Laboratory Diagnosis of Lyme Disease

Determining Pretest Probability for Lyme Disease

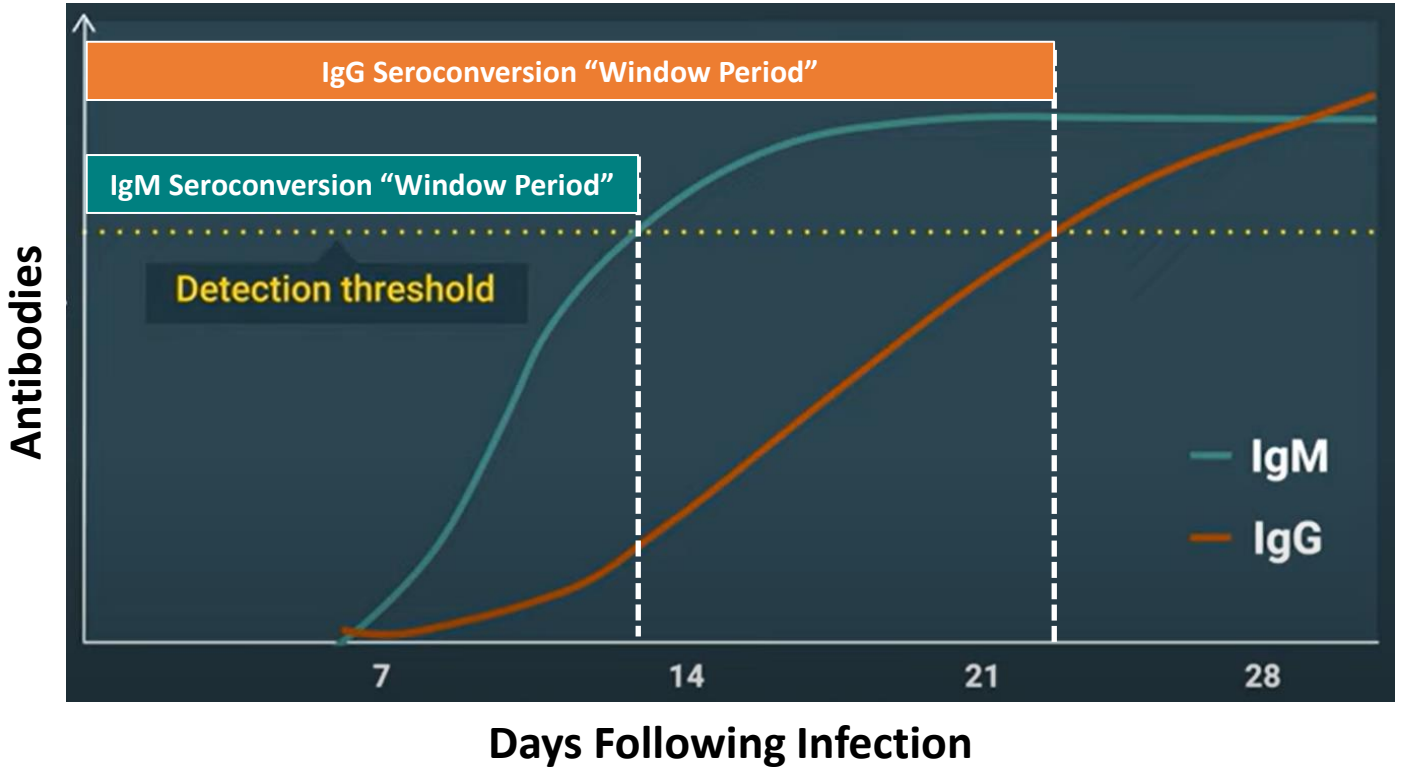
Pretest probability can help inform when testing for Lyme disease is most helpful

- Has the patient been in an area where Lyme disease is common?
- Was the patient likely exposed to ticks?
- Does the patient have symptoms characteristic of Lyme disease?
    - What is the disease stage?

