

Lyme Disease Diagnosed by Alternative Methods and Similar Syndromes: Research Approaches to Take us Forward

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**We're Here Because
People are Sick**

For Progress to Occur, Ideas Must be Tested

- “We should not be justified in devoting further time to opinions which are not supported by any serious experiment.”
 - Louis Pasteur, 1879



Scientific Problems with Imperfect Case Definitions

- Within a group given a “Lyme disease” or other label, there may be several groups of people sick for different reasons
- Imperfect case definition → misclassification
- Misclassification makes it harder to find key differences between sick and healthy people
- This makes it harder to find good tests
- This also makes it harder to test treatment options

Can we be more precise about what we mean by “Lyme Disease”?

Patient Category	Basis for Diagnosis
Undisputed Lyme Disease	Diagnosed on appropriate clinical grounds in early disease or by reference laboratory testing in later stages (33)
Post-Treatment Chronic Lyme Syndrome (PTCLS)	Diagnosed as above but failing to experience complete symptom resolution after standard antibiotic therapy (34)
Alternatively Diagnosed Chronic Lyme Syndrome (ADCLS)	Diagnosed on clinical grounds supported only by alternative tests, the validity of which is questioned by major reference laboratories and the CDC (25)
Seronegative Lyme Disease	Diagnosed on purely clinical grounds (a controversial category outside of early disease)

What would Pasteur be doing if he were alive today?

- **Metagenomics – microbial discovery**
- Understanding of Gut Microbiome
- **Transcriptomics – gene expression**
- Epigenetics – gene alteration
- **Immunosignature Assay – comprehensive overview of antibody expression**

*Xu GJ, Kula T, Xu Q, Li MZ, Vernon SD, Ndung'u T, Ruxrungtham K, Sanchez J, Brander C, Chung RT, O'Connor KC, Walker B, Larman HB, Elledge SJ. Viral immunology. Comprehensive serological profiling of human populations using a synthetic human virome. *Science*. 2015 Jun 5;348(6239):aaa0698. doi: 10.1126/science.aaa0698. PubMed PMID: 26045439.

Views Promoted by Lyme advocates in British Columbia - 2010

- Borrelia bacteria are everywhere in ticks in BC with plenty of strain variation
- “Specialty labs” do a better job of finding LD
- People need more antibiotics than they get
- Well designed studies produced findings that lead to rejection of each of these hypotheses
- But that does not change the fact that people feel sick

BC Tick Surveillance

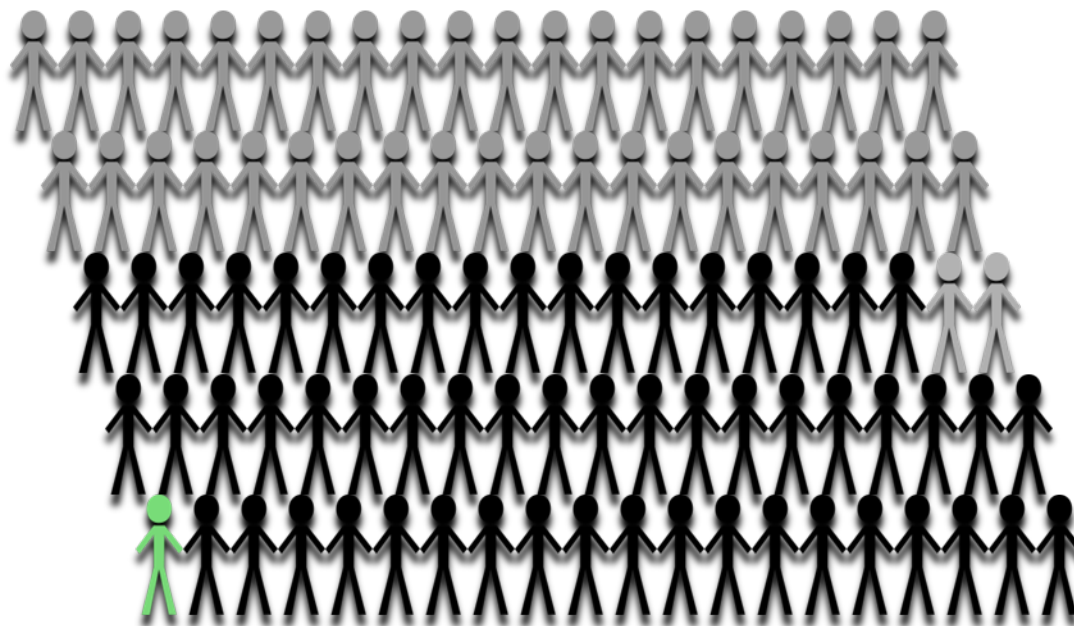
- Sites based on ecological niche modeling
- Rodents trapped, ticks pooled by life-stage
- Screening 23S ribosomal gene
- Then ospA gene and sequencing
- 0.56% Positivity in ticks (50-100 times lower than high prevalence areas)
- Same rate from ongoing passive surveillance

