



MASSACHUSETTS

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Medical Policy

Intravenous Antibiotic Therapy and Associated Diagnostic Testing for Lyme Disease

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Policy Number: 171

BCBSA Reference Number: 5.01.08 (For Plan internal use only)

Related Policies

None

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

TESTING

Polymerase chain reaction (PCR) - based direct detection of *B burgdorferi* in CSF samples may be **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.

Repeat PCR-based direct detection of *B burgdorferi* is **INVESTIGATIONAL** in the following situations:

- As a justification for 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 **INVESTIGATIONAL** in all clinical situations.

Genotyping or phenotyping of *B burgdorferi* is **INVESTIGATIONAL**.

Other diagnostic testing is **INVESTIGATIONAL** including but not limited to “stand-alone” C6 peptide ELISA determination of levels of the B lymphocyte chemoattractant CXCL13, or Outer surface protein A (OspA) antigen testing for diagnosis or monitoring treatment.

TREATMENT¹

Short-term IV antibiotic use (2-4 weeks) for the treatment of Lyme disease is considered **MEDICALLY NECESSARY**. The ordering provider must attest that the member has Lyme disease through confirmatory testing or based on the patient's clinical presentation.

Per State Mandate¹[Chapter 183 of the Acts of 2016, "An Act Relative to Long-Term Antibiotic Therapy for the Treatment of Lyme Disease"](#):

- a. For the purposes of this section, "long-term antibiotic therapy" and "Lyme disease" shall have the meaning ascribed to them in section 12DD of chapter 112 (see below).
- b. A policy, contract, agreement, plan or certificate of insurance issued, delivered or renewed within the commonwealth that provides medical expense coverage shall provide coverage for long-term antibiotic therapy for a patient with Lyme disease when determined to be medically necessary and ordered by a licensed physician after making a thorough evaluation of the patient'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; provided, however, that a drug, including an experimental drug, shall be covered for an off-label use in the treatment of Lyme disease if the drug has been approved by the United States Food and Drug Administration.

[Section 12DD: Administration of long-term antibiotic therapy upon diagnosis of Lyme disease](#)¹

- a. As used in this section, the following words shall have the following meanings unless the context clearly requires otherwise:

"Long-term antibiotic therapy," the administration of oral, intramuscular or intravenous antibiotics singly or in combination, for periods of time in excess of 4 weeks.

"Lyme disease," the clinical diagnosis of a patient by a physician licensed under [section 2](#) of the presence of signs or symptoms compatible with acute infection with *Borrelia burgdorferi*; late stage, persistent or chronic infection with *Borrelia burgdorferi*; complications related to such infection; or with such other strains of *Borrelia* that become identified or recognized by the National Centers for Disease Control and Prevention as a cause of Lyme disease; provided, however, that "Lyme disease" shall also include an infection that meets the surveillance criteria set forth by the National Centers for Disease Control and Prevention and a clinical diagnosis of Lyme disease that does not meet the National Centers for Disease Control and Prevention surveillance criteria but presents other acute and chronic signs or symptoms of Lyme disease as determined by the treating physician; and provided further, that clinical diagnosis shall be based on knowledge obtained through medical history and physical examination only or in conjunction with testing that provides supportive data for such clinical diagnosis.

- b. A licensed physician may prescribe, administer or dispense long-term antibiotic therapy for a therapeutic purpose to eliminate infection or to control a patient's symptoms upon making a clinical diagnosis that the patient has Lyme disease or displays symptoms consistent with a clinical diagnosis of Lyme disease, if such clinical diagnosis and treatment are documented in the patient's medical record by the prescribing licensed physician.

Prior Authorization Information

Inpatient

- For services described in this policy, precertification/preauthorization **IS REQUIRED** for all products if the procedure is performed **inpatient**.

Outpatient

- For services described in this policy, see below for products where prior authorization **might be required** if the procedure is performed **outpatient**.

	Outpatient
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Commercial Managed Care (HMO and POS)	Prior authorization is not required.
Commercial PPO and Indemnity	Prior authorization is not required.
Medicare HMO BlueSM	Prior authorization is not required.
Medicare PPO BlueSM	Prior authorization is not required.

