

"Research Update on Adult ME/CFS"



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Stanford ME/CFS Advisory Board

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The ME/CFS field appears to be at a historical crossroad

NIH funding

Research findings continue to shed further light into what is biologically abnormal in ME/CFS

Non-ME/CFS meetings have opened the doors to ME/CFS themes

However, all this potential cascade of good news can be threatened by the fact that many of the traditional ME/CFS investigators and clinicians are retiring and a cadre of young crusaders is needed

NIH centers for ME/CFS syndrome research

Three Collaborative Research Centers (CRC) and a Data Management Coordinating Center (DMCC).

These important grants will provide a strong foundation for expanding research in ME/CFS, and lead to knowledge about the causes and ways to treat people affected by this mysterious, heartbreaking, and debilitating disease," said NIH Director Francis S. Collins, M.D., Ph.D.

CRCs embrace community engagement and involvement of the ME/CFS advocacy groups and individuals with ME/CFS.

Four major NIH grants were awarded

Cornell ME/CFS Collaborative Research Center. Maureen Hanson, Ph.D., Cornell University: brain imaging, genetic, immunological tools in the setting of PEM.

Center for Solutions for ME/CFS. W. Ian Lipkin, M.D., Columbia University: Role of bacteria and viruses, genetics, metabolomics to define ME/CFS subgroups and diagnostic tests.

Topological Mapping of Immune, Metabolomic and Clinical Phenotypes to Reveal ME/CFS Disease Mechanisms. Derya Unutmaz, M.D., The Jackson Laboratory, Farmington, Connecticut.

Data Management and Coordinating Center (DMCC) for the ME/CFS Collaborative Research Centers. Principal Investigator: Rick L. Williams, Ph.D. Research Triangle Institute, Research Triangle, North Carolina

Thousands of published papers show objective abnormalities

2015 IOM: 2-day exercise testing, tilt table, natural killer cell activity supportive of an ME/CFS diagnosis. More studies/ replication needed.

Abnormalities (preliminary, high signal/noise ratio) in immunological, metabolomic, microbiome, brain imaging studies

Obstacles: multi-system/chronic disease, heterogeneity among patients, lack of standardization of research methods, sample sizes, appropriate technology.

Prospective studies: $\approx 10\%$ of patients develop ME/CFS after EBV, Q fever, West Nile virus fever, Ross river virus, influenza etc.).

Retrospective studies: Up to 80% of patients recall their ME/CFS started after infectious event.

Recent findings from ME/CFS studies

2016 to 2017

Metabolic profiling indicates impaired pyruvate dehydrogenase function in myalgic encephalopathy/chronic fatigue syndrome.

JCI Insight. 2016;1(21): e89376. doi:10.1172/jci.insight.89376.

Øystein Fluge, Olav Mella, Karl J. Tronstad et al

Reduction of amino acids that fuel oxidative metabolism via the Krebs cycle, mainly in female ME/CFS patients.

The amino acid pattern suggested functional impairment of pyruvate dehydrogenase (PDH, critical enzyme for cellular respiration), in PBMCs from both sexes.

Myoblasts grown in presence of serum from patients with severe ME/CFS showed metabolic adaptations, including increased mitochondrial respiration and excessive lactate secretion.

Inadequate ATP generation by oxidative phosphorylation and excessive lactate generation upon exertion.

Antibodies to β adrenergic and muscarinic cholinergic receptors in patients with Chronic Fatigue Syndrome.

Brain, Behavior, Immunity. 2016 Feb;52:32-39. Loebel M, Scheibenbogen C, et al.

Antibodies against β_2 , M3 and M4 receptors were significantly elevated in CFS patients

Antibodies against α adrenergic, dopamine, serotonin, angiotensin, and endothelin receptors were not different between patients and controls.

29.5% of patients with CFS had elevated antibodies against one or more M acetylcholine and β adrenergic receptors which are potential biomarkers for response to B-cell depleting therapy.

Myalgic encephalomyelitis/chronic fatigue syndrome and gulf war illness patients exhibit increased humoral responses to the herpesviruses-encoded dUTPase: Implications in disease pathophysiology.

Halpin P, Ariza ME et al. J Med Virol. 2017 Sep;89(9):1636-1645. doi: 10.1002/jmv.24810. Epub 2017 Apr 26.

A significant percentage of patients with ME/CFS (30.91-52.7%) and GWI (29.34%) simultaneously produce antibodies against multiple human herpesviruses-encoded dUTPases and/or the human dUTPase when compared to controls (17.21%).

GWIs patients exhibited significantly higher levels of antibodies to the HHV-6 and human dUTPases than controls ($P = 0.0053$ and $P = 0.0036$, respectively)

ME/CFS cohort had higher anti-EBV-dUTPase antibodies than in both GWI patients ($P = 0.0008$) and controls ($P < 0.0001$) as well as significantly higher anti-human dUTPase antibodies than in controls ($P = 0.0241$).

Clinically proven mtDNA mutations are not common in those with chronic fatigue syndrome.

Schoeman EM, Elson JL et al. BMC Medical Genetics (2017) 18:29.

Fatigue is common and often severe in patients with mitochondrial disease

It has been suggested that some CFS patients harbor clinically proven mtDNA mutations.

MtDNA sequencing of 93 CFS patients from the United Kingdom (UK) and South Africa (RSA) was performed using an Ion Torrent Personal Genome Machine (more than 200 clinically proven mtDNA mutations point mutations have been identified).

