The Lyme Disease Controversy

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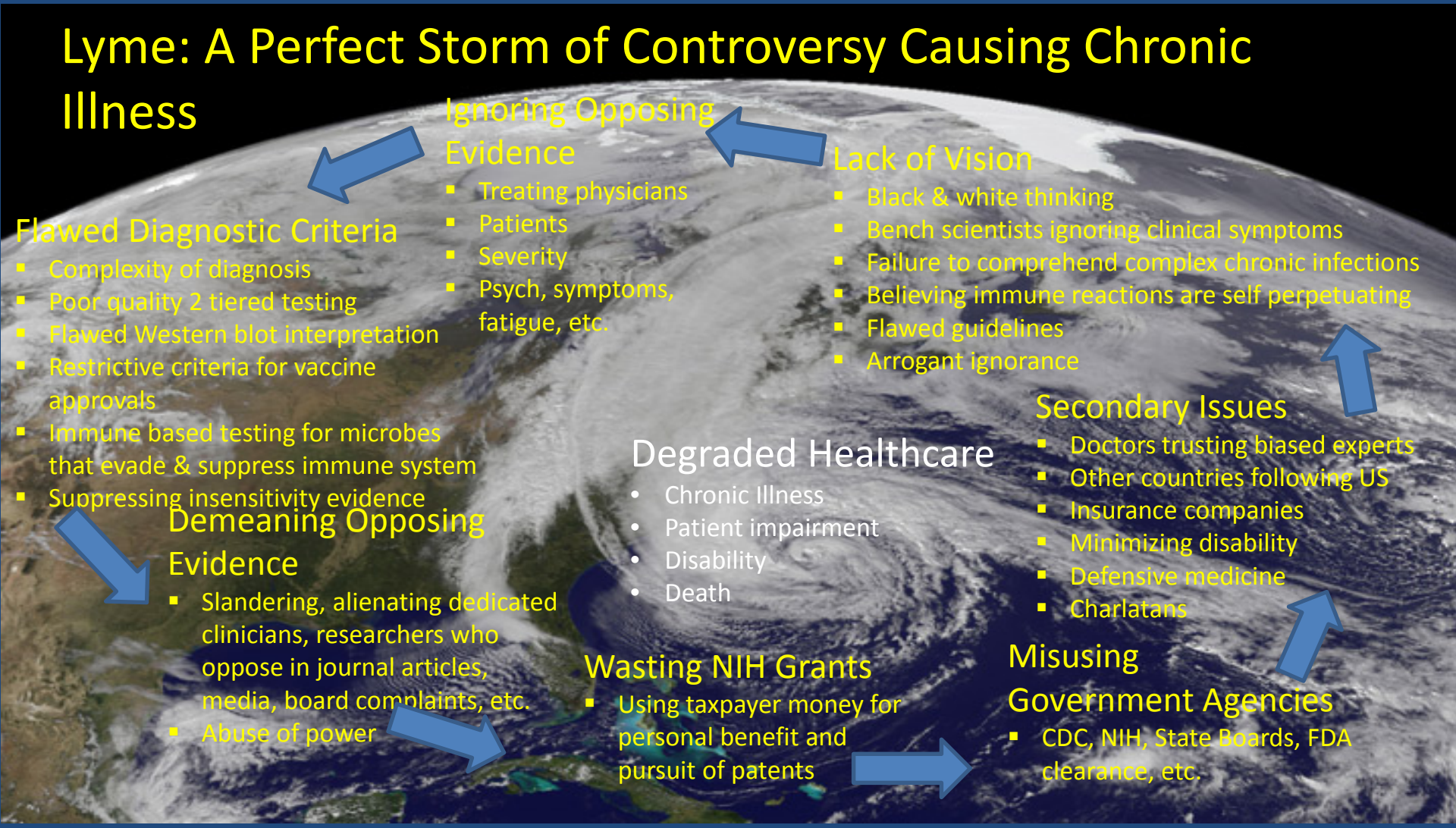
Lyme: A Perfect Storm of Controversy Causing Chronic Illness



Flawed Diagnostic Criteria

- Complexity of diagnosis
- Poor quality 2 tiered testing
- Flawed Western blot interpretation
- Restrictive criteria for vaccine approvals
- Immune based testing for microbes that evade & suppress immune system
- Suppressing insensitivity evidence

Ignoring Opposing Evidence

- Treating physicians
- Patients
- Severity
- Psych, symptoms, fatigue, etc.

Lack of Vision

- Black & white thinking
- Bench scientists ignoring clinical symptoms
- Failure to comprehend complex chronic infections
- Believing immune reactions are self perpetuating
- Flawed guidelines
- Arrogant ignorance

Demeaning Opposing Evidence

- Slandering, alienating dedicated clinicians, researchers who oppose in journal articles, media, board complaints, etc.
- Abuse of power

Degraded Healthcare

- Chronic Illness
- Patient impairment
- Disability
- Death

Secondary Issues

- Doctors trusting biased experts
- Other countries following US
- Insurance companies
- Minimizing disability
- Defensive medicine
- Charlatans

Wasting NIH Grants

- Using taxpayer money for personal benefit and pursuit of patents

Misusing Government Agencies

- CDC, NIH, State Boards, FDA clearance, etc.

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Outline

- Overview
- Defining and Assessing Lyme Disease
- Assessment and Testing
- The Role of Third Parties
- Medical Knowledge
- Medical Standards and Guidelines
- Conclusion

Overview

I would have never seen it if I hadn't believed it.

Yogi Berra

The good physician teats the disease; the great physician treats the patient who has the disease.

Sir William Osler

OVERVIEW OF LYME DISEASE: A CRITIQUE OF AN IGNORED PANDEMIC

- A seemingly stealthy pandemic of epic proportions, causing untold misery and suffering for millions, thrives amidst a culture of politics, greed, corruption, incompetence and arrogance. Endemic in many parts of the world Lyme disease and its associated coinfections doesn't even exist in the minds of some in the medical community, can't be easily diagnosed, treatment regimens are often confusing and not evidence based. When treatment is attempted it is often inadequate or substandard leaving many with chronic persistent infections. While not fitting a vaccine model, paradoxically the quest for finding a vaccine seems to have superseded all other priorities. The evidence of neuroborreliosis being causative in Alzheimer's disease has been sidelined presumably because that information is financially threatening to some controlling faction of our civilization. To complicate matters further there are many pathogenic Borrelia, some that may even rival Borrelia burgdorferi in causing illness, and almost nothing is being done to significantly advance either our ability to diagnose and treat this group of infections that are as problematic as they are pernicious.

Stoller KP. International Journal of Current Advanced Research. Vol 4, Issue 10, pp 409-414, October 2015

Seizing an Opportunity

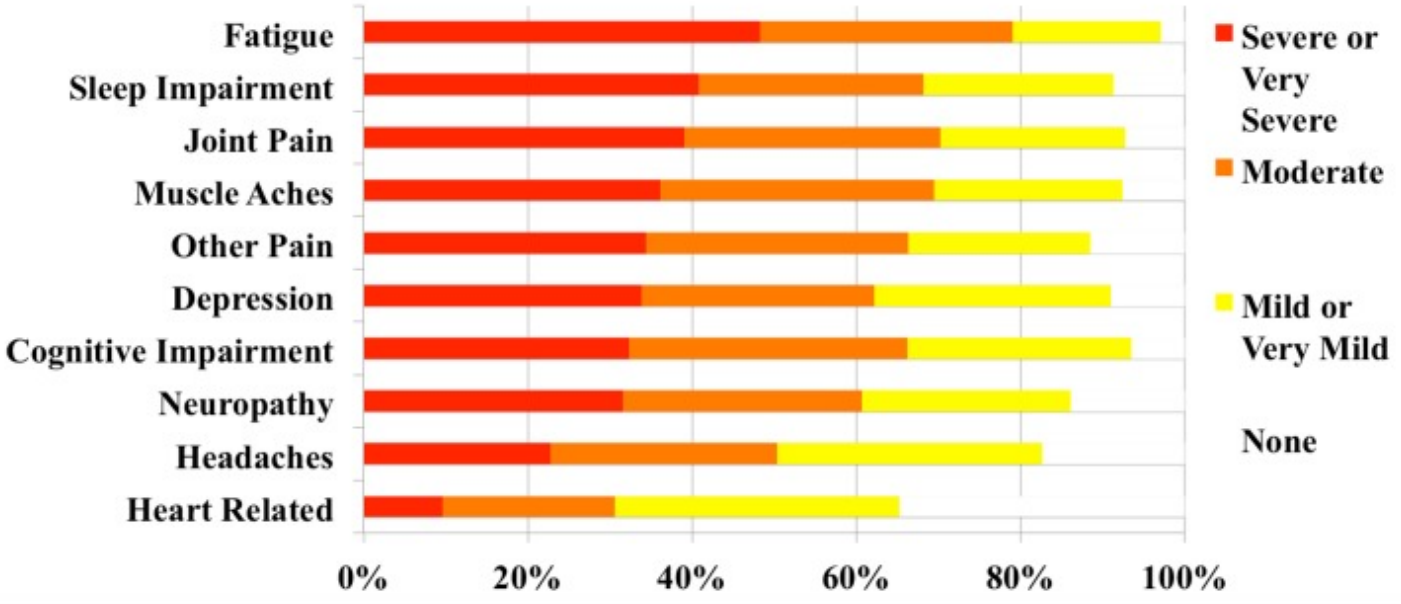
- Lyme/tick-borne disease has a significant impact in great severity, in great numbers and is difficult to diagnose.
- Prevention, recognition, early effective treatment and monitoring to prevent relapse is an opportunity to prevent a significant burden of disease that includes functional impairment, lost potential and productivity, healthcare costs, caretaker burden and suffering.
- Healthcare providers are in a unique position to help.

The Most Common Presentation

- Most commonly a previously health individual has a recognize or unrecognized tick bite and then experiences a gradual progression of increasing symptoms over a period of months and years. These symptoms ranked in order of severity include fatigue, sleep impairments, joint pain, muscle aches, other pain depression, cognitive impairments, neuropathy, headache and heart related symptoms.*

*Johnson L, et al. 2014

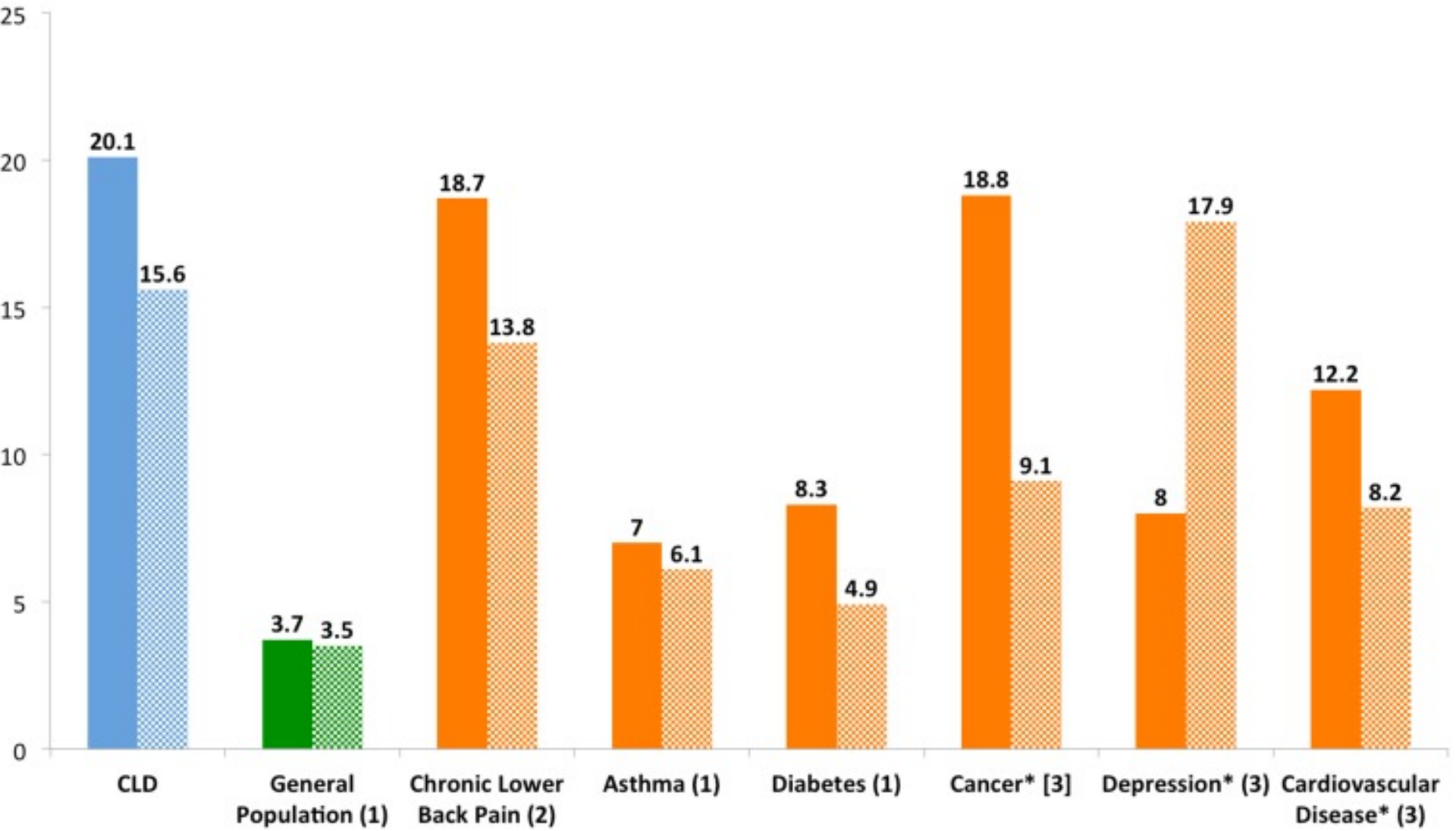
(A): CLD symptoms by severity



(B) CDC symptom days (out of 30)

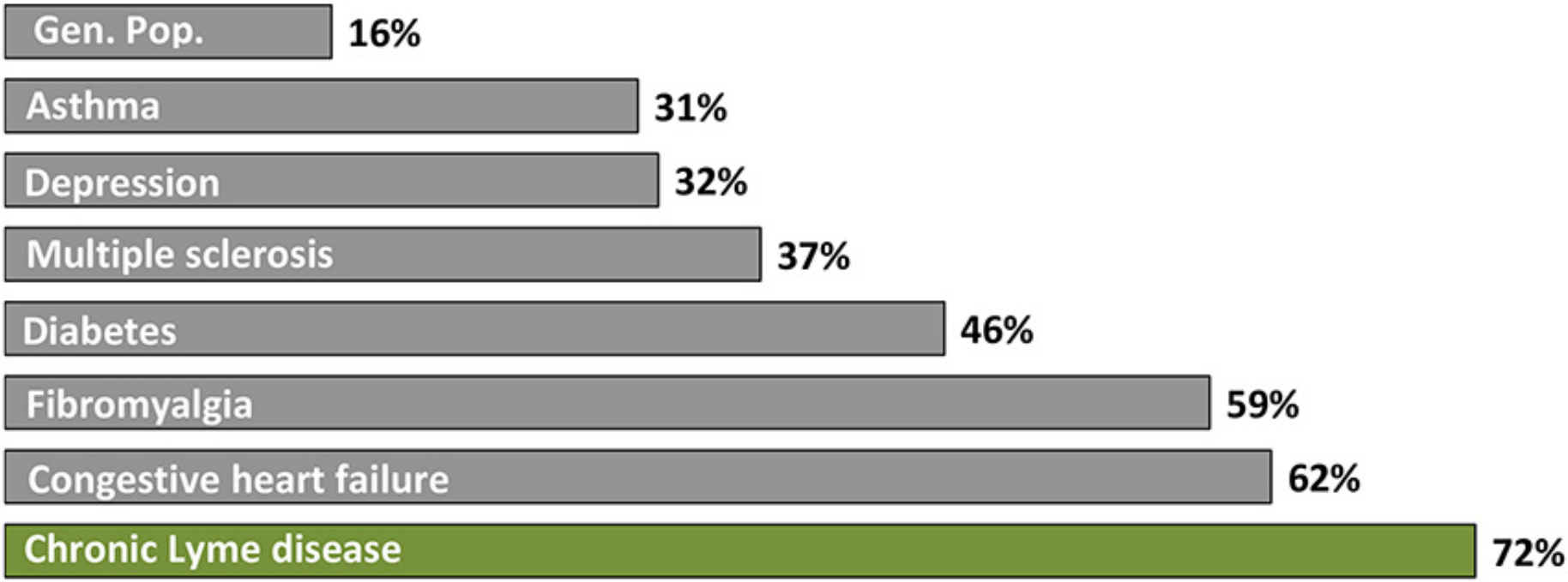
Johnson L et al. 2014

Number of poor physical and mental days per month of patients with Chronic Lyme Disease compared to the general population and other chronic diseases



Quality of Life

Chronic Lyme patients suffer worse quality of life compared to most other chronic diseases. 72% report their health status as fair or poor.



NIH Chronic Lyme Study

- "Based on objective tests of physical impairment, we found that the patients had levels of:
  - **Functional disability** comparable to what you would see with congestive heart failure,
  - **Pain** comparable to what you might expect in patients coming out of surgery, and
  - **Fatigue** comparable to patients with multiple sclerosis."
- Sustained improvement from antibiotics 10 years later!

Fallon , BA. Neurology. 2008 Mar 25;70(13):992-1003.
Fallon, BA Makousa M. Poster presentation. Drexel ILADS Symposium. April 11, 2015.

History of Lyme Disease

Historical Timeline

- Bb. found in amber, Iceman & ancient American Indian
- Described in Europe early 1900s
- Hellerstrom: Psych symptoms 1930
- Hellerstrom described in USA 1949
- Scrimenti: bulls eye rash 1971
- Polly Murray: Lyme CT 1975
- Burgdorfer discovers cause—Borrelia burgdorferi 1982
- Burrascano: clinical description
- Clinical diagnosis with pattern recognition, can be chronic
- MacDonald, Miklossy, Mattman, Sapi: coinfections, cysts, biofilms
- Barthold, Hodzic, Straubinger, Embers: persistence after treatment
- Psych symptoms immune basis
- At least 300,000 cases/year in US

Historical Errors

- New illness CT, only arthritis
- Steere: virus, leptospira, steroid tx
- Testing degraded at Dearborn
- Antibody testing reliable
- Dx by certain “objective” & ignore “subjective, non-specific” symptoms
- Symptoms are mild, self limiting
- Flawed Klempner studies
- Restrictive IDSA guidelines
- Vaccine is safe and effective
- Post infection immune symptoms
- No coinfections, cysts or biofilms
- Easily treated, no chronic infections
- No psychiatric symptoms
- 30,000 cases/year in US

Historical Failure

- Many policymakers controlling Lyme disease have been microbiologists, rheumatologists, bench scientists and bureaucrats. Their lack of expertise in clinical medicine and psychoimmunology prevents them from understanding the association between Lyme/tick-borne infections and fatigue and the cognitive, psychiatric, subtle neurological and other multi-systemic symptoms.

Significant controversy over Lyme disease exists for three main reasons

- Lack of accurate and/or universally accepted testing for the disease
- Disagreement about symptoms associated with persistent infection in chronic Lyme disease
- Misinterpretation and misrepresentation of underpowered Lyme antibiotic treatment trials
- While many studies describe the constellation of musculoskeletal, neurocognitive and/or cardiac symptoms associated with chronic Lyme disease, Shapiro views these as "medically unexplained symptoms" not necessarily related to persistent B. burgdorferi infection.

Stricker R. http://www.ncbi.nlm.nih.gov/pubmed/25705394

Lyme Disease Definition

- Some phrases used to describe this condition include—Lyme/Tick-Borne Disease, Lyme and Associated Diseases, Early Stage Lyme Disease, Disseminated Lyme Disease, Late Stage Lyme Disease, Lyme Borreliosis, Lyme Disease Complex, Lyme Encephalopathy, Neuro-Lyme, Lyme Neuroborreliosis, Neuropsychiatric Lyme, Chronic Lyme, Post Treatment Lyme, Latent Lyme, Latent Lyme/Tick-Borne Disease, Lyme Disease based upon CDC surveillance criteria, Lyme Disease based upon clinical assessment, Stanford definition, Chinese definition, CDC/ASPHLD Dearborn criteria, Two Tier definition, ILADS definition, Southern Tick Associated Rash Illness, etc.
- A failure to agree upon definitions adds to confusion when discussing this disease.

Tick-Borne Disease vs. Lyme Disease

Tick-Borne Disease

- Constantly evolving definition based on clinical observations & science. Pathophysiology is complex, interactive infection of multiple pathogens, opportunistic infections & other contributors. Diagnose with comprehensive clinical exam & pattern recognition. Recognition of limitations of current testing. Can be severe & chronic. Regional variability. Clinically relevant to all physicians globally.

Burgdorfer, Cameron, Stricker, Philips, Liegner, Bransfield, Johnson, et al.

