BlueCross BlueShield of North Carolina

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Corporate Medical Policy

Lyme Disease AHS – G2143

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Description of Procedure or Service

A. Definitions
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, 2019). 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, 2019).

B. Related Policies
Testing for Mosquito-or Tick-Related Infections AHS – G2158

C. Scientific 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 Midwest, cases have been associated with *B. mayonii* (Beard, 2018; 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, Kugeler, & Mead, 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 the nervous system. Months to years after exposure to *B, burgdorferi*, affected individuals can experience different manifestations including neuroborreliosis, Lyme carditis, and/or arthritis (Hyde, 2017).

In 2018, 33,666 cases of confirmed and probable Lyme disease were reported in the United States, 21% less than in 2017 (CDC, 2018c). However some studies suggest that closer to 300,000 people are diagnosed with Lyme disease each year in the United States. Lyme

disease cases are concentrated in the Northeast and upper Midwest, with 14 states accounting for over 96% of cases (CDC, 2018a).

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, 2019). Weitzner et al (2015) found that "PTLDS may persist for >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, 2019). 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. The best indicator of early infection (erythema migrans) is presented in the majority of US cases and should prompt treatment without testing (Schriefer, 2015) as the lesion appears prior to development of a diagnostic, adaptive immune response (Hu, 2019).

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, 2019; John & Taege, 2019). Standardized 2-tier testing (STTT) is the recommended diagnostic technique for Lyme disease in clinical practice (CDC, 2019a). Although STTT detection of early, localized infection is poor, STTT detection of late disease is very good (Schriefer, 2015). Evidence of seronegative late Lyme disease is unconvincing (Halperin, 2015). A recent 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, 2019b). 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).

PCR 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 (John & Taege, 2019). Other

potential techniques for Lyme disease diagnostics include cell culture, ELISA, and multiplex testing techniques.

D. Clinical Validity and Utility

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 (5 studies, 6 lines) had a sensitivity of 79.1% and specificity of 97.7%, and Stage 3 (9 studies, 20 lines) had a sensitivity of 94.7% and specificity of 96.1%. The CDC immunoblots (second tier, 2 studies, 4 lines) were estimated at 91% sensitivity and 99% specificity (Waddell et al., 2016).

Other diagnostic tests have been created but not widely validated (Hu, 2018). 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 also 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) states that urine tests for *B. burgdorferi* "have been found to be invalid on the basis of independent testing or to be too nonspecific to exclude false-positives (AAP, 2018)." The CDC also includes urine testing for Lyme disease within their list of laboratory tests that are not recommended (CDC, 2018b).

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).

Joung et al. (2019) note that while the CDC recommends serological methods for Lyme disease testing, it is expensive (>$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).

A total of 379 whole blood samples were used to evaluate ChromaCode's Research Use Only (RUO) nine target High-Definition PCR (HDPCR™) Tick-Borne Pathogen (TBP) panel (Shakir, Mansfield, Hays, Couturier, & Hillyard, 2019). 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.

E. State and Federal Regulations, as applicable

A search for "Lyme Disease" on the FDA website on January 06, 2021 yielded 16 results. Additionally, 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.

******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 all patients with a history of travel to a Lyme region (with or without a history of a tick bite) with compatible symptoms of Lyme disease.

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 Lyme region presenting with any of the following disorders:

a. Acute myocarditis/pericarditis of unknown cause
b. Meningitis, encephalitis, or myelitis
c. Painful radiculoneuritis
d. Mononeuropathy multiplex including confluent mononeuropathy multiplex
e. Acute cranial neuropathy

When Lyme disease testing is not covered

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

a. In patients with an erythema migrans (EM) rash. Patients with skin rashes consistent with EM who reside in or have recently traveled to an endemic area should be treated for Lyme disease.
b. For screening of asymptomatic patients living in endemic areas.
c. For patients with non-specific symptoms only (eg, fatigue, myalgias/arthralgias). The use of serologic testing in populations with a low pre-test probability of Lyme disease results in a greater likelihood of false positive test results than true positive test results.
d. In patients with amyotrophic lateral sclerosis
e. In patients with relapsing-remitting multiple sclerosis
f. In patients with Parkinson's disease
g. In patients with dementia or cognitive decline, or new-onset seizures
h. In patients with psychiatric illness

PCR-based direct detection of *Borrelia burgdorferi* is not considered medically necessary.