Complete mtDNA sequence of 93 CFS patients from the UK and RSA, without finding evidence of clinically proven mtDNA mutations.

Cytokine Inhibition in Patients With Chronic Fatigue Syndrome: A Randomized Trial

Roerink ME, Van der Meer JWM, et al. Annals of Internal Medicine. 2017
2017 Apr 18;166(8):557-564. doi: 10.7326/M16-2391

50 women aged 18 to 59 years with CFS and severe fatigue leading to functional impairment.

Participants were randomly assigned to daily subcutaneous anakinra, 100 mg (n = 25), or placebo (n = 25) for 4 weeks and were followed for an additional 20 weeks after treatment (n = 50).

There were no clinically important or statistically significant differences between groups in CIS-fatigue score at 4 weeks (mean difference, 1.5 points [95% CI, -4.1 to 7.2 points]) or the end of follow-up.

Physiological measures in participants with chronic fatigue syndrome, multiple sclerosis and healthy controls following repeated exercise: a pilot study

Hodges LD, Nielsen T, Baken D. Clin Physiol Funct Imaging 2017 Aug 7. doi: 10.1111/cpf.12460

To compare physiological responses of chronic fatigue syndrome (CFS/ME), multiple sclerosis (MS) and healthy controls (HC) following a maximal incremental cycle exercise test on day 1 and again 24 h later

On day 2, both CFS and MS had significantly reduced max workload (WL) compared to HC.

On day 2, significant differences were apparent in WL between CFS and CFS HC (93 ± 37 W, 132 ± 42 W, $P < 0.042$).

MS demonstrated a decreased WL compared to MS HC on both days of the study (D1 81 ± 30 W, 116 ± 30 W; D2 84 ± 29 W, 118 ± 36 W); however, patients with MS were able to achieve a higher WL on day 2 alongside MS HC.

Immune network analysis of cerebrospinal fluid in myalgic encephalomyelitis/chronic fatigue syndrome with atypical and classical presentations

Hornig M, Lipkin WI, et al. Transl Psychiatry 2017 Apr 4;7(4):e1080. doi: 10.1038/tp.2017.44.

Cerebrospinal fluid (CSF) from 32 cases with classical ME/CFS and 27 cases with atypical ME/CFS using a 51-plex cytokine assay.

Associations between the atypical ME/CFS phenotype and lower CSF levels of the inflammatory mediators, interleukin 17A and CXCL9.

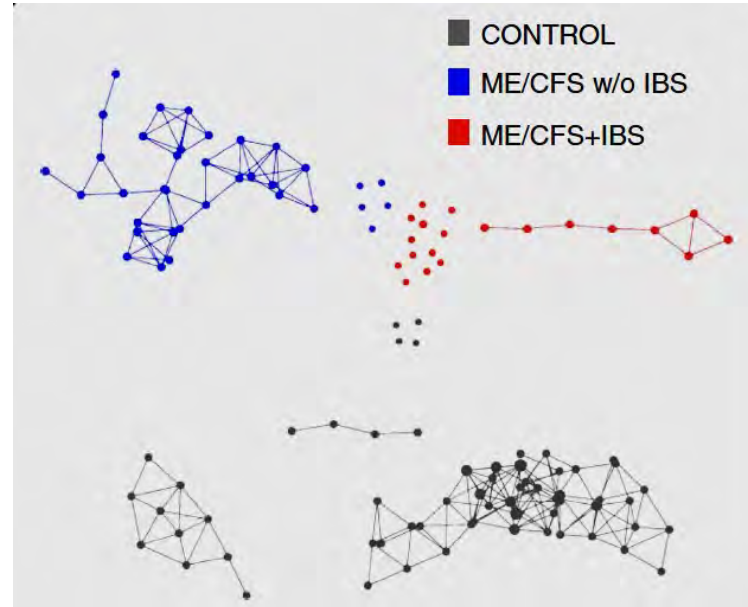
Interleukin 1 receptor antagonist appeared to be a negative regulator in classical ME/CFS, with patterns suggestive of disturbances in interleukin 1 signaling and autoimmunity-type patterns of immune activation.

Fecal metagenomic profiles in subgroups of patients with myalgic encephalomyelitis/chronic fatigue syndrome.

Nagy-Szakal D, Lipkin WI et al. Microbiome 2017 Apr 26;5(1):44. doi: 10.1186/s40168-017-0261-y

Rigorous clinical characterization, fecal bacterial metagenomics, and plasma immune molecule analyses in 50 ME/CFS patients and 50 healthy controls frequency-matched for age, sex, race/ethnicity, geographic site, and season of sampling.

Diagram with molecular patterns: ME/CFS w/o IBS ME/CFS+ IBS, and Control.



Cytokine signature associated with disease severity in chronic fatigue syndrome patients.

Montoya JG and Davis MM. PNAS 2017 Aug 22;114(34):E7150-E7158. doi: 10.1073/pnas.1710519114. Epub 2017 Jul 31.

