

REPORT OF THE NANDS COUNCIL WORKING GROUP FOR ME/CFS RESEARCH

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National Institute of
Neurological Disorders
and Stroke

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EXECUTIVE SUMMARY

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic, complex, debilitating disease that can have a profound impact on people's lives. Symptoms can include pain; severe exhaustion that is not alleviated by rest; cognitive impairment, including difficulty with concentration and short-term memory; and orthostatic intolerance. A distinctive feature of the disease is post-exertional malaise, which is the worsening of symptoms 12-48 hours after physical exercise or mental activity. Many people with ME/CFS experience significant disability, often do not return to their pre-disease levels of activity, and a number of severely affected individuals become home- or bed-bound. The causes and biological mechanism(s) remain unknown, there is no laboratory diagnostic test, and no FDA-approved treatment for ME/CFS. Exact numbers are unknown, but it is estimated that between 836,000 to 2.5 million people in the United States have ME/CFS (Jason et al., 1999, 2006) and direct and indirect economic costs associated with the disease may range from \$18 billion to \$51 billion annually in the U.S. (Reynolds et al., 2004; Jason et al., 2008; Lin et al., 2011).

In the fall of 2015, NIH initiated a variety of activities to stimulate research on ME/CFS. The Trans-NIH ME/CFS Working Group, composed of representatives from 23 Institutes, Offices, and Centers, was reinvigorated to coordinate the extramural research efforts at NIH. This group supported administrative supplement grants in 2016 and issued RFAs that resulted in the funding of three ME/CFS Collaborative Research Centers and a Data Management and Coordinating Center in 2017. NIH funding for ME/CFS research increased from \$5.4 million in Fiscal Year 2014 to more than \$14 million in Fiscal Years 2017 and 2018. In addition, NINDS and CDC facilitated the creation of ME/CFS Common Data Elements (CDEs) for use in clinical research. In April 2019, the Trans-NIH Working Group held a research conference on ME/CFS and a workshop for early career ME/CFS investigators, both at NIH. The NIH Intramural Research Program began a comprehensive study of individuals with post-infectious ME/CFS who have been ill for less than five years. Despite these efforts, there are still significant gaps in our understanding of the disease and there is an urgent need to expand the research field.

The NANS Council Working Group for ME/CFS Research was convened in the summer of 2018 to provide scientific guidance on how best to advance research in ME/CFS at NIH. The working group included individuals representing ME/CFS stakeholders: individuals with ME/CFS, representatives from non-profit advocacy organizations, health care providers, scientists, and representatives from the CDC and NIH. The group identified key gaps and opportunities in ME/CFS research, as well as strategies to address those gaps. Critical gaps include lack of knowledge of the underlying biological mechanisms of ME/CFS and insufficient information about clinical aspects of the disease; the low number of investigators and NIH grant applications focusing on ME/CFS, particularly from early-career investigators; and the lack of an overall research plan.

Detailed strategies to address these gaps are included throughout the report. Key overarching recommendations are the creation of a research strategic plan and the formation of an

interagency group to increase research cooperation between relevant stakeholders, including researchers, clinicians, federal agencies, and non-profit advocacy organizations. These are considered necessary steps to break down silos and stimulate coordinated, field-wide research progress. The group also recommends extensive outreach to solicit ME/CFS grant applications through wide distribution of ME/CFS program announcements as one strategy to help expand this research field. Additional recommendations focus on strategies to facilitate basic and clinical research; approaches to bringing more researchers, including early-career investigators, into the field; and ways to raise awareness and decrease stigma of the disease among researchers and health care providers. Following approval by the NANS Council, next steps include dissemination of the report to other NIH Institutes, Offices, and Centers, prioritization of the recommendations and development of an implementation plan by the Trans-NIH ME/CFS Working Group.

INTRODUCTION

Background

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic, complex, debilitating disease that can have a profound impact on people's lives. Symptoms can include pain, severe exhaustion that is not alleviated by rest, cognitive impairment, including difficulty with concentration and short-term memory, and orthostatic intolerance. A distinctive feature of the disease is post-exertional malaise (PEM), which is the worsening of symptoms 12-48 hours after physical exercise or mental activity. Many people with ME/CFS experience significant disability, often do not return to their pre-disease levels of activity, and a number of severely affected individuals become home- or bed-bound. The causes and biological mechanism(s) remain unknown, there is no laboratory diagnostic test, and no FDA-approved treatment for ME/CFS. Exact numbers are unknown, but it is estimated that between 836,000 to 2.5 million people in the United States have ME/CFS (Jason et al., 1999, 2006) and direct and indirect economic costs associated with the disease may range from \$18 billion to \$51 billion annually in the U.S. (Reynolds et al., 2004; Jason et al., 2008; Lin et al., 2011).

Over the past 35 years, many studies have found abnormalities in the central and autonomic nervous systems, chronic immune activation or exhaustion, and abnormalities of energy metabolism, in people with ME/CFS. Clinical ME/CFS research has identified the wide range of symptoms experienced by people with ME/CFS, and the increased frequency of certain comorbid conditions, such as fibromyalgia and irritable bowel syndrome. Clinical research also has identified some potential physical examination findings and standard laboratory test results that may distinguish people with ME/CFS from healthy controls and is examining whether past medical history or family history findings may be characteristic of ME/CFS. Many recent laboratory and clinical research findings were presented in April 2019 at the “Accelerating Research on ME/CFS” conference held on the NIH campus¹. The conference and general ME/CFS research landscape were summarized in a recent JAMA publication (Komaroff, 2019)²

Despite recent progress, ME/CFS research continues to face many challenges. An understanding of what generates the abnormalities in different systems remains elusive, as does the question of how or whether the abnormalities in different organ systems are linked. Since the 1980s, several case definitions have been used, making cross-study comparisons difficult. In addition, methods of data collection used to determine whether subjects meet case definitions have not been standardized. Some scientific publications have been unclear in their descriptions of research participants, including controls, making it difficult to determine who was being studied. Finally, the ME/CFS research workforce suffers from a paucity of investigators at every level of career development.

¹ Day 1 of the videocast is available at <https://videocast.nih.gov/launch.asp?27422>, and Day 2 is available at <https://videocast.nih.gov/launch.asp?27424>.

² Komaroff AL. Advances in Understanding the Pathophysiology of Chronic Fatigue Syndrome. JAMA. Published online July 05, 2019; 322(6):499–500. doi:10.1001/jama.2019.8312

In the fall of 2015, NIH initiated a variety of activities to stimulate research on ME/CFS. The Trans-NIH ME/CFS Working Group, composed of representatives from 23 Institutes, Offices, and Centers, was reinvigorated to coordinate the extramural research efforts at NIH³. This group supported administrative supplement grants in 2016 and issued RFAs that resulted in the funding of three ME/CFS Collaborative Research Centers and a Data Management and Coordinating Center in 2017. NIH funding for ME/CFS research increased from \$5.4 million in Fiscal Year 2014 to more than \$14 million in Fiscal Years 2017 and 2018. In addition, NINDS and CDC facilitated the creation of ME/CFS Common Data Elements (CDEs) for use in clinical research⁴. In April 2019, the Trans-NIH Working Group held a research conference on ME/CFS and a workshop for early career ME/CFS investigators, both at NIH. The NIH Intramural Research Program began a protocol to comprehensively study individuals with post-infectious ME/CFS who have been ill for less than five years. A full description of NIH activities is provided in Appendices A-F of this report. Non-profit organizations including #MEAction, the Open Medicine Foundation, and the Solve ME/CFS Initiative also play an important role in supporting ME/CFS research. Summaries of non-profit activities are included in Appendix G of this report.

Despite these efforts, ME/CFS still imposes a substantial burden on individuals, significant gaps remain in our understanding of the disease, and there are no FDA approved therapies. There is an urgent need to expand the field, at all levels of research, including basic, translational, and clinical studies. NIH funding for ME/CFS from 2015 to 2018 ranged from \$6.5 million to \$14.8 million (Figure 1). Across this time period, 36 unique extramural PIs were funded (Figure 2). Of particular concern was the small number of training grants in ME/CFS research, with only one Fellowship (F) award and no Career Development (K) awards during this time. Detailed information about NIH funding of ME/CFS research is provided in Appendix H.

³ <https://www.nih.gov/research-training/medical-research-initiatives/mecfs>

⁴

<https://www.commondataelements.ninds.nih.gov/Myalgic%20Encephalomyelitis/Chronic%20Fatigue%20Syndrome>

Figure 1. NIH ME/CFS Research Funding from FY 2015-2018

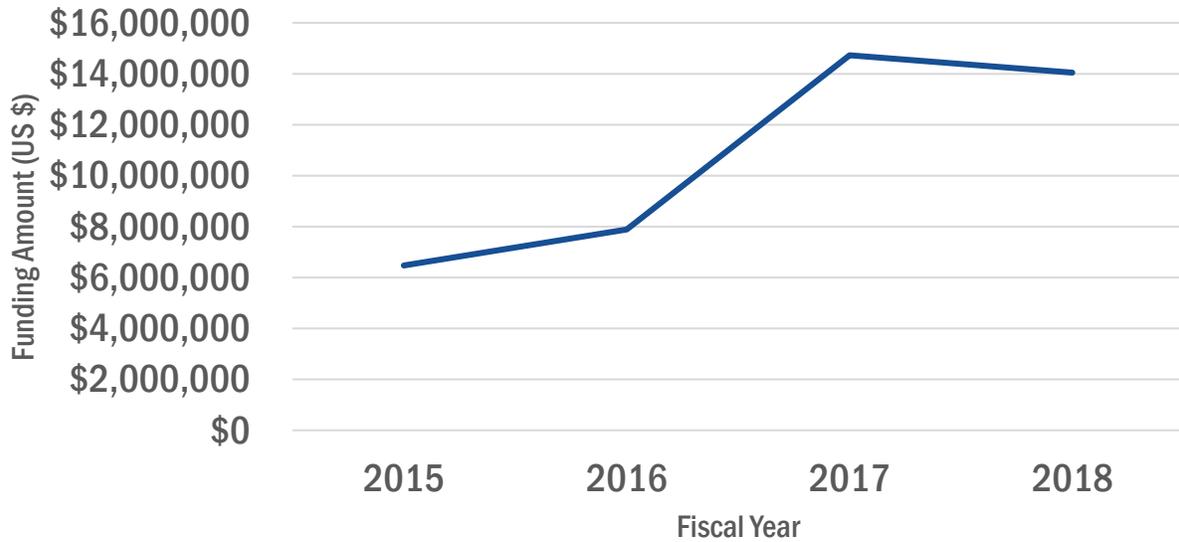
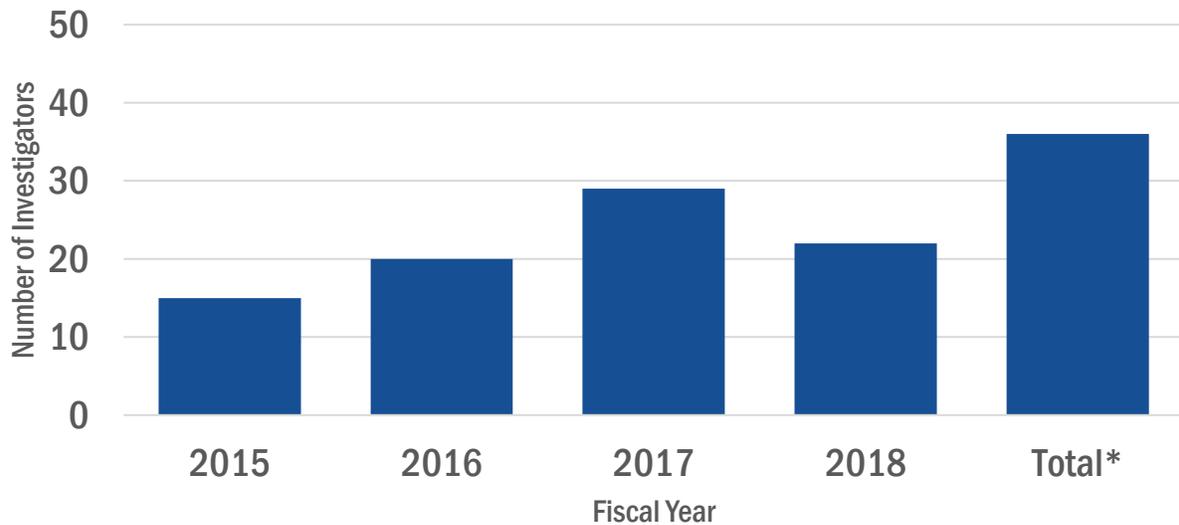


Figure 2. Number of Principal Investigators of Extramural NIH ME/CFS Grants



**Total - This represents the total number of unique principal investigators across all of FYs 2015-2018. PIs that were funded in multiple years were only counted once.*

Purpose and Charge of the NINDS Council Working Group for ME/CFS Research

The NINDS Council Working Group for ME/CFS Research was convened in the summer of 2018 and was charged with providing scientific guidance on how best to advance research in ME/CFS at NIH (see Appendix I for full charge). This included identifying gaps and opportunities in ME/CFS research, considering unique strategies for NIH-supported ME/CFS research to attract and train a pipeline of new and young investigators in this field, and identifying potential approaches to enhance ongoing research collaboration and communication between relevant advocacy organizations, individuals with ME/CFS, researchers, and federal agencies focused on supporting research in ME/CFS.

Committee Processes

The working group was chaired by Steve Roberds, Ph.D., a member of the NINDS Council. The group initially held a series of introductory calls followed by an in-person meeting in December 2018 (see Appendix J for agenda). During this meeting, working group members discussed NIH and non-profit research activities, how to increase stakeholder communication and collaboration, how to expand the research pipeline, and how to gather stakeholder input to inform the working group. Based on these discussions, the group formed several sub-committees focused on key areas. Sub-committee topics were:

1. Gathering stakeholder input
2. Structure for ongoing biomedical research collaboration between federal agencies, patient advocacy groups, and other ME/CFS stakeholders
3. Create new knowledge – pathobiology of ME/CFS
4. Create new knowledge – clinical information
5. Exploratory: identification of potential federal research programs that may be more broadly related to ME/CFS

Working group members volunteered for sub-committee(s) that aligned with their interests and expertise. Many working group members served on multiple sub-committees. Each sub-committee held regular calls, during which members discussed the gaps, opportunities, and strategies presented in this report. The entire working group participated in monthly calls to discuss progress of the sub-groups and the overall process culminating in this report.

