



GETTING STARTED WITH IGENEX

March 2022



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- Why IGeneX?
- Patient journey
- How to order tests and panels
- Discuss which tests to order and why
- Quality of test results
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Why IGeneX?

- Servicing the Lyme and tick-borne disease community for nearly 30 years
- **Comprehensive Testing**
 - **More diseases:** Lyme, TBRF, Bartonella, Babesia, Anaplasma, Ehrlichia, Rickettsia, COVID-19
 - **More methods:** PCR, Western Blots, IgXSpot, ImmunoBlots, FISH, IFA
 - **Most accurate:** ImmunoBlots have proven to be nearly twice as sensitive as two-tier testing
- **Certified** – IGeneX is fully CLIA/CMS certified, as well as being licensed to perform testing from all 50 states, including New York

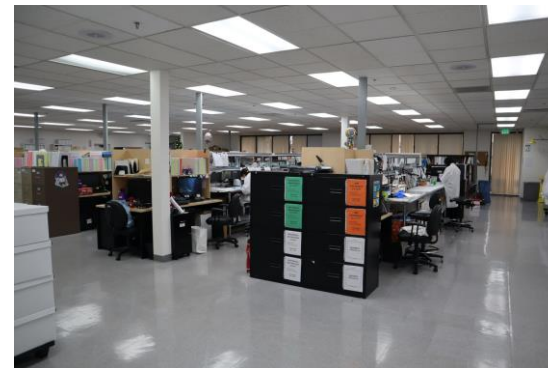


*Dr. Jyotsna Shah
President & Laboratory Director
IGeneX, Inc.*



Why IGeneX?

- Headquartered in the San Francisco Bay Area
- 70 employees
- Quality leader
- All R&D and testing is done on site



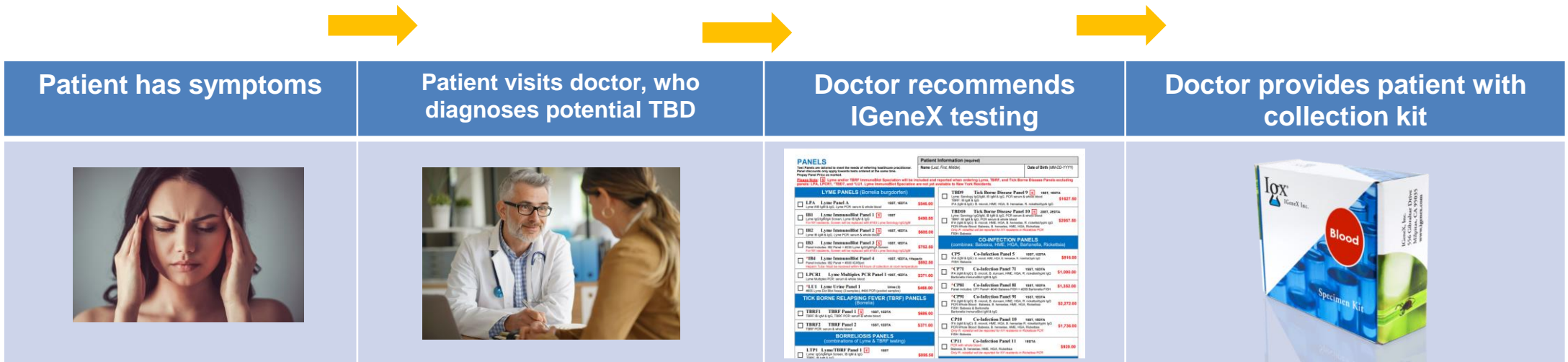


Two ways patients find IGeneX

Patient driven



Doctor driven





Next steps

Patient gets blood drawn at doctor's office or other facility. (Visit igenex.com for Blood Draw locator)

Igx
IGeneX Inc.

556 Gibraltar Drive | Milpitas | CA 95035 - 6315 | T: (800) 832-3200 | F: (408) 935-8272 | www.igenex.com
CLIA Number: 05D0643914 • NPI: 1396837605 • CA License: CLF4033 • Federal Tax ID: 94-3147701

Processing of test(s) may be delayed if the following required information is incomplete:
 • PATIENT INFORMATION: Patient's demographic, Patient's signature, and Patient/Responsible party's signature.
 • REFERRING PHYSICIAN'S INFORMATION: Referring Physician's practicing location address, EIN, Code, NPI, and Physician's signature.

