Lyme Infection-Associated Chronic Illness

National Academies of Science, Engineering and Medicine

Perspectives from the Steven & Alexandra Cohen Foundation

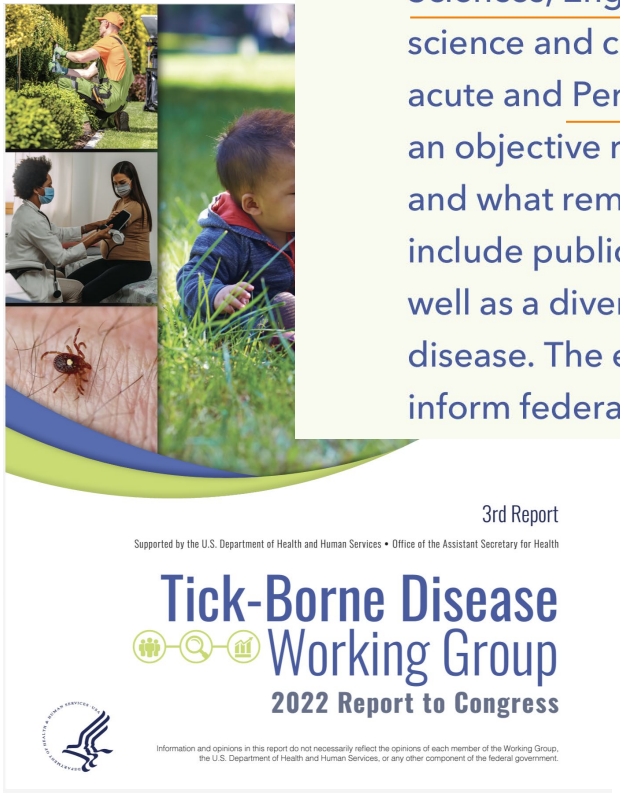
Bennett Nemser, PhD
Chief Program Officer

April 22, 2024

Shared Goal

Chapter 3: Access to Care and Education

Recommendation 3.1: Provide funding for the U.S. Department of Health and Human Services to sponsor the National Academy of Medicine (NAM) within the National Academies of Sciences, Engineering, and Medicine to conduct an objective, comprehensive review of the basic science and clinical evidence for diagnosis and treatment of Lyme disease, with emphasis on acute and Persistent Lyme Disease/Chronic Lyme Disease (PLD/CLD). The purpose for conducting an objective review would be to establish what is definitely known, what is partially understood, and what remains unknown about Lyme disease. The review mechanism shall be transparent and include public stakeholders and patient representatives, experts in trial design and execution, as well as a diversity of experts who represent the full spectrum of scientific perspectives on Lyme disease. The expert panel will produce a comprehensive public report, which will be used to inform federal and state initiatives.



[1] Tick-Borne Disease Working Group. 2022 Report to Congress. Submitted to Congress in February 2023.

Patient Experience with Lyme and Chronic Symptoms

health+ Lyme Disease

Human-Centered Design Report

"So seven-and-a-half years to get to diagnosis. And I'm at about seven-and-a-half years of treatment. I went from literally incapacitated, bed bound, housebound, completely dysfunctional... while trying to raise two children."

—Patient

"If you're diagnosed with Lyme, nobody believes you. They think it's all in your head, you're making up your symptoms. I've had doctors tell me, you know, honey, put some makeup on, get out of bed and go back to school."

—Patient

"I felt like I was dying and there were some days I prayed to the maker to take me because it was terrible. I eventually joined a Lyme group and learned that's how everybody felt at one point in their journey and I thought maybe these are the people I need to talk to."

—Patient

"You know if you have four hours where you feel well enough to be with the world and that's it, how do you portion that? How do you have a job and make a living? How do you have a marriage? How do you be a father? How do you be a son?"

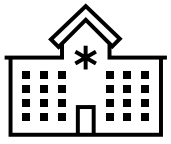
—Patient

PATIENT QUOTE

"And they would read the note like I wasn't there, whispering to each other, reaching for psychological disorder. I'd be like, 'Guys, I know what the health records say I brought them to you. Obviously, I disagree. Look at her, she's running a fever. She's blue. Can we investigate?'"

[1] Health+ Lyme Disease: Human-Centered Design Report. April 2021. Created by Coforma and sponsored by HHS as part of LymeX.

System Breakdown



Funders

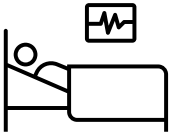
Fund enough of the right research

Researchers

Provide tools to diagnose & treat

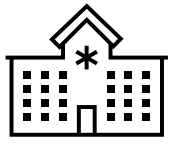
Clinicians

Properly identify and give care



Patients

System Breakdown



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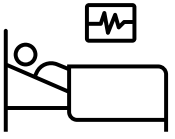


Patients

Collectively, our research results speak for themselves – Lyme IACI has:
no validated diagnostics and no proven treatment options.