To gather broader input, the working group issued a Request for Information (RFI) (NOT-NS-19-057) that was open to all members of the public from March 15, 2019 to May 1, 2019⁵. There were 281 total responses, including 23 from researchers, 14 from healthcare providers, 195 from individuals with ME/CFS, 61 from patient advocates, and 25 from other interested parties. RFI respondents could self-identify in more than one of the above response groups. RFI responses helped inform working group discussions of how to advance research on ME/CFS. A summary of the RFI responses is included in Appendix K, and all of the full responses are posted on NINDS's website.

Although this report is submitted to the NINDS Council, the strategies outlined in this report are intended to help inform all of the NIH Institutes, Offices, and Centers that make up the Trans-

⁵ <https://grants.nih.gov/grants/guide/notice-files/NOT-NS-19-045.html>

NIH ME/CFS Working Group. Dr. Walter Koroshetz, NINDS director and Chair of the Trans-NIH ME/CFS Working Group, will take this report to the Trans-NIH Working Group for prioritization of the recommendations and development of an implementation plan. The strategies in this report use “NIH” as shorthand for “NINDS, in partnership with the other Institutes and Centers from the Trans-NIH ME/CFS Working Group.”

GAPS AND OPPORTUNITIES IN ME/CFS RESEARCH, AND STRATEGIES TO ADVANCE ME/CFS RESEARCH

The working group identified a series of gaps in current knowledge, opportunities for future action, and a series of potential strategies to pursue for each gap/opportunity.

- **Gap/Opportunity: Devising an overarching research strategy to address the complex nature of ME/CFS**

ME/CFS is a multi-system disease requiring research in numerous scientific areas. There is currently no overarching research strategy to prioritize and integrate research within and across these diverse fields.

Potential Strategies:

- The Trans-NIH ME/CFS Working Group should coordinate a research prioritization and strategic planning process to create an overarching roadmap for ME/CFS research. The process should identify key research priorities across relevant scientific areas. Scientists and clinicians with relevant outside expertise should be included in the process, as well as other stakeholders such as individuals with ME/CFS, advocates, and caregivers. Several key questions and priorities for such an effort are detailed below and included in the “Strategic Planning” section of Appendix L.

- **Gap/Opportunity: Enhancing cooperation among federal agencies and other interested stakeholders**

There is a need to increase research cooperation and coordination between relevant federal agencies, non-profits, health care providers, investigators and individuals with ME/CFS.

Potential Strategies:

- NIH should create a group that includes members from federal agencies involved in ME/CFS research, nonprofit foundations supporting ME/CFS research, and other interested stakeholders. The group should promote increased collaboration toward common research goals, monitor progress of the overall ME/CFS research field, share information on ME/CFS research activities, highlight advances, and discuss research gaps and opportunities. Additional details on a potential collaborative structure are included in Appendix M.

- **Gap/Opportunity: Promoting increased awareness in the medical and scientific community**

Clinicians and clinician-scientists typically have limited awareness about ME/CFS and how it overlaps with their medical specialties, which is a barrier to enrolling well-defined patients for studies and generating research resources such as biospecimens.

Potential Strategies:

- NIH should offer information and feedback to stakeholders who are engaged in outreach and medical education.
- When appropriate for its mission, NIH should partner with other federal agencies, such as CDC, and professional organizations to disseminate information about research on ME/CFS.

- **Gap/Opportunity: Reducing disease stigma by promoting the importance and value of research on ME/CFS**

Stigma around ME/CFS may impact interest in conducting research on the disease. When ME/CFS was first described, little was known about its underlying biology. Many clinicians and investigators are still unaware of the literature that has since developed about the underlying pathobiology. A history of claims of psychosomatic origins continues to perpetuate a reputation that the disease lacks a biologic etiology and/or is difficult to study, which also creates barriers to publication of ME/CFS research in high quality journals. The field would benefit from proactive approaches to reduce stigma around research on this disease and to demonstrate pathobiologic etiology.

Potential Strategies:

- NIH should leverage events to publicize information about ME/CFS.
- NIH should continue to publicize its ME/CFS research efforts, such as the NIH ME/CFS intramural study and the ME/CFS Research Network.
- NIH should provide materials about ME/CFS, including information from the CDC, at exhibit booths during professional conferences.

- **Gap/Opportunity: Increasing the number of ME/CFS research grant applications submitted to NIH**

A low number of grant applications hampers research progress on ME/CFS.

The widespread perception of lack of interest by NIH in ME/CFS research may discourage potential grant applicants from submitting proposals and early career investigators from choosing a dedicated career path in this disease area.

Potential Strategies:

- NIH should solicit ME/CFS proposals through targeted outreach to investigators in relevant scientific and medical fields identified by the Trans-NIH ME/CFS Working

Group to be relevant to ME/CFS, regardless of whether those investigators have previously studied ME/CFS.

- As part of its outreach efforts, the Trans-NIH ME/CFS Working Group should develop a resource guide for investigators, which should include information from Institute/Center websites related to grant and training opportunities.
- NIH should actively encourage investigators to contact program staff with questions related to their grant applications, including identifying appropriate Funding Opportunity Announcements (FOA) for their basic, translational and clinical research studies.

- **Gap/Opportunity: Promoting a more multidisciplinary and collaborative approach to the study of ME/CFS**

ME/CFS research is often conducted in silos, but an integrated, multidisciplinary research approach is needed for such a complex, multi-system disease. The Funding Opportunity Announcement for the NIH Collaborative Research Centers (CRCs) required collaborative multidisciplinary teams with wide-ranging scientific, clinical, and technical expertise. These CRC teams are applying their different skills to simultaneously study multiple biological systems within the same individuals with ME/CFS. Wider encouragement of multidisciplinary approaches is needed to accelerate progress towards a more complete understanding of the multi-system nature of the disease.

Potential Strategies:

- NIH should continue to encourage multidisciplinary approaches in grant proposals.
- NIH should increase awareness among the researcher community about current multi-PI funding opportunities that encourage investigators with diverse skills and expertise to work together on projects.

- **Gap/Opportunity: Expanding the number of new researchers entering the ME/CFS field**

Many investigators from areas relevant to ME/CFS do not expand their research to include ME/CFS.

Potential Strategies:

- NIH should solicit ME/CFS proposals through targeted outreach to investigators in relevant scientific and medical fields identified by the Trans-NIH ME/CFS Working Group to be relevant to ME/CFS, regardless of whether those investigators have previously studied ME/CFS.
- NIH should facilitate wider availability of ME/CFS biospecimens, as detailed below. Access to biospecimens will help reduce barriers to new and early career investigators entering the ME/CFS field.

- As part of a strategic planning process, the NIH should include scientists with relevant outside expertise.
 - NIH should continue to hold ME/CFS conferences on a regular basis.
 - NIH should continue to provide information on both the NIH ME/CFS website as well as on the ME/CFS Network website about ongoing research efforts.
 - NIH should continue to issue press releases when significant NIH-funded ME/CFS research is published.
- **Gap/Opportunity: Expanding the number of early career investigators entering the ME/CFS field**

Currently, very few early career investigators have sought to enter the field. There are few ME/CFS investigators and clinicians available as mentors to support career training for junior researchers or to collaborate with established investigators interested in studying ME/CFS.

Potential Strategies:

- NIH should partner with nonprofit research organizations to create training resources for early career investigators interested in becoming ME/CFS researchers.
 - NIH should continue to hold events geared towards early career investigators to provide guidance on how to apply for NIH research support and navigate the peer review process.
 - NIH should continue to actively participate in efforts to support early career investigators such as the “Thinking the Future: Early Career Network (Invest in ME).”
 - NIH should provide a list of currently funded ME/CFS research, including the Principal Investigator(s) for each grant award to enable trainees to identify potential mentors.
- **Gap/Opportunity: Enabling access to bioresources for ME/CFS research**

A major obstacle for ME/CFS researchers, including those considering the study of ME/CFS, may be difficulty in recruiting and characterizing patients, and in obtaining and preserving biospecimens.

A lack of available data and bioresources hampers progress in the ME/CFS field. In the absence of *in vitro/in vivo* disease model systems, all ME/CFS research depends upon primary patient samples or participation. In the absence of objective biomarker(s), patient selection for studies relies upon clinical experts who are scarce, overburdened, and nearing retirement. NIH has already created biorepositories with samples linked to clinical information about well-characterized patients. Increased access to bioresources will allow for more extensive hypothesis-driven, exploratory, and replication studies.

Potential Strategies:

- NIH should continue to support expansion of ME/CFS biorepositories that also include detailed clinical data about the study participants.
 - NIH should encourage funded research projects to provide biospecimens to existing biobanks for sharing with qualified investigators.
 - NIH should partner with stakeholders to develop a registry through which potential study participants can be identified.
 - NIH should work with funded investigators to ensure that steps are taken to enable future data sharing and biobanking. Examples include writing consent forms to allow for biobanking and wider data sharing, as well as the use of Globally Unique Identifiers (GUIDs) to track research subjects who are participants in multiple studies.
- **Gap/Opportunity: Continuing and strengthening the NIH ME/CFS Special Emphasis Panel (SEP)**

The NIH ME/CFS Special Emphasis Panel (SEP)⁶ allows for focused scientific review of ME/CFS grant applications. However, the limited number of investigators with substantial ME/CFS research experience limits the pool of reviewers, especially given that some of these potential reviewers also may have applications under review.

- NIH should continue to ensure that the ME/CFS SEP includes reviewers with relevant ME/CFS expertise. Reviewers with other relevant subject matter expertise, including experts in tools and methodologies being proposed, should also be included.
 - NIH should consider study section formats that provide for productive interactions between members of the review panel, for example face-to-face or video conference meetings.
 - NIH should consider inviting members of the SEP to be reviewers in multiple grant cycles to build a sense of community within the SEP.
- **Gap/Opportunity: Using case definitions that facilitate broader research utility and data sharing**

Several case definitions for ME/CFS have been proposed, and different studies have used different case definitions, making it difficult to compare studies addressing a similar question.

Potential Strategies:

- NIH should encourage all NIH grant applications on ME/CFS to clearly state which case definition is being used and what data collection instruments will be used to obtain the data needed to apply that case definition.
- NIH should encourage applications proposing to use one particular case definition to also obtain sufficient clinical data so that the subjects can be categorized according to any of the primary case definitions of ME/CFS.

⁶ <https://public.csr.nih.gov/StudySections/DNDA/IFCN/CFSSEP>

- **Gap/Opportunity: Building consensus on inclusion/exclusion criteria for control groups in ME/CFS research**

The published literature sometimes contains little discussion or methodological details on how *healthy controls* were assessed and determined to be “healthy.” There is a need for standardized data collection instruments that can be completed by potential healthy control subjects in any ME/CFS study. Simultaneously, there is a need for associated criteria (linked to those instruments) for defining a potential control subject as “healthy.” For example, must a subject be entirely free of all of the chronic symptoms that are part of the case definitions of ME/CFS in order to be considered “healthy?”

In addition, people with ME/CFS typically have considerably impaired levels of activity, but some studies have not used control groups who have equivalent levels of activity, such as sedentary controls. Physical fitness and the presence of other diseases are common potential confounding factors.

Potential Strategies:

- NIH should encourage ME/CFS studies to assess the health status of control groups using valid data collection instruments, such as those recommended in the ME/CFS CDE guidelines and the NIH toolbox⁷.
- NIH should encourage studies to formally assess physical activity levels of all cases and controls, using validated and standardized instruments. Justification for using fit controls (e.g. comparison to model systems) should be provided when appropriate.
- NIH should encourage studies to rigorously assess and control for confounding factors in all studies of ME/CFS that may influence the results and comparisons between those with ME/CFS and the chosen controls. Physical fitness and the presence of other diseases are common potential confounding factors.

- **Gap/opportunity: Achieving consistent data collection, analysis, and reporting**

There is wide variability in how studies enroll people with ME/CFS and measure, collect, use, analyze, and report data. Many published studies collect and report insufficient clinical information on ME/CFS cohorts. For example, published studies often contain minimal description of potentially important information such as average symptom severities, age of onset, disease duration, pre-disease exposures, and overall level of disability. In addition, standardized instruments are not always used to collect clinical data, or they do not exist. For instance, while the ME/CFS CDE instruments collect data on the presence of post-exertional malaise (PEM), research is hampered by a lack of a universally agreed-upon definition and/or a validated measurement tool to assess PEM. There is also a need for a standardized measure of disease severity.

Potential Strategies:

⁷ <http://www.healthmeasures.net/explore-measurement-systems/nih-toolbox>

- NIH should urge investigators to use the ME/CFS CDEs, to both characterize comorbid conditions and details of the disease.
- NIH should work with the CDC and other stakeholders to identify additional required data elements and instruments that will facilitate more detailed ME/CFS phenotyping and improve data sharing.
- NIH should support development and validation of new instruments where needed to measure disease features of importance to people with ME/CFS (e.g., PEM).

- **Gap/opportunity: Increasing understanding of different stages of ME/CFS**

Some studies indicate that there may be important biological differences between newly ill individuals with ME/CFS and those who have been sick for a long time. This is not often accounted for in the published research. In addition, people with ME/CFS are often sick for many years before they receive a diagnosis.

Potential Strategies:

- Investigators should be encouraged to take into account the onset and length of disease in all ME/CFS studies.

- **Gap/Opportunity: Addressing the heterogeneous and multifactorial nature of ME/CFS**

ME/CFS is likely a heterogenous condition with 1) multiple potential triggers, rather than a single, novel etiologic agent; 2) abnormalities of multiple different interacting organ systems; 3) signs and symptoms of the disease that often wax and wane, and that may progress over time. Current research efforts have largely been limited to testing single biological systems, thereby limiting discovery of pathophysiological mechanisms that may involve multiple physiological processes and/or the interaction of multiple biological systems. There is a need for multidisciplinary research to better understand how reported abnormalities relate across systems. There is also a need for large-scale studies and data aggregation to resolve heterogeneity and, as mentioned below, study potential subtypes.

Potential Strategies:

- NIH should encourage ME/CFS research that evaluates the interactions between multiple biological systems that, individually, have been found to have abnormalities within the same cohort of people with ME/CFS.