Note:

- Testing is recommended only when there is existing clinical and epidemiological support for a diagnosis
- Testing asymptomatic patients who have not had the potential for exposure to ticks is strongly discouraged

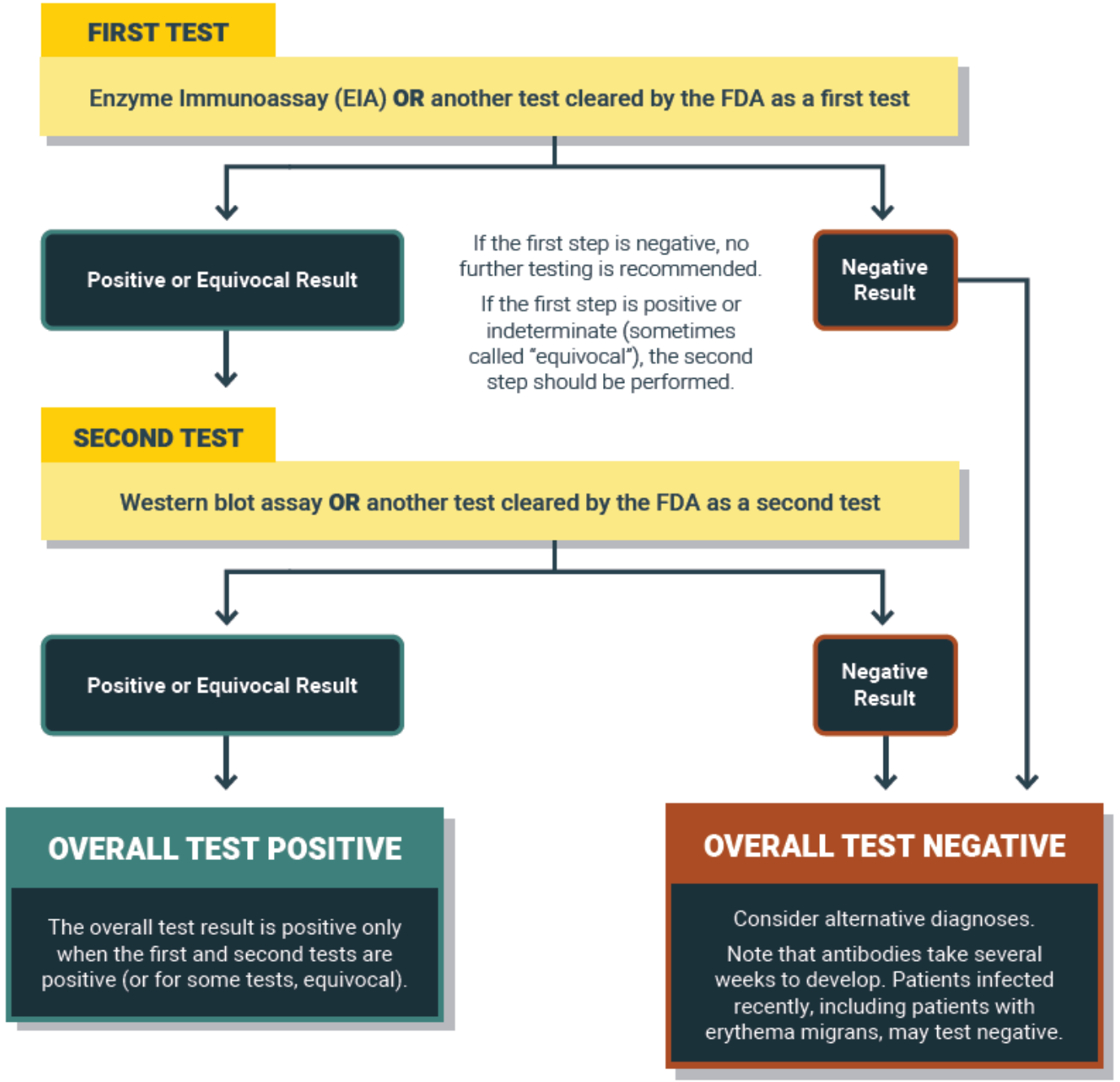
Kinetics of Antibody Response Following Infection



