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Medical Policy Manual Laboratory, Policy No. 83

Lyme Disease Testing

Effective: July 1, 2026

Next Review: May 2026
Last Review: May 2027

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Lyme disease is a tick-born illness that may be diagnosed based on the presence of a characteristic rash and a known tick exposure, or through laboratory testing. A number of proprietary tests for Lyme disease have been developed and marketed but have limited data validating their use.

MEDICAL POLICY CRITERIA

Note: This policy applies only to the proprietary Lyme disease tests listed below.

The following Lyme disease tests are considered **investigational:**

A. Babesia ImmunoBlot IgG Test (IGeneX)
B. Babesia ImmunoBlot IgM Test (IGeneX)
C. Bartonella ImmunoBlot IgG Test (IGeneX)
D. Bartonella ImmunoBlot IgM Test (IGeneX)
E. iDart™ Lyme IgG ImmunoBlot Kit (ID-FISH Technology)
F. iDart™ Lyme IgM ImmunoBlot Kit (ID-FISH Technology)

G. Lyme Borrelia NanoTrap® Urine Antigen Test (Galaxy Diagnostics)

H. Lyme ImmunoBlot IgG (IGeneX)

I. Lyme ImmunoBlot IgM (IGeneX)

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Investigational Gene Expression, Biomarker, and Multianalyte Testing, Laboratory, Policy No. 77
2. Screening Laboratory Testing, Laboratory, Policy No. 80

BACKGROUND

LYME DISEASE

Lyme disease is a bacterial infection caused by the *Borrelia burgdorferi* organism (and occasionally closely related species). It is the most common tick-borne illness in North America and is particularly prevalent in the Northeastern, mid-Atlantic, and upper-Midwest regions in the United States. Peak transmission occurs in late spring and summer, when ticks are most active.

B. burgdorferi infection generally requires a tick to be attached to the skin for at least 24 hours. In the days following infection, a characteristic “bull’s eye” rash called erythema migrans often develops. The presence of an erythema migrans rash in an individual who has possibly been exposed to ticks is considered sufficient to begin treatment with antibiotics, and additional diagnostic testing is not generally needed. Other early symptoms of infection are less specific and include headache, neck stiffness, fever, malaise, and joint and muscle pain.

Early treatment is important for preventing additional manifestations and complications of the disease. If left untreated, late-stage Lyme disease may develop months after the initial infection. This late-stage disease is characterized by joint inflammation and swelling, known as Lyme arthritis, heart inflammation (carditis), and neuroborreliosis, which describes the neurological symptoms of late infection, such as numbness, weakness, facial palsy/droop, and meningitis symptoms (e.g., fever, stiff neck, headache). Even after treatment, some people will continue to experience

LYME DISEASE TESTING

The Centers for Disease Control and Prevention (CDC) recommends a two-step serologic testing process for Lyme disease.[1] The first step is an enzyme immunoassay (EIA), and if this is negative, no further testing is indicated. If the EIA is positive or equivocal, a second test (either EIA or western blot) is performed. These serological assays detect antibodies in the blood, which may not be detectible for weeks following the initial infection, limiting the usefulness of the testing in the early stages of infection. Antibody titers can also persist for years following successful treatment of the infection, so serologic testing is of limited use for assessing cure or reinfection. False-positive results are also possible, particularly for individuals with conditions such as relapsing fever, rheumatoid arthritis, and Epstein-Barr virus infection, due to cross-reactivity.[1] Some laboratories offer urine testing for Lyme disease, however these are not currently recommended by the CDC or the American Academy of Pediatrics (AAP).[1, 2]

REGULATORY STATUS

Several tests, including the ZEUS ELISA Borrelia VlsE1/pepC10 IgG/IgM Test System, ZEUS ELISA Borrelia burgdorferi IgG/IgM Test System, ZEUS ELISA Borrelia burgdorferi IgM Test System, and the ZEUS ELISA Borrelia burgdorferi IgG Test System, iDart™ Lyme IgM ImmunoBlot Kit, and iDart™ Lyme IgG ImmunoBlot Kit have received 510(k) marketing clearance from the U.S. Food and Drug Administration (FDA). Other tests are offered as laboratory-developed tests (LDTs), which must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).

EVIDENCE SUMMARY

There is limited evidence to support the use of the proprietary Lyme disease tests in this policy.

Data from the FDA on the iDart™ Lyme IgG test (ID-FISH Technology) included a comparison of the test with an FDA-cleared EIA.[3] Testing was performed on 768 samples procured from vendors, including a cohort of 290 samples from Lyme disease patients in endemic areas and two cohorts with a total of 478 samples from patients with “Lyme-like” symptoms in endemic areas. The percent positive agreement ranged from 90.1% (62.27% to 98.38%) to 95.00% (89.52% to 97.69%) in the cohorts.