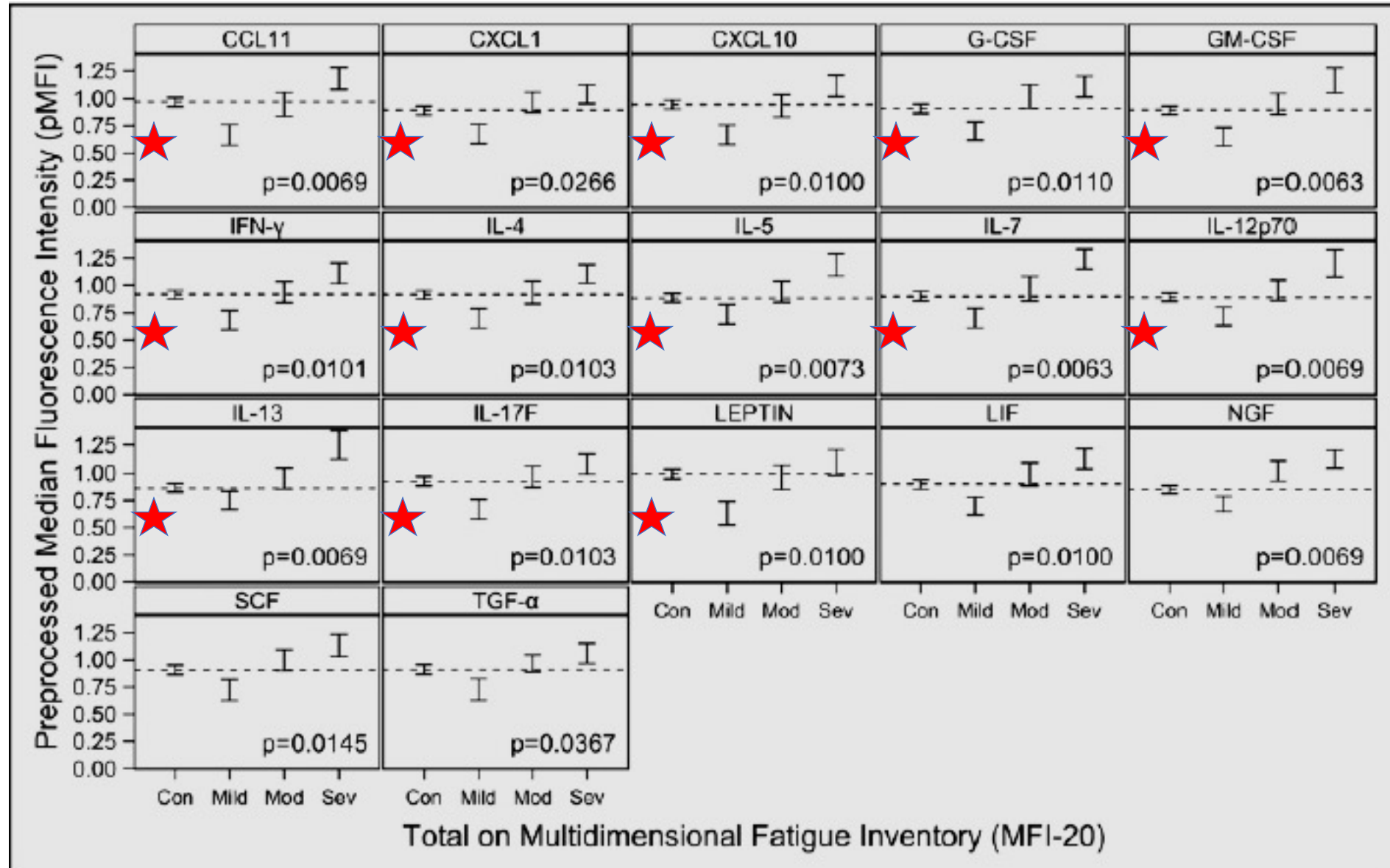
Cytokines of 192 ME/CFS patients and 392 healthy controls were measured using a 51-multiplex array on a Luminex system.

On average, TGF- β was elevated ($P = 0.0052$) and resistin was lower ($P = 0.0052$) in patients.

Seventeen cytokines had a statistically significant upward linear trend that correlated with ME/CFS severity.

Of the 17 cytokines that correlated with severity, 13 are proinflammatory
Only CXCL9 (MIG) inversely correlated with fatigue duration.

Seventeen cytokines correlate with severity, thirteen are pro-inflammatory



Metabolic features of chronic fatigue syndrome.

Naviaux RK, Gordon E, et al. PNAS 2016 Sep 13;113(37):E5472-80. doi: 10.1073/pnas.1607571113

Targeted, broad-spectrum metabolomics in 45 ME/CFS patients (23 women) vs. 39 age- and sex- matched normal controls (21 women)

Patients with CFS showed abnormalities in 20 metabolic pathways.

Eighty percent of the diagnostic metabolites were decreased, consistent with a hypometabolic syndrome.

Pathway abnormalities included sphingolipid, phospholipid, purine, cholesterol, microbiome, pyrroline-5-carboxylate, riboflavin, branch chain amino acid, peroxisomal, and mitochondrial metabolism.

Can patients with chronic fatigue syndrome really recover after graded exercise or cognitive behavioural therapy? A critical commentary and preliminary re-analysis of the PACE trial.

Wilshire C and McGrath S. (2017). Fatigue: Biomedicine, Health & Behavior, 5:1, 43-56, DOI: 10.1080/21641846.2017.1259724

The PACE trial is the largest clinical trial ever conducted on patients with CFS

PACE trial reported recovery rates for GET, CBT, and non-therapy group were: 22%, 22%, 7%, respectively.

New figures based on a definition of recovery specified in the original trial protocol: 4%, 7% and 3%, respectively.