- Antibodies can take several weeks to develop
- ***False negative results may occur in patients who are tested very early following infection***
- Antibodies may persist in the blood for months or even years resolution of infection
  - Cannot be used to determine cure

Lyme Disease Serologic Testing Guidelines

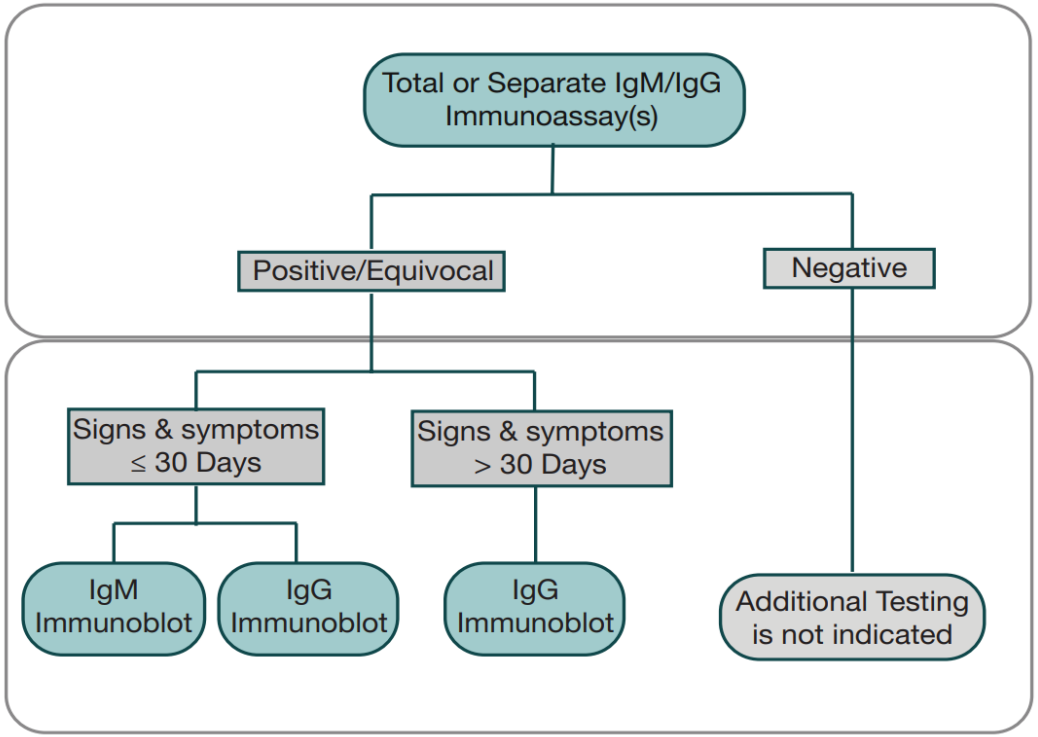
- CDC recommends a **two-step testing process** for Lyme disease using FDA approved tests
- APHL published suggested laboratory reporting and clinician interpretation for Lyme disease serologic test results



https://www.cdc.gov/lyme/resources/pdfs/lyme-testing-aid_prior-pretest_combined-low-ink-P.pdf

Standard vs Modified Two-tiered Testing

Standard
(Circa 1995)