Lyme Disease

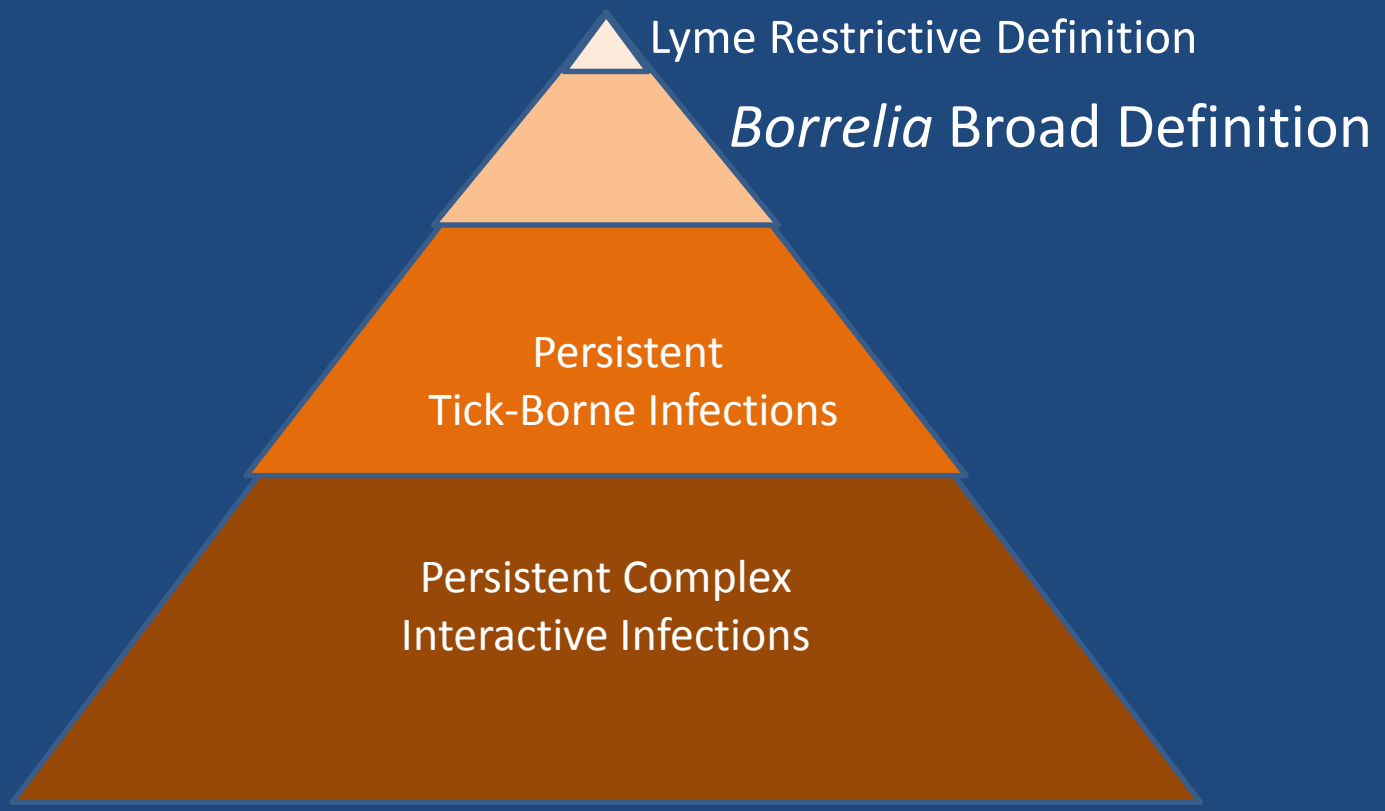
- Defined by highly restrictive clinical and laboratory criteria, based on symptoms seen in a 1975 juvenile arthritis epidemic in Lyme CT & *Bbss.* B-31 Shelter Island, NY USA laboratory reference strain & two-tiered testing with restrictive Dearborn criteria, “mild, never chronic & easily treated.”

Wormser, Steere, Shapiro, McSweegan et al.

Lyme: How Much is Bb or Other Microbes

- About 20+ years ago there was the phrase of “Lyme-like bacteria.” Some of us give more weight to lab tests, some give more weight to clinical presentation. For 20+ years clinical presentation frequently did not coincide with the highly controversial two tiered testing based upon the *Bbss* shelter Island B31 laboratory strain and the restrictive Dearborn criteria. So now that we know more—what is Lyme-like bacteria? Is it *Bartonella, Babesia, Anaplasma, Ehrlichia, Mycoplasma, Rickettsia*, opportunistic viruses, etc., or other *Borrelia* species such as *Borrelia miyamotoi*?

Nomenclature



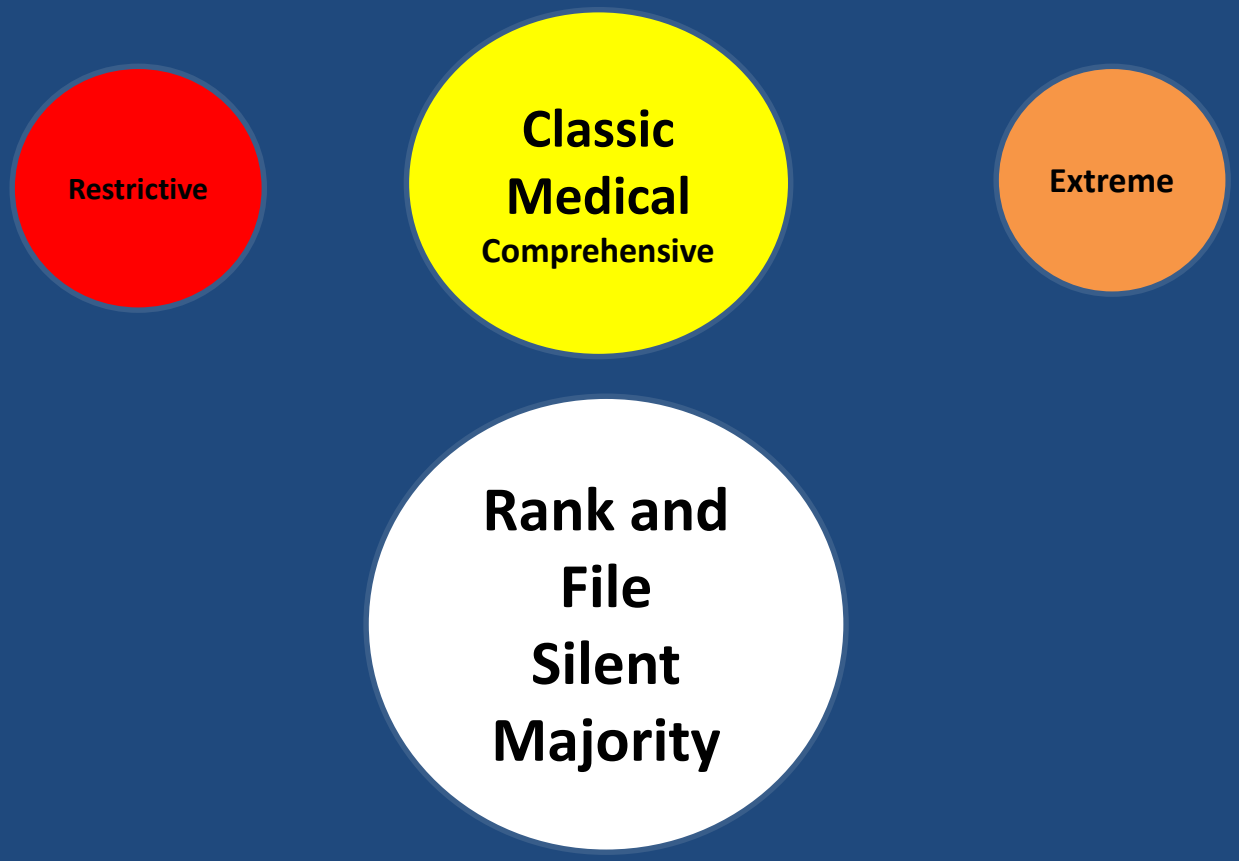
Defining and Assessing Lyme Disease

- Lyme disease may currently be the most controversial issue in medicine.
- Defining the disease, assessment and testing are at the core of the Lyme disease controversy.

CDC: Clinical Diagnosis Not Lab Diagnosis

- Lyme disease is a clinical diagnosis. This immune based test for Lyme disease requires complex interpretation. Positive reactivity does not always prove the presence of infection and negative reactivity does not always prove the absence of infection. The CDC states— "Two-step positive results provide supportive evidence of exposure to *B. burgdorferi*, which could support a clinical diagnosis of Lyme disease but **should not be used as a sole criterion for diagnosis**." [CDC]

Lyme/TBD Medical Views



Classic Medical: Comprehensive Definition of Lyme

- Comprehensive clinical assessment & pattern recognition.
- Comprehensive clinical definition needed for diagnosis.
- Psychiatric, cognitive symptoms from Lyme/TBD.
- Reactivity of specific bands on Western blot demonstrate exposure to *Bb*.
- Can be severe.
- Culture, PCR, CD-57 support diagnosis.
- Two tiered testing is highly unreliable for diagnosis.
- Coinfections are significant.
- If previously treated, it can relapse, can be chronic.
- Physician's primary responsibility to patient, clinical judgment and ethics supersedes third party authority.

Individualized Assessment

- Classic medical and standard evidence based medicine is based upon the long-standing traditions of Hippocrates and Osler emphasizing a thorough exam and individualized treatment with a balanced weight given to best evidence available, clinical expertise and patient preferences.
- Efforts by some to shift experience based decision making* away from the physician patient relationship towards third party empowerment jeopardizes the effective treatment of complex, poorly understood conditions.

*Includes clinical experience, published research, critical review of studies, international conference, CME, interacting with colleagues to gain knowledge, review and writing of guidelines, governmental actions etc. Includes clinical experience, published research, critical review of studies, international conference, CME, interacting with colleagues to gain knowledge, review and writing of guidelines, governmental actions etc.

Osler: History, Examination & Judgment

- "There is no more difficult art to acquire than the art of observation."
- "The good observer is not limited to the large hospital.“
- "If you listen long enough, the patient will give you the diagnosis."
- "Medicine is learned by the bedside and not in the class room. Let not your conception of manifestations of disease come from work heard in the lecture room or read from the book: see and then research, compare and control. But see first.“
- “The greater the ignorance, the greater the dogmatism.”

The Restrictive Definition of Lyme

- Definition is the original definition of Lyme arthritis from 1970s that includes only a few of the neurological symptoms. Other symptoms are subjective, nonspecific, "medically unexplained symptoms.," post treatment Lyme.
- No psychiatric symptoms.
- Severity is no more than "aches and pains of daily living."
- Antibody testing based upon B31 laboratory mutated strain of *Borrelia burgdorferi sensu lato* from Shelter Island, NY.
- Two tiered testing is highly reliable & needed for diagnosis.
- Dearborn interpretation of Western blot.
- Coinfections are mostly insignificant.
- If previously treated, it's cured, never chronic.
- Physicians defer to authority of third parties—CDC, etc.

Can you follow this "logic"?

- "Because most symptoms are accompanied by subjective signs, to test patients who have only those symptoms without objective signs such as nerve palsy, frank arthritis and so on, the vast majority of the test results are going to be false positive results," Shapiro said. "That is the reason there is this myth that chronic Lyme disease is common and difficult to treat. Such patients do not have Lyme disease in the overwhelming majority of cases."
- Teaching physicians unfamiliar with Lyme to manage medically unexplained symptoms without diagnosing an illness proves challenging, Shapiro said.
  "It is important to integrate psychological and biological factors associated with fatigue and anxiety when managing symptoms without a diagnosis in a patient who may have a 'chronic' disease," he said.

Shapiro ED. "Lyme Disease: old and new". Presented at: IDC NY; Nov. 19-20, 2016; New York

“Medically Unexplained Symptoms”

- Outdated, not included in DSM-5.
- No medical condition is totally explained or unexplained. Instead, knowledge is on a continuum and all conditions are partially explained to different degrees.
- This label is impacted by the bias and level of knowledge of anyone calling it “unexplained.” These symptoms are often unexamined rather than unexplained.

Diagnostic and Statistical Manual 5, American Psychiatric Association

Restrictive Advocates Debate Disease Definition, Testing & Antibiotic Effectiveness, Safety, Cost

- Feder HM Jr, Johnson BJ, O'Connell S, Shapiro ED, Steere AC, Wormser GP; Ad Hoc International Lyme Disease Group, (Agger WA, Artsob H, Auwaerter P, Dumler JS, Bakken JS, Bockenstedt LK, Green J, Dattwyler RJ, Munoz J, Nadelman RB, Schwartz I, Draper T, McSweegan E, Halperin JJ, Klempner MS, Krause PJ, Mead P, Morshed M, Porwancher R, Radolf JD, Smith RP Jr, Sood S, Weinstein A, Wong SJ, Zemel L.) A critical appraisal of "chronic Lyme disease". N Engl J Med. 2007 Oct 4;357(14):1422-30.
- Halperin JJ, Baker P, Wormser GP. Common misconceptions about Lyme disease. Am J Med. 2013 Mar;126(3):264.e1-7.
- Auwaerter PG, Bakken JS, Dattwyler RJ, Dumler JS, Halperin JJ, McSweegan E, Nadelman RB, O'Connell S, Shapiro ED, Sood SK, Steere AC, Weinstein A, Wormser GP. Antiscience and ethical concerns associated with advocacy of Lyme disease. Lancet Infect Dis. 2011 Sep;11(9):713-9.
- Auwaerter PG, Bakken JS, Dattwyler RJ, Dumler JS, Halperin JJ, McSweegan E, Nadelman RB, O'Connell S, Sood SK, Weinstein A, Wormser GP. Scientific evidence and best patient care practices should guide the ethics of Lyme disease activism. J Med Ethics. 2011 Feb;37(2):68-73.

“Post Treatment Lyme Disease Syndrome”

- A poorly defined invalid concept
- Was there sufficient treatment?
- More accurately called Post Inadequate Treatment Lyme Disease Syndrome.
- Unproven that persistent infection was eradicated.
- If there are no progressive symptoms, it would suggest the infection was either latent or eradicated.
- Progressive symptoms are caused by either:
  - Persistent infection (273 peer reviewed articles support this)
  - Speculated persistent immune process without persistent infection, but no evidence supports this hypothesis.

What Makes Sense?

- Clinicians place higher credibility on symptom patterns.
- Bench scientists and economic interests place higher credibility on biological markers.
- Clinically relevant research pulls together both perspectives.
- There is a high level of variability between individual predisposing contributors to disease, different combinations of coinfections, different pathophysiological processes and different symptom manifestations. When there are many variables a comprehensive perspective is needed.

One Way of Viewing the Debate

- The definition of Lyme disease is critical in the debate.
- Using the highly restrictive IDSA Lyme group definition, Lyme disease as defined by two tiered testing with Dearborn criteria based upon the Borrelia burgdorferi sensu lato B-31 Shelter Island laboratory strain and acknowledging the validity of only a few symptoms is a very limited condition of limited concern.
- Using the broader ILADS definition, Lyme/tick-borne disease as defined by broader clinical and laboratory criteria is a highly significant condition of serious concern.

Go round up the usual suspects…

Tick-borne Pathogens

- Borreliosis: *Borrelia burgdorferi* (multiple species and strains) *also B. americana*, *B. andersonii*, *B. bissettii*, *B. carolinensis, B. afzelii, B. garinii, B. spielmanii, B. lonestari, B. bissetti, B. kurtenbachii, B. chilensis, B. lusitaniae, B. valaisiana, B. sinica, B. bavariensis, B. finlandensis, B. japonica, B. miyamoti, B. Yangtze, B. tanukii, B. turdi*
- Babesiosis: *Babesia microti, Babesia duncani, etc.*
- Other Piroplasm Diseases: Theileria and Cytauxzoon
- Ehrlichiosis: *Ehrlichia chaffeensis, Anaplasma phagocytophilum, and Ehrlichia ewingii.*
- Human Monocytic Ehrlichiosis: *Ehrlichia chaffeensis*
- Rocky Mountain Spotted Fever: *Rickettsia rickettsia*
- Tick-borne Relapsing Fever: *Borrelia turicatae, B. hermsi*
- Tularemia: *Francisella tularensis*
- Q Fever: *coxiella burnetii*
- Tick Paralysis (Tick Toxicosis): Unknown
- Powassan/Deer Tick Virus Encephalitis: Powassan and deer tick viruses
- Colorado Tick Fever: Colorado tick fever virus
- Southern Tick-Associated Rash Illness (STARI) or Master's Disease : unknown
- Bartonellosis: *Bartonella species*
- Mycoplasosis: *Mycoplasma species*
- Tick-borne Encephalitis: *Flavivirus*
- Maculatum Disease: *Rickettsia parkeri*
- Relapsing Fever: *Borrelia hermsii*
- *Rickettsia philipii*
- Bourbom virus
- Who knows what else?

Bransfield, Burrascano

Tick-Borne Disease Testing

- **Lyme**-Western blot-use CLIA approved labs that report *all* Western blot bands, not just CDC reportable bands, Advanced Laboratory *Bb.* culture.
- **Lyme**-PCR, culture, antigen capture, antibody response.
- **Babesia**-blood smears, IFA (IgG & IgM), FISH (Fluorescent in-situ Hybridization) and PCR may be ordered.
- **Anaplasma**-blood smears, IFA (IgG & IgM), PCR. Recommended to use more than one type of test.
- **Ehrlichia**-blood smears, IFA (IgG & IgM) & PCR for E. equii (HGE) and/or E. chaffeensis (HME) and PCR for HGE & HME are available.
- **Bartonella heselae**-an IFA, FISH & PCR are available.
- **Other**-Mycoplasma Pneumonia, Chlamydia, Q-fever, Parvovirus, Tularemia, CD-57, C3A, C4A, RMSF.

Only 1/100 Lab Tests Are CDC Positive

- Yearly statistics:
  - 3,400,000 Lyme lab tests ordered yearly.
  - 300,000 to 1,000,000 estimated yearly cases.
  - 30,000 meet CDC surveillance definition.
- Negative lab tests don't rule out Lyme disease.
- A serious national and international health crisis in all 50 states and more than 80 countries.

Hinckley A, et al.. (2013) TickNET: A survey of testing practices for Lyme disease by large commercial laboratories –United States, 2008. Presented at the 13th International Conference on Lyme Borreliosis and other Tick-Borne Diseases, Boston, MA, August 19, 2013. Available: http://www.poughkeepsiejournal.com/assets/pdf/BK211782914.pdf.

Ahern H. Comparison of Lyme Disease Prevalence and Disease Reporting in an Endemic Area Journal of Microbiology Research 2013, 3(6): 261-265.

Nelson C, Saha S, Shankar M, Kugeler K, Hinckley A, et al.. (2013) Epidemiology and clinical characteristics of Lyme disease diagnosed by health care providers: Results from a large national database study. Presented at the 13th International Conference on Lyme Borreliosis and other Tick-Borne Diseases, Boston, MA, August 19, 2013. Available: http://www.poughkeepsiejournal.com/assets/pdf/BK211781914.pdf

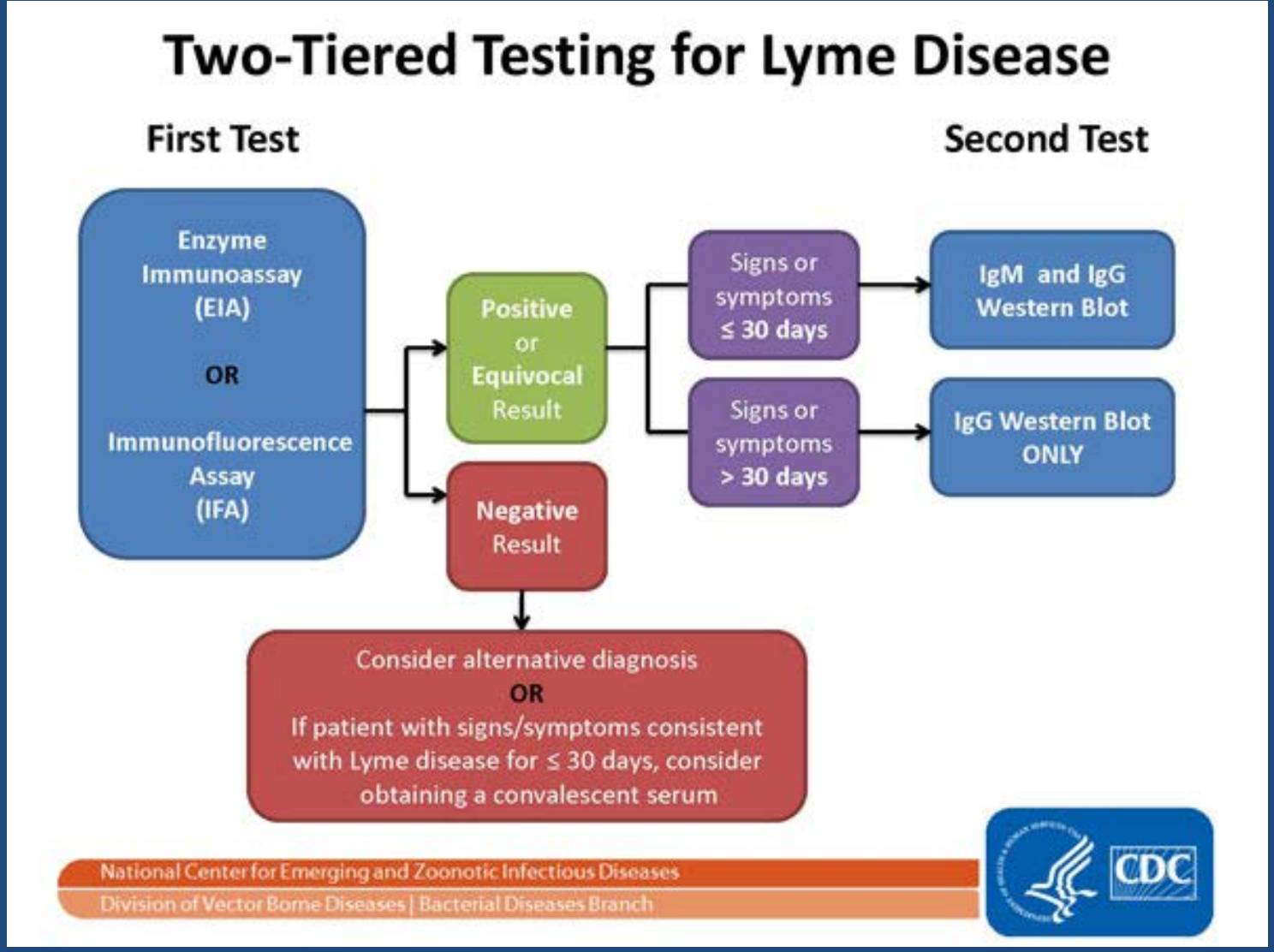
TRADITION

Just Because You've Always Done It That Way
Doesn't Mean It's Not Incredibly Stupid.

