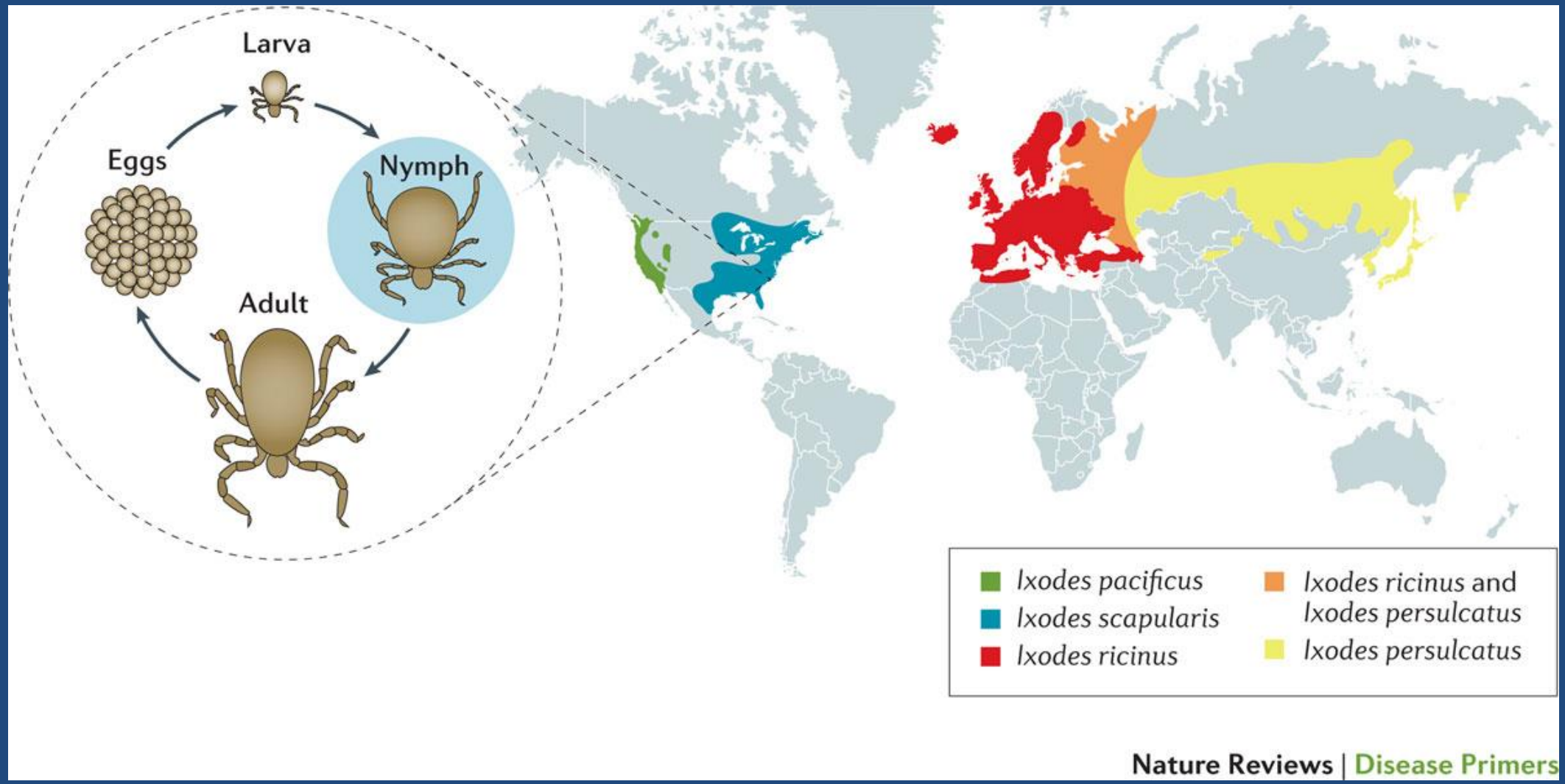
Current Status and Challenges in Research for Lyme Infection-Associated Chronic Illnesses (IACI) Treatment

John Aucott, MD
Barbara Townsend Cromwell Professor in Lyme Disease and Tickborne Illness
Director, Lyme Disease Research Center
Associate Professor of Medicine
Division of Rheumatology
Johns Hopkins University School of Medicine