"So it's really easy to get pissed and throw spears at doctors, but we give them four hours in medical school to learn that Lyme disease is easy to treat. I empathize with their lack of knowledge, with the lack of resources, diagnostic tools."

—Lyme Leader [1]

Patients suffer with:
- Severe Fatigue
- Brain fog, memory loss
- Chronic Pain
- Neuro-psychiatric
- Dysautonomia / POTS
- …many others

- Putting **clinicians in a very difficult position** with no proven diagnostics nor treatment option for Lyme IACI
- **Ethical dilemma for clinicians**: "Do no harm", but **doing nothing *is* harmful**.
- Lyme IACI patients suffer endlessly, and **suicide rate increases by 75%** with a Lyme diagnosis. [2]

[1] Health+ Lyme Disease: Human-Centered Design Report. April 2021. Created by Coforma and sponsored by HHS as part of LymeX.
[2] Fallon et al. Lyme Borreliosis and Associations With Mental Disorders and Suicidal Behavior: A Nationwide Danish Cohort Study. Am J Psychiatry 178:10, October 2021

What is in a Name?

"Lyme Infection-Associated Chronic Illnesses"

- Umbrella term encompassing:
  - Persistent Lyme Disease
  - Chronic Lyme Disease
  - Post-treatment Lyme Disease Syndrome (PTLDS)
  - Post-treatment Lyme Disease (PTLD)
  - Long Lyme
  - Any other term for Lyme disease patients who experience prolonged symptoms after initial infection.

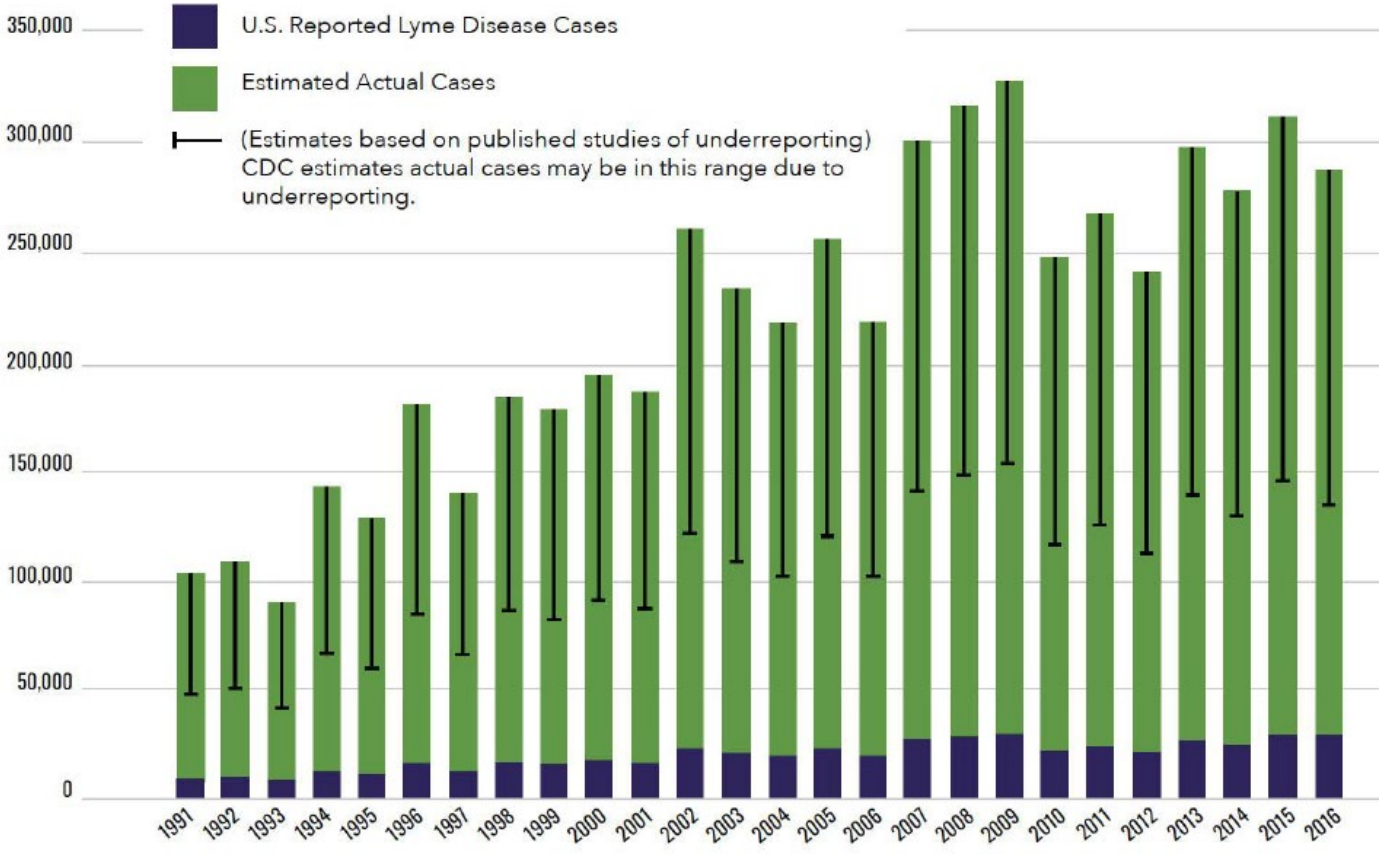
- **Recommendation:** Focusing the Committee's time and energy on improving diagnostics and treatment options for patients is better than renaming the illness.

