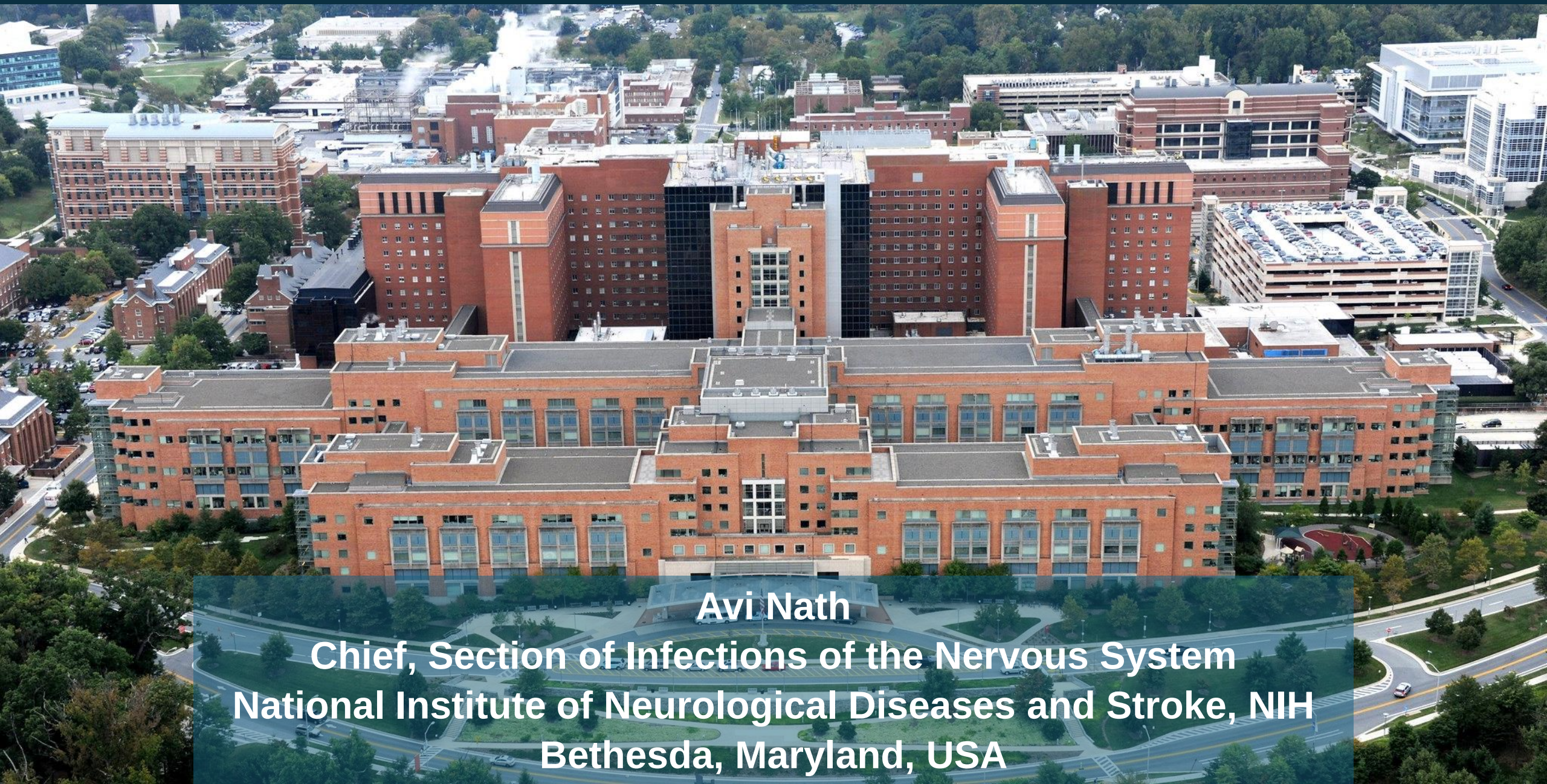
Elucidating Pathophysiology: Lessons from ME/CFS



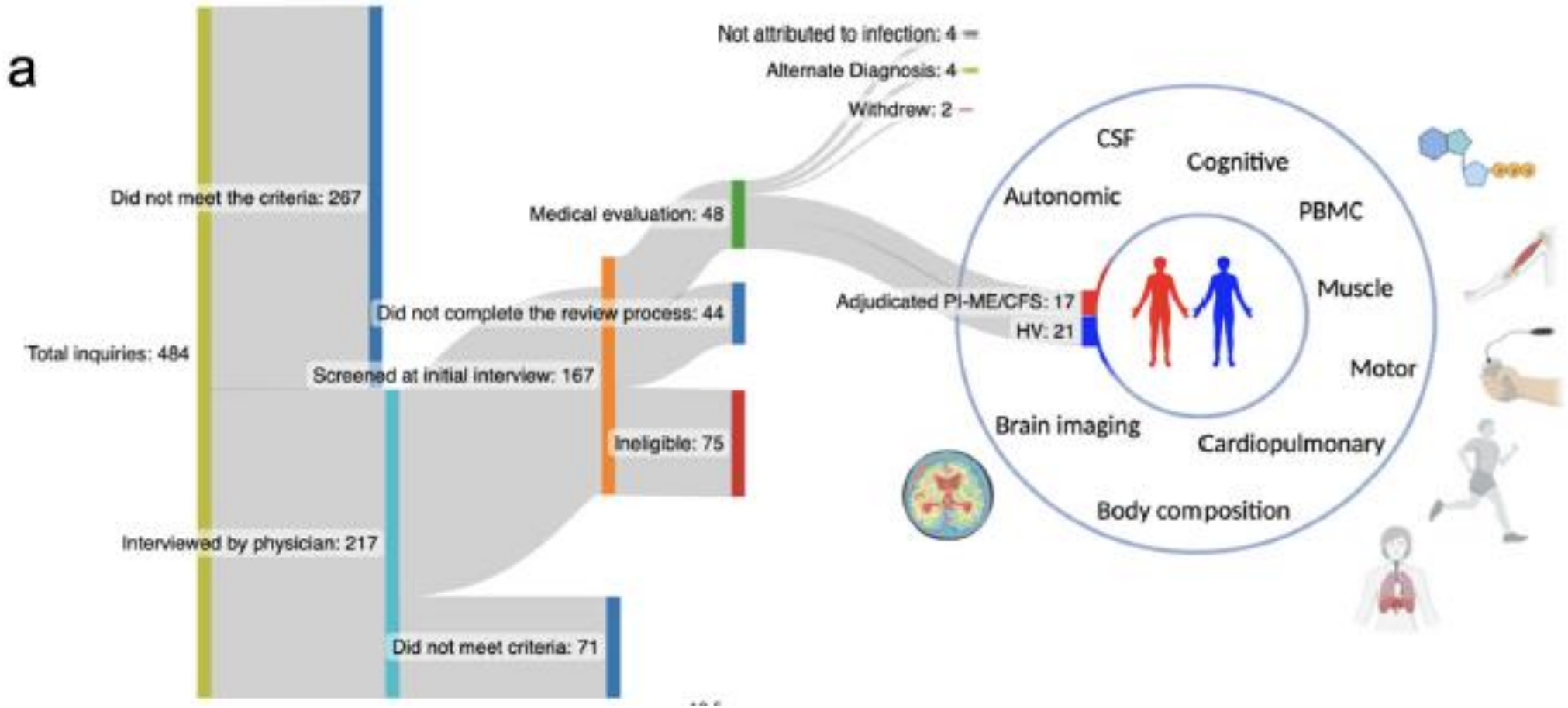
Avi Nath

Chief, Section of Infections of the Nervous System

National Institute of Neurological Diseases and Stroke, NIH

Bethesda, Maryland, USA

Recruitment of Post-Infection ME/CFS cohort



Walitt et al., Nat Commn 2024

Alternative diagnoses in persons with ME/CFS

ME/CFS Participants (27):