CDC removes GET and CBT as treatment options

Defining and measuring recovery from myalgic encephalomyelitis and chronic fatigue syndrome: the physician perspective.

Devendorf AR, Jason AL, et al. Disabil Rehabil. 2017 Oct 5:1-8. doi: 10.1080/09638288.2017.1383518.

For physicians,

Recovery: complete symptom remission and a return to premorbid functioning (adjusted for with age)

Significant improvement: substantial reduction in symptoms with considerable functional gains, where patients may operate in daily life but still must cope or be treated.

Provide recommendations and approaches for measuring: daily functioning, symptomatology, quality of life, and physical functioning.

Recovery from ME/CFS should be viewed as multidimensional, considering patients' daily life, psychosocial functioning, and overall physical functioning.

Access to Medical Care for Individuals with Myalgic Encephalomyelitis and Chronic Fatigue Syndrome: A Call for Centers of Excellence

Sunnquist M, Nicholson L, Jason LA, Friedman KJ. Mod Clin Med Res 2017 Apr;1(1):28-35

Chronic, multi-system, disabling nature of ME and CFS calls for expert care.

Fifty-four percent of U.S. patients report dissatisfaction with their medical care for ME/CFS: Physicians' inadequate training in treating ME/CFS patients.

Seventy-one percent of participants need to see four or more physicians in order to receive a diagnosis.

Of 898 participants, less than half had ever seen an ME or CFS specialist, though 99% of participants were interested in specialist care.

Patients cite geographic and financial barriers as most frequently precluding access to ME/CFS specialists.

Satisfaction with specialist care greatly exceeded satisfaction with non-specialist care.

ME/CFS patients are a medically-underserved population, due to lack of available care.

Mortality in Patients with Myalgic Encephalomyelitis and Chronic Fatigue Syndrome.

McManimen SL, Jason LA et al. Fatigue 2016; 4(4):195-207. doi: 10.1080/21641846.2016.1236588

Significantly increased risk of earlier mortality?

	ME/CFS	US Pop.
All-cause	55.9	73.5
Cardiovascular-related	58.8	77.7
Suicide	41.3	47.4
Cancer-related	66.3	71.1

The results suggest there is an increase in risk for earlier mortality in patients with ME and CFS. Due to the small sample size and over-representation of severely ill patients, the findings should be replicated to determine if the directional differences for suicide and cancer mortality are significantly different from the overall U.S. population

Mortality of people with chronic fatigue syndrome: a retrospective cohort study in England and Wales from the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) Clinical Record Interactive Search (CRIS) Register

Roberts E, Hotopf M et al. The Lancet 2016; 387: 1638-1643.

Calculated standardised mortality ratios (SMRs) for all-cause, suicide-specific, and cancer-specific mortality for a 7-year observation period using the number of deaths observed in SLaM records compared with age-specific and sex-specific mortality statistics for England and Wales

2147 cases of chronic fatigue syndrome from CRIS and 17 deaths from Jan 1, 2007, to Dec 31, 2013.

A significant increase in suicide-specific mortality (SMR 6·85, 95% CI 2·22-15·98; p=0·002).

FOCiS[®]2017

CHICAGO JUNE 14-17

Precision in Immunology 

SCIENTIFIC PROGRAM



12:45pm – 4:45 pm

Insights into the Immunology of Chronic Fatigue Syndrome

Organized by the Division of Allergy, Immunology & Transplantation, National Institute of Allergy and Infectious Diseases, National Institutes of Health
Stevens Salon C-3 (lower level)



12:45 pm Welcome and Objectives

Joseph Breen, PhD, National Institutes of Health and Vicky Whittemore, PhD, National Institute of Neurological Disorders and Stroke

12:50 pm The Public Health Problem of ME/CFS

Elizabeth Unger, MD, Centers for Disease Control and Prevention

1:15 pm Evidence of T Cell Activity in ME/CFS

Mark Davis, PhD, Stanford University

1:45 pm Immunological Characterization of ME/CFS Cases and Controls from the UK ME/CFS Biobank

Eleanor Riley, PhD, University of London

2:35 pm Coffee Break

2:55 pm Pathobiology of ME/CFS

Ian Lipkin, MD, Columbia University

3:35 pm Circulating Cytokine Signatures Associated with ME/CFS Severity and Duration

Jose Montoya, MD, Stanford University

4:15 pm Question/Answer Forum

SESSION - PANEL DISCUSSION



3038.0: Special Session in Epidemiology: Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Fact, Fiction, Findings

Moderator



Lily Chu
Stanford University School of Medicine

Presentations

08:30 AM

3038.0 Introductory Remarks

08:35 AM



3038.0 What Do We Know About the Epidemiology of ME/CFS? Fact vs. Fiction
José Montoya, MD, FACP, FIDSA, Stanford University School of Medicine, Stanford, CA