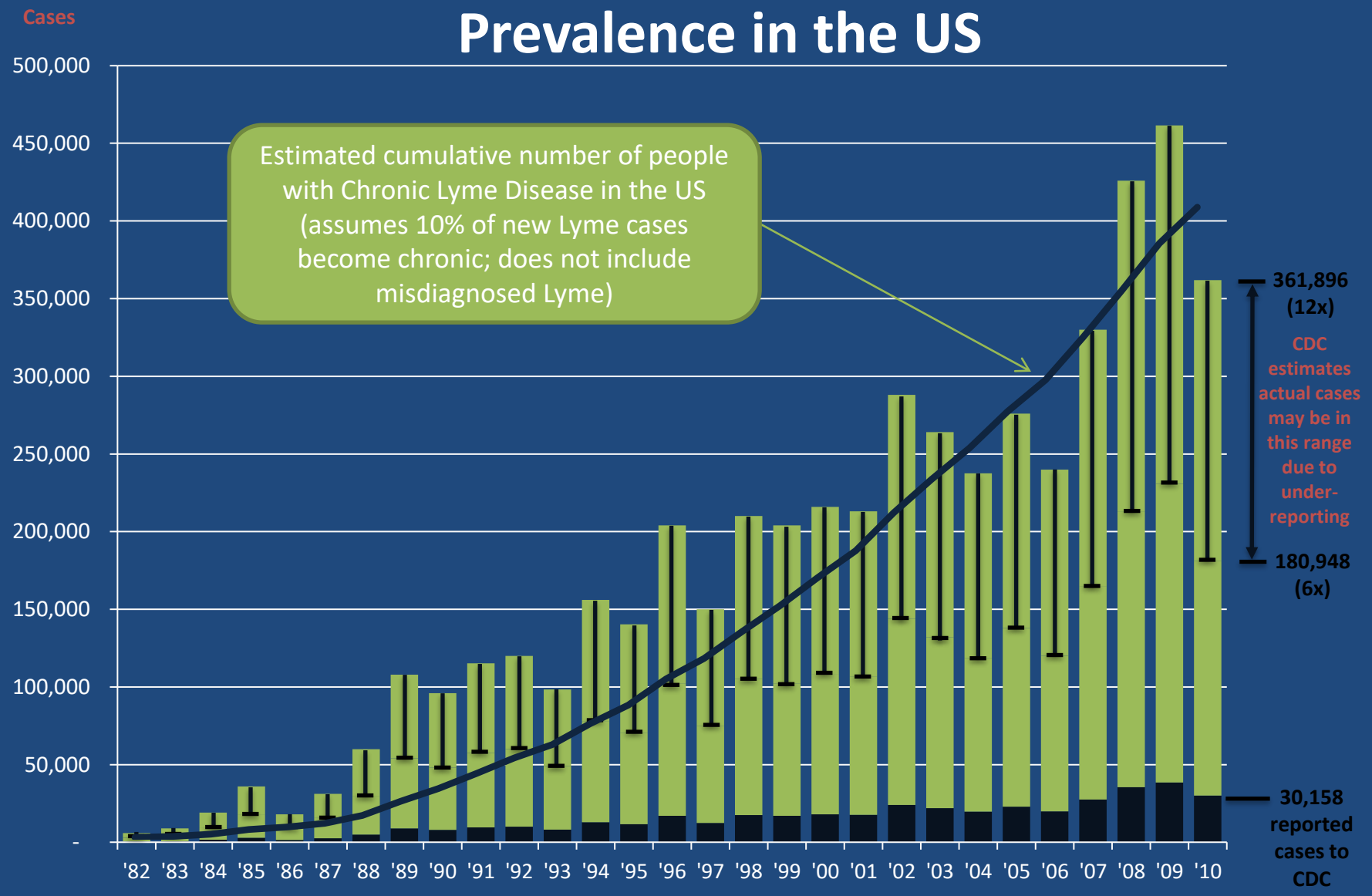
JOHNS HOPKINS
MEDICINE

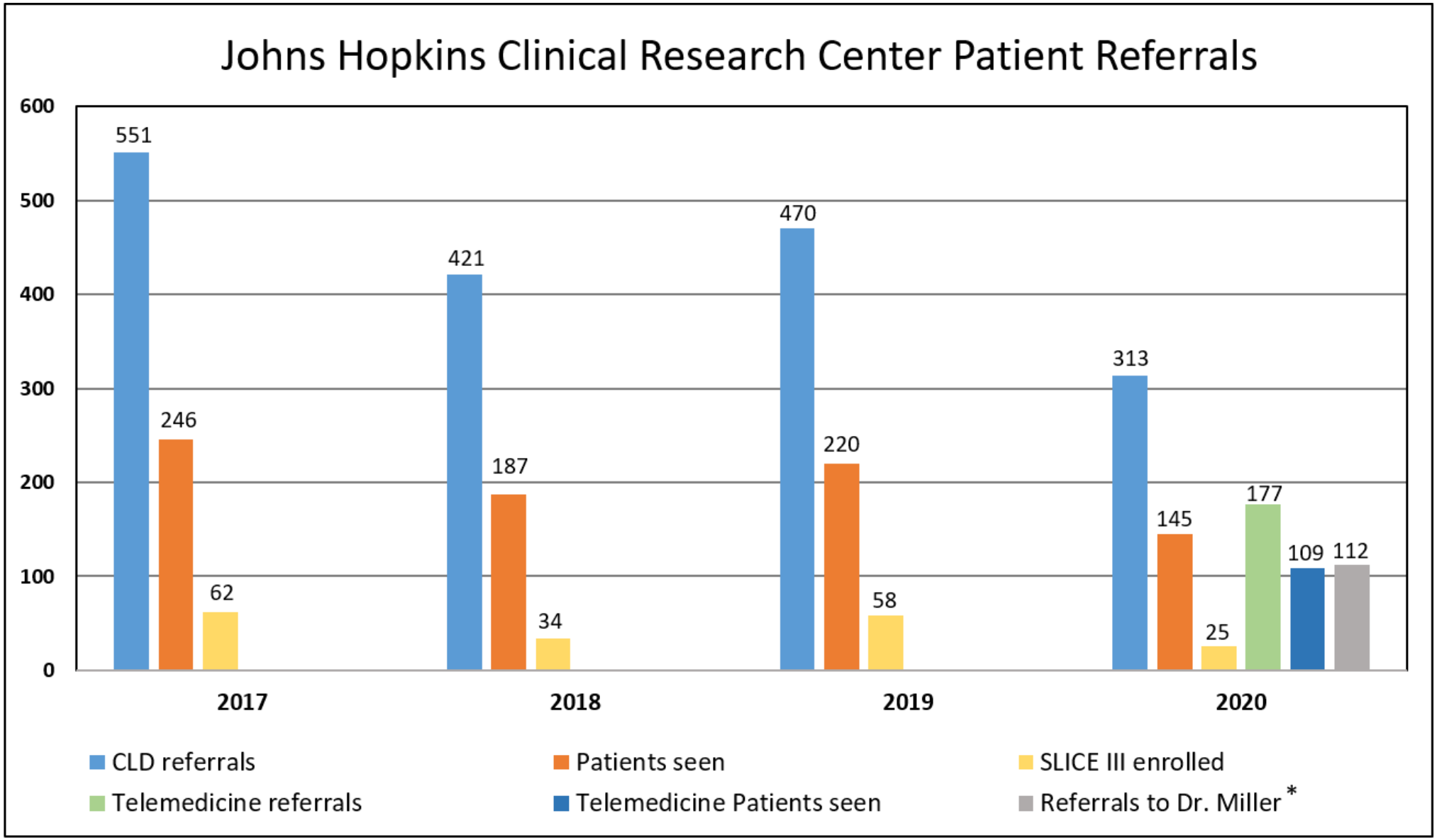
Global Distribution of *Ixodes* ticks that transmit *Borrelia burgdorferi* s.l.



Steere, A. C. *et al.* (2016) Lyme borreliosis
Nat. Rev. Dis. Primers doi:10.1038/nrdp.2016.90