TEST REQUISITION FORM
(Domestic Use Only)

Lab Use Only

PATIENT INFORMATION (Please Print Clearly) Visit www.igenex.com for the most up-to-date billing and payment information.

| | | | | |
|-----------------|------------|---------------------------------|-------------------------------|-----|
| Last Name | First Name | City | State | Zip |
| Mailing Address | | Middle Initial | | |
| Telephone | Email | Gender | Date of Birth (MM/DD/YYYY) | |
| | | <input type="checkbox"/> Female | <input type="checkbox"/> Male | |

BILLING INFORMATION – Please select one of the following payment methods (REQUIRED):
 Please note, IGeneX, Inc. does not bill Health Insurance Providers, Medi-Cal or Medicaid.

YES, I have Medicare – Medical (Part B) Coverage
 MBI (Medicare Number):
 • Please attach a copy of your Medicare Card
 • Review Medicare paperwork included in specimen collection kit
 • Please complete and sign the attached Medicare Patient Insurance Information Form

NO, I do not have Medicare – Medical (Part B) Coverage

Check Number:
 Credit Card: Visa, MasterCard, Discover or American Express ONLY
 We DO NOT accept Healthcare Financing CareCredit or Credit Cards.

Credit Card Number:
 Card Holder's Name:
 Expiration Date (MM/YYYY) Billing Zip Code:

SIGN HERE:
(Required to process tests)

PATIENT or RESPONSIBLE PARTY'S SIGNATURE (REQUIRED)

Please charge my credit card for additional test(s) requested by my Referring Physician: YES NO



Domestic kits are shipped to IGeneX in a prepaid mailer.





Billing



- Insurance is not accepted except for Medicare Part B. However, IGeneX does provide paperwork for 3rd party filing.
- Competitive pricing, with significant discounts on test panels
- Organizations such as LymeTap offer grants for low-income individuals
- We offer Client Bill and Patient Bill





How does a physician order IGeneX tests?

- **You do not need to create an account before ordering from IGeneX.** An account will be created when your first requisition is received.
- Complimentary kits can be requested through the website or by calling 1-800-832-3200
- The Test Requisition Form (TRF) has over 60 individual tests and 30 panels to choose from



Which tests should a physician order?

Two important issues:

1. Testing for the right pathogens
2. Test performance

Both must be considered to prevent false negative tests and missed diagnoses.



Testing for the right pathogens-

Many “Lyme” patients are co-infected

A 2018 study of 10,000+ patient samples from nearly every state:

- 37.3% were positive for Babesia species
- 32.1% for Lyme Borrelia
- 27.7% for TBRF Borrelia
- 19.1% for Bartonella
- 16.7% for Anaplasma
- 12.8% for Rickettsia
- 6.9% for Ehrlichia

Co-infections

- 40% tested positive for two pathogens
- 15% tested positive for three pathogens
- 4.6% tested positive for four pathogens
- 0.7% tested positive for five pathogens



Borrelia: More than just Lyme - must also include TBRF

They ALL presented as Lyme patients, not “relapsing fever” patients

543 US patients with suspected Lyme:

- 32% were positive for Antibodies to Lyme Borrelia
- 22% were positive for Ab to Relapsing Fever Borrelia
- 7% were positive for Ab to **both** LB and RFB

321 California residents:

- 33% were positive for Ab to LB
- 27% were positive for Ab to RFB
- 11% were positive for Ab to **both** LB and RFB



Within each group are multiple species

The IGeneX ImmunoBlots can detect and identify them

Lyme Borrelia

- *B. burgdorferi B31*
- *B. burgdorferi 297*
- *B. californiensis*
- *B. mayonii*
- *B. spielmanii*
- *B. valaisiana*
- *B. afzelii*
- *B. garinii*

TBRF Borrelia

- *B. hermsii*
- *B. miyamotoi*
- *B. turcica-like*
- *B. turicatae*
- *B. texasensis*
- *B. coriaceae*
- *B. parkeri*