Why many doctors have a problem with Alternative Lab Testing

- Specialty labs were not better at finding Lyme disease when it was there
- However, a specialty lab using “in-house interpretive criteria” labeled 23/40 healthy people as having Lyme disease – 57%
- Such an approach is reported by most people presenting with alternatively-diagnosed Lyme syndrome in BC

Fallon BA, Pavlicova M, Coffino SW, Brenner C. A comparison of lyme disease serologic test results from 4 laboratories in patients with persistent symptoms after antibiotic treatment. Clin Infect Dis **2014**; 59(12): 1705-10.

Expected test results when an alternative laboratory employs “in-house” interpretation (Fallon, CID)



Correct – 43%
Incorrect – 57%



True Lyme
Disease 1%



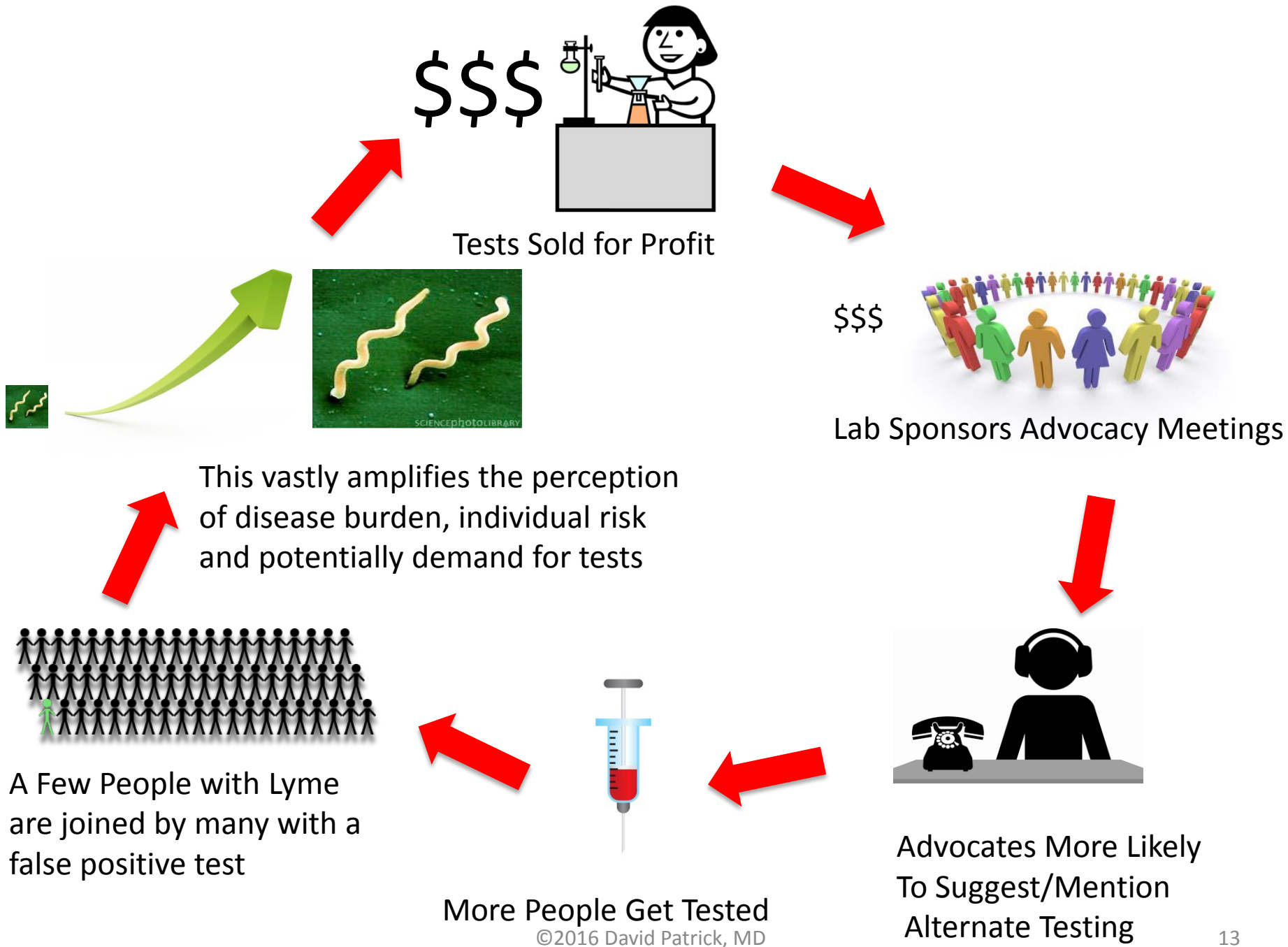
True Negative
42%



False Positive
57%

More accuracy, Fraction of the Cost





Any Canadian lab reporting with this much error would be required to issue recall warnings to its clients, even if it did move forward to change its testing platform.

