Corporate Medical Policy

Lyme Disease Testing AHS – G2143

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Description of Procedure or Service

Lyme disease is a common multisystem inflammatory disease caused by spirochetes of the family *Borreliaceae* transmitted through the bite of an infected tick of the genus *Ixodes* (Barbour, 2022). Lyme disease affects the skin in its early localized stage, and spreads to the joints, nervous system, and other organ systems in its later disseminated stages (Hu, 2022).

Related Policies
Testing for Vector-Borne Infections AHS – G2158

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

BCBSNC will provide coverage for Lyme disease testing when it is determined the medical criteria or reimbursement guidelines below are met.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Lyme disease testing is covered

Reimbursement is allowed for serologic testing (2-tier testing strategy using a sensitive enzyme immunoassay (EIA) or immunofluorescence assay, followed by a western immunoblot assay or FDA-cleared second EIA assay) for individuals with symptoms of Lyme disease and a history of travel to a region endemic for Lyme (with or without a history of a tick bite).

Reimbursement is allowed for serologic testing (2-tier testing strategy using a sensitive enzyme immunoassay (EIA) or immunofluorescence assay, followed by a western immunoblot assay or FDA-cleared second EIA assay) for individuals with a history of travel to a region endemic for Lyme in **any** of the following situations:

a. For individuals with acute myocarditis/pericarditis of unknown cause.
b. For individuals with meningitis, encephalitis, or myelitis.
c. For individuals with painful radiculoneuritis.
d. For individuals with mononeuropathy multiplex including confluent mononeuropathy multiplex.
e. For individuals with acute cranial neuropathy.

When Lyme disease testing is not covered

Reimbursement is not allowed for serologic testing in **any** of the following situations:

a. For individuals with an erythema migrans (EM) rash (individuals with skin rashes consistent with EM who reside in or who have recently traveled to an endemic area should be treated for Lyme disease).
b. To screen asymptomatic individuals living in endemic areas.
c. For individuals with non-specific symptoms only (e.g., fatigue, myalgias/arthralgias).
d. For individuals with amyotrophic lateral sclerosis.
e. For individuals with relapsing-remitting multiple sclerosis.
f. For individuals with Parkinson's disease.
g. For individuals with dementia or cognitive decline, or new-onset seizures.
h. For individuals with psychiatric illness.

Reimbursement is not allowed for detection of *Borrelia burgdorferi* by nucleic acid identification techniques (direct or amplified probe).

Reimbursement is not allowed for repeat serologic testing for individuals who have previously tested positive for Lyme disease.

Reimbursement is not allowed for all other testing for *Borrelia burgdorferi* not described above.

Testing of the individual tick is considered investigational for the diagnosis of Lyme disease.

Policy Guidelines

Background

Lyme disease can be caused by several species in the spirochete family *Borreliaceae*; however, infection in North America is predominately caused by *B. burgdorferi*. Much less commonly, in the upper midwestern United States, cases have been associated with *B. mayonii* (Mead & Schwartz, 2022; Pritt et al., 2016). The taxonomic classification system for this species is undergoing revision, and the genus name may be represented as either *Borrelia* or *Borreliella* (Adeolu & Gupta, 2014; Margos et al., 2017). Borrelia burgdorferi occurs naturally in reservoir hosts, including small mammals and birds (Hyde, 2017). *Ixodes scapularis* and *I. pacificus* become infected with *B. burgdorferi* while feeding on the blood of natural reservoir hosts. Transmission to humans results from the bite of an infected tick (Bacon et al., 2008). Spirochete transmission times and virulence depend upon the tick and *Borrelia* species, and infection can never be excluded after a tick bite irrespective of the estimated duration of attachment time (Cook, 2015).

In the earliest stage of Lyme disease, *B. burgdorferi* disseminates from the site of the tick bite resulting in the colonization of dermal tissue and localized infection characterized by a painless bulls-eye rash called erythema migrans, experienced by approximately 70–80% of patients at the site of the tick bite. This is accompanied by non-specific flu-like symptoms, including headache, neck stiffness, malaise, fatigue, myalgia, and fever. During localized infection, the number of *B. burgdorferi* cells increases in the dermal tissue. If left untreated, *B. burgdorferi* can disseminate from the site of the tick bite through the bloodstream and/or lymphatic system to invade and colonize various tissues days to weeks after infection. This can affect the heart, joints, and nervous system. Months to years after exposure to *B. burgdorferi*, affected individuals can experience different manifestations, including neuroborreliosis, Lyme carditis, and arthritis (Hyde, 2017).