Bartonella testing

Similar story as Borrelia- multiple species

- The Bartonella ImmunoBlot has multispecies capability
 - Able to detect antibodies to the most commonly found species
 - Will further name the following species if present: *B. henselae*, *B. quintana*, *B. elizabethae* and *B. vinsonii*
- The Bartonella FISH also has multispecies capability
 - Designed to detect Bartonella at the genus level
 - Is a direct test that detects the organism's RNA
 - Potential to detect organisms hidden in biofilms
- The PCR and IgXSpot likewise test at the genus level



Babesia testing

Again, multiple species may infect your patient!!

- Babesia IFA
 - IgM and IgG antibodies to *B. microti* and *B. duncani*
- Babesia FISH also has multispecies capability
 - Designed to detect Babesia at the genus level
 - Is a direct test that detects RNA
 - Potential to detect organisms hidden in biofilms
- Babesia PCR
 - Is a direct test that detects DNA
 - Also detects at genus level



The obvious conclusion:

Testing for multiple pathogens is often necessary

Co-infections:

Because of symptom overlap, often it is not possible to separate out the major TBDs on clinical grounds alone

- **EXAMPLE:** Many of the co-infections mimic Borreliosis
 - Symptoms of Lyme and TBRF overlap
 - Bartonella can cause joint pain, fatigue and neurologic issues
 - Babesiosis can cause headaches, dizziness and fatigue
 - All of these can become chronic
 - All of these may be missed if not properly tested

*Testing for **multiple pathogens** maximizes diagnostic accuracy*



Test performance- insist upon maximal accuracy!

- **ImmunoBlots** use *multiple recombinant protein antigens* genetically engineered to detect a large number of species with far higher sensitivity and specificity
- **FISH assays** use specific RNA probes
 - Said to be orders of magnitude more sensitive than direct smears
 - Outperform PCR
 - Able to detect organisms trapped in biofilms
- **PCR:** When you order an IGeneX Lyme PCR, FOUR PCRs are done:
 - Genomic and plasmid
 - Whole blood and serum



EXAMPLE: The Lyme ELISA performs poorly

Sensitivity averages 49% (range 29% to 75%)

(Stricker, BMJ 2007; 335 (7628): 1008)

| Study/Year | Sensitivity | Specificity |
|------------------------|---------------|-------------|
| Schmitz et al, 1993 | 66% | 100% |
| Engstrom et al, 1995 | 55% | 96% |
| Ledue et al, 1996 | 50% | 100% |
| Bakken et al. 1997 | 75% | 81% |
| Trevejo et al, 1999 | 29% | 100% |
| Nowakowski et al, 2001 | 66% | 99% |
| Bacon et al, 2003 | 68% | 99% |
| Coulter et al, 2005 | 18% | - |
| Wormser et al, 2008 | 14.1% | - |
| MEAN TOTAL | 49.01% | 96% |

1. Schmitz et al. *Eur J Clin Microbiol Infect Dis.* 1993;12:419-24
2. Engstrom et al. *J Clin Microbiol.* 1995;33:419-27.
3. Ledue et al. *J Clin Microbiol.* 1996;34:2343-50.
4. Bakken et al. *J Clin Microbiol* 1997; 35(3): 537-543.
5. Trevejo et al. *J Infect Dis.* 1999;179:931-8.
6. Nowakowski et al. *Clin Infect Dis.* 2001;33:2023-7.
7. Bacon et al. *J Infect Dis.* 2003;187:1187-99.
8. Coulter et al. ., *J Clin Microbiol* 2005; 43: 5080-5084.
9. Wormser et al. *Clin Vaccine Immunol.* 2008;(10):1519-22.



Lyme ImmunoBlot has far greater sensitivity!