- **Gap/opportunity: Addressing heterogeneity within individuals with ME/CFS**

The disease not only differs between patients, there can be tremendous symptom variability within the same individual over time.

Potential Strategies:

- NIH should encourage clinical characterizations of study participants that better inform the scope of the disease and the changes in symptoms over time.
- NIH should encourage investigators to measure symptoms from multiple perspectives (e.g. assessing current, peak, and typical symptom levels; and/or assessing different timeframes and situational frames) to gather a more complete picture of the symptom complex of people with ME/CFS.

- **Gap/Opportunity: Increasing knowledge about disease subtypes**

Although ME/CFS has long been considered a heterogeneous disease, the existence and clinical/biological relevance of disease subtypes is unclear. Clinicians have discussed their observations regarding potential subtypes, but it is unknown whether the subtypes are different in meaningful ways, such as in their underlying etiology, the subsequent pathophysiology, their response to treatment, or their prognosis.

Potential Strategies:

- NIH should encourage research to identify and validate ME/CFS subtypes. Researchers examining subtypes should be encouraged to consider relevant clinical information including (but not limited to) onset triggers, disease severity, stage of disease, and symptom presentation, as well as combinations of clinical and biological data.
- A strategic planning process should include discussions, informed by knowledge from clinicians and people with ME/CFS, about clinical phenotypes and studies that may reveal ME/CFS subtypes. This should be coordinated with efforts at the CDC.

- **Gap/opportunity: Increase understanding of overlapping syndromes and comorbid conditions related to ME/CFS**

The role of comorbid or overlapping syndromes in ME/CFS remains understudied and their relevance to core ME/CFS pathobiology is unclear. Overlapping syndromes (for example, fibromyalgia, irritable bowel syndrome, multiple chemical sensitivities, postural orthostatic tachycardia syndrome, and hypermobile Ehlers-Danlos syndrome) have not been systematically assessed in most studies or have been evaluated using differing criteria. Other potentially relevant medical issues are also infrequently assessed in ME/CFS clinical studies. Examples include mast cell activation, immune activation, small fiber neuropathy, cognitive dysfunction, neurological symptoms (including orthostatic intolerance), and neurostructural findings. The relevance of comorbidities to ME/CFS should be assessed.

Potential Strategies:

- NIH should encourage multidisciplinary ME/CFS studies to examine and report on comorbid conditions utilizing the appropriate ME/CFS CDEs.

- If CDEs for the comorbid conditions do not exist in the ME/CFS CDEs, they should be co-opted from other disease CDEs.
- NIH should inform ME/CFS investigators when relevant NIH Funding Opportunity Announcements are available in related fields and conditions (such as chronic pain, etc.).
- NIH should explore ways to coordinate ME/CFS research efforts with ongoing activities in overlapping syndromes.

- **Gap/Opportunity: Clarifying the specificity of research findings**

There is a lack of studies using comparison groups with diseases in which fatigue is a prominent symptom and that are often confused with ME/CFS. Such comparison groups are necessary in order to determine the specificity of biomarkers and clinical symptoms of ME/CFS.

Potential Strategies:

- When scientifically appropriate, NIH should encourage investigators to include disease comparison groups with other fatiguing illnesses (e.g., multiple sclerosis, systemic lupus erythematosus, major depression, Sjogren’s syndrome) as well as healthy control subjects.

- **Gap/Opportunity: Taking advantage of big data approaches to create widely shared large datasets**

There is a need for large studies or databases that comprehensively study different disease subgroups (e.g. early and late disease, different disease severities, etc.). This should include exhaustive medical workups and large-scale biological testing (e.g. pathogen testing and multi-omic analyses from all relevant sources including blood, CSF, and brain tissue). Strategies to combine data for comprehensive analysis may help address several of the research gaps mentioned in this report.

Potential Strategies:

- NIH should urge investigators to use the ME/CFS CDEs. These instruments standardize the collection of data about symptoms, past medical history, family medical history, physical examination, and common laboratory test results. These instruments may also help to categorize patients into certain disease subtypes, and to identify comorbid diseases. Standardized data collection and reporting through the CDEs is critical to enable cross study comparison, aggregation, and replication.
- NIH should partner with nonprofit and private organizations to develop a platform for ME/CFS researchers to facilitate data sharing.
- NIH should work with funded investigators to ensure steps are taken to enable future data sharing and biobanking, as detailed above.
- Once a comprehensive database is created, NIH should encourage secondary data analysis of aggregated existing datasets.

- **Gap/Opportunity: Addressing barriers to ME/CFS clinical trials**

There are various overarching issues that may be obstacles to the design and implementation of ME/CFS clinical trials.

Firstly, there are currently no FDA-approved treatments for ME/CFS. Expert ME/CFS clinicians prescribe a variety of off-label pharmaceuticals, many of them off-patent. These medications have not been evaluated in double-blind, randomized, placebo-controlled trials to assess potential efficacy.

Secondly, appropriate clinical trial cohort enrichment and patient selection strategies are currently unclear. This is partly a result of insufficient knowledge about potential subgroups of ME/CFS patients. There is also a lack of validated biomarkers that could be used for patient selection and/or cohort enrichment in clinical trials.

Finally, it is unclear whether symptoms or objective biomarkers are the most appropriate outcome measures to use in clinical trials.

Potential Strategies:

- A strategic planning process should consider clinical trial design, patient selection and enrichment strategies, outcome measures, and sources of heterogeneity across patients and within the same patient over time.
- The planning process should more rigorously assess the relative merits of different patient-reported outcome measures (such as alternative scales for determining fatigue severity, post-exertional malaise, or functional capacity).
- A strategic planning process should also discuss the scientific rationale for potential studies of off-label treatments used by clinicians.
- NIH should encourage research proposals to better understand the proposed mechanism of action of currently utilized therapeutics in either clinical research or mechanistic clinical trials. The primary outcome would be mechanistic information for further study and potentially larger separate clinical trial(s) designed for efficacy, etc.
- As indicated above, NIH should encourage research to identify and validate ME/CFS subtypes.

- **Gap/Opportunity: Addressing barriers to clinical research participation**

Some individuals with ME/CFS are entirely home- or bed-bound, making it difficult or impossible to travel to receive healthcare and/or participate in research studies. There are very few studies that include severely ill patients. There is currently not a registry or list of homebound or bedbound individuals in the US who are willing to participate in research.

Potential Strategies:

- NIH should encourage the use of telemedicine or home visits for research on home- or bed-bound people with ME/CFS to include this group of individuals in research studies when feasible.
- NIH should encourage the use of validated wearable devices and/or apps for symptom tracking of individuals with ME/CFS outside the research lab/clinic setting.
- NIH should encourage measurement of symptom severity.

- **Gap/Opportunity: Deciphering the underlying mechanisms specific to ME/CFS**

While the current published ME/CFS literature reports many biological abnormalities that are *associated* with ME/CFS, the studies typically have not established that they cause the symptoms of the disease. In addition to descriptive studies, other research strategies will be needed to gain understanding of disease etiology and pathophysiology. For example, such studies may be prospective in nature to follow disease trajectory or test treatments, compare different phases of disease, or assess responses to specific stimuli and stressors, such as physical or cognitive exertion.

Potential Strategies:

- A strategic planning process should include discussions of the state of knowledge about the possible etiologies for ME/CFS and how to identify findings that are likely to be disease causes versus physiological responses (i.e. epiphenomena and thus not the underlying cause(s) of ME/CFS).

- **Gap/Opportunity: Leveraging provocation study designs**

Provocation by physical exertion or other stressors (cognitive challenges, orthostatic stress) worsens the symptoms of ME/CFS, and may also uncover the underlying biological causes of the symptoms. Studies employing such provocations to date have been shown to be scientifically productive. However, investigators need to consider the concerns of individuals with ME/CFS about participating in such provocation studies, given that the studies may cause a temporary, or long-lasting, worsening of symptoms.

Potential Strategies:

- When scientifically appropriate, NIH should encourage provocation studies. These may help to reveal the underlying cause(s) of ME/CFS.

- **Gap/Opportunity: Developing ME/CFS biomarkers with diagnostic and prognostic utility**

Because ME/CFS is defined primarily by a patient's self-report of symptoms, it is important to find objective biomarkers for the disease. However, there are many nuanced issues that need to be considered in the development and usage of biomarkers.

Given the heterogeneity of ME/CFS, multiple biomarkers may be needed: some biomarkers for the disease, and other biomarkers that help define ME/CFS subgroups or are specific to progression of disease.

Potential Strategies:

- NIH should encourage research leading to the identification of objective measures that can be utilized as biomarkers for diagnosis, disease progression, and response to treatment.
- NIH should encourage investigators to consider information provided by the FDA-NIH Biomarker Working Group⁸.

- **Gap/opportunity: Improving understanding of onset, triggers, etiology, and pathogenesis**

There are important unresolved questions regarding ME/CFS onset, triggers, etiology and pathogenesis. Not all patients progress along the same pathway, and little is known about the disease natural history.

The ambiguity of disease onset also poses a challenge to understanding triggers, etiology, and pathogenesis. Some patients report a clear, acute onset (often with an “infectious-like” illness) but it is unclear how common this is. Clinicians and the individual may have missed or not considered previous medical events as relevant to the diagnosis of ME/CFS. Understanding predisposing or triggering factors may be difficult to accomplish with retrospective studies—particularly if the disease onset occurred years or decades ago and there are no medical records available to corroborate medical histories. Studies are needed to more carefully and thoroughly examine stressors, events and environmental exposures in the period leading to disease onset.

Potential Strategies:

- Where scientifically appropriate, NIH should encourage systematic clinical and epidemiological research to better characterize disease onset, triggers, etiology, and pathogenesis.
- NIH should encourage researchers to consider study designs, such as prospective and longitudinal studies, that may improve our understanding of ways in which ME/CFS develops.

- **Gap/Opportunity: Development of preclinical models relevant to ME/CFS**

There currently is a lack of *in vitro* and animal models of ME/CFS and mechanistic and translational research of some symptoms cannot be conducted in humans. Moving beyond observational assays in primary human tissues, development of *in vitro* models and experimental systems are promising avenues of study in determining potential

⁸ <https://www.ncbi.nlm.nih.gov/books/NBK326791/>

underlying mechanisms of disease. Development of *in vitro* systems that do not rely on primary patient samples is ultimately critical in overcoming the bottleneck of limited clinical resources. Similarly, development of animal models could create research momentum and incentivize researchers from related fields to begin conducting ME/CFS research.

However, creating animal models of a disease, such as ME/CFS, that is defined primarily or exclusively by the self-reported expression of symptoms is very challenging. It will be difficult to determine whether putative potential animal models accurately reflect ME/CFS in terms of both phenotypic symptoms and pathophysiology. Lessons may be learned from other symptomatically defined diseases, such as fibromyalgia, that have developed animal models primarily focused on specific disease phenomena, including exercise abnormalities, rather than on holistic disease models.

Potential Strategies:

- A strategic planning process should identify key issues related to the development and usage of *in vitro* and *in vivo* ME/CFS models.
- NIH should encourage research to develop *in vitro* and *in vivo* models of ME/CFS.

APPENDICES

Appendix A. NIH ME/CFS Activities: 2015 to Present

In the fall of 2015, NIH initiated a variety of activities to stimulate research on ME/CFS. Each key activity from 2015 until the present is described as a separate subsection below:

Trans-NIH ME/CFS Working Group

The Trans-NIH ME/CFS Working Group was reinvigorated in 2015 with Dr. Walter Koroshetz, Director of NINDS, taking over as the Chair. Representatives from 23 Institutes, Offices, and Centers across NIH developed short- and long-term goals for the group with the overarching goal of stimulating and supporting research on ME/CFS. Additional activities of the Trans-NIH ME/CFS Working Group are detailed below and a list of the current members of the working group is provided in Appendix B.

Request for Information

In May 2016, a [Request for Information](#) was released seeking input on the identification and consideration of research areas and topics to be included in future NIH efforts on ME/CFS. Input was solicited from researchers, health care providers, patient advocates and health advocacy organizations, scientific or professional organizations, federal agencies, and other interested parties. NIH received a [tremendous response](#) from the community that was utilized by the Trans-NIH ME/CFS Working Group to formulate both short- and long-term goals for research on ME/CFS.

Administrative Supplements

In order to bolster research on ME/CFS, NIH released a [Notice](#) informing the research community of the availability of administrative supplements to existing NIH-funded research grant awards. As a result, seven administrative supplements were awarded to provide additional support to investigators with grant awards on ME/CFS or related research areas. A list of the funded administrative supplement awards is contained in Appendix C.

Request for Applications for Collaborative Research Centers and Data Management Coordinating Center

The Trans-NIH ME/CFS Working Group released two Request for Applications (RFAs) in January 2017: one [RFA](#) requesting applications for Collaborative Research Centers and one [RFA](#) requesting applications for a Data Management Coordinating Center. Three Collaborative Centers and one Data Management Coordinating Center were [funded in September 2017](#) with support from multiple NIH Institutes, Offices and Centers. A list of the funded Centers is provided in Appendix D.

Professional Conferences

NIH Program Staff have participated in and/or organized sessions on ME/CFS at professional society meetings including a session on ME/CFS at the [SLEEP 2017 Conference](#) and one at the [FOCIS meeting in 2017](#). In addition, NIH staff participated in a Grant Writing Session at the [International CFS Annual meeting](#) in Florida in 2016.

Common Data Elements for ME/CFS

Working with Emmes, the contractor for the NINDS Common Data Elements project, NINDS and the CDC supported the development of [common data elements \(CDEs\)](#) for use in clinical research on ME/CFS. Working groups made up of ME/CFS stakeholders (individuals with ME/CFS, caregivers, health care professionals, and investigators) developed CDEs across the spectrum of symptoms of the disease.

NIH Conference on ME/CFS

NIAID took the lead in organizing a conference on ME/CFS entitled “Accelerating Research on ME/CFS,” which was held on the NIH Campus on April 4-5, 2019 (agenda provided in Appendix E). The conference was attended by over 300 individuals with more than 4500 viewing the conference live online. More than 2000 people have viewed the archived videos. On April 3, 2019, NINDS hosted a workshop for early career investigators in ME/CFS entitled “Thinking the Future: Early Career Investigators” that was attended by over 40 early career investigators, NIH program staff, and senior investigators. The workshop provided early career investigators opportunities to present their research and network with colleagues.

