Community Advisory Committee

ME/CFS Research Priorities

Community Advisory Committee, Research Priorities Working Group

NIH ME/CFS Collaborative Research Centers

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Overview

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating, chronic, complex disease that most often follows an infection and is associated with neurological, autonomic, immunological, and metabolic abnormalities. Patients experience a substantial impairment in functioning, and a range of symptoms, including sleep dysfunction, cognitive impairment, orthostatic intolerance, pain, flu-like symptoms, fatigue, sensory sensitivities, and the hallmark post-exertional malaise (PEM). PEM is an exacerbation of symptoms and a further reduction in functioning following even small amounts of previously tolerated activity. The National Academy of Medicine (NAM) estimated 836,000 to 2.5 million Americans of all ages, genders, races and ethnicities have ME/CFS with a greater prevalence in females, adults and possibly people who are Black and Latinx. There are no validated biomarkers, no FDA-approved treatments and patients can struggle to access adequate clinical care. Recovery is rare and patients can remain ill for decades, with an estimated 25% homebound or bedbound and 75% unable to work.

Progress in understanding the etiology of ME/CFS and developing biomarkers and treatments have been constrained by a number of interrelated challenges:

- Inherent heterogeneity and complexity of the disease;
- Failure to reach consensus on the criteria and methods to assess and characterize the disease, and a lack of sensitive and specific biomarkers;
- Challenges in collaborating across scientific and clinical disciplines, across academic centers, and between researchers, clinicians, and people with lived experience;
- Disbelief and misunderstanding about the nature of the disease;
- Lack of research funding and interested researchers and clinicians;

In spite of these barriers, the field has made substantial progress in understanding some of the underlying pathology, including abnormalities in metabolism and in the immune, neurological, and autonomic nervous systems. Our understanding of how ME/CFS and other post-infectious illnesses might be caused by factors such as persistent infection, infection-triggered autoimmunity, an aberrant immune response by the host to infection, neuroinflammation, or changes in energy metabolism is growing rapidly. But research has not yet translated into the treatments that produce a meaningful difference in patients' quality of life or biomarkers that enable swift and accurate diagnosis.

The SARS-CoV-2 pandemic has left a significant number of people with persistent illness, some for as long as two years following COVID-19. These long-term symptoms are referred to as post-acute sequelae of COVID-19 (PASC) or Long COVID. Dr. Anthony Fauci noted the disease is "strikingly similar" to ME/CFS. Studies have shown nearly half of people with Long COVID meet

diagnostic criteria for ME/CFS and many Long COVID patients have already been diagnosed with ME/CFS. It cannot be denied that the pandemic has led to individual suffering and a national and international crisis in clinical care. While tragic, the pandemic has created an unprecedented opportunity as well as a mandate to accelerate progress, offering answers for both Long COVID and for associated conditions such as ME/CFS and other post-infectious illnesses. Historic deficits in research on post-infectious illnesses such as ME/CFS has produced a dearth of the scientific and clinical resources needed to study and care for the current surge of PASC patients. However, the pandemic has brought the level of funding and focused attention required to finally unravel how an acute infection can trigger a prolonged post-infectious illness and what can be done to resolve it.

Leveraging this opportunity for ME/CFS requires ME/CFS-specific funding and a strategic plan to expedite progress. It also requires the integration of learnings from ME/CFS research into the PASC strategy, not only to help accelerate research in Long COVID but to better understand ME/CFS onset, natural history, and pathology. A natural experiment is underway which cannot be replicated, and this calls for swift, decisive action. Early in the disease is not only a critical time for sample collection; it is also the best opportunity for interventions that may change outcomes for patients.

This document outlines the long-standing barriers that have constrained progress in ME/CFS, as well as the research priorities that need to be progressed to achieve outcomes for people with ME/CFS, including those whose ME/CFS developed following COVID-19.

Upstream Barriers to Successful ME/CFS Research

A number of barriers have constrained progress in ME/CFS research. The field lacks basic resources and instrumentation required to study ME/CFS, such as a lack of agreement on methods for selecting patients; a lack of reliable, objective biomarkers; a lack of knowledgeable and willing researchers and clinicians; and a lack of sufficient financial support from government, corporate, and private funders. Further, the field lacks the level of collaboration across academic centers, across scientific and clinical disciplines (e.g., neurology, immunology, infectious disease, rheumatology, endocrinology/metabolism, cardiology, etc.), and among researchers, clinicians and patient partners required to tackle a disease of this complexity.

