title changed from Lyme Disease ( <i>Borrelia Burgdorferi</i> ) Management.
06/15/2014	Document updated with literature review. The following statement was added to the experimental, investigational, and/or unproven coverage position: "All other diagnostic testing for Lyme disease are considered experimental, investigational and/or unproven including but not limited to..." and the following were added to the listing of experimental, investigational, and/or unproven indications: C6 peptide ELISA and Determination of levels of the B lymphocyte chemoattractant CXCL13 for diagnosis or monitoring treatment.
05/01/2011	Document updated with literature review. The following changes were made: 1) The "detection and diagnostic testing" section of coverage was removed, and the testing criteria are now included with the treatment

	<p>criteria; 2) Specific IgG and IgM titer amounts were removed, and the CDC recommendations for the ELISA and Immunoblot tests were moved to the Description section; 3) The criteria for documentation of early skin lesions and arthritis were removed; 4) The following was added as not medically necessary: Patients with chronic (&gt;6 months) subjective symptoms ("post-Lyme syndrome") after receiving recommended treatment regimens for documented Lyme disease; Bell's palsy without clinical evidence of meningitis; Antibiotic-refractory Lyme arthritis; 5) The following was added as experimental, investigational and unproven: Immunofluorescent staining for cell wall-deficient forms of <i>B burgdorferi</i>, and lymphocyte transformation tests.</p>
08/15/2008	Revised/updated entire document.
07/15/2006	Revised/updated entire document.
06/01/1999	Revised/updated entire document.
02/01/1996	Revised/updated entire document.
04/01/1994	Revised/updated entire document.
05/01/1990	New medical document.