Reimbursement is not allowed for repeat serologic testing in individuals who have tested positive previously since positive results may not distinguish between past and possible current infection(s).

Reimbursement is not allowed for repeat PCR-based direct detection of *Borrelia burgdorferi* in the following situations.

a. As a justification for continuation of IV antibiotics beyond one month in patients with persistent symptoms
b. As a technique to follow a therapeutic response.
c. Via urine sample.

Other testing for Borrelia burgdorferi is investigational, including but not limited to

a. Genotyping and phenotyping
b. Determination of levels of the B lymphocyte chemoattractant CXCL13
c. Urine assays, including urinary-based antigen capture assays
d. Panel immunoblot testing, such as Lyme Immunoblot IgM, Lyme Immunoblot IgG, and Lyme Dot Blot

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

Policy Guidelines

Guidelines and Recommendations:

The Centers for Disease Control(CDC) (CDC, 2017, 2018b; P. Mead, Petersen, & Hinckley, 2019)

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, 2019a; 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:

1. Capture assays for antigens in urine
2. Culture, immunofluorescence staining, or cell sorting of cell wall-deficient or cystic forms of *B. burgdorferi*
3. Lymphocyte transformation tests
4. Quantitative CD57 lymphocyte assays
5. "Reverse Western blots"
6. In-house criteria for interpretation of immunoblots
7. Measurements of antibodies in joint fluid (synovial fluid)
8. IgM or IgG tests without a previous ELISA/EIA/IFA (CDC, 2018b)

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 (P. Mead et al., 2019)."

The Infectious Diseases Society of America (IDSA), The American Academy of Neurology (AAN), and The American College of Rheumatology (ACR) (Lantos et al., 2020)

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) (Lantos et al., 2020)."

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."

International Lyme and Associated Diseases Society (Cameron, Johnson, & Maloney, 2014)

The International Lyme and Associated Diseases Society have published guidelines on the assessment and treatment of Lyme disease; no method of testing has been recommended over STTT.

The American College of Rheumatology (ACR, 2013)

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, American Academy of Pediatrics, 31st Edition (2018-2021, Red Book) (AAP, 2018)

The Committee on Infectious Diseases released joint guidelines with the American Academy of Pediatrics. They state that the standard testing method for Lyme disease is the two-tier testing algorithm. The initial test is an ELISA or EIA or an immunofluorescent antibody test (IFA) followed by a Western immunoblot. Only specimens that test positive or equivocal on the first test need to be tested with the immunoblot.

The Red Book states that no PCR tests for *B. burgdorferi* are FDA-approved and are not routinely recommended, although PCR testing of joint fluid from a patient with Lyme arthritis may establish a diagnosis. Other tests, such as urine tests for *B. burgdorferi,* the CD57 assay, novel culture techniques, and antibody panels are considered "invalid" as they are not accurate enough to exclude false positive results. The Red Book also notes that the specificity of the C6 EIA does not exceed the specificity of immunoblot (AAP, 2018).

National Institute for Health and Care Excellence (NICE, 2018, 2019, 2020)

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 in November 2020 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, 2020).

Canadian Paediatric Society (CPS) (Onyett, 2020)

The CPS states that the diagnosis of Lyme disease is generally a clinical one, is based on erythema migrans, and may be supported by the fact that the patient was in an area where tick bites are common; however, since tick populations are expanding, the CPS suggests that all patients with erythema migrans "be diagnosed and treated without laboratory confirmation, because antibodies against *B. burgdorferi* are often not detectable by serodiagnostic testing within the first four weeks after infection (Onyett, 2020)."

