Lyme Disease
Case Classification and Two-Tiered Testing

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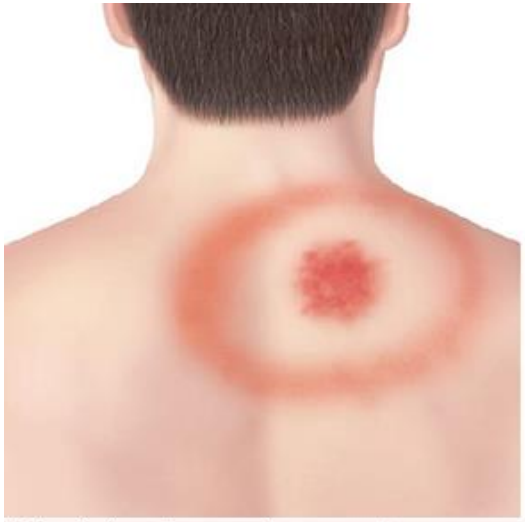
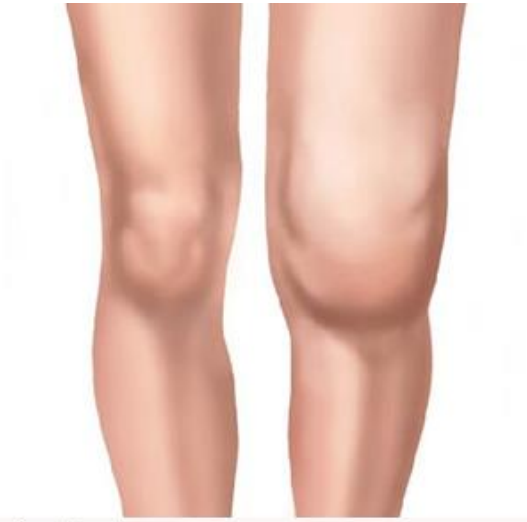
Lyme Disease
2016 Case Definition/Case Classification

A systemic, tickborne disease with protean manifestations, including dermatologic, rheumatologic, neurologic, and cardiac abnormalities. The best clinical marker for the disease is the initial skin lesion, erythema migrans (EM). For most patients, the expanding EM lesion is accompanied by other acute symptoms, particularly fatigue, fever, headache, mildly stiff neck, arthralgia, or myalgia.



"Classic" erythema migrans rash

Facial palsy



Swollen knee

http://www.cdc.gov/lyme/signs_symptoms/index.html

Lyme Disease
Case Definition/Case Classification (cont.)

***Confirmed**:* A case with physician-diagnosed EM >= 5cm in size with an exposure in a high-incidence state or country*

OR

a case of physician-diagnosed EM of any size with laboratory confirmation,

OR

a case with at least one late manifestation** that has laboratory confirmation

*Texas is considered a low-incidence state for Lyme disease. Therefore, a positive/equivocal screen is required prior to running IgM/IgG Immunoblots and additional testing is required to accompany an EM.

In 2014, 96% of confirmed Lyme disease cases were reported from 14 states:
Connecticut, Delaware, Maine, Maryland, Massachusetts, Minnesota, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont, Virginia, Wisconsin
Lyme disease is the most commonly reported vector-borne illness in the United States. However this disease does **not** occur nationwide and is concentrated heavily in the northeast and upper Midwest.

www.cdc.gov/lyme/stats/index.html

Lyme Disease
Case Definition/Case Classification (cont.)

Confirmed: a case with at least one **late manifestation**** that has laboratory confirmation

For purposes of surveillance, late manifestations include any of the following **when an alternate explanation is not found:

- Musculoskeletal system: recurrent, brief attacks (weeks or months) of objective joint swelling in one or a few joints, sometimes followed by chronic arthritis in one or a few joints.
- Nervous system: any of the following, alone or in combination: lymphocytic meningitis; cranial neuritis, particularly facial palsy (can be bilateral); radiculoneuropathy; or, rarely, encephalomyelitis. Encephalomyelitis must be confirmed by demonstration of antibody production against *Borrelia burgdorferi* in the cerebrospinal fluid (CSF), evidenced by a higher titer of antibody in CSF than in serum.
- Cardiovascular system: acute onset of high-grade (2nd or 3rd-degree) atrioventricular conduction defects that resolve in days to weeks and are sometimes associated with myocarditis.