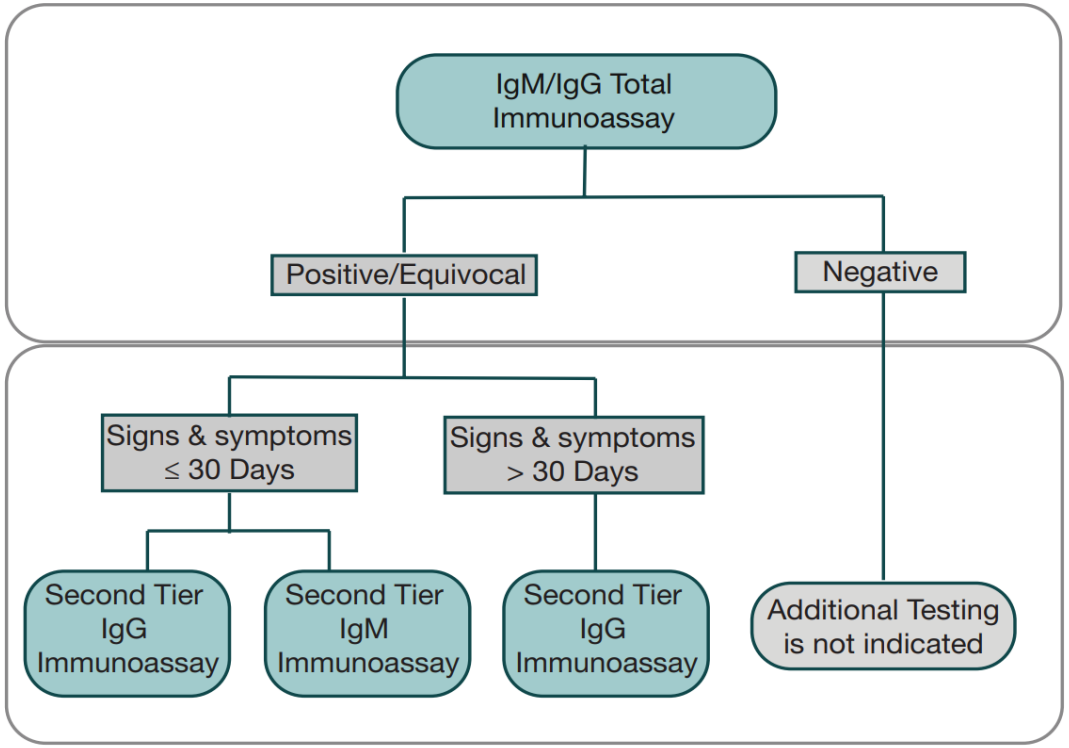
https://www.cdc.gov/mmwr/preview/mmwrhtml/00038469.htm

Western immunoblot as tier 2 test

Tier 1

Tier 2

Modified
(Circa 2019)



https://www.cdc.gov/mmwr/volumes/68/wr/mm6832a4.htm?s_cid=mm6832a4_w

Enzyme immunoassay acceptable as tier 2 test.

The modified two-tiered testing approach is used at Northwell Labs

https://www.aphl.org/aboutAPHL/publications/Documents/ID-2021-Lyme-Disease-Serologic-Testing-Reporting.pdf

Updated CDC Recommendation for Serologic Diagnosis of Lyme Disease

Paul Mead, MD[1]; Jeannine Petersen, PhD[1]; Alison Hinckley, PhD[1]

Lyme disease is a tickborne zoonosis for which serologic testing is the principal means of laboratory diagnosis. In 1994, the Association of State and Territorial Public Health Laboratory Directors, CDC, the Food and Drug Administration (FDA), the National Institutes of Health (NIH), the Council of State and Territorial Epidemiologists, and the National Committee for Clinical Laboratory Standards convened the Second National Conference on Serologic Diagnosis of Lyme Disease (*1*).

The conference proceedings recommended a two-test methodology using a sensitive enzyme immunoassay (EIA) or immunofluorescence assay as a first test, followed by a western immunoblot assay for specimens yielding positive or equivocal results (*1*,*2*). Regarding the development of future tests, the report advised that evaluation of new serologic assays include blind testing against a comprehensive challenge panel, and that new assays should only be recommended if their specificity, sensitivity, and precision equaled or surpassed the performance of tests used in the recommended two-test procedure. To assist serologic test developers, CDC has made available, with support from NIH, a comprehensive panel of sera from patients with various stages of Lyme disease and other conditions, as well as healthy persons (*3*).

On July 29, 2019, FDA cleared several Lyme disease serologic assays with new indications for use based on a modified two-test methodology (*4*). The modified methodology uses a second EIA in place of a western immunoblot assay. Clearance by FDA of the new Lyme disease assays indicates that test performance has been evaluated and is "substantially equivalent to or better than" a legally marketed predicate test.

Recommendation

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.

Summary

What is already known about this topic?

Serologic testing is the principal means of laboratory diagnosis of Lyme disease. Current recommendations include using a sensitive enzyme immunoassay (EIA) or immunofluorescence assay, followed by a western immunoblot assay for specimens yielding positive or equivocal results.