High Burden of Disease

Annual Cases of Lyme Disease in U.S.

> 476,000 cases per year [2]

[1]



[1] Tick-Borne Disease Working Group. 2018 Report to Congress. November 2018.
[2] Kugeler et al. Estimating the frequency of Lyme disease diagnoses, United States, 2010–2018. Emerg Infect Dis. 2021 Feb
[3] Marques A. Chronic Lyme Disease: An appraisal. Infect Dis Clin North Am. 2008 June ; 22(2): 341–360
[4] DeLong et al. Estimation of cumulative number of post treatment Lyme disease cases in the US, 2016 and 2020. BMC Public Health (2019)

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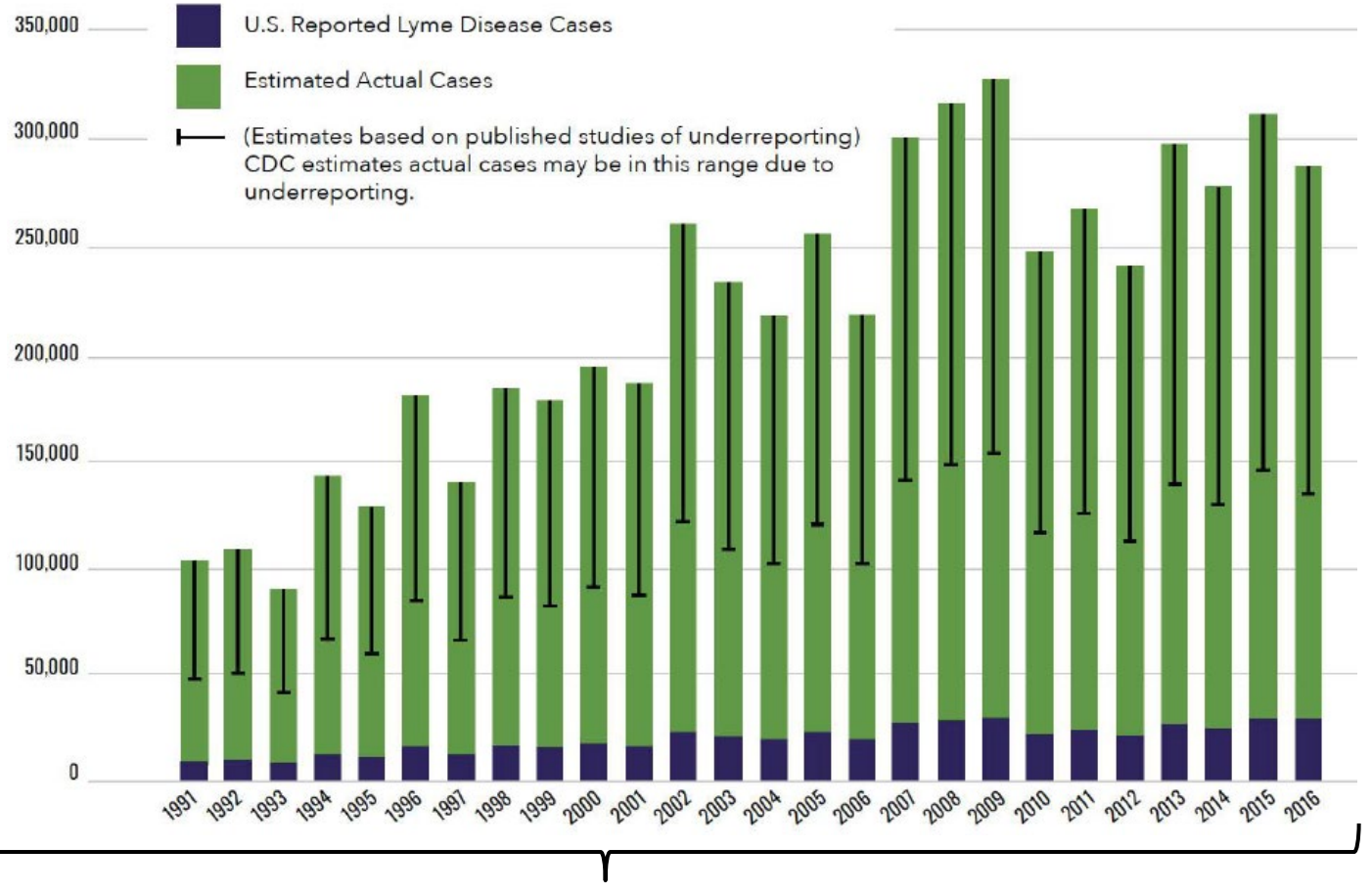