- Met criteria for substantial fatigue and post-exertional malaise (27)
- Withdrawal: 2
- Excluded based on NIH evaluation: 4
  - Cancer (1)
  - Atypical myositis (1)
  - Parkinsonism (1)
  - Primary Biliary Cholangitis (1)
- Adjudicated Out: 4
  - Not Post-Infectious (4)
- Total cases that meet IOM ME/CFS criteria: 25

- **Total Adjudicated PI-ME/CFS cases: 17**

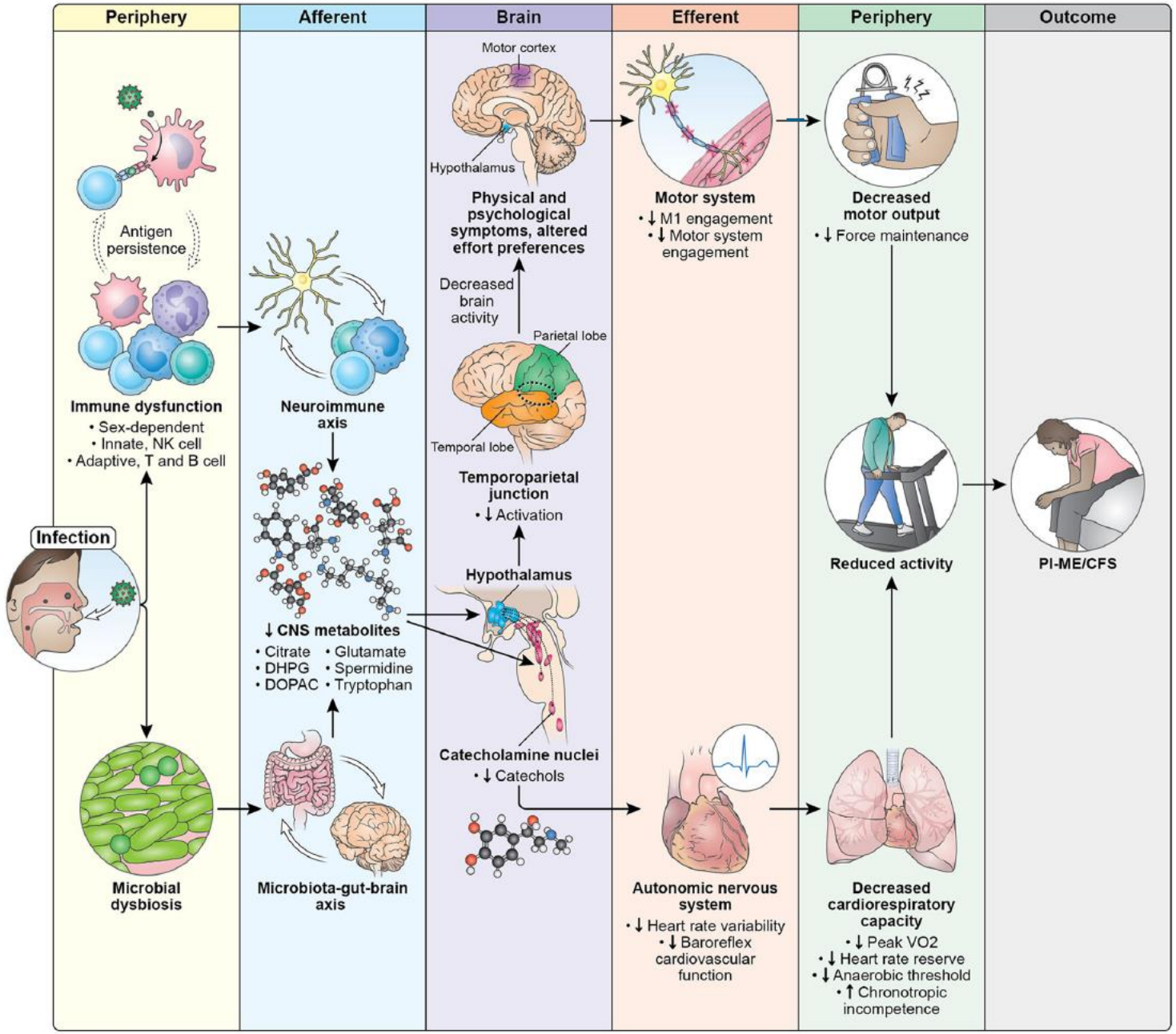
Types of Infections associated with ME/CFS

ME/CFS Participants (27):

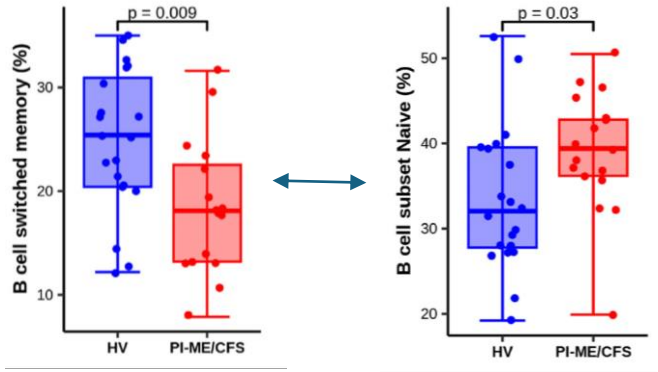
- 10 cases of mixed upper respiratory tract infections:
  - 8 pharyngitis
  - 2 sinusitis
  - 2 bronchitis
  - 2 otitis
- 3 cases of acute Epstein-Barr Virus infection
- 1 case of gastroenteritis
- 1 case of atypical hepatitis
- 2 cases of herpes zoster:
  - 1 herpes zoster ophthalmicus
  - 1 Ramsay Hunt syndrome