Back of Envelope Calculation of PTLDS Prevalence in the US





*Since March 2020

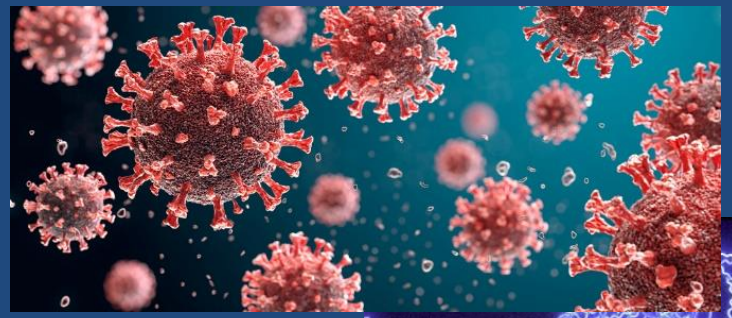
A Clinician's Perspective on Lyme IACI

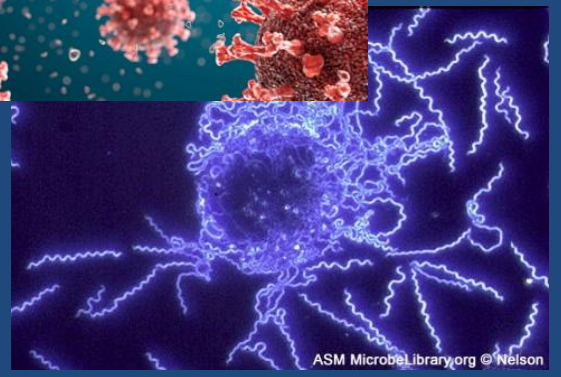
- Multidisciplinary background gives some insights from infectious diseases, rheumatology and general internal medicine.
- Continuity of care gives insights into impact and suffering in patient I knew when they were healthy.
- How I became involved.
  - Recognizing there was more to the story.
  - The map doesn't give fit what I was seeing

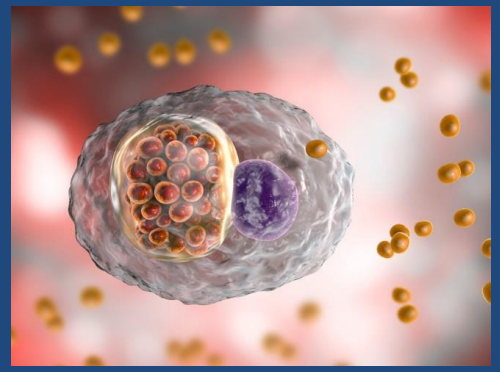
California Map 1620 -1747

Infection Associated Illnesses and Syndromes

- Past epidemics of infection triggered fatigue
  - Post-Ebola syndrome
  - SARS-COV1
  - ME/CFS after Epstein-Barr virus (mono)
  - Post-treatment Lyme Disease/Chronic Lyme
  - COVID-19 and Long Haul COVID
- Infection triggered Autoimmunity
  - Rheumatic Heart Disease and strep
  - Guillain-Barre syndrome
  - Reactive arthritis and chlamydia







PERSONAL HEALTH

When Lyme Disease Lasts and Lasts

BY JANE E. BRODY JULY 8, 2013 12:01 AM 54

Ellen Weinstein

Email

Share

Tweet

Chronic Lyme disease is a highly controversial catch-all term for a host of long-lasting symptoms that may or may not stem from prior infection with the bacterium that causes acute Lyme disease. Often misdiagnosed and mistreated, chronic Lyme disease leaves thousands of people physically and mentally debilitated and without a medically established recourse.

IDSA 2006 Proposed Case Definition for Post Treatment Lyme Disease Syndrome

- Evidence of physician documented Lyme disease preceding onset of illness (CHAPTER 1 of Illness)
- Adequate prior treatment
  - Lyme disease, Babesia
- Patient Reported Symptoms > 6 months duration
  - Fatigue (sleep disruption)
  - Cognitive Complaints
  - Musculoskeletal Pain (tingling, twitching, cramps)
- Significant severity/Functional impact of symptoms
- Exclusion other causes of symptoms
  - Good history physical and basic labs
- Laboratory tests
  - (+) Lyme convalescent Serology NOT part of case definition
  - Lack of other objective laboratory data (culture, PCR, for Bb or other cause of illness), normal ESR

Study Timeline of Lyme Disease Immunology and Clinical Events (SLICE II)

Uniform Entry Point Allows Study of Early Events in Infection and Immediately Post Treatment and Over Time

Lyme Cases (N= 234)

Skin Biopsy Visit 1

Neurocognitive Visit 2

Visit 3

Visit 4-5

Doxycycline Treatment

Acute Lyme Disease (0- 72 hours treatment)

Post-Treatment

2 months Post-Treatment

6-12 months Post-Treatment

Screening

Visit 1

Neurocognitive

Visit 2

57%

30%

14%

Defining Outcomes

Return to Health
No symptoms, No impact on QOL

Symptoms Only
No impact on QOL (SF36)

PTLDS
Defined at 6 months using IDSA criteria of persistent symptoms with impact on QOL

Controls

Rate of "PTLDS" in matched control population in study was 4%

Aucott JN, Yang T, Yoon I, Powell D, Geller SA, Rebman AW. Risk of post-treatment Lyme disease in patients with ideally-treated early Lyme disease: A prospective cohort study. Int J of Inf Dis, 2022 V116, p 230-237. doi: 10.1016/j.ijid.2022.01.033

Figure 1. Distribution of average symptom scores between two visits and percentage of moderate or severe symptoms, by group. Symptoms of most interest in this study selected by the clinical expert on the study are marked red.

