Tick-borne Diseases

Laboratory Support of Diagnosis and Management

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INTRODUCTION

This Topic Brief describes the various tick-borne diseases and their incidence, prevalence, and geographic distribution across the United States; it also describes disease symptoms as well as available tests and their interpretation. After describing availability of general tests for all tick-borne diseases, sections follow that include Lyme disease, non-Lyme bacterial tick-borne diseases, and parasitic and viral tick-borne diseases.

The information provided is not intended as medical advice. Test selection and interpretation, diagnosis, and patient management decisions should be based on the physician's education, clinical expertise, and assessment of the patient. The treating healthcare professional should refer to the manufacturer's approved labeling for prescribing, warnings, side effects, and other important information relating to treatment options.

ALL TICK-BORNE DISEASES

Tick-borne diseases are caused by infections transmitted to humans via a tick vector, such as the deer tick, dog tick, wood tick, or lone star tick. Causative agents include bacteria, viruses, and parasites. The incidence varies by geographic location and causative agent (**Table 1**).[1-7] Clinical manifestations also vary depending on the causative agent but frequently include fever, chills, sweating, headaches, myalgia, arthralgia, nausea, and vomiting; because of similar symptomology, tick-borne diseases have substantial clinical overlap.[2,5,8,9] Some patients develop a rash or lesion at the site of the bite. More severe disease may lead to hematologic, respiratory, cardiac, and neurologic complications as well as kidney or liver failure and arthritis. Although tick-borne illnesses can be fatal, antimicrobial agents are usually effective for treating bacterial tick-borne diseases. Some ticks can harbor more than 1 infectious agent that can be transmitted to humans, and coinfection may complicate the diagnosis and affect treatment selection.[10]

All tick-borne diseases: test availability

Laboratory tests that can help confirm the clinical diagnosis include tick identification, microscopic visualization of the causative organism in blood or other clinical specimens, various serologic techniques, culture, and polymerase chain reaction (PCR)-based assays (**Table 2**). Panel components may be ordered individually.

All tick-borne diseases: test selection and interpretation

In most cases, presumptive diagnosis of tick-borne illness is based on clinical grounds. Submitting the removed tick for species identification (test code 3946[X]) is recommended as it allows for the determination of tick characteristics (ie, species, life stage, degree of blood engorgement) that can inform additional testing and treatment.[9] Identification of the tick is recommended by the Infectious Diseases Society of America (IDSA),[9] as some disease pathogens are carried by specific tick species.

Table 1. Incidence of Tick-borne Diseases, United States

Disorder (reported cases, 2022)	Disease geographic distribution[1,2,4,5,a]	Causative organism	Primary vector tick(s)
Lyme disease (62,551)[3]	Upper Midwest, Northeast, Mid-Atlantic, Northern California, Oregon, Washington	*Borrelia burgdorferi, Borrelia mayonii*	Black-legged tick, also known as deer tick (*Ixodes scapularis* Western black-legged tick (*Ixodes pacificus*)
Anaplasmosis (5,633)[3]	Upper Midwest, Northeast, Pacific Coast states, Eastern states	*Anaplasma phagocytophilum*	Black-legged tick, also known as deer tick (*Ixodes scapularis*) Western black-legged tick (*Ixodes pacificus*)
Ehrlichiosis (HME) (1,557)[3]	South-Central, Southeast, East Coast extending to Texas	*Ehrlichia chaffeensis*	Lone star tick (*Amblyomma americanum*)
Human ewingii ehrlichiosis (25)[3]		*Ehrlichia ewingii*	
Spotted fever rickettsioses (1,271)[3,b]	Nationwide; Arkansas, North Carolina, Alabama, Missouri and Tennessee account for over 50% of cases	*Rickettsia rickettsii*	American dog tick (*Dermacentor variabilis*) Brown dog tick (*Rhipicephalus sanguineus*) Rocky Mountain wood tick (*Dermacentor andersoni*)
		Rickettsia parkeri	Gulf Coast tick (*Amblyomma maculatum*)
Babesiosis (1,915)[3,c]	Most common in New York, Massachusetts, Connecticut; cases reported on the West Coast	*Babesia microti* and other *Babesia* species (eg, *Babesia duncani*)	Black-legged tick, also known as deer tick (*Ixodes scapularis*)
Tularemia (167)[3]	Nationwide; predominately Midwest	*Francisella tularensis*	Lone star tick (*Amblyomma americanum*) Rocky Mountain wood tick (*Dermacentor andersoni*) American dog tick (*Dermacentor variabilis*)
Colorado tick fever (11)[6,d]	Rocky Mountain region	Colorado tick fever virus	Rocky Mountain wood tick (*Dermacentor andersoni*)
Hard tick relapsing fever (unknown)	Upper Midwest, Northeast, Mid-Atlantic, Northern California, Oregon, Washington	*Borrelia miyamotoi*	Black-legged tick, also known as deer tick (*Ixodes scapularis*) Western black-legged tick (*Ixodes pacificus*)

HME, human monocytic ehrlichiosis; RMSF, Rocky Mountain spotted fever.

[a] See reference 1 for detailed geographic distribution maps.

[b] As of 2010, cases of Rocky Mountain spotted fever (RMSF), *Rickettsia parkeri* rickettsiosis, Pacific Coast tick fever, and rickettsialpox are reported under a category called Spotted Fever Rickettsiosis (SFR). Categorization under SFR is due to the inability to differentiate between spotted fever group *Rickettsia* species using commonly available serologic tests.[7]

[c] Reported cases in 2021.