FDA approved tests for the diagnosis of Lyme disease?

- FDA approval for lab testing requires clarification as *there are currently no FDA approved Lyme tests.* States have Clinical Laboratory Improvement Amendments (CLIA) offices which ensure that labs adhere to certain standards.
- FDA test approval is required when a test kit is sold across state lines in the US and does not, per se, indicate improved accuracy compared to CLIA approval. In the absence of a lengthy FDA approval process, tests can be cleared by FDA and given similar treatment if they are demonstrated to be roughly equivalent to a former comparator test. The first Lyme Western blot to receive FDA clearance was the MarDx Lyme Western blot. A review of the FDA's database reveals that this test was compared to the Lyme Western Blot performed by Dr. Steere's lab at Tufts. It's not clear to me if the comparator test was ever FDA approved, but it appears from my interpretation of the data that it was not. Because most doctors don't know what this actually means, they view the lack of FDA approval or FDA clearance of a test as a bad thing. Lyme antibody assays offered by even the major universities that perform research in Lyme disease are not FDA approved. Historically, these tests have not even been cleared by FDA.

Phillips S. **Yale-Trained Doctor Refutes Dangerous Misinformation Given by CDC's Dr. Paul Mead on Fox 5 Lyme Special. http://www.huffingtonpost.com/dana-parish/yale-trained-doctor-refut_b_11291116.html**



Note: Surveillance case definitions establish uniform criteria for disease reporting and should not be used as the sole criteria for establishing clinical diagnoses, determining the standard of care necessary for a particular patient, setting guidelines for quality assurance, or providing standards for reimbursement.

CDC. http://www.cdc.gov/lyme/healthcare/clinicians.html

Surveillance Is Not Diagnosis

- Federal Public Law 107-116 passed by the Senate and House and signed by President Bush on January 10, 2002; Wording on that bill states that the CDC's case surveillance definition is "misused as a standard of care for healthcare reimbursement, product (test) development, medical licensing hearings, and other legal cases." It also instructs the CDC to correct this misuse. This is the statement that enables the CDC to prevent the misuse: *"This surveillance case definition was developed for national reporting of Lyme disease; it is not intended to be used in clinical diagnosis"*

Dearborn Criteria Eliminated the Bands Most relevant to Neurological Symptoms

- At the Dearborn Conference in 1995 the two-tiered protocol was adopted by the CDC for surveillance, not diagnostic purposes.
- 31 (OspA) and 34 (OspB) bands, associated with neurological and psychiatric symptoms, were removed from the Western blot.

Alaedini A, Latov N. Antibodies against OspA epitopes of *Borrelia burgdorferi* cross-react with neural tissue. J Neuroimmunol. 2005 Feb;159(1-2):192-5.

Fallon BA, Levin ES, Schweitzer PJ, Hardesty D. Inflammation and Central Nervous System Lyme Disease. *Neurobiol Dis*. (2010) 37(3):534-41.

Bransfield RC. The Psychoimmunology of Lyme/Tick-Borne Diseases and its Association with Neuropsychiatric Symptoms. *The Open Neurology Journal.* (2012) *6,* (Suppl 1-M3) 88-93.

Kuhn M, Bransfield R. Divergent Opinions of Proper Lyme Disease Diagnosis and Implications For Children CoMorbid with Autism Spectrum Disorder. Med Hypotheses. 2014 Sep;83(3):321-5.

Anticipated Vaccine Income Compromised Diagnostic Accuracy

- The highly subjective criteria established for two-tiered testing with the removal of the 31 & 34 bands from the Western blot created a highly specific Lyme disease test that raised the bar for the diagnosis of Lyme disease and facilitated success in vaccine trials but compromised diagnostic criteria.

Subjective, Non-Specific Symptoms?

- Late stage symptoms Lyme/TBD are dismissed by some as being subjective and non-specific.
- Two-tiered testing criteria is highly subjective and non-specific to active infection.
- The only symptoms specific for *Bb* infections are the erythema migrans rash and acrodermatitis chronica atrophicans. The diagnosis is mostly based upon pattern recognition.
- Many late stage symptoms are neuropsychiatric and can be demonstrated objectively with mental status evaluations, psychological testing and brain imaging.

Western Blot Interpretation

- Some labs use only the B31 strain (a mutated lab strain) to standardize their testing. IGENEX [CLIA approved] also uses the 297 strain, a wild strain from Connecticut, which increases the sensitivity
- "Reactivity of *B burgdorferi*–specific bands on Western blot without the full number of bands meeting the CDC surveillance criteria is a more reliable indicator of prior exposure to *B burgdorferi.*" [1]

1. Bransfield RC, Kuhn M. *JAMA*. 2013; 310(8):856.

Two-Tiered Testing

- As of January 1, 2008, the CDC requirements for laboratory confirmation of a surveillance case diagnosis were changed; ELISA testing is no longer required.
- Surveillance case definitions establish uniform criteria for disease reporting and should not be used as the sole criteria for establishing clinical diagnoses, determining the standard of care necessary for a particular patient, setting guidelines for quality assurance, or providing standards for reimbursement.[1]
- FDA advises against overreliance on serological testing.[2.3]

[1] CDC 2011 Case Definition CSTE Position Statement Number: 10-ID-06
[2] Lyme disease--United States, 2003-2005. *MMWR Morb Mortal Wkly Rep.* Jun 15 2007;56(23):573-576.
[3] Brown SL, Hansen SL, Langone JJ. Role of serology in the diagnosis of Lyme disease. *JAMA.* Jul 7 1999;282(1):62-66.

The CDC looses sensitivity by excluding a IGM response beyond 1 month since an IgM Western blot response to Lyme disease can persist

- "IgM levels rose during exacerbations and fell during remission" for 6 to 18 months after treatment of an EM rash. Steere, 1979
- 56% of patients with early Lyme disease had detectable IgM responses 6 months later Massarotti 1992
- "serum IgM levels correlated directly with disease activity (p = 0.025) Craft, Yale J Biol Med 1984
- "Persistence of specific IgM antibodies may also be associated with more severe disease." Craft, 1984

Sensitivity/Specificity of Commercial Two-Tier Testing for Lyme Disease 2007

Study/Year	Sensitivity	Specificity
• Schmitz et al, 1993	66%	100%
Engstrom et al, 1995	55%	96%
• Ledue et al, 1996	50%	100%
• Trevejo et al, 1999	29%	100%
• Nowakowski, 2001	66%	99%
• Bacon et al, 2003	68%	99%
• MEAN TOTAL	56%	99%

AIDS testing has a sensitivity of 99.5% Would an AIDS test with a sensitivity of 56% be satisfactory?

Stricker and Johnson BMJ 2007; 335:1008

Sensitivity/Specificity of Commercial Two-Tiered Testing for Late Stage Lyme 2010

Study/Year	Sensitivity	Specificity
Schmitz et al, 1993	66%	100%
Engstrom et al, 1995	55%	96%
Ledue et al, 1996	50%	100%
Trevejo et al, 1999	29%	100%
Nowakowski, 2001	66%	99%
Bacon et al, 2003	68%	99%
Binnicker et al, 2008	49%	100%
Steere et al, 2008	18%	99%
MEAN TOTAL	**46%**	99%

(Total Patients/Controls 435/951)

Stricker & Johnson, *Minerva Med*. 2010;101:419-25).

Flawed Two Tier Lyme Testing

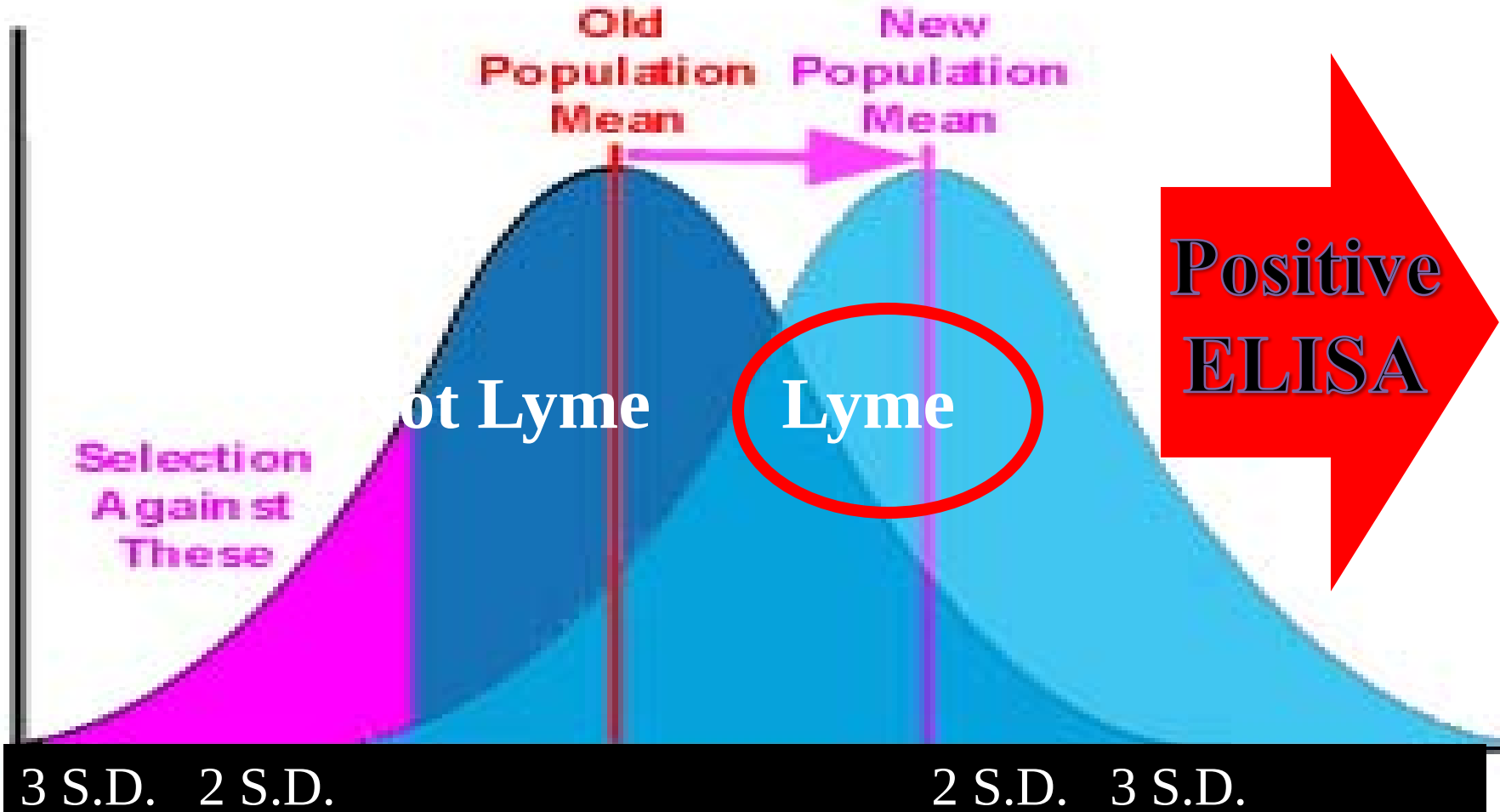
- Recent papers detail the results from more than 70 independent studies of the sensitivity of Lyme disease test kits. Soon after an infected tick bite they typically identify 20% of cases, (80% of cases misdiagnosed) and with samples that were proven positive, only 59% were found to be positive (41% of cases misdiagnosed).
- The tests are more accurate at this later stage. However one analysis demonstrates that the test widely recommended by medical authorities where positive samples from an initial test are submitted to a second test (the so called two-tier test) misdiagnosed 74.9% of cases, a sensitivity of 25.1%.

Cook MJ

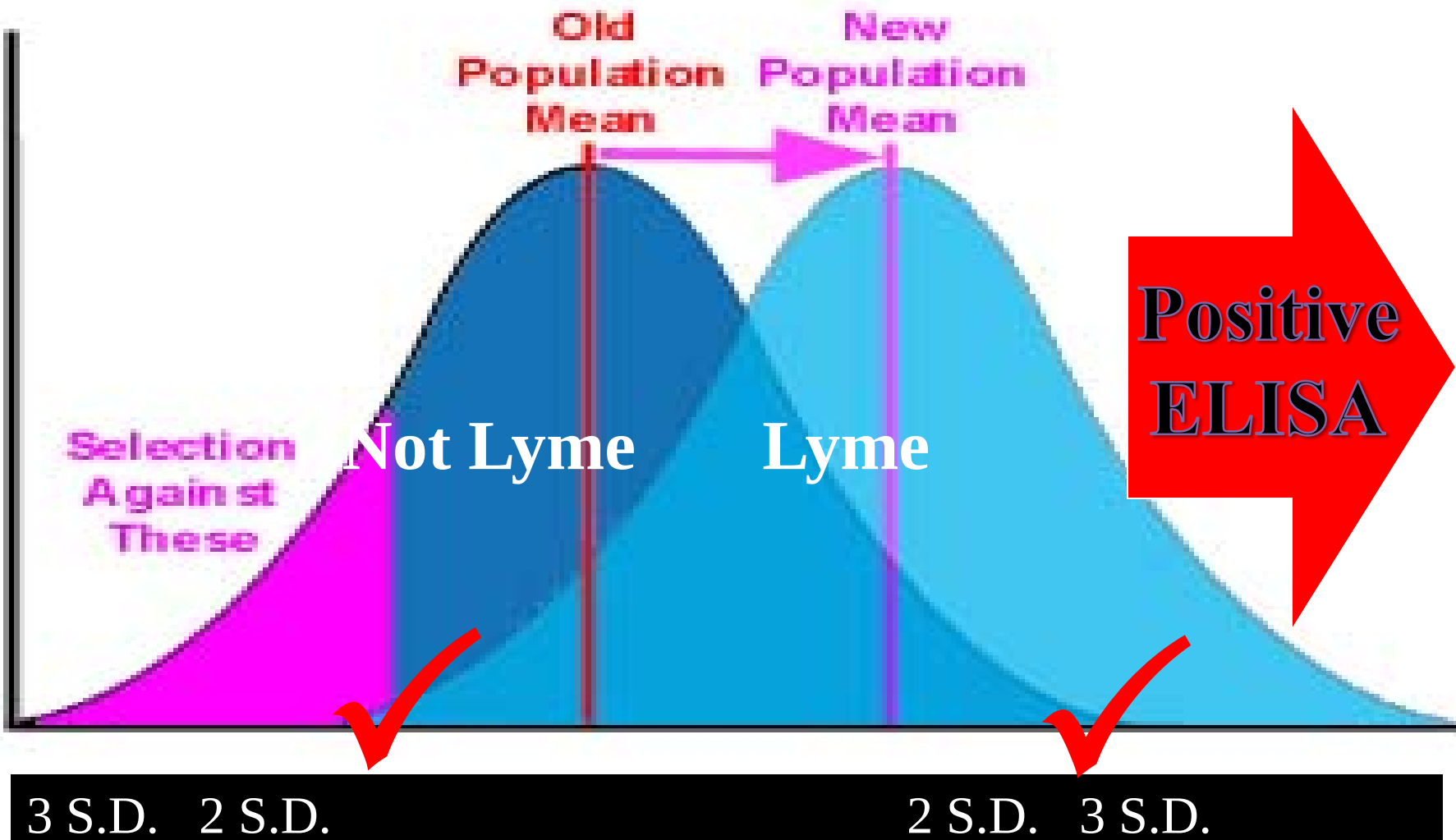
Flawed Two Tier Testing
Recent European References

- Leeflang M, Ang C, Berkhout J, Bijlmer H, Van Bortel W, Brandenburg H, et al. The diagnostic accuracy of serological tests for Lyme borreliosis : a systematic review and meta-analysis . BMC Infect Dis. BMC Infectious Diseases; 2016;16: 1–17. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4807538
- Cook MJ, Puri BK. Commercial test kits for the detection of Lyme borreliosis: a meta-analysis of test accuracy. Int J Gen Med. 2016;9: 427–440. https://www.ncbi.nlm.nih.gov/pubmed/27920571.
- Zeller H, Van Bortel W. A systematic literature review on the diagnosis accuracy of serological tests for Lyme borreliosis [Internet]. 2016 (Based on Leeflang et al). http://ecdc.europa.eu/en/publications/Publications/lyme-borreliosis-diagnostic-accuracy-serological-testssystematic-review.pdf
- Cook MJ, Puri BK. Application of Bayesian decision-making to laboratory testing for Lyme disease and comparison with testing for HIV Application of Bayes to Lyme disease testing. Int J Gen Med. 2017;10: 113– 123. https://www.ncbi.nlm.nih.gov/pubmed/28435311

The ELISA for Lyme disease patients must be 3 S.D. above the mean to be positive



The ELISA for Lyme disease patients often fall short of the 3 SD for 10 controls – instead most ELISAs fall between the two check marks



Lyme Disease Two-Tiered Testing

1. ELISA/IFA

- A Lyme disease ELISA must be higher then 3 SD above the mean for ten controls to be positive which gives high specificity but poorly sensitivity
- Based on one laboratory strain of *B. burgdorferi*
- Large variation in commercial test quality

2. Western blot

- More sensitive in theory
- Criteria for positive test too stringent
- Large variation in laboratory proficiency
- Men and women react differently

Stricker R, Johnson LB.

Two-Tiered False Negatives I

- Recent infection before immune response
- Antibodies are in immune complexes
- Spirochete encapsulated by host tissue (i.e.: lymphocytic cell walls)
- Spirochete is deep in host tissue (i.e.: fibroblasts, neurons, etc.)
- No spirochetes in body fluid on day of test
- Genetic heterogeneity (300 strains, 100 in U.S.)
- Antigenic variability
- Surface antigens change with temperature
- Utilization of host protease instead of microbial protease
- Spirochete in dormancy phase (L-form) with no cell walls
- Recent antibiotic treatment
- Recent anti-inflammatory treatment
- Concomitant infections may cause immunosuppression
- Females have less immune reactivity

Bransfield R. 1996

Two-Tiered False Negatives II

- Other causes of immunosuppression
- Lab with poor technical capability for Lyme disease
- Lab tests not standardized for late stage disease
- CDC criteria is surveillance not a diagnostic criteria
- Lack of standardized control
- Most labs use only one strain as reference point
- Few organisms are sometimes present
- Encapsulated by glycoprotein "S-layer" which impairs immune recognition
- "S"- layer binds to IgM
- Immune deficiency
- Possible down regulation of immune system by cytokines
- Revised W.B. criteria fails to include most significant antibodies
- Ignoring IgM reactivity

Bransfield R. 1996

ILADS remains concerned with the poor sensitivity of the CDC‘s sero-surveillance criteria

- The CDC’s continues to advise:
  - A positive culture with Bb.
  - Two-tier testing interpreted with CDC criteria.
  - Single-tier immunoglobulin G, immunoblot seropositivity interpreted using their criteria.
  - A positive IgM beyond 4 weeks is considered a false positive test.
  - The only exception is an EM rash but only if an endemic area.

Surveillance vs. Diagnosis

- The following statement is from the testimony of Dr. Paul Mead, Medical Epidemiologist with the Division of Vector-Borne Infectious Disease, CDC.
- "No surveillance case definition is 100% accurate. There will always be some patients with Lyme disease whose illness does not meet the national surveillance case definition. For this reason, CDC has stated repeatedly that the surveillance case definition is not a substitute for sound clinical judgment. Given other compelling evidence, a physician may choose to treat a patient for Lyme disease when their condition does not meet the case definition."

C6 ELISA

- Some hoped the C6 ELISA (VlsE surface antigen) would be more sensitive. The main advocate of the C6 ELISA is Dr Gary Wormser, who has significant financial interests in both companies that promote the test, has demonstrated it misses 31% of positive cases. In addition C6 assay tests IgG, not IgM, fails to include the highly specific 39 band and probably will not detect any late stage persistent infection.

Wormser GP, Liveris D, Hanincová K, Brisson D, Ludin S, Stracuzzi VJ, Embers ME, Philipp MT, Levin A, Aguero-Rosenfeld M, Schwartz I. Effect of Borrelia burgdorferi genotype on the sensitivity of C6 and 2-tier testing in North American patients with culture-confirmed Lyme disease. *Clin Infect Dis*. 2008 1;47(7):910-4.