What is added by this report?

On July 29, 2019, the Food and Drug Administration (FDA) cleared several Lyme disease serologic assays with new indications for use, allowing for an EIA rather than western immunoblot assay as the second test in a Lyme disease testing algorithm.

What are the indications for public health practice?

When cleared by FDA for this purpose, serologic assays that utilize a second EIA in place of western immunoblot assay are acceptable alternatives for the serologic diagnosis of Lyme disease.

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All authors have completed and submitted the ICMJE form for disclosure of potential conflicts of interest. No potential conflicts of interest were disclosed.

References

1. Association of State and Territorial Public Health Laboratory Directors. In: proceedings of the Second National Conference on Serologic Diagnosis of Lyme Disease; October 27–29, 1994; Dearborn, MI. Washington, DC: Association of State and Territorial Public Health Laboratory Directors; 1994.
2. CDC. Notice to readers: recommendations for test performance and interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease. MMWR Morb Mortal Wkly Rep 1995;44:590–1.
3. Molins CR, Sexton C, Young JW, et al. Collection and characterization of samples for establishment of a serum repository for Lyme disease diagnostic test development and evaluation. J Clin Microbiol 2014;52:3755–62. https://doi.org/10.1128/JCM.01409-14
4. Food and Drug Administration. FDA clears new indications for existing Lyme disease tests that may help streamline diagnoses. [News release]. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2019. https://www.fda.gov/news-events/press-announcements/fda-clears-new-indications-existing-lyme-disease-tests-may-help-streamline-diagnoses

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Executive Deputy Commissioner

December 16, 2019

Dear LABORATORY DIRECTOR,

The Centers for Disease Control and Prevention (CDC) has reported that three enzyme immunoassays (EIA) from Zeus Scientific have recently been cleared by the Food and Drug Administration (FDA) for use in an alternative two-tier testing protocol for Lyme disease diagnosis. These EIAs may be used sequentially for Lyme disease diagnosis rather than the standard two-tier Lyme testing algorithm which uses an EIA or IFA screening test followed by IgM and IgG western blots.

Based upon the updated CDC recommendation (MMWR 68:703 (2019)) and our own evaluation of these FDA cleared EIAs approved for the alternative testing algorithm, the Diagnostic Immunology Laboratory at the Wadsworth Center will begin using the alternative two-tiered Lyme testing algorithm on January 1, 2020. Lyme IgM and IgG western blots will no longer be used for serologic testing for Lyme disease.

The alternative two-tiered algorithm performed at the Wadsworth Center will employ an initial screening using one Zeus EIA to detect antibodies reactive with ***Borrelia burgdorferi***, followed by second-step, using two separate EIAs to detect ***Borrelia burgdorferi***-reactive IgM and IgG, respectively.

Please note that EIAs from other companies that are FDA approved may still be used by labs for Lyme disease testing. However, if a lab chooses to use the alternative Lyme disease testing algorithm now recommended by CDC then only the Zeus kits are permissible.