Samples supplied by the CDC; interpreted with IGeneX criteria

| Patients with: | n | 2-tier Serological Testing for LD (ELISA followed by Western blots) | | | Lyme ImmunoBlots | | |
|-----------------------------------|----|---|--------|--------|------------------|--------|--------|
| | | IgM | IgG | G+M | IgM | IgG | G+M |
| Early Lyme Acute (Stage 1) | 15 | 20.0% | 0.0% | 20.0% | 66.7% | 46.7% | 93.3% |
| Early Lyme Convalescent (Stage 1) | 15 | 66.7% | 33.3% | 80.0% | 86.7% | 46.7% | 100.0% |
| Neurological Lyme (Stage 2) | 9 | 100.0% | 55.6% | 100.0% | 100.0% | 77.8% | 100.0% |
| Lyme arthritis (Stage 3) | 10 | 10.0% | 100.0% | 100.0% | 30.0% | 100.0% | 100.0% |
| Total | 49 | 46.9% | 40.8% | 69.4% | 71.4% | 63.3% | 98.0% |

GAME CHANGER!

IGeneX Lyme ImmunoBlot picked up **93% of early cases!!**

No other test *of any kind* has been demonstrated to do this.



Lyme ImmunoBlot specificity

Unlike standard serologies, no tradeoff between sensitivity and specificity

| Samples | Negatives | Lyme IB (In-House) | | | Lyme IB (CDC) | | |
|----------------------|-----------|--------------------|-------------|-------------|---------------|-------------|-------------|
| | | IgM | IgG | IgM+IgG | IgM | IgG | IgM+IgG |
| | | | | | | | |
| CDC Set 1* | 5 | 0 | 0 | 0 | 0 | 0 | 0 |
| CDC Set 2* | 20 | 0 | 1 | 1 | 0 | 0 | 0 |
| PT Samples | 11 | 0 | 0 | 0 | 0 | 0 | 0 |
| Autoimmune | 42 | 0 | 0 | 0 | 0 | 0 | 0 |
| Viral Infections | 46** | 1 | 1 | 2 | 0 | 0 | 0 |
| RPR + | 28 | 0 | 2 | 2 | 0 | 1 | 1 |
| Total False + | | 0 | 4 | 5 | 0 | 1 | 1 |
| Total True - | 152 | 151 | 148 | 147 | 152 | 151 | 151 |
| Specificity % | | 99.3 | 97.4 | 96.7 | 100 | 99.3 | 99.3 |

*Western blot results were provided by CDC

**Out of 46 samples with antibodies to viruses, 11 had antibodies to CMV; 24 to EBV, 7 to HSV; and 4 to HCV

**Only 2 of 24 samples with antibodies to EBV were positive by Lyme IB

PT = proficiency test



Testing by **multiple methods** also increases diagnostic accuracy

| Direct Testing These tests look for the pathogen in the specimen | Indirect Testing These tests look for antibodies or T-cell reactivity in the blood |
|---|--|
| Why use direct tests: <ul style="list-style-type: none">• Not every patient has detectable antibodies• Patients may be immune-suppressed• Antibodies may be bound in immune complexes• Some patients are challenging blood draws (i.e. young kids) so urine specimens can be tested instead | Why use indirect tests: <ul style="list-style-type: none">• Pathogens not always in the bloodstream• Superior at detecting early and/or late stage disease• Certain tests can detect T-cell response, an early disease indicator and useful in B-cell immune deficiencies |
| Types of direct tests: <ul style="list-style-type: none">• PCR (DNA)- multiple sources possible• FISH (RNA)- blood samples only• Urine antigen capture | Types of indirect tests: <ul style="list-style-type: none">• ImmunoBlot• Western Blot• IFA• IgXSpot (T-cell response) |



Testing by multiple methods- *Example: Bartonella*

| N | 130 | % (+) |
|---------|-----|-------|
| FISH | 15 | 11.5% |
| WB | 51 | 39.2% |
| IgX | 23 | 17.7% |
| Overall | 69 | 53.1% |

Note: ImmunoBlots are more sensitive than Western Blots. Therefore, we expect the overall sensitivity to improve using FISH, ImmunoBlot and IgXSpot test.