Biorepository

NINDS accepted biospecimens from a project funded by a private foundation, the Chronic Fatigue Initiative funded by the Hutchins Family Foundation. The biospecimens were collected from study participants at five clinical sites and had been stored at Duke University. The biospecimens are now housed at BioSEND, the NINDS-contracted biorepository, and they will be available together with clinical data to qualified investigators in the near future. Biospecimens from additional studies will be added to the biorepository going forward.

Outreach Activities

NIH used a variety of outreach strategies – including telebriefings, blogs, websites, listserv, and media opportunities – to keep the ME/CFS community informed of efforts to advance research in this disease area as well as to invite feedback and input from interested stakeholders. A full list of outreach activities is provided in Appendix F.

Intramural Activities

The NIH Intramural Research Program began a comprehensive multisystem ME/CFS study at the Clinical Center. The study focuses on post-infectious ME/CFS that has developed within the past five years in order to closely examine the clinical and biological characteristics of the disorder and improve understanding of its cause and progression.

Appendix B. Trans-NIH ME/CFS Working Group Members

Walter Koroshetz, M.D., Chair

National Institute of Neurological Disorders and Stroke

Vicky Whittemore, Ph.D.

National Institute of Neurological Disorders and Stroke

Andrew Breeden, Ph.D.

National Institute of Neurological Disorders and Stroke

Barbara McMakin

National Institute of Neurological Disorders and Stroke

Avindra Nath, M.D.

National Institute of Neurological Disorders and Stroke

Christine Torborg, Ph.D.

National Institute of Neurological Disorders and Stroke

Brian Walitt, M.D.

National Institute of Nursing Research / National Center for Complementary and Integrative Health

Guadalupe Aquino

National Center for Advancing Translational Research

Catherine Bennett, Ph.D.

NIH Center for Scientific Review

Joseph Breen, Ph.D.

(Alternate: Joshua Milner, M.D.)

National Institute of Allergy and Infectious Diseases

Milton Corn, M.D.

National Library of Medicine

Emmeline Edwards, Ph.D.

National Center for Complementary and Integrative Health

Basil Eldadah, M.D., Ph.D.

National Institute on Aging

Yolanda Vallejo-Estrada, Ph.D.

National Institute of Dental and Craniofacial Research

Adam Felsenfeld, Ph.D.

National Human Genome Research Institute

Rohan Hazra, M.D.

Eunice Kennedy Shriver National Institute of Child Health and Human Development

Mike Humble, Ph.D.

(Alternate: Jonathan Hollander, Ph.D.)

National Institute of Environmental Health Sciences

Joyce Hunter, Ph.D.

National Institute on Minority Health and Health Disparities

Kathy Jung, Ph.D.

National Institute on Alcohol Abuse and Alcoholism

Martha Matocha, Ph.D.

(Alternate: Leorey Saligan, Ph.D., RN, CRNP)

National Institute of Nursing Research

Cheryl L. McDonald, M.D.

(Alternate: Catherine Levy, RN)

National Heart, Lung, and Blood Institute

Christopher Mullins, Ph.D.

National Institute of Diabetes and Digestive and Kidney Diseases

TBD

National Cancer Institute

Matthew Rudorfer, M.D.

National Institute of Mental Health

Dana M. Greene, Ph.D.

Office of Behavioral and Social Science Research

Shelley Su, Ph.D.

National Institute on Drug Abuse

David Thomas, Ph.D.

Office of Research on Women's Health

James Witter, M.D., Ph.D.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

Steve Zullo, Ph.D.

National Institute on Biomedical Imaging and Bioengineering

Appendix C. ME/CFS Administrative Supplement Awards

The National Institute of Allergy and Infectious Diseases funded the following supplements:

- **A longitudinal immunological and virological study for ME CFS biomarker discovery;** PI: Luis Nacul; Project number: 3R01AI03629-03S1
- **A prospective study of CFS following infectious mononucleosis in college students;** PIs: Ben Z. Katz, Leonard A. Jason; Project number: 5R01AI105781-03S1
- **Immune cell gene expression and predictive models in CFS;** PIs: Fabien Campagne, Maureen Hanson; Project number: 4R01AI107762-04S1
- **Adaptive and innate immunity, memory and repertoire in vaccination and infection;** PI: Mark Davis; Project number: 5U19AI057229-13S1
- **Administrative supplement on ME/CFS;** PI: W. Ian Lipkin; Project number: U19AI109761-03S1

The National Institute of Neurological Disorders and Stroke funded the following administrative supplements:

- **Genomic approach to find novel biomarkers and mechanisms of CFS/ME;** PI: Lubov Nathanson; Project number: 3R15NS087604-01A1S1
- **Gender differences in myalgic encephalomyelitis/chronic fatigue syndrome;** PI: Mary A. Fletcher; Project number: 3R01NS090200-03S1

Appendix D. NIH-Funded ME/CFS Collaborative Research Centers and Data Management and Coordinating Center

In 2017, the NIH funded a network of three Collaborative Research Centers and a Data Management and Coordinating Center. In addition to the descriptions below, more information can be found on the MECFSnet website: <https://mecfs.rti.org/>.

The grants are managed by NIAID and NINDS. Additional participating NIH Institutes and Centers include: the National Heart, Lung, and Blood Institute; the National Human Genome Research Institute; the National Institute on Alcohol Abuse and Alcoholism; National Institute of Arthritis and Musculoskeletal and Skin Diseases; the National Institute on Drug Abuse; the National Institute of Mental Health; the National Center for Advancing Translational Sciences; and the National Center for Complementary and Integrative Health; and the Office of the Director.

The grants were awarded to:

- *Cornell ME/CFS Collaborative Research Center*

Principal Investigator: Maureen Hanson, Ph.D., Cornell University, Ithaca, New York; 1U54NS105541

The Cornell ME/CFS Collaborative Research Center conducts and promotes interdisciplinary research to identify the causes, biomarkers, and pathophysiology of ME/CFS with the goal of developing diagnostic and treatment methods. The Center draws expertise from Cornell's flagship campus and medical college, a local research institute, Ithaca College, and medical practices, utilizing their collective scientific and clinical expertise in advanced neuroimaging techniques, proteomics, metabolism, molecular biology, and genetics. Cornell is focusing on three main research projects designed to provide unique insights into ME/CFS by studying brain images, molecular markers in blood, and biologic and physiologic characteristics of exercise-induced post-exertional malaise (PEM). PEM is a hallmark symptom of ME/CFS. To simulate PEM for data-gathering purposes, researchers are conducting cardiopulmonary exercise tests using stationary bikes at Weill Cornell Medicine, the Ithaca College Wellness Clinic, and at the medical practice of John Chia, MD, in Los Angeles. The first project is using advanced brain imaging techniques, including MRI and PET, to look for markers of neuroinflammation and oxidative stress before and after exercise, to see if differences in the markers are linked with the disease. The second project is examining proteins, small molecules, and microRNAs in extracellular vesicles before and after exercise to find out whether the contents of vesicles are associated with ME/CFS symptoms. In the third project, Cornell researchers are sequencing the RNA in individual white blood cells in people with ME/CFS and healthy individuals before and after exercise, to learn more about the role of gene regulation and the immune system in the disease.

- *Center for Solutions for ME/CFS*

Principal Investigator: W. Ian Lipkin, M.D., Columbia University, New York City; 1U54AI138370

The Center for Solutions for ME/CFS ([CfS for ME/CFS](#)) is an interdisciplinary, inter-institutional center comprising [clinicians, clinical investigators, and basic scientists](#) who are committing to working together to understand the pathogenesis of ME/CFS and develop evidence-based strategies for interventions that prevent and mitigate disease. The team initially coalesced with an NIH call to respond to spurious reports linking xenotropic murine leukemia virus-related virus (XMRV) to ME/CFS. The team consolidated with support from the Hutchins Family Foundation Chronic Fatigue Initiative (CFI) and a crowd-funding initiative, the Microbe Discovery Project, to explore the role of infection and immunity in disease and identify biomarkers for diagnosis through functional genomic, epigenetic, proteomic, and metabolomic discovery. The Center's three main projects are [exploring the role of infection and immunity in ME/CFS](#), working to [understand the roles of metabolomics and gene expression in ME/CFS](#), and working with the ME/CFS community and clinicians to design a mobile app ("[myME/CFS](#)") to help patients and physicians acquire valuable longitudinal data and to personally as well as clinically manage the illness.

- *Topological Mapping of Immune, Metabolomic and Clinical Phenotypes to Reveal ME/CFS Disease Mechanisms*

Principal Investigator: Derya Unutmaz, M.D., The Jackson Laboratory, Farmington, Connecticut; 1U54NS105539

The Jackson Laboratory (JAX) is an independent, nonprofit biomedical research institution whose mission is to discover precise genomic solutions for human disease. JAX is bringing together experts in computational biology, statistics, chemistry, immunology, metabolomics, and microbiology to test an emerging hypothesis about the interplay between a patient's immune system, metabolism, and microbiome in the onset and progression of ME/CFS. Blood and stool samples from individuals with ME/CFS and healthy controls are being collected at multiple time points at the Bateman Horne Center in Salt Lake City, UT. Samples are then being analyzed at the JAX CRC to explore changes in the immune system, metabolome, and gut microbiome of individuals with ME/CFS over time and in comparison to healthy individuals. The role of the gut microbiome, or the collection of microorganisms that live in the digestive tract of each individual, has become an area of particular interest in ME/CFS. The CRC is investigating how the gut microbiome interacts with the immune system to cause disease and how it contributes to disease severity. The research project is generating a highly detailed longitudinal collection of clinical and biological ME/CFS data that will be analyzed using advanced computational technologies such as machine learning approaches. Finding a biological basis for ME/CFS and related biomarkers could lead to faster diagnosis and personalized treatment approaches.

- *Data Management and Coordinating Center (DMCC) for the ME/CFS Collaborative Research Centers*

Principal Investigator: Linda Morris Brown, MPH, DrPH, Research Triangle Institute, Research Triangle, North Carolina; 1U24NS105535

RTI International (RTI) leads the Data Management and Coordinating Center (DMCC) for the multi-center ME/CFS Collaborative Research Network. In this capacity, RTI provides

advanced computing systems and expertise to bring together research data from the CRCs into a unified multi-omic database, which combines information from studies looking at genes, proteins, immune function, etc. This data management, analytic support, and coordination will promote the development of new ideas to enhance ME/CFS research by augmenting existing CRC expertise and fostering partnerships among the CRCs and the broader research community. RTI is fostering increased transparency and collaboration within the ME/CFS community by coordinating the network's community outreach activities and hosting a public website. RTI, a large nonprofit research institute, has served as a data coordinating center for more than 40 multi-site/multi-study research networks, including networks focused on maternal and child health, traumatic brain injury, pelvic floor disorders, blood banking and transfusion medicine, sickle cell disease, Zika virus, and other emerging health challenges.

Appendix E. “Accelerating Research on ME/CFS” Conference Agenda

Goal: Present high-quality science studies of ME/CFS to better understand the state of the science and help drive the field forward by identifying gaps and opportunities. Presentations should emphasize newer work or in some cases critical previous work that fits with current models of ME/CFS. Audience is expected to be scientists, clinicians, patients and other ME/CFS stakeholders. Conference will be webcast and publicly available.

Day 1: April 4, 2019

Masur Auditorium, NIH Clinical Center

9-9:20 AM Welcome/Introductions – NINDS and NIAID Staff

9:20-10:00 AM Setting the stage – ME/CFS 101- Lucinda Bateman

Metabolomics/Metabolism of ME/CFS

Joe Breen (NIAID) - moderator

10-10:30 AM *“Metabolic features of chronic fatigue syndrome”* Robert Naviaux (UCSD)

11-11:30 AM *“Informatics tools for investigating metabolic dysregulation in ME/CFS”* Oliver Fiehn (UC Davis)

11:30-12 NOON *“The Biochemistry to Support the Evidence of Neuroinflammatory Involvement in ME/CFS”* Jonas Bergquist (Uppsala Univ)

Immunology of ME/CFS

Nancy Klimas (NOVA SE) – moderator

1-1:30 PM *“TBD”* Jose Montoya (Stanford)

1:30-2 PM *“Potentially important T cell activity in CFS/ME”* Mark Davis (Stanford University)

2-2:30 PM *“Disturbance of the immune system during ME/CFS”* Derya Unutmaz (Jackson Labs)

2:30-3PM *“Cellular Metabolism of Immune Cells”* Maureen Hanson (Cornell University)

Provocation Studies

Andrew Breeden (NINDS) - moderator

3:30-4 PM *“Accelerating to Clinical Trials – Modeling to Predict Intervention”* Nancy Klimas (NOVA SE)

4:00-4:30 PM *“Pathophysiology and treatment of exertional intolerance in ME/CFS: insights from cardiopulmonary exercise testing”* David Systrom (BWH/Harvard)

4:30-5 PM *“Exertion intolerance: What is the evidence telling us?”* Betsy Keller (Ithaca)

5-5:30 PM *“Role of circulating microRNAs in ME/CFS pathogenesis: From molecular stratification to therapeutic targets”* Alain Moreau (U. de Montreal)

Group Discussion Q&A

5:30-6PM - Terri Wilder (#MEAction) - moderator

6:00-7PM – Poster Session – posters from Workshop for Young Early Career ME/CFS Investigators – **FAES Terrace, NIH Clinical Center**

Day 2: April 5, 2019

Masur Auditorium, NIH Clinical Center

8:30-9:30 AM Clinician Panel Discussion Tony Komaroff- moderator

Lucinda Bateman – *Orthostatic intolerance*

Susan Levine – *Mast cell activation syndrome and incidence; quick overview of biology, diagnosis, and treatment*

Jose Montoya – *Is there a role for anti-herpes therapy in ME/CFS?*

Daniel Peterson – *Precision medicine and artificial intelligence in the diagnosis and treatment of ME/CFS*

Peter Rowe – *Neurodynamic dysfunction*

9:30-10AM Q and A session with Clinician Panel – Open mic questions

10-10:10 AM Welcome and Remarks - Francis Collins (NIH Director), introduced by Walter Koroshetz (NINDS Director)

NINDS Intramural study update

Vicky Whittemore – introduction

10:15-10:45 AM Avi Nath (NINDS)

10:45-11:15 AM BREAK

Microbiome/Virome

Sadie Whitaker (Solve ME/CFS) - moderator

11:15-11:45 AM *“Center for Solutions for ME/CFS: 18 months in...”* Ian Lipkin (Columbia)

11:45-12:15 NOON *"From metagenomes to therapeutics: decoding the interactome* Julia Oh (Jackson Labs)

1-1:30 PM *"Pathogenic alterations of mitochondrial dynamics: A working model for ME/CFS"* Bhupesh Prusty (Wuerzburg)

New Technology for ME/CFS Research

Joe Breen (NIAID) - introduction

1:30-2 PM *The Molecular Basis of ME/CFS* - Ron Davis (Stanford Genome Center)

Imaging of the CNS and ME/CFS

Fred Friedberg (Stony Brook) - moderator

2:00-2:30 PM *"Neuroinflammation in ME/CFS"* Jarred Younger (UAB)

2:30-3:00 PM *"Optimizing techniques for neuroimaging brainstem in ME/CFS during post-exertional malaise and neuroinflammation"* Mike VanElzakker (Harvard)

Orthostatic/Autonomic Disorders

David Systrom (BWH/Harvard) - moderator

3:30-4:00 PM *"Orthostatic Intolerance in ME/CFS: Gains and Gaps"* Peter Rowe (JHU)

4:00-4:30 PM *"Small Fiber Neuropathy; A Common Contributor"* Anne Oaklander (MGH)

4:30 - 5:15 PM – Summary of Conference – Tony Komaroff (Harvard)

5:15 – 6:15 PM – Next Steps for ME/CFS Research (30 min) and Open Question/Answer with Panel (30 min)

Panel: Joe Breen (NIAID), Vicky Whittemore (NINDS), Maureen Hanson (Cornell), Sadie Whitaker (SMCI), Jose Montoya (Stanford)

Appendix F. NIH Outreach Activities

NIH uses a variety of outreach strategies to keep the ME/CFS community informed about efforts to advance research in this disease area as well as to invite feedback and input from interested stakeholders.

