The most compelling ME/CFS research needs

Immune system research-to find out what immune system responses occur during flu-like illnesses. Research on immune system and the way it can affect the brain. Genetic defects in the immune system of ME/CFS patients. Research on why severely affected patients cannot walk. Brain inflammatory responses to infection. Biomarker. Way to identify ME/CFS at the onset of illness. Reseearch to find out the similarities between MS and ME/CFS.
Biomedical research into cause, biomarker, and possible treatment. Please stop doing "behavioral/psychological" research, it's a waste of time and money. You may as well be doing behavioral/psychological research to figure out what causes AIDS or cancer.
Many patients believe that overexertion in the early stage of the illness worsens the prognosis. If true then early recognition and sensible advice could prevent much harm. A study where patients wear an activity and heart rate tracking device for several months could reveal whether the illness is associated with particular patterns of physical activity and heart rate. An objective diagnostic test is very important and is probably key to developing effective treatments.
Dr. Kent Holtorf has the most compelling research with peptide therapy and stem cells and immune modulating techniques.
Glean more understanding on what worked for people who have recovered from ME/CFS. The numbers seem to be few, and the path to recovery has been varied. We need a way to distinguish the variations in illness and generate a database of these success stories to scientifically study the common themes of recovery.
there were a couple of days at the beginning of my illness, a week perhaps, when i thought I may die, I had such excrutiating and unusual pains in my head. I think if you can catch patients at the acute stage and brain scan them would be great.
More centres of excellence. There were many great applications a few years ago but only 3 were allowed. We need all of them funding. You complain there aren't enough researchers in the field but when they apply with amazing applications for research centres, you say sorry, only a maximum of three independent of their merits. Please put another call for centres of excellence and fund all of those considered worthy and not restricted by arbitrary numbers.
To be biomedical - and based on appropriate data sets clearly identifying people with the illness and its severity. Not spin off from other conditions. It needs to focus on the lack of energy, inflammation and PEM as the key defining features of ME.
1) RFA's or other research funds dedicated specifically to ME/CFS to attract researchers into the field. 2) The use of stricter diagnostic criteria that require the presence of post-exertional malaise. 3) Training of ME/CFS specialists, because many are reaching retirement ages and we need them to make reliable diagnoses in research. 4) ME/CFS taught in United States Medical Schools. Not only 5% of Medical Schools 5) More funding. More funding.

Finding a biological marker for accurate and quick diagnosis. This will allow people to identify that they need to rest to avoid a more severy illness & give those of us suffering access to disability benefits and care giving. Once a biological marker is found, finding a cure.
All reseaech s vital.
Biomarker(s) that can guide the success or failure of treatments. A connected database so researchers and clinicians can access known successes and failures for both diagnosis, ongoing treatments, and biomarker assays.
Physiological self management using objective data e..g HRV, morning resting HR, sleeping HR and quantity/quality, orthostatic intolerance versus activity - all of which patients are using to manage the disease but which are under utilised due to a lack of large scale trials etc... The Workwell Foundation have a wealth of knowledge as do other exercise physiologists. The zephr body harness can be used to collect data and one speaker at the recent Emerge Australia said he could source the $600 meters from one of the manufacturers for free. CPET and 2 day CPET tests where appropriate and safe for the participants. Build on what experts know about over training syndrome as the physiological responses to exertion are the same they just get more and more extreme in people with ME/CFS because at least in part they are told to be more active. There is also a lack of research into the food/chemical intolerances as detailed in the Australian NSW Royal Prince Alfred Hospital Elimination Diet. Food intolerances also affect the HR and can be identified and managed objectively.
I have recently done this exercise, together with Derya Unutmaz and Maureen Hanson, for UK MRC as an advisory board so I thought I would just offer some bullet points along the same lines here. Vicky Whittemore knows that I am a retired biomedical scientist with a major interest in ME research as a sort of 'disinterested uncle'. Chris Ponting has convinced me that pushing genetic studies is worth doing. We need to draw on the really big datasets (hundreds of thousands or more if possible for 'first pass' trawling. We also need to verify using smaller carefully recruited population based cohorts like the UK ME biobank cohort. I think there are likely to be serious confounding ascertainment factors in cohorts that are not truly population representative and I am not yet convinced that people are aware just how serious they are. But I don't think they preclude getting a valid answer with careful methodology. The other idea is something that came from a 'citizen scientist' patient. The key clinical problem in ME/CFS is exertion intolerance. I think we need to be able to measure that objectively. I think there is an analogy with the inability to move rapidly and smoothly in Parkinsonism. The neurologists have made progress in documenting this with actimetry - including describing on-off phenomena. Actimetry in ME/CFS has mostly looked at just quantity of activity but I think it needs to be used to look at PATTERNS of impaired activity so that these can be tracked objectively over long periods. The technical term for this is apparently 'motor fatigue'. That is to say not a sense of fatigue but a behavioural pattern that can be studied objectively. Only when we understand these patterns will we know what we are trying to explain. I think it very likely that if we really knew what the activity deficit was we would know we are not looking for a metabolic defect, for instance.
I have just submitted a suggestion from the email **[…]**. I now realise that I did not say who I was, although it might be possible to guess. I think it would be helpful to state that I am indeed **[…]**.

