Challenges in Developing Diagnostics and Criteria for ME/CFS and Other Infection-Associated Chronic Illnesses: Lessons for Lyme

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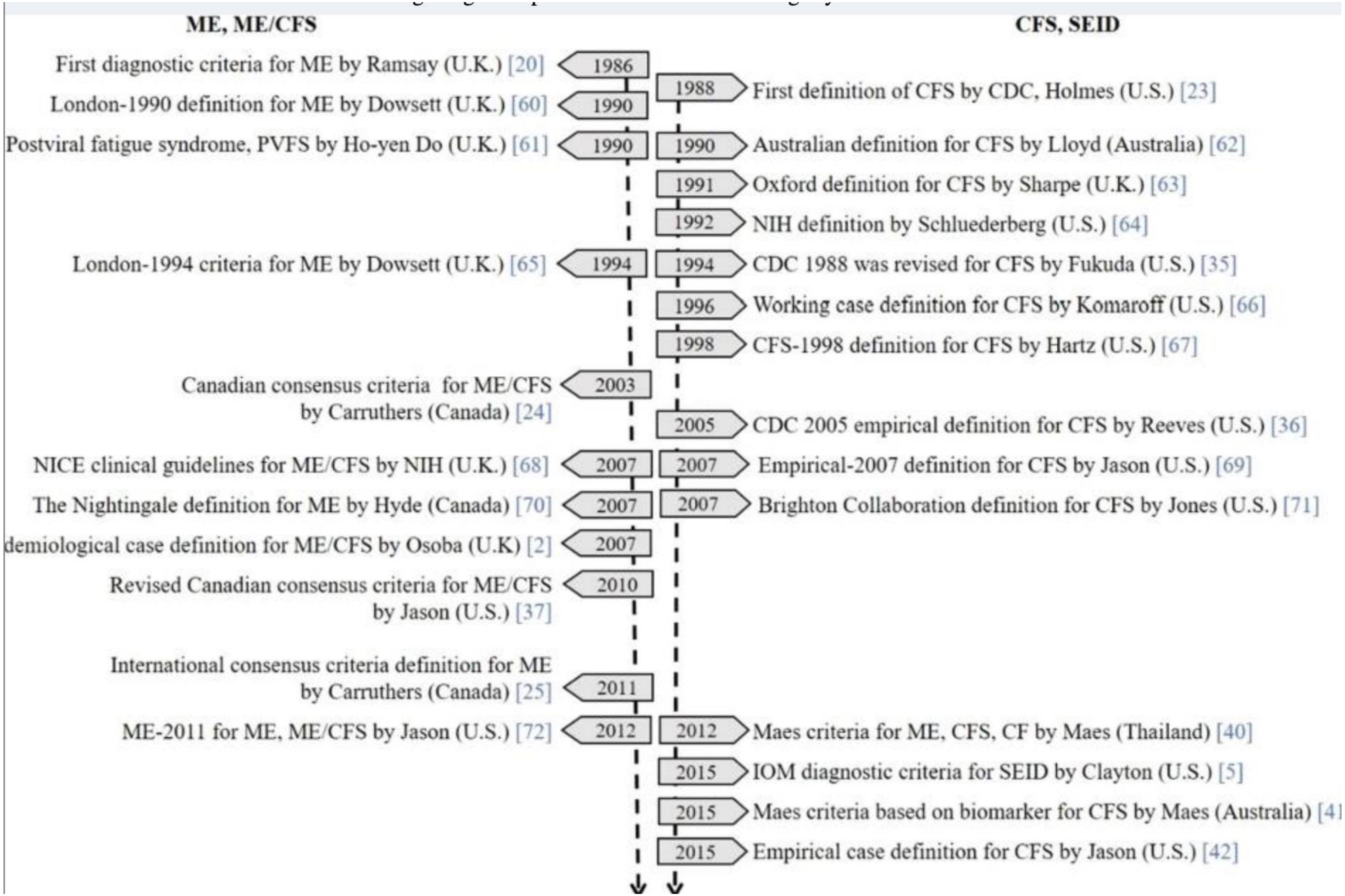
Importance of accurate diagnostics and criteria development