Telebriefings. On March 8, 2016, NIH hosted its first telebriefing with the ME/CFS community. NIH now holds these calls three times a year. The calls provide NIH staff an opportunity to update the community on ME/CFS-related activities. In addition, the phone line opens during the second half of the call, encouraging the community to engage directly with NIH staff. A recording and transcript of the calls are posted online.

List Serv. To help keep the ME/CFS community informed about NIH activities in this disease, NIH created a list serv to send out announcements of upcoming events and relevant updates. There are currently more than 400 subscribers to the list serv. Anyone who is interested in receiving announcements and updates from NIH is invited to sign up for the list serv.

Trans-NIH ME/CFS website. The Trans-NIH ME/CFS Working Group has a website (www.nih.gov/mecfs) that includes announcements, events, resources, and funding information. The website is regularly updated and is a valuable source of information about NIH work in this area.

NIH Director's Blog. On March 21, 2017, NIH Director Dr. Collins and NINDS director Dr. Koroshetz co-authored "[Moving Toward Answers in ME/CFS](#)," a piece for the NIH Director's blog that focused on the disease. The NIH Director's Blog is very popular and this post provided a lot of visibility and awareness for the disease.

Media opportunities. To inform the public about NIH's efforts in advancing ME/CFS research and to help raise awareness in general about the disease, NIH staff have participated in several media interviews, discussing ME/CFS. Examples of ME/CFS stories in the press that featured NIH staff are:

- "['Milestone' Meeting Highlights NIH Efforts to Combat ME/CFS](#)," Medscape, April 17, 2019
- "[NIH Striving to Avoid False Hope in Chronic Fatigue](#)," MedPage Today, January 16, 2018
- "[NIH Study Takes the Deepest Dive Yet Into Baffling Condition](#)," NBC News, May 3, 2017
- "[NIH Study Aims To Unravel The Illness Known As 'Chronic Fatigue Syndrome'](#)," NPR, May 1, 2017

NIH continues to explore media opportunities to describe our activities related to ME/CFS and to help bring attention to the general public about this debilitating disease.

One strategy that NIH uses to invite media engagement is by issuing press releases on important scientific findings or announcements of activities or policies that will have widespread impact. Recent ME/CFS-related press releases issued by the NIH include a statement of renewed emphasis on ME/CFS ([NIH takes action to bolster research on Myalgic Encephalomyelitis/Chronic Fatigue Syndrome](#)) and the announcement of the CRCs and DMCC

[*\(NIH announces centers for myalgic encephalomyelitis/chronic fatigue syndrome research\)*](#). NIH plans for publications of significant NIH-funded ME/CFS research to be promoted by NIH, through press releases and media outreach.

ECI Website. NIH is working closely with RTI to develop a website geared towards Early Career Investigators. The website will provide information about finding and applying for grants as well as news and upcoming events.

RFI Comments. In an effort to increase transparency, NIH posted full comments received in response to the following Requests for Information and Comments:

- [Request for Information: Soliciting Input on How Best to Advance Myalgic Encephalomyelitis/Chronic Fatigue Syndrome \(ME/CFS\) Research](#)
- [Common Data Elements for ME/CFS Research](#)
- [Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome \(ME/CFS\)](#)

Appendix G. ME/CFS Nonprofit Research Activities (Listed Alphabetically)

Bateman Horne Center

Bateman Horne Center (BHC) is a 501(c)3 nonprofit clinic and research center, modeled as a Center of Excellence, devoted to advancing research and improving clinical care for people with ME/CFS. In addition to numerous clinical collaborations with NIH funded scientists at the University of Utah (Kathleen Light PhD, Alan Light PhD, Akiko Okifuji PhD), BHC is the clinical core of the NIH funded ME/CFS Collaborative Center Grant awarded to Derya Unutmaz, M.D., at The Jackson Laboratory and a clinical site participating with the NIH Collaborative Center Grant to W. Ian Lipkin, M.D., Center for Solutions, Columbia University. The BHC Research Center was also a site for the Center for Disease Control and Prevention Multi-site Clinical Assessment of CFS.

The research team at BHC has built a rich multidimensional research database created by the combined data of almost 200 ME/CFS subjects whose biological samples have been separately analyzed by several NIH-funded scientists looking at epigenetics, whole gene sequencing, gene expression, immune function, metabolism, microbiome, and immune evidence of prior infections. Additional primary research at BHC is aimed at “operationalizing” the National Academy of Medicine 2015 core clinical diagnostic criteria such as impaired function, PEM and orthostatic intolerance as clinical tools for more accurate and rapid diagnosis.

#MEAction

#MEAction is a grassroots international network of patients and healthy allies focused on building public awareness of ME, facilitating patient and caregiver support venues, advocating for increased public investment in research and medical education, promoting compassionate and effective medical care, and generating researcher interest in ME. #MEAction facilitates patient engagement by actively recruiting for participation in research studies, publishing an annual Research Review, and attending and reporting on ME conferences. #MEAction also supports several young researcher and clinical fellowships, produces medical education materials including a nationally accredited CME, engages in epidemiological research for the ME community, and partners with the NIH-supported Research Centers project with Columbia University. Finally, #MEAction hosts MEpedia, an ME wiki that provides context for every aspect of the history and biology of the disease.

Open Medicine Foundation

Open Medicine Foundation (OMF) is currently funding three research centers – one at Stanford University under the direction of Ronald W. Davis, PhD, one at the Harvard University Affiliated Hospitals under the direction of Ronald G. Tompkins, MD, ScD, and Wenzhong Xiao, PhD, and one at Uppsala University in Sweden under the direction of Jonas Bergquist, MD, PhD.

The OMF-funded **ME/CFS Collaborative Research Center at Stanford University** is currently targeting the molecular cause of ME/CFS, establishing a diagnostic test, and

identifying effective treatments. The Stanford Center is accelerating the development of diagnostics with two recent publications for the nanoneedle (<https://www.pnas.org/content/116/21/10250>) and the red blood cell deformability test (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6398549/>).

New publications are expected soon on OMF's first major funded research project, the Severely ill Big Data Study (SIPS), the deep dive omics analysis of severely ill patients. This study has unveiled several potential areas that have led to further projects including a hypothesis that was published recently (<https://www.mdpi.com/2075-4418/9/3/82>) that is known as the metabolic trap hypothesis, led by Robert Phair, PhD. The team at Stanford is also engaged in other research projects including the examination of heavy metals in ME/CFS patients, the study of T-cells and their role as master immune regulators, and the comprehensive study of ME/CFS patients and their family members who are either healthy or have an associated disease.

The OMF-funded **ME/CFS Collaborative Research Activities at MGH and the Harvard Affiliated Hospitals** is a new initiative bringing together faculty from three Harvard institutions (MGH, Beth Israel and Brigham and Women's) and other international collaborators. The major projects are in the planning and IRB application phases, however, several key collaborators in the group are observing ME/CFS patients undergoing iCPET. This research is resolving cardiopulmonary anomalies in ME/CFS patients as well as neurological impairments via brain imaging applied to patients before and after the physical stress of the iCPET. The major projects in planning will extend this research on circulation and neuroinflammation anomalies with a particular focus on post-muscular stress by conducting a multi-omic characterization of muscle tissue before and after exercise to monitor their recovery. The new Collaborative Center at Harvard is also seeking to develop the infrastructure required to conduct rigorous clinical investigations. An initial project to build towards this endeavor is the development of a symptom diagnostic using Computerized Adaptive Testing (CAT).

The OMF-funded **ME/CFS Collaborative Research Center at Uppsala University** is the newest Collaborative Center and seeks to focus its attention on the targeted molecular diagnosis of ME/CFS with the future goal of evidence-based strategies for intervention. Two major projects underway at Uppsala is the analysis of cerebrospinal fluid as a unique source of ME/CFS neurochemical biomarkers and the search for autoantibodies in the blood of ME/CFS patients. This group is also very innovative, exploring new tools for extracting biofluids (CSF and blood) from patients and developing new methods to target specific proteins and metabolites using high-resolution mass spectrometry.

Solve ME/CFS Initiative

Founded in 1987, the Solve ME/CFS Initiative is a nonprofit organization focused on supporting research and advocating for increased federal spending on behalf of millions of ME/CFS patients and their families. The organization's research programs are designed to improve the ME/CFS research infrastructure and support work that will identify and untangle the complex causes and symptoms so that approaches to treatment and prevention can be developed.

Through the Ramsay Grant Program, the Solve ME/CFS Initiative invests in pilot studies, with a particular emphasis on engaging young investigators and researchers new to the field. The availability of this funding is intended to address the lack of researchers working on ME/CFS

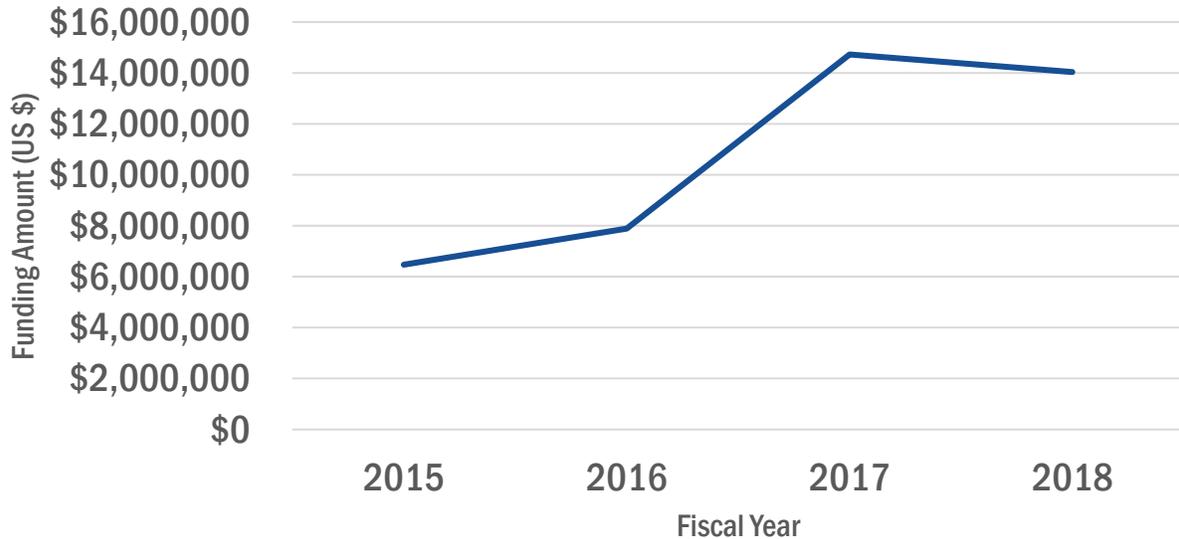
and to produce pilot data for larger grant applications. The Solve ME/CFS Initiative is building infrastructure to take the Program from a series of individual projects to a strong network of researchers, who can learn from each other, build on each other's findings, and collaborate to better decipher this disease.

The You + M.E. Registry and Biobank is a resource of clinical data and biosamples. You + M.E. is designed to be a community tool that leverages digital health and technology to facilitate both data capture and data sharing. The Registry includes a mobile app for ongoing reporting of symptoms, factors, and activity to help people living with ME/CFS to better track and understand their disease and contribute vital data for research. Working with a consortium, the Solve ME/CFS Initiative aim to make a rich, longitudinal dataset and paired biosamples available to researchers from around the world.