IqGeneX test panels simplify ordering and save money

- A test panel is a logical grouping of tests that increases accuracy and completeness of results, while saving large amounts of money
- Simplifies ordering tests for multiple pathogens using multiple methods
- Designed to make ordering quick and easy!
- Good “memory jogger” so you are more likely to be complete in your assessments

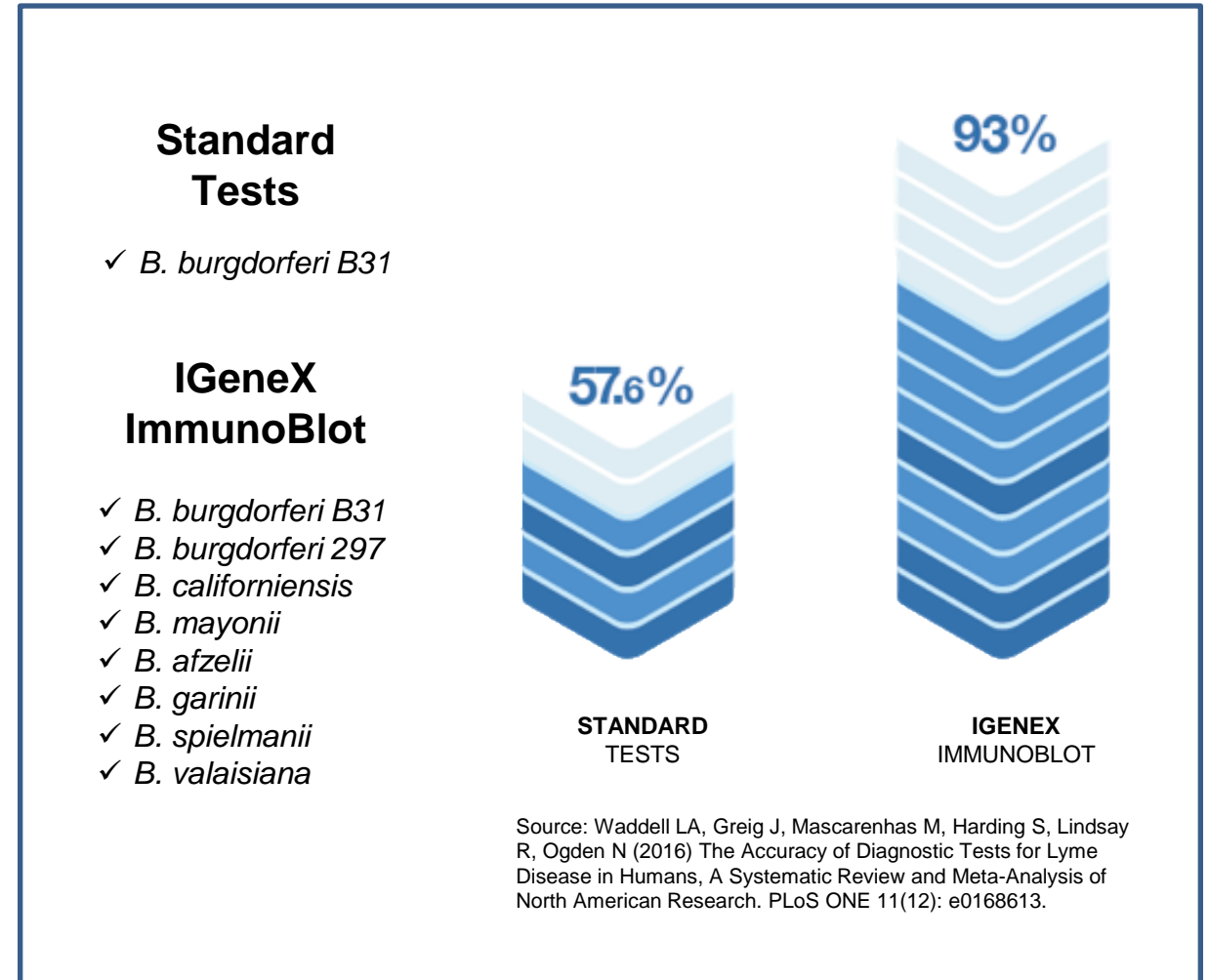
Examples of most popular panels

- LTP1 - LYME/TBRF PANEL 1
 - Includes IgM and IgG ImmunoBlots for Lyme and TBRF Borrelia
 - Adds a screening IFA to satisfy two-tier requirements needed for some cases of insurance coverage
 - **Saves \$204.50** over ordering tests individually
- TBD61 - TICK BORNE DISEASE PANEL 61
 - LB, TBRF, Babesia microti and duncani, Bartonella, HME, HGA, R. rickettsia, R. typhi
 - Includes IFA, ImmunoBlot, PCR, FISH; serum + whole blood
 - **Saves \$1,308.50!!**