- ME/CFS is defined by its clinical presentation, and has had dozens of case definitions confounding the literature before efforts at consensus resulted a consistent application of a research case definition.
- The field had a slow start, with an early focus on psychologic factors and interventions; this slowed funding of the pathogenesis studies that have since demonstrated the biologic underpinnings of the illness. This emphasis still remains in the UK, with clinical guidelines adopted in the UK and much of the EU that emphasize coping, pacing and exercise (NICE Guidelines), while the US moves to mediator targeted therapies.
- At a policy level, changing the focus of the program announcements that result in funding to biologic underpinnings and subgrouping strategies resulted in the big advances in the field



Lim EJ, Son CG. Review of case definitions for myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). J Transl Med. 2020 Jul 29;18(1):289.

Challenges in ME/CFS Diagnostics

- Heterogeneous nature of ME/CFS symptoms, subgrouping strategies: focus on groupings that make clinical sense and direct interventive approaches (e.g. neuroinflammatory predominant, dysautonomia predominant, FM tender points, restorative sleep indices etc)
- Lack of biomarkers and objective diagnostic tests to define the overall group, though biomarkers to define subgroups exist. (eg MRS spectroscopy and lab measures for oxidative stress; poor NK cell function, cytokine panels, and immune senescence markers for chronic antigen exposure)

1994 International Research Case Definition

Overview of Inclusions

- Fatigue + 4 out of 8 case-defining symptoms:
- PEM lasting more than 24 hours
- Unrefreshing sleep
- Significant impairment of short-term memory or concentration
- Muscle pain
- Pain in the joints without swelling or redness
- Headaches of a new type, pattern, or severity
- Tender lymph nodes in the neck or armpit
- A sore throat that is frequent or recurring

Duration

- ≥ 6 months (clinical evaluation starts at one month – prolonged fatigue)

References

Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: A comprehensive approach to its definition and study. *Ann Intern Med* 121:953-959, 1994.

Reeves WC, Lloyd A, Vernon SD, Klimas N, Jason LA, Bleijenberg G, Evengard B, White PD, Nisenbaum R, Unger ER; International Chronic Fatigue Syndrome Study Group. Identification of ambiguities in the 1994 chronic fatigue syndrome research case definition and recommendations for resolution. BMC Health Serv Res. 2003 Dec 31;3(1):25

2003 Canadian Consensus

Overview of Inclusions

Fatigue, post-exertional malaise ±fatigue, sleep dysfunction, and pain; have 2 or more neurological/cognitive manifestations and 1or more from 2 categories of autonomic, neuroendocrine and immune manifestations

Duration

- ≥ 6 months (preliminary diagnosis can be earlier)

Fatigue

Significant new onset persistent or recurrent physical or mental fatigue

- Unexplained after clinical evaluation
- Substantially reduces activity level

Post-exertional malaise

- Required

Minimum number of symptoms—8

Reference

Carruthers BM, Jain AK, DeMeirleir KL, et al. Myalgic encephalomyelitis/chronic fatigue syndrome: Clinical working case definition, diagnostic and treatment protocols. *J Chronic Fatigue Syndrome* 11:7-115, 2003.

2015 IOM Clinical Case Definition: Evidence based

- The 2015 IOM diagnostic criteria for ME/CFS in adults and children state that **three symptoms and at least one of two additional manifestations are required** for diagnosis. The three required symptoms are:

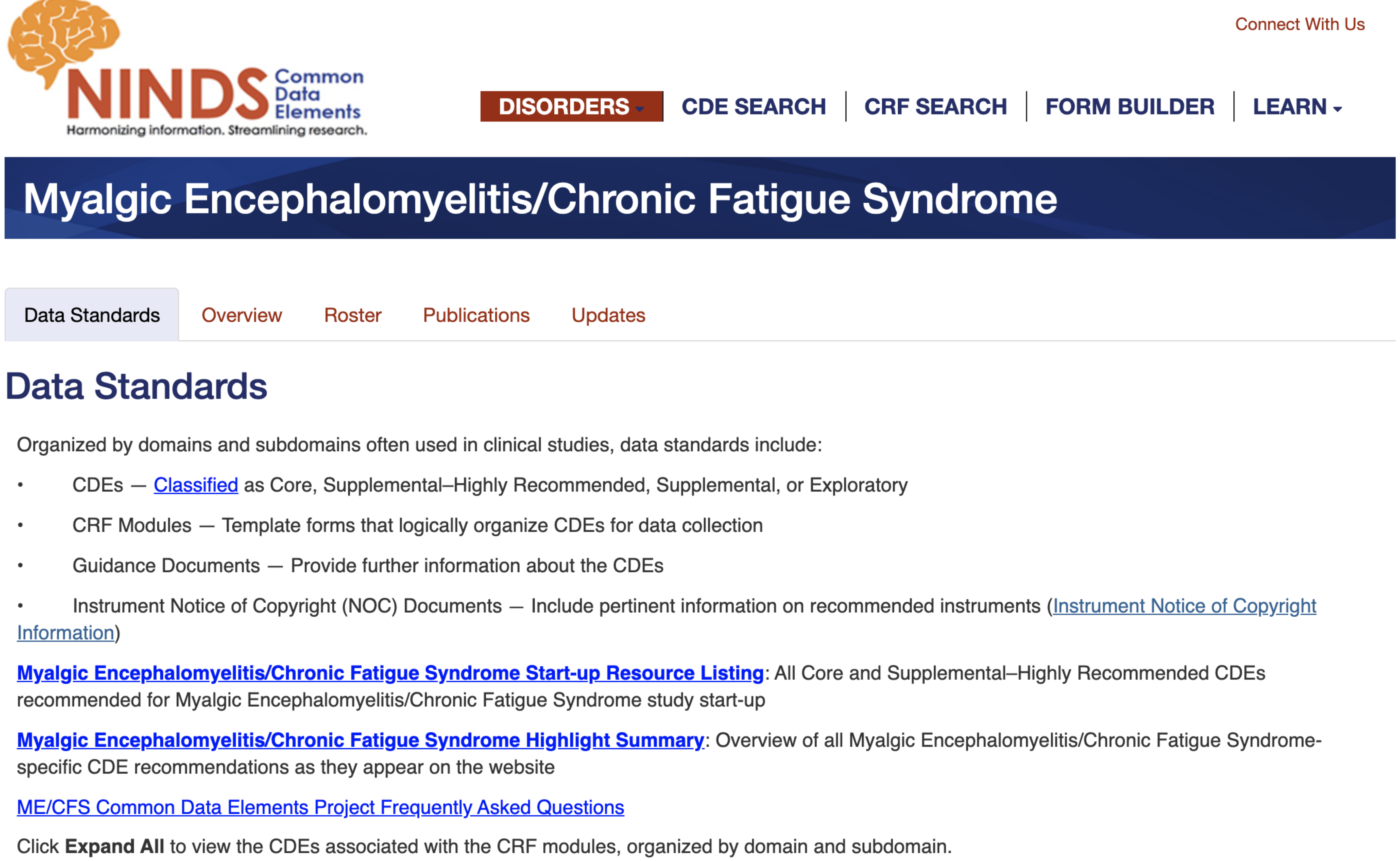
1. **A substantial reduction or impairment in the ability to engage in pre-illness levels of activity** (occupational, educational, social, or personal life) that:
    1. lasts for more than 6 months
    2. is accompanied by fatigue that is often profound, of new onset, not relieved by rest and not caused by excessive exertion
2. **Post-exertional malaise (PEM)***—worsening of symptoms after physical, mental, or emotional exertion that would not have caused a problem before the illness.
3. **Unrefreshing sleep*—**patients with ME/CFS may not feel better or less tired even after a full night of sleep despite the absence of specific objective sleep alterations.