[d] Median number of cases per year, 2013-2022.[6]

Table 2. Tests Available for Diagnosis and Management of All Tick-borne Diseases

Test code	Assay[a]	Method	Clinical use
3946(X)	Tick (and Other Arthropods) Identification	Microscopy	Identify tick to determine risk of tick-borne disease; assist with differential diagnosis
94322	Tick-borne Disease, Acute Molecular Panel[b] Includes *Anaplasma phagocytophilum*, *Babesia microti*, *Borrelia miyamotoi*, *Ehrlichia chaffeensis*, and Lyme disease (*Borrelia* spp).	Real-time PCR (qualitative for *A phagocytophilum* and *Borrelia* spp [blood])	Diagnose tick-borne diseases when selecting tests for individual pathogen is challenging due to overlapping geographic distributions and clinical presentations of illness; especially useful to diagnose mixed infections
32338	Tick-borne Disease, Acute Molecular Panel, Non-Lyme[b] Includes *A phagocytophilum*, *B microti*, *B miyamotoi*, and *E chaffeensis*.		
16220	Tick-borne Disease, Antibody Panel WIth Reflexes[b,c] Includes Lyme disease Ab with reflex to immunoassay (IgG, IgM) and A *phagocytophilum* antibodies (IgG and IgM), B microti antibodies (IgG, IgM), and *E chaffeensis* (IgG, IgM) with reflexes to titers.	IFA, immunoassay	Diagnose tick-borne diseases when selecting tests for individual pathogens is challenging due to substantial clinical overlap and coinfection

IFA, immunofluorescence assay; PCR, polymerase chain reaction.
[a] Panel components may be ordered individually.
[b] This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics. It has not been cleared or approved by the US Food and Drug Administration. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.
[c] Reflex tests are performed at an additional charge and are associated with an additional CPT® code(s).

Because of rapid disease progression associated with some tick-borne infections (eg, Lyme disease, tick-borne rickettsial diseases), treatment should not be delayed in symptomatic patients pending the results of laboratory tests or the development of more serious symptoms.[2] For prophylaxis after a tick bite, antibiotic therapy for Lyme disease is only recommended by the IDSA if the bite is considered high risk by meeting 3 criteria: (a) being caused by an *Ixodes* vector species, (b) occurring in a highly endemic area, and (c) the tick being attached for ≥36 hours.[9]

The clinical symptoms and type of rash or lesion, if present, guide the initial differential diagnosis among patients exposed to a tick-endemic area (**Figure**).[1-5,8,9,11-14] This, in turn, guides appropriate test selection, which can include test panels for multiple organisms (test codes 94322, 32338, 16220) or confirmatory tests for specific organisms. Absence of a rash should not rule out a disease from the differential diagnosis.

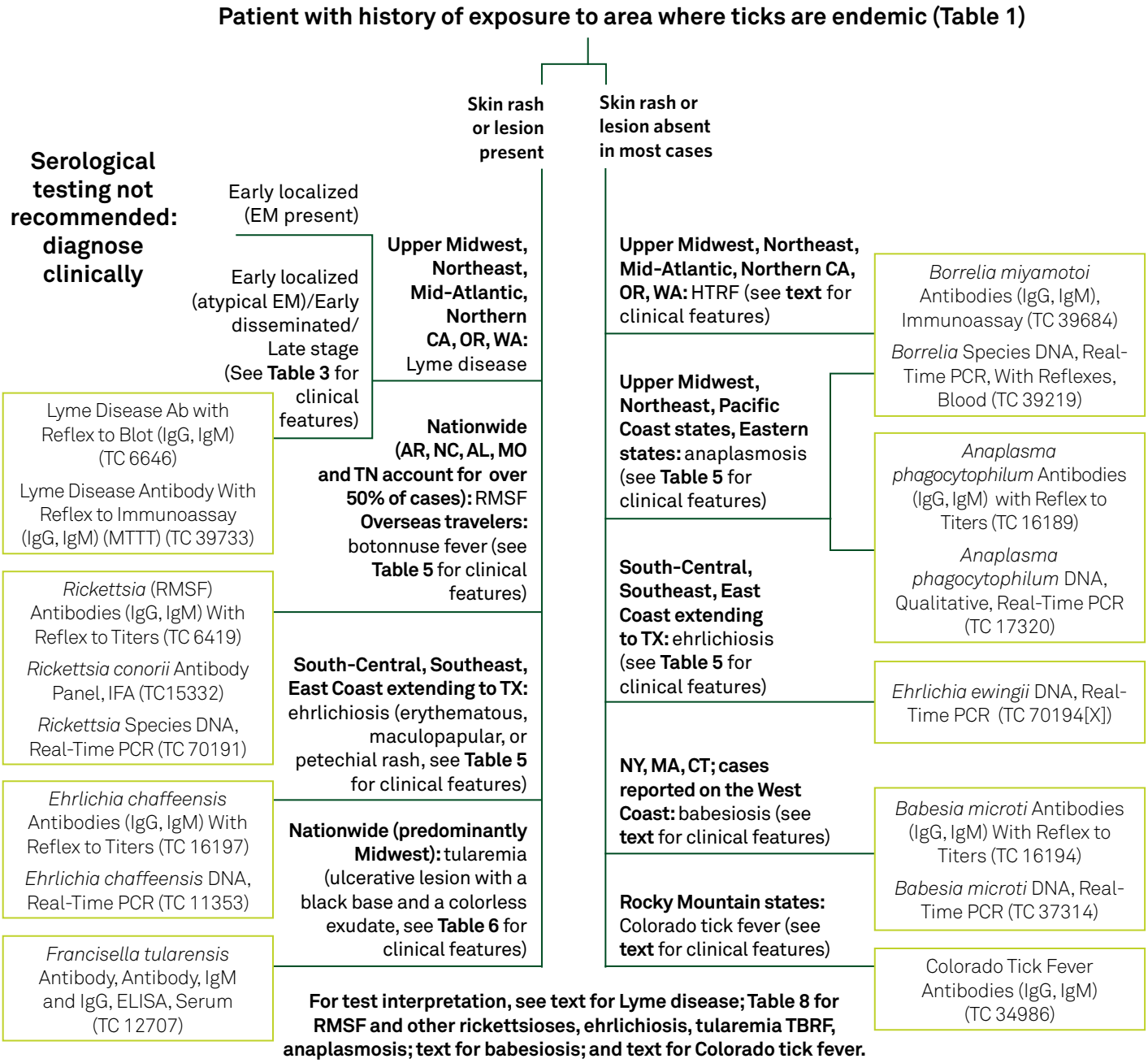
LYME DISEASE

Lyme disease or Lyme borreliosis is by far the most common tick-borne disease in the United States. It is caused by the bacterium *Borrelia burgdorferi* and transmitted from the deer tick (*Ixodes scapularis* or *Ixodes pacificus*). In 2023, approximately 90,000 cases of Lyme disease were reported to the CDC by healthcare providers[15] but, based on insurance claims data, the annual number of patients diagnosed and treated could be as high as 476,000 per year.[16]