Compared to the control group, after adjusting for gender, race, life events, heart disease or hypertension, LD group had significantly higher scores in joint pain, memory changes and depression (p-values = 0.022, 0.033, and 0.021), and significantly higher odds of developing moderate or severe fatigue (odd ratio: 3.81, p-value=0.011).

SLICE Study Conclusions

- 13.7% of participants with a history of prior LD met criteria for PTLD compared with 4.1% of those without a history of prior LD.
- Patients with a history of early LD were significantly more likely to meet criteria for PTLD than controls (5.3 times risk), even after controlling for relevant co-morbidity, demographic, and psychosocial factors..
- Risk of meeting PTLD criteria was also independently increased among females and those with higher exposure to previous traumatic life events

- Limitations of Study
  - Clinical assessment may be more sensitive to the diagnosis of PTLD than patient reported surveys. 20% of patients identified with PTLD by chart review
    - Wormser, Gary P., et al. *Clinical Infectious Diseases* 71.12 (2020): 3118-3124. DOI: 10.1093/cid/ciz1215
  - Ideal setting of early diagnosis may not generalize to community setting
  - Does not take into account impact of potential co-infection

Is Chronic Lyme/PTLD a Psychosomatic Illness?

1. No.
   - Psychosomatic illnesses are distinct clinical entities (conversion, malingering, pseudosiezures)
2. Depression alone isn't adequate explanation for range of symptoms seen in PTLDS (for example the multiple organs impacted by post-infectious dysautonomia)
3. PTLD is primarily a range of symptoms reported by patients with a range of life experiences and personality types that shapes the illness presentation
   - Doesn't mean that that the mind and emotions and personality don't affect manifestations of underlying illness
   - Means that the underlying cause/pathophysiology isn't solely due to psychiatric or mental health disorders

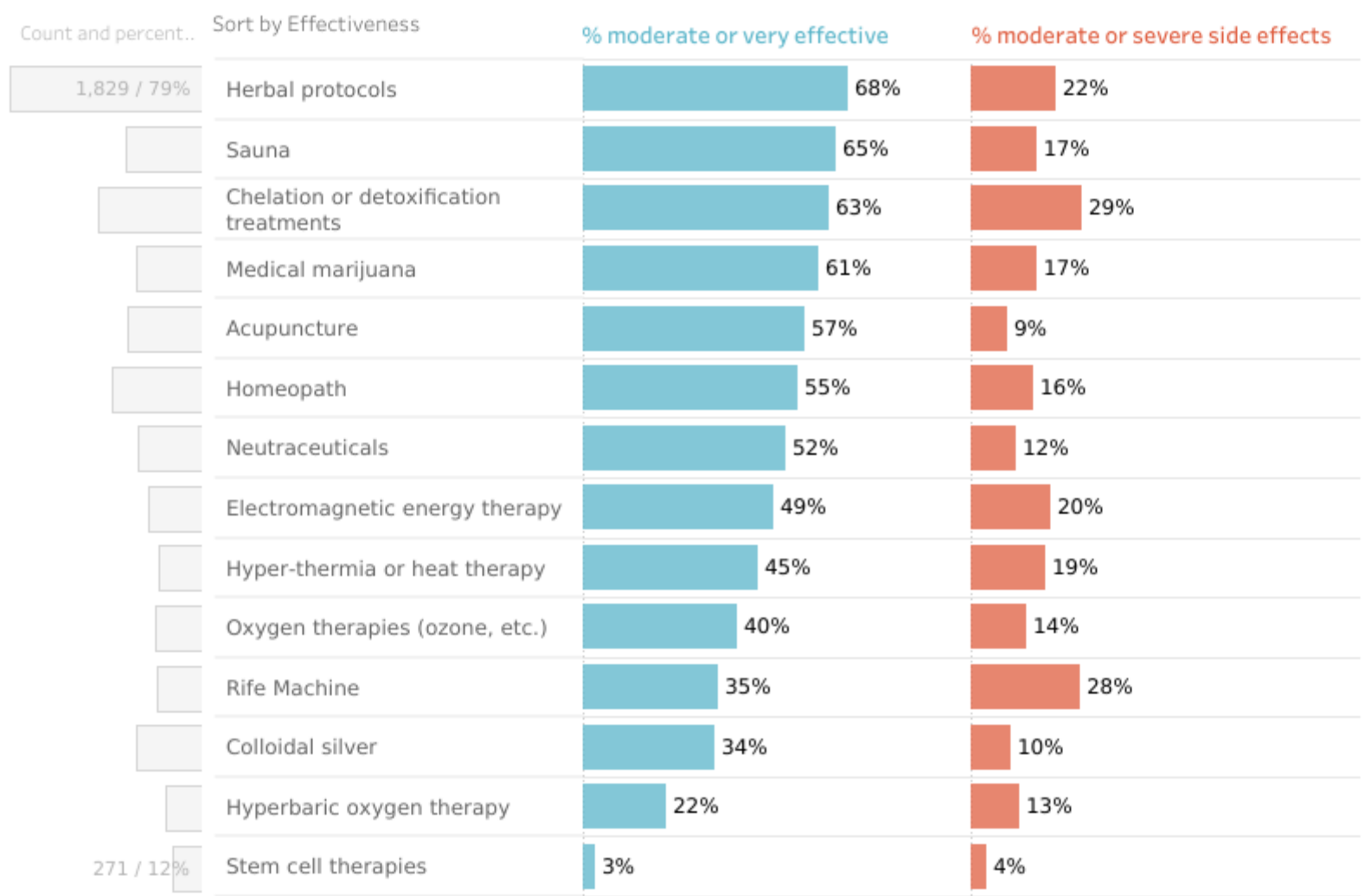
Dr. Glenn Treisman, Professor, Johns Hopkins Department of Psychiatry