The CDC reports that about 476,000 Americans are diagnosed with Lyme disease each year, but they estimate that only about 300,000 people get Lyme disease each year. The CDC notes that these numbers likely differ because the 476,000 people treated for Lyme disease, and patients are often treated presumptively and without proper testing (CDC, 2021b).

Even following antibiotic treatment, a subset of patients continue to present with arthritic symptoms; this has been designated as postinfectious, antibiotic-refractory Lyme arthritis (Hyde, 2017). The term "post-Lyme disease syndrome" (PTLDS) is often used to describe the nonspecific symptoms (such as headache, fatigue, and arthralgias) that may persist for months after treatment of Lyme disease. For the majority of patients, these symptoms improve gradually over six months to one year (Hu, 2022). Weitzner et al. (2015) found that "PTLDS may persist for over 10 years in some patients with culture-confirmed early Lyme disease. Such long-standing symptoms were not associated with functional impairment or a particular strain of *B. burgdorferi*."

The diagnosis of Lyme disease is based on an individual's history of possible exposure to ticks, the presence of characteristic signs and symptoms, and blood test results (Hu, 2022). Direct detection of *Borrelia burgdorferi* has limited applications (Marques, 2015). Thus, most laboratory confirmation of Lyme disease involves the detection of antibody responses against *B. burgdorferi* in serum (Schriefer, 2015). Serology testing is not recommended for patients who do not have symptoms typical of Lyme disease (Marques, 2015), as current assays do not distinguish between active and past infection, thus a positive result is more likely to be a false positive. Early diagnosis of erythema migrants should be made without testing because the lesion appears prior to development of a diagnostic, adaptive immune response (Hu, 2022).

Serological testing using the two-tier algorithm, comprising a first screening enzymatic immunoassay (EIA), followed by a confirmatory Western blot test, is the gold standard for Lyme disease diagnoses (Bunikis & Barbour, 2002; Hu, 2022; John & Taege, 2019). Standardized two-tier testing (STTT) is the recommended diagnostic technique for Lyme disease in clinical practice (CDC, 2021a). Although STTT detection of early localized infection is poor, STTT detection of late disease is excellent (Schriefer, 2015). Evidence of seronegative late Lyme disease is unconvincing (Halperin, 2015). A systematic review has shown that the sensitivity of serology for Lyme disease in early localized infection is 50%, but the algorithm performs well in late stages of the infection, where the sensitivity approaches 100% (Waddell et al., 2016).

On July 29, 2019, the FDA approved several Lyme disease serologic assays, including ZEUS ELISA, allowing for an EIA rather than Western blot as the second test in the two-tier algorithm (CDC, 2019). ZEUS ELISA is a Modified Two-Tiered Testing (MTTT) Algorithm that replaces the second-tier Western blot with a more sensitive and specific methodology, such as ELISA. According to ZEUS Scientific, MTTT reduces the number of missed clinically positive patient samples and improves lab efficiency (ZEUS Scientific, 2019). Compared to the traditional STTT, the MTTT algorithms improve sensitivity to detect early infections and have equivalent sensitivity for detecting late-stage infections and comparable specificity. In addition, MTTT may have the benefit of improved sensitivity in identifying positive cases in patients infected with related strains of *Borrelia*. In a study by Davis, one case of infection with a European genospecies of *Borrelia* was detected by MTTT, which was missed by STTT (Davis et al., 2020). The Canada Communicable Disease Report (CCDR) agrees with the FDA recommendation, advising that "Diagnostic improvements in sensitivity of [Lyme disease] testing without significant loss of specificity have been consistently reported when MTTT is compared with STTT in studies conducted in highly [Lyme disease] endemic regions" (CCDR, 2020).

Polymerase chain reaction (PCR) testing may be useful in the early stages of a Lyme disease infection before an immune response occurs and is also helpful when testing for reinfection. Other potential techniques for Lyme disease diagnostics include cell culture, ELISA, urine testing, and multiplex testing techniques (John & Taege, 2019).