Ticks transmitting Lyme disease are generally distributed in the Eastern United States and the Pacific Coast states. Lyme disease cases are most frequently reported from the upper midwestern, northeastern, and mid-Atlantic states.[2] However, cases are also reported from Northern California, Oregon, and Washington. Lyme disease is most common among children and middle-aged adults.[17]

The clinical presentation of Lyme disease is categorized as 1 of 3 stages: early localized, early disseminated, and late (**Table 3**).[2,5,8,9] In 70% to 80% of infected persons, early localized disease is characterized by erythema migrans (EM), a round or oval skin lesion at least 4 cm to 5 cm in diameter that may appear in a "bulls-eye" pattern and expand up to 30 cm across.[2] In the absence of EM, the differential diagnosis may include other tick-borne diseases such as hard tick relapsing fever (HTRF), which is often misdiagnosed as Lyme disease owing to overlapping symptoms.[18]

Figure. Serological Test Selection for the Differential Diagnosis of Tick-borne Diseases Based on Geographic Origin and Symptoms of Infection



EM, erythema migrans; HTRF, hard tick relapsing fever (also called BMD, *Borrelia miyamotoi* disease); RMSF, Rocky Mountain spotted fever; TBRF, tick-borne relapsing fever; TC, test code.

Note: The commonly seen EM rash is not observed in some people with Lyme disease (<30%). Panels are also available to simultaneously test for multiple tick-borne diseases (TC 94322, TC 32338, TC 16220, **Table 2**). Reflex testing may be performed at additional charge with additional CPT® code(s). This figure was developed by Quest Diagnostics based on references 1-5, 8, 9, and 11-14. It is provided for informational purposes only and is not intended as medical advice. Test selection and interpretation, diagnosis, and patient management decisions should be based on the physician's education, clinical expertise, and assessment of the patient.

Table 3. Clinical Features of Lyme Disease and Recommended Laboratory Testing

Stage of disease[2,5]	Symptom onset[2]	Signs and symptoms[2]	Laboratory testing[8,9]
Early localized (acute phase)	3-30 days after tick bite	• EM • Fever, myalgia, headache, nausea, fatigue	If EM is identified in a patient where Lyme disease is endemic, serologic testing is not recommended (ie, a clinical diagnosis of Lyme disease is recommended) STTT or MTTT may be considered (weakly recommended) for patients with 1 or more skin lesions suggestive of, but atypical for EM; however, serologic testing during the acute phase of infection is less sensitive and specific than testing at later stages of infection
Early disseminated	3-12 weeks after tick bite	• Dermatologic: multiple EM rashes that are distant from bite • Neurologic: Lyme neuroborreliosis (LNB) - common symptoms include Bell's palsy, lymphocytic meningitis, painful radiculoneuritis (1 or more dermatomes), and others such as painful peripheral motor and sensory neuropathy (mononeuritis multiplex), and intracranial hypertension (rare) • Cardiac: Lyme carditis leading to conduction abnormalities, such as AV node block; can be fatal (rare) • Rheumatologic: transient and/or migratory arthritis; effusion in 1 or more joints, often large joints; Baker's cysts; migratory pain in tendons, bursae, muscle, and bones	When assessing for possible LNB affecting either the PNS or CNS, STTT or MTTT, serum is recommended If LNB or 1 or more acute symptoms (eg, meningitis, painful radiculoneuritis) of LNB are suspected, guideline recommendations include obtaining simultaneous samples of CSF and serum for measuring CSF:serum antibody index STTT or MTTT is recommended when assessing for rheumatologic symptoms of Lyme disease; PCR is recommended in seropositive patients
Late-stage	Months to years after tick bite	• Patients may not have a history of EM; however, may present with sensory axonal polyneuropathy, encephalomyelitis (rare), or mononeuropathy • Cognitive deficits, personality changes, extreme irritability, and depression • Lyme arthritis • Bluish red rash (acrodermatitis chronica atrophicans) in women	STTT or MTTT is recommended with IgG only considered >30 days after symptom onset

AV, atrioventricular; CNS, central nervous system; CSF, cerebrospinal fluid; EM, erythema migrans; LNB, Lyme neuroborreliosis; MTTT, modified 2-tiered testing; PCR, polymerase chain reaction; PNS, peripheral nervous system; STTT, standard 2-tiered testing.

The first sign of early disseminated disease is often additional smaller skin lesions that may develop if Lyme disease is untreated; however, a recognized skin lesion does not always occur. Extracutaneous involvement in early disseminated disease can include cardiac, rheumatologic, and/or neurologic manifestations (**Table 3**).[2,5,8,9] About 10% to 15% of patients with untreated Lyme disease will develop Lyme neuroborreliosis (LNB).[19] Lyme arthritis may also occur during late-stage disease and is the most common manifestation of Lyme disease months after initial tick exposure.[20] Left untreated, Lyme arthritis usually affects the knees over a period of several years.[20]

If initiated in the early stages of Lyme disease, treatment with appropriate antibiotics is usually effective.[9,21] Prophylaxis or serologic testing after a tick bite is usually not indicated in areas where less than 20% of ticks are infected; however, in areas where infected ticks are endemic, laboratory testing, including tick identification, is recommended.[9,21]

Lyme disease: test availability

Laboratory tests that can help confirm the clinical diagnosis of Lyme disease include tick identification, various serologic techniques and polymerase chain reaction (PCR)-based assays (**Table 4**).

Lyme disease: test selection and interpretation

A timeline of tick exposure in a tick-endemic area and symptoms of Lyme disease guide appropriate test selection (**Table 3**).[2,5,8,9] Guideline recommendations include testing for IgM and/or IgG antibodies using either standard 2-tiered testing (STTT, test code 6646) or modified 2-tiered testing (MTTT, test code 39733)[8,9,22]; in MTTT, the second tier of testing is performed by a second enzyme immunoassay instead of a Western blot. MTTT detects up to 30% more cases compared to STTT in patients with early Lyme disease.[23,24] The following sections outline appropriate test selection based on the stage of disease along with characteristic test results.