Deep Phenotyping Measurements

- History and Physical Examination
  - NINDS (Walitt)
  - CC (Solin/Deming)
- Neurological Examination
  - NINDS (Smith/Reoma/Nath)
- Neuropsychological Assessment:
  - NIMH: SCID-5 (Sinclair)
  - NIMH: Neurocognitive Testing (Snow/Tierney/Madian)
- Patient Reported Outcome Measures
  - NINDS: Questionnaires (Walitt, Calco, Chigurupati, Coleman, Horan, Vetter, Williams)
  - NINR: Symptom Interviews (Walitt, Kreskow)
  - NCCIH: Post-exertional malaise qualitative interviews (Stussman/Gavin)
- Dietary Evaluation:
  - CC Nutrition (Yang/Courville/Turner)
- Neuroimaging
  - CC Radiology: Contrast MRI (Butman)
- Body Composition
  - NIDDK: Dual-energy Xray absorptiometry (Chen/Brychta/Lamunion)
- Sleep
  - NIMH: Polysomnography (Buckley)
- Neurophysiology
  - Transcranial magnetic stimulation (Hallett/Horovitz/Bedard/Popa/McGurrin)
  - Functional magnetic resonance imaging (Hallett/Horovitz/Bedard/Popa/Knutson)
- Autonomic Testing
  - NINDS: Provocative Tilt Table Testing (Goldstein)
  - NHLBI: Heart Rate Variability (Levin/Cathay)
- Blood
  - DTM: Clinical laboratory testing
  - CHI: Proteomics (Apps, Chen, Cheung, Mukherjee, Sellers)
  - NIA: Lipidomics, Cellular Senescence (Ferruci, Moaddel)
  - NIDCR: Autoantibody testing (Burbelo)
  - NK cell function (Cincinnati Children's Hospital)
- Peripheral Blood Mononuclear Cells:
  - NINDS: iPSCs for neuronal disease and mouse disease models (Malik)
  - NINR: Mitochondrial Function (Saligan/Feng)
  - Transcriptomics: (Sack/Hassanzadeh/Singh)
- Cerebrospinal Fluid
  - NINDS: Flow cytometry (Jacobson, Akahata)
  - CHI: Proteomics (Apps, Chen, Cheung, Mukherjee, Sellers)
  - NINDS: Catecholamines (Goldstein)
  - Metabolomics: (Metabolon)
- Stool Measurements
  - NCI: Microbiome (McCulloch, Trincheri), NINR (Vizioli), CC (Barb)
  - NIEHS: Metabolomics (Mueller, Gabel)
- Skin Biopsy
  - JHU: Small fiber and sympathetic fiber density (Polydefkis)
- Muscle Biopsy
  - NIAMS: Pathology (Mammen, Pak, Munoz-Braceras)
  - NINDS: Transcriptomics (Mammen, Pinal-Fernandez)
  - Mitochondrial genetics (GeneDx)
  - NHLBI: Endoplasmic Reticular Stress (Hwang/Wang)



Walitt et al., Nature Commun 2024



Decreased ability to switch B cells from IgM to IgG

Poor immune response against a microbial antigen

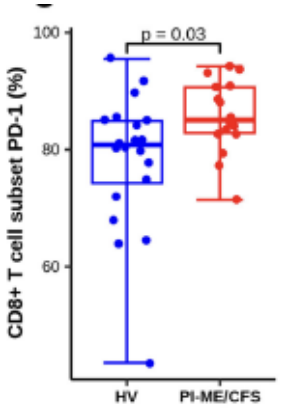
Persistence of microbial antigen (?)

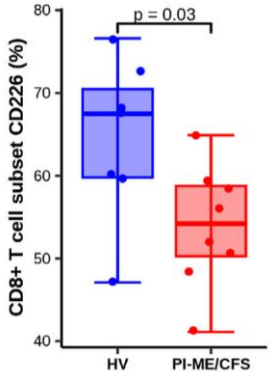
T cell exhaustion

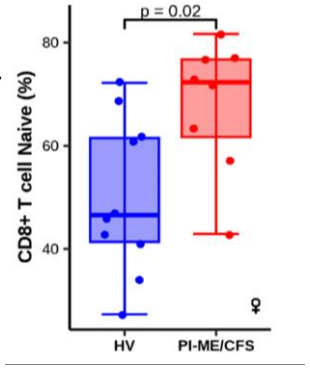
Innate immune activation

Decreased cytotoxic T cell activ

Increased naïve T cells (females)







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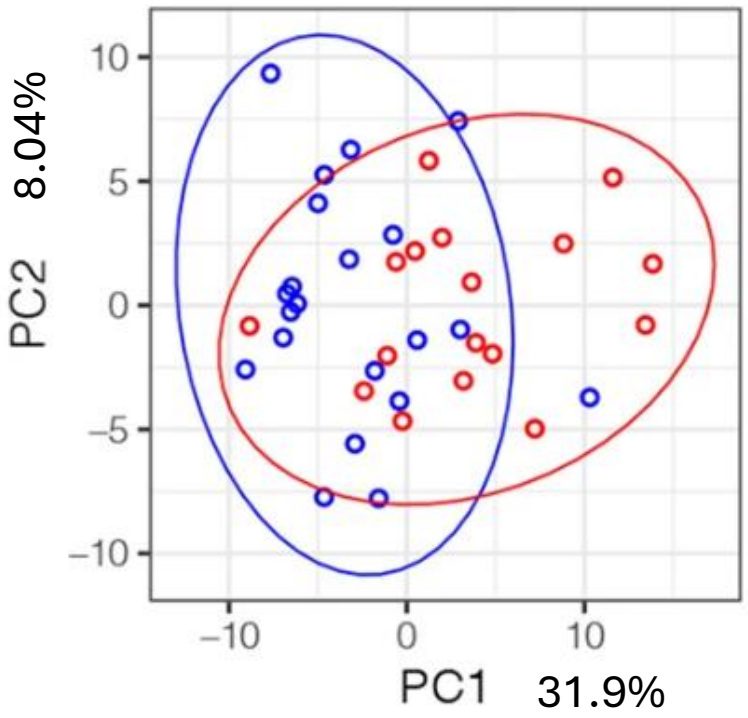
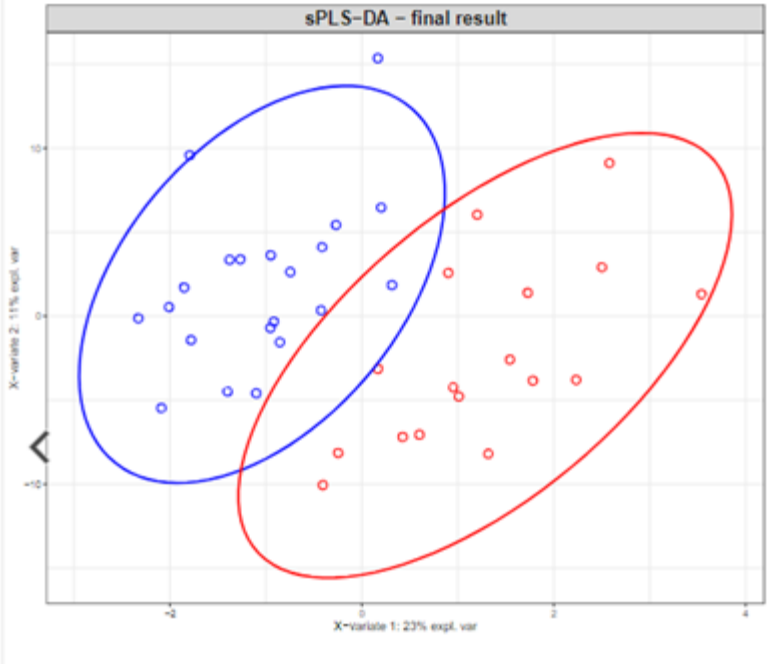
Cerebrospinal Fluid Metabolomics (445 features)