These gaps reinforce and perpetuate each other. For example, the 2011 NIH ME/CFS State of the Knowledge report concluded that failure to reach consensus on case criteria and methods creates problems for “the entire scientific enterprise.” While consensus has been reached on clinical criteria, there is no such consensus on research criteria. This results in research cohorts who may include people with other conditions, making it difficult to compare findings and to identify subtypes and biomarkers.

Key barriers that must be addressed include:

Case Criteria and Selection Methods: The field lacks agreement on what key features must be present, what conditions must be excluded, and how those features should be evaluated to diagnose ME/CFS in research. This includes lack of agreement on whether even PEM is required, despite its being required clinically in the US and the UK for a diagnosis of ME/CFS. As a result,

diagnostic criteria such as Fukuda, which does not require PEM, are still being used to identify ME/CFS cases in research, including in Long COVID studies. This lack of agreement on diagnostic criteria and assessment methods results in an artificially induced heterogeneity. Study publications rarely distinguish findings for those who met one criteria versus another or who experience PEM or not. This makes it challenging to compare findings across studies, produces findings that conflict from one study to the next, and can result in treatment recommendations based on studies using non-specific diagnostic criteria that are then inappropriately applied to people with ME/CFS. A lack of consensus on diagnostic criteria for use in research also makes it difficult to identify subtypes and biomarkers specific to ME/CFS. While NIH's Common Data Elements(CDE) Initiative made recommendations on what data to collect, it did not address what diagnostic criteria or assessment methods to use.

Objective Biomarkers and Measures: While there have been several publications suggesting possible biomarkers, replication and validation of those biomarkers in larger populations, in other disease populations, and in subtypes of ME/CFS are required. And while a few outcome measures have been used in clinical trials, few are objective, and few have been FDA-qualified for ME/CFS. The lack of a validated diagnostic biomarker(s) complicates the identification of ME/CFS study participants, putting a premium on the availability of a small pool of clinicians knowledgeable about ME/CFS to ensure accurate cohort selection and creating a critical bottleneck to achieving robust sample sizes. A dearth of objective biomarkers and outcome measures is a significant barrier to the pharmaceutical industry undertaking drug development.

Complexity and Heterogeneity of the Disease: Aside from the artificial heterogeneity induced by non-specific or inconsistent methods of case identification, the disease has a high level of intrinsic heterogeneity due to its inherent complexity. Some of the sources of this heterogeneity include:

- **Multisystem illness:** Research has shown that ME/CFS is associated with abnormalities in multiple physiological systems but there needs to be more focus on how these systems interact in creating and perpetuating these abnormalities.
- **Chronicity and fluctuation over time:** The chronicity of ME/CFS and its variability in features (signs and symptoms) and intensity over days, months and years significantly complicates the conduct of research. For example, some studies show differences in immune function in those with short versus long-term disease, and patients can experience unpredictable improvement and deterioration that require approaches that account for the waxing and waning of disease presentation.
- **Heterogeneous symptomatology:** ME/CFS patients display a wide range of symptom constellations. Most of these clinical data are not captured by standard instrumentation.
- **Presence of comorbidities:** Comorbidities can be present at disease onset and additional comorbidities have been shown to develop over time. When present, they can reduce functioning, change symptom profiles and treatment response, and influence biological markers.
- **Sex and age differences:** There is a greater prevalence in females over males and in adults over adolescents over younger children. For example, studies have shown sex-based differences in ME/CFS in areas such as metabolic profiles and neuroendocrine changes.
- **Spectrum of severity:** The disease has a wide spectrum of severity, from those who can work with accommodations to those who are bedbound and need total care. Many research protocols require in-clinic attendance, which excludes severely ill subjects from research, introduces selection bias, and results in a profound gap in knowledge about the disease.

- **Black, Indigenous, and People of Color (BIPOC) populations:** While most ME/CFS studies are in Caucasian people, studies have indicated that BIPOC populations are also affected, potentially at greater prevalence. As with the severely ill, the exclusion of these groups from research cohorts introduces bias, results in a profound knowledge gap, and magnifies the health equity issues BIPOC patients experience.