Early localized Lyme disease

Diagnosis of early localized Lyme disease can sometimes be made on the basis of EM alone without laboratory testing.[2] Importantly, serologic testing during the acute phase of Lyme disease is less sensitive than at later stages of disease.[8] When testing is done too soon (≤14 days) following infection, negative or equivocal results may occur due to the time needed for the immune system to develop a serologic response.[8] Positive or repeat testing (test codes 29477, 8593) on another sample collected in 7 to 14 days is recommended.[8] Serologic testing (MTTT or STTT) may also be considered in patients with 1 or more skin lesions suggestive of, but atypical for, EM.[9]

If first-tier testing performed 14 days after suspected infection is negative, then second-tier testing is not required.[8] If first-tier testing is positive or equivocal, then second-tier testing is required.[8] For samples collected from patients with symptoms lasting ≤30 days, positive IgM is consistent with infection regardless of IgG seropositivity.[8]

Early disseminated Lyme disease

Two-tiered testing is recommended when clinical findings are suggestive of early disseminated Lyme disease (**Table 3**).[2,5,8,9] For specimens collected at 2 to 4 weeks after onset of symptoms, 2-tiered testing that is positive for IgM and negative for IgG indicates early infection, unless obtained on a specimen collected more than 1 month after onset of symptoms.[8] If the specimen was collected more than 1 month after onset of symptoms, a positive IgM finding is more likely to represent a false-positive result unless IgG is also positive; vaccination or other diseases may also cause false-positive results.[8] A positive IgG result by 2-tiered testing is required to confirm the diagnosis of early disseminated Lyme disease, but it does not differentiate between active and past *B burgdorferi* infection.[9,25]

A diagnosis of LNB involving either the peripheral nervous system or central nervous system (CNS) can be supported if *Borrelia* antibody or DNA are detected in serum or cerebrospinal fluid (CSF); however, serum antibody testing is recommended over PCR due to low clinical sensitivity (38%).[9,26] If LNB involving the CNS is suspected and CSF testing is performed, a validated laboratory method for the determination of the CSF:serum antibody index using simultaneously obtained CSF and serum samples is recommended.[9] The antibody levels in the CSF that are compared to control levels (ie, serum antibody or albumin) in the CSF:serum antibody index can be measured by enzyme-linked immunosorbent assay (ELISA) or nephelometry (test code 34194); an elevated antibody index strongly supports a diagnosis of LNB.[27]

Negative serology results may indicate lack of infection or lack of seroconversion, which may occur if samples are collected too early after disease onset or when early antibiotic therapy blunts the antibody response.[8] PCR-based assays (test codes 94322, 39209, 15777, 39219, 39218, 15510, 90558) can be useful in the workup of *B burgdorferi*

Table 4. Tests Available for Diagnosis and Management of Lyme Disease

Test code	Assay[a]	Method	Clinical use
Lyme disease			
39209	*Borrelia burgdorferi* DNA, Qualitative Real-Time PCR, Miscellaneous[b,c]	Real-time PCR	Diagnose Lyme disease using whole blood, synovial fluid, or CSF
15777	*Borrelia* Species DNA, Qualitative Real-Time PCR, Miscellaneous[b]		Detect *Borrelia* spp DNA in whole blood, synovial fluid, or CSF
15510	*Borrelia* Species DNA, Qualitative Real-Time PCR, Tick[b]		Detect *Borrelia* spp DNA in ticks
39219	*Borrelia* Species DNA, Real-Time PCR, With Reflexes, Blood[b,c,d]		Detect *Borrelia* spp DNA in whole blood
39218	*Borrelia* Species DNA, Real-Time PCR, With Reflexes, Synovial Fluid/CSF[b,c,d]		Detect *Borrelia* spp DNA in synovial fluid or CSF
6646	Lyme Disease Ab with Reflex to Blot (IgG, IgM)[d]	Immunoassay	Diagnose Lyme disease by standard 2-tiered test
39733	Lyme Disease Antibody with Reflex to Immunoassay (IgG, IgM)(MTTT)[d] Includes reflex to Lyme disease supplemental antibodies (IgG, IgM) if Lyme disease antibody is positive or equivocal.		Diagnose Lyme disease by modified 2-tiered test
34194	Lyme Disease Antibody Index for CNS Infection	ELISA; nephelometry	Diagnose Lyme neuroborreliosis
29477	Lyme Disease Antibody (IgG), Immunoblot	Immunoblot	Diagnose Lyme disease when ELISA results are positive or equivocal
8593	Lyme Disease Antibodies (IgG, IgM), Immunoblot		
90558	Tick ID with Reflex to Lyme Disease DNA, Real-Time PCR, Tick[d]	Microscopy; reflex to PCR	Identify tick and *B burgdorferi* to assess risk of tick-borne disease and assist with differential diagnosis

CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; PCR, polymerase chain reaction.
[a] Panel components may be ordered individually.
[b] This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics. It has not been cleared or approved by the US Food and Drug Administration. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.
[c] Please refer to the Quest Test Directory for your service area for test availability.
[d] Reflex tests are performed at an additional charge and are associated with an additional CPT code(s).

infection if seroconversion has not yet occurred; these assays, however, are limited by low clinical sensitivity (18%).[28] Untreated patients who continue to be symptomatic but are seronegative for 6 to 8 weeks are unlikely to have Lyme disease, and a differential diagnosis should be considered.[9]

Late-stage Lyme disease

In patients with suspected Lyme disease that has been left untreated for months to years after a tick bite, symptoms that are characteristic of late-stage disease such as Lyme arthritis or LNB can help guide diagnostic test selection. Detection of *Borrelia* DNA in synovial fluid, commonly from the knees, supports the diagnosis of Lyme arthritis (sensitivity, 78%; specificity, 100%).[20,28]

NON-LYME BACTERIAL TICK-BORNE DISEASES

Tick-borne diseases caused by bacterial agents other than Lyme disease include tick-borne rickettsial diseases (TBRDs), tick-borne relapsing fevers, and tularemia. Each disease is discussed in the following sections.