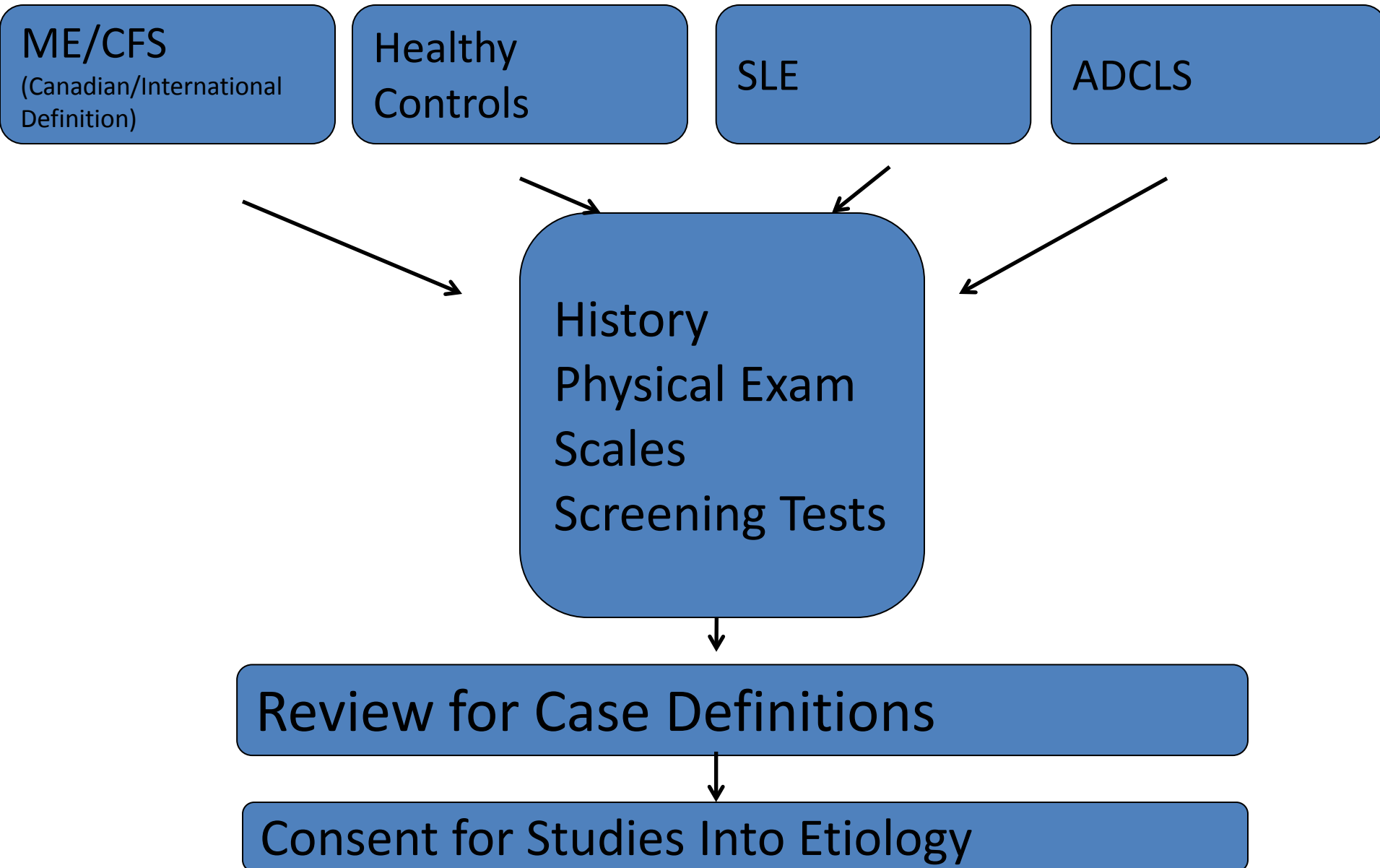
Diagnostic misdirection has its risks

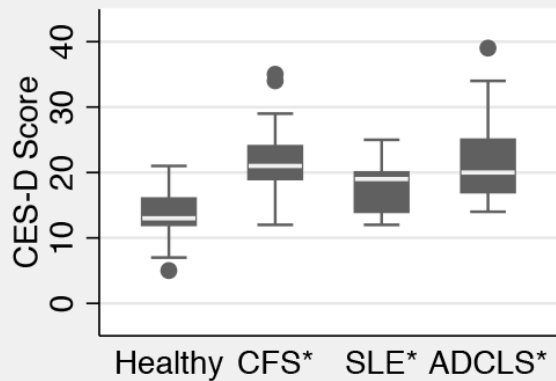
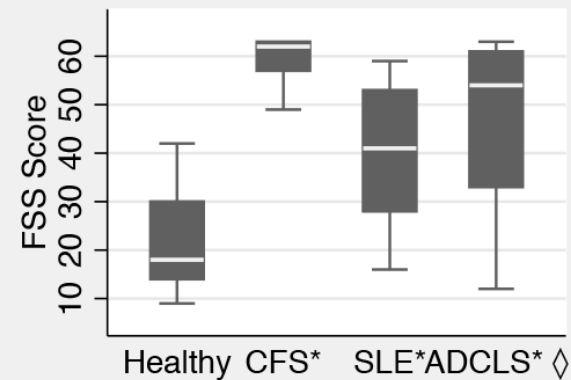
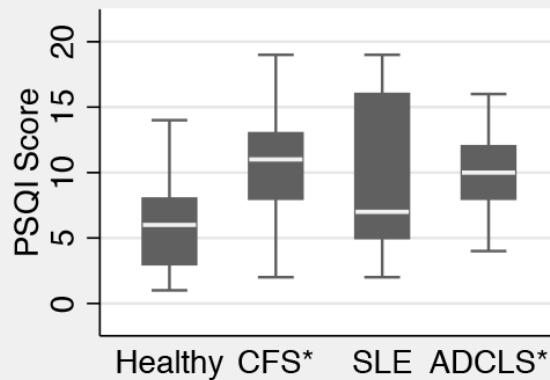
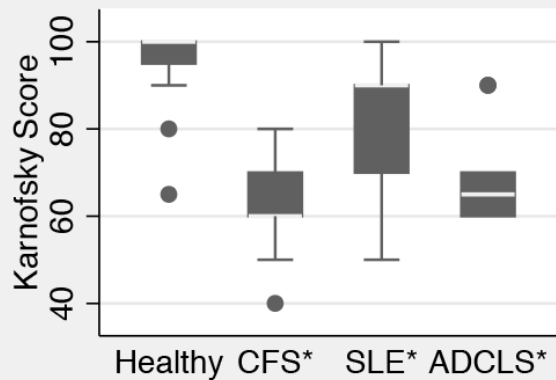