Inadequate Instrumentation, Study Design, and Study Approaches: Current instrumentation, study design, and study approaches are underdeveloped, inconsistently applied, and do not adequately account for the unique features, the inherent complexity and heterogeneity of the disease, and the range of severity and populations affected. Strong collaboration with patients in study design could help mitigate some of these issues by incorporating insights gained from patients' lived experience.

In addition to inadequate instrumentation, studies have often lacked the study power and integration across disciplines and academic/clinical centers required for a disease of this complexity. The small size of most studies also impedes subset analysis needed to better understand the intrinsic heterogeneity of the disease by stratifying objective findings by key clinical variables (e.g., disease duration, onset type, severity, comorbidities, symptom profiles, PEM, sex, race, ethnicity, etc.).

Another important issue is with the use of methods to provoke PEM. These have provided valuable insight into disease pathology by revealing abnormal responses to a challenge on one's physiological systems. But they risk worsening the patient's illness. Further, these have typically used physical exercise as a provocation to the exclusion of other stressors such as cognitive exertion. Additional provocation methods are needed that cover the breadth of PEM triggers (physical, cognitive, social, emotional, sensory exertion) and minimize the risk of worsening patients' health.

Academic Institutions, Clinicians, Researchers, and Funding: The field has failed to grow as much as needed. Reasons for the lack of engaged researchers and clinicians are complex: institutional bias, stigma, and misunderstanding; lack of accurately diagnosed patients; the unresolved barriers cited above; and difficulty securing adequate funding for ME/CFS research studies. Resolving these issues will require dedicated funding from the NIH and other funders, stronger political leadership to engage the research and medical communities, and consensus on critical methods.

Short Term Research Priorities

These priorities are listed in rough priority order but will need to be pursued in parallel for reasons of expediency and interrelatedness. Many of these priorities are also important for Long COVID research and their resolution will benefit PASC initiatives.

Collaborative Approaches

- Create and invest in the structures necessary to achieve meaningful, effective partnerships with patients in shaping and prioritizing the research agenda and designing and implementing research studies. Patients' lived experience, diverse and complementary skills, and deep connection to the broader ME community are critical assets that must be leveraged to successfully move the field.
- Strengthen and support the engagement of clinicians in research. Learnings from clinical practice can expedite achieving outcomes most meaningful to patients while providing key insights to the nature of the disease pathology and its subtypes that can inform data analysis and help drive the overall research agenda.
- Increase targeted funding for collaborative research centers to increase the number of centers and the level of support for each, and to support the development of the infrastructure, data sharing, and instrumentation needed to research such a complex illness. Current NIH funding for collaborative research centers is not adequate.
- Understanding a chronic, multisystem disease requires merging relevant domains of expertise to develop a framework for the interrelated effects of dysfunction across systems. Enhanced collaboration across relevant domains of clinical research such as neurology, immunology, infectious diseases, rheumatology, endocrinology/metabolism, cardiology/dysautonomia, pain, and sleep is needed. Bridges must be built between ME/CFS and those researching other related diseases, particularly other post-infectious illnesses.

PASC Integration

Numerous studies have demonstrated that ME/CFS is one of the significant sequelae of acute COVID-19. This must be examined in Long COVID research. At the same time, the integration of knowledge gained from ME/CFS and other post-infectious illnesses into the PASC strategy could help expedite progress in Long COVID. This should be done in the following ways:

- Use either the National Academy of Medicine (NAM) Criteria or the Canadian Consensus Criteria (CCC) along with the DePaul Symptom Questionnaire plus other ME/CFS CDEs as needed to accurately identify ME/CFS cases in Long COVID cohorts. It is particularly important to determine the presence of PEM, as this is a key symptom of ME/CFS in all modern definitions and is reported by a significant portion of Long COVID patients. Use of criteria that require PEM will ensure the best translation to US clinical care where PEM is required for a diagnosis. Fukuda and other criteria that do not require PEM should not be used to identify ME/CFS patients, as they can capture a very different cohort of patients without PEM.
- Include patients with ME/CFS and other post-viral illnesses as comparator groups in PASC studies. Include ME/CFS patients with both short and long duration illness and no evidence of SARS-CoV-2 infection.
- Include in the PASC research strategy those areas of ME/CFS research that are proving fruitful, including metabolic abnormalities; mitochondrial dysfunction, redox imbalance; systemic immune dysfunction; viral reactivation and potential pathogen persistence; autoimmunity; neuroinflammation; neuropathies including small fiber neuropathy (SFN);

autonomic nervous system dysfunction, vascular dysfunction including endothelial dysfunction and hypoperfusion in the brain; ion channelopathies; gut microbiota abnormalities; and hypothalamic-pituitary-adrenal (HPA) axis abnormalities.