C6-ELISA

- In eight samples, the C6-ELISA and the IgG-ELISA were negative, whereas the Western blot was positive. In three of these samples, p39 was detected with Western blot. This antibody is not recognized by the IgG-ELISA, which explains the discrepancy. In the remaining five samples, Western blot recognized bands for p100, p18 and p41/internal, which are included in the IgG-ELISA analysis, but the concentration of the antibodies appeared to be below the threshold of sensitivity claimed for the IgG-ELISA method. [1]
- Research papers from 1999 to 2011 show that Whole cell and C6 peptide tests demonstrate average sensitivity between 50% and 69%. [2]

1. Jansson, C., S-A. Carlsson, H. Granlund, P. Wahlberg, and D. Nyman. "Analysis of Borrelia burgdorferi IgG antibodies with a combination of IgG ELISA and VlsE C6 peptide ELISA." *Clinical microbiology and infection* 11, no. 2 (2005): 147-150.
2. Cook MJ. unpublished and does not include data from the past three years.

Summary of Serology Test data using C6 Peptide ELISA

Author	Year	Samples	Test	Sensitivity	Range		
Liang(5)	1999	Post treat	C6	80%	62%	-	95%
Bacon(2)	2003	CDC	C6	66%	-	-	-
Marangoni(6)	2005	Culture	C6	62%	-	-	-
Mogilyansky(7)	2005	CDC Panel	C6	100%	-	-	-
Smismans(8)	2005	Sero pos	C6	86%	80%	-	91%
Tjernberg(10)	2007	Clinical	C6	63%	34%	-	88%
Steere(9)	2008	CDC+clinical	C6	55%	-	-	-
Vermeersch(12)	2008	Sero Pos	C6	65%	61%	-	68%
Ang(1)	2011	Clinical	C6	41%	37%	-	41%
Chandra(3)	2011	Clinical	C6	87%	-	-	-
Average and Range of studies				69%	34%		95%

C6 Vs. ELISA/Two-Tiered

- Now there are 10 studies evaluating the sensitivity of the C6 ELISA. When the sensitivity of the C6 ELISA is evaluated with patients diagnosed with the other 46% reliable ELISA/Two-Tired testing, it superficially appears to perform well, but what about the 54% of patient that were not detected by the two-tiered testing? Ten different independent studies of commercial C6 test indicate that they have an overall sensitivity from 34% to 95% with a mean of 69%. The studies used both culture positive and CDC serum panels and clinical cases. When the C6 ELISA is combined with the second stage Western blot it further lowers the probability of detection of true positives. Five independent studies range from 17% to 100% sensitivity with a mean of 63%. Although 63% sensitivity is better than 46% sensitivity, it is still very, very poor.

From David Volkman, PhD MD to CDC

- “Lyme disease (LD) is enormously under-diagnosed and under-treated. The CDC bears a major responsibility for this under-diagnosis as they actively promote the risible, 20 year old “two-tier” criteria for reporting a positive serology when, as all investigators know a single IgG antibody anti-p41 reactivity is sufficient to confirm an infection. Please revise our reporting criteria to a less stringent requirement.
- Individuals at the CDC in Fort Collins, CO have egregious conflicts of interest, they have patented and actively promoted an insensitive C6 serologic test for LD and intransigently refused to revise their diagnostic criteria.”

Confusion Regarding FDA & Lyme Testing

- FDA approval for lab testing requires clarification as there are currently no FDA approved Lyme tests. Each state has a Clinical Laboratory Improvement Amendments (CLIA) office which ensures that labs adhere to certain standards. FDA test approval is required when a test kit is sold across state lines in the US and does not, per se, indicate improved accuracy compared to CLIA approval. In the absence of a lengthy FDA approval process, tests can be cleared by FDA and given similar treatment if they are demonstrated to be roughly equivalent to a former comparator test. A search of the FDA's database reveals that he first Lyme antibody test to receive FDA clearance was the MarDx Lyme antibody test and this was compared to the Lyme Western Blot performed by Dr. Steere's lab at Tufts. It's not clear to me if the comparator test was ever FDA approved, but it appears from my interpretation of the data, that it was not. Because most doctors don't know what this actually means, they view the lack of FDA approval or FDA clearance for a test as a bad thing, but Lyme antibody assays offered by even the major universities that perform research in Lyme disease are not FDA approved. Historically these tests have not even been cleared by FDA.

S Phillips

Antigens of Borrelia burgdorferi recognized during Lyme disease. Appearance of a new immunoglobulin M response and expansion of the immunoglobulin G response late in the illness

- Using immunoblots, we identified proteins of Borrelia burgdorferi bound by IgM and IgG antibodies during Lyme disease. In 12 patients with early disease alone, both the IgM and IgG responses were restricted primarily to a 41-kD antigen. This limited response disappeared within several months. In contrast, among six patients with prolonged illness, the IgM response to the 41-kD protein sometimes persisted for months to years, and late in the illness during arthritis, a new IgM response sometimes developed to a 34-kD component of the organism. The IgG response in these patients appeared in a characteristic sequential pattern over months to years to as many as 11 spirochetal antigens. The appearance of a new IgM response and the expansion of the IgG response late in the illness, and the lack of such responses in patients with early disease alone, suggest that B. burgdorferi remains alive throughout the illness.

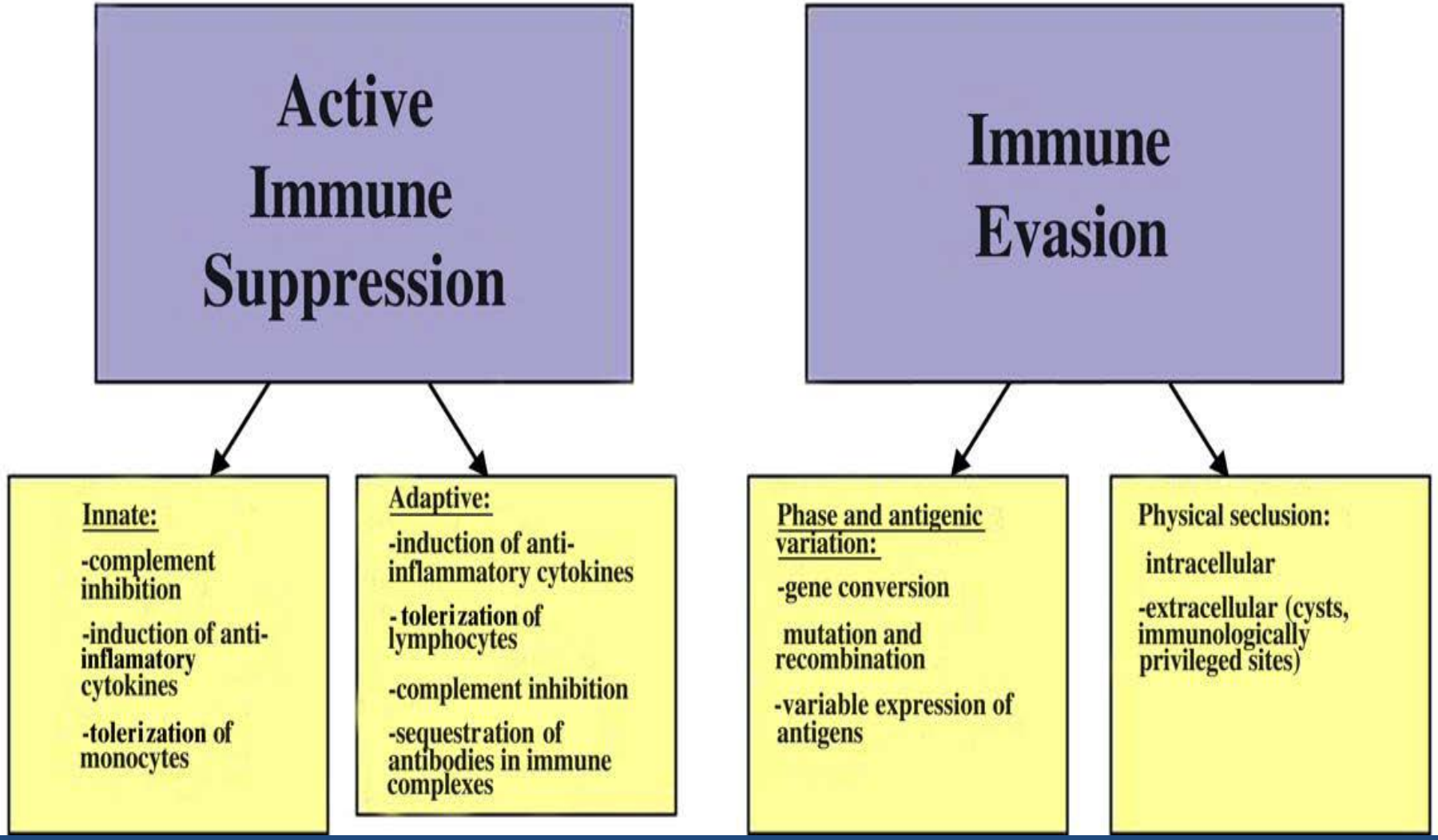
J E Craft, D K Fischer, G T Shimamoto, and A C Steere. J Clin Invest. 1986 Oct; 78(4): 934–939.

The spinal tap is poorly sensitive in chronic neurologic Lyme disease

- 27 subjects presenting with neurologic Lyme disease presenting to Tufts Univ. School of Medicine, Boston
- 1 of 27 with antibodies to Lyme disease
- 1 of 27 with abnormal spinal tap (7 white cells)

Logigian and Steere 1990 NEJM

Proposed Mechanisms of *Borrelia burgdorferi* Persistence



M Embers, MT Philipp et al, Microbes and Infection, 2004 Survival strategies of *Borrelia burgdorferi*, the etiologic agent of Lyme disease

Effects of *Borrelia* on host immune system: Possible consequences for diagnostics

- The immune status of the borreliosis patient needs to be considered, especially in Stage 3 in conjunction with clinical symptoms in the diagnosis. *Borrelia* has the ability to manipulate both the innate and active immunity and alter the cytokines secreted hence alter the path of the immune response. Immune parameters such as IFN-gamma/IL-10, lymphocyte markers, complement C3a, C4a, and total immunoglobulin levels may help to discriminate between stages and monitor treatment outcomes. The level of immune dysfunction in Stage 3 may depend on the number of co-infections delivered by a tick bite, such as Babesia, and Rickettsia, the genospecies of *Borrelia*, other pathogens, the patients' biome and immunogenetics.

McManus M. Cincotta A. Annals of Integrative Medicine. 2015

Persistence of the Lyme Disease Spirochete

- 301 peer reviewed articles supporting the persistence of the Lyme disease spirochete: http://canlyme.com/2013/11/01/persistence-of-lyme-disease/
- Intracellular location of Borrelia:

  http://lymerick.net/Bb-intracellular.htm

Immune Based Testing: Serious Limitations

- ”Bb infection suppresses the development of long-lived antibody production and immunological memory formation and may achieve this by suppressing the function and/or causing the rapid and global collapse of germinal centers.” [1]
- “Antibodies disappear rapidly when infection is controlled by antibiotic treatment.” [1]
- Clearly the future of Lyme disease diagnostics is not in immune based testing but instead culture techniques, PCR and antigen based testing. [2]

1. Elsner RA, et al. The immune system cannot generate immunological memory during infection with the Lyme disease agent *B. burgdorfer.* Cytokine. (2013) 63(3):261.).
2. Coulter P, Lema C, Flayhart D, Linhardt AS, Aucott JN, Auwaerter PG, Dumler JS. Two-year evaluation of Borrelia burgdorferi culture and supplemental tests for definitive diagnosis of Lyme disease. J Clin Microbiol. 2005 43(10):5080-4.

Lab Test vs. Clinical Impression

- Some of us give more weight to lab tests, some give more weight to clinical presentation. For 20+ years clinical presentation frequently did not coincide with the highly controversial two tiered testing based upon the *Bbss* shelter Island B31 laboratory strain and the restrictive Dearborn criteria. So now that we know more—what is Lyme-like bacteria? Is it *Bartonella, Babesia, Anaplasma, Ehrlichia, Mycoplasma, Rickettsia*, *Borrelia burgdorferi* not demonstrated by the testing, opportunistic viruses, etc., or other *Borrelia* species such as *Borrelia miyamotoi*?

Don’t Ignore the Complexity

- **The controversial science and politics of Lyme disease have created barriers to reliable diagnosis and effective treatment of this protean illness.** Two major clinical hurdles are the absence of a therapeutic end point in treating *Borrelia burgdorferi*, the spirochetal agent of Lyme disease, and the presence of tick-borne coinfections with organisms such as *Babesia*, *Anaplasma, Ehrlichia* and *Bartonella* that may complicate the course of the disease. From a pathophysiologic standpoint, the affinity of *Borrelia burgdorferi* for multiple cell types and the presence of non-replicating forms of the Lyme disease spirochete have contributed to persistent infection and failure of simple antibiotic regimens. Newer approaches to the treatment of Lyme disease should take into account its clinical complexity in coinfected patients and the possible need for prolonged combination therapy in patients with persistent symptoms of this potentially debilitating illness. The optimal antibiotic regimen for chronic Lyme disease remains to be determined.

Stricker RB, Lautin A, Burrascano JJ. Expert Review of Anti-infective Therapy. 2005 3:2
http://www.tandfonline.com/doi/abs/10.1586/14787210.3.2.155

Third Parties

- Let’s not confuse who has what responsibility in what area.
- The CDC and FDA have no license to practice medicine, have no clinical experience, do not see patients and do not correct their errors by feedback as clinical experience does. The CDC and FDA are not laboratories that perform quality assurance and are not acceptable as references for how to CLINICALLY interpret serological tests or any tests in the office.

The Role of Government Agencies

- The CDC has responsibility for surveillance of infectious diseases.
- The FDA approves drugs and the labelling of drugs.
- CLIA (Clinical Laboratory Improvement Amendment) approves medical laboratories, not the FDA. A CLIA approved lab has been proven to be proficient by federal standards.
- The CDC and FDA are not licensed to practice medicine, do not see patients, have no clinical experience, do not correct their errors from feedback as experienced clinicians do, are not laboratories that perform quality assurance and are not acceptable authorities for the clinical interpretation of serological or any office tests.

FDA & Lab Testing

- FDA clearance of a lab test device is not approval or testing or certification that a device is medically accurate at confirming a diagnosis. It is a small business license to compete with other approved devices when it is tested against previously positive/negative known device result samples and it certifies that a facility can offer a test without laboratory technician expertise.
- It does not certify that the test is more reliable than laboratories certified to offer highly complex tests.
- If it clears a test compared to a previously approved but flawed test it does not demonstrate the test is accurate.

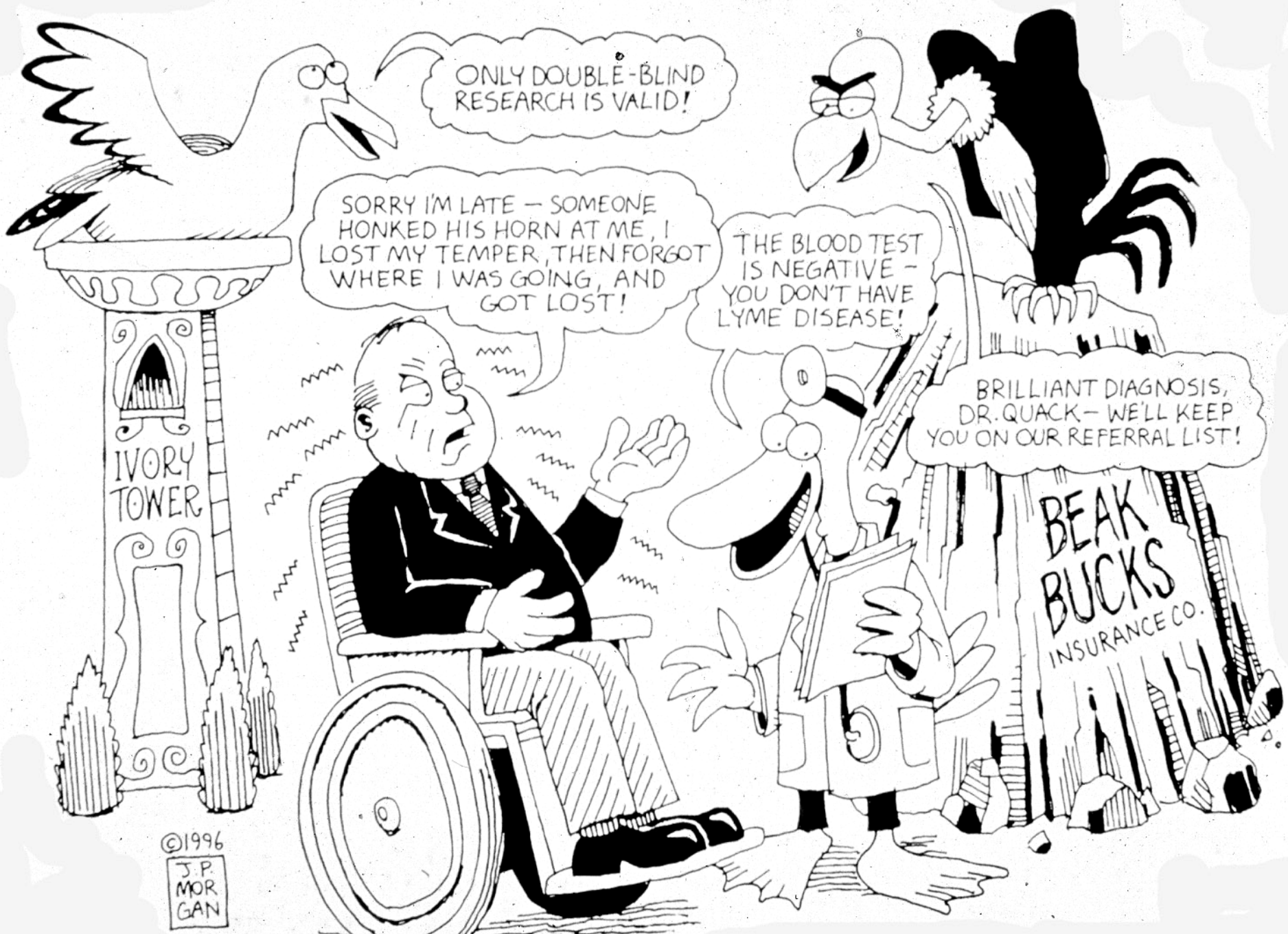
FDA Labeling Issues

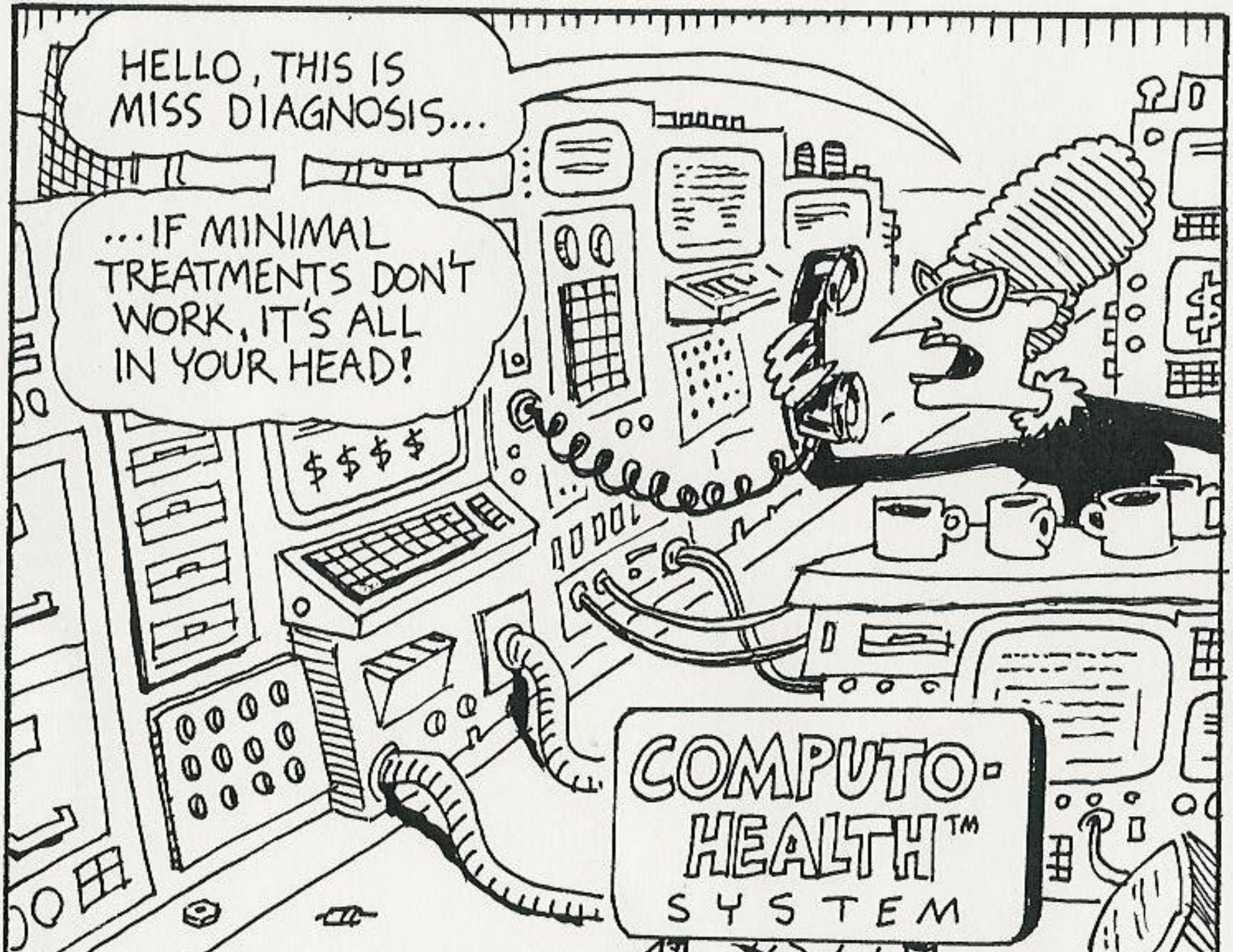
- "The FDA does not regulate the practice of medicine and physicians may use a drug in ways other than indicated on the labeling when, in their professional judgment, it is warranted in a particular case." [FDA]
- "The standard of care is often not the same as the FDA labeling for any particular treatment. Good medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and judgment." [FDA]
- "The FDA recognizes that off-label use of drugs by prescribers is often appropriate and may represent the standard of practice." [FDA]

Insurance Companies

- Insurance companies are often quick to support the view that an illness has only a psychiatric basis, since they find it easier to evade responsibility for mental illness. “Compensation neurosis,” “symptom magnification,” and “stress” are favorite terms of consultants paid to give so-called second opinions or paper reviews.