If money is an issue, choose the ImmunoBlot

- Considered the gold standard in Lyme testing
 - **Better testing saves money in the long run**
 - ImmunoBlots replace the Western Blot
- Most Lyme tests detect only a single *Borrelia* species, *B. burgdorferi B31*. The ImmunoBlot tests for eight species.
 - Eight Western blots needed to duplicate this
- ImmunoBlots are available for Lyme, Tick-Borne Relapsing Fever, Bartonella and COVID-19 (more to come)
- **Broad Coverage Assays – Only \$195!**
 - Available for Lyme and TBRF
 - Similar to ImmunoBlots, but without speciation
 - BCAs replace the ELISA





Remember, using insensitive tests can cause trouble!!

Seronegativity can be due to missed pathogens and also due to insensitive tests.

- Because of seronegativity:
 - Missed diagnoses
 - Incorrect diagnoses, especially neuropsychiatric ones
 - Patients are told they need psychiatric help!!
 - Patients are told to just live with their symptoms ☹️
- Because of seronegativity:
 - Insurance companies may deny covering treatment
- Because of seronegativity:
 - If the clinician diagnoses on clinical grounds despite negative tests, then not only may your peers question you, state Medical Boards may pay a visit!

THEREFORE, YOU MUST INSIST UPON USING THE MOST ACCURATE TESTS AVAILABLE!

IGeneX offers the highest quality and broadest range of tests than any other lab.



Examples of Test Results



Copy of an actual report - *Bartonella ImmunoBlot*

Interpretation:

- Positive: two or more bands
- Indeterminate: one band
- Negative: no bands

Speciation:

- Report species if any of these are found:
 - *B. elizabethae*
 - *B. vinsonii*
 - *B. henselae*
 - *B. quintana*
- Report as genus-positive if other species are found
- May find and report more than one species (surprisingly common!)

The patient is positive for both Bartonella IgM and Bartonella IgG.

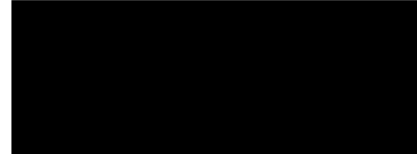


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NPI: 1396837605

Referring Physician



Collected: 09/29/2021 UNK
Received: 10/06/2021 15:09
Reported: 10/14/2021 16:56
Reprinted: 12/02/2021 16:34

Patient



BARTONELLOSIS

| | | | |
|---------------------------|---------|-----------------|---|
| Bartonella FISH | W blood | Negative | |
| BARTONELLA IMMUNOBLOT IGM | | | |
| Bartonella genus | Serum | Positive | Positive: Detected 2 or more Bartonella genus or species-specific antibody. Indeterminate: Detected only 1 Bartonella genus or species-specific antibody. Negative: No Bartonella specific antibody detected. |
| <i>B. elizabethae</i> | Serum | Negative | |
| <i>B. vinsonii</i> | Serum | Negative | |
| <i>B. henselae</i> | Serum | Positive | |
| <i>B. quintana</i> | Serum | Negative | |
| BARTONELLA IMMUNOBLOT IGG | | | |
| Bartonella genus | Serum | Positive | Positive: Detected 2 or more Bartonella genus or species-specific antibody. Indeterminate: Detected only 1 Bartonella genus or species-specific antibody. Negative: No Bartonella specific antibody detected. |
| <i>B. elizabethae</i> | Serum | Positive | |
| <i>B. vinsonii</i> | Serum | Positive | |
| <i>B. henselae</i> | Serum | Positive | |
| <i>B. quintana</i> | Serum | Negative | |

End of Report





Copy of an actual report - *Babesia* IFA

The patient is Indeterminate for *B. microti* IgM, and negative for *B. microti* IgG, Babesia FISH, and *B. duncani* IgM and IgG.