- Leverage ME/CFS clinical learnings and pathophysiological findings to accelerate selected clinical treatment trials for Long COVID. Such trials can be designed to advance understanding of disease mechanisms in parallel with establishing evidence for treatments that reduce patients' symptom burden and improve their quality of life.
- Create a formal ME/CFS advisory group to provide input on all federal PASC/Long COVID initiatives, including NIH's PASC and Long COVID strategy and CDC's INSPIRE study. This group would consist of federal agencies; federal, commercial, and private funders; and ME/CFS stakeholders including researchers, clinicians, patients, caregivers and patient organizations. It would provide input on ways to integrate what has been learned from ME/CFS research into the strategy for studying Long COVID, and vice versa.
- Assess patients for the emergence of ME/CFS and other post-infectious illnesses/conditions [e.g., dysautonomia including postural orthostatic tachycardia syndrome (POTS), mast cell activation syndrome (MCAS)] at multiple time points (from time of infection through 2 years post-infection) in Long COVID prospective longitudinal studies. Follow those who develop ME/CFS and other Long COVID-associated conditions for an extended duration beyond 2 years to elucidate the natural history of ME/CFS and other post-infectious diseases.
- Undertake large scale whole genome sequencing/genome-wide association studies (WGS/GWAS) to identify predisposing and symptom-associated risk variants that may indicate causal pathways, with cluster analysis for major subgroup identification, including ME/CFS cases.

Consensus Meetings

Hold a series of federally funded meetings among federal agencies and ME/CFS expert researchers, clinicians, patients, and caregivers to achieve consensus on:

- **Core Selection Criteria and Assessment Methods to be used in all research studies**
  - Agree to a core set of inclusion and exclusion criteria to be used across all research studies. This includes the research case definition(s) and/or specific required criteria (e.g., PEM). This is a core set to identify ME/CFS cases and may be supplemented by additional inclusion and exclusion requirements specific to the needs of a given study.
  - Identify and agree to methods to operationalize these inclusion and exclusion criteria, including standardizing procedures for assessing symptoms. Threshold or scoring methods for evaluating the presence or absence of each of the case-defining ME/CFS symptoms must be applied consistently across studies (including frequency and severity).
- **Illness Severity and BIPOC populations**
  - Agree to a common definition for the range of severity (e.g., functional severity of mild, moderate, severe, very severe).
  - Identify and agree to existing methods that could be used to score severity (e.g., Karnofsky, SF-36, Bell).
  - Recommend approaches to include BIPOC and the most severely ill in studies.
- **Major Subtypes**
  - Document any prominent clinical phenotypes learned from current research and clinical care, and if they exist, any associated biomarkers. Prominent phenotypes could include the presence of important comorbidities that could influence findings (e.g., ME/CFS patients with and without fibromyalgia (FM) in pain studies).

- **Methods**
    - Review status of the existing CDEs and the open issues as documented in the ME/CFS CDE Initiative. Refine and update these recommendations as needed to gain greater consensus on the tools used to assess various domains of illness (e.g., fatigue, PEM, sleep, cognition, etc.) and how they should be applied. Propose areas where targeted research is needed to resolve issues.
    - Recommend an appropriate instrument(s) to best assess comorbid anxiety and depression in ME/CFS research to ensure somatic symptoms are not inappropriately attributed to mental health issues.
    - Review existing provocation methods and recommend existing tools and/or future research to establish a set of methods that can be used to assess PEM at all levels of severity, that cover the range of triggers (e.g., cognitive, social, emotional, sensory, and orthostatic as well as physical), and that are gentler to the study participants.
- **Outcome Measures**
    - Agree to a set of initial outcome measures (both patient-reported and objective if available) to use in clinical treatment trials. Identify areas where further research is needed and recommend a plan to address.