Lyme Disease
Case Definition/Case Classification (cont.)

***Probable**:* Any other case of physician-diagnosed Lyme disease that has laboratory confirmation
{Clinically compatible: fatigue, fever, headache, mildly stiff neck, arthralgia, or myalgia}

Suspect: A case of EM with no known exposure and no laboratory evidence of infection, **OR** a case with laboratory evidence of infection, but no clinical information available

Note: Lyme disease reports will not be considered cases if the medical provider specifically states this is not a case of Lyme disease, or the only symptom listed is "tick bite" or "insect bite".

Laboratory Confirmation Tests

Positive culture for *Borrelia burgdorferi*

OR

IgG immunoblot seropositivity using established criteria*
with Positive/Equivocal EIA or IFA test
~~**AND** Specimen collected > 30 days after symptom onset,~~

OR

(*NEW for 2016!*) IgG immunoblot seropositivity using established criteria*
with an exposure in a high-incidence state or country

OR

IgM immunoblot seropositivity using established criteria*
with Positive/Equivocal EIA or IFA test,
AND Specimen collected ≤30 days after symptom onset

Note: *CDC Immunoblot interpretation criteria

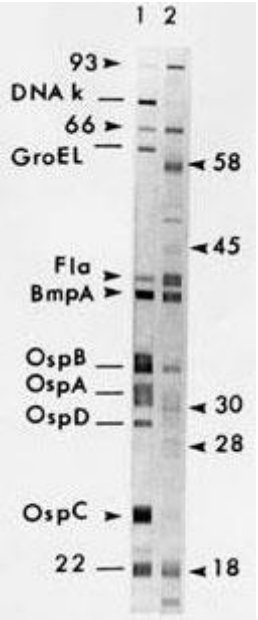
Lyme disease (*Borrelia burgdorferi*) 2011 National Case Definition

- **Laboratory Criteria for Diagnosis**
- For the purposes of surveillance, the definition of a qualified laboratory assay is
- Positive Culture for *B. burgdorferi*, **OR**
- Two-tier testing interpreted using established criteria[1], where:
  - Positive IgM is sufficient only when ≤30 days from symptom onset
  - Positive IgG is sufficient at any point during illness
- **Single-tier IgG immunoblot seropositivity using established criteria.[1-4]**
- CSF antibody positive for *B. burgdorferi* by Enzyme Immunoassay (EIA) or Immunofluorescence Assay (IFA), when the titer is higher than it was in serum