Proprietary Testing

Other diagnostic tests have been created but not widely validated (Hu, 2022). For instance, Wormser et al. (2013) evaluated a C6 enzyme-linked immunosorbent assay (ELISA) as a single-step, serodiagnostic test that uses a reference standard of two-tier testing. This test provided increased

sensitivity in early Lyme disease with comparable sensitivity in later manifestations of the disease. Four hundred and three samples were compared to the sensitivities of the traditional two-tier tests, and the C6 ELISA was measured to have a 66.5% sensitivity and a 35.2% sensitivity, both of which were more sensitive than the individual steps of the STTT approach. The specificity was evaluated with over 2200 blood donors, and the C6 ELISA was evaluated at 98.9% specificity (Wormser et al., 2013).

Urine testing for diagnosis of Lyme disease is available from multiple laboratories. For example, Igenex (2017b) claims that the urine tests "are useful during the acute phase of infection before antibodies are present, in seronegative patients, in patients with vague symptoms of long duration, and previously-treated patients with recurring symptoms." However, the American Academy of Pediatrics (AAP) asserts that "A number of tests for Lyme disease have been found to be invalid on the basis of independent testing or to be too nonspecific to exclude false-positive results", including "urine tests for *B burgdorferi*, CD57 assay, novel culture techniques, and antibody panels that differ from those recommended as part of standardized 2-tier testing" (AAP, 2021). The CDC also includes urine testing for Lyme disease within their list of laboratory tests that are not recommended (CDC, 2023).

Igenex's proprietary Immunoblot has been used to detect IgM and IgG antibodies to diagnose Lyme disease. From the sample report, Igenex has stated that "Recombinant *B. burgdorferi* species antigens are sprayed at specific positions onto a nitrocellulose membrane and cut into strips. These strips are used to detect *B. burgdorferi* specific antibodies in patient serum" (Igenex, 2017b). Eight total species of *Borrelia* are detected by this test; based on 174 samples, the ImmunoBlot was found to have a sensitivity of 90.9% and specificities of 98% (IgM) and 98.7% (IgG) (Igenex, 2017b). Igenex also has a PCR-based test for the detection of B. burgdorferi. Four hundred and two positive samples for *B. burgdorferi* were evaluated based on Igenex's proprietary PCR test and the CDC diagnostic criteria (the traditional two-tiered test). Out of the 402 samples, 236 were considered positive by the proprietary PCR test and 70 were considered positive per the CDC criteria (Igenex, 2017a).

Clinical Utility and Validity

Waddell et al. (2016) assessed the accuracy of the traditional diagnostic tests of Lyme disease. A total of 11 studies with 34 lines of data were evaluated for the overall accuracy. The overall sensitivity was found to be 82%, and the overall specificity was found to be 94.2%. Fifteen studies were examined for Stage 1 of Lyme disease, and the sensitivity was found to be 54%; however, the specificity was calculated to be 96.8%. Stage 2 (five studies, six lines) had a sensitivity of 79.1% and specificity of 97.7%, and Stage 3 (nine studies, 20 lines) had a sensitivity of 94.7% and specificity of 96.1%. The CDC immunoblots (second tier, two studies, four lines) were estimated at 91% sensitivity and 99% specificity (Waddell et al., 2016).

Joung et al. (2019) note that while the CDC recommends serological methods for Lyme disease testing, it is expensive (over $400/test) and can take longer than 24 hours to obtain results; therefore, a cost-effective and rapid assay was developed to address these challenges. This assay can detect early stage Lyme disease and "assays for antibodies specific to seven *Borrelia* antigens and a synthetic peptide in a paper-based multiplexed vertical flow assay (xVFA)"; the specificity of this test was identified at 87% and sensitivity at 90.5% (Joung et al., 2019).

Shakir et al. (2019) used a total of 379 whole blood samples to evaluate ChromaCode's Research Use Only (RUO) nine target High-Definition PCR (HDPCR™) Tick-Borne Pathogen (TBP) panel. Results were compared to clinically validated real-time PCR assays and laboratory developed tests. The final positive percent agreement and negative percent agreement "for the TBP panel was 97.7% (95% CI 95.2% - 99.0%) and 99.6% (95% CI 99.3% - 99.8%), respectively, with an overall agreement of 99.5% (95% CI 99.2% -99.7%)" with the laboratory developed tests" (Shakir et al., 2019).

Nigrovic et al. (2019) evaluated the Lyme disease PCR test compared to the traditional two-tier assessment method (a positive or equivocal EIA and a positive immunoblot test). In total, 124 were tested and 54 had Lyme disease. However, only 23 of the Lyme disease patients had a positive PCR

test, giving a sensitivity of 41.8% and specificity of 100% (Nigrovic et al., 2019). These results show that the Lyme disease PCR test has low sensitivity.

