MOSAIC DIAGNOSTICS

Clinical Algorithm: Selecting Serology vs. Direct Detection for *Borrelia*

Critical First Distinction: *Borrelia* Is Not One Diagnostic Entity

Before selecting a test, clinicians must distinguish which Borrelia group is biologically plausible, as this determines where the organism resides and which specimen is meaningful.

Two Clinically Relevant *Borrelia* Groups

1. *Lyme Borreliosis Group (Borrelia burgdorferi sensu lato)*

- Tissue-tropic
- Rapidly exits bloodstream
- Extremely low or absent circulating bacteremia
- Poor candidate for blood-based PCR
- Best approached with serology with blood testing and or antigen detection using urine

2. Relapsing Fever Borrelia (e.g., Borrelia miyamotoi and other relapsing fever species)

- Blood-borne during febrile episodes
- Cyclic bacteremia
- Amenable to direct detection in blood using PCR or dPCR

Diagnostic strategy depends on the *Borrelia* group suspected, not simply the genus name.

Clinical Algorithm

✓ **Step 1:** Assess Clinical Stage and Presentation

✓ **Step 2:** Evaluate Reliability of Serologic Response (Lyme)

✓ **Step 3:** Choose Diagnostic Modality Based on *Borrelia* Biology

✓ **Step 4:** Interpret Results in Full Clinical Context

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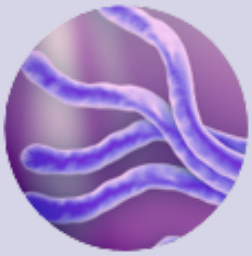
Steps 1 & 2

Step 1: Assess Clinical Stage and Presentation

Early Localized or Early Disseminated Lyme (days to weeks)

- Erythema migrans often absent or unrecognized
- Flu-like illness, headache, fatigue
- Neurologic or cardiac symptoms may already emerge



Key biologic consideration for Lyme *Borrelia*

- Antibody production is delayed, often 2 to 6 weeks
- IgM and IgG responses may be absent or incomplete
- Organisms disseminate rapidly into tissues and collagen-rich sites
- Circulating organisms are exceedingly rare
- Serology may be negative despite active infection
- Blood PCR is not expected to be positive in Lyme disease
- Antigens Lyme *Borrelia* sheds are excreted in urine and can be detected in this phase

Step 2: Evaluate Reliability of Serologic Response (Lyme)

Factors that impair antibody detection include:

- Delayed or ineffective IgM to IgG class switching
- Antigenic variation such as VlsE expression changes
- Immune suppression or immune distraction
- Early antibiotic exposure

These factors are DUE TO the microbiology of how Lyme Borrelia species behave, not human biology itself. These factors also increase the risk of false-negative serology, especially in early or atypical disease.

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Step 3

Step 3: Choose Diagnostic Modality Based on *Borrelia* Biology

When Serology Is Most Informative for Lyme Borrelia

- Later disseminated disease, weeks to months
- Adequate time for antibody development
- Used to support exposure history

Limitations: Reflects immune response, not organism presence, cannot distinguish active versus past infection, cross-reactivity possible, cannot localize infection or confirm persistence

Limitations of Blood-Based PCR for Lyme *Borrelia*

Lyme *Borrelia (Borrelia burgdorferi sensu lato)*

- Organisms rapidly leave blood
- Blood-based PCR has extremely low yield

Failure to detect Lyme *Borrelia* DNA in blood does not argue against infection and is biologically expected.*

**Borrelia burgdorferi has been reported at concentrations as low as ~0.1 organisms per 1 mL of blood, which is 3–4 orders of magnitude below the detection limits of conventional PCR. As a result, the probability of detecting Borrelia in blood using conventional PCR is exceedingly low—comparable to the lifetime probability of being struck by lightning.*

When Direct Detection Adds Value and Which Direct Test Matters

Appropriate Direct Approach for Lyme

- Detection relies on non-blood specimens such as urine
- Urine antigen detection
- Targets shed bacterial proteins rather than intact organisms
- Aligns with tissue sequestration biology

Relapsing Fever *Borrelia*

- True blood-borne *spirochetemia*
- Cyclic high-level *bacteremia*
- Best detected during symptomatic periods

Appropriate Direct Approach for Replapsing Fever

- Blood-based PCR or digital PCR
- Especially useful during febrile episodes

This distinction explains why *BBB* Direct Detect testing is relevant for relapsing fever *Borrelia*, not classical Lyme *Borrelia*

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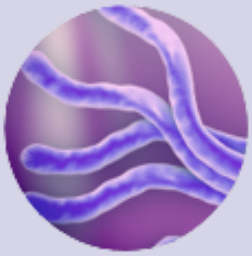
Step 4

Step 4: Interpret Results in Full Clinical Context

- Negative Lyme serology does not exclude early or immune-evasive infection
- Negative blood PCR does not exclude Lyme disease
- Negative direct tests do not exclude tissue-sequestered organisms
- Concordance with clinical findings is essential



Key principle

Diagnostic testing should support clinical judgment, not replace it.
Educational use only. This algorithm does not mandate testing or treatment.

Mosaic offers tests and combination panels to meet every patient's needs

Lyme + Co-infections

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Test ID		Lyme Borrelia Direct Detect	Bartonella IgG Detect – IFA	Tickborne BBB Direct Detect (1 or 3 day)
	Methodology	Nanotrap® Direct	Immunofluorescence (IFA) Indirect	Digital PCR (dPCR) Direct
	Sample Type	Urine	Serum (yellow top)	Blood (lavender top)
	Description	Confirms current presence of OspA antigen in easy-to-collect urine samples.	Confirms antibodies against the four most common species of inection based on published research.	Confirms current presence of pathogens by detecting DNA for a broad range of Bartonella, Borrelia, and Babesia species in whole blood.
	INDIVIDUAL PROFILES			
1	Lyme Borrelia Direct Detect	✓		
2	Bartonella IgG Detect – IFA		✓	
3	Tickborne BBB Direct Detect – 1 day			✓
7	Tickborne BBB Direct Detect – 3 day			✓
	COMBINATION PROFILES			
4	Lyme + Bartonella IgG Detect	✓	✓	
5	Tickborne BBB Plus – 1 day		✓	✓
8	Tickborne BBB Plus – 3 day		✓	✓
6	Lyme + Co-infections Comprehensive – 1 day	✓	✓	✓
9	Lyme + Co-infections Comprehensive – 3 day	✓	✓	✓

Test (by clinical suspicion)

Lyme-only suspicion

1 **Lyme Borrelia Direct Detect (Nanotrap)**
Best matrix for Lyme; validated in acute (EM rash) and chronic/PTLDS populations.

Bartonella suspicion

5 1 day | 8 3 day

Tickborne BBB Plus
= Tickborne BBB Direct Detect + Bartonella IgG Detect

Babesia suspicion

3 1 day | 7 3 day

Tickborne BBB Direct Detect
Triple (3 day) vs single (1 day) blood draw - When feasible, choose triple draw for Tickborne BBB Direct Detect—serial sampling increases the probability of detecting low-abundance pathogens.

Tick-borne illness, unsure which pathogen

6 1 day | 9 3 day

Lyme + Co-infections Comprehensive
= Lyme Borrelia Direct Detect + Bartonella IgG Detect + BBB Direct Detect

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