NEUROPSYCHIATRIC LYME DISEASE




HELLO, THIS IS MISS DIAGNOSIS...
...IF MINIMAL TREATMENTS DON'T WORK, IT'S ALL IN YOUR HEAD!
$ $ $ $
COMPUTO-HEALTH™ SYSTEM

Disease Definition Impacted by Conflicting Interests

- It is apparent there is an attempt to use a narrow definition of Lyme disease to facilitate approval of a Lyme disease vaccines, test kits and NIH grants. Recognizing it as a chronic relapsing disease that can be seronegative, defined by a complex clinical assessment rather than immune based testing, would prevent cost-effective approval of Lyme vaccines and mass produced test kits by the FDA. Post-treatment Lyme disease syndrome is simply a contrived medical condition disguising treatment failure. Authors of the IDSA Lyme guidelines were principle investigators of vaccine trials, test kits and NIH grants.

Virginia Law: Required Labeling

- "YOUR HEALTH CARE PROVIDER HAS ORDERED A LABORATORY TEST FOR THE PRESENCE OF LYME DISEASE FOR YOU. CURRENT LABORATORY TESTING FOR LYME DISEASE CAN BE PROBLEMATIC AND STANDARD LABORATORY TESTS OFTEN RESULT IN FALSE NEGATIVE AND FALSE POSITIVE RESULTS, AND IF DONE TOO EARLY, YOU MAY NOT HAVE PRODUCED ENOUGH ANTIBODIES TO BE CONSIDERED POSITIVE BECAUSE YOUR IMMUNE RESPONSE REQUIRES TIME TO DEVELOP ANTIBODIES. IF YOU ARE TESTED FOR LYME DISEASE, AND THE RESULTS ARE NEGATIVE, THIS DOES NOT NECESSARILY MEAN YOU DO NOT HAVE LYME DISEASE. IF YOU CONTINUE TO EXPERIENCE SYMPTOMS, YOU SHOULD CONTACT YOUR HEALTH CARE PROVIDER AND INQUIRE ABOUT THE APPROPRIATENESS OF RETESTING OR ADDITIONAL TREATMENT."

Ohio Law: Patient Must Sign

- "Your health care provider has ordered a test for the presence of Lyme disease. Current testing for Lyme disease can be problematic and may lead to false results. If you are tested for Lyme disease and the results are positive, this does not necessarily mean that you have contracted Lyme disease. In the alternative, if the results are negative, this does not necessarily mean that you have not contracted Lyme disease. If you continue to experience symptoms or have other health concerns, you should contact your health care provider and inquire about the appropriateness of additional testing or treatment."

Maryland Law: Must Give to Patient when Blood is Drawn

- "Your health care provider has ordered a laboratory test for the presence of Lyme disease for you. Current laboratory testing for Lyme disease can be problematic and standard laboratory tests often result in false negative and false positive results and, if done too early, you may not have produced enough antibodies to be considered positive because your immune response requires time to develop antibodies. If you are tested for Lyme disease and the results are negative, this does not necessarily mean you do not have Lyme disease. If you continue to experience unexplained symptoms, you should contact your health care provider and inquire about the appropriateness of retesting or initial or additional treatment."

Maine Law: Lyme Disease Testing Information Disclosure

- Lyme disease may be difficult to diagnose and treat.
- A negative result for a Lyme disease test does not necessarily mean that Lyme disease is not present and if symptoms continue, the patient should contact a health care provider and inquire about the appropriateness of retesting or additional treatment.

Improved culture conditions for the growth and detection of Borrelia from human serum

- In this report we present a method to cultivate Borrelia spirochetes from human serum samples with high efficiency. This method incorporates improved sample collection, optimization of culture media and use of matrix protein. The method was first optimized utilizing Borrelia laboratory strains, and later by demonstrating growth of Borrelia from sera from fifty seropositive Lyme disease patients followed by another cohort of 72 Lyme disease patients, all of whom satisfied the strict CDC surveillance case definition for Lyme disease. The procedure resulted in positive cultures in 47% at 6 days and 94% at week 16. Negative controls included 48 cases. The positive identification of Borrelia was performed by immunostaining, PCR, and direct DNA sequencing.

Sapi E, Pabbati N, Datar A, Davies EM, Rattelle A, Kuo BA. Int J Med Sci. 2013;10(4):362-76.

A technology backed by Bill Gates may revolutionize diagnostics for Lyme disease

- Ceres Nanosciences has developed the urine-based Nanotrap Lyme Antigen test developed at George Mason University for detecting Lyme disease.
- The nanotrap technology looks for the biomarker of the infection — a vastly different approach from the current two-tiered method that tests the antibodies.

Diana Pryor, CNBC news. http://www.cnbc.com/2017/02/07/technology-backed-by-bill-gates-may-improve-testing-for-lyme-disease.html

POCKit

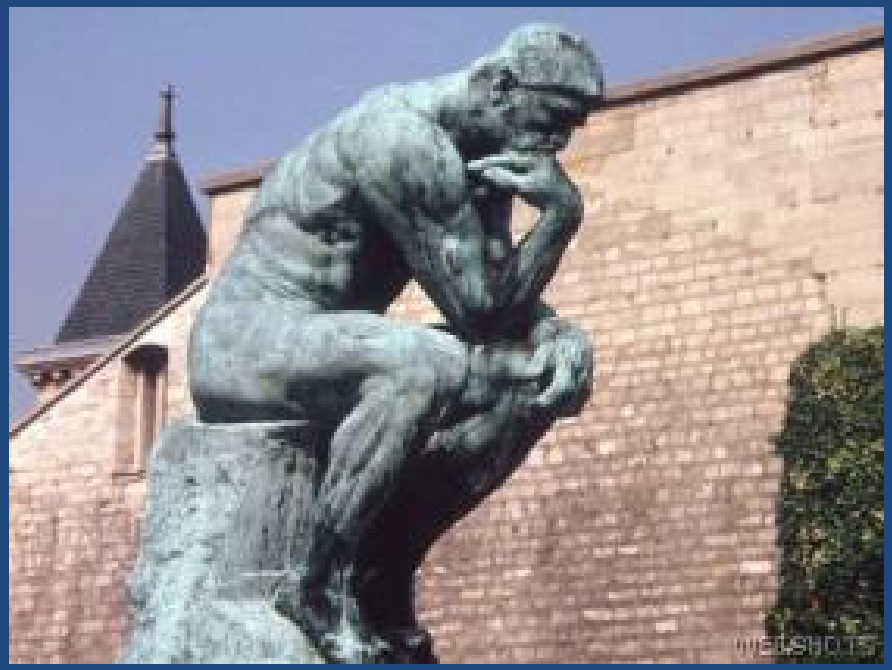
- POCKit is creating a device for patients to test for multiple microbes and different stages of disease all at once.*
- This test will include other Borrelia genospecies and/or other tick-borne coinfections. Early indications are that the test has good specificity and there is an improvement in sensitivity (the rate of true positives) over the standard serological tests.

*http://challenge.helsinki.fi/blog/title-team-pockit-we-want-to-put-the-power-of-diagnostics-in-the-hands-of-the-patients

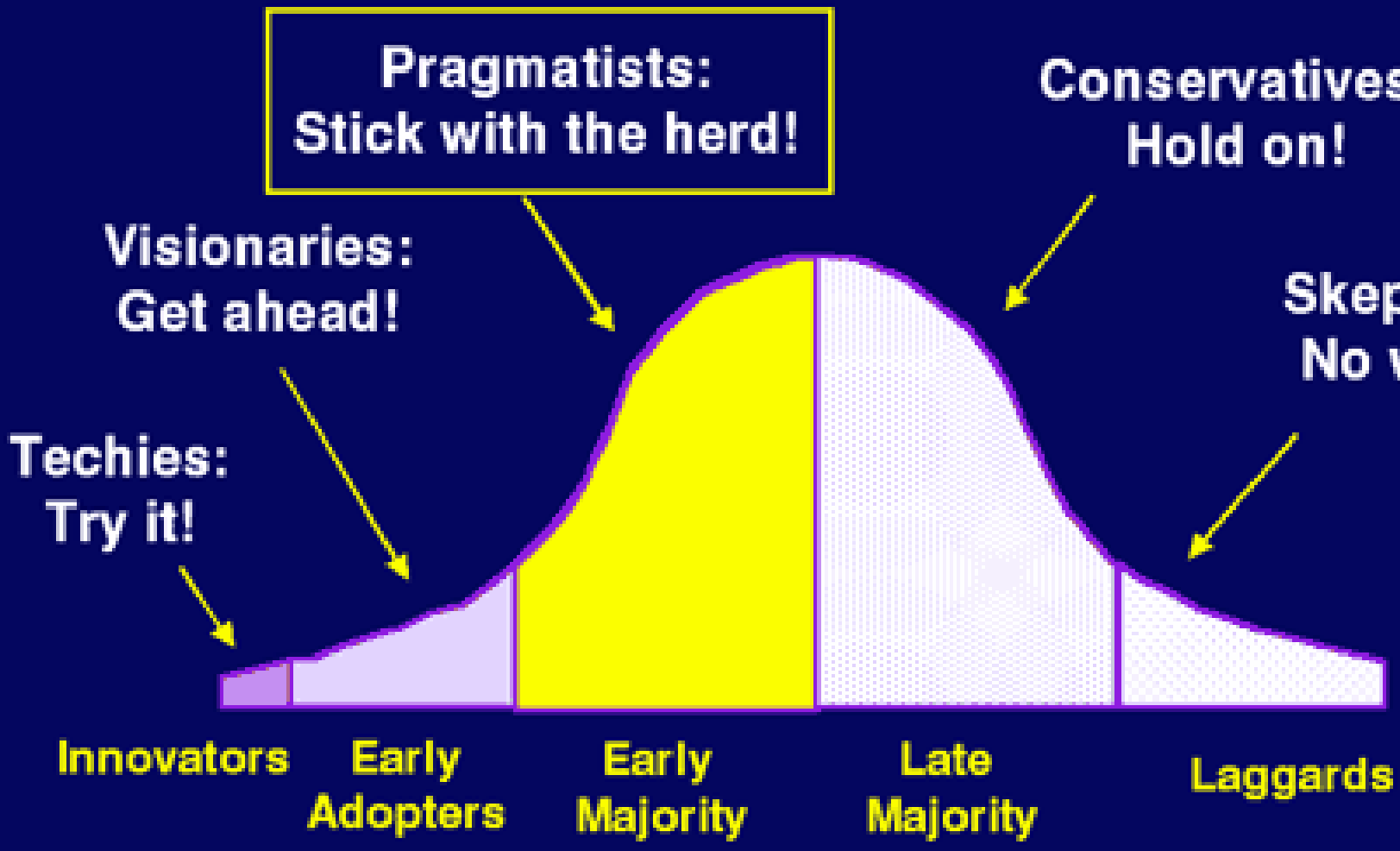
Medical Knowledge

- “Science advances one funeral at a time.”
  — Max Planck
- “A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it.”
  — Max Planck

With Emerging Diseases Think Outside the Box



Technology Adoption Life Cycle



Pragmatists cast the deciding vote

What's the cause?

- Complex, poorly understood diseases are often considered to predominately have a psychological basis until proven otherwise. Tuberculosis, hypertension, and stomach ulcers were once considered to be psychosomatic. A failure to make a diagnosis based upon various so-called "objective tests" is not a basis for a psychiatric diagnosis. The diagnosis of any psychiatric syndrome requires the presence of clearly defined signs and symptoms consistent with each diagnostic category. The presence of a psychiatric diagnosis does not eliminate the possibility of a comorbid somatic diagnosis. Many patients are given a psychiatric diagnosis as a result of an inadequate medical exam.

Patient's Health vs. Definitive Evidence

- Unfortunately, patients cannot put their chronic illness on hold until the medical scientists come to a consensus on whether the evidence suggesting infectious causation is or is not close enough to "definitive." the chronic condition that have been associated with Lyme disease are at the current fuzzy edge off the expansion of the germ theory. Making wise decisions in the uncertain environment requires balanced reasoning, critical thinking, compassion, and common sense.

Ewald P. Preface, In The Crucible of Chronic Lyme Disease: Collected Writings & Associated Materials. Liegner KB.

Lyme: Not Black & White but Shades of Gray

- Some players in the Lyme controversy seem to pride themselves in their acceptance of a conclusion only when the evidence overwhelmingly supports it. This approach does not require much insight. The decisions that demand wisdom are those in which the correct answer is not so clear, when the various explanations need to be evaluated with many bit of sometimes conflicting evidence, when erring on one side or the other will be costly to patients, but the evidence is not sufficiently complete to know with certainty the best course of action. These certainly apply to Lyme disease at every turn.

Ewald P. Preface, In The Crucible of Chronic Lyme Disease: Collected Writings & Associated Materials. Liegner KB.

What obstructs forward progress?

- Dr Willie Burgdorfer, who discovered Borrelia burgdorferi, the spirochete causing Lyme, stated—"The controversy in the Lyme disease research is a shameful affair and I say this because the whole thing is politically tainted. Money goes to the same people who have for the last 30 years produced the same thing—nothing."*

*Under Our Skin

“Tribalism Among Scientists”

- “The first step to the Lyme disease solution is to cut out the tribalism among the scientists whose careers were built on Lyme disease research.”

Sin Hang Lee, F.R.C.P.(C). PLOS One.

IDSA Founding Member Faults CDC Lyme Policy

- Individuals at the CDC in Fort Collins, CO have egregious conflicts of interest, they have patented and actively promoted an insensitive C6 serologic test for LD and intransigently refused to revise their diagnostic criteria. I would not like to see the integrity of the CDC tarnished by the behavior of a few. It is imperative that the CDC's criteria for reporting LD be revised to reflect our current ability to detect LD cheaply, with sensitivity, and specificity. David J. Volkman, Ph.D., M.D. Emeritus Professor of Medicine and Pediatrics, SUNY, Stony Brook

Letter to CDC Director Dr Frieden August 6, 2014.

A Lack of Clinically Relevant Research

- Even though there are over 100,000 cases of CHRONIC Lyme each year—three times more than hepatitis C – only three government treatment trials have ever been conducted. And those three trials didn't look at treatments actually used by physicians treating chronic Lyme disease, but were instead limited to 90 days of a single form of antibiotics. And, they didn't study ordinary patients. One screened over 32,000 patients to finally enroll just 23, who met the researchers' highly specific criteria. Patients in these treatment trials are by definition not typical.
- The last government treatment trial was over 15 years ago and it took four years to recruit, five to complete, seven to publish. It cost nearly $5 million dollars. And there's currently no research—not a single treatment study on chronic Lyme disease treatment– in the pipeline.
- Patients with chronic Lyme disease can't afford to wait for tomorrow's research –which may never come. They have a worse quality of life than patients with multiple sclerosis; 43% can't work and 20% are on disability.

Johnson L. https://www.lymedisease.org/lymepolicywonk-my-speech-at-medx-on-lyme-disease/

Looking for Lyme in All the Wrong Places

- To date, every penny of Lyme research money has disappeared down a deep dark hole. The only treatments available have come from the anecdotal observations and experience of physicians. Biologists and epidemiologists are looking in the wrong place for the pathogens causing the symptoms of Chronic Lyme.
  Luc Montagnier, the Nobel laureate, says he has never seen AIDS without secondary (apparently causative) pathogens. And neither has he seen Lyme without pathogens other than *Borrelia*.
  The secondary causative pathogens reside in the tissue Microbiome, where 99.9% of species cannot be detected with PCR or culture.
- Because the suppression of some innate pathways in these diseases is so complete, the co-infections can be viewed a result of the disease process, rather than the cause.

This raises critical questions

- How much NIH and CDC Lyme disease research has help patients in the past 30 years?
- Could this disease have been improperly defined by a group of researchers to maintain the flow of research grant money to themselves, their institutions and their collaborators?

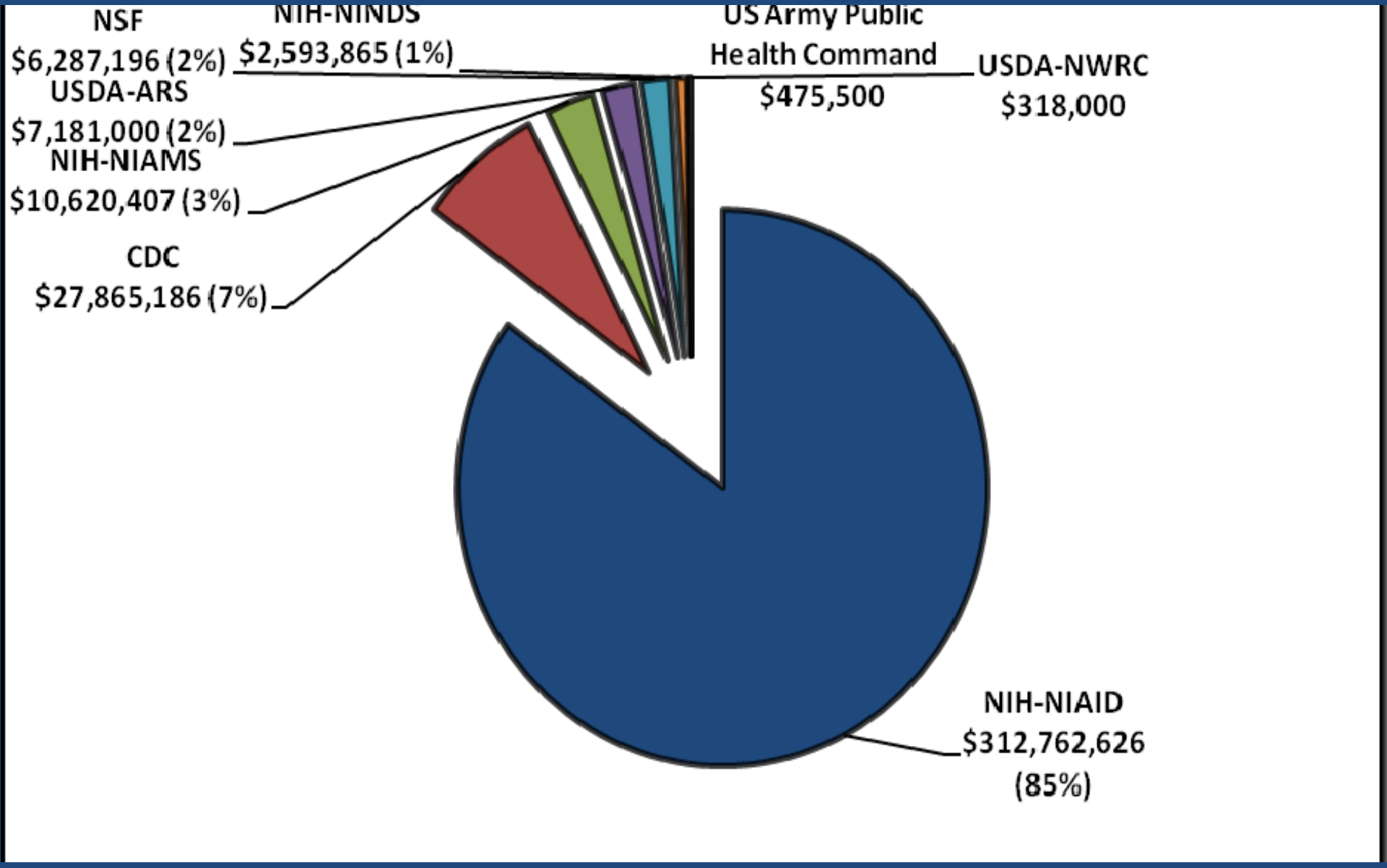
Why is there is resistance to forward progress?

- Healthy skepticism
- A reluctance to adapt to new ideas
- Some who err by accepting the credibility of inaccurate sources of information
- Conflicting imbedded interests, finances and reputations invested in erroneous views
- Profiting by restricting health and access to care
- Some process information in a black and white manner and cannot adapt to a complex model.