PCA: All participants

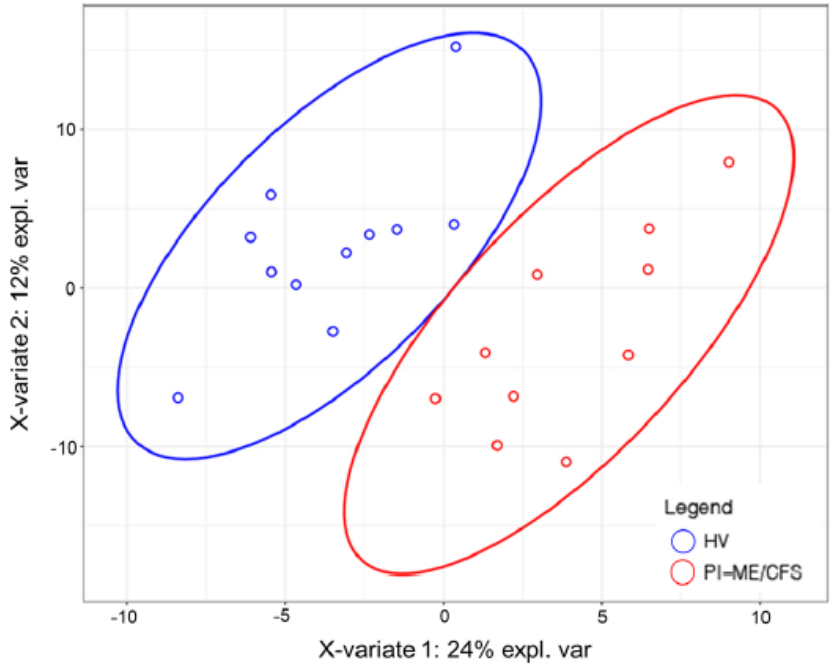


PLS-DA: All participants



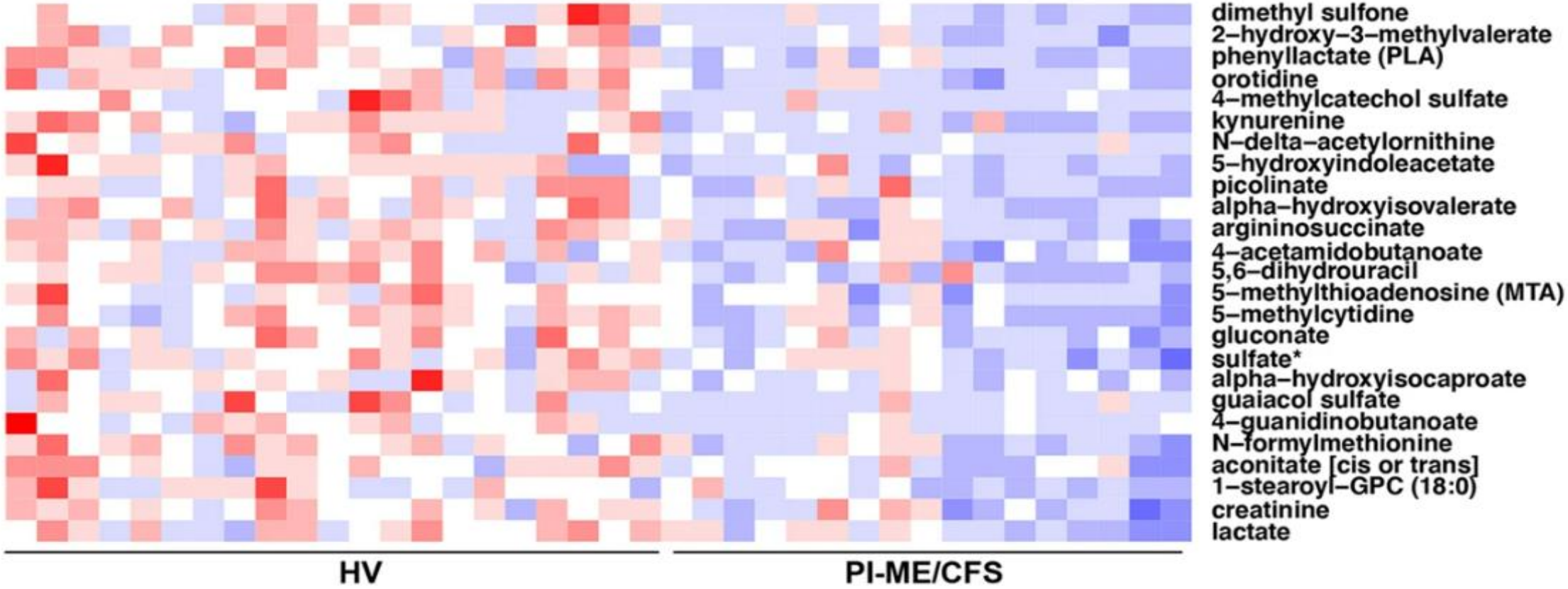
Explains 44% variance

PLS-DA: All participants, Differential Expression



Explains 36% variance

Cerebrospinal fluid metabolites discriminate PI-ME/CFS from HV the best of all the Omics measures



PI-ME/CFS: Decreased

glutamate,
dopamine 3-O-sulfate,
butyrate,
polyamine,
tricarboxylic acid (TCA) pathway metabolites

biomedicines

MDPI

Article

Tryptophan Metabolites, Cytokines, and Fatty Acid Binding Protein 2 in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Manuela Simonato [1], Stefano Dall'Acqua [2], Caterina Zilli [3], Stefania Sut [2], Romano Tenconi [4], Nicoletta Gallo [5], Paolo Sfriso [4], Leonardo Sartori [4], Francesco Cavallin [6], Ugo Fiocco [4], Paola Cogo [7], Paolo Agostinis [8], Anna Aldovini [9,10], Daniela Bruttomesso [4], Renzo Marcolongo [4], Stefano Comai [2,11,12,13,*,†] and Aldo Baritussio [4,†]

Aging and Disease
www.aginganddisease.org

Volume 13, Number 3; 698-711, June 2022
http://dx.doi.org/10.14336/AD.2021.0824

Review

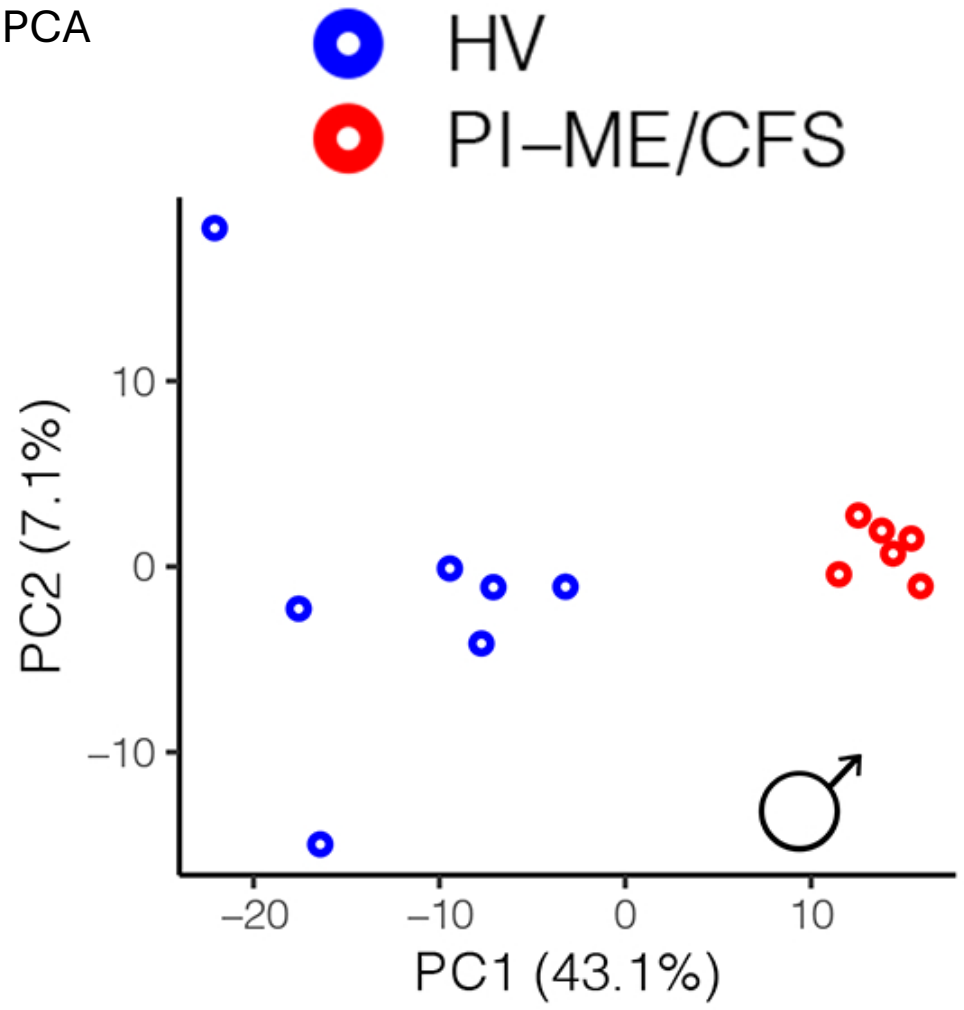
The Role of Kynurenine Pathway and NAD+ Metabolism in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