> 476,000 cases per year [2]

10-20% of cases result in persistent symptoms

(aka. Chronic Lyme or PTLDS: 'Post-treatment Lyme Disease Syndrome') [3]

→ Up to 1.9 million cases of PTLDS (prevalence by 2020) [4]

[1] Tick-Borne Disease Working Group. 2018 Report to Congress. November 2018.
[2] Kugeler et al. Estimating the frequency of Lyme disease diagnoses, United States, 2010–2018. Emerg Infect Dis. 2021 Feb
[3] Marques A. Chronic Lyme Disease: An appraisal. Infect Dis Clin North Am. 2008 June ; 22(2): 341–360
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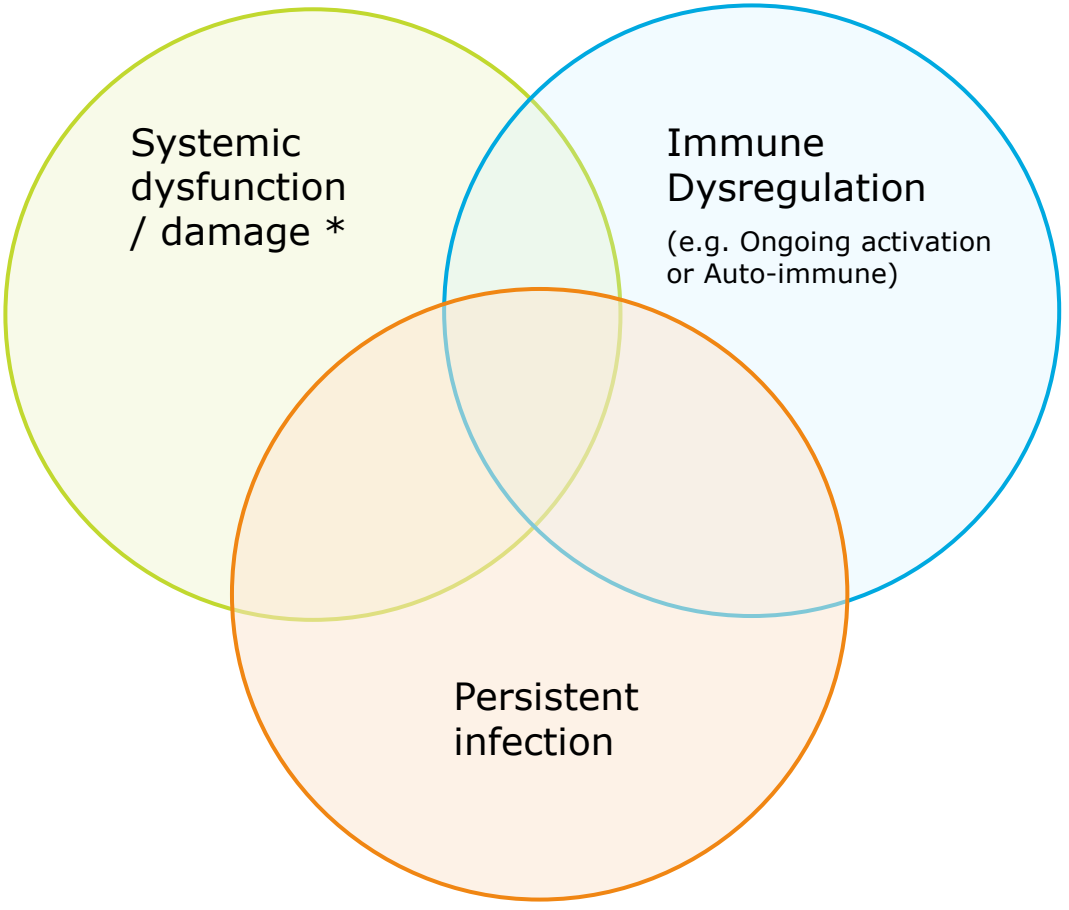
Genesis of Persistent Symptoms

Potential causes (or theories) for Lyme IACI symptoms:



* Could include microclots, altered GI microbiome, mitochondrial dysfunction and/or byproducts of past infection, such as residual peptidoglycan.