(1) establishing a biomarker to facilitate early diagnosis
(2) research existing pharmaceutical interventions on established symptoms (I.e. use of drugs for neuroinflammatory disorders that may have crossover to me/cfs
(3) establish proper standard of care for primary care physicians to follow for me/cfs patients, including checking for co-occurring conditions (such as POTS, Ehlers Danlos Syndrome, MCAS, fibro), as well as commonly used medical intervention for me/cfs patients (such as antivirals, low dose naltrexone, heart rate monitoring, treatment for dysautonomia etc).

CFS / ME inhibits brain function due to various causes, and most of our bodies are not functioning normally. There is a problem with the production of brain signals, or a problem with the transfer, which causes abnormal operation due to a failure of the cell or the organ to receive a normal command.

Up to date research using The ME-ICC specifically. Using cells or patients who meet the strict requirements of the ICC

- More research into multidisciplinary rehabilitation.

- Research into CBT and GET, to see which variations of CBT and GET are effective, and what type of exercise helps vs which makes patients worse.

1) BDNF gene

2) SIBO correlation, gut microbiome disruption

3) Can it be determined that the EBV retrovirus is real or not real

4) Train more doctors in more states regarding the complexity of symptoms so that we do not feel so very unsupportive.

***There is something wrong in the nervous system sending random improper signals. Send a survey for a trial, send to a thousand of us, provide choices of the 10 top reliable sources of the start of the disease as we've been told (so many). Take the top 5-7 commonalities from the ten of that survey, study us, we don't need crazy isolated synthetic medications to fix us, we need support and strategy to regain control of our neurons and pathways.

5) Where are the system breakdowns, where are the kinks, where is the inflammation, how can the connections be corrected? I had SIBO for a year before the retrovirus was able to get through my destroyed and emaciated microbiome and ME/CFS quickly killed my career, my family life, my ability to complete simple tasks... in a matter of months.

6) We are the disregarded, the unsolvable, we are the patients that sit in so many different doctor's offices imagining a glint of hope and get told we just need depressant medication and walk out so very disappointed. Our systems are depressed, not our hope, not our will, not our drive. If we had trained doctors that understood some of what is going on and diligently have us track relateable symptoms in a sample of us, then you'll get some serious real data.

7) You need patterns, strong data in order to get to the bottom of this terrible heartbreaking life-breaking disease.

Let's research a plan to help us Recover from this living death disease. Having no answers is the worst,

wait, second to worse, first is that we don't know if this is degenerative because of lack of long term data.
Funding.
Increased funding for ME research is the greatest need! Provide increased funding for ME research and the ME researchers will come! NIH devotes about one-tenth of its budget to AIDS/HIV and those affected enjoy a far better quality of life than do ME patients thanks to vast amounts having been spent on AIDS/HIV research. A tiny fraction of NIH's budget has been devoted to ME research, and ME patients suffer dreadfully!
bio marker, drug to target the source of the disease, drugs to help relieve symptoms
Genes and biological, cellular-level research. Finding the cause of the widespread energy deficiency.
Multifocal studies combining immunology, neurology, EDS patients, gynecology, endocrinology, genetics, etc. We need to know why this has affected 3 women in the family.
Brain imaging studies of the brainstem area. An objective diagnostic test is urgently needed.
Identifying markers for diagnosis, identifying and establishing a link between causes of ME and contracting the disease. Researching and identifying treatment plans and protocols, especially for PCP's to follow since their knowledge of this disease is so poor.
Members of the Working Group are probably not aware of the research published in 1994 and 1995 on the isolation and characterization of an African green monkey simian cytomegalovirus (SCMV)-derived stealth adapted virus from a CFS patient. The references are: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1887390/pdf/amjpathol00056-0208.pdf and https://ac.els-cdn.com/0928019795000209/1-s2.0-0928019795000209-main.pdf?_tid=0e743f8b-576a-463c-8c7e-2e5fba0ceed4&acdnat=1553016254_b85ba731cff4d9fad7d225d4aa3b6972 These and subsequent articles explain CFS as a virus encephalopathy. The causative viruses, some of which are monkey-derived, do not evoke inflammation. They can, however, be suppressed via the alternative cellular energy (ACE) pathway.
Infectious viral, endogenous retrovirus, and altered immune response-related risk factors in ME/CFS.
For a way for doctors to be able to definitively diagnose ME/CFS. They greatly struggle with seeing ME as a legitimate organic illness, and are currently doing great harm in their ignorance.
(1) identification of some sort of a biomarker to diagnose people with ME/CFS; (2) how to use currently available medications to treat ME/CFS patients and ameliorate symptoms and improve quality of life; (3) development of new drugs to treat ME/CFS
The possibility that a portion of cases of CFS are due to persistence of aluminum adjuvant in the body should be investigated. See RK Gherardi et al for more details.

Funding. Funding. Funding. It's as simple as that. Disease specific RFAs, no strings attached funding increases to the top research groups such as the Open