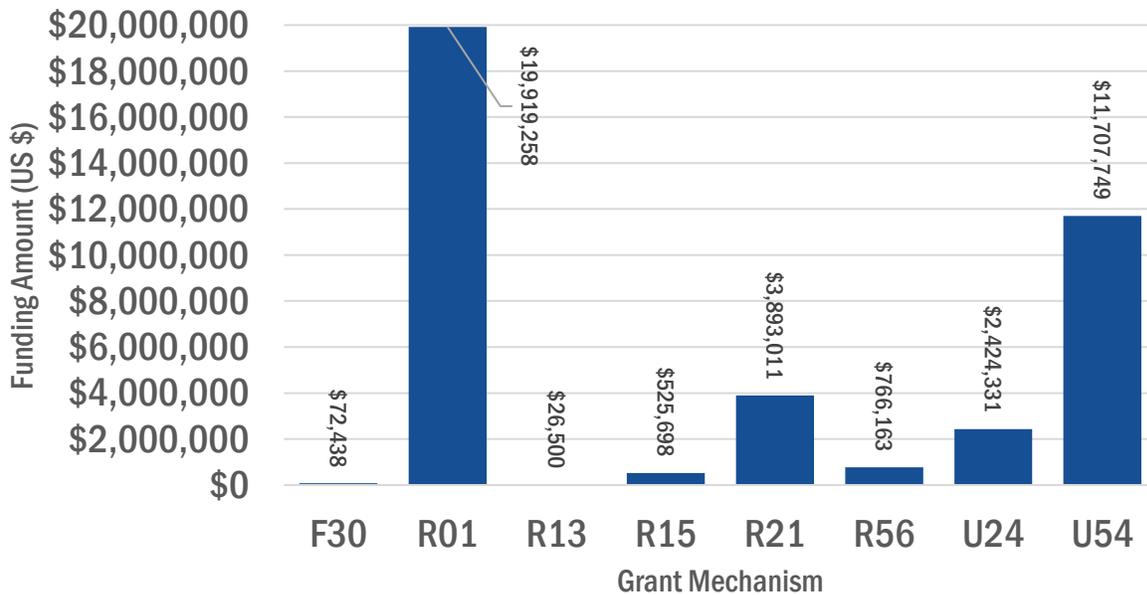
Appendix H. NIH ME/CFS Funding

Data obtained from the NIH Research, Condition, and Disease Categorization (RCDC) website.

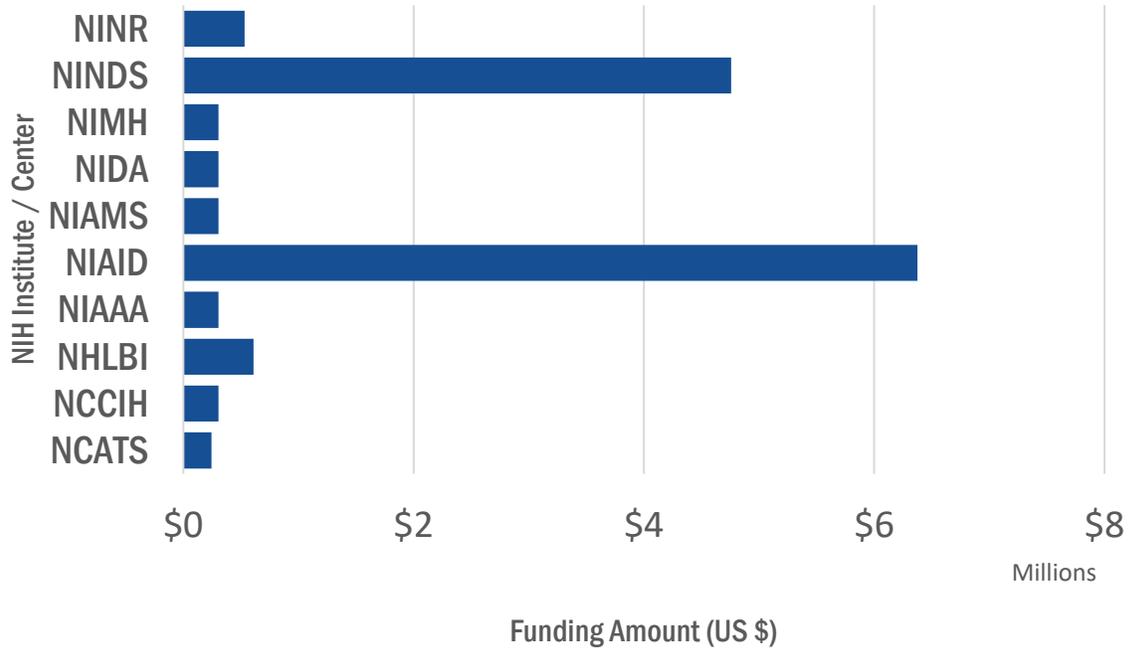
NIH ME/CFS Research Funding from FY 2015-2018



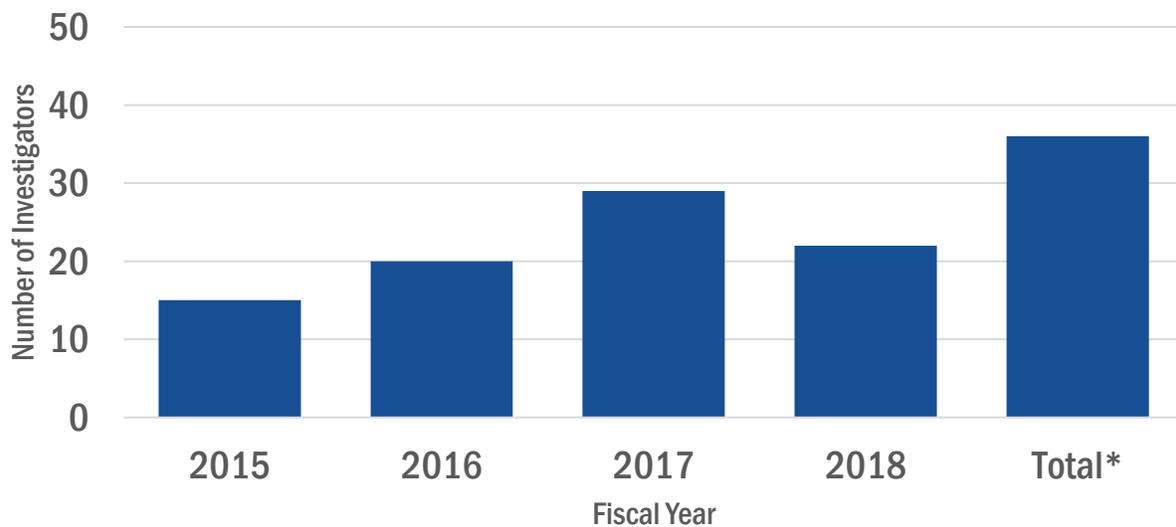
NIH ME/CFS Extramural Research Funding by Grant Mechanism FY 2015-2018



NIH ME/CFS Research Funding by NIH Institute/Center in FY 2018

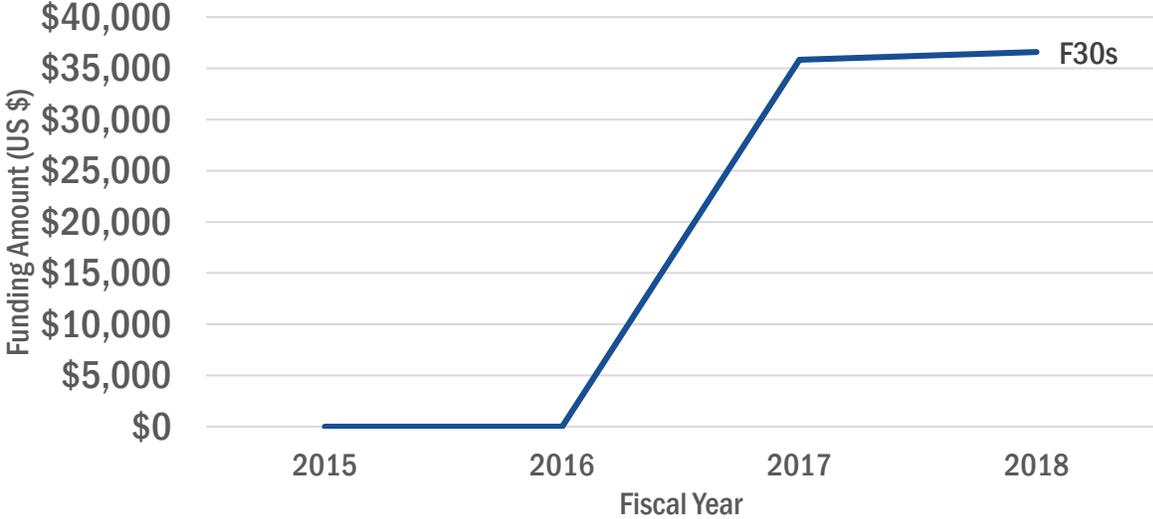


Number of Principal Investigators on Extramural NIH ME/CFS Grants



**Total - This represents the total number of unique principal investigators across all of FYs 2015-2018. PIs that were funded in multiple years were only counted once.*

NIH ME/CFS Training Award Funding from FY 2015-2018



Appendix I. NANS Council Working Group for ME/CFS Research Charge

Background

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic, complex, multi-faceted condition characterized by substantial reduction or impairment in the ability to engage in pre-illness levels of occupational, educational, social or personal activities due to post-exertional malaise; unrefreshing sleep, and at least one of the following symptoms: cognitive impairment and/or orthostatic intolerance (Beyond Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome: Redefining an Illness, 2015). Many individuals with ME/CFS experience significant disability, and some become homebound or bedbound. The etiology and pathogenesis remain unknown, there is no laboratory diagnostic test, and no FDA-approved treatment for ME/CFS. An estimated 836,000 to 2.5 million people in the United States have ME/CFS (Jason et al., 1999, 2006). ME/CFS is an unmet public health need with direct and indirect economic costs estimated to range from \$18 billion to \$51 billion annually in the US (Reynolds et al., 2004; Jason et al., 2008; Lin et al., 2011). Limited knowledge about the underlying cause(s) of ME/CFS creates an additional burden for individuals with the disease, their families and caregivers, as well as for health care providers.

Since the fall of 2015, the Trans-NIH ME/CFS Working Group has coordinated the extramural research efforts at NIH. This working group is composed of representatives from 24 NIH Institutes, Offices, and Centers who meet monthly. Chaired by Walter Koroshetz, M.D., director of the National Institute of Neurological Disorders and Stroke (NINDS), this group came together to issue two RFAs that resulted in the funding of three ME/CFS Collaborative Research Centers and a Data Management and Coordinating Center as well as administrative supplement grants in 2016. In addition, there is a portfolio of research grants on ME/CFS that are administered across NIH, primarily by the National Institute of Allergy and Infectious Disease (NIAID) and NINDS.

There is a significant need to grow the research portfolio on ME/CFS and to identify ways in which to attract both young investigators and investigators from other research fields to focus their research efforts on and develop strategies to advance research on this disease.

Charge

This new NANS Working Group will provide scientific guidance to the NANS Council on how best to advance research on ME/CFS at the National Institutes of Health (NIH).

Consistent with this charge, this NANS-WG will:

- With reports from the P2P workshop and the IOM report as a guide:
 - Assess current NIH ME/CFS research activities and the extent to which they address opportunities and gaps in ME/CFS research
 - Suggest specific goals to further address opportunities and gaps in ME/CFS research, given the evolving scientific landscape
- Consider unique opportunities for NIH-supported ME/CFS research to train and empower a pipeline of young investigators, as well as investigators new to the field

- Identify an effective potential structure to enhance ongoing biomedical research collaboration and communication between relevant advocacy organizations, individuals with ME/CFS, researchers, and federal agencies

Process, Deliverables, and Timeframe

This working group of the NANS Council will:

- Seek input broadly from stakeholders (including people with ME/CFS, researchers and clinicians, and advocacy organizations) and other federal agencies
- Hold workshops to assess current efforts in areas outlined in the working group charge and identify opportunities for research
- Present its final report to the full NANS Council at its September 2019 meeting

Appendix J. December Working Group Meeting Agenda

December 19, 2018

Rockville, MD

8:00 – 8:15 AM	Registration – <i>Gather at security desk to be escorted into NSC building</i>
8:15 – 8:30	Opening Remarks <ul style="list-style-type: none"> • <i>Walter Koroshetz, MD</i>
8:30 – 8:45	Review of Agenda and Goals of Meeting <ul style="list-style-type: none"> • <i>Steve Roberds, PhD</i>
8:45 - 9:00	<u>Session 1: ME/CFS Research: Setting the Stage</u> <i>Meeting Chair: Steve Roberds, PhD</i>
9:00 – 9:20	The Institute of Medicine Report: High-Level Findings <ul style="list-style-type: none"> • <i>Lucinda Bateman, MD</i>
9:20 – 9:30	The Pathways to Prevention Workshop: High-Level Research Recommendations <ul style="list-style-type: none"> • <i>Kate Winseck, MSW and Carrie Klabunde, PhD</i>
9:30 – 9:50	Recommendations from the Federal Partner Meetings <ul style="list-style-type: none"> • <i>Vicky Whittemore, PhD</i>
9:50 – 10:10	Discussion <ul style="list-style-type: none"> • Review of the high-level categories of recommendations from both the IOM and P2P. • Which are appropriate categories to adopt or adapt, given the Working Group’s charge? • What categories of output should the Working Group plan to generate for the final report?
10:10 – 10:25	Overall NIH ME/CFS Activities and Research Funding <ul style="list-style-type: none"> • <i>Vicky Whittemore, PhD and Andrew Breeden, PhD</i>
10:25 – 10:40	The Centers for Disease Control and Prevention (CDC) ME/CFS Research <i>Elizabeth Unger, MD, PhD</i>
10:25 – 10:40	Break
10:40 – 10:55	Solve ME/CFS Initiative Research Funding <ul style="list-style-type: none"> • <i>Carol Head</i>
10:55 – 11:10	The Open Medicine Foundation (OMF) ME/CFS Research Funding <ul style="list-style-type: none"> • <i>Linda Tannenbaum</i>
11:10 – 11:25	The 2019 Accelerating ME/CFS Research Conference <ul style="list-style-type: none"> • <i>Joe Breen, PhD</i>