Few Recent Randomized Control Trials (RCTs)

NIH Funding	Lead [1]	Publish	Treatment	Screened	PLD Enrolled	Yield	PLD Treated
1998-2000	Klempner	2001	IV Ceftriaxone (4 weeks) followed by oral Doxycycline (8 weeks)	1,966	129	7%	64
1997-1999	Krupp	2003	IV Ceftriaxone (4 weeks)	512	55	11%	28
1999-2003	Fallon	2008	IV Ceftriaxone (10 weeks)	3,368	37	1%	23
			Total	**5,846**	**221**	**4%**	**115**

- Few RCTs conducted on Lyme IACI patients – no NIH-funded RCTs in last ~20 years
- Assessed only monotherapy (one antibiotic) or sequential monotherapy
- Low sample size and mixed results - generally held null hypotheses with exceptions (e.g., fatigue)
  - Limited power to detect meaningful change and limited subgroup analyses.

[1] Based on table from Johnson et al. Removing the Mask of Average Treatment Effects in Chronic Lyme Disease Research using Big Data and Subgroup Analysis. Healthcare 2018, 6, 124; doi:10.3390/healthcare6040124
[2] Based on table from Stricker RB. Counterpoint: Long-term Antibiotic Therapy Improves Persistent Symptoms Associated with Lyme Disease. Clinical Infectious Disease 2007.

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- Other diseases required (much) longer-term and/or combined antibiotics

			Duration of Treatment	
Disease [2]	**Organism**	**Treatment**	**Months**	**Weeks**
Drug-susceptible tuberculosis	M. tuberculosis	2-4 antibiotics	6-9	26-39
Multidrug-resistant tuberculosis	M. tuberculosis	3-5 antibiotics	18-24	78-104
Leprosy	M. leprae	3-4 antibiotics	24	104
Q fever endocarditis	Coxiella burnetii	2 antibiotics	36	156

[1] Based on table from Johnson et al. Removing the Mask of Average Treatment Effects in Chronic Lyme Disease Research using Big Data and Subgroup Analysis. Healthcare 2018, 6, 124; doi:10.3390/healthcare6040124
[2] Based on table from Stricker RB. Counterpoint: Long-term Antibiotic Therapy Improves Persistent Symptoms Associated with Lyme Disease. Clinical Infectious Disease 2007.