A clinician's view of Lyme IACI and Treatment

- Physicians and care givers need tools to care for their patients.
  - No FDA approved therapies for Lyme IACI.
  - No consensus on off label use of medications
  - No Current Standard of Care for Treatment of PTLD
    - UpToDate: No recommendation, states only no evidence for effectiveness of antibiotic use
    - ChatGPT: Symptom management, CBT, diet and exercise, alternative therapies

Effectiveness and side effects of alternative treatments for Lyme disease

Hover over a bar for details



Filters

Gender
All

State
All

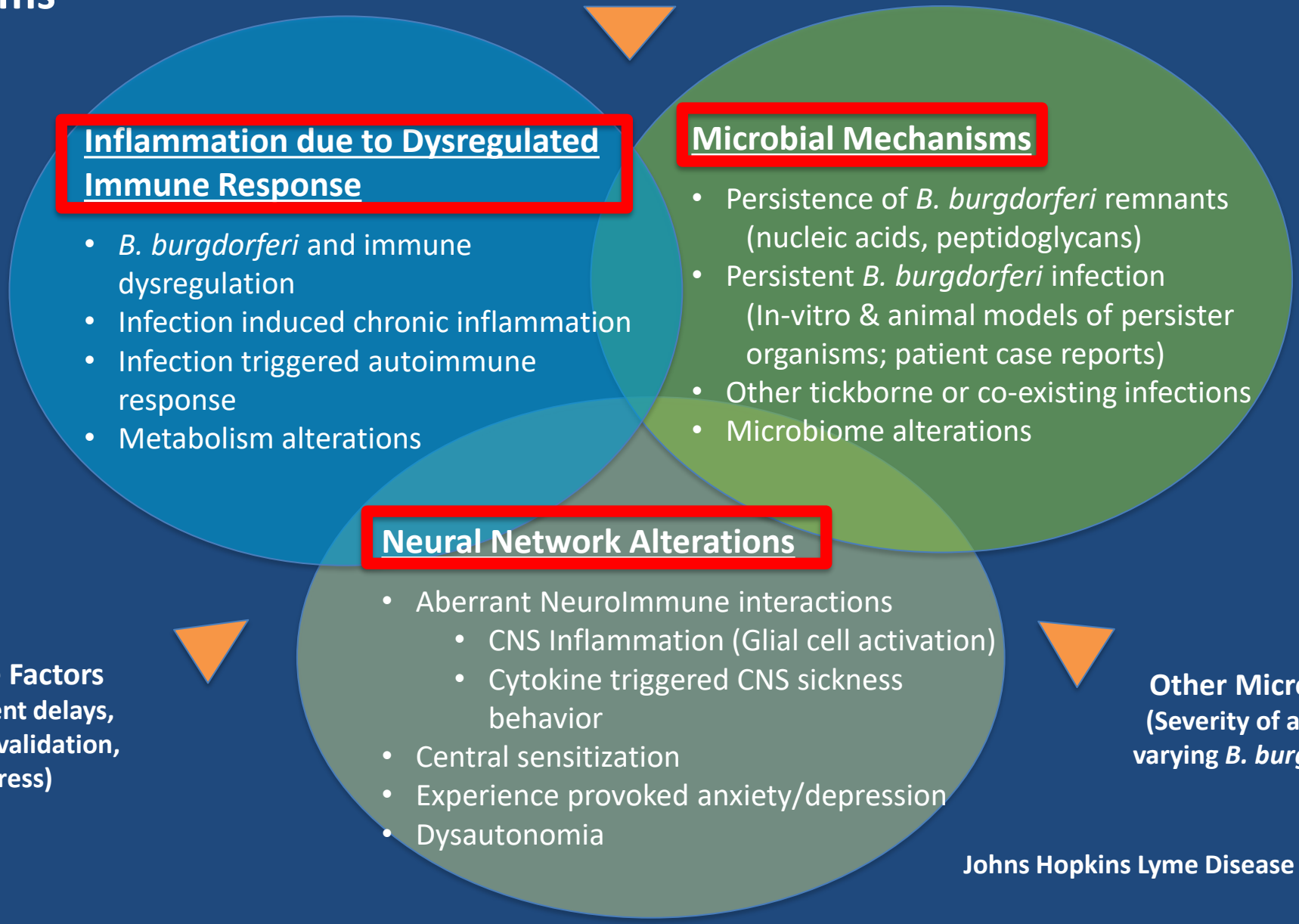
MyLymeData
A PROJECT OF LYMEDISEASE.ORG

What is the current evidence base toward understanding and developing treatments for Lyme IACI? Setting the stage for session 2

- Current understanding
  - Heterogenous population.
- Knowledge gaps
  - Role of persistent pathogen.
  - Viable infection vs. “amber theory”
    - Translation of animal model data to humans
  - Role of infection triggered pathologies.
    - Persistent immune dysregulation/inflammation/autoimmunity
    - Interferon alpha, cytokines
    - Autonomic dysfunction and POTS
- Emerging biology – brain imaging, autoimmunity, peptidoglycan biology

Multifactorial Potential Mechanisms of Lyme Disease Associated Chronic Illness

Host, Genetic, and Environmental Factors
(Genetic variation in key immune system mediators, epigenetic changes, sex, age, race/ethnicity, environmental exposures, co-morbidities)