08:55 AM



3038.0 Onset Patterns and Course of ME/CFS
Lily Chu, MD, MSHS, Stanford University School of Medicine, Stanford, CA

09:15 AM



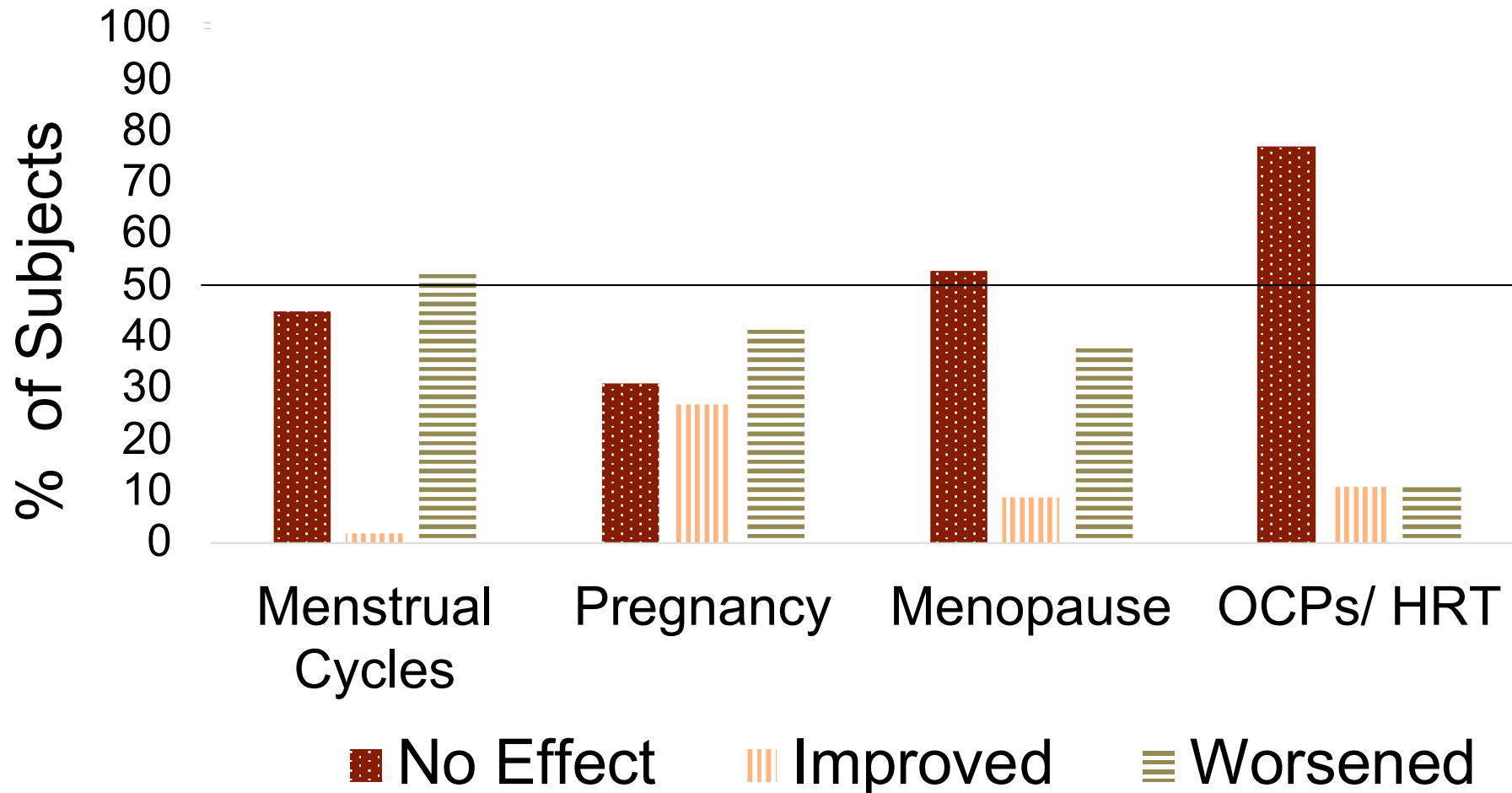
3038.0 Epidemiologic Approaches to Capturing the Heterogeneity of ME/CFS
Elizabeth Unger, MD, PhD, US Centers for Disease Control and Prevention, Atlanta, GA