Magni (2015) reported on the development of the NanoTrap® assay (Ceres Biosciences/Galaxy Diagnostics) for Lyme disease detection in urine samples.[4] The test, which is designed to detect the *Borrelia* Outer surface protein A (OspA) was run on 268 samples from patients being evaluated for Lyme disease in Lyme-endemic areas. Of these, 117 samples were from patients considered not to have Lyme disease due to lack of symptoms and negative serology testing, and these samples were all negative by the NanoTrap® assay. All of the 34 samples from patients with an erythema migrans rash tested positive with the assay, while 11 of these were negative by serology testing.

No randomized controlled trials or prospective studies have been published that compare health outcomes for patients based on the results of the tests in this policy

PRACTICE GUIDELINE SUMMARY

Centers for Disease Control and Prevention (CDC)

The recommendations from the CDC for serological Lyme disease testing state the following:[1]

“CDC currently recommends a two-step testing process for Lyme disease serologic testing. Both steps are required and can be done using the same blood sample. If this first step is negative, no further testing is recommended. If the first step is positive or indeterminate (sometimes called “equivocal”), the second step should be performed. The overall result is positive only when the first test is positive (or equivocal) and the second test is positive (or for some tests equivocal). Standard two-tier testing (STTT) uses enzyme immunoassay (EIA) as the first step and western blotting (WB) for the second step. Increasingly, laboratories are using modified two-tier testing (MTTT) in which both assays are EIAs.”

In the 2019 update concerning the CDC recommendations for serologic diagnosis of LD, 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."

INFECTIOUS DISEASES SOCIETY OF AMERICA, THE AMERICAN ACADEMY OF NEUROLOGY, AND THE AMERICAN COLLEGE OF RHEUMATOLOGY

Joint guidelines on the prevention, diagnosis, and treatment of Lyme disease from the Infectious Diseases Society of America (IDSA), the American Academy of Neurology (AAN), and the American College of Rheumatology (ACR) include the following recommendations:[5]

- 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).
- 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).*

SUMMARY

There is not enough research to show that testing for Lyme disease using the iDart™ Lyme IgG or IgM tests (ID-FISH Technologies), the Babesia, Bartonella, or Lyme ImmunoBlot IgG or IgM tests (IGeneX), or the Lyme Borrelia NanoTrap® Urine Antigen Test (Galaxy Diagnostics) can improve health outcomes for individuals suspected of having the disorder compared with standard testing. Therefore, the use of these tests is considered investigational.

REFERENCES

1. Centers for Disease Control and Prevention (CDC). Clinical Testing and Diagnosis for Lyme Disease. [cited 5/12/2026]. 'Available from:' https://www.cdc.gov/lyme/hcp/diagnosis-testing/index.html.
2. American Academy of Pediatrics (AAP). (2024). Lyme Disease. In D. Kimberlin, M. Brady, M. Jackson, & S. Long (Eds.), Red Book: 2024-2027 Report of the Committee on Infectious Diseases: 33rd Edition.
3. U.S. Food and Drug Administration (FDA). 510(k) Substantial Equivalence Determination Decision Summary K233367, IDart Lyme IgG ImmunoBlot Kit. 2024. [cited. 'Available from:' https://www.accessdata.fda.gov/cdrh_docs/reviews/K233367.pdf.
4. Magni R, Espina BH, Shah K, et al. Application of Nanotrap technology for high sensitivity measurement of urinary outer surface protein A carboxyl-terminus domain in early stage Lyme borreliosis. *J Transl Med.* 2015;13:346. PMID: 26537892
5. Lantos PM, Rumbaugh J, Bockenstedt LK, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), American Academy of Neurology (AAN), and American College of Rheumatology (ACR): 2020 Guidelines for the Prevention, Diagnosis and Treatment of Lyme Disease. *Clin Infect Dis.* 2021;72(1):1-8. PMID: 33483734

CODES

Codes	Number	Description
CPT	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
	0580U	Borrelia burgdorferi (Lyme disease), antibody detection of 31 recombinant protein groups, by immunoassay, IgG
	0615U	Borrelia burgdorferi (Lyme disease), antibody detection of 26 recombinant protein groups, by immunoassay, IgM
	0636U	Babesia (Babesiosis), antibody detection of 20 recombinant protein groups, by immunoassay, IgG
	0637U	Babesia (Babesiosis), antibody detection of 20 recombinant protein groups, by immunoassay, IgM
	0638U	Bartonella (Bartonellosis), antibody detection of 32 recombinant protein groups, by immunoassay, IgG
	0639U	Bartonella (Bartonellosis), antibody detection of 32 recombinant protein groups, by immunoassay, IgM
HCPCS	None	

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