Davis et al. (2020) evaluated the effectiveness of the MTTT algorithm compared to the STTT algorithm. Modified two-tiered testing (MTTT) algorithm uses a second enzyme immunoassay (EIA) instead of the immunoblots for samples that test positive or equivocal on the first EIA. Retrospective chart reviews were performed on 10,253 specimens tested for Lyme disease (LD) serology. "Patients were classified as having Lyme disease if they had a positive STTT result, a negative STTT result but symptoms consistent with Lyme disease, or evidence of seroconversion on paired specimens" (Davis et al., 2020). Of the 10,253 specimens, 9,806 (95.6%) were negative for Lyme disease and 447 patients tested positive. Of the 447 patients, 227 were classified as patients with Lyme disease. "Of the 227 patients classified as having LD, 65 (28.6%) had early localized infections, 67 (29.5%) had early disseminated infections, 26 (11.5%) had late LD, 61 (26.9%) had evidence of old infections, and 8 (3.5%) had posttreatment LD syndrome. Of the remaining 63 patients with early localized disease, 16 (25.4%) were positive by MTTT but negative by STTT. The MTTT identified an additional four (6.6%) cases of early disseminated infection and one case (3.8%) in late LD" (Davis et al., 2020). Overall, MTTT identified additional cases in early localized and early disseminated infections and detected 25% more early infections with a specificity of 99.56% (99.41 to 99.68%) compared to the STTT (Davis et al., 2020).

van Gorkom et al. (2020) evaluated the utility of an in-house and a commercial enzyme-linked immunosorbent spot (ELISpot) assay for the diagnosis of Lyme neuroborreliosis (LNB). Peripheral blood mononuclear cells (PBMCs) were isolated from eighty-seven patients diagnosed with LNB at Diakonessenhuis Hospital, Utrecht, and the St Antonius Hospital, Nieuwegein, the Netherlands between March 2014 and November 2017. In-house *Borrelia* ELISpot assay and the commercial LymeSpot assay. However, it was found that both tests performed unsatisfactorily—the sensitivity for the Borrelia ELISpot yielded a sensitivity of 61.1% (95% CI: 38.9-77.8%) and a specificity of 66.7(42.0-81.2%), while the LymeSpot assay produced 66.7% (95% CI: 44.4-88.9%) and 59.4% (95% 44.9-72.5%), respectively. Moreover, low PPVs for ELISpot and LymeSpot were observed (30.6% vs. 29.7%, respectively), further corroborate their poor diagnostic performance. The researchers do acknowledge a few shortcomings in their study, namely that the isolation procedure for the PBMC deviated from that of the LymeSpot assay—however, the deviations from protocol were allowed for the technician to minimize differences when comparing across assays to allow for fairer comparison of results. Though this was the case, they believe still that the deviations "from the recommended protocol are not critical", and as such they uphold "the conclusion stands that both ELISpot assays cannot help to diagnose active LNB" (van Gorkom et al., 2020).

Sabin et al. (2023) compared the MTTT algorithm to the STTT. The authors compared samples from 320 patients. "The MTTT confirmed the illness in 116 subjects (36%, P = 0.007), and 30 (26%) were negative by the STTT." MTTT sensitivity was increased in early infection, but insufficiently sensitive to non-*Borrelia* species infections. The authors concluded that "Routine adoption of MTTT would improve sensitivity for early Lyme disease attributable to *B. burgdorferi*, but may not capture illness attributed to *B. mayonii* and *B. miyamotoi*" (Sabin et al., 2023).

Pratt et al. (2022) believed that the concurrent use of molecular and serologic testing could broaden the diagnostic window for early Lyme disease. Of the 33,199 specimens submitted for review by antibody capture EIA and WB-RTPCR, 1,379 tested positive, and of those positive, "1,179 were positive by serology only, 131 were positive by molecular testing only, and 69 were positive by both serology and molecular testing." Overall, they found that "4.2% of all specimens were positive and nearly 10% were detected by WB-RTPCR alone." The authors reported that "Of the 131 specimens that tested positive for *B burgdorferi* DNA only, 29 had follow-up samples submitted for follow-up serology testing". Most importantly, "Eighty-six percent (25/29) of the patients with follow-up testing demonstrated seroconversion, 3% (1/29) were equivocal, and 10% (3/29) tested negative" (Pratt et al., 2022). The researchers also examined "2526 specimens submitted for concurrent MTTT and molecular testing" and found that "The two data sets showed a similar percentage of molecular-positive,