Methods and Study Design

- Develop a standardized disease severity scale that reflects the spectrum of severity. Develop severity indicators and measures with minimal ceiling/floor effects.
- Adopt study design approaches that account for the complexity of the disease (e.g., duration, fluctuation, comorbidities, heterogeneous symptomatology, good day/bad day, severity, PEM, etc.) and the populations affected (e.g., BIPOC, the severely ill, pediatric as well as adult).
- Routinely capture sufficient clinical data (e.g., via DePaul Symptom Questionnaire) to fully characterize ME/CFS features, support retroactive fitting to various definitions, and facilitate exploratory subset analysis via stratification across key variables (e.g., duration, onset type, severity, symptoms, etc.)

Biomarkers

- Provide targeted funding to identify and validate sensitive and specific diagnostic biomarker(s) and if applicable and if possible, the disease subsets to which they apply.
    - This should include validating biomarkers for clinical use as well as for research. Measures that improve diagnostic certainty could be helpful clinically even if they are not 100% sensitive and specific to ME/CFS and need to be used in conjunction with additional clinical parameters. Potential examples include serum transfer nanoneedle assay, hand grip strength, NASA lean test, wearable activity measures, online cognitive tests, etc.
- Expand and diversify study populations to evaluate specificity, sensitivity and subgroup relevance. This includes studies with larger cohorts, studies of BIPOC patients, the severely ill, and pediatric patients as well as adults, and studies that compare ME/CFS to other chronic conditions.
- Stratify datasets across key clinical variables (e.g., illness duration, onset type, severity, symptoms, etc.) to identify biomarkers for subgroups, correlation with disease severity, and potentially for treatment response. Establishing clinical subgroups of ME/CFS is essential for facilitating meaningful associations with biomarker profiles, which could then be amenable to therapeutic intervention.

Clinical Treatment Trials

- Conduct symptom-based treatment trials in subgroups targeting major symptoms (e.g., orthostatic intolerance, sleep, cognitive function, pain, etc.) using existing FDA-approved interventions.
- Conduct disease-modifying treatment trials in subgroups that leverage current understanding of the underlying pathophysiology of the disease (e.g., neuroinflammation, viral reactivation) and drugs with known pharmacological mechanisms that target such pathophysiology.
- For both, use study designs that expedite delivery of treatments to reduce disease burden and improve long term outcomes in parallel with further elucidating disease pathology and subtypes. Advance methods of assessing efficacy and safety outcomes.

Epidemiological and Longitudinal studies

- Comprehensive basic epidemiologic survey to define prevalence, severity spectrum, onset types, triggers, risk factors, prognosis, etc.

Advance Understanding of Disease Pathology

- Advance and integrate the substantial knowledge gained from research on ME/CFS; including: metabolic abnormalities, mitochondrial dysfunction, redox imbalance, systemic immune dysfunction, viral reactivation and potential pathogen persistence, autoimmunity, neuroinflammation, neuropathies including small fiber neuropathy, autonomic nervous system dysfunction, HPA axis abnormalities, vascular dysfunction including endothelial dysfunction and hypoperfusion in the brain, ion channelopathies, and gut microbiota abnormalities.
- Undertake large scale WGS/GWAS to identify predisposing and symptom-associated risk variants that may indicate causal pathways, with cluster analysis for major subgroup identification.

Clinical Studies to Demonstrate Disability

- Evaluate available tools and make recommendations for new tools to assess the functional impairment seen in ME/CFS. Tools being used in ME/CFS today include cardio-pulmonary exercise tests (CPET), the 10 minute NASA lean test, tests for cerebral hypoperfusion, activity meters, and neuropsychological testing for assessment of cognitive function. Tools from other fields may be useful. People with ME/CFS have struggled immensely to access social services, disability benefits, school and work accommodations, and other needed services, and are often met with denial due to lack of objective measures of functional impairment. Clinical studies to demonstrate disability and functional impairment is an urgent need that should be addressed in parallel with other initiatives outlined here.