Tick-borne rickettsial diseases

TBRDs include Rocky Mountain spotted fever (RMSF), *Rickettsia parkeri* rickettsiosis, anaplasmosis, and ehrlichiosis. TBRDs commonly manifest with an acute onset of nonspecific symptoms that mimic benign viral infections, making diagnosis difficult (**Table 5**).[2] The presence or absence of a rash can be a useful diagnostic aid.

Because antibiotic treatment is most effective when given early, therapy for symptomatic patients with clinically suspected TBRDs should not be delayed pending confirmatory laboratory results.[2,29,30] Once the presumptive diagnosis of TBRD is made based on endemic exposure and clinical signs and symptoms, doxycycline is generally the drug of choice for both children and adults.[29,31,32]

Anaplasmosis

Anaplasmosis is caused by infection with *Anaplasma phagocytophilum*. In 2021, 6,729 anaplasmosis cases were reported, the most since being a nationally notifiable disease in 1999.[33] Anaplasmosis is most frequently reported in the upper Midwest and Northeast[33]; however, ticks that transmit anaplasmosis can also be found in the Pacific Coast states in addition to the Eastern United States.[2] Anaplasmosis has substantial overlap of features with early Lyme disease but tends to be a more severe illness.[34] The incidence (per million population) is highest in adults 70 to 84 years (more than 50 per million population) and in those with compromised immune systems.[33]

The ticks that carry *A phagocytophilum* can also harbor *B burgdorferi*, *B miyamotoi*, or *B microti*, and detection of coinfection is recommended as it may affect treatment choices.[31]

Ehrlichiosis

Ehrlichiosis is mostly caused by *Ehrlichia chaffeensis* (human monocytic ehrlichiosis [HME]) and *Ehrlichia ewingii* (human ewingii ehrlichiosis) to a lesser extent.[2] These ehrlichioses are most identified in South-Central and Southeastern

Table 5. Clinical Features of Tick-borne Rickettsial Diseases

Disease	Incubation period, days[2]	Signs and symptoms[2]	Rash[2]
Anaplasmosis	5-14	Fever, chills, rigors, severe headache, malaise, myalgia, gastrointestinal symptoms	Rare (<10%)
Ehrlichia chaffeensis ehrlichiosis	5-14	Fever, chills, headache, malaise, muscle pain, gastrointestinal symptoms, altered mental status	More commonly reported in children
Ehrlichia ewingii	5-14	Fever, chills, headache, malaise, muscle pain, gastrointestinal symptoms, altered mental status	Rare
Mediterranean spotted fever (boutonneuse fever)	5-7	Fever, headache, muscle pain	Eschar (usually single)
Rickettsia parkeri rickettsiosis	2-10	Fever, headache, muscle aches	Sparse maculopapular or papulovesicular eruptions on the trunk and extremities
Rocky Mountain spotted fever	3-12	Early signs/symptoms (1-4 days) include fever, headache, malaise, myalgia, edema around eyes and back of hands, nausea/vomiting	Early (2-5 days after symptom onset) maculopapular rash initially appearing on the wrists, forearms, and ankles
		Late signs/symptoms (5 days or later) include altered mental state, coma, cerebral edema, respiratory compromise, necrosis, multiorgan system damage	Late (after day 6 of symptom onset) petechial rash that indicates progression to severe disease

states, and from the East Coast extending to Texas.[35] In recent decades, cases of HME have increased 10-fold, from 200 reported cases in 2000 to 2,093 cases in 2019.[35] In comparison, only 353 cases of ehrlichiosis caused by *E ewingii* were reported to the CDC from 2008 to 2023.[35]

Mediterranean spotted fever

Mediterranean spotted fever (boutonneuse fever) is an emerging TBRD of the spotted fever group, and the causative agent is *Rickettsia conorii*.[36] It has been reported in US patients who recently travelled to Europe (Mediterranean basin), the Middle East, the Indian subcontinent, or Africa.[2] Symptoms of boutonneuse fever are moderately severe (**Table 5**) and can include a single eschar rash.[2] The illness, which can be fatal, is transmitted from several species of *Ixodes* ticks.[2]

Rickettsia parkeri rickettsiosis

The first case of human *R parkeri* infection was documented in 2014; as of 2015, at least 40 cases have been identified.[12] It is carried by the Gulf Coast tick (*Amblyomma maculatum*), and its geographic distribution extends from the Southern and Mid-Atlantic regions. The first established population of the Gulf Coast tick was reported in Connecticut in 2021, and other populations were reported in New York in 2022 and in New Jersey in 2024; over 30% of these populations of Gulf Coast ticks were infected with *R parkeri*.[37]

Rocky Mountain spotted fever

RMSF is a TBRD of the spotted fever group and is the most severe of the rickettsial diseases in the United States.[11] The disease is caused by the bacterium *Rickettsia rickettsii*, which infects endothelial cells and causes small-vessel vasculitis resulting in maculopapular or petechial rash.[2] Symptoms tend to appear 3 to 12 days after a bite.[2] Vasculitis in organs such as the brain or lungs can lead to life-threatening complications.[2]

Since 2010, RMSF has been reported as spotted fever rickettsiosis, which also includes other spotted fever rickettsioses (SFR) such as *Rickettsia parkeri* rickettsiosis. SFR have been reported throughout the United States, including Arizona where RMSF had not been previously seen.[7] Five states (Arkansas, North Carolina, Alabama, Tennessee, and Missouri) accounted for more than 50% of cases during 2019 to 2023.[7] The peak season for infection coincides with tick activity level for the region, but infection has been reported throughout the year.[7] The reported incidence has increased in recent decades to about 19 cases per million population in 2017[7]; however, the increase in incidence has been accompanied by a decrease in case fatality rate to <0.5% in 2017.[7] Although infection is most common in people over the age of 40 years, children younger than 10 years have the highest case-fatality rate.[7]