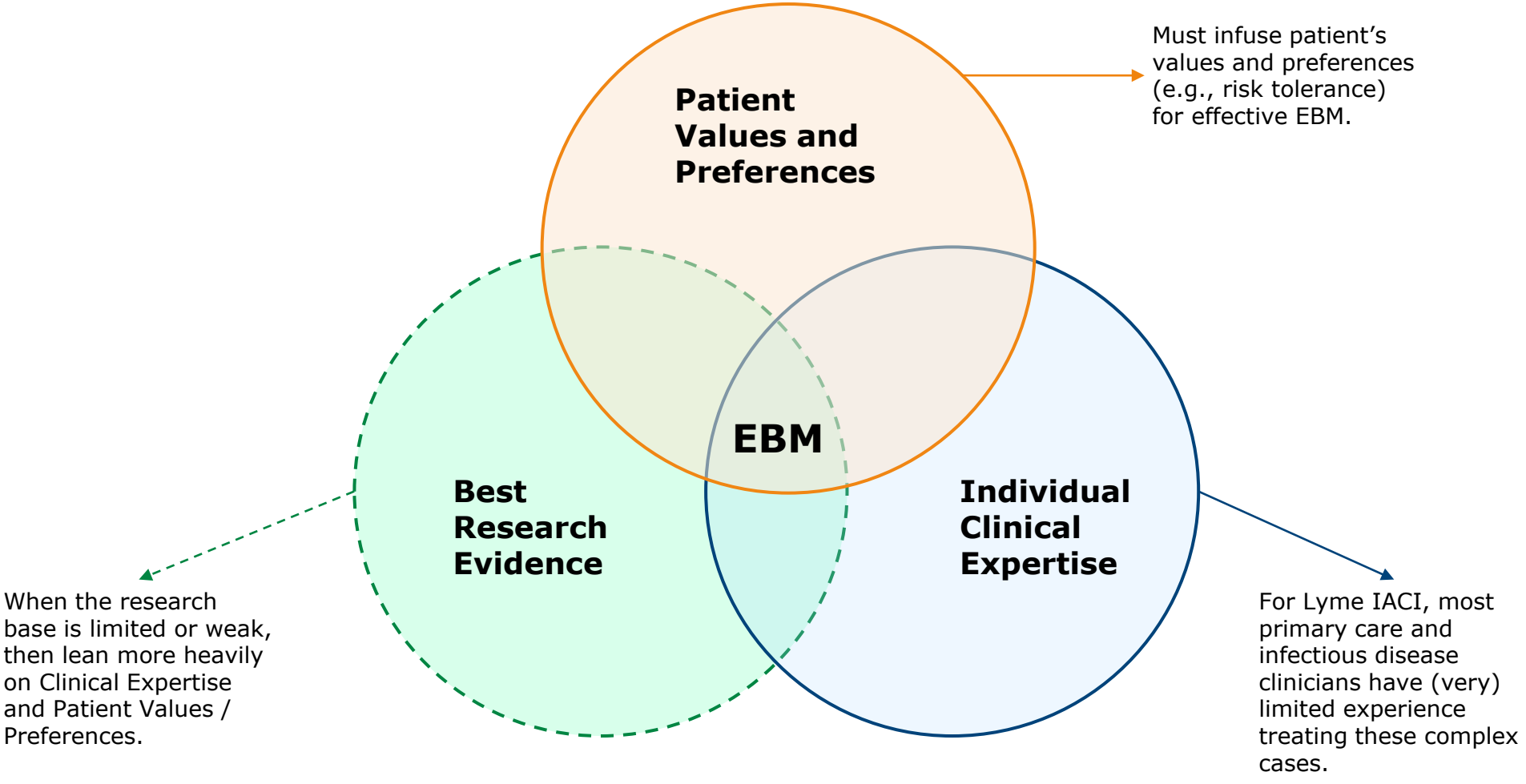
Lyme Clinical Trials Network

- Established in 2021 with a grant from the Steven & Alexandra Cohen Foundation
- CTN Sites:
  - **Columbia University, NY** (PI: Brian Fallon, Coordinating Center)
  - **Johns Hopkins University, MD** (PI: John Aucott)
  - **Children's National Hospital, DC** (PI: Roberta DeBiasi)
  - **State University of New York – Upstate** (PI: Kris Paolino)
  - **University of California, San Francisco** (PI: Charles Chiu)
  - **Mt. Sinai Health System, NY** (PI: David Putrino)
  - And adding more…

Pilot Study	Design
Tetracycline treatment tolerability trial for PTLD	RCT
Vagus nerve stimulation for persistent fatigue	RCT
Transcranial direct current stimulation and cognitive retraining for brain fog	RCT
Early neurodevelopmental outcomes of exposure to Lyme in pregnancy	Observational
Mast cell treatment in post-tick bite illness	RCT
Proteolytic enzymes as potential treatments for fibrin/amyloid deposition and platelet hyperactivation	Open-label
Pulse IV ceftriaxone therapy for patients with persistent symptoms	RCT

Evidence-based Medicine (EBM) Triad

Practicing evidence-based medicine requires three (3) equal elements:



Accuracy of Lyme Diagnostics

Sensitivity/specificity of commercial two tier testing for convalescent/late stage Lyme disease in the US*			
Study/Year	**Patients/Controls**	**Sensitivity**	**Specificity**
Schmitz (1993)	25/28	66%	100%
Engstrom (1995)	55/159†	55%	96%
Ledue (1996)	41/53	44%	100%
Tilton (1997)	23/23	45%	100%
Trevejo (1999)	74/38	29%	100%
Bacon (2003)	106/559	67%	99%
Binnicker (2008)	35/5	49%	100%
Steere (2008)	76/86††	18%	99%
TOTAL	435/951	46%	99%
*Limited to studies from the US that included negative controls; †Non-commercial ELISA and Western blot; ††Non-commercial ELISA			

- (Very) Low sensitivity of diagnostics in acute and later stage Lyme disease. Less than 50% of cases could test positive
- Minimal innovation in the last 30 years have reached patients

* Note: NIH recently funded five (5) long-term projects on PTLDS, which focus on diagnostics (i.e., no projects on treatment).