For IV therapy, providers are required to complete the [Home Infusion Therapy Prior Authorization Form #430](#)

CPT Codes / HCPCS Codes / ICD Codes

Inclusion or exclusion of a code 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 as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

The above **medical necessity criteria MUST** be met for the following codes to be covered for **Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:**

CPT Codes

CPT codes:	Code Description
86617	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

The following CPT codes are considered investigational for **Commercial Members: Managed Care (HMO and POS), PPO, Indemnity, Medicare HMO Blue and Medicare PPO Blue:**

CPT Codes

CPT codes:	Code Description
0041U	Borrelia burgdorferi, antibody detection of 5 recombinant protein groups, by immunoblot, IgM
0042U	Borrelia burgdorferi, antibody detection of 12 recombinant protein groups, by immunoblot, IgG
0316U	Borrelia burgdorferi (Lyme disease), OspA protein evaluation, urine

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 (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.

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

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 1 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, 1 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.

SUMMARY

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.

Summary of Evidence

Suspected Lyme Disease

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 and a United States-based retrospective 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* Outer surface protein A (OspA) testing, the evidence includes a single cohort study. 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 (eg, 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.

Confirmed Lyme Disease

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.

Additional Information

It is well established that the optimum method of testing for Lyme disease depends on the stage of the disease. Guidelines from the Centers for Disease Control and Prevention and other sources have

supported policy statements related to a tiered diagnostic testing strategy. 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. When laboratory testing is indicated, 2-tiered serologic testing is recommended. The PCR may be clinically useful as a second approach in patients with a short duration of neurologic symptoms (<14 days).

Policy History

Date	Action
12/2023	Annual policy review. Policy updated with literature review through August 23, 2023; no references added. Minor editorial refinements to policy statements; intent unchanged.
12/2022	Annual policy review. Updated policy statement to mention this testing method as follows: "Other diagnostic testing is considered investigational including but not limited to...Outer surface protein A (OspA) antigen testing for diagnosis or monitoring treatment." Intent unchanged.
4/2022	Clarified coding information.
12/2021	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
6/2021	Clarified coding information.
12/2020	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
11/2019	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
10/2019	Policy statement on short-term IV antibiotic use (2-4 weeks) for the treatment of Lyme disease was edited for clarity. Policy statements unchanged. 10/22/2019 Policy clarified to indicate that prior authorization for IV therapy is not required.
11/2018	Annual policy review. Description, summary, and references updated. Policy statements unchanged.
8/2018	Medically necessary statements under Roman numeral V. State Mandate Chapter 183 of the Acts of 2016, An Act Relative to Long-Term Antibiotic Therapy for the Treatment of Lyme Disease clarified. 8/8/2018
4/2018	Clarified coding information.
12/2016	Annual policy review. Policy clarified to add "stand-alone" to the statement on C6 peptide ELISA. 12/1/2016
11/2016	Clarified coding information.
10/2016	Policy updated to include mandated coverage for repeat or prolonged courses of IV antibiotic therapy. Effective 10/1/2016.
1/2016	Annual policy review. New references added
11/2015	Added coding language.
3/2015	Annual policy review. New references added
4/2014	Annual policy review. New references added
2/2013	Annual policy review. Changes to policy statement. Effective 2/4/2013.
11/2011-4/2012	Medical policy ICD 10 remediation: Formatting, editing and coding updates. No changes to policy statements.
1/2011	Updated - Medical Policy Group - Neurology and Neurosurgery. No changes to policy statements.
3/1/2010	Medical policy 171 effective 3/1/2010.

Information Pertaining to All Blue Cross Blue Shield Medical Policies

Click on any of the following terms to access the relevant information:

[Medical Policy Terms of Use](#)

[Managed Care Guidelines](#)

[Indemnity/PPO Guidelines](#)

[Clinical Exception Process](#)

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Endnotes

¹ Based on [State Mandate Chapter 183 of the Acts of 2016, "An Act Relative to Long-Term Antibiotic Therapy for the Treatment of Lyme Disease" \("Chapter 183"\)](#) was enacted, retroactively effective as of July 1, 2016.

[Section 12DD: Administration of long-term antibiotic therapy upon diagnosis of Lyme disease](#)