- At least one of the following **two additional manifestations** must be present:

1. **Cognitive impairment*—**patients have problems with thinking, memory, executive function, and information processing, as well as attention deficit and impaired psychomotor functions. All can be exacerbated by exertion, effort, prolonged upright posture, stress, or time pressure, and may have serious consequences on a patient’s ability to maintain a job or attend school full time.
2. **Orthostatic intolerance—**patients develop a worsening of symptoms upon assuming and maintaining upright posture as measured by objective heart rate and blood pressure abnormalities during standing, bedside orthostatic vital signs, or head-up tilt testing.

Primary and Secondary Outcome Variables

- Common Data Elements project – now in its first revision; used as a starting point for the Gulf War Illness CDE
- No consensus on a single primary outcome variable, this is slowing clinical trials approvals and allowing comparable results
- Need to correlate biomarkers with clinical outcomes for accurate surrogates of clinical response (eg HIV Viral load rather than death/ infection rate moved the needle faster)



Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Data Standards

Organized by domains and subdomains often used in clinical studies, data standards include:

- CDEs — Classified as Core, Supplemental–Highly Recommended, Supplemental, or Exploratory
- CRF Modules — Template forms that logically organize CDEs for data collection
- Guidance Documents — Provide further information about the CDEs
- Instrument Notice of Copyright (NOC) Documents — Include pertinent information on recommended instruments (Instrument Notice of Copyright Information)

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Start-up Resource Listing: All Core and Supplemental–Highly Recommended CDEs recommended for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome study start-up

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Highlight Summary: Overview of all Myalgic Encephalomyelitis/Chronic Fatigue Syndrome-specific CDE recommendations as they appear on the website

ME/CFS Common Data Elements Project Frequently Asked Questions

Click **Expand All** to view the CDEs associated with the CRF modules, organized by domain and subdomain.

Lessons Learned from ME/CFS

- Importance of stakeholder involvement (patients, clinicians, researchers).
- Need for multidisciplinary approaches (biomedical, psychosocial)
- Iterative refinement of criteria based on new evidence
- A process to perform gaps analyses, realigns priorities, and focuses funding in ways that will improve the health of patients suffering rom these illnesses

Learning from the the ME/CFS experience: basic principles

- The importance of an easily taught **clinical** case definition that is more inclusive. (impact on confidence of clinicians in recognizing he illness, as well as impact on patient in other issues e.g. disability eligibility)
- The need of a **research** case definition to be tighter with potential subgrouping criteria that assist in finding key pathogenesis features and defining subgroups that would be more likely to respond to proposed treatments (eg autoimmune or viral reactivation subgroup criteria in trial designs that target these mediators)
- The Common Data Elements (NINDS) process also greatly assisted the research process in requiring comparable measures of domains, severity and outcomes. The ME/CFS studies remain complicated by having several acceptable research case definitions

Conclusion

- Early consensus on research case definitions and common data element platforms are important to prevent long delays in comparable studies and allow meta analyses in a rapidly evolving literature
- Clinical case definitions are equally important in allowing medical education to go forward and allowing patients from experience long delays and misdiagnoses.
- ME/CFS research methodologic advances can be a starting point, the evolution of case definitions and the Common Data Elements Platform have allowed critical advances
- Research priorities should include improving Lyme disease diagnostics
- Role of advanced technologies (e.g., proteomics, genomics) in biomarker discovery
- Potential impact on patient outcomes and treatment strategies

Conclusion

- Lumping vs splitting - lumping the post infectious illnesses together for the purpose of advancing our understanding of common pathways and intervention points; but understanding that their may be important differences
- Splitting into subgroups that allow targeted treatments to be developed
- Importance of lessons learned from ME/CFS research, what slowed it down and what is speeding it up
- Call to action for continued research and collaboration