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To: NANDS Council Working Group
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Friday, March 8, 2024

Subject: Feedback on the ME/CFS Research Roadmap priorities

To whom it may concern,

Thank you for the opportunity to contribute to the ME/CFS Research Roadmap priorities. At Solve M.E., we are thrilled to witness the roadmap's development and are particularly proud of our former CEO Oved Amitay's involvement in the process up to this point. Our organization is deeply committed to funding research, with a special emphasis on supporting early career investigators. This focus is part of our broader strategy to accelerate and enhance these researchers' success within the NIH ecosystem, thereby contributing to the field's overall growth and bridging the gaps that fall outside NIH's scope. We value the opportunity to work in community with the NIH.

We view this chance to offer input on the NIH's research direction in this area as a reflection of the significant progress made in the ME/CFS field. While we recognize and celebrate this advancement, it's also crucial to acknowledge that the growth, despite being substantial, has yet to fully meet patients' needs for effective clinical care or yield the transformative therapies we desperately seek. With this in mind, our comments, though not exhaustive, are specifically tailored to provide insights into potential areas for NIH's future investment, aiming to foster further growth and innovation in research that could lead to life-changing treatments for ME/CFS patients.

Note: Please feel free to post the below comments attributed to Emily Taylor, Solve M.E.

Nervous System

When considering the role of the nervous system in ME/CFS, it's essential to incorporate insights from key research and discussions, including the foundational work by Freeman and Komaroff (1997), which underscored the involvement of the autonomic nervous system in ME/CFS, providing a critical link between autonomic dysfunction and the disease's characteristic symptoms such as orthostatic intolerance. Additionally, research conducted by VanElzakker et al. (2018) enriches our understanding by suggesting neuroinflammation as a potential underpinning of ME/CFS symptoms. Their research provides compelling

evidence of alterations in sympathetic and parasympathetic nervous system function in ME/CFS patients, offering a physiological basis for symptoms like orthostatic intolerance. In a related study, Wirth et. al. (2021) outlines tentative mechanisms of impaired cerebral blood flow, increase in intracranial pressure and central adrenergic hyperactivity and describes how they can explain the key symptoms of cognitive impairment (e.g., brain fog), headache, hypersensitivity, sleep disturbances and dysautonomia seen in ME/CFS.

By exploring the relationship between autonomic dysfunction and ME/CFS symptoms, such as the significant increase in heart rate upon standing and tilting observed in patients, we can begin to unravel the complexities of this condition. A deeper understanding of the nervous system's involvement in ME/CFS will not only enhance our knowledge of the disease mechanism but also open up new avenues for treatment and management strategies. Therefore, prioritizing research on the nervous system within the ME/CFS Research Roadmap is essential for making meaningful progress in combating this debilitating condition.

The nervous system is especially relevant to ME/CFS as evidenced by the symptoms of brain fog/cognitive dysfunction, tremors, speech and language problems, poor temperature control and sensory sensitivity.

Based on our own research findings in this area and what we are seeing in the field, this is an area that holds the potential to drive better diagnostics and therapeutics for patients and improve quality of life.

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Immune System

The immune system is one of the most commonly implicated systems in patients with ME/CFS. Evidence for immune system involvement in the disease is abundant and the immune system dysregulation is often cited as one of the potential causes of ME/CFS. Solve believes the immune system is one of the most promising areas of research and has focused heavily in this area as one with the best opportunities to produce treatments and precision medicine markers.

The evidence is indisputable at this point that the immune system is involved in ME/CFS. More research in this area has the potential to drive interventions, therapeutics, and diagnostics. Because potential treatment options are already widely researched, this is an area where targeted clinical trials should be prioritized,

particularly by repurposing FDA approved drugs. Of all the categories, the immune system deserves more translational funding to inch the field closer to an effective treatment.

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Metabolism

Metabolic disturbances in ME/CFS are well documented, including reduced energy supply and increased lactate production in multiple cellular functions. Failures in the metabolic system are one of the key culprits in the hallmark symptom of the disease, post-exertional malaise, or PEM. Studies on metabolism and CFS suggest irregularities in energy metabolism, amino acid metabolism, nucleotide metabolism, nitrogen metabolism and others.

Post exertional malaise is a critical diagnostic measure that needs to be included in any research or clinical criteria regarding ME/CFS. Our understanding of the metabolic dysfunction in ME/CFS has accelerated greatly thanks to exceptional research in this area. Keeping in mind the variability of this disease, PEM is one of the core symptoms of ME/CFS and needs to be accounted for in the inclusion criteria for any metabolic research studies conducted.

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Genomics/Genetic Susceptibility

While many genes are linked to key elements of ME/CFS symptoms, no specific genetic predisposition or inheritable traits have been verified. This area of study holds promise to enable precision medicine for ME/CFS and other infection associated chronic illnesses. We encourage the NIH to invest more on genomics-informed development of both diagnostics and treatments, instead of only focusing on identifying predispositions and risk factors. The whole community is eagerly calling for tangible treatments for patients already suffering.