09:35 AM

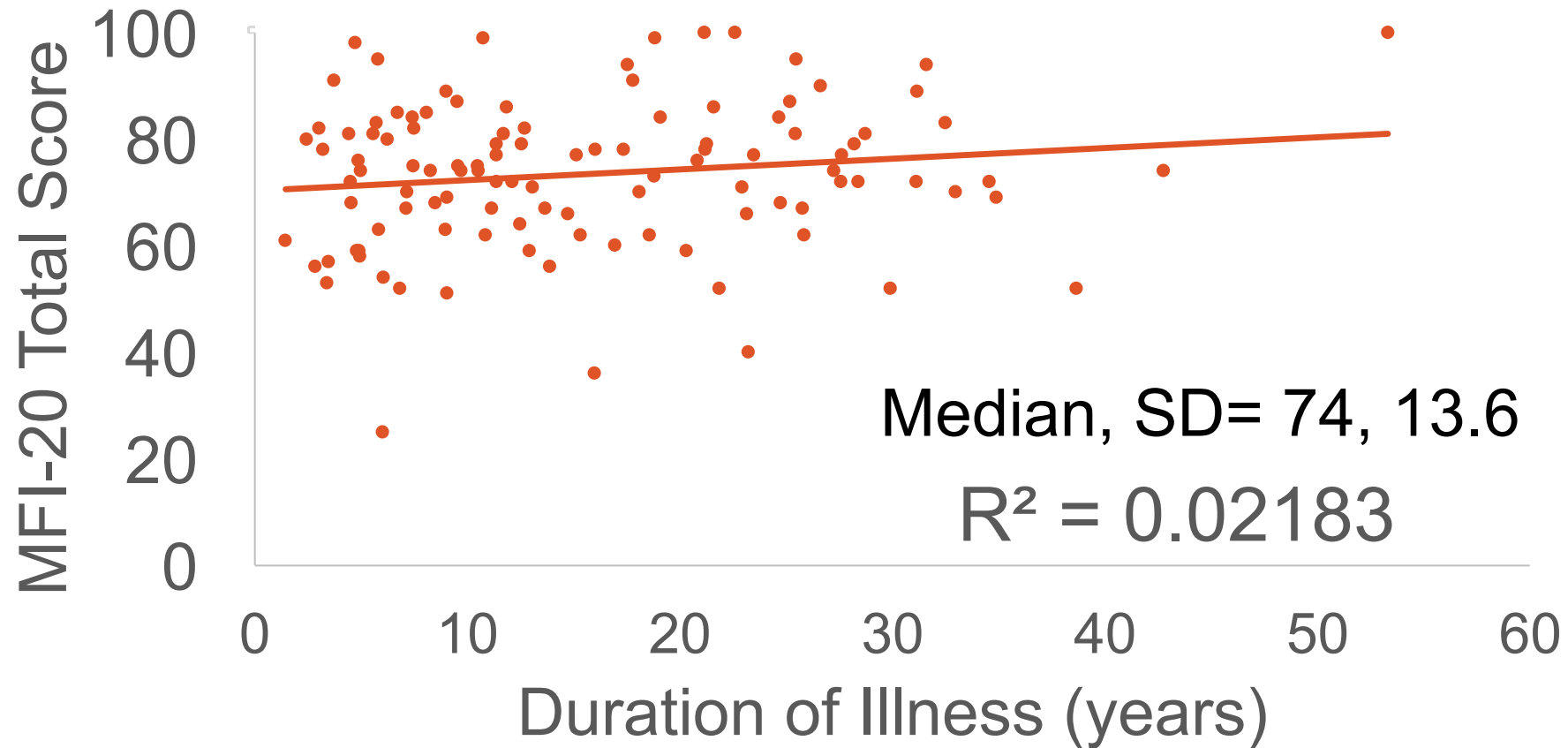


3038.0 Research and Service Needs for ME/CFS
Luis Nacul, MD, PhD, London School of Hygiene and Tropical Medicine, London WC1E 7HT, United Kingdom

Female Reproductive Events and ME/CFS



Fatigue Does Not Worsen With Illness Duration



Patients diagnosed with Myalgic encephalomyelitis/chronic fatigue syndrome also fit systemic exertion intolerance disease criteria.
Chu L et al. Fatigue: Biomedicine, Health & Behavior 2017; 5;2: 114-28

A total of 131 subjects fitting 1994 Fukuda CFS criteria at the time of study recruitment completed a survey of symptoms they experienced during their first 6 months of illness.

When severity/frequency thresholds were added to the Fukuda criteria, CCC and ME-ICC, the percentage of these subjects also fitting SEID criteria increased to 93%, 97%, and 95%.

SEID criteria categorize a similar percentage of subjects as Fukuda criteria. The advantage of SEID may be in its ease of use.

We must not desire all to begin by perfection. It matters little how we begin provided we be resolved to go on well and end well.

GET and CBT, or compelling patients to exercise is the wrong advice when patients are sick, at a plateau, or worsening

Abnormalities in ATP production, metabolomics, microbiome

Chronic inflammation as underlying pathophysiological process

Central and Autonomic nervous system

Role of Herpes viruses and other pathogens (known or unknown)

Exercise testing (single or repeated)



BEFORE ME/CFS

- Student Body President in HS
- Sorority
- Secretary of Fitness Club
- Hospital Volunteering
- Clinic Volunteering
- Pre-med Classes
- Social Life
- Mother had had ME/CFS but has fully recovered with valganciclovir



Back to almost normal but, how did it happen?

- 17 yr old: Hashimoto's Thyroiditis & Celiac Disease
 - 18 yr old: some fatigue.. Thyroid?
 - 19 yr old: Sophomore year final exams... crashed
 - 20 yr old: VERY SICK... but recovered through Valcyte and Colchicine
 - 21 yr old: back to school... over did it... relapse
 - 22 yr old: recovering again Valcyte and Celebrex
-



These observational studies led to the design and execution of
a randomized, double-blind, placebo controlled clinical trial

Journal of Medical Virology 85:2101–2109 (2013)

Randomized Clinical Trial to Evaluate the Efficacy and Safety of Valganciclovir in a Subset of Patients With Chronic Fatigue Syndrome

Jose G. Montoya,^{1,2*} Andreas M. Kogelnik,² Munveer Bhangoo,² Mitchell R. Lunn,^{2,3†} Louis Flamand,⁴ Lindsey E. Merrihew,^{2,3} Tessa Watt,² Jessica T. Kubo,^{1,3,5} Jane Paik,^{1,3,5} and Manisha Desai^{1,3,5}

¹*Department of Medicine, Stanford University School of Medicine, Stanford, California*