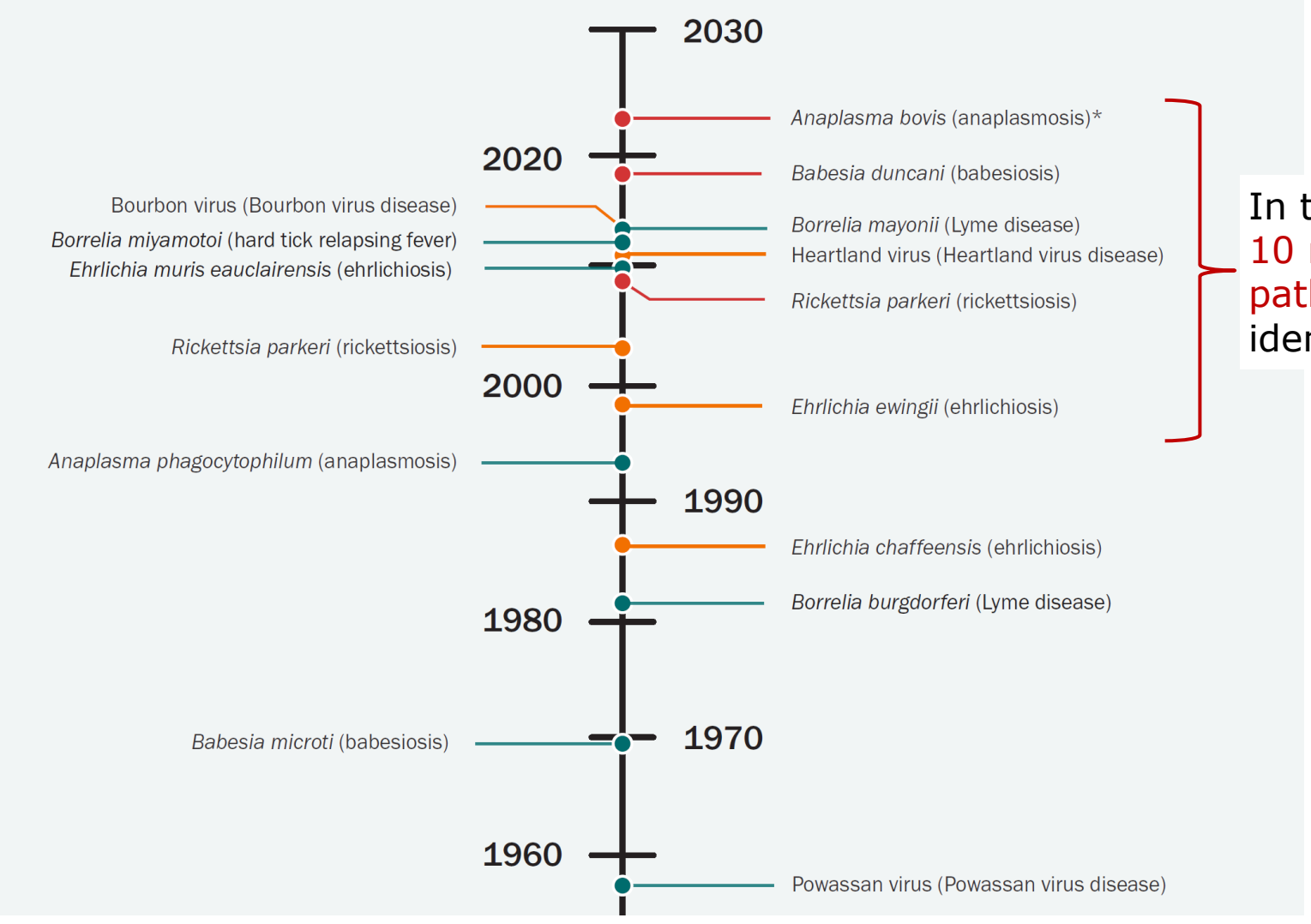
[1] Stricker RB, Johnson L.: Lyme disease diagnosis and treatment: lessons from the AIDS epidemic. Minerva Med. 2010.
https://www.lymedisease.org/wp-content/uploads/2014/08/Image10-sensitivity.pdf

LymeX Innovation Accelerator

- LymeX established in 2019
- Public-private partnership between Department of Health and Human Service (HHS) and the Steven & Alexandra Cohen Foundation
- $10+ million competition to **develop diagnostics** for Lyme disease
- Currently in Phase 3 of competition with six (6) teams of innovators:
  - BlueArc Biosciences Inc. (La Jolla, CA)
  - Drexel University College of Medicine (Philadelphia, PA)
  - HelixBind Inc. (Boxborough, MA)
  - Massachusetts General Hospital (Boston, MA)
  - Northwestern University, Feinberg School of Medicine (Chicago, IL)
  - Tufts University (Boston, MA)

Discovery of Tickborne Pathogens

That Cause Human Disease in the United States, 1900–2023



In the past 30 years, 10 new tick-borne pathogens have been identified.