http://wwwn.cdc.gov/nndss/conditions/lyme-disease/case-definition/2011/

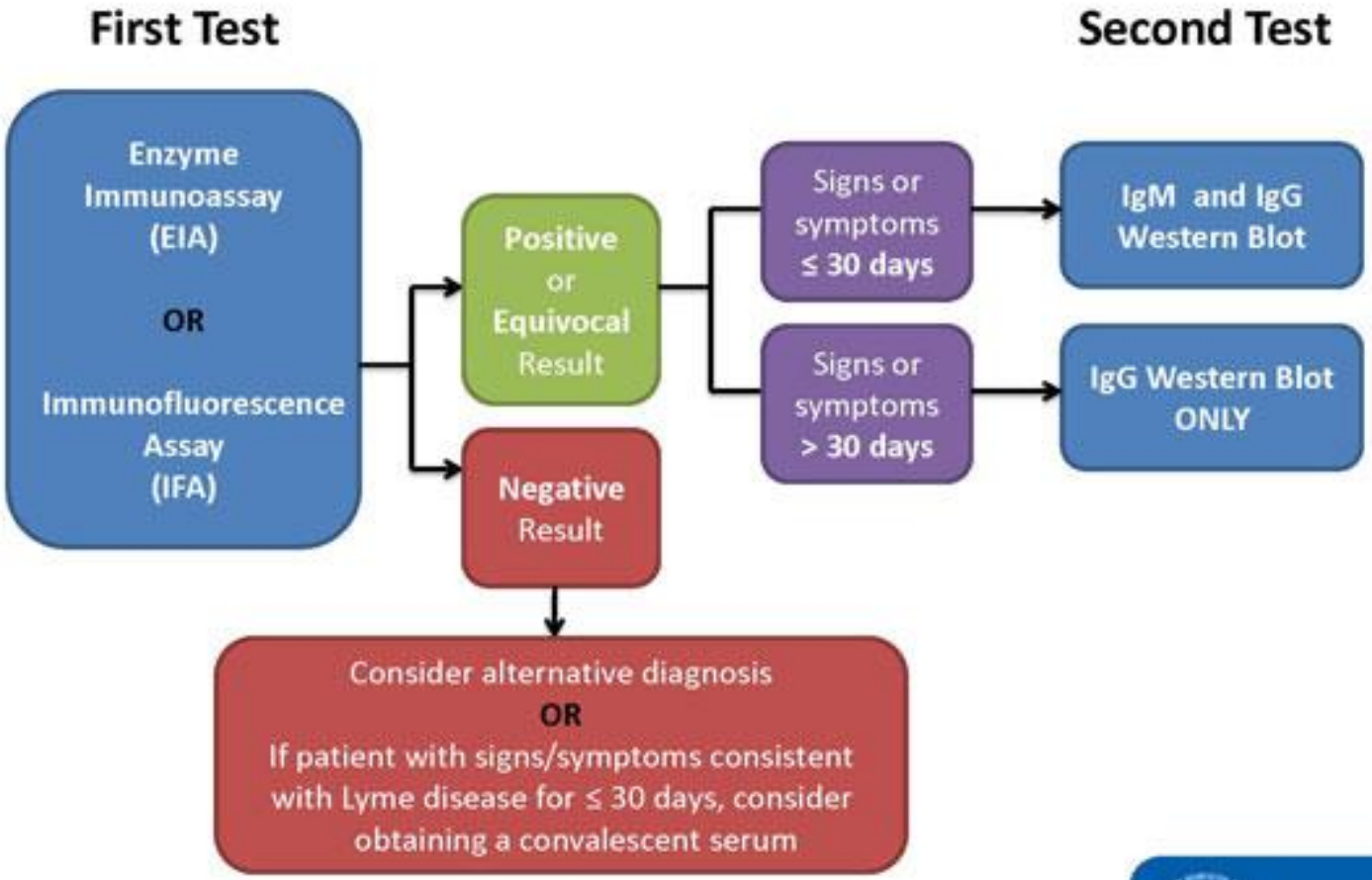
Immunoblot (Western Blot) Interpretation Criteria

- **IgM immunoblot**
  - Considered positive if 2 of the following 3 bands are present: 23-25 kDa (OspC), 39 kDa (BmpA), and 41 kDa (Fla)
- **IgG immunoblot**
  - Considered positive if 5 of the following 10 bands are present: 18 kDa, 23-25 kDa (OspC), 28 kDa, 30 kDa, 39 kDa (BmpA), 41 kDa (Fla), 45 kDa, 58 kDa, 66 kDa, and 83-93 kDa



http://www.cdc.gov/mmwr/preview/mmwrhtml/00038469.htm (Updated 1995)

Two-Tiered Testing for Lyme Disease



Two-Tier Testing for Lyme Disease

- **Lyme Screens (EIA/ELISA):**
  - Examples:
    - **Lyme disease (Borrelia burgdorferi) Antibody Screen:**
      1.22 - (Final)
    - **Borrelia burgdorferi Ab.IgG+IgM:**
      1.47 index
    - **Borrelia burgdorferi Ab.IgM:**
      0.94 index

- **Immunoblots (Western Blots)**
  - Examples:
    - **Borrelia burgdorferi Ab.IgM band pattern:**
      Positive
    - **B BURGDOR IGG SER QL IB:**
      Positive
    - **Borrelia burgdorferi antibody band pattern:**
      Lyme IgG Western Blot - bands 30, 39, 41, 45, and 58 present positive

Lyme ELISA (screen)

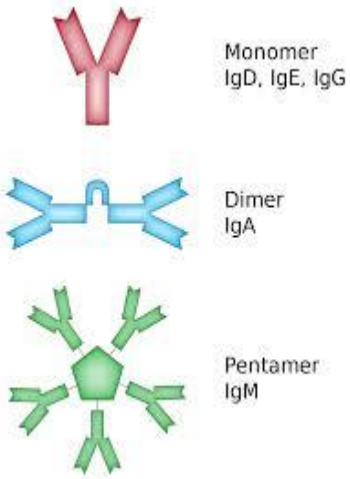
- **False-negative results common if tested too early**
  - Only 50% sensitivity if test taken within first two weeks of infection
  - Patients with EM typically seronegative

- **Sensitivity of screen is very good AFTER the EM stage of illness**
  - Ab levels may remain elevated for months to years after treatment!