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Chronic Infection

In general, scientific consensus agrees that ME/CFS is most likely caused by two or more possible factors working together to trigger the illness. One of these likely factors is the presence of chronic infection or previous infectious agents reactivating. This particular area of research presents many unique challenges and is further conflated by the extremely high infection rates of COVID-19. While a worthwhile area of research, prevention and treatment options remain limited for this line of inquiry.

If areas of chronic infection are identified, it would hold the potential to drive immediate treatments and potentially offer options for prevention of long term illness resulting from infections. Because potential treatment options are already widely researched, this is an area where targeted clinical trials should be prioritized, particularly by drug repurposing. It should be a moderate priority area of research.

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Physiology

This area of research is one of the most sensitive and must be approached cautiously. This area also could potentially be responsible for the wide variety of presentations of ME/CFS. In order to study potential physiological causes of ME/CFS, extreme caution must be taken with patient inclusion criteria. Patients who have experienced physiological triggers (e.g., spinal injury, head trauma) or environmental factors may potentially fall into a different subtype from infection-associated forms of the disease. There is some promising research in this area, such as surgical treatment. It's important to also note the high overlap with ME/CFS and connective tissue diseases and the potential subtyping opportunities.

This area holds the potential to be extremely impactful for several subsets of ME/CFS patients and the opportunities for diagnostics are especially promising.

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Less Studied Pathologies

The area of research that truly stands out in this category is that of mast cell activation. A well documented area of dysfunction in the existing ME/CFS literature, mast cells have been implicated in symptom severity and presence.

These areas show promise, and should continue to be explored by NIH research. Future research exploring the overlap with connective tissue diseases and the impact of viruses on connective tissue diseases may significantly impact quality of life for subsets of ME/CFS patients. Research into Mast Cell Activation Syndrome holds the potential to deliver treatment options for ME/CFS patients.

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Circulation

ME/CFS research in this area is in its infancy. While ME/CFS patients have been found to have low blood flow and circulatory dysfunction, microclotting issues were only recently found in ME/CFS. Long COVID findings helped bring this area of research into the light for patients with ME/CFS and these findings necessitate further investigation. Solve recommends additional investigation into this area, with a clear focus on treatments.

This is an area that has only recently become prominent in the ME/CFS space. It is one of the areas that highlights the similarities between ME/CFS and Long COVID, and where research holds the potential to help multiple infection associated chronic illnesses. This could potentially be a fruitful line of inquiry due to the easily available treatment options that already exist in this area.

Crosscutting

We encourage the NIH to invest at least $200 million of extramural funding per year in the following areas of ME/CFS research to effectively address this huge public health burden:

- Expanding the use of real-world data (RWD) and digital twins to improve precision patient-subtyping
- Validating surrogate clinical trial endpoints that can minimize potential harms/burdens to ME/CFS patients during study participation
- Promoting decentralized trial designs to extend the access to clinical studies to ME/CFS patients who are house-bound/bed-ridden
- Ranking drug repurposing candidates based on biology-informed probabilities of success
- Exploring the discovery of digital biomarkers, especially based on medical imaging results

Patient Engagement

Drawing upon our organization's nearly four decades of experience, Solve strongly supports and encourages meaningful patient engagement in all stages of the research process. A requirement for our own grants, Solve strongly urges the NIH to add similar patient engagement requirements to its studies. Again and again, we see that studies with better patient engagement and stronger ties to the community have better and more usable outcomes. Solve M.E. can create and implement bespoke patient engagement processes into a variety of study designs, and our platform, Solve Together, is specifically designed to improve data collection and foster improved patient engagement. We cannot emphasize strongly enough that in order for NIH studies to be successful, the patient and stakeholder community must be a meaningful partner with shared decision making authority. See Patient-Led Research Patient Engagement Scorecard for reference: http://cmss.org/wp-content/uploads/2023/01/11231_CMSS_Plybk_Scorecards_V3.pdf

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Conclusion

As we grapple with the challenges posed by ME/CFS, Long COVID, and other surging infection associated chronic illnesses like the recent Dengue Fever outbreak in Brazil, the urgency to understand and address ME/CFS and other related illnesses continues to escalate. These factors contribute to a scenario where more individuals will continue to fall ill and remain chronically unwell, highlighting the critical need for research that can stem the tide of infection-associated chronic conditions.

In response, the NIH's role is paramount in pioneering research that leads to effective treatments. By concentrating investments on treatment trials and ensuring tangible outcomes that directly impact patient quality of life, the NIH can make a significant difference. It is *crucial to continue including patient perspectives*, and we offer our gratitude to the NIH for the opportunity to add public comments to this roadmap. We believe there is a significant opportunity to mitigate the growing impact of these conditions. We hope our contributions underscore the importance of directing resources towards ME/CFS research, fostering a future where these debilitating illnesses no longer sideline individuals from their lives.

All the best,

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