[1] DHHS, CDC: The National Public Health Strategy to Prevent and Control Vector-Borne Diseases in People. U.S. DHHS, CDC; 2024

Multiple infections

www.nature.com/scientificreports

OPEN

Evaluating polymicrobial immune responses in patients suffering from tick-borne diseases

Received: 11 July 2018
Accepted: 15 October 2018
Published online: 29 October 2018

Kunal Garg[1,2], Leena Meriläinen[1], Ole Franz[1], Heidi Pirttinen[1], Marco Quevedo-Diaz[3], Stephen Croucher[4] & Leona Gilbert[1,2]

There is insufficient evidence to support screening of various tick-borne diseases (TBD) related microbes alongside Borrelia in patients suffering from TBD. To evaluate the involvement of multiple microbial immune responses in patients experiencing TBD we utilized enzyme-linked immunosorbent assay. Four hundred and thirty-two human serum samples organized into seven categories followed Centers for Disease Control and Prevention two-tier Lyme disease (LD) diagnosis guidelines and Infectious Disease Society of America guidelines for post-treatment Lyme disease syndrome. All patient categories were tested for their immunoglobulin M (IgM) and G (IgG) responses against 20 microbes associated with TBD. Our findings recognize that microbial infections in patients suffering from TBDs do not follow the one microbe, one disease Germ Theory as 65% of the TBD patients produce immune responses to various microbes. We have established a causal association between TBD patients and TBD associated co-infections and essential opportunistic microbes following Bradford Hill's criteria. This study indicated an 85% probability that a randomly selected TBD patient will respond to Borrelia and other related TBD microbes rather than to Borrelia alone. A paradigm shift is required in current healthcare policies to diagnose TBD so that patients can get tested and treated even for opportunistic infections.

Patients suffering from tickborne disease do not follow the one microbe, one disease germ theory as **65%** of the TBD patients produce immune responses to various microbes. (from US and European samples)

Ticks carry multiple pathogens

Contents lists available at ScienceDirect

Ticks and Tick-borne Diseases

journal homepage: www.elsevier.com/locate/ttbdis

Microbiome analysis of *Ixodes scapularis* ticks from New York and Connecticut

Rafal Tokarz[a,*], Teresa Tagliafierro[a], Stephen Sameroff[a], D. Moses Cucura[b], Alexandra Oleynik[a], Xiaoyu Che[a], Komal Jain[a], W. Ian Lipkin[a]

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[b] Division of Vector Control, Suffolk County Department of Public Works, Yaphank, NY, 11980, United States

ARTICLE INFO

Keywords:
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Metagenomics
High-throughput sequencing
Borrelia
Bartonella
Ixodes scapularis

ABSTRACT

We employed high throughput sequencing to survey the microbiomes of *Ixodes scapularis* collected in New York and Connecticut. We examined 197 individual *I. scapularis* adults and pools from 132 adults and 197 nymphs. We detected *Borrelia burgdorferi* sensu stricto in 56.3% of individual ticks, *Anaplasma phagocytophilum* in 10.6%, *Borrelia miyamotoi* in 5%, *Babesia microti* in 7.6%, and Powassan virus in 3.6%. We did not detect *Borrelia mayonii*, *Ehrlichia muris eauclairensis*, *Bartonella* spp. or pathogenic *Babesia* species other than *B. microti*. The most abundant bacterium (65%), and only rickettsial species identified, was the endosymbiont *Rickettsia buchneri*. A filarial nematode was found in 13.7% of adult ticks. Fourteen viruses were detected including South Bay virus (22%) and blacklegged tick phlebovirus 1 and 2 (73%). This study provides insight into the microbial diversity of *I. scapularis* in New York State and Connecticut.

From *Ixodes scapularis* ticks collected in NY and CT during 2015-17:

56% had Borrelia burgdorferi (Lyme)

19% had co-infections

Multiple tickborne infections

1. Anaplasmosis
2. Babesiosis
3. Borrelia burgdorferi (Lyme)
4. Borrelia mayonii
5. Borrelia miyamotoi
6. Bourbon virus
7. Colorado tick fever
8. Ehrlichiosis
9. Heartland virus
10. Powassan disease
11. Rickettsia parkeri rickettsiosis
12. Rocky Mountain spotted fever (RMSF)
13. STARI (Southern tick-associated rash illness)
14. Tickborne relapsing fever (TBRF)
15. Tularemia
16. 364D rickettsiosis

(among various tick species)

Number of clinical treatment trials conducted on participants with multiple tickborne infections?

Multiple infections

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(among various tick species)

Number of clinical treatment trials conducted on participants with multiple tickborne infections?

0

(zero)

Positioning for Success

1. **Critically evaluate** the available science including design and interpretation
2. **Identify gaps** in Lyme IACI knowledge base and questions to be answered
3. **Build a strategic framework** for future scientific exploration. How does each study fit into a wider strategy to fill gaps and improve patient lives?
4. **Outline specific research projects** for immediate implementation and recommend design, size, and interventions where feasible
5. **Focus on treatments and diagnostics** for Lyme IACI (not new naming conventions)
6. **Learn from other IACIs**

- **Accept our past failures**
- **Be humble**: this disease has vexed researchers / decisionmakers for decades
- **Be agnostic**: openness to new theories and treatment options
- **Transcend the stigma, our egos, and historic indifference**
- **Center the work on patient experience**
- **You are supported**: Know the Lyme patient community is rooting for you