serology-negative results (8.7% for MTTT and 9.5% for ACEIA)". Moreover, using the $\chi 2$ test, they found "no statistically significant difference between the antibody-capture and MTTT data sets was observed when analyzing the Lyme-positive results" ($\chi 2 = 0.2765$, $P = .871$). Consequently, it was concluded that "WB-RTPCR, in clinically suspected cases of ELD, can identify *B burgdorferi* infection that serology testing could otherwise miss". Though a retrospective review of paired samples was used to confirm their results, the lack of clinical information to associate with the results motivates the need for a future prospective study (Pratt et al., 2022).

Guidelines and Recommendations:

Centers for Disease Control and Prevention (CDC)

The CDC currently recommends a two-step process when testing blood for evidence of antibodies against the Lyme disease bacteria. Both steps can be done using the same blood sample.

- **The first step** uses a testing procedure called "EIA" (enzyme immunoassay) or rarely, an "IFA" (indirect immunofluorescence assay).
- **If this first step is negative**, no further testing of the specimen is recommended.
- **If the first step is positive** or indeterminate (sometimes called "equivocal"), the second step should be performed.
- **The second step** uses a test called an immunoblot test, commonly, a "Western blot" test.
- Results are considered positive only if the EIA/IFA and the immunoblot are both positive (CDC, 2021a; Mead et al., 2019).

CDC Guidelines on Non-Recommended Lab Tests:

Some laboratories offer Lyme disease testing using assays whose accuracy and clinical usefulness have not been adequately established. Examples of unvalidated tests include:

- Capture assays for antigens in urine
- Immunofluorescence staining, or cell sorting of cell wall-deficient or cystic forms of *B. burgdorferi*
- Lymphocyte transformation tests
- Quantitative CD57 lymphocyte assays
- "Reverse Western blots"
- IgM or IgG tests without a previous enzyme immunoassay

The CDC additionally notes that:

- If a laboratory uses "in-house" criteria for interpretation of FDA-cleared tests for Lyme disease, this indicates the laboratory has modified the test and the clinical validity and safety is not certain.
- Test results for Lyme disease should always be interpreted in the broader context of a person's illness and medical history, exposure likelihood, and other test results.
- Do not seek testing without consulting a healthcare provider (CDC, 2023).

In the 2019 update concerning the CDC recommendations for serologic diagnosis of Lyme disease, they state, "When cleared by FDA 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. Based on the criteria established at the 1994 Second National Conference on Serologic Diagnosis of Lyme Disease, clinicians and laboratories should consider serologic tests cleared by FDA as CDC-recommended procedures for Lyme disease serodiagnosis" (Mead et al., 2019).

The Infectious Diseases Society of America (IDSA), The American Academy of Neurology (AAN), and The American College of Rheumatology (ACR)

The IDSA, AAN and ACR have published clinical practice guidelines for the prevention, diagnosis, and treatment of Lyme disease. The guidelines include the following statements:

- Following a tick bite, "We recommend submitting the removed tick for species identification. (good practice statement)
- We recommend against testing a removed *Ixodes* tick for *B. burgdorferi* (strong recommendation, moderate quality evidence). The presence or absence of *B. burgdorferi* in an Ixodes tick removed from a person does not reliably predict the likelihood of clinical infection.
- We recommend against testing asymptomatic patients for exposure to *B. burgdorferi* following an *Ixodes* spp. tick bite (strong recommendation, moderate-quality evidence).
- 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 recommendation, moderate quality evidence).
- 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 recommendation, low-quality evidence). Comment: If needed, the convalescent-phase serum sample should be collected at least 2–3 weeks after collection of the acute-phase serum sample.
- 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 recommendation, moderate-quality evidence).
- If CSF testing is performed in patients with suspected Lyme neuroborreliosis involving the CNS, we (a) recommend obtaining simultaneous samples of CSF and serum for determination of the CSF: serum antibody index, carried out by a laboratory using validated methodology, (b) recommend against CSF serology without measurement of the CSF: serum antibody index, and (c) recommend against routine PCR or culture of CSF or serum (strong recommendation, moderate-quality evidence).
- In patients presenting with 1 or more of the following acute disorders: meningitis, painful radiculoneuritis, mononeuropathy multiplex including confluent mononeuropathy multiplex, acute cranial neuropathies (particularly VII, VIII, less commonly III, V, VI, and others), or in patients with evidence of spinal cord (or rarely brain) inflammation, the former particularly in association with painful radiculitis involving related spinal cord segments, and with epidemiologically plausible exposure to ticks infected with *B. burgdorferi*, we recommend testing for Lyme disease (strong recommendation, moderate-quality evidence).
- In patients with typical amyotrophic lateral sclerosis, relapsing-remitting multiple sclerosis, Parkinson's disease, dementia or cognitive decline, or new-onset seizures, we recommend against routine testing for Lyme disease (strong recommendation, low-quality evidence).
- In patients with neurological syndromes other than those listed… in the absence of a history of other clinical or epidemiologic support for the diagnosis of Lyme disease, we recommend against screening for Lyme disease (strong recommendation, low-quality evidence)
- In patients presenting with nonspecific magnetic resonance imaging white matter abnormalities confined to the brain in the absence of a history of other clinical or epidemiologic support for the diagnosis of Lyme disease, we suggest against testing for Lyme disease (weak recommendation, low-quality evidence).
- In patients with psychiatric illness, we recommend against routine testing for Lyme disease (strong recommendation, low-quality evidence).
- In children presenting with developmental, behavioral, or psychiatric disorders, we suggest against routinely testing for Lyme disease (weak recommendation, low-quality evidence).

- In patients with acute myocarditis/pericarditis of unknown cause in an appropriate epidemiologic setting, we recommend testing for Lyme disease (strong recommendation, low-quality evidence)
- In patients with chronic cardiomyopathy of unknown cause, we suggest against routine testing for Lyme disease (weak recommendation, low-quality evidence)
- When assessing for possible Lyme arthritis, we recommend serum antibody testing over PCR or culture of blood or synovial fluid/tissue (strong recommendation, moderate quality of evidence)
- In seropositive patients for whom the diagnosis of Lyme arthritis is being considered but treatment decisions require more definitive information, we recommend PCR applied to synovial fluid or tissue rather than *Borrelia* culture of those samples (strong recommendation, moderate quality of evidence)".

The guideline also made several relevant comments on the above recommendations:

- The guideline commented that knowing tick characteristics (such as "species, life stage, and an assessment of the degree of blood engorgement") is helpful for early guidance, such as antibiotic management.
- "Serologic testing of asymptomatic patients following a tick bite does not help with treatment decisions."
- "Association of Lyme disease with meningitis, cranial neuritis, radiculoneuritis, and other forms of mononeuropathy multiplex is well established…The few systematic studies that have been performed have failed to identify consistent associations between Lyme disease and amyotrophic lateral sclerosis, multiple sclerosis, Alzheimer's disease, or Parkinson's disease…These recommendations place a high value on avoiding false positive Lyme disease test results, which can delay appropriate medical evaluation and treatment of other disorders and lead to unnecessary antibiotic exposure and potential side effects."
- "The main disadvantage of this approach [the traditional 'two-tiered approach'] is that seroreactivity after successfully treated Lyme borreliosis may persist for years, complicating test interpretation in patients with known previous exposure and/or in patients from highly endemic areas where background seroprevalence is substantial. In such patients, after seroreactivity has been demonstrated, synovial fluid or synovial tissue *B. burgdorferi* PCR may improve diagnostic specificity" (Lantos et al., 2021).

The American College of Rheumatology (ACR)

The ACR also recommends that "the musculoskeletal manifestations of Lyme disease include brief attacks of arthralgia or intermittent or persistent episodes of arthritis in one or a few large joints at a time, especially the knee. Lyme testing in the absence of these features increases the likelihood of false positive results and may lead to unnecessary follow-up and therapy. Diffuse arthralgias, myalgias or fibromyalgia alone are not criteria for musculoskeletal Lyme disease" (ACR, 2013).

Committee on Infectious Diseases of the American Academy of Pediatrics, 32nd Edition

The Committee on Infectious Diseases of the American Academy of Pediatrics states that "Diagnosis of Lyme disease rests first and foremost on the recognition of a consistent clinical illness in people who have had plausible geographic exposure. Early Lyme disease in patients with erythema migrans is diagnosed clinically on the basis of the characteristic appearance of this skin lesion. Although erythema migrans is not pathognomonic for Lyme disease, it is highly distinctive and characteristic. In areas with endemic Lyme disease, it is expected that the vast majority of erythema migrans occurring in the appropriate season is attributable to *B burgdorferi* infection" (AAP, 2021).