BABESIOSIS

B. microti IFA - IgM

Serum

20

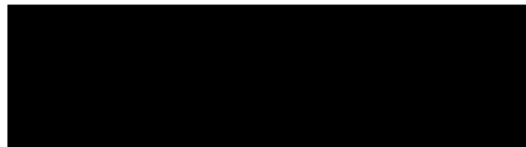
< 20 : Negative Titer
= 20 : May or may not indicate active infection
>=40 : Indicates active infection

Testing performed at IGeneX 556 Gibraltar Drive Milpitas CA 95035 (800) 832-3200

Diagnosis should not be based on laboratory results alone. Results should be interpreted in conjunction with clinical symptoms and patient history.

NOTE: Western Blots, ImmunoBlots, Lyme Dot Blot, Epitope, PCR, IFA, FISH, C. pneumoniae IgG/IgA, CD57, IGXSpot, Broad Coverage Antibody, COVID-19 Test - These tests were developed and their performance characteristics determined by IGeneX, Inc. They have not been cleared or approved by the FDA. The FDA has determined that such approval is not necessary. These tests are used for clinical purposes and should not be regarded as investigational or for research. IGeneX, Inc. is licensed by CMS and NYS to perform high complexity clinical laboratory testing.

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Amended:
Corrected:

| TEST | SPECIMEN | RESULT | REFERENCE RANGE | UNITS |
|----------------------|----------|----------|--|-------|
| B. microti IFA - IgG | Serum | <40 | < 40 : Negative < 160 : May or may not suggest active infection >=160 : Indicates active infection | Titer |
| Babesia FISH | W blood | Negative | | |
| B. duncani IFA - IgM | Serum | <20 | < 20 : Negative = 20 : May or may not indicate active infection >=40 : Indicates active infection | Titer |
| B. duncani IFA - IgG | Serum | <40 | < 40 : Negative < 160 : May or may not suggest active infection >=160 : Indicates active infection | Titer |



Copy of an actual report - Lyme ImmunoBlot

The patient is positive for Lyme IgM by both IGeneX and CDC criteria.

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 Amended:
 Corrected:

| TEST | SPECIMEN | RESULT | REFERENCE RANGE | UNITS | | |
|--|----------|----------|-----------------|-------|-----|----|
| Lyme ImmunoBlot IgM | Serum | Positive | | | | |
| IGX Criteria: | | Positive | | | | |
| CDC/NYS Criteria: | | Positive | | | | |
| *** [REVISED REPORT: EFFECTIVE APRIL 10, 2019] | | | | | | |
| Lyme ImmunoBlot IgM detects antibodies to B. burgdorferi strains and species | | | | | | |
| Band (kDa) | 23* | 31* | 34* | 39* | 41* | 93 |
| Intensity | + | - | - | - | + | + |

Band Intensity: Positive: + to +++++, Indeterminate: Ind, Negative: (-)

| INTERPRETATION | IGX CRITERIA | CDC/NYS CRITERIA |
|----------------|---|---|
| Positive | 2 or more of the starred bands are present (+): 23*, 31*, 34*, 39*, 41* kDa | 2 or more of the following bands are present (+): 23*, 39*, 41* kDa |
| Negative | Does not meet IGX criteria for a positive. | Does not meet CDC/NYS criteria for a positive. |

LIMITATION: Bands 31* and 34* kDa are present in Lyme vaccinated patients. Viral antibodies cross react with the 93 kDa antigen.

LYME IMMUNOBLOT IGM SPECIATION

B. burgdorferi US(genus) Serum Positive
 B. burgdorferi US Spp Serum Positive

BbSs: Borrelia burgdorferi sensu stricto includes but not limited to B. burgdorferi B31 and B. burgdorferi 297.

BbSl: Borrelia burgdorferi sensu lato includes but not limited to B. mayonii and B. californiensis.



Additional resources

- Customer service personnel are well trained and knowledgeable
- Sales reps have a high degree of expertise and can address most questions
- Dr. Shah and other senior scientists are always happy to help
- Visit igenex.com for reference material, patient stories, webinars, and a Symptom Checker



Thank you!

QUESTIONS?