Mona Dehhaghi[1,2], Hamed Kazemi Shariat Panahi[1], Bahar Kavyani[1], Benjamin Heng[1,2], Vanessa Tan[1,2], Nady Braidy[3], Gilles J. Guillemin[1,2*]

Transcriptomics in peripheral blood mononuclear cells

Males vs Males

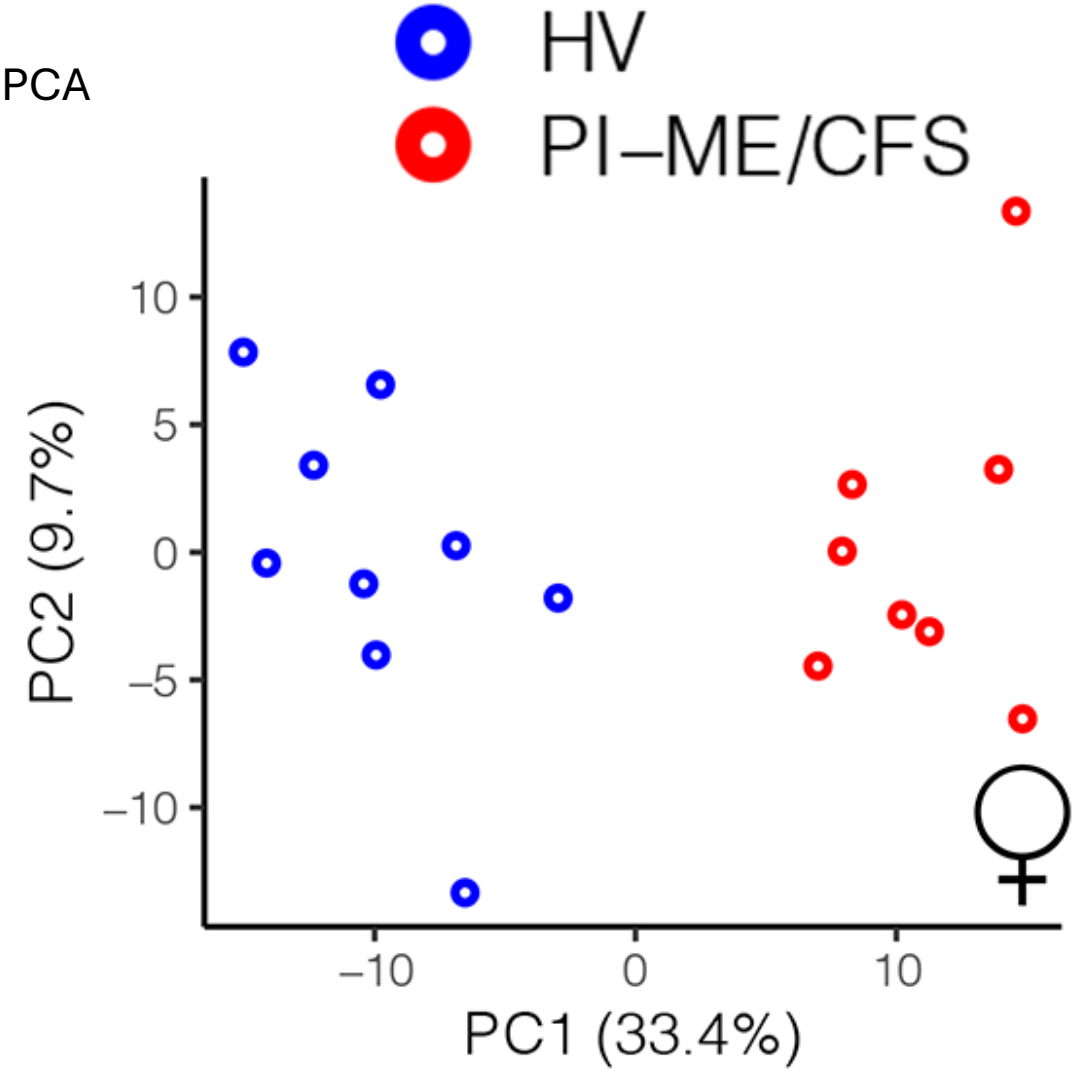
PCA



Explains 50.2% variance

Females vs Females

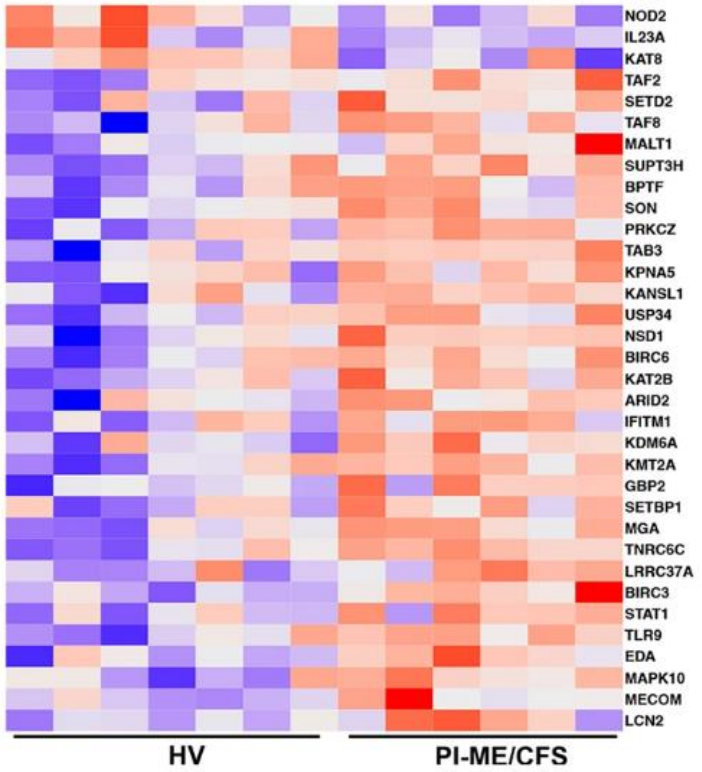
PCA