The AAP report a 2-tier serologic algorithm as the standard testing method for Lyme disease, in which "The initial screening test identifies antibodies to a whole-cell sonicate, to peptide antigen, or to recombinant antigens of B burgdorferi using an enzyme-linked immunosorbent assay (ELISA or EIA)

or immunofluorescent antibody (IFA) test. It should be noted that clinical laboratories vary somewhat in their description of this test. It may be described as "Lyme ELISA," "Lyme antibody screen," "total Lyme antibody," or "Lyme IgG/IgM." Many commercial laboratories offer EIA/IFA with reflex to Western immunoblot if the first-tier assay result is positive or equivocal. Although the initial EIA or IFA test result may be reported quantitatively, its sole importance is to categorize the result as negative, equivocal, or positive" (AAP, 2021).

Then, "If the first-tier EIA result is negative, the patient is considered seronegative and no further testing is indicated. If the result is equivocal or positive, then a second-tier test is required to confirm the result. There are 2 options for second tier testing: (1) a western immunoblot, which is the standard 2-tiered testing algorithm; or (2) an EIA test that has been specifically cleared by FDA for use as a second-tier confirmatory test, which is the modified 2-tiered testing algorithm". However, the AAP also reports that "Some assays marketed in the United States have reduced sensitivity for European strains of B burgdorferi. For patients potentially infected in Europe, check with the test provider or laboratory director to select tests that have been validated for this purpose" (AAP, 2021).

The AAP Red Book also delineates for whom and when testing is appropriate.

They caution against the use of serologic testing for Lyme disease in children "without symptoms or signs suggestive of Lyme disease and plausible geographic exposure."

They recommend against Western immunoblot testing "the initial EIA or IFA test result is negative or without a prior EIA or IFA test, because specificity of immunoblot diminishes if the test is performed alone."

"No polymerase chain reaction (PCR) test for *B.burgdorferi* currently is cleared by the FDA. PCR testing of joint fluid from a patient with Lyme arthritis often yields positive results and can be informative in establishing a diagnosis of Lyme arthritis. The role of a PCR assay on blood is not well established; test results usually are negative in early and late Lyme disease and is not recommended routinely. Yield of PCR testing on cerebrospinal fluid samples from patients with neuroborreliosis is too low to be useful in excluding this diagnosis."

"A number of tests for Lyme disease have been found to be invalid on the basis of independent testing or to be too nonspecific to exclude false-positive results. These include urine tests for *B.burgdorferi*, CD57 assay, novel culture techniques, and antibody panels that differ from those recommended as part of standardized 2-tier testing. Although these tests are commercially available from some clinical laboratories, they are not FDA cleared and are not appropriate diagnostic tests for Lyme disease" (AAP, 2021).

Moreover, the interpretation of the results of diagnostic testing can be fraught with difficulties. The notable scenarios are reported below.

"Some patients treated with antimicrobial agents for early Lyme disease never develop detectable antibodies against B burgdorferi; they are cured and are not at risk of late disease. Development of antibodies in patients treated for early Lyme disease does not indicate lack of cure or presence of persistent infection. Ongoing infection without development of antibodies ("seronegative Lyme") has not been demonstrated. Most patients with early disseminated disease and virtually all patients with late disease have antibodies against B burgdorferi. Once such antibodies develop, they may persist for many years. Tests for antibodies should not be repeated or used to assess success of treatment."

"A positive IgM immunoblot result can be falsely positive. The IgM assay is useful only for patients in the first 4 weeks after symptom onset. The IgM immunoblot result should be disregarded (or, if possible, not ordered) in patients who have had symptoms for longer than 4 weeks, or symptoms consistent with late Lyme disease, because false-positive IgM assay results are common, and because

most untreated patients with disseminated Lyme disease will have a positive IgG result by week 4 of symptoms."

"Lyme disease test results for B burgdorferi in patients treated for syphilis or other spirochete diseases are difficult to interpret."

"Standardized 2-tier testing can be expected to have positive results in patients with *B mayonii* infection", as "patients with *B mayonii* infection develop a serologic response similar to that of patients infected with B burgdorferi" (AAP, 2021).