Hard tick relapsing fever

Borrelia miyamotoi is the causative agent of HTRF (also known as *Borrelia miyamotoi* disease [BMD]) and has been detected in both *Ixodes* species ticks (*I scapularis* and *I pacificus*) that transmit *B burdorferi* in Lyme disease. Hard tick relapsing fever may share the same geographic distribution as Lyme disease; however, unlike Lyme disease, which most commonly occurs in June and July, HTRF occurs mostly in July and August.[2]

The clinical presentation of HTRF is variable but shares a similar spectrum with other tick-borne diseases such as Lyme disease, anaplasmosis, and babesiosis.[38] A constellation of nonspecific symptoms includes fever, severe headache, myalgia, fatigue, and arthralgia. These symptoms are also characteristic of Lyme disease, babesiosis, and anaplasmosis, which may be included in a differential diagnosis.[38] A "toxic" appearance suggestive of sepsis is common on presentation in patients hospitalized for suspected infection and is often accompanied by elevated liver enzyme levels, neutropenia, and thrombocytopenia.[39]

Tularemia

Ticks that transmit tularemia are widely distributed east of the Rocky Mountains; however, cases have been reported from nearly all US states and are most commonly found in parts of Massachusetts, including Martha's Vineyard, the South Central United States, the Great Plains regions, and the Pacific Northwest.[2] It is caused by the bacterium *Francisella tularensis* and transmitted through varying portals of entry, including tick bites, deer fly bites, skin contact with infected animals, ingestion of contaminated food or water, and inhalation of contaminated aerosols or agricultural dust (**Table 6**).[2,40]

General symptoms of tularemia include fever, chills, malaise, anorexia, myalgia, chest discomfort, cough, sore throat, vomiting diarrhea, and abdominal pain. Ulceroglandular tularemia is the most common form of tularemia and usually occurs following a tick bite or after handling an infected animal.[40] Infection via tick bites is characterized by an ulcerative lesion at the site of the tick bite and lymphadenopathy. An erythematous, tender, or pruritic papule typically appears within 3 to 5 days and subsequently enlarges to form an ulcer with a black base. Pneumonic tularemia, a pulmonary form that may be contracted by inhalation, is the most serious form of tularemia and may spread through the bloodstream to the lungs if left untreated.

Table 6. Clinical Consequences of Tularemia

Manifestation (portal of entry)[2,40,41]	Signs and symptoms[2]
Oculoglandular (eyes)	Photophobia, vision impairment/loss, conjunctivitis, regional lymphadenopathy
Oropharyngeal (ingestion)	Severe throat pain, exudative pharyngitis or tonsilitis, regional lymphadenopathy
Pneumonic (inhalation)	Non-productive cough, substernal tightness, pleuritic chest pain; hilar adenopathy, infiltrate, or pleural effusion may be present on chest X-ray; most serious form of tularemia
Typhoidal (any)	Combination of general symptoms without the localized symptoms of other tularemia syndromes; infiltrates may be seen in chest X-ray even in the absence of respiratory symptoms
Ulceroglandular (skin)	Localized lymphadenopathy, cutaneous ulcer with a black base at site of infection (not always present)

Non-Lyme bacterial tick-borne diseases: test availability

Laboratory tests that can help diagnose non-Lyme bacterial disease include culture, immunoassays and PCR-based assays (**Table 7**).

Non-Lyme bacterial tick-borne diseases: test selection and interpretation

Tick-borne rickettsial diseases

Diagnosis of TBRDs is primarily clinical. However, laboratory testing can play an important role in distinguishing among closely related TBRDs and confirming infection. Confirmatory laboratory testing for TBRDs is primarily through serology and nucleic acid testing (**Table 8**).[2,31,42] Immunofluorescence antibody assays (test codes 37507, 15332, 37478, 6419, 37503) are considered the gold standard for TBRD serology testing.[31] A 4-fold rise in titer of IgG or IgM in paired acute and convalescent samples is essential to confirm infection; the acute sample should be taken within the first 2 weeks of illness and the convalescent sample should be taken 2 to 4 weeks later.[2]

Note: although most patients have positive IgG or IgM antibody by the second week of illness, many people will be seronegative at the time of the first test, especially if done within the first week or so of illness. Therefore, negative results on serologic tests should not lead to discontinuation of therapy.[31]

Detection of DNA in whole blood is especially useful for confirming anaplasmosis and ehrlichioses because these organisms infect circulating leukocytes. In patients with suspected RMSF, detection of *R rickettsii* in blood is more likely in advanced disease or fulminant infection. Positive results confirm TBRD, but negative results do not exclude the diagnosis.

Hard tick relapsing fever

Laboratory diagnosis of HTRF is supported by molecular and serology testing and by visualization of spirochetes by microscopy of peripheral blood obtained during a febrile episode (**Table 8**).[2] PCR amplification of *B miyamotoi* DNA is part of an acute molecular panel of tests used to confirm a presumptive diagnosis of HTRF (BMD) based on clinical presentation. Cerebrospinal fluid, synovial fluid, whole blood, or urine are acceptable specimen types for analysis. Detection of *B miyamotoi* DNA in suspected tick specimens is supportive for the diagnosis of infection.[2] Guidelines also indicate serologic testing to confirm the diagnosis of HTRF.[2] Positive results on serology by ELISA or IgM and IgG immunoblot, however, may indicate coinfection by *Borrelia* species such as *B burgdorferi* and/or *B hermsii*.[2] Negative results do not rule out infection and may be due to testing prior to seroconversion during the acute phase of infection.[43]

Tularemia

Various methods are available to assist in the diagnosis of tularemia. Culture (test code 11873) of *F tularensis* from appropriate sites provides definitive evidence of tularemia but can be challenging due to the slow-growing, fastidious nature of the organism.[2] Serology test results indicating seroconversion from negative to positive IgM and/or IgG antibodies in paired acute and convalescent specimens confirms a diagnosis of tularemia (**Table 8**, test codes 12707).[2,13] Tests that can support a diagnosis of tularemia include immunohistochemical staining, sequencing (eg, PCR), or single serologic tests performed on serum samples collected at least 14 days after the onset of symptoms.[13]