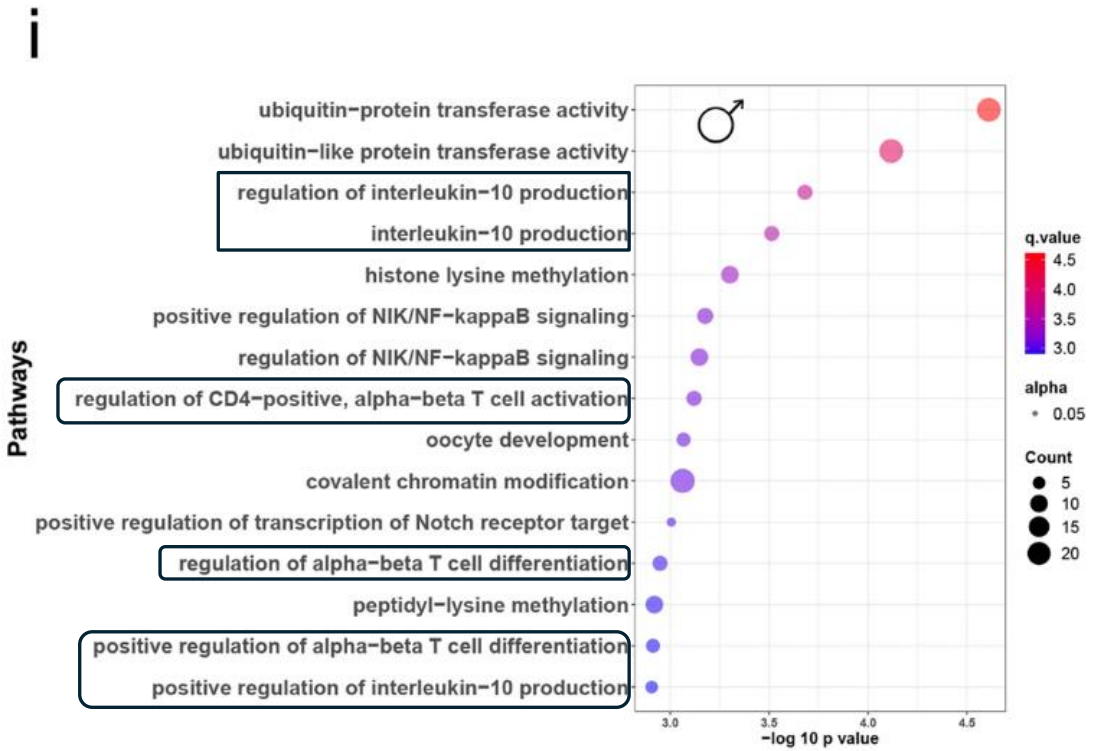


Explains 43.1% variance

Walitt et al., 2024

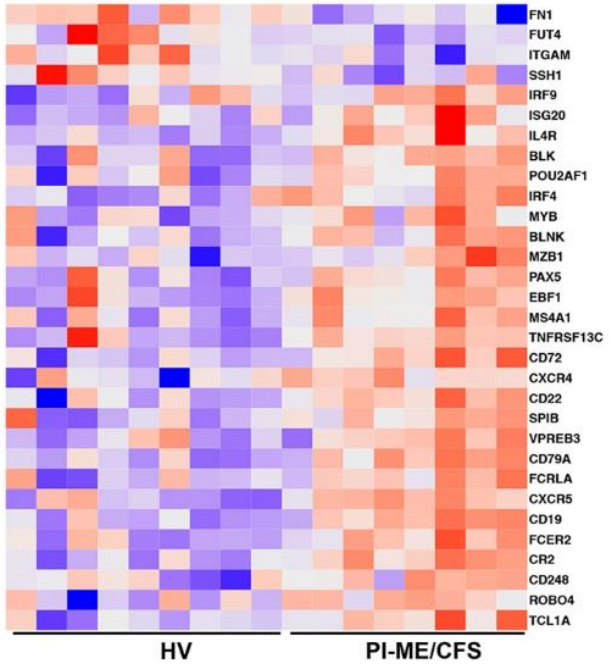
Peripheral Blood Mononuclear Cell RNA Sequencing in **Males**

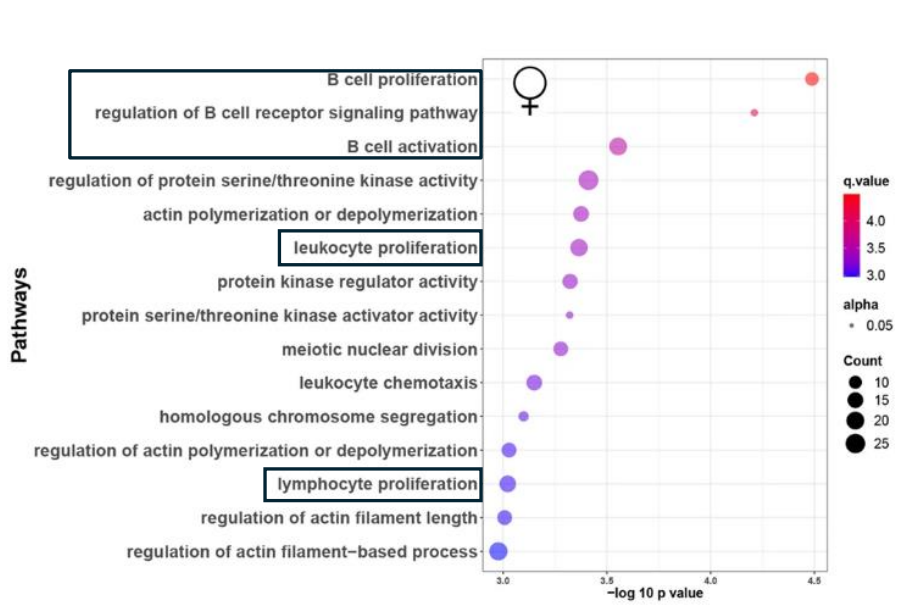


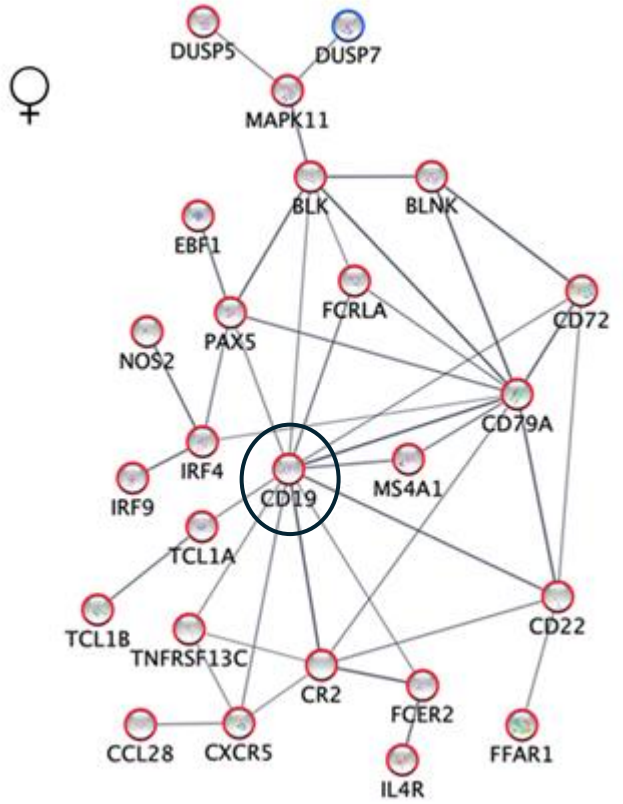


- Shows dysregulation of antigen specific T cells
- and Interleukin-10 (anti-inflammatory)