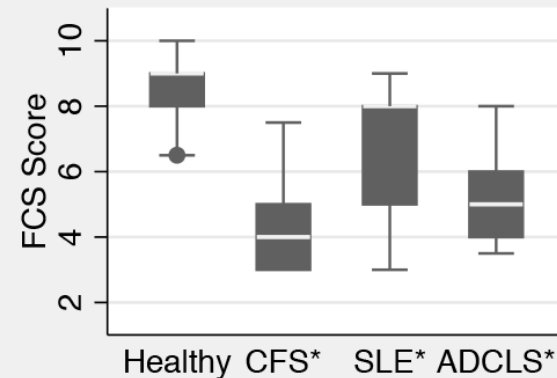
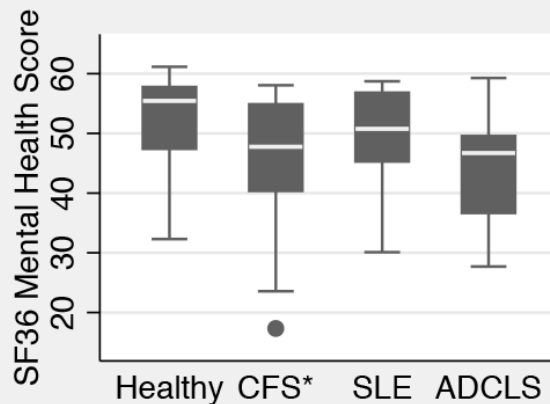
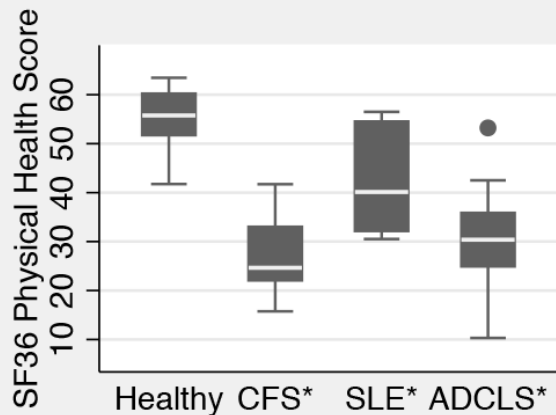
- Delay in finding the underlying cause
- Risks associated with certain treatments
- Exclusion from involvement in research that may come up with a better answer
- A challenge for Advocacy groups
- Is being perceived as correct more important than finding a better answer for some of those we represent?

Why Research Alternately Diagnosed Chronic Lyme Syndrome or PTCLS?