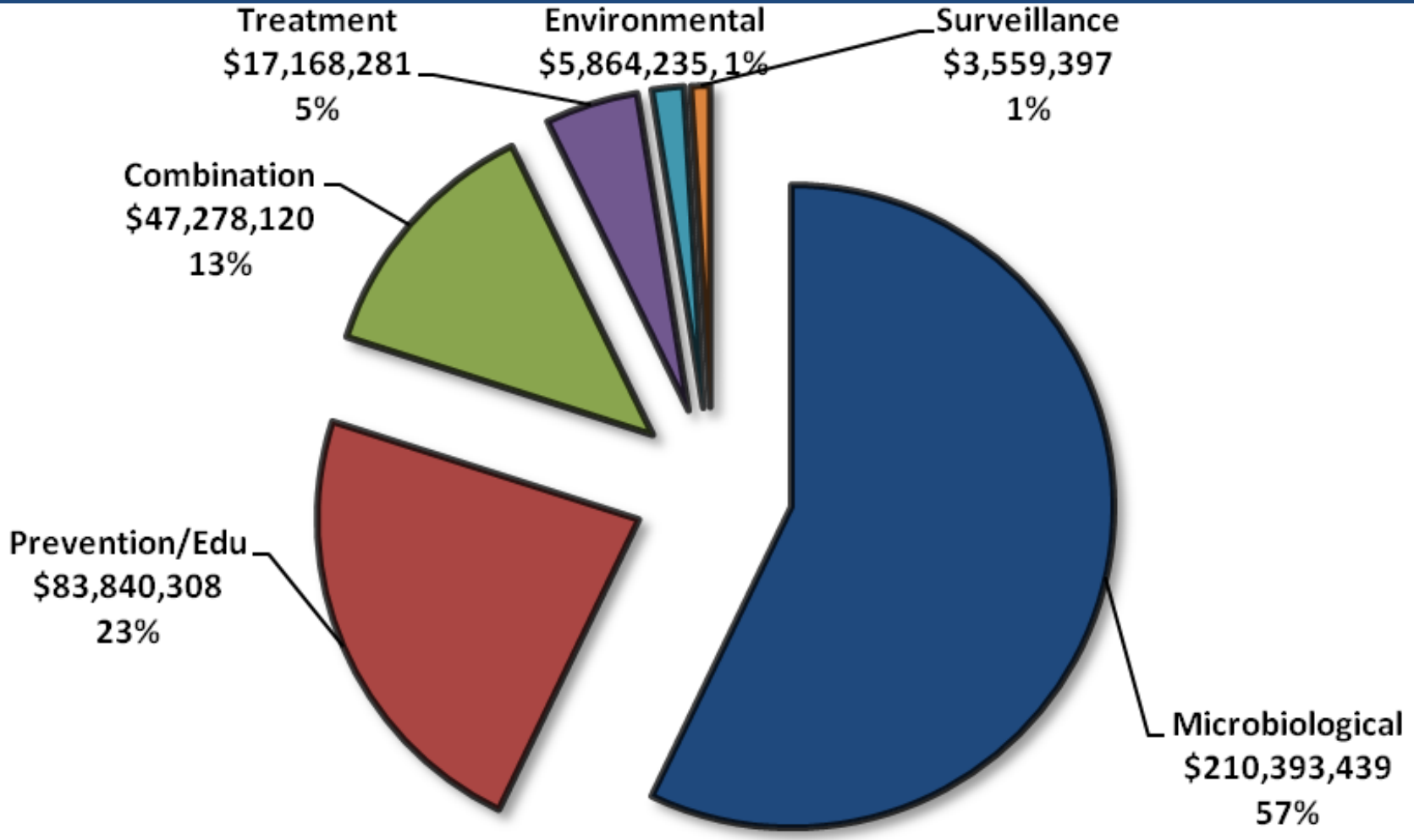
Who has the ELISA Patent?

- Barbara Johnson: CDC Fort Collins, advisor IDSA Lyme guidelines
- William T. Golde: seems to be with USDA and Plum Island.
- Dr. John T. Roehrig: chief of the Arbovirus Diseases Branch, Division of Vector-Borne Infectious Diseases, CDC.
- Tom Burkot, PhD: CDC Atlanta Division of Parasitic Diseases
- Joseph F. Piesman: CDC Ft. Collins DHHS Microbiology
- Leonard W. Mayers: CDC Atlanta Meningitis and Special Pathogens Branch, Division of Bacterial and Mycotic Diseases, National Center for Infectious Diseases
- Mark G. Keen: is/was with CDC Ft. Collins Division of Vector Borne Infectious Diseases.
- Ann R. Hunt: CDC Ft. Collins Division of Vector-Borne Infectious Diseases

Total allocation of funding for tick-borne disease studies by agency/organization, 2006-2010



Total allocation of funding for tick-borne disease studies by study type, 2006-2010



The IDSA Lyme disease guidelines authors had:

- $92,000,000 in NIH & CDC Lyme grants
- $113,000,000 in NIH & CDC Lyme grants to their institutions & more to other collaborators
- 200 Lyme related patents (including Lyme ELISA)

[The IDSA Lyme disease guidelines review panel considered income of $10,000 from treating Lyme patients to be a conflict of interests.]

The Bayh-Dole Act Further Increased the Financial Gain from NIH Grant Money

- The legislation offered universities the opportunity to patent the results of federally funded research on license campus-based inventions and earning royalties in return. After the act was passed in 1980,many of the doctors in academic research shifted their research away from the clinical aspects of Lyme Disease towards research focused upon acquiring patents on different parts of *Borrelia* etc.
- Money is made from NIH grants, patents and royalties only if it is a laboratory rather than clinically based definition.

Press E, Washburn J. The Kept University. The Atlantic Monthly; March 2000.

Missed Opportunity

- The failures of NIH and CDC to effectively deal with Lyme disease results in missed opportunity to prevent impairment, disability and sometimes death.
- Other countries follow the lead of American healthcare policies which magnifies the consequences of our actions.

Should we accept outdated approaches that fail?

- When many fail from treatments recommended by others it is our responsibility and our calling to constantly advance and improve our scientific and medical capabilities and the standard if care.
- Forward progress should never be deterred by the need of individuals or groups for power, money or ego.

Finding Answers

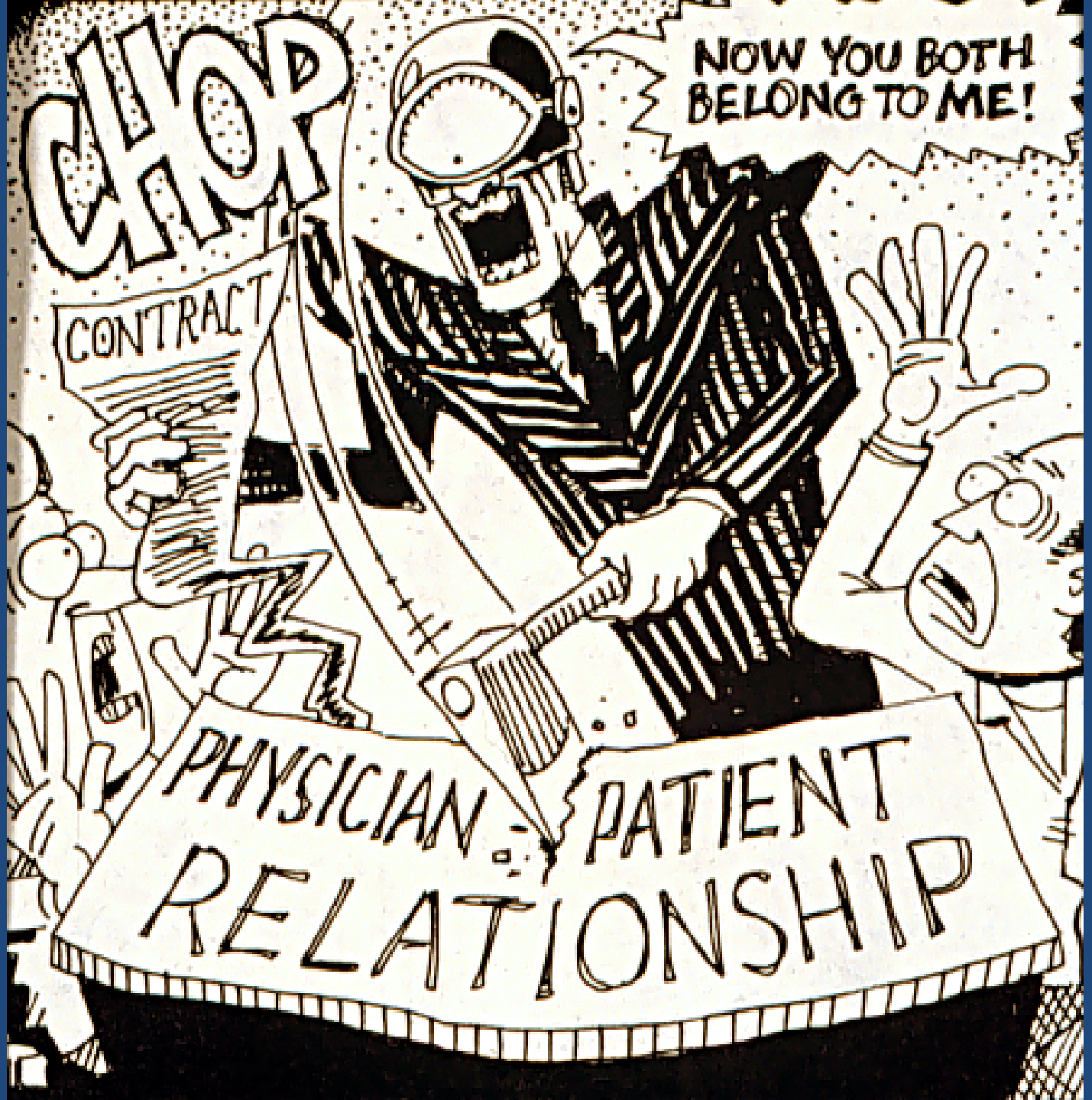
- **Religion** is based upon *faith*
- **Governments** are based upon *authority* or *majority*
- **Science** is based upon *evidence*
- **Medicine** is based upon a combination of the *best evidence available*, *clinical judgment*, *patient preferences* and *ethics*
- **Authority** is the lowest form of knowledge in the philosophy of knowledge.

Always move forward

- Medicine is undergoing a paradigm shift.
- High level researchers and some community physicians recognize the importance of infections and immune reactions to them towards causing many previously unexplained chronic diseases.
- Just as mathematics shifted from Newton to Einstein, we need to make a similar shift in medicine to use more complex models to understand complex disease.

Black Box Warning: Healthcare Middlemen

- What facets of healthcare are most critical and who is now having the greatest impact—patients, doctors or middlemen?
- Mergers and acquisitions of healthcare middlemen (insurance companies, pharmaceutical benefit management companies, etc.) and their powerful lobbying impact on the political process for financial opportunism have has shifted decision making away from the physician patient relationship.


CHOP
CONTRACT
NOW YOU BOTH BELONG TO ME!
PHYSICIAN - PATIENT RELATIONSHIP

Freedom in Medicine

- Dr. Benjamin Rush, signer of the Declaration of Independence and personal physician to George Washington stated—“Unless we put medical freedom into the Constitution, the time will come when medicine will organize into an undercover dictatorship to restrict the art of healing to one class of men and deny equal privileges to others: The Constitution of this Republic should make a special privilege for medical freedom as well as religious freedom.”

Medical Standards and Guidelines

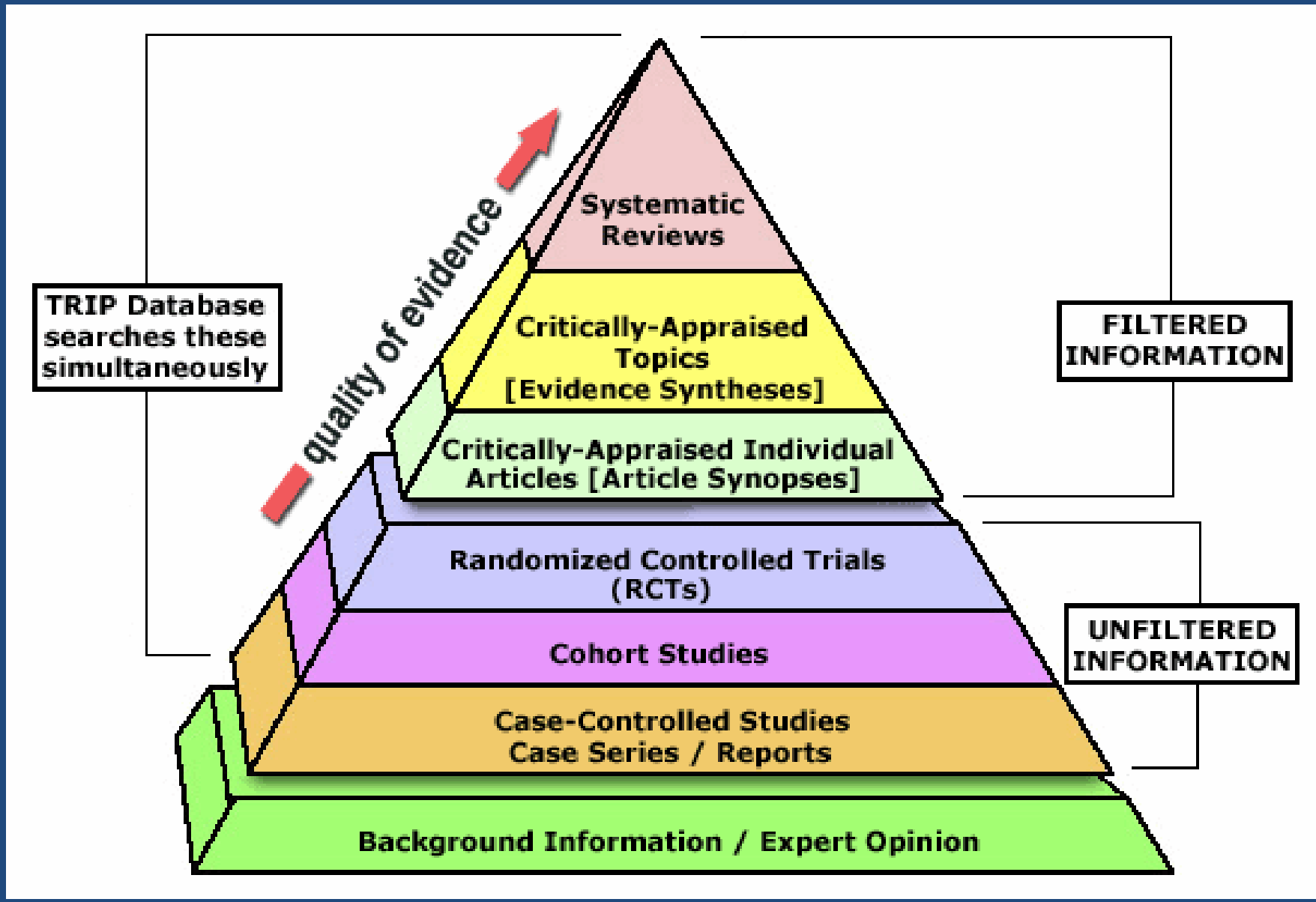
Defining Medical Necessity by AMA

- Healthcare products or services that a prudent physician would provide to a patient for the purpose of diagnosing or treating an illness, injury, disease, or its symptoms in a manner that is: (1) in accordance with generally accepted standards of medical practice; (2) clinically appropriate in type, frequency, level, site, and duration; and (3) not primarily for the convenience of the patient, physician, or other health care provider. [AMA Council on Medical Service]

Evidence-Based Practice

- ***Evidence-based practice*** (EBP) is defined by the Institute of Medicine as - the integration of best-researched evidence and clinical expertise with patient values. [Institute of Medicine Committee on Quality of Health Care in America (2001). *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: National Academies Press. Institute of Medicine Committee on Quality of Health Care in America (2001). *Crossing the Quality Chasm: A New Health System for the 21st Century*. Washington, DC: National Academies Press.]

Quality of Medical Evidence



Osler: History, Examination & Judgment

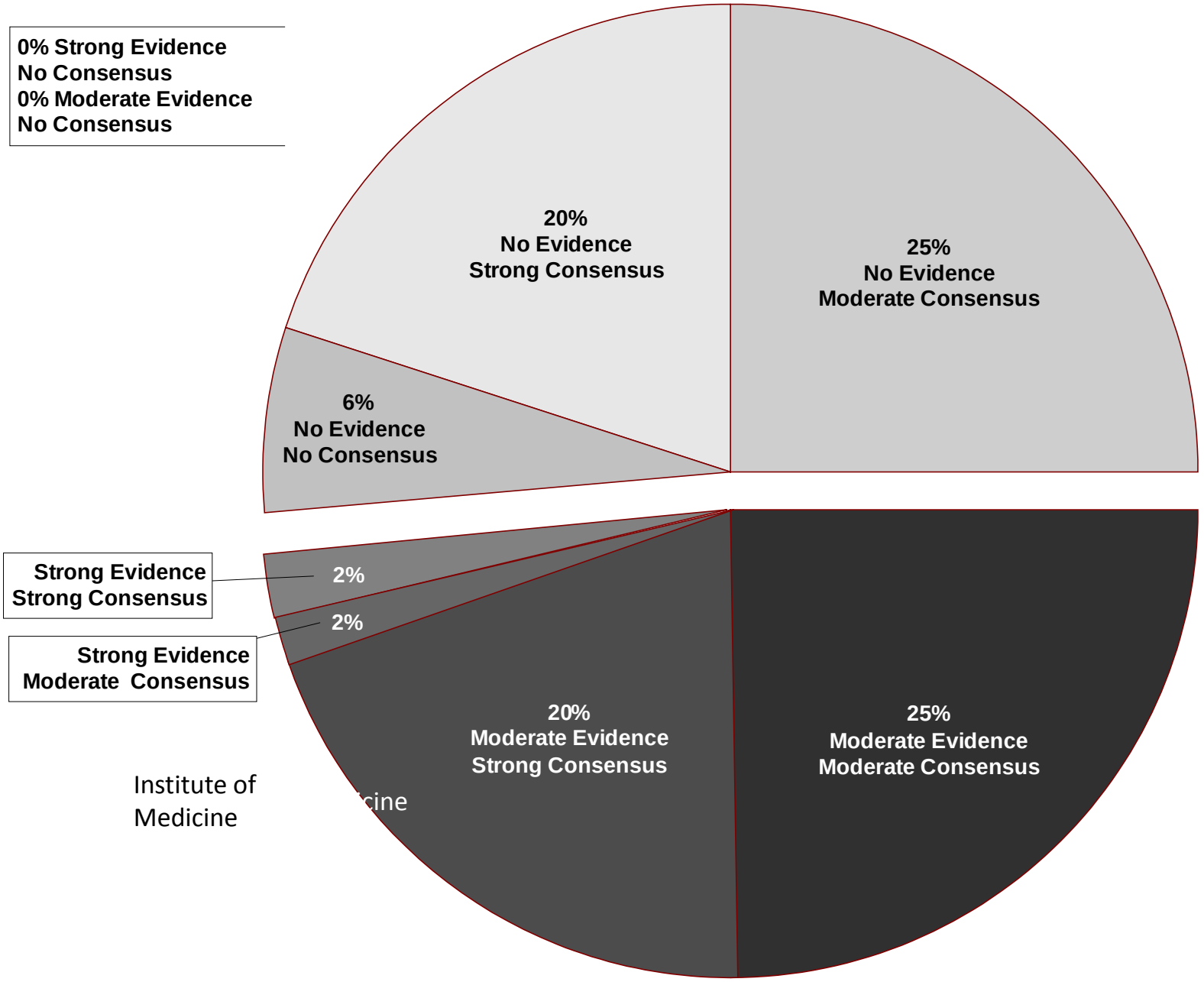
- "There is no more difficult art to acquire than the art of observation."
- "The good observer is not limited to the large hospital.“
- "If you listen long enough, the patient will give you the diagnosis."
- "Medicine is learned by the bedside and not in the class room. Let not your conception of manifestations of disease come from work heard in the lecture room or read from the book: see and then research, compare and control. But see first.“

Doctors should treat patients, not diseases

- In his recent book, “The Finest Traditions of My Calling,” Abraham Nussbaum, makes the case that doctors and patients alike are being shortchanged by medical practices that emphasize population-based standards of care rather than individual patient needs and experiences.
- Physicians need to rely less on clinical guidelines for managing single diseases and more on their own clinical judgment to create treatment plans that are tailored to meet the needs of individual patients.
- Current clinical practice guidelines followed by doctors are aimed primarily at managing single diseases. These guidelines, therefore, are of little help in aiding physicians when it comes to treating patients who have multiple conditions.
- A lot of the clinical guidelines are written by disease-specific specialists who may not take into account the whole clinical picture.