Peripheral Blood Mononuclear Cell RNA Sequencing in Females





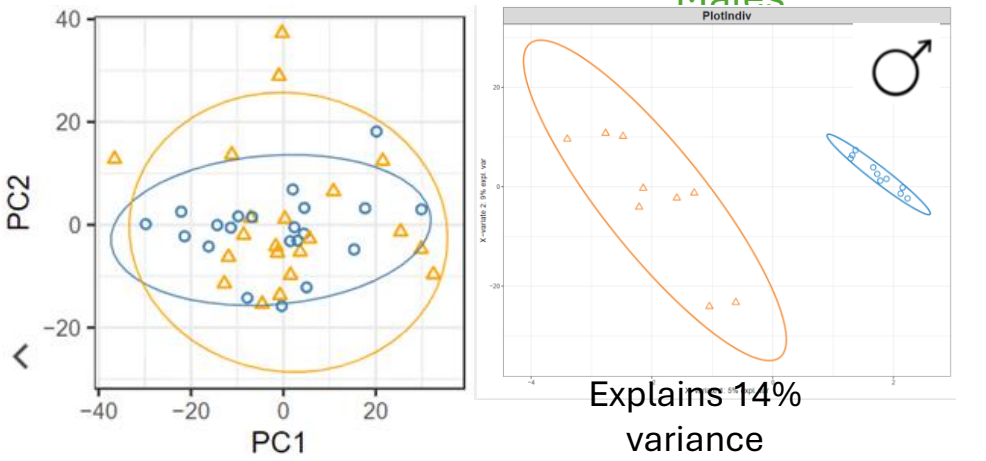


- Shows dysregulation of proliferation and activation
- Upregulation of B-cell interactome
- Consistent with expansion of naïve B-cells and decreased switched memory B-cells noted on flow cytometry