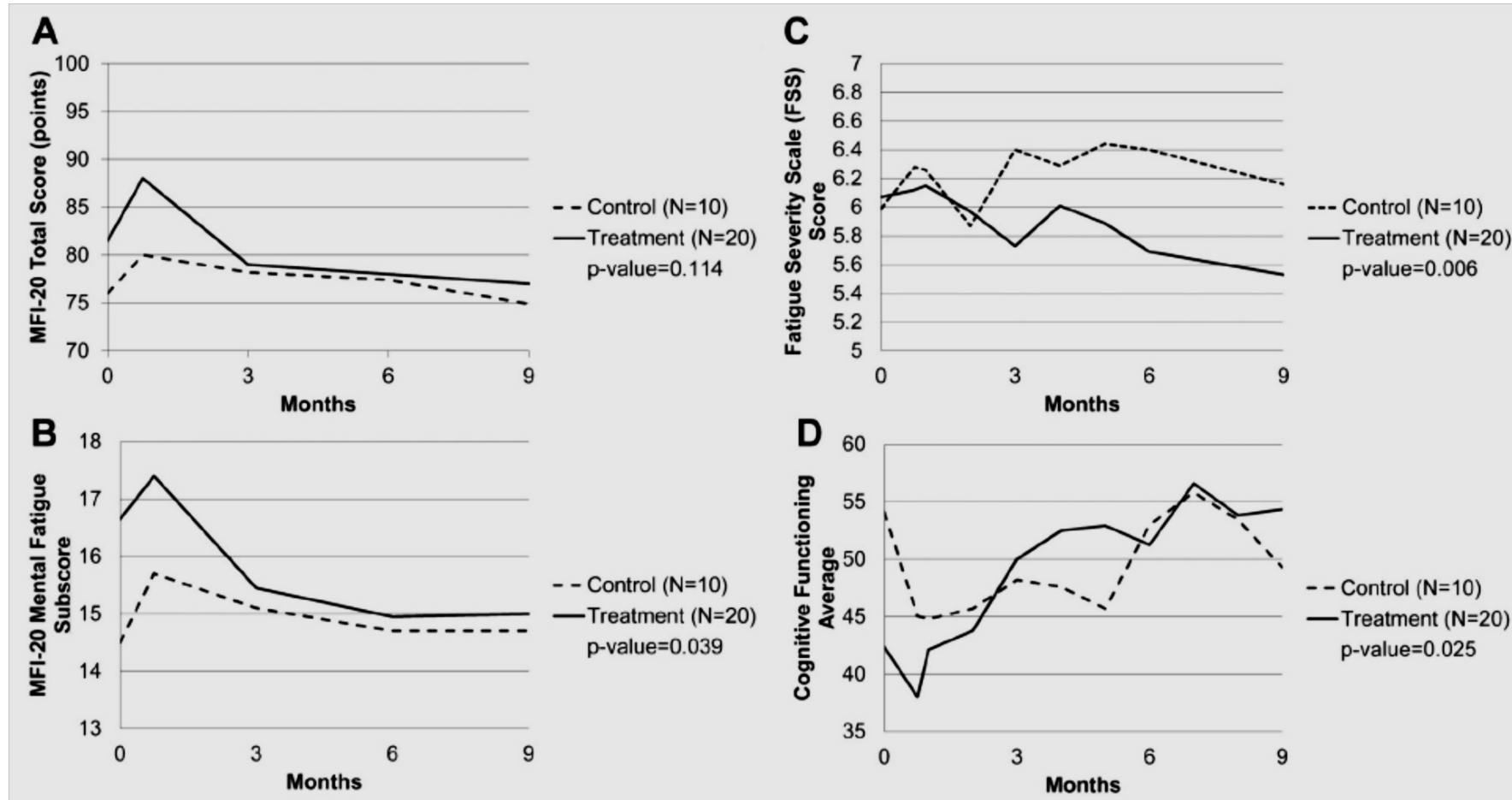
²*Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine, Stanford, California*

³*Stanford University School of Medicine, Stanford, California*

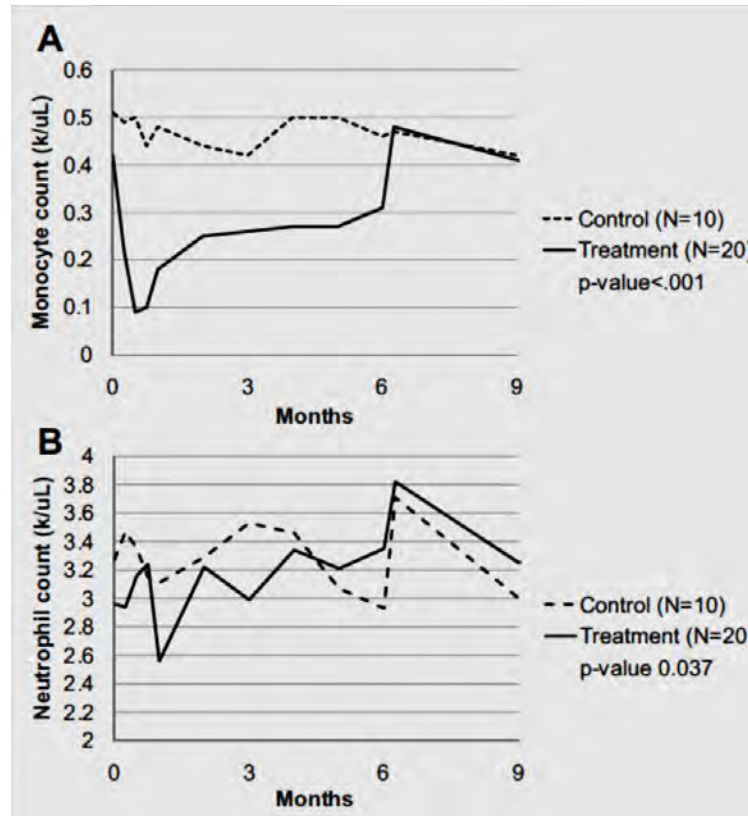
⁴*Department of Microbiology, Infectious Diseases and Immunology, Faculty of Medicine, Laval University, Québec, Canada*