11:25 – 12:00	<p>Discussion</p> <ul style="list-style-type: none"> • How can the Working Group best compile and review progress on recommendations from the Federal Partners meeting? What additional information does the Working Group feel it needs in order to identify new and emerging research opportunities? • How can the 2019 ME/CFS Research Conference be used as an information gathering opportunity? Can any outputs from this conference feed into the Working Groups efforts?
12:00 – 12:30	<p>Break – Lunch orders will be delivered during the break and Session 2 will be a working lunch</p>
12:30 – 12:35	<p><u>Session 2: Identifying an Effective Structure for Collaboration</u></p> <p>Background of Collaborative Structure</p> <ul style="list-style-type: none"> • Vicky Whittemore, PhD <p>12:35 – 12:50</p> <p>The Interagency Collaborative to Advance Research in Epilepsy (ICARE) as an Example Collaborative: Structure, Activities, and Examples of Research Issues Addressed</p> <ul style="list-style-type: none"> • Miriam Leenders, PhD <p>12:50 – 1:15</p> <p>Discussion</p> <ul style="list-style-type: none"> • How can the Working Group identify a potential structure or mechanism to enhance ongoing biomedical research collaboration and communication between relevant advocacy organizations, individuals with ME/CFS, researchers, and federal agencies?
12:35 – 12:50	
12:50 – 1:15	
1:15 – 1:30	<p><u>Session 3: Working Lunch and Discussion of Expanding the Research Pipeline</u></p> <p>Thinking the Future: Developing a Pipeline of Young/Early Career ME/CFS Investigators</p> <ul style="list-style-type: none"> • Vicky Whittemore, PhD <p>1:30 – 2:00</p> <p>Discussion</p> <ul style="list-style-type: none"> • How can the Working Group identify NIH activities that could be utilized to train and empower a pipeline of young investigators? • How can the Working Group identify opportunities to attract and retain investigators new to the field? • How can the workshop for young / early career ME/CFS investigators be used as an information gathering opportunity? • Are there other disease research areas we can learn from to develop a young investigator pipeline? • Is there additional information the Working Group needs to inform its findings related to training and expanding the research pipeline?
1:30 – 2:00	
2:00 – 2:15	<p>Break</p>
	<p><u>Session 4: Gathering Stakeholder Input</u></p>

2:15 – 2:30	<p>Experiences of the TS Alliance in Using Patient Input to Inform a Research Strategy</p> <ul style="list-style-type: none"> • <i>Steven Roberds, Ph.D.</i>
2:30 – 2:40	<p>Outreach Activities of the Solve ME/CFS Initiative</p> <ul style="list-style-type: none"> • <i>Carol Head</i>
2:40 – 2:50	<p>Outreach Activities of MEAction</p> <ul style="list-style-type: none"> • <i>Jennifer Brea or Rochelle Joslyn, PhD</i>
2:50 – 3:15	<p>Discussion</p> <p>How should the Working Group seek input broadly from stakeholders (including people with ME/CFS, researchers and clinicians, and advocacy organizations) and other federal agencies?</p>
3:15 – 3:45	<p><u>Wrap up and Next Steps</u></p>
	<ul style="list-style-type: none"> • Formulating an overall workplan, timeline and priorities for future Working Group activities.

Appendix K. Summary of Responses to Request for Information (RFI): Soliciting Input on How Best to Advance Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) Research

To gather broad input from the public, patient, medical, and scientific communities, the working group issued a Request for Information (RFI) (NOT-NS-19-057) that was open to all members of the public from March 15 to May 1, 2019. There were 281 total responses, including 23 from researchers, 14 from healthcare providers, 195 from individuals with ME/CFS, 61 from patient advocates, and 25 from other interested parties. RFI respondents could self-identify in more than one of the above response groups. RFI responses helped inform working group discussions of how to advance research on ME/CFS.

The below summary includes only the most commonly mentioned topics and responses. Full responses are posted on the NINDS website at <https://www.ninds.nih.gov/About-NINDS/Who-We-Are/Advisory-Council/ME-CFS-Working-Group>. Not all of the topics or suggestions listed in this summary fall within the mission of NINDS. However, they were included in this summary because these are the issues that were commonly cited as important.

Summary of Responses by Topic

Funding. Increased funding for ME/CFS research was the highest priority stated by most respondents. Most of the responses stated that insufficient funds are hindering the progress in ME/CFS research and preventing researchers from entering the field. Most respondents did not suggest a specific amount of funding that is needed, instead commenting that funding should be commensurate with the burden of disease. Of those who did give specific amounts of funding needed, suggestions ranged from \$200 million/year to funding levels on par with HIV/AIDS [~\$3 billion in FY 2018]. Several respondents advocated for ME/CFS-specific funding opportunity announcements (FOAs) or explicitly mentioning ME/CFS in funding opportunity announcements for comorbid conditions. Some responses suggested specific topics for FOAs, such as exploratory/early-stage research, clinical trials, and cross-disciplinary research. Some respondents also encouraged increased funding for the ME/CFS Collaborative Research Centers (CRCs). Some respondents advocated for additional funds or specific FOAs to encourage new investigators to enter the field and to encourage mid-career investigators from other fields to do research on ME/CFS. A few responses suggested increasing funding through nongovernmental sources including community fund-raising, philanthropy, start-ups and big pharmaceutical companies, and public-private partnerships.

Medical and Graduate Education. Many respondents emphasized the importance of educating medical professionals and researchers about ME/CFS and dispelling the misconception that it is a psychological disease. A number of responses noted that the stigma surrounding ME/CFS and doctors' lack of knowledge have led to misdiagnosis, delayed proper treatments, and stopped individuals with ME/CFS from receiving disability benefits. A few respondents said that increased medical education would lead to more people being diagnosed with ME/CFS who

could then participate in research studies. The proposed strategies for promoting ME/CFS education include:

- supporting ME/CFS education in medical and graduate schools, as well as continuing medical education for primary care physicians.
- using documentaries about ME/CFS or having people with ME/CFS directly interact with students so they learn about how the disease affects people.
- working with advocacy organizations, medical associations, and state medical boards to create curricula.
- including ME/CFS in medical board exams.
- supporting more fellowships and internships for ME/CFS or pairing trainees with established ME/CFS clinicians.
- creating a ME/CFS-specific journal that would allow physicians and researchers to communicate the most recent findings.

Public Awareness and Stigma. Many responses emphasized the negative impact of stigma surrounding ME/CFS. Respondents stressed that stigma causes the medical community and the general public to dismiss the needs of people with ME/CFS. Stigma affects an employer's willingness to accommodate the needs of a person with ME/CFS, and it leads to reduced social support and increased social isolation of people with ME/CFS, severely affecting their mental and physical health. Respondents advocated for public service announcements, documentaries, media engagement, scientific publications, and education starting at the high school level. They would like the public to become aware of the number of people living with this disease and to understand how severely debilitating the disease can be, affecting every aspect of a person's life. Respondents strongly emphasized the need to dispel the misconception that ME/CFS is a psychological disease or the result of physical deconditioning and highlighted the importance of developing biomarkers and other objective diagnostic methods to increase recognition of ME/CFS as a biological disease, in addition to facilitating accurate diagnosis. A few people also commented that the current name focuses on only one symptom and minimizes the severity of the disease. They would like the name to not include "fatigue," as they feel that the word further stigmatizes the disease.

Biomarkers/Diagnosis. Accurate diagnostic tests, specifically biomarkers, was a top priority for many respondents. An objective diagnostic test would facilitate proper diagnosis and timely treatment and would increase the public and medical recognition of ME/CFS as a biological disease. Respondents emphasized that any diagnostic test that is developed should be easily accessible for general clinical practice. In the absence of objective diagnostic tests or biomarkers, several respondents advocated for using the International Consensus Criteria (ICC) and/or the Canadian Consensus Criteria (CCC) for defining ME/CFS. Others stressed the need for creating consensus on a case definition specifically for research. Many people noted that post-exertional malaise (PEM) should be included in any definition of ME/CFS.

Treatments. Many responses said that the top ME/CFS research need is finding effective treatments to prevent the disease, alleviate symptoms, and find a cure. Respondents suggested that researchers develop new drugs, repurpose currently available medications, and investigate

hormone therapy, nutritional supplements, immunoglobulin treatments, plasmapheresis, antiviral treatments and stem cell therapy as potential interventions. Respondents also advocated for research into lifestyle interventions such as nutrition, stress reduction, and removing environmental triggers. Some respondents urged research into functional or holistic approaches to treating ME/CFS. Respondents also encouraged more research into physiological self-management techniques such as heart rate monitoring and pacing, to help them improve symptoms and improve their quality of life.

Causes. Respondents emphasized that research into the causes of ME/CFS will facilitate treatment development. Potential causes noted in the responses include genetic mutations, neurological dysfunction, immune dysfunction, vaccines, stress, viruses or other pathogens, microbiome, and metabolic or mitochondrial defects. Other responses suggested that ME/CFS is triggered and modified by environmental factors such as mold, chemicals, foods, and wireless technology.

Epidemiology. Many people noted that large, longitudinal epidemiological studies are needed to better understand the disease and to determine how many people are living with ME/CFS. This information may help to identify possible causes of and treatments for ME/CFS. Respondents noted that this may also help to convince the public and medical communities of the severity of the disease and the economic and public health impact.

Post-exertional Malaise (PEM). Many respondents considered PEM to be a defining feature of ME/CFS and advocated for careful characterization of PEM in people with ME/CFS, studying the causes and physiology of PEM, and developing treatments for PEM. A few respondents noted that PEM can occur in people with other diseases or disorders so PEM shouldn't be the sole symptom that defines ME/CFS. Additional research is needed to determine if PEM associated with ME/CFS is distinct from PEM and exertional intolerance in other diseases. Some respondents pointed out that research is needed to help people with ME/CFS determine the maximal level of activity that they can maintain without triggering PEM.

Suicide. Respondents noted that ME/CFS is associated with increased risk for suicide and that the risk of suicide among people with ME/CFS make the need to find effective treatments for ME/CFS even more pressing. Respondents identified the need for more research into suicide rate and prevention and suggested increased public awareness of ME/CFS to prevent suicide.

New ME/CFS Researchers. Many respondents noted that the best ways to get new researchers into the field are to increase funding for ME/CFS and to improve ME/CFS education in medical and graduate schools (as noted above in the **Medical or Graduate Education** section). They also identified the need to increase awareness among trainees through additional blogs and outreach programs, funding of trainees and young investigators to attend conferences, loan repayment programs for ME/CFS investigators, and establishment of ME/CFS-specific fellowship and training programs.

Specific ME/CFS Researchers/Organizations. Several respondents suggested funding specific researchers or organizations.

Medical Specialties. Responses emphasized that ME/CFS is a multi-system disease that requires many different medical specialties to be engaged in the research and care. Funding policies, programs, and consortia should be used to facilitate collaboration and communication across specialties. The most commonly mentioned specialties were cardiology, endocrinology, exercise physiology, functional medicine, gastroenterology, hematology, immunology, infectious disease, integrative medicine/physiology, neurology, rheumatology, and virology.

Comorbid Conditions or Diseases with Overlapping Symptoms. Many respondents noted that diseases that may be comorbid or share common symptoms with ME/CFS should also be studied. Respondents listed a wide range of diseases and conditions that fell into the general categories of brain and nervous system disorders, cardiovascular and blood diseases, connective tissue disorders, endocrine diseases, environmental intolerances, fatigue and pain disorders, immunological diseases, infectious diseases and their sequelae, and rare genetic diseases.

Data Sharing, Centralized Databases, and Biobanks. Respondents advocated for open databases for ME/CFS research that include past and ongoing treatments, diagnostic tests, and medical records from individuals with ME/CFS. They also advocated for biobanks that would store and distribute biospecimens to researchers. To facilitate comparison across studies they encouraged standardization of data and biospecimen collection both within the context of databases and biobanks and in studies that don't use these resources. They suggested that this would promote communication between ME/CFS clinicians and researchers and help advance progress in ME/CFS studies. Respondents advocated for open databases of all ME/CFS studies and encouraged data sharing even before research is published. Some respondents suggested utilizing big data and artificial intelligence techniques to analyze the data.

Rigorous Research. Many respondents urged funding of large studies and for replicating the results of the small studies that are currently in the ME/CFS literature. They advocated for a clear research case definition of ME/CFS to ensure consistency across studies and careful selection of appropriate control groups. They also advocated for ensuring that researchers are ethical and do not have conflicts of interest.

Diversity. Respondents urged inclusion of a diverse population of individuals with ME/CFS in clinical studies. They advocated for including people of all ages (including children), genders, racial and ethnic groups, geographic locations, socioeconomic classes, and disease severities.

Conferences. Many respondents advocated for NIH to host annual conferences like the April 2019 "Accelerating Research on ME/CFS" Conference and for NIH to support conferences hosted by other organizations. They encouraged videocasting to increase the ability of people to be engaged without travelling and to have an archive of the conference presentations. They also encouraged NIH to support travel to conferences, particularly for young investigators.

Web-based Communication. Many respondents suggested using webinars, forums, and other sources of web-based communication to facilitate information sharing and collaborations between stakeholders including individuals with ME/CFS, health care providers and researchers. Some respondents suggested hosting registries for researchers and potential participants to facilitate communication and collaboration. Others suggested creating web-based platforms for

researchers to share data with each other or for people with ME/CFS to share their medical information. Some suggested that there should be a single entity that takes responsibility for communicating information about current research on ME/CFS, research opportunities, and resources for people with ME/CFS so that they don't have to go to multiple sources.

Research Participation. Many respondents said that they are very eager to participate in research and that researchers should include people with ME/CFS or their caregivers and advocates in all stages of research. In particular, they stressed that researchers should reach out to people with ME/CFS when designing study protocols and symptom assessment tools to ensure that the studies are focused on the aspects of the disease that are most disabling and that protocols are designed to accommodate the unique needs and limitations of people with ME/CFS. Many respondents advocated for a registry to connect researchers to people with ME/CFS and to capture data from these individuals. They also advocated for researchers to share the data and results of the studies, even before publication.

Travel. Many respondents pointed out that clinical studies of ME/CFS are only found at a few locations across the country. Long distance travel is often difficult or impossible for people with ME/CFS because of the expense, stress, exertion, and lack of control over the environment. Travel, in and of itself, could worsen symptoms both immediately and in the long term, making study participation risky for the health of the individual and potentially reducing the validity of the studies. Several responses included potential strategies for reducing the burden of traveling to and being in a research facility such as:

- funding more **research centers in all regions of the country** and providing alternative off-site locations for testing and blood draws.
- providing **funds for travel and hotel accommodations**. Some suggested supporting travel for a caregiver to accompany the person with ME/CFS. Others suggested providing a car and driver for people who are local to the study site. A couple respondents mentioned that hotel accommodations should be provided both before the study to allow people to recover from travel and after the study to allow people to recover from the participation in the study before traveling back home.
- offering simple and clear **forms and questionnaires in advance** of the appointment so participants can take as much time as they need to read, understand, and fill out the forms in their own homes.
- ensuring that the **research facility** provides quiet, low-light, chemical/scent free spaces both for testing and resting, provides food that considers individual dietary sensitivities, and trains staff to understand and accommodate the unique needs and limitations of people with ME/CFS.