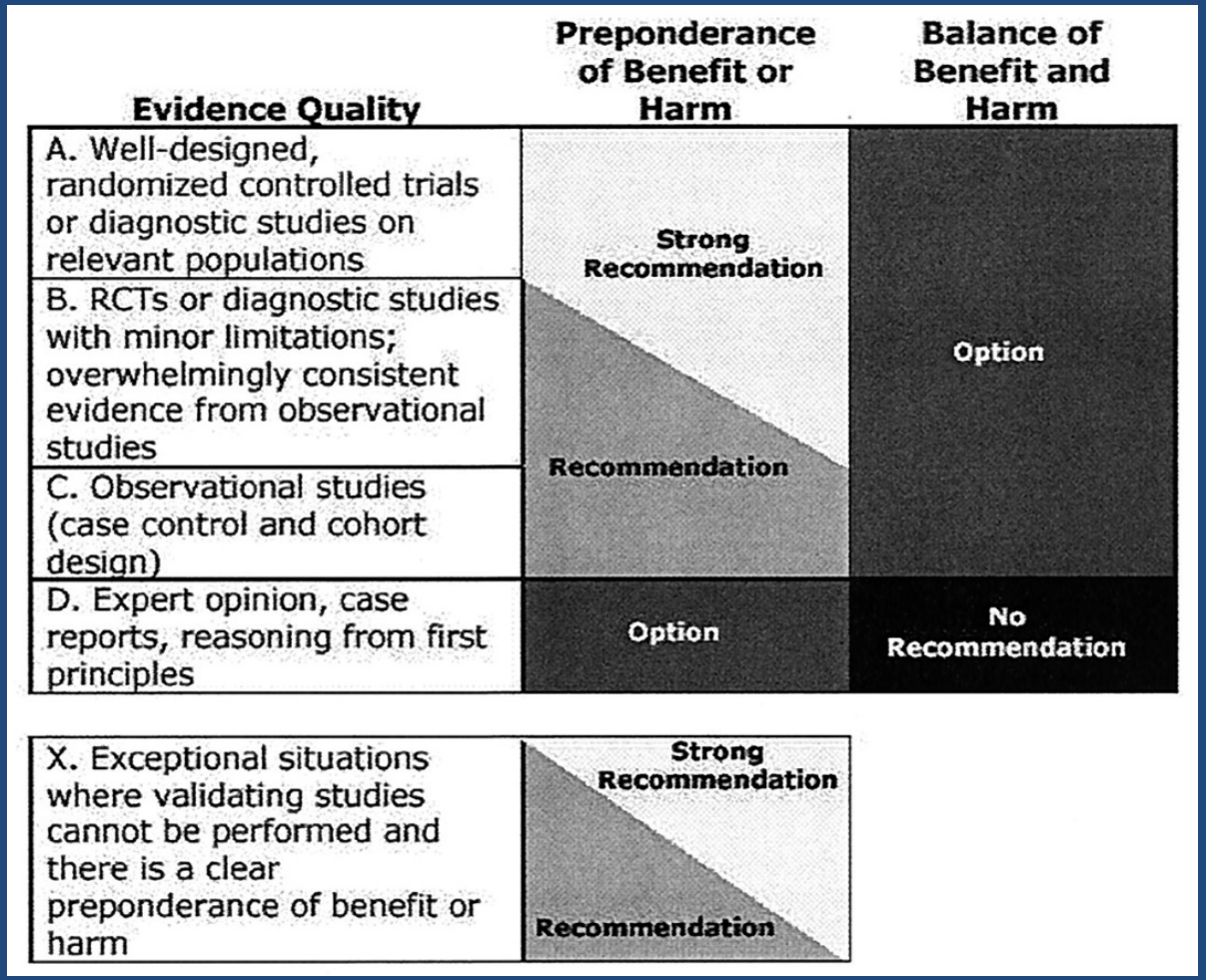
Boyd et al. *JAMA.* 2005;294:716-724.

The Role of Evidence and Consensus in Medicine



Institute of
Medicine

Integrating evidence quality appraisal with an assessment of the anticipated balance between benefits and harms if a policy is carried out leads to designation of a policy as a strong recommendation, recommendation, option, or no recommendation



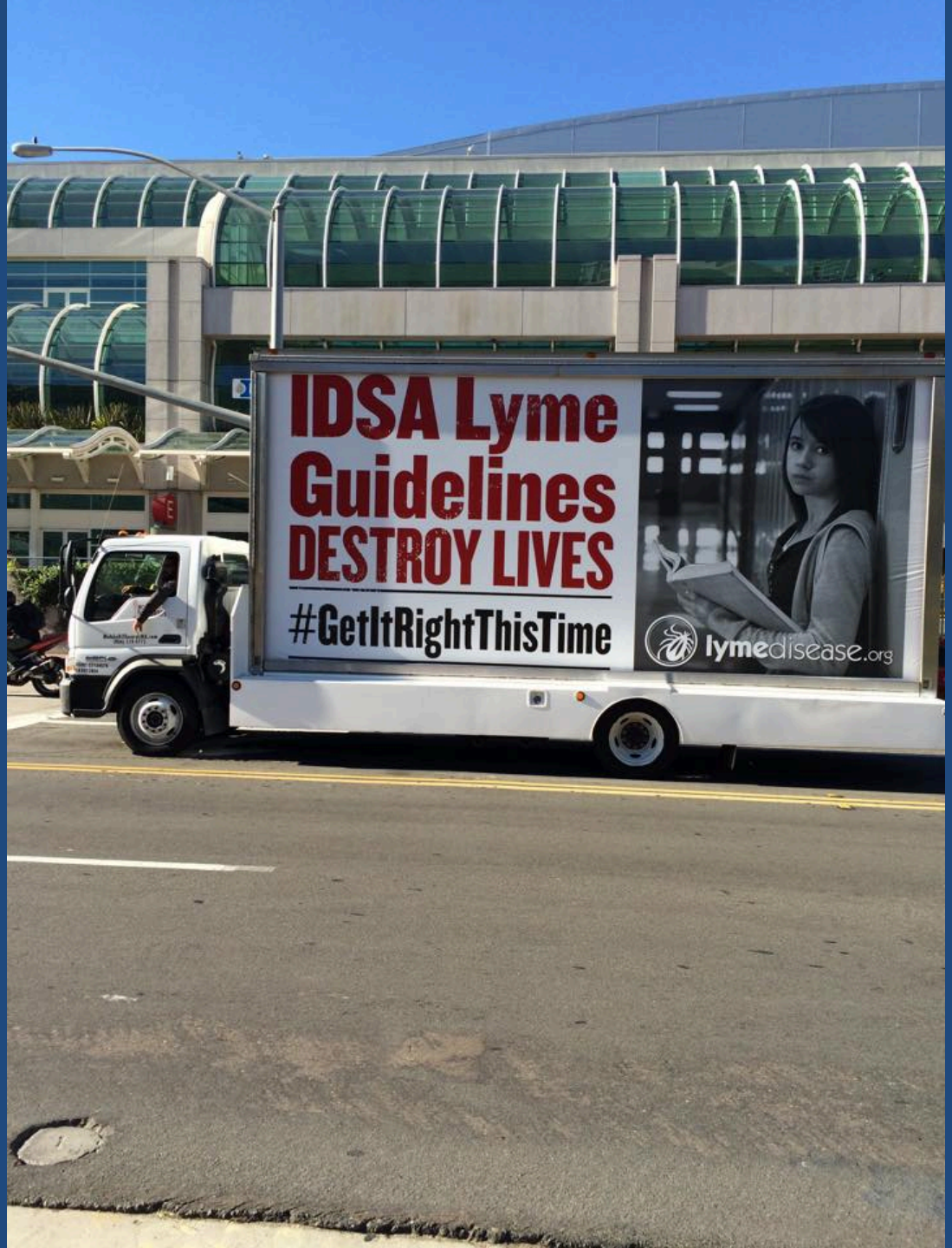
Steering Committee on Quality Improvement and Management, Pediatrics 2004;114:874-877

PEDIATRICS®

When evidence is unsettled and when there is a lack of consensus, guidelines and standards of practice cannot be rigid.

Divergent Guidelines

- Guidelines reflect both the evidence base and value judgments of the guidelines panel. Factors associated with divergent guidelines include a weak evidence base, clinical experience, patient preferences, treatment availability, and clinician values.
- The main difference between the guidelines of the IDSA and those of ILADS is that in the face of scientific uncertainty, the ILADS guidelines defer to clinical judgment and patient preferences while those of the IDSA make very strong recommendations against treatment and severely restrict the use of clinical judgment.


IDSA Lyme
Guidelines
DESTROY LIVES
#GetItRightThisTime
lymedisease.org

Long Term Antibiotics for a Tick-Borne Infection

- "Adequate antibiotic treatment reduces the mortality rate for Q fever endocarditis to <5%. Treatment preferably consists of a combination of doxycycline and hydroxychloroquine for at least 18 months (nonprosthetic infection) to 24 months (prosthetic infection) and is recommended to be continued in case of unfavorable clinical or serologic response."

Kampschreur LM et al. Chronic Q Fever Diagnosis—Consensus Guideline versus Expert Opinion. Emerg Infect Dis. 2015 Jul; 21(7): 1183–1188.

Who Makes Treatment Decisions?

"*In all we do, we must remember that* the best health care decisions are made not by government and insurance companies, but by patients and their doctors."

-President George W. Bush
State of the Union Address
January 23, 2007

Our goals are to enhance and protect the physician-patient relationship and to preserve the physician's ability to make clinical decisions to benefit patients

- Adversaries promote incorrect and outdated information. Evidence exists both for the persistence of viable bacteria after antibiotic treatment and for the benefits of extended treatment.
- Dr. Nevena Zebcevek cited three antibiotic retreatment studies in which patients demonstrated improved cognition and fatigue. Dr. Brian Fallon also cites retreatment studies in which patients showed improvement.
- Several studies have demonstrated persistence of infection. Researcher Kim Lewis has reported on viable Lyme persister cells which survive and thrive in the laboratory after antibiotic treatment. Zhang and his colleagues in their recent xenodiagnosis study, found evidence of infection in humans previously treated with antibiotics. Several published clinical case reports further attest to persistence in patients after antibiotic treatment.
- Patients' needs are being submerged by unnecessary and bitter controversy and cannot wait for care while the "experts" hash out their differences and lobbyists promote their special interests. In the face of scientific uncertainty or controversy, evidence-based medicine upholds the importance of the clinical judgement of the treating physician, and respects the role of patient values which is consistent with an evidence-based approach.

https://www.lymedisease.org/mms-opposes-lyme-insurance-bill/

Legal Standard of Care

- The legal standard of care for treating a condition is determined by the consensus of physicians who actually treat patients, not by treatment guidelines.[1] In view of the uniqueness of individuals; biological heterogeneity; the complexity of conditions and individual differences in safety, tolerability and efficacy; treatment provided by rigid adherence to treatment guidelines without exercising clinical judgment is clearly below the standard of care. [2,3]

[1] Hurwitz, B. Clincal Guidelines and the law. BMJ,1995. 311:p.1517-1518.
[2] Johnson L, Stricker R. Treatment of Lyme disease: a medicolegal assessment; Expert Rev. Anti-infec. Ther. 2(4). (2004)
[3] Wilson v. Blue Cross of Southern California, 271 Cal. Rptr. 876 (1990).

Lyme Disease: Two Standards of Care

- In Lyme disease, opinion within the medical community is deeply divided regarding the best approach for treating Lyme disease, particularly when patients remain ill after short-term protocols. This split has resulted in two standards of care: one advanced by the Infectious Diseases Society of America (IDSA) and the other advanced by the International Lyme and Associated Diseases Society (ILADS). Both viewpoints are reflected in peer-reviewed, evidence-based guidelines and constitute medically recognized standards of care.

The Standard of Care is Longer Treatment of Lyme

- A recent study funded by the Centers for Diseases Control and Prevention (CDC) surveyed a representative sample of people in the US population and found that only 39% of those with Lyme disease were treated in accordance with blanket short term recommendations in the IDSA guidelines. The majority were treated for longer periods.
- Therefore short term treatment advocated by IDSA represents the minority position.
- The actual standard of care is more reflected by the majority of how physicians actually treat a disease.

"My dermatologist gave me a prescription for 6 months of antibiotics for my acne, but when I was diagnosed with Lyme I was told by my primary doctor that they could only give me 3 weeks of antibiotics to treat the disease or they could get into trouble. Why is my disease less severe than my cosmetic issue?"-*An Iowa Lyme Sufferer*

iowalymelaw.org

CDC Says Doxycycline Safe for Extended Periods of Time

- QUOTE- "CDC has no limits on the use of doxycycline for the prevention of malaria. There is **no evidence of harm** when the drug has been used for **extended periods of time**."
-
- Quote- "**Doxycycline can also prevent some additional infections** and so it may be preferred by people planning to do lots of hiking, camping, and wading and swimming in fresh water."
-
- Quote- "Doxycycline tends to be the least expensive of all the antimalarial medicines, so it might be **preferred especially for trips of long duration.**"
-
- Link Here- http://www.cdc.gov/malaria/resources/pdf/fsp/drugs/doxycycline.pdf

Hope for Clinically Relevant Research

- The Tick-borne Disease Research Transparency and Accountability Act, authored by Congressman Gibson, prioritizes federal research on Lyme and related diseases and creates a working group that includes patients, advocates, and physicians to enhance cooperation among federal agencies seeking improved treatment, detection, and prevention.

Lyme: A Perfect Storm of Controversy Causing Chronic Illness

Flawed Diagnostic Criteria

- Complexity of diagnosis
- Poor quality 2 tiered testing
- Flawed Western blot interpretation
- Restrictive criteria for vaccine approvals
- Immune based testing for microbes that evade & suppress immune system
- Suppressing insensitivity evidence

Ignoring Opposing Evidence

- Treating physicians
- Patients
- Severity
- Psych, symptoms, fatigue, etc.

Lack of Vision

- Black & white thinking
- Bench scientists ignoring clinical symptoms
- Failure to comprehend complex chronic infections
- Believing immune reactions are self perpetuating
- Flawed guidelines
- Arrogant ignorance

Secondary Issues

- Doctors trusting biased experts
- Other countries following US
- Insurance companies
- Minimizing disability
- Defensive Medicine
- Charlatans

Degraded Healthcare

- Chronic Illness
- Patient impairment
- Disability
- Death

Demeaning Opposing Evidence

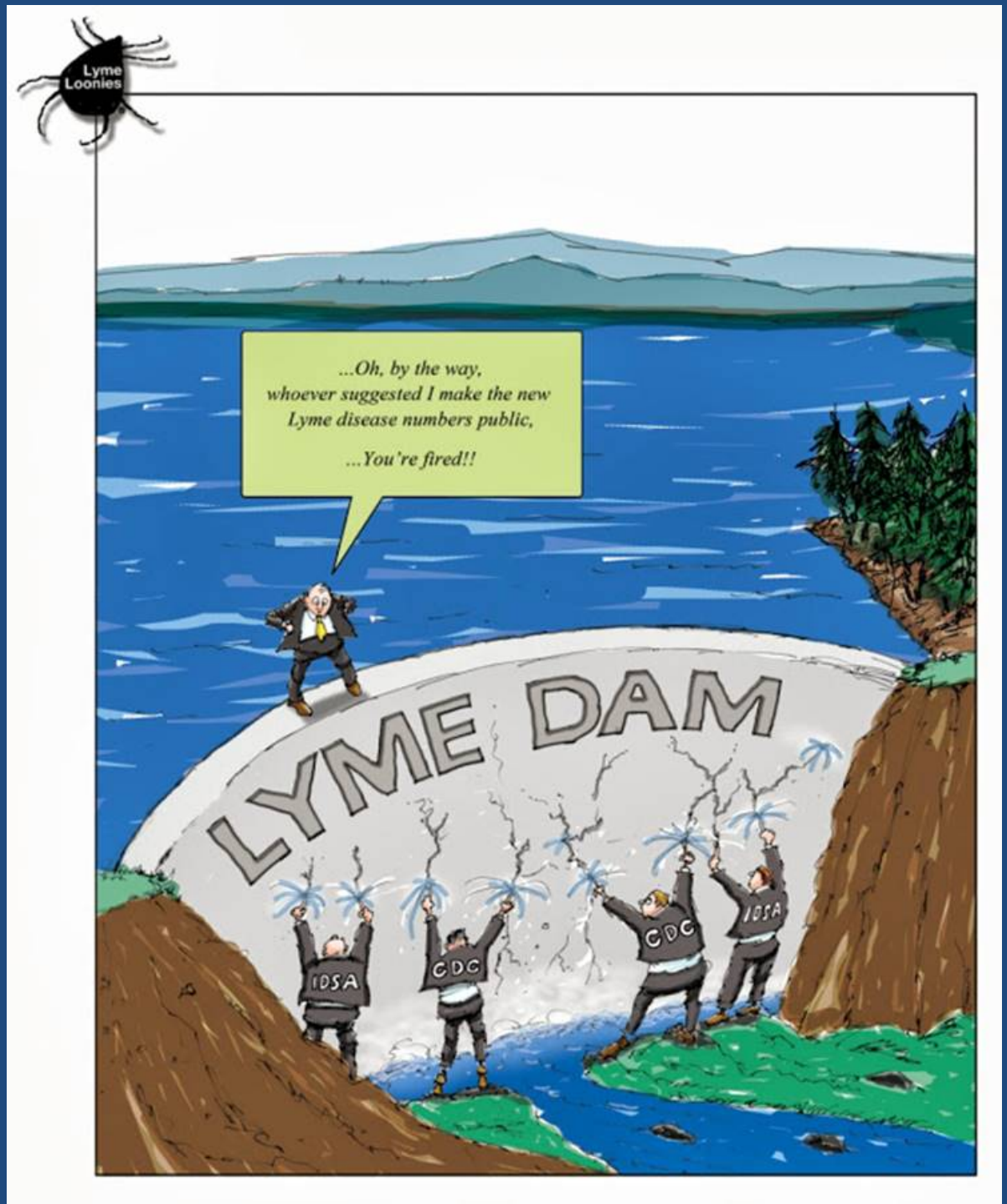
- Slandering, alienating dedicated clinicians, researchers who oppose in journal articles, media, board complaints, etc.
- Abuse of power

Wasting NIH Grants

- Using taxpayer money for personal benefit and pursuit of patents

Misusing Government Agencies

- CDC, NIH, State Boards, FDA clearance, etc.



David Skidmoor

Key Contributors to the Controversy

- There are many contributors to the Lyme disease controversy. One issue is honest differences of medical opinion, particularly differences of opinion between bench scientists and physicians who have the long term responsibility for caring for these patients. A major issue is the diagnosis with inappropriate reliance by some upon immune based testing to diagnose an infection with immune suppressant an evasion capabilities while overlooking symptom patterns and declaring them to be “subjective and non-specific.” the controversy is further intensified by protecting reputations, NIH research grant money, patents and vaccine trails that are dependent upon upholding the flawed disease definition. Others give credibility to perceived though leaders and follow the folly.

Conclusion

- Lyme/tick-borne disease requires comprehensive clinical assessment & pattern recognition for diagnosis.
- The ELISA, Western blot, C-6, and two-tier tests have poorly sensitivity. No lab test is a gold standard.
- Immune based lab tests alone can never rule out a diagnosis of Lyme/tick-borne disease.
- Reliance upon CDC surveillance criteria for diagnosis has created confusion and impeded forward progress.
- There are two evidenced based standards of care for Lyme disease. The treatment decision regarding which approach to use rests within the physician patient relationship in a medical system that respects freedom.

Further Resources

Debate: How Common is the Rash?

- **Mead:** "typically people with early stages of disease get a rash..."
  Phillips: I don't actually think it's accurate to say that this is typical. The initial published findings by Steere documented that 25% of patients recalled a history of rash compatible with erythema migrans (EM). Other published research has pegged the rate of prior EM in late Lyme patients at 22%. Part of the problem with some of the research that demonstrates a very high rate of EM in Lyme disease is that it's part of the CDC reporting criteria as well as being a common diagnostic criterion. So the CDC's statistics on the rates of EM in early Lyme may be inherently skewed. It may be likened to publishing a study that 95% of people in prison have committed a crime.

http://www.huffingtonpost.com/dana-parish/yale-trained-doctor-refut_b_11291116.html

Debate: The Great Imitator

- **Mead:** "well, actually 'the great imitator' is a term used to refer to syphilis which is a different disease"
  Phillips: Well, actually, although syphilis was a previous illness given this nickname, Lyme disease has also carried the moniker in the medical literature. A Pubmed search of 'great imitator' and 'lyme' returned 23 results. This is because Lyme can present in so many varied ways, able to mimic a broad array of diseases.