⁵*Division of General Medicine Disciplines and Quantitative Sciences Unit, Stanford University School of Medicine, Stanford, California*

Results in this study support the view that CFS is a real disease that necessitates sound translational research and that can be amenable to medical interventions



This study also supports the view that CFS/ME is an inflammatory disease likely treatable with immunomodulation

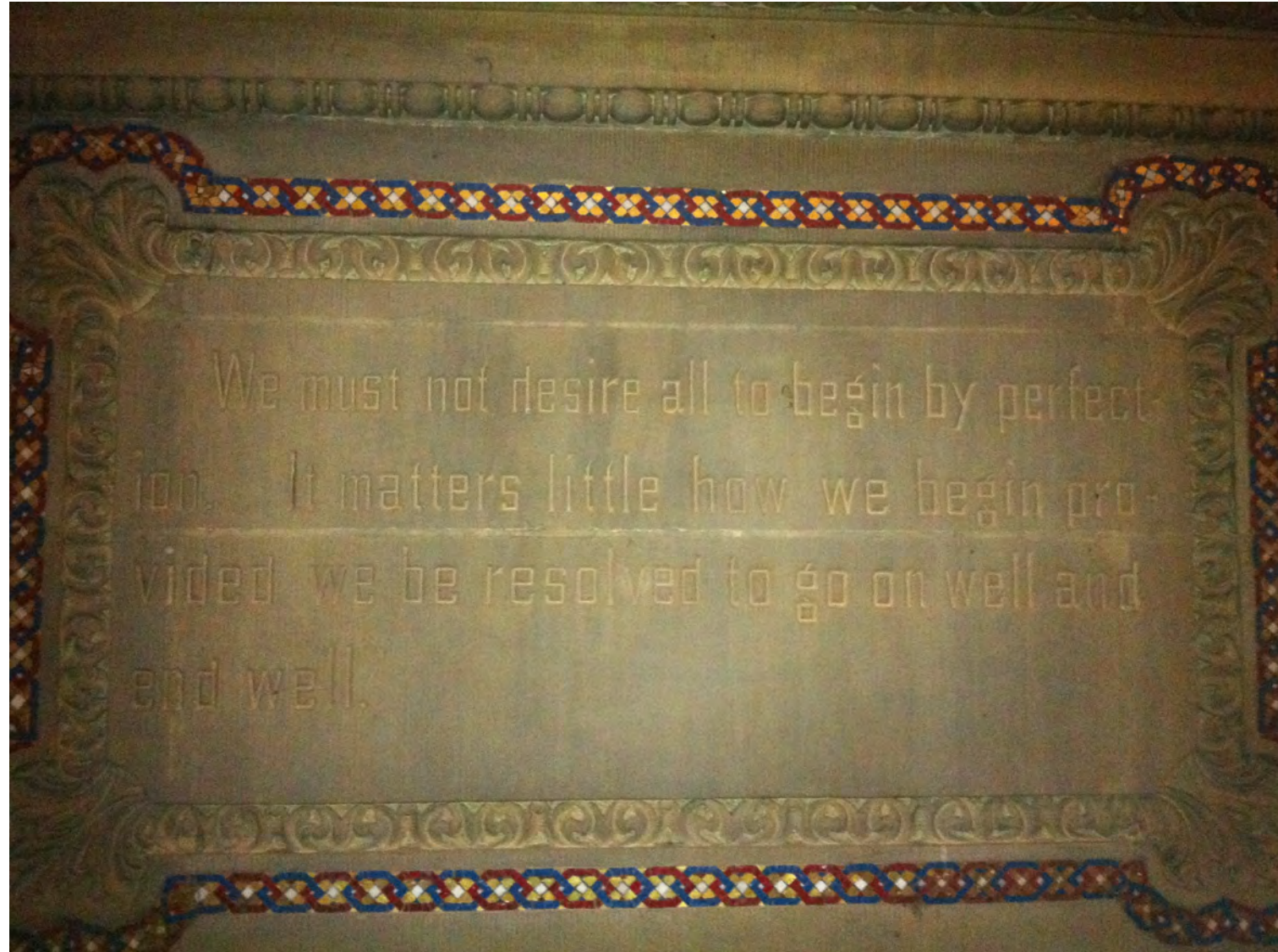


Th1 (IL-2, IL-12, IFN-g)

Th2 (IL-4, IL-5, IL-6, IL-10, IL-13)

A 2.52-fold increase over a 9-month period in Th1-type cytokines in the VGCV arm and a 1.48-fold decrease in the placebo arm ($P < 0.001$) was Found.

We must not desire all to begin by perfection. It matters little how we begin provided we be resolved to go on well and end well.



Daily cytokine fluctuations, driven by leptin, are associated with fatigue severity in chronic fatigue syndrome: evidence of inflammatory pathology.

Stringer EA, Younger JW, et al. J Transl Med 2013