National Institute for Health and Care Excellence (NICE)

NICE recommends diagnosis without laboratory testing in patients with erythema migrans. For patients without erythema migrans, NICE states to consider using an ELISA test. If this ELISA is positive or equivocal, then an immunoblot may be performed. If both tests are positive, then Lyme disease may be diagnosed (NICE, 2018).

NICE also published guidelines in 2019 with the following recommendations:

- "People presenting with erythema migrans are diagnosed and treated for Lyme disease based on clinical assessment, without laboratory testing.
- People with suspected Lyme disease without erythema migrans who have a negative enzyme-linked immunosorbent assay (ELISA) test carried out within 4 weeks of their symptoms starting may have the test repeated 4 to 6 weeks later if Lyme disease is still suspected" (NICE, 2019).

NICE also produced a diagnostic algorithm with the following recommendations:

- "If Lyme disease is still suspected in people with a negative ELISA who have had symptoms for 12 weeks or more, perform an immunoblot test.
- Carry out an immunoblot test, despite an initial negative ELISA, when there is clinical suspicion of Lyme disease. Diagnose Lyme disease in people with symptoms of Lyme disease and a positive immunoblot test.
- If the immunoblot test for Lyme disease is negative (regardless of the ELISA result) but symptoms persist, consider a discussion with or referral to a specialist, to: review whether further tests may be needed for suspected Lyme disease, for example, synovial fluid aspirate or biopsy, or lumbar puncture for cerebrospinal fluid analysis or consider alternative diagnoses (both infectious, including other tick-borne diseases, and non-infectious).
- Initial testing with a combination IgM and IgG ELISA for Lyme disease should be offered because the evidence generally showed better accuracy (both sensitivity and specificity) for combined tests compared to IgM-only and IgG-only tests. The evidence was best for tests based on purified or recombinant antigens derived from the VlsE protein or its IR6 domain peptide (such as a C6)."

This diagnostic algorithm was primarily based off of NICE's 2018 guidelines (NICE, 2018).

Federal Regulations, as applicable

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 86617, 86618, 87475, 87476, 0041U, 0042U, 0316U

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

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Medical Director review 4/2024

Policy Implementation/Update Information

For policy titled: Lyme Disease

1/1/19 New policy developed. BCBSNC will provide coverage for Lyme disease testing when it is determined to be medically necessary because the medical criteria and guidelines are met. Medical Director review 1/1/2019. Policy noticed 1/1/2019 for effective date 4/1/2019. (sk)

5/14/19 Reviewed by Avalon 1st Quarter 2019 CAB. Related policy added. Background section updated. Clinical Utility and Validity section added. Federal Regulations section updated. Policy Guidelines updated. New codes 0041U, 0042U, 0043U, and 0044U added. Medical Director review 4/2019. References added. (sk)

10/29/19 Wording in the Policy, When Covered, and/or Not Covered section(s) changed from Medical Necessity to Reimbursement language, where needed. .(gm)

3/10/20 Specialty Matched Consultant Advisory Panel review 2/19/2020. (sk)

5/12/20 Reviewed by Avalon 1st Quarter 2020 CAB. Description section updated. State and Federal Regulations section updated. When Covered section updated. When Not Covered section updated. Policy Guidelines updated. Codes 0043U and 0044U deleted. Medical Director review 4/2020. References added. (sk)

3/9/21 Specialty Matched Consultant Advisory Panel review 2/17/2021. (sk)

5/4/21 Reviewed by Avalon 1st Quarter 2021 CAB. Description section updated. When Covered section updated. When Not Covered section updated. Policy Guidelines updated. Medical Director review 4/2021. References added. (sk)

5/17/22 Reviewed by Avalon 1st Quarter 2022 CAB. Description section updated. Policy Guidelines updated. Code 0316U added to Billing/Coding section. Medical Director review 4/2022. References added. (sk)

For policy titled: Lyme Disease Testing

5/30/23 Reviewed by Avalon 1st Quarter 2023 CAB. Deleted Related Policies section. Description, Policy Guidelines, and References updated. Table of Termiology added. Policy title changed from Lyme Disease to Lyme Disease Testing. Medical Director review 4/2023. (sk)

5/15/24 Reviewed by Avalon 1st Quarter 2024 CAB. Updates to Description, Policy Guidelines, and References sections. No change to policy intent. Added Related Policies. Removed Table of Terminology. Medical Director review 4/2024. (ldh)