- **False positive results are an issue also - some possible causes of false-positive screening tests include:**
  - Relapsing fever
  - Syphilis (*Treponema pallidum*)
  - Periodontal disease (*Treponema denticola*)
  - Systemic lupus erythematosus
  - Acute Epstein-Barr virus infection
  - *Helicobacter pylori*
  - Subacute bacterial endocarditis
  - Rheumatoid arthritis

Lyme IgM Western Blot Issues

- Omitting the screen and using IB only decreases specificity of serological testing!
- Why?
  - Western Blot will NOT be done if screen is negative
  - With NO screen, more Western Blots will be run – some will be false positives
  - Erroneous scoring of a faint band is a common reason for false-positive readings
  - IgM results more affected by this problem:
    - IgM Abs are more non-specifically "sticky" than IgG Abs
    - Only 2 of 3 bands are required for an IgM to be reported as positive (as opposed to 5 of 10)
    - "A single erroneously scored faint band will affect IgM results more readily than it will affect IgG results"

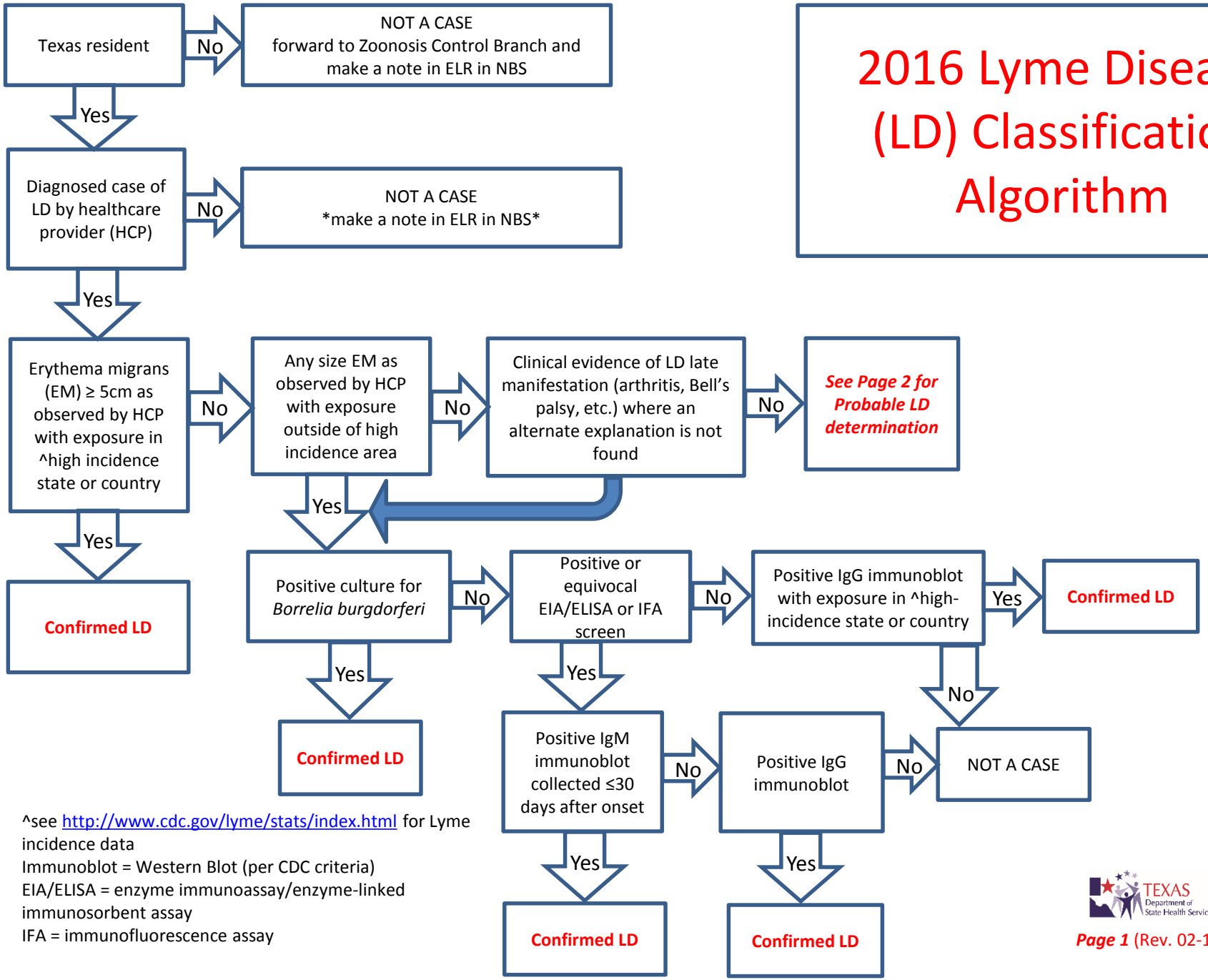