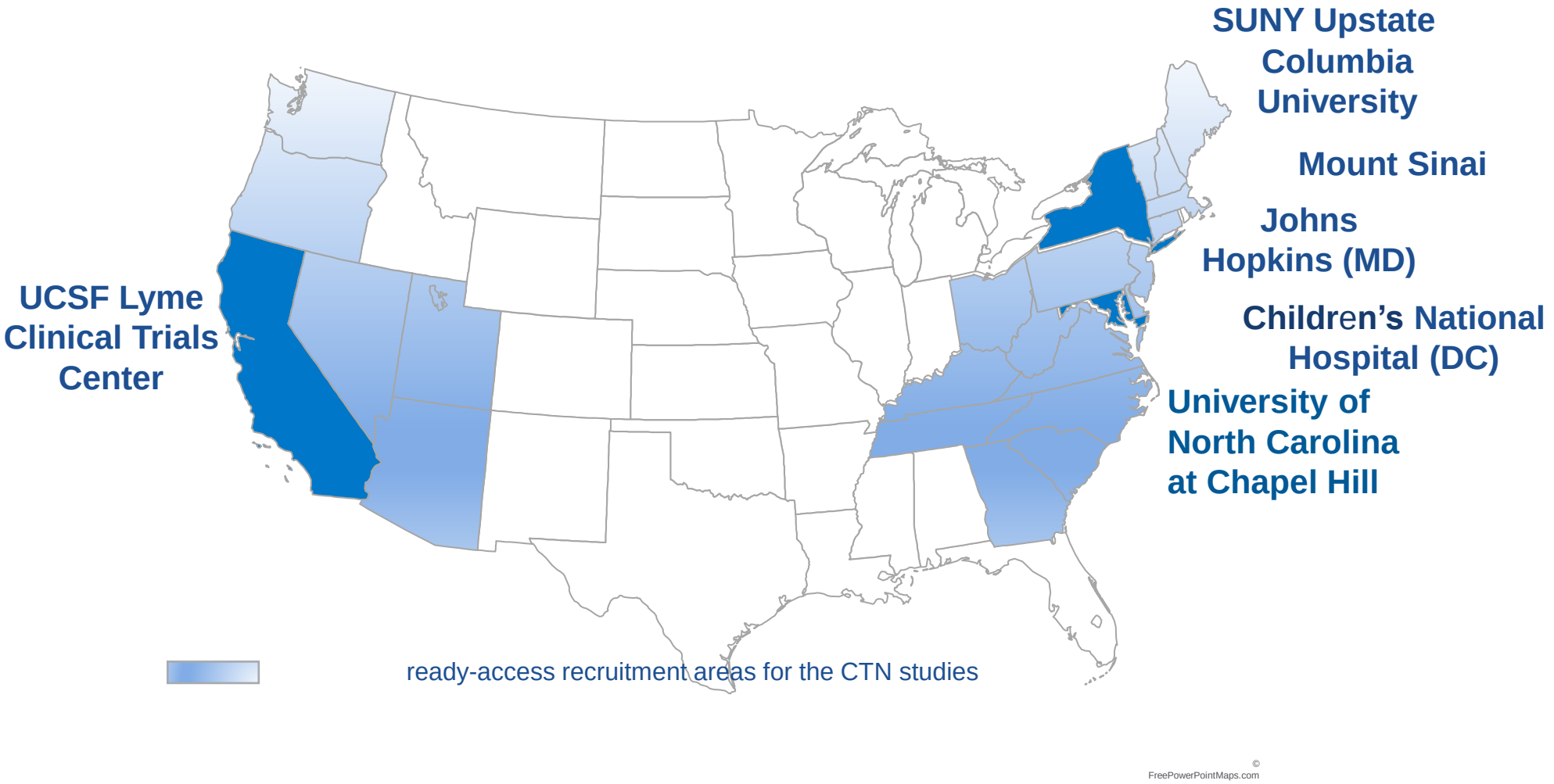


Illness Experience Factors
(Diagnosis & treatment delays, uncertainty, illness invalidation, psychosocial stress)

Other Microbial Factors
(Severity of acute infection, varying *B. burgdorferi* strains)

Johns Hopkins Lyme Disease Research Center

A Map of the Clinical Trials Network (CTN) nodes (2021-2023)



Mechanisms of Disease tested in CTN Pilot studies

Persistent Infection

Pulse IV Ceftriaxone (PI: Paolino, SUNY Upstate Medical)

Infection and Inflammation

Tetracycline (PI: Aucott; Hopkins)

Dysautonomia and Inflammation and CNS Network dysregulation

Transauricular Vagus nerve stimulation (PI: Fallon & Kuvaldina, Columbia)

CNS Neural Network dysfunction

Transcranial direct current brain stimulation & Cognitive retraining

(PI: Gorlyn, NYSPI; Co-PIs- Chiu, Chow, UCSF)

Immune Dysregulation related to Post-tick bite Illness

Mast Cell modulation (PI: Commins, UNC)

Microclots & platelet hyperactivation

Proteolytic Enzyme (PI: Putrino, Mount Sinai)

Prenatal Bb infection may impact neurodevelopmental outcomes

Pregnancy observational study (PI: Mulkey, Children's National)

Other Potential New Therapeutics

- Psilocybin (Johns Hopkins pilot study)
- Hygromycin A (Flightpath Biosciences)
- Dapsone and antibiotic combination therapies (Richard Horowitz)
- TNF inhibitors and biologics for inflammatory arthritis and enthesitis (Rheumatologists)
- Medical management of dysautonomia and POTS

What are key scientific or technical barriers in addressing challenges to develop new treatments?

- Don’t know mechanisms of disease
- Main challenges to conducting treatment research
  - Case definitions
  - Outcome measures
  - Enrollment in studies
  - Multisite networks (CTN established)
  - Including children, pregnant women
  - Funding

Complexity
Uncertainty
Persistence
and Hope

Maggie on my Mind, 2015, acrylic on canvas.
Carol Brown Goldberg, used with permission