Debate: Making the Diagnosis

- **Mead:** "there are really two parts to diagnosis, there are the clinical features of the disease that is what the physician can see, a large joint, a red rash, a fever, that sort of thing, and then there is laboratory testing."
  Phillips: Most of the clinical features of Lyme disease are subjective, i.e., symptoms that the physician can't see. There is robust data in the medical literature which documents that in patients diagnosed with Lyme disease based on the presence of EM or of B. burgdorferi and/or its components obtained from body tissues and/or fluids, the subjective symptoms of Lyme disease outnumber the objective signs by very significant numbers.
- So to restrict clinical diagnosis to those patients who have the several objective features included in the CDC reporting criteria would mean that a great many patients would go undiagnosed.
- I don't think it's justified to exclude subjective symptoms from the reporting criteria just because such symptoms can't be seen. More alarming, in my view, is that this practice reinforces a medical paradigm of not believing the patient. When do we start believing patients again?
- I see lots of patients in my office who come in with the 'not-Lyme diagnosis'. When I ask the primary care physicians further about this, I'm frequently told that they don't know what the patient has, but that it's not Lyme. The exclusion of this diagnosis is most often predicated upon failure to meet CDC surveillance criteria. I find it really sad and frustrating. It's like we're speaking different languages.

http://www.huffingtonpost.com/dana-parish/yale-trained-doctor-refut_b_11291116.html

Debate: Surveillance vs. Diagnosis

- **Mead:** "So the recommended way of diagnosing Lyme disease in the laboratory is by the use of serologic tests primarily and in general we recommend a two-step process to this where the blood is tested essentially in two steps to identify whether or not the person has evidence of infection with Borrelia burgdorferi." "If a patient has been ill for just a few days or weeks the test may in fact be negative. However if a patient has been ill for months or years, if the test is negative, that's good evidence that their illness may be caused by something other than Borrelia burgdorferi infection."
  Phillips: It's interesting to me that CDC currently recommends laboratory surveillance criteria for diagnosis since they've historically been recommending it for standardization purposes as below, which is still listed on their website:
- "This surveillance case definition was developed for national reporting of Lyme disease; it is not intended to be used in clinical diagnosis." http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5623a1.htm
- Further, this is Dr. Mead's testimony excerpted from the State of Connecticut Department of Public Health Public Hearing on Lyme Disease January 29th, 2004: http://www.ct.gov/ag/lib/ag/health/0129lyme.pdf
  "Let me now say a few words about clinical diagnosis. The clinical diagnosis is made for the purpose of treating an individual patient and should consider the many details associated with that patient's illness. Surveillance case definitions are created for the purpose of standardization, not patient care. They exist so that health officials can reasonably compare the number and distribution of cases over space and time. Whereas physicians appropriately err on the side of over-diagnosis, thereby assuring they don't miss a case, surveillance case definitions appropriately err on the side of specificity, thereby assuring they do not inadvertently capture illnesses due to other conditions."
- "...CDC has stated repeatedly that the surveillance case definition is not a substitute for sound clinical judgment. Given other compelling evidence, a physician may choose to treat a patient with Lyme Disease when their condition does not meet the case surveillance definition."
- If Dr. Mead has previously stated that surveillance case definitions are not to be used for patient care, then why is Dr. Mead now recommending the opposite? I'm not aware of any groundbreaking medical literature in the past 12 years which should have radically changed the opinion of the CDC on this matter.
- To the contrary, since 2004, there have been even more published medical journal articles demonstrating Lyme disease with negative Lyme antibody tests, further raising questions about the validity of CDC surveillance criteria for diagnosis. In fact, there are now over 50 medical journal articles documenting Lyme disease despite negative antibody tests. This research spans all stages of illness, including late stage disease, at which time Dr. Mead opines that Lyme antibody testing should be positive.
- Further, as additional pathogenic species of borrelia are continually being discovered, the term 'Lyme disease' is being thought of more and more in a collective sense. It is logical to conclude that the Lyme ELISA would cross-react with at least some of these species. By restricting diagnosis to CDC two-tier serologic reporting criteria, a greater truth may be missed in that diagnoses of such patients with non-Lyme borrelial infections would not be possible in the absence of species-specific testing for the new species, which is largely unavailable.
- Another important question regarding diagnosis relates to the use of polymerase chain reaction (PCR). PCR is a very well-established and reliable technology that has been in continuous use for more than 30 years. It replicates DNA many times over so that it can be picked up on a test. If a PCR test is positive, this means that the DNA of a microbe is present and is considered definitive proof of infection for virtually every other infectious disease known in medicine. Yet for Lyme disease, it appears to me that there may be a double standard.
- I recently saw a video from the CDC in which Dr. Christina Nelson advised against using Lyme PCR to evaluate Lyme disease. She spoke of its relatively low sensitivity in vivo presumably as a motivation to avoid its use. However, if this test is positive, then active infection is confirmed, which is exactly what's needed to clarify persistent infection in Lyme disease. So it's curious that she would advise against its use, even with a less than perfect sensitivity.
- It should be further noted that PCR is a very specific technology, meaning that even small differences in the targeted snippets of DNA can result in a negative test. Coupled with strain heterogeneity and highly variable gene expression in B. burgdorferi in the tick vs. the mammal, it appears that some PCR assays be may going after the wrong target. It's not clear from the video to which Lyme PCR tests Dr. Nelson is referring. Newer PCR's using multiple targets and other improved technologies may have better sensitivities.
- She also expressed concern that PCR tests might be falsely positive and represent dead DNA. However published data demonstrates that injection of dead borrelial DNA into dogs did not produce positive Lyme PCR tests in as little as even a few days after inoculation. This means that dead Lyme DNA does not remain in the absence of a continual resupply by a live infection. So I'd like to know from where this concern springs? And if PCR false positivity is so problematic, then why has PCR emerged as the cornerstone for diagnosing and monitoring a multitude of infectious diseases and where are the warnings from CDC about false positive PCR for these other infectious diseases?

http://www.huffingtonpost.com/dana-parish/yale-trained-doctor-refut_b_11291116.html

Debate: False Positive Testing?

- **Mead:** "It's most valuable to order the test in people who have or who are likely to have the disease. If a person is unlikely to have the disease there's a chance that if the test comes back positive that it's more likely a false positive than a true positive"
  Phillips: This statement appears to have its roots in Bayes' Theorem. Bayesian methods are one of the more controversial approaches in statistics, with the inherent limitations of being a closed system of logic. For example, who is likely to have the disease?
- Everything depends on the initial assumption of probability based on clinical criteria that are under dispute. We know that the objective clinical signs described by CDC surveillance criteria are restrictive in that they do not capture the majority of Lyme diagnoses, which is echoed by CDC itself below: "...the total number of people diagnosed with Lyme disease is roughly 10 times higher than the yearly reported number"nu http://www.cdc.gov/me.../releases/2013/p0819-lyme-disease.html
- So whereas patients having the objective clinical signs described by CDC surveillance reporting criteria are likely to have Lyme disease, it appears from CDC's own statement that these represent only the minority of patients. We'd therefore be missing the majority of diagnoses if we followed a Bayesian approach.

http://www.huffingtonpost.com/dana-parish/yale-trained-doctor-refut_b_11291116.html

Debate: FDA Approved Tests?

- **Mead:** "CDC recommends that people rely on FDA approved tests for the diagnosis of Lyme disease"
  "FDA approved tests are various forms of the two tier assay that I just mentioned, the serologic antibody testing"
  Phillips: FDA approval for lab testing requires clarification as *there are currently no FDA approved Lyme tests.* States have Clinical Laboratory Improvement Amendments (CLIA) offices which ensure that labs adhere to certain standards.
- FDA test approval is required when a test kit is sold across state lines in the US and does not, per se, indicate improved accuracy compared to CLIA approval. In the absence of a lengthy FDA approval process, tests can be cleared by FDA and given similar treatment if they are demonstrated to be roughly equivalent to a former comparator test.
- The first Lyme Western blot to receive FDA clearance was the MarDx Lyme Western blot. A review of the FDA's database reveals that this test was compared to the Lyme Western Blot performed by Dr. Steere's lab at Tufts. It's not clear to me if the comparator test was ever FDA approved, but it appears from my interpretation of the data that it was not. Because most doctors don't know what this actually means, they view the lack of FDA approval or FDA clearance of a test as a bad thing. Lyme antibody assays offered by even the major universities that perform research in Lyme disease are not FDA approved. Historically, these tests have not even been cleared by FDA.

http://www.huffingtonpost.com/dana-parish/yale-trained-doctor-refut_b_11291116.html

Debate: ILADS Guidelines

- **Mead:** "The ILADS Guidelines advance two basic ideas: The first is that there really is not any adequate scientific information about the management of Lyme disease; and the second is that in the absence of that sort of information, healthcare providers should be free to do and treat patients in whatever way they see fit. Our concerns are that misrepresents or does not give full credit to the amount of scientific evidence there is about management of Lyme disease..."
  Phillips: In response to the claim regarding the first basic idea, I think that this is a *highly* inaccurate statement. ILADS (International Lyme and Associated Diseases Society) is a multi-specialty medical society made up of physicians and researchers. Its members are well-published in the medical literature and the society holds large, very well-attended, CME-approved medical conferences annually both in the US and abroad.
- ILADS Guidelines provide an evidence-based approach to the management of Lyme disease. They are published in the peer-reviewed medical literature and are presently the only Lyme disease treatment guidelines listed on Guidelines.gov, an agency which is under the auspices of the U.S. Department of Health and Human Services.Guidelines.gov was created by the Agency for Healthcare Research and Quality in partnership with the American Medical Association and the American Association of Health Plans, (which is now known as America's Health Insurance Plans) in order to provide physicians, other healthcare providers, and health plans with detailed information on clinical practice guidelines and to further their use. Despite this, both CDC and insurance companies do not endorse or refer to ILADS Guidelines.
- The ILADS Guidelines assess the medical literature on the topic of Lyme disease and associated infections. There are many shortcomings with the state of research in the field, but the purpose of the ILADS Guidelines is not to bemoan this fact but to improve the welfare of a suffering population who may be the most disenfranchised patients in medicine.
- What is very clear is that B. burgdorferi has been isolated alive from both animals and humans *despite administration of antibiotics that are deemed curative by IDSA and CDC. More alarmingly, this organism has also been isolated alive from humans after antibiotic therapies measured in many months to years, when the administered therapies are far in excess of what is declared curative by these same agencies.*
- Much of the medical literature in which B. burgdoferi was isolated from patients despite "appropriate" antibiotic therapy was penned by IDSA Guidelines authors. These medical journal articles were either not referenced in the IDSA Guidelines, or when they were, they did not specifically refer to the aspects that document persistent borrelial infection despite antibiotic therapy. Despite this, CDC gives preference to IDSA Guidelines and does not endorse ILADS Guidelines.
- In response to the claim regarding the second basic idea, ILADS Guidelines provide a heuristic algorithm for optimal treatment of an extremely heterogeneous group of very ill patients given the best available published medical literature on the topic. Inherent to this, there must be a place for sound clinical judgment, which may be the freedom to which Dr. Mead is referring. I fear the day when individualized clinical judgment is replaced by medical guidelines of any kind. You simply can't rigidly standardize Lyme disease treatment due to strain heterogeneity, co-infections, and differences in immune system types among patients.

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Debate: Unproven Therapies?

- **Mead:** "...and perhaps more importantly, we are concerned about patients who are being treated with unproven therapies; with therapies that are sometimes harmful. There are case reports of patients who died as the result of long term therapies for Lyme disease when in fact there wasn't even necessarily evidence that they were infected."
  Phillips: I think one thing that we can all agree upon is that we want to minimize risks to patients from treatments and maximize benefits, which is why ILADS has physician training programs.
- Therapies for most serious diseases likewise have potentially serious side effects, but the risk of fatality from long-term antibiotic therapy is quite low. For example, far *more* fatalities have been caused by Lyme disease than by its treatment.
- The risk of fatal outcomes in the treatment of inflammatory diseases with immunosuppressive agents and cancer with chemotherapy is far higher than that with antibiotic therapy, but the difference in those diseases is that they are well accepted by CDC as legitimate so that the risk is deemed worthy. I would further counter that in the rare case reports of patients who died during therapy for Lyme disease, there was indeed evidence of infection, albeit not meeting strict CDC surveillance reporting criteria in all cases.
- Although it's correct that some therapies being used to treat chronic Lyme patients are of unproven efficacy, the high rates of treatment failures of even early, and most certainly late Lyme, are quite well-documented in the medical literature. It has been demonstrated in study after study without equivocation that short-term antibiotics are not effective in a great many cases. This, coupled with the documentation of microbial persistence despite such short term antibiotic therapies, makes the case for longer and better treatments. It's not uncommon in medicine for innovative therapies to be used in patients before well-designed trials document their utility. I see it all the time in other diseases.

Debate: Lyme Misdiagnosis?

- **Mead:** "the reports of cases of Lyme being mistaken for other diseases are really quite rare"
  Phillips: There are a great many cases in the published medical literature where Lyme disease has been mistaken for other diseases. Of course, in these cases the diagnosis of Lyme was eventually made, hence the ability to have the published reports. The natural question which follows is how many patients never get appropriately diagnosed with Lyme, never get treated, and remain in the category of 'other disease'.
- In my clinical experience of treating over 20,000 patients, I see patients come in with diagnoses of fibromyalgia, chronic fatigue syndrome, various inflammatory disorders, cardiac symptoms, and MS on a regular basis. When I find evidence for Lyme and/or other zoonotic infection such as bartonella, the large majority of these patients markedly improve with antibiotic therapy.

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Debate: Misdiagnosis?

- **Mead:** "...patients who have been told they have Lyme and are then treated for Lyme, when in fact they have other things: pituitary adenomas, other types of malignancy, and some of those patients were seriously harmed by being given a diagnosis and long term therapy for Lyme disease when in fact their underlying condition went untreated."
  Phillips: Medical mistakes will occur as long as the practice of medicine exists. Of that I'm certain. It's crucial for physicians in any area of medicine to pursue the correct diagnoses. But again, if we examine the published literature, there are relatively few reports of Lyme being diagnosed instead of another serious diagnosis which was missed.

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Debate: Why the Controversy?

- **Mead:** "Why there seems to be so much controversy, I'm not really entirely clear."
  "There is a lot of misinformation about Lyme disease, about basic facts about it that are spread a great deal on the internet."
  "I fear that sometimes if people have heard something enough times, they come to really believe that it must be true."
  Phillips: I very much believe that Dr. Mead is earnest in his statements. But then again, I'm conflicted because such statements appear to me to be myopic at best. How could this intelligent physician working at the highest levels of CDC not realize why there is so much controversy?
- Bias blind spot in medical terminology refers to recognizing the impact of biases on the judgment of others, while failing to see the impact of biases on one's own judgment. Published studies demonstrate that bias blind spot is pervasive in humans, begins in childhood, and is greater in individuals with greater cognitive ability. Confirmation bias in medical terminology refers to the tendency to interpret new evidence as confirmation of one's existing beliefs or theories. Published evidence documents that confirmation bias is very common and can lead to implacable decision making.
- I think that it's all too easy for intelligent individuals in large groups to fall prey to these biases.

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Debate: Value of Treatment

- **Mead:** "There have been a number of studies, including one just published recently in the New England Journal from the Netherlands, which have looked at longer courses of antibiotic therapy for these patients, and of course what they find is that when patients get that therapy that they improve. The problem is that the patients who got the placebo also improved at the same rate. So I think it's a little bit misleading to suggest that there's been no science done on this problem."
  "We can't just dismiss out of hand the numerous studies that have been done."
  "We certainly do recognize that there are patients who've had Lyme disease and who have been treated and who will have persistent subjective symptoms, as I mentioned fatigue, some difficulty with their sleep, and with thinking, and with muscle aches and pains.
- Those patients we refer to has having 'post-treatment Lyme disease syndrome'. So we recognize that that condition exists. The fundamental question is what is the cause of that condition? Is it a persistent infection? Or is it a complication of prior infection? And what is the best treatment for it. Is it long-term antibiotics or not? On the first question, we don't know the answer. It's possible that it's either one of those. We do have data on the second question. As I mentioned, a number of placebo-controlled trials which have looked at patients with 'post-treatment Lyme disease syndrome' and given them various courses of prolonged antibiotic and the bottom line of those studies is that overall they do not seem to benefit those patients in the long run."
  Phillips: The gold standard in microbiology for diagnosing an infectious disease has always been to culture the organism alive. Despite notorious difficulties in culturing B. burgdorferi, in about 30 studies this organism has been cultured alive from patients despite at least standard antibiotic therapy, and in many cases after antibiotics far in excess of what is deemed curative by IDSA and CDC.

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Debate: Value of Treatment II

- If the pathogen that causes a disease is still present in conjunction with symptoms compatible with that infection, it would appear to me that these 'fundamental questions about the cause of long term symptoms' should have been answered a very long time ago. To add insult to injury, recent studies from Tulane, Johns Hopkins, and Northeastern University all demonstrate that we can't even kill B. burgdorferi in the test tube with the currently recommended antibiotics.
- I cannot in good conscience use the term 'post-treatment Lyme disease syndrome' given the wealth of published information that this organism persists. It is, I believe, by its very definition, an illogical construct. What are the chances that a second disease of mysterious etiology but with the same symptoms as the first disease, would come and replace the first disease when there is published evidence that the pathogen which causes the first disease persists despite both short and long-term antibiotics?
- There are numerous chronic bacterial infections which require long-term combination antibiotic therapies: Tuberculosis, leprosy, coxiella endcocarditis, brucellosis, Whipple's. Why should Lyme be different?
- By referring to patients with persistent symptoms of Lyme disease after a short course of antibiotics as 'post-treatment Lyme disease syndrome' this may produce a de facto fait accompli, in that such patients, when desperately searching for answers on the CDC website, may feel that antibiotics can't possibly help them.
- This may only delay their care further and increase the likelihood of subsequent antibiotic treatment failure. Because semantics guide patient care, I believe that the term 'post-treatment Lyme disease syndrome' is harmful.
- In response to the second question, it's true that there have been a number of studies addressing the response to antibiotics vs placebo of patients with persistent symptoms after Lyme disease, but I think that it's very important to specify what that number is and what those studies showed. There have only been 3 NIH-funded randomized placebo controlled studies looking at this problem since 2001. New Lyme infections as estimated by CDC are over 329,000 cases per year, which is more than new diagnoses of invasive breast cancer and HIV combined, yet the NIH has only funded 3 studies on this topic, and two of those 3 studies have demonstrated responses to antibiotics, albeit imperfect responses, as explored in the following discussion.
- The first study was by Klempner. This study evaluated antibiotic vs placebo. The study was terminated early due to the determined likelihood that a beneficial effect would not be found. When this was critically analyzed with biostatistical methods, an article was published which I believe demonstrates that Klempner's study was so poorly designed and analyzed that in order for a treatment effect to have been observed, the antibiotic treated patients would have had to improve to a level of health which was a full standard deviation better than the average health of the general population. It's a reasonable hope for antibiotics to return a patient to a somewhat normal life; it's not a reasonable hope that they would improve that patient's health status to better than average.
- The second study was by Krupp. It showed a reduction in fatigue in patients treated with antibiotics and not with placebo. There was no improvement in cognitive functioning. A biostatistical analysis demonstrated that fatigue was the only outcome of the study for which it was properly designed.
- The third study was by Fallon. This was, in my opinion, the best designed of the 3 trials. It demonstrated improved cognition in antibiotic treated patients and not placebo, but these patients relapsed when antibiotics were discontinued. There were also benefits to antibiotic treated patients in fatigue and body pain by subgroup analysis.
- Another study was performed by Cameron, which demonstrated benefits to antibiotics and not placebo across quality of life assessments. However, this study may have had statistical issues with baseline randomization.
- The PLEASE study from The Netherlands to which Dr. Mead is referring is, in my opinion, a study looking for a question to answer but failing to find one. When studies are designed, they must be designed thoughtfully to answer important questions. An important question which requires further study is whether longer and innovative antibiotic treatment regimens are superior to placebo in patients with chronic Lyme symptoms after a previous short course of antibiotics. The PLEASE study did not have a true placebo group in that all patients were treated with antibiotics. Further, the patient population was heterogeneous in that although most patients had been treated previously with antibiotics, some had not been previously treated.
- The placebo aspect of this study was such that after 2 weeks of IV antibiotics, the patients then received further oral antibiotics vs placebo. There was no benefit to oral antibiotics piggybacked directly onto the IV antibiotics. Again, very little useful information, if anything, in my opinion, can be gleaned from a study using a heterogeneous patient population in which all of them received some form of antibiotic.

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Debate: Differences of Opinion

Mead: "We are very concerned about patients who are ill, both those patients with 'post-treatment Lyme disease syndrome as well as those patients who may have been misdiagnosed with it."
Phillips: The only way for real progress to be made is to consider a problem from all sides with, to paraphrase from Buddhism, the proverbial 'new eyes'. Abraham Lincoln famously countered confirmation bias by forming his cabinet with those that publicly disagreed with him. Why isn't the CDC doing something similar? Why isn't the IDSA?
IDSA physicians, assuming that they follow IDSA Guidelines, are not able to see the beneficial effect of following ILADS Guidelines because they don't treat in that way. However, ILADS physicians see the other side of the equation every day in the form of innumerable treatment failures after short term and limited range antibiotic treatment options.
I think it's very compelling that a study funded by CDC and published in 2015 demonstrated that the majority of US physicians polled treat Lyme disease with antibiotics for longer than 4 weeks, which is in excess of what IDSA Guidelines recommend.
If someone of a CDC/IDSA centric view were to have confirmation bias, they may interpret this data as a wake-up call to better educate physicians on the proper way to treat Lyme disease.
However, a more neutral approach might be to ask oneself if there is a reason that most physicians aren't following IDSA Guidelines. Perhaps it's because they don't work well in curing patients.

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Lyme Case Definition is Stagnant

- Overall, most diseases' case definitions were revised to include new disease knowledge and many added new diagnostic options for confirmation.
- For 26 years, the Lyme case definition has proved to be the clear exception to this practice.
- The CDC Lyme policy fails its own standards for disease surveillance and prevention. Overall, CDC practices surrounding Lyme case definition, surveillance, clinical guidance, clinical descriptions and treatments guidance stand in stark contrast to other conditions, particularly those illnesses with similar symptoms.
- The misapplication of Medically Unexplained Symptoms is an inept and transparent effort to blame patients for treatment failures.
- The Post Lyme Treatment Syndrome is a fraudulent term with potentially dangerous and costly consequences.
- The CDC has not learned from its botched stigmatizing of certain groups during the AIDS epidemic.
- The stigmatizing of certain groups, the arbitrary exclusion of certain patients from diagnosis, and treatment and the under-reporting of the Lyme epidemic will not make it disappear.
- Altogether, such practices shine doubt on both the institutional credibility and competence of the CDC and indicate it is a political organization unconcerned with science and public health.

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https://caudwelllyme.com/2016/08/30/problems-with-current-uk-care-for-tick-sick-patients/