Table 7. Tests Available for Diagnosis and Management of Non-Lyme Bacterial Tick-Borne Diseases

Test code	Assay[a]	Method	Clinical use
Spotted fever rickettsiosis			
91121	Febrile Antibodies Panel[b,c] Includes *Brucella* IgG and IgM with reflex to agglutination (test code 91068), *Rickettsia* (RMSF) IgG and IgM with reflex to titer, *Rickettsia typhi* IgG and IgM with reflex to titer, and *Salmonella* total antibody (*Salmonella* H types A, B, D; *Salmonella* O types D, Vi; test code 10582).	See individual tests	Differential diagnosis of RMSF or *Rickettsia typhi* as a cause of febrile disease vs other infectious causes
37507	*Rickettsia* Antibody Panel With Reflex to Titers[b] Includes IgG and IgM to causative organisms of RMSF and typhus fever.	IFA	Differential diagnosis of rickettsial disease
15332	*Rickettsia conorii* Antibody Panel, IFA[c] Includes IgG and IgM.	IFA	Diagnose *Rickettsia conorii* infection
37478	Rickettsial Disease Panel Includes *Rickettsia* (RMSF) IgG and IgM with reflex to titer; *Rickettsia* (typhus fever) IgG and IgM with reflex to titer; and Q fever (*Coxiella burnetii*) IgG and IgM phase I and phase II with reflex to titers.	IFA	Differential diagnosis of rickettsial disease
70191	*Rickettsia* Species DNA, Real-Time PCR[c]	Real-time PCR	Diagnose RMSF
6419	*Rickettsia* (RMSF) Antibodies (IgG, IgM) With Reflex to Titers[b]	IFA	
37503	*Rickettsia* (Typhus Fever) Antibodies (IgG, IgM) With Reflex to Titers[d] Includes *Rickettsia* (RMSF) IgG and IgM with reflex to titer and *Rickettsia* (typhus fever) IgG and IgM with reflex to titer.	IFA	Differential diagnosis of rickettsial disease (tick-borne vs other organisms)
Anaplasmosis			
16212	*Anaplasma phagocytophilum* and *E. chaffeensis* Antibody Panel Reflex to Titers[b,c] Includes IgG and IgM for both organisms with reflex to titers.	IFA	Diagnose anaplasmosis and ehrlichiosis
16189	*Anaplasma phagocytophilum* Antibodies (IgG, IgM) With Reflex to Titers[b,c]	IFA	Diagnose anaplasmosis
17320	*Anaplasma phagocytophilum* DNA, Qualitative, Real-Time PCR[d]	Real-time PCR	
Ehrlichiosis			
16197	*Ehrlichia chaffeensis* Antibodies (IgG, IgM) With Reflex to Titers[b,c]	IFA	Diagnose ehrlichiosis
11353	*Ehrlichia chaffeensis* DNA, Real-Time PCR[d]	Real-time PCR	
70194(X)	*Ehrlichia ewingii* DNA, Real-Time PCR[d]	Real-time PCR	
Tularemia			
11873	Culture, Select Agent[d]	Culture	Screen for tularemia
12707	*Francisella tularensis* Antibody, Antibody, IgM and IgG, ELISA, Serum[d]	ELISA	Diagnose tularemia

(Continued)

Table 7. Tests Available for Diagnosis and Management of Non-Lyme Bacterial Tick-Borne Diseases *(Continued)*

Test code	Assay[a]	Method	Clinical use
Hard tick relapsing fever (*Borrelia miyamotoi* disease)			
39684	*Borrelia miyamotoi* Antibodies (IgG, IgM), Immunoassay[d]	Immunoassay	Diagnose *B miyamatoi* infection
93795	*Borrelia miyamotoi* DNA, Real-Time PCR, Miscellaneous[d]	Real-time PCR	Confirm diagnosis of *B miyamotoi* infection
93794	*Borrelia miyamotoi* DNA, Real-Time PCR, Tick[d]		Detect *B miyamotoi* in tick to assess risk of human infection
39219	*Borrelia* Species DNA, Real-Time PCR, With Reflexes, Blood[b,c,d]	Real-time PCR	Detect *Borrelia* spp DNA; diagnose Lyme disease or *B miyamotoi* disease
39218	*Borrelia* Species DNA, Real-Time PCR, With Reflexes, Synovial Fluid/CSF[b,c,d]		

ELISA, enzyme-linked immunosorbent assay; IFA, immunofluorescence assay; PCR, polymerase chain reaction; RMSF, Rocky Mountain spotted fever.

[a] Panel components may be ordered individually.

[b] Reflex tests are performed at an additional charge and are associated with an additional CPT code(s).

[c] This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics. It has not been cleared or approved by the US Food and Drug Administration. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.

[d] Please refer to the Quest Test Directory for your service area for test availability.

PARASITIC AND VIRAL TICK-BORNE DISEASES

Babesiosis

Babesiosis is a tick-borne disease caused by infection of erythrocytes by *Babesia* spp parasites. Most cases are caused by *B microti*, which is transmitted by *Ixodes scapularis* ticks.[2] During 2011 to 2019, more than half of the 16,456 cases of babesiosis reported to the CDC were reported from New York (4,738), Massachusetts (4,136), and Connecticut (2,200);[44] however, cases linked to *B duncani* have occurred on the West Coast.[2] Infection is primarily transmitted by ticks, although it can also be transmitted congenitally or through transfusion.[2]

Symptoms may appear 1 to 6 weeks after the tick bite but some infected persons remain asymptomatic.[2] Symptoms vary widely but may include a gradual onset of irregular fever, chills, sweating, myalgia, arthralgia, nausea/vomiting, fatigue, and dark urine.[2] Mild hepatosplenomegaly or jaundice may develop.[2] Less common symptoms include photophobia and conjunctival injection.[2] Treatment is not usually required for people without symptoms.[2]

Colorado tick fever

Colorado tick fever (CTF) is caused by an arbovirus (Colorado tick fever virus) that infects erythrocytes. It is found throughout the Rocky Mountain region, primarily in Colorado, Utah, Montana, and Wyoming (**Table 1**).[2] Although CTF is not a nationally notifiable condition, a total of 223 cases of CTF were reported to the CDC from 2003 through 2022.[45]

Symptoms of CTF occur 1 to 14 days after a tick bite and include fever, chills, headache, body aches, and lethargy.[2] In about half of patients, a "biphasic" fever may occur in which a fever lasting 2 to 3 days disappears then reappears for another 2 to 3 days. In rare instances, severe complications may affect the central nervous system, resulting in symptoms that may include stiff neck and confusion.[46] Specific antiviral treatment is not available for CTF.[46]

Parasitic and viral tick-borne diseases: test availability

Laboratory tests that can help diagnose parasitic and viral tick-borne diseases include microscopy, immunoassay, and PCR-based assays (**Table 9**).