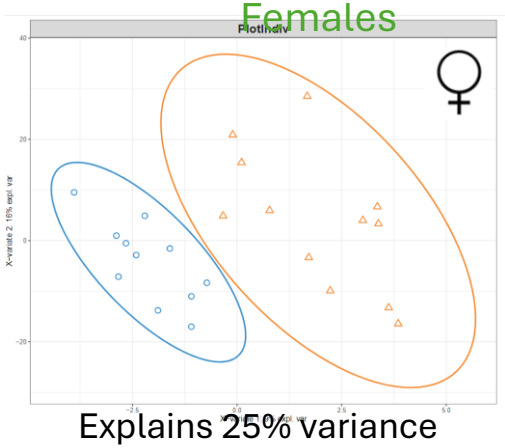
PCA,
All participants

PLS-DA,
HV Males vs PI-ME/CFS Males

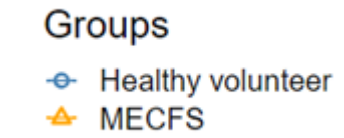
PLS-DA,
HV Females vs PI-ME/CFS Females



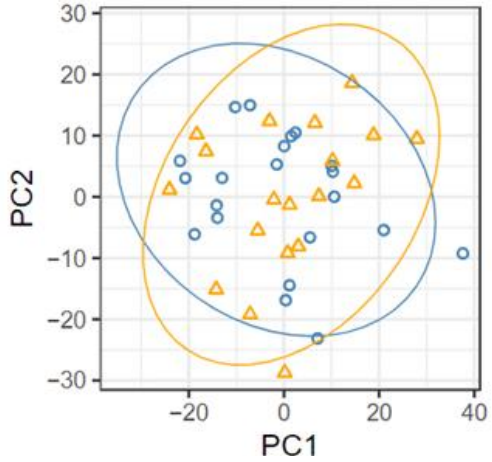
Explains 14% variance

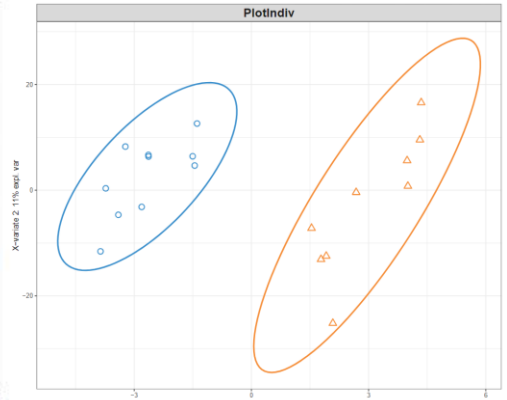


Explains 25% variance

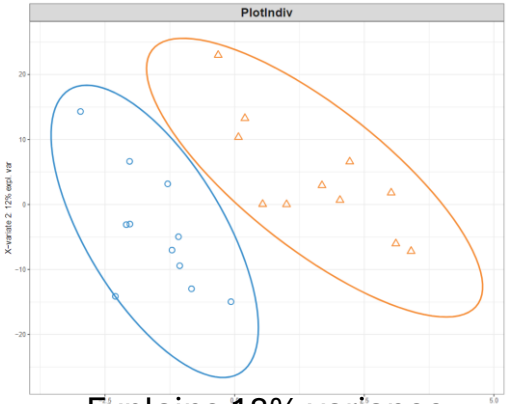


Plasma Proteomics



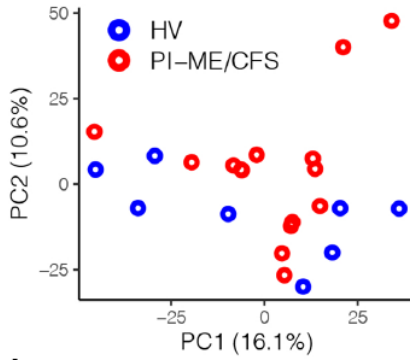


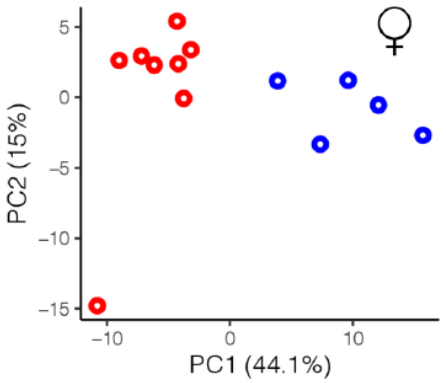
Explains 19% variance

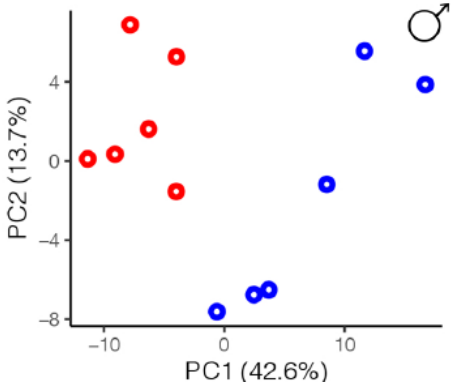


Explains 18% variance

CSF Proteomics



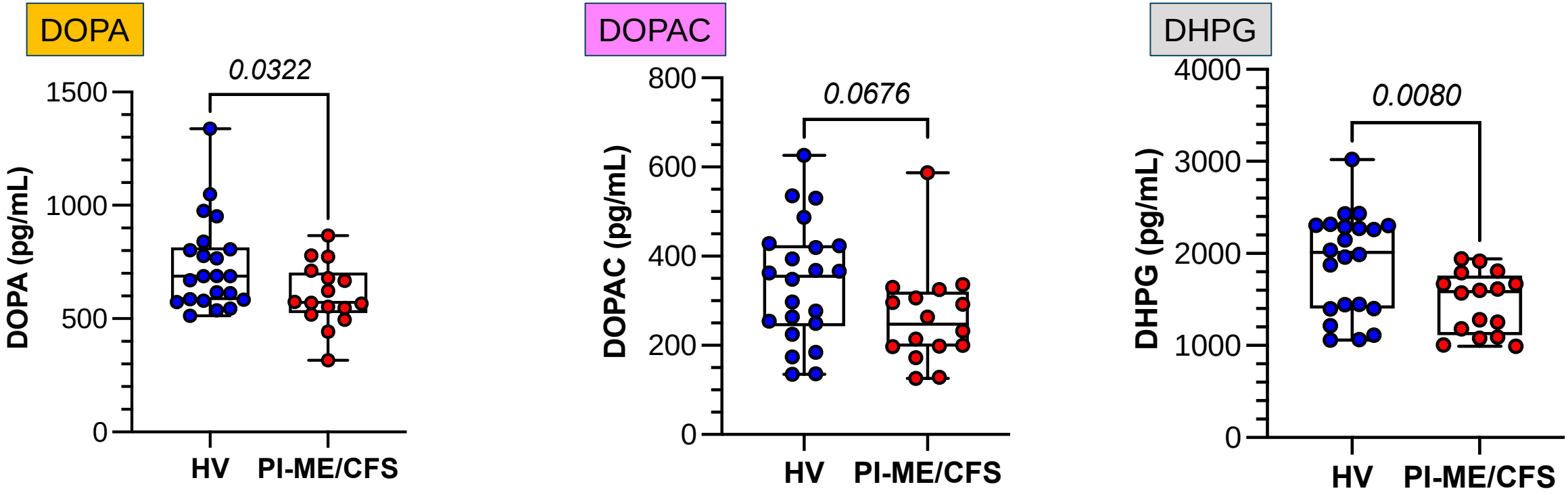




Muscle RNA

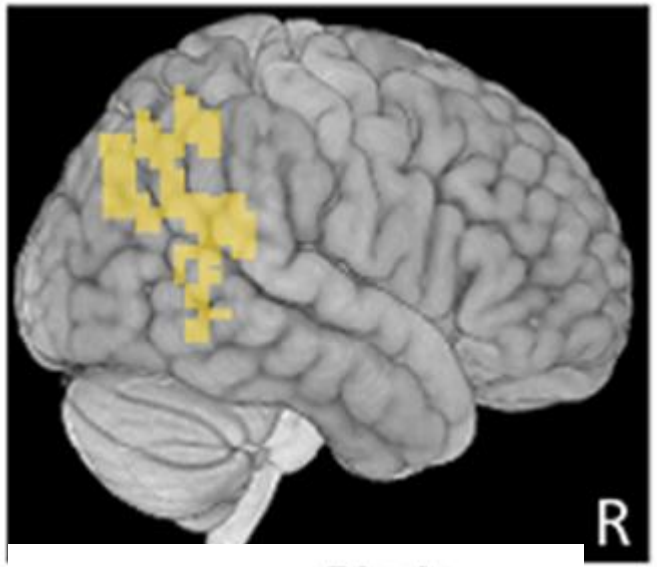
Differences are evident only when separated by sex

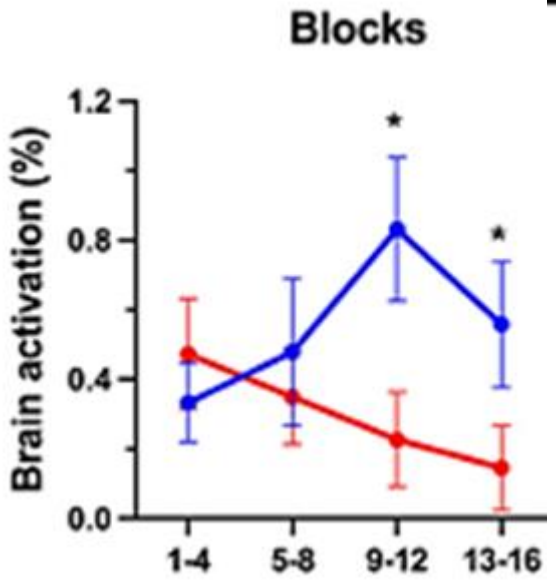
Catechol neurotransmitters were decreased in PI-ME/CFS



- Catechol neurotransmitters are important compounds in the regulation of autonomic function
- The decreased levels of catechol metabolites suggest decreased central catecholamine biosynthesis

Functional MRI showed circuit dysfunction of integrative brain regions that drive the motor cortex





- No difference in motor system activation was noted between groups
- The right temporoparietal junction (TPJ) activated differently between the groups
- The TPJ is responsible for high order integration of brain function and ‘mismatch’ detection

Conclusions

- Can be precipitated by multiple infections
- Likely driven by persistent microbial antigen as reflected by defect in
  - B cell maturation
  - T cell exhaustion
  - Innate immune activation
- Decreased central catecholamine synthesis
- Circuit dysfunction of integrative brain regions
- Sex dependent differences

THANK YOU!

Authors: Brian Walitt, Komudi Singh, Mark Hallett, Steve Jacobson, Kong Chen, Yoshimi Enose-Akahata, Richard Apps, Jennifer J. Barb, Patrick Bedard, Robert J. Brychta, Ashura Williams Buckley, Peter D. Burbelo, Brice Calco, Brianna Cathay, Li Chen, Jinguo Chen, Foo Cheung, Snigdha Chigurupati, Lisa MK Chin, Benjamin W. Coleman, Amber B. Courville, Madeleine S. Deming, Bart Drinkard, Li Rebekah Feng, Luigi Ferrucci, Scott A Gabel, Angelique Gavin, David S. Goldstein, Shahin Hassanzadeh, Sean C. Horan, Silvina G. Horovitz, Kory R. Johnson, Anita Jones Govan, Kristine M. Knutson, Joy D Kreskow, Samuel R. LaMunion, Mark Levin, Jonathan J. Lyons, Nicholas Madian, Nasir Malik, Andrew L. Mammen, John A. McCulloch, Patrick M. McGurrin, Joshua D. Milner, Ruin Moaddel, Geoffrey A Mueller, Amrita Mukherjee, Sandra Muñoz-Braceras, Gina Norato, Katherine Pak, Iago Pinal-Fernandez, Traian Popa, Lauren B. Reoma, Michael N. Sack, Leorey N. Saligan, Brian A. Sellers, Stephen Sinclair, Bryan Smith, Joseph Snow, Stacey Solin, Barbara J. Stussman, Giorgio Trinchieri, Sara A. Turner, C. Stephenie Vetter, Felipe Vial, Carlotta Vizioli, Ashley Williams, Shanna B. Yang, and Avindra Nath

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