Further, the CPS then states that "All other clinical manifestations of possible Lyme disease (LD) should be supported by laboratory confirmation. Two-tiered serological testing, including an ELISA screening test followed by a confirmatory Western blot test, is used to supplement clinical suspicion of extracutaneous LD. Two-tiered testing is necessary because the ELISA may yield false-positive results from antibodies directed against other spirochetes, viral infections or autoimmune diseases… Supplemental tests can detect Borrelia species that cause LD outside of North America. Therefore, travel history should be documented (Onyett, 2020)."

"Tests of joint fluid for antibody to B burgdorferi and urinary antigen detection have no role in diagnosis. In suspected Lyme meningitis, testing for intrathecal immunoglobulin M or immunoglobulin G antibodies may be helpful (Onyett, 2020)."

Public Health Agency of Canada (PHAC, 2020)

The PHAC has published guidelines regarding laboratory testing for Lyme disease. These guidelines state that "Laboratory testing should only be used to supplement clinical findings, not as a basis for diagnosis of early Lyme disease (PHAC, 2020)."

Further, when laboratory testing is used, a two-teared serological testing method is validated and used in Canada. This "two-tiered serological testing approach is recommended when testing a patient's blood for antibodies against the bacterium causing Lyme disease" and includes the use of an EIA screening test and a confirmatory immunoblot test (if the EIA is positive or equivocal) (PHAC, 2020).

For patients with illness lasting over a month, only IgG testing should be performed (not IgM). A positive IgM test alone is not sufficient to diagnose current disease in these patients, as a positive test cannot distinguish between active and a past infection. PHAC advises that the EIA test has low specificity, may yield false positive test results if used as a stand-alone test, and may cross-react with antibodies to commensal or pathogenic spirochetes. In suspected Lyme meningitis, testing for intrathecal IgG or IgM antibodies may be helpful (PHAC, 2020).

Infectious Disease Expert Group (IDEG) of Nova Scotia (IDEG, 2020)

IDEG has published guidelines regarding diagnostic testing for Lyme disease. IDEG recommends that:

- "Physicians need to be aware that the diagnosis of early Lyme disease with localized EM in season (anytime temperature reaches > 4° C, with the greatest risk of transmission during summer months) is a clinical one. Serological tests have poor sensitivity during the first four weeks of infection and are not recommended for management decisions.
- Patients with an EM-like rash out of season (regardless of exposure area) should undergo serological testing using the two-tiered algorithm. If the test result is negative, serological testing should be repeated in 4-6 weeks.
- Patients presenting with a nonspecific febrile illness, but no EM-like rash, AND a recent, clear exposure in an area at moderate or higher risk for Lyme disease should be tested and monitored for other symptoms suggestive of Lyme disease. Repeat testing in 4-6 weeks is suggested if there are still concerns that the patient has Lyme disease.
- Patients presenting with only a nonspecific febrile illness and exposure in an area at lower risk for Lyme disease should NOT be tested.
- Patients with signs and symptoms suggestive of early disseminated and late Lyme disease should undergo serologic testing using the two-tiered algorithm. These presentations take time to manifest and may present out of season.
- Patients in whom there is a concern for neuroborreliosis should undergo a lumbar puncture to look for cerebrospinal fluid abnormalities, in addition to serological testing at the same time. Consultation with an infectious diseases physician or neurologist would be appropriate (IDEG, 2020)."

IDEG does not recommend testing in the absence of signs or symptoms of Lyme disease, testing in asymptomatic patients who have a blacklegged tick bite as antibodies to B. burgdorferi are not detected until a few weeks after infection, or repeat testing after treatment. IDEG does not recommend bypassing ELISA and using immunoblots alone. Immunoblots done in the absence of preceding ELISA testing have been associated with a reduction in specificity. Lastly, IDEG does not recommend the use of PCR on blood, serum, or plasma or the use of urinary antigen as these tests have not been validated (IDEG, 2020).

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

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.

Scientific Background and Reference Sources

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Policy Implementation/Update Information

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)