Table 8. Confirmatory Diagnostic Testing for Non-Lyme Bacterial Tick-borne Diseases

Disease	Confirmatory laboratory tests offered by Quest[a]	Criteria for confirmation of diagnosis[a]
Tick-borne rickettsial diseases[2,31,36,42]		
Anaplasmosis	Acute and convalescent serology (test codes 16212, 16189)	4-fold increase in antibody titer[b,c]
	or	
	A *phagocytophilum* DNA (test code 17320)	Detected
Human monocytic ehrlichiosis (HME)	Acute and convalescent serology (test code 16197, 16212,	4-fold increase in antibody titer[b,c]
	or	
	E chaffeensis DNA (11353)	Detected
Human ewingii ehrlichiosis	Acute and convalescent serology (test code 16197) *or*	4-fold increase in antibody titer[b,c]
	E ewingii DNA (70194[X])	Detected
Mediterranean spotted fever (boutonneuse fever)	Acute and convalescent serology (test code 15332)	4-fold increase in antibody titer
Rickettsia parkeri rickettsiosis	Acute and convalescent serology (test codes 37505, 37478, 6419, 37503) *or*	4-fold increase in antibody titer[d]
	Rickettsia species DNA (test code 70191)	Detected
Rocky Mountain spotted fever (*Rickettsia rickettsii*)	Acute and convalescent serology (test codes 37507, 37478, 6419, 37503, 91121) *or*	4-fold increase in antibody titer[b,c]
	R rickettsii DNA (test code 70191)	Detected
Non-rickettsial diseases		
Hard tick relapsing fever[2]	Acute and convalescent serology (test code 39684)	Increase in antibody titer
	B miyamotoi DNA[e] (test codes 93795, 93794, 39219, 39218, 15777, 15510)	Detected[e]
	B hermsii DNA, *B turicatae* DNA[e] (test codes 15777, 15510, 39218)	Detected[e]
Tularemia	Serology (test code 12707)	Seroconversion from negative to positive IgM and/or IgG
	Culture[13] (test code 11873)	*F tularensis* detected in samples taken from ulcers, lymph node aspirates or biopsies, pharynx, pleural fluid (respiratory specimens)

[a] Confirmation of the diagnosis is based on laboratory testing, but antibiotic therapy should not be delayed in a patient with suspected infection.[2]
[b] Titers are often negative in the first 7-10 days of illness. Results from acute serology alone cannot be relied upon for confirmation of infection.[2]
[c] IgM results alone should not be used for laboratory diagnosis.[2]
[d] Results may not be specific to *R parkeri*; RMSF antibody tests often cross-react.[2]
[e] Supportive of diagnosis.[13]

Table 9. Tests Available for Diagnosis and Management of Parasitic and Viral Tick-Borne Diseases

Test code	Assay[a]	Method	Clinical use
Babesiosis			
16194	*Babesia microti* Antibodies (IgG, IgM) With Reflex to Titers[b,c]	IFA	Diagnose babesiosis
37314	*Babesia microti* DNA, Real-Time PCR[b]	Real-time PCR	
17231	*Babesia duncani* (WA1) Antibody (IgG), IFA[b]	IFA	
831	Malaria/*Babesia*/Other Blood Parasites	Microscopy	
Colorado tick fever			
34986	Colorado Tick Fever Antibodies (IgG, IgM)[b]	IFA	Diagnose Colorado tick fever

IFA, immunofluorescence assay; PCR, polymerase chain reaction; RMSF, Rocky Mountain spotted fever.
[a] Panel components may be ordered individually.
[b] This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics. It has not been cleared or approved by the US Food and Drug Administration. This assay has been validated pursuant to the CLIA regulations and is used for clinical purposes.
[c] Reflex tests are performed at an additional charge and are associated with an additional CPT code(s).

Parasitic and viral tick-borne diseases: test selection and interpretation

Babesiosis

The diagnosis of babesiosis should be based on epidemiological risk factors and clinical evidence and confirmed by microscopic identification (test code 831) or detection of *Babesia* species (ie, *B microti*, *B duncani*) DNA by nucleic acid amplification (test code 37314).[2,47] Serologic testing may also confirm or support a diagnosis depending on antibody titers (test codes 16194, 17231).[2] A 4-fold increase in IgG levels seen in paired acute and convalescent specimens is confirmatory, while an IgG antibody titer of ≥1:1024 or the presence of IgM antibody are supportive of active or recent *B microti* infection.[47] Also supportive of infection are general laboratory findings that are consistent with hemolysis: hemolytic anemia with decreased haptoglobin, elevated lactate dehydrogenase, reticulocytosis, thrombocytopenia, elevated creatinine and blood urea nitrogen, elevated transaminase, and proteinuria.[2]

Colorado tick fever

Leukopenia is characteristically seen in a CBC, and moderate thrombocytopenia may be present.[2] Laboratory diagnosis by molecular testing (PCR) is preferred for serum (CSF if suspected CNS involvement) specimens collected at fewer than 14 days after symptom onset.[2] For specimens collected on or after day 14, acute and convalescent serology (test code 34986) is preferred but PCR should be considered for specimens collected up to 21 days after symptom onset.[2] A 4-fold rise of IgG or IgM titer in paired acute and convalescent specimens supports a diagnosis of CTF.[2] Paired specimens should be collected at least 2 weeks apart, with the convalescent specimen collected at least 3 weeks after symptom onset.[2]

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