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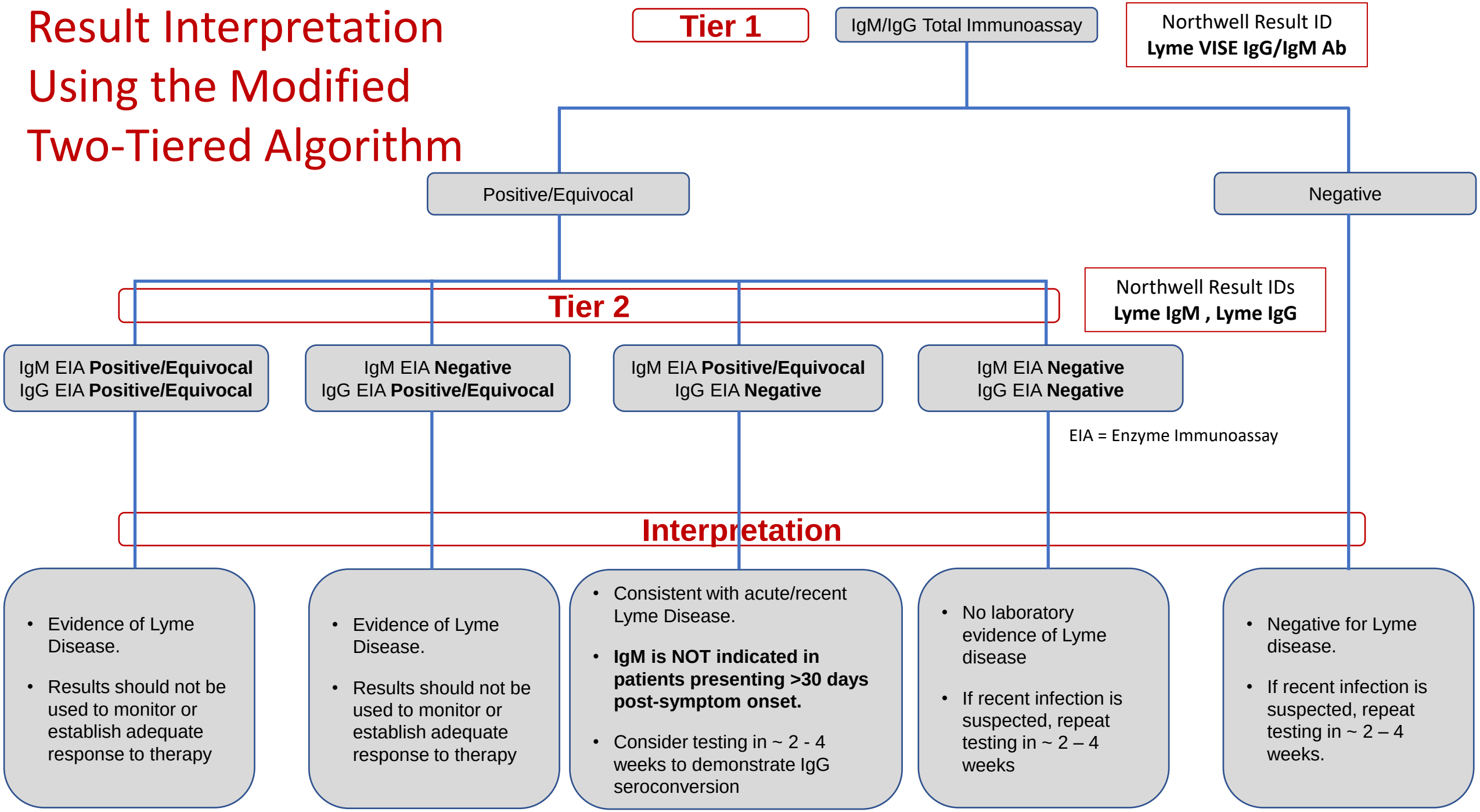
Result Interpretation Using the Modified Two-Tiered Algorithm



Educational Resources for Clinicians

- Lyme Disease Serologic Testing (https://www.youtube.com/watch?v=Dei-8na9wZU)
- Pretest Probability of Lyme Disease (https://www.youtube.com/watch?v=LhF7vX5RynA)
- Lyme Disease Prophylaxis After Tick Bite (https://www.youtube.com/watch?v=kpxsfb7pOEY)
- APHL Suggested Reporting Language, Interpretation and Guidance Regarding Lyme Disease Serologic Test Results https://www.aphl.org/aboutAPHL/publications/Documents/ID-2021-Lyme-Disease-Serologic-Testing-Reporting.pdf
- Lyme Disease Updates and New Educational Tools for Clinicians ***25:14 to 30:00*** (https://emergency.cdc.gov/coca/calls/2021/callinfo_052021.asp)
- Caring for Patients after a Tick Bite https://www.cdc.gov/lyme/resources/FS-Guidance-for-Clinicians-Patients-after-TickBite-508.pdf
- Tickborne Diseases of the US: A Reference Manual for Health Care Providers https://www.cdc.gov/ticks/tickbornediseases/TickborneDiseases-P.pdf