Home-based Research. Many respondents advocated for home-based research which would not only eliminate the burden of travel but would also allow more severely affected individuals to participate in studies. Inclusion of more severely ill individuals may produce insights not seen by only studying mild to moderate cases. Examples of home-based research include:

- researchers and medical professionals **visiting people with ME/CFS in their homes**.

- **interacting remotely** with participants via Skype or other virtual platforms.
- employing **web-based platforms** to collect medical histories or track daily symptoms.
- utilizing **activity trackers** and other wearable data-gathering devices.
- providing **kits for biospecimens** (e.g. hair, saliva, feces) to be mailed to a research facility.
- contracting with **local hospitals and clinics** for blood draws.
- developing **mobile clinics**.

Post-study Monitoring and Supportive Therapies. Some testing, particularly exercise studies, can cause worsening of symptoms. Respondents suggested providing post-study monitoring and supportive therapies to help individuals with ME/CFS manage post-testing symptoms.

Strategic Plan. Respondents advocated for NIH to develop a strategic plan for research on ME/CFS to address a critical need for diagnostics, treatments, and improved understanding of the disease. They urged NIH to commit funding and resources to implementing such a strategic research plan.

Government Agencies. Several respondents commented that a single NIH institute should be designated as the “home” institute for ME/CFS. A few respondents noted that ME/CFS symptoms and comorbidities fall under the purview of several NIH institutes and all those institutes should be involved in ME/CFS research. A few people said that NIH should hire more staff to work on ME/CFS and that they should receive more support and resources. A few respondents urged CDC to change the way they communicate about ME/CFS. A few respondents advocated for reinstating the Chronic Fatigue Syndrome Advisory Committee (CFSAC) at the Department of Health and Human Services.

Grant Review. Respondents advocated for continued use of the ME/CFS Special Emphasis Panel study section (<https://public.csr.nih.gov/StudySections/DNDA/IFCN/CFSSEP>), for developing educational materials for reviewers on the study section, and for ensuring that the reviewers are open-minded and objective in their reviews.

Social Services Many respondents noted a lack of social services available to assist people with ME/CFS. Suggestions include:

- improving access to medical care.
- increasing access to education.
- providing housing and ME/CFS-focused communities.
- promoting the development of a helpline for people with ME/CFS.

Appendix L. List of Strategies

Strategic Planning

- The Trans-NIH ME/CFS Working Group should coordinate a research prioritization and strategic planning process to create an overarching roadmap for ME/CFS research. The process should identify key research priorities across relevant scientific areas. Scientists and clinicians with relevant outside expertise should be included in the process, as well as other stakeholders such as individuals with ME/CFS, advocates, and caregivers.
- A strategic planning process should include discussions, informed by knowledge from clinicians and people with ME/CFS, about clinical phenotypes and studies that may reveal ME/CFS subtypes. This should be coordinated with efforts at the CDC.
- A strategic planning process should consider clinical trial design, patient selection and enrichment strategies, outcome measures, and sources of heterogeneity across patients and within the same patient over time.
- The planning process should more rigorously assess the relative merits of different patient-reported outcome measures (such as alternative scales for determining fatigue severity, post-exertional malaise, or functional capacity).
- A strategic planning process should also discuss the scientific rationale for potential studies of off-label treatments used by clinicians.
- A strategic planning process should include discussions of the state of knowledge about the possible etiologies for ME/CFS and how to identify findings that are likely to be disease causes versus physiological responses (i.e. epiphenomena and thus not the underlying cause(s) of ME/CFS).
- A strategic planning process should identify key issues related to the development and usage of *in vitro* and *in vivo* ME/CFS models.

Encouragement of Research Topics and Approaches

- NIH should continue to encourage multidisciplinary approaches in grant proposals. NIH should increase awareness among the researcher community about current multi-PI funding opportunities that encourage investigators with diverse skills and expertise to work together on projects.
- NIH should encourage all NIH grant applications on ME/CFS to clearly state which case definition is being used and what data collection instruments will be used to obtain the data needed to apply that case definition.
- NIH should encourage applications proposing to use one particular case definition to also obtain sufficient clinical data so that the subjects can be categorized according to any of the primary case definitions of ME/CFS.
- NIH should encourage ME/CFS studies to assess the health status of control groups using valid data collection instruments, such as those recommended in the ME/CFS CDE guidelines and the NIH toolbox.

- NIH should encourage studies to formally assess physical activity levels of all cases and controls, using validated and standardized instruments. Justification for using fit controls (e.g. comparison to model systems) should be provided when appropriate.
- NIH should encourage studies to rigorously assess and control for confounding factors in all studies of ME/CFS that may influence the results and comparisons between those with ME/CFS and the chosen controls. Physical fitness and the presence of other diseases are common potential confounding factors.
- Investigators should be encouraged to take into account the onset and length of disease in all ME/CFS studies.
- NIH should encourage ME/CFS research that evaluates the interactions between multiple biological systems that, individually, have been found to have abnormalities within the same cohort of people with ME/CFS.
- NIH should encourage clinical characterizations of study participants that better inform the scope of the disease and the changes in symptoms over time.
- NIH should encourage investigators to measure symptoms from multiple perspectives (e.g. assessing current, peak, and typical symptom levels; and/or assessing different timeframes and situational frames) to gather a more complete picture of the symptom complex of people with ME/CFS.
- NIH should encourage research to identify and validate ME/CFS subtypes. Researchers examining subtypes should be encouraged to consider relevant clinical information including (but not limited to) onset triggers, disease severity, stage of disease, and symptom presentation, as well as combinations of clinical and biological data.
- NIH should encourage multidisciplinary ME/CFS studies to examine and report on comorbid conditions utilizing the appropriate ME/CFS CDEs.
- When scientifically appropriate, NIH should encourage investigators to include disease comparison groups with other fatiguing illnesses (e.g., multiple sclerosis, systemic lupus erythematosus, major depression, Sjogren's syndrome) as well as healthy control subjects.
- NIH should encourage research proposals to better understand the proposed mechanism of action of currently utilized therapeutics in either clinical research or mechanistic clinical trials. The primary outcome would be mechanistic information for further study and potentially larger separate clinical trial(s) designed for efficacy, etc.
- NIH should encourage the use of telemedicine or home visits for research on home- or bed-bound people with ME/CFS to include this group of individuals in research studies when feasible.
- NIH should encourage the use of validated wearable devices and/or apps for symptom tracking of individuals with ME/CFS outside the research lab/clinic setting.
- NIH should encourage measurement of symptom severity.
- When scientifically appropriate, NIH should encourage provocation studies. These may help to reveal the underlying cause(s) of ME/CFS.
- NIH should encourage research leading to the identification of objective measures that can be utilized as biomarkers for diagnosis, disease progression, and response to treatment.

- NIH should encourage investigators to consider information provided by the FDA-NIH Biomarker Working Group.
- Where scientifically appropriate, NIH should encourage systematic clinical and epidemiological research to better characterize disease onset, triggers, etiology, and pathogenesis.
- NIH should encourage researchers to consider study designs, such as prospective and longitudinal studies, that may improve our understanding of ways in which ME/CFS develops.
- NIH should encourage research to develop *in vitro* and *in vivo* models of ME/CFS.

Instruments and Common Data Elements

- NIH should urge investigators to use the ME/CFS CDEs. These instruments standardize the collection of data about symptoms, past medical history, family medical history, physical examination, and common laboratory test results. These instruments may also help to categorize patients into certain disease subtypes, and to identify comorbid diseases. Standardized data collection and reporting through the CDEs is critical to enable cross study comparison, aggregation, and replication.
- NIH should work with the CDC and other stakeholders to identify additional required data elements and instruments that will facilitate more detailed ME/CFS phenotyping and improve data sharing.
- NIH should support development and validation of new instruments where needed to measure disease features of importance to people with ME/CFS (e.g., PEM).
- If CDEs for the comorbid conditions do not exist in the ME/CFS CDEs, they should be co-opted from other disease CDEs.

Data Sharing and Biobanking

- NIH should continue to support expansion of ME/CFS biorepositories that also include detailed clinical data about the study participants.
- NIH should encourage funded research projects to provide biospecimens to existing biobanks for sharing with qualified investigators.
- NIH should partner with stakeholders to develop a registry through which potential study participants can be identified.
- NIH should work with funded investigators to ensure that steps are taken to enable future data sharing and biobanking. Examples include writing consent forms to allow for biobanking and wider data sharing, as well as the use of Globally Unique Identifiers (GUIDs) to track research subjects who are participants in multiple studies.
- NIH should partner with nonprofit and private organizations to develop a platform for ME/CFS researchers to facilitate data sharing.
- Once a comprehensive database is created, NIH should encourage secondary data analysis of aggregated existing datasets.

Increasing Collaboration and Cooperation

- NIH should create a group that includes members from federal agencies involved in ME/CFS research, nonprofit foundations supporting ME/CFS research, and other interested stakeholders. The group should promote increased collaboration toward common research goals, monitor progress of the overall ME/CFS research field, share information on ME/CFS research activities, highlight advances, and discuss research gaps and opportunities. Additional details on a potential collaborative structure are included in Appendix M.
- NIH should explore ways to coordinate ME/CFS research efforts with ongoing activities in overlapping syndromes.

Outreach to Scientific Investigators

- NIH should provide materials about ME/CFS, including information from the CDC, at exhibit booths during professional conferences.
- NIH should solicit ME/CFS proposals through targeted outreach to investigators in relevant scientific and medical fields identified by the Trans-NIH ME/CFS Working Group to be relevant to ME/CFS, regardless of whether those investigators have previously studied ME/CFS.
- As part of its outreach efforts, the Trans-NIH ME/CFS Working Group should develop a resource guide for investigators, which should include information from Institute/Center websites related to grant and training opportunities.
- NIH should actively encourage investigators to contact program staff with questions related to their grant applications, including identifying appropriate Funding Opportunity Announcements (FOA) for their basic, translational and clinical research studies.
- NIH should inform ME/CFS investigators when relevant NIH Funding Opportunity Announcements are available in related fields and conditions (such as chronic pain, etc.).

General Outreach

- NIH should offer information and feedback to stakeholders who are engaged in outreach and medical education.
- When appropriate for its mission, NIH should partner with other federal agencies, such as CDC, and professional organizations to disseminate information about research on ME/CFS.
- NIH should leverage events to publicize information about ME/CFS.
- NIH should continue to publicize its ME/CFS research efforts, such as the NIH ME/CFS intramural study and the ME/CFS Research Network.
- NIH should continue to provide information on both the NIH ME/CFS website as well as on the ME/CFS Network website about ongoing research efforts.
- NIH should continue to issue press releases when significant NIH-funded ME/CFS research is published.

Conferences and Workshops

- NIH should continue to hold ME/CFS conferences on a regular basis.
- NIH should continue to hold events geared towards early career investigators to provide guidance on how to apply for NIH research support and navigate the peer review process.

Research Training

- NIH should partner with nonprofit research organizations to create training resources for early career investigators interested in becoming ME/CFS researchers.
- NIH should continue to actively participate in efforts to support early career investigators such as the “Thinking the Future: Early Career Network (Invest in ME).”
- NIH should provide a list of currently funded ME/CFS research, including the Principal Investigator(s) for each grant award to enable trainees to identify potential mentors.

Scientific Review

- NIH should continue to ensure that the ME/CFS SEP includes reviewers with relevant ME/CFS expertise. Reviewers with other relevant subject matter expertise, including experts in tools and methodologies being proposed, should also be included.
- NIH should consider study section formats that provide for productive interactions between members of the review panel, for example face-to-face or video conference meetings.
- NIH should consider inviting members of the SEP to be reviewers in multiple grant cycles to build a sense of community within the SEP.

Appendix M. Potential Structure of Collaborative Group

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) research needs reach across the missions of multiple NIH Institutes, Offices and Centers and across organizations outside the NIH. This working group will have broad representation from the NIH, other federal agencies, and the research and patient advocacy communities.

Goals:

- Provide a forum for sharing information on ME/CFS research activities, highlight advances, and discuss gaps and opportunities.
- Promote increased and ongoing collaboration toward common research goals.
- Monitor progress of the overall ME/CFS research field.

Meetings:

- An annual face-to-face meeting supplemented by an additional annual conference call.
- As needed, working groups will be formed that will hold conference calls to discuss and track progress on specific collaborative activities.

Membership:

- Members of NIH Trans-NIH ME/CFS Working Group, other federal agencies, Canadian Institute of Health Research (CIHR), professional and advocacy non-profit organizations.

Criteria for membership:

1. Federal Agencies:

At least one of the following criteria:

- a. Provide funding support for ME/CFS research; and/or
- b. Are interested in promoting research on ME/CFS; and/or
- c. Are interested in collaborating with other organizations to stimulate and support research on ME/CFS.

Potential Members: NIH: NIAID, NINDS, NCI, NIA, NHLBI, NIMH, NIEHS, NICHD, NIAAA, NIDA, CSR, NINR, NIDCR, OBSSR, OD, NIDDK, NCATS, NIBIB, NHGRI, NCCIH, NIMHD, NIAMS; AHRQ, CDC, FDA, HRSA, DoD, VA, CMS, SSI, CIHR

2. Professional Organizations:

- a. 501(c)3 status with the IRS
- b. Maintains a Scientific/Medical Advisory Board to assist in research and other programs
- c. National (and/or international) in scope and range of activities

At least one of the following criteria:

- a. Provides funding for peer-reviewed research through a granting mechanism; and/or
- b. Are interested in promoting research on ME/CFS; and/or
- b. Are interested in collaborating with other organizations to stimulate and support research on ME/CFS.

3. Patient Advocacy Organizations:

- a. 501(c)3 status with the IRS
- b. Maintains a Scientific/Medical Advisory Board to assist in research and other programs
- c. National (and/or international) in scope and range of activities

At least one of the following criteria:

- d. Provides funding for peer-reviewed research through a granting mechanism; and/or
- e. Are interested in promoting research on ME/CFS; and/or
- f. Are interested in collaborating with other organizations to stimulate and support research on ME/CFS.