- People are sick and often disabled
- They've had a hard time finding a solid model of care -> causing outrage/skepticism
- Disagreement on cause should not cause people to be selected away from health care or studies

UBC Complex Chronic Disease Study





Performance on Functional Scales By Group

Clinical Findings

- People with ME/CFS and people with alternately diagnosed Lyme syndrome look very similar in this study
 - History and physical
 - Laboratory testing
- No patient diagnosed with Lyme Disease by alternate methods could be confirmed by any form of reference testing
- People are sick enough that it is worthwhile trying to better understand causes

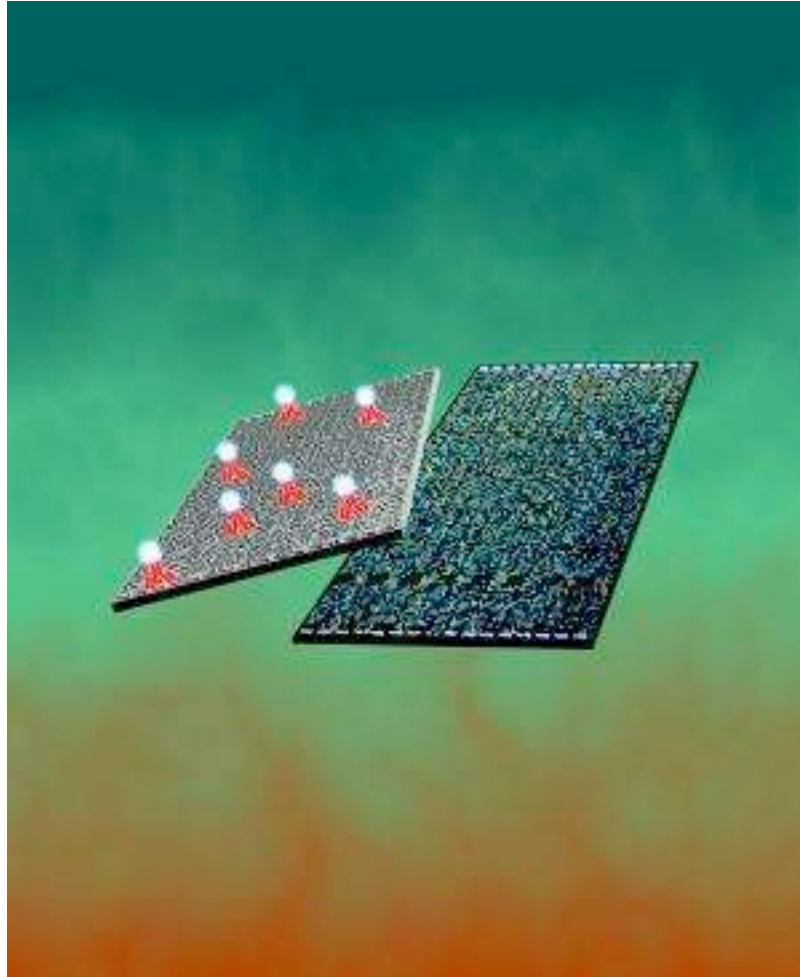
Alternative Test False Positive or Reference Test False Negative?

- 12 diagnosed by one alternative lab
- What's the likelihood of seeing 12 false positive Alternative Tests?
- $.98^{12} = 78\%$
- Likelihood Reference Test False Negative?
- $0.6^{12} = 0.2\%$
- Not very likely

Early Report on RNA Seq Transcriptomics

- Chiu and Bouquet (UCSF) have found a unique transcriptional signature for acute Lyme disease
- In the same hands, relatively few differentially expressed genes between ME/CFS, ADCLS and Healthy (SLE had many)
- Currently correlating these with core co-variates (fatigue severity, age etc)

Immunosignature Work



Where Etiological Studies Really Need to Go

- Multi-centre efforts
- New cases within large population based prospective cohort studies (Canadian Partnership for Tomorrow)
- Nested Case control approach
- But married to state of the art bio-banking and full spectrum “omics” platforms on banked material
 - Blood
 - Stabilized RNA
 - Hair
 - Stool

If there is consensus that solving problems for patients is more important than complete agreement on current theory – then we increase the likelihood that the future of research and care will be better than the past.

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