ME/CFS Targeted Funding and Research Strategic Plan

- Achieving these priorities will require a significant increase in ME/CFS-targeted funding. This includes funding opportunities with set-aside funding to incentivize researchers, clinicians, and academic centers to enter the field.
- It also requires the development of a research strategic plan, as recommended by the 2019 NINDS NANDS Council Working Group for ME/CFS but not yet accomplished. This plan will need to proactively address the long-standing barriers and capitalize on current learnings to accelerate research and delivery of treatments to patients. To ensure progress, the plan will need defined milestones and benchmarks.
- While tighter integration into the PASC strategy is critical, that alone doesn't substitute for ME/CFS-targeted funding and a research strategic plan.

Longer Term Research Priorities

Methods Development

- Develop *in vitro* and animal disease models.
- Further develop and validate disease-specific instrumentation, subjective and objective assessment methods, and patient-reported and objective outcome measures.
- Further develop and validate a suite of objective and subjective measures of PEM that cover the range of triggers and provocation methods that are gentler to patients. Some objective measures might include serum metabolites, cytokines, gene expression, extracellular vesicles, tissue cellular composition, and neuroimaging.

Advance Disease Knowledge

The areas outlined in Short Term Priorities will likely require continued effort. While these are listed as separate bullets, the interaction of these systems will also need to be evaluated. These include but are not limited to:

- Characterize metabolic dysfunction, mitochondrial function in energy metabolism and innate host defense.
- Identify mechanisms of central and peripheral asthenia.
- Characterize neurocognitive dysfunction relative to other neurodegenerative diseases.
- Characterize autonomic, orthostatic and vascular dysfunction.
- Characterize immunologic dysfunction (e.g., autoreactivities, immunodeficiencies, chronic inflammation, cellular exhaustion).
- Characterize neurological changes (e.g., neuroinflammation, hypoperfusion and hypometabolism in the brain)
- Characterize microbiome changes and their role, if any, in persistence of the disease.
- Define prevalence and mechanistic relationships of frequent comorbidities and overlapping syndromes: MCAS, dysautonomia, POTS, Ehlers-Danlos syndrome (EDS), FM, SFN, structural abnormalities, etc.
- Comprehensively characterize symptom constellations and clinical variables in a large study population and identify significant subgroups.

Clinical Treatment Trials

- Conduct disease-modifying treatment trials using existing and new therapeutic targets that emerge as the understanding of underlying disease mechanisms and/or relevant biological pathways become available.

Epidemiological and Longitudinal studies

- Prospective longitudinal studies following triggering events (infectious and non-infectious).
- Retro- and prospective longitudinal observational studies to define disease progression (develop a prognosis framework), incidence of progression to other diseases (e.g., autoimmune disease, cancer, cardiac disease, endocrine dysfunction, metabolic disease), causes of premature death.
- Prospective study of impacts of hormonal change (e.g., pregnancy, menopause, HRT, puberty) on disease status.

Data Capture and Sharing

- Support further development of existing patient-reported data capture platforms and patient registries (e.g., You + ME Registry and Biobank (https://youandmeregistry.com/, Chronic Illness Survey https://www.meaction.net/epi/).

- Develop and validate methods of longitudinal biometric data capture (e.g., wearable activity meters, heart rate and VO2 monitors, etc.).
- Expand volume and access to centralized data and biospecimen repositories to enable wider collaboration and facilitate stronger study power.
- Utilize study designs that allow harmonization to Map ME/CFS and Search ME/CFS databases. Expand the sources of data for these repositories to include all ME/CFS researchers.
- Fix ICD-10-CM coding for ME/CFS, ME, and CFS so electronic health records are usable for research. Currently, ME/CFS does not exist, ME is not used, and CFS has been given the same code as the symptom of "chronic fatigue, unspecified."

Resources

Selected Resources about ME/CFS:

2015 National Academy of Medicine Report on ME/CFS

Bateman et al, ME/CFS: Essentials of Diagnosis and Treatment

Komaroff, Lipkin, Insights from ME/CFS may help unravel the pathogenesis of postacute COVID-19 syndrome

Recommendations for Research:

2020 Patient Led Research: Long COVID Research: Findings & Recommendations

2019 Report of the NANDS Council Working Group for ME/CFS

2019 MEAction Response to NINDS NANDs Council Report

2016 NIH Pathways to Prevention Report

Earlier Resources:

HHS CFS Advisory Committee Recommendations from 2004 to 2015

NIH 2019 Summary of Community Responses to its Request for Information

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