Johnson, B.J. "Chapter 4: Laboratory diagnostic testing for *Borrelia burgdorferi* infection" in Lyme disease: An Evidence-based Approach, J.J. Halperin, Ed. (CAB International, 2011). Complete Article Reproduced with Permission

Lyme Disease Case Investigation

- Onset date important
  - IgM + blot only relevant if specimen collected ≤30 days after symptom onset
- Make sure all lab reports are in NEDSS
- Physician does not have to definitively diagnose patient with Lyme ("will not be considered cases if the medical provider specifically states this is *not* a case of Lyme disease")
- Inquire about travel history!
- Consider "alternate explanation"
  - Rheumatoid arthritis, Lupus, etc.
- Make sure all required fields are completed in NEDSS (*refer to Data Entry Guidelines – Quick Reference section for patient demographics/lab report*)

2016 Lyme Disease (LD) Classification Algorithm



^see http://www.cdc.gov/lyme/stats/index.html for Lyme incidence data
Immunoblot = Western Blot (per CDC criteria)
EIA/ELISA = enzyme immunoassay/enzyme-linked immunosorbent assay
IFA = immunofluorescence assay

TEXAS Department of State Health Services

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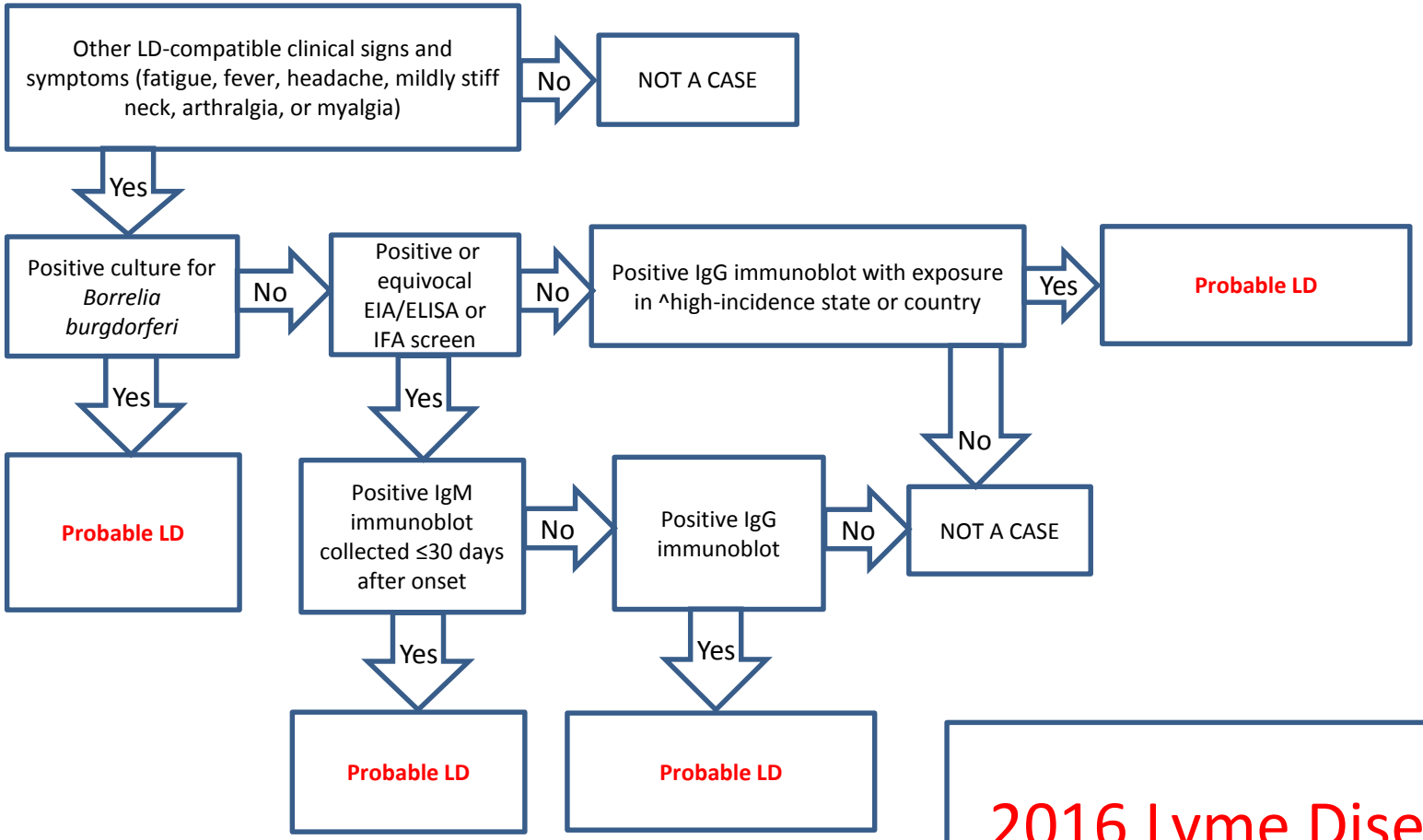

2016 Lyme Disease (LD) Case Classification Algorithm

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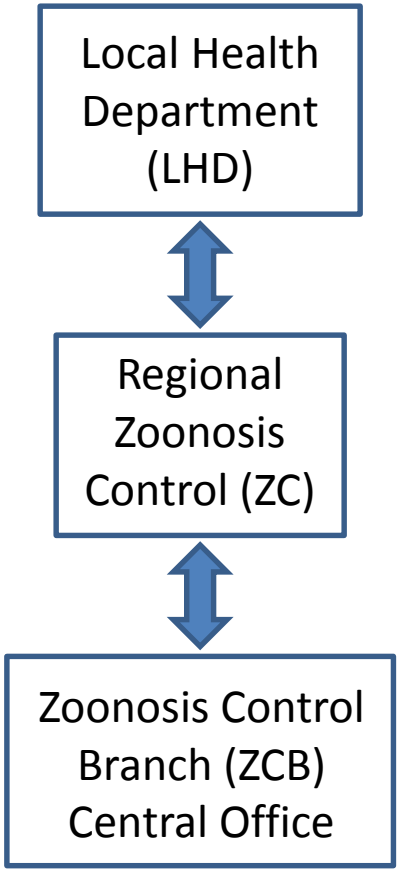
Immunoblot = Western Blot (per CDC criteria)
EIA/ELISA = enzyme immunoassay/enzyme-linked immunosorbent assay
IFA = immunofluorescence assay

Disease Reporting/Communication



- **Regional ZC should be the liaison between the LHDs and ZCB – if responsible jurisdiction is LHD, information should flow through regional ZC office**
  - Completed case investigation forms
  - Questions
  - Issues with classification or missing documentation/information
- **Regional ZC all have different preferences and are involved to varying degrees**
- **If ZCB communicates directly with LHD, regional ZC should at least be notified (cc'd if email)**

Useful Resources

- DePietropaolo DL, Powers JH, Gill JM. **Diagnosis of Lyme Disease.** Am Fam Physician. 2006 Mar 1;73(5):776.
  - clinical recommendations, how to determine pre-test probability, interpretation of serologic testing
- www.cdc.gov/lyme/
  - signs and symptoms, treatment, diagnosis and testing, data and statistics, transmission, post-treatment Lyme disease syndrome, info for healthcare providers, educational materials, tick bite/removal/testing info
- www.dshs.state.tx.us/idcu/disease/lyme/
  - overview, data, resources
- Lantos PM, et al. **Poor Positive Predictive Value of Lyme Disease Serologic Testing in an Area of Low Disease Incidence**. Clin Infect Dis. 2015 Nov 1;61(9):1374-80. doi: 10.1093/cid/civ584. Epub 2015 Jul 20.
  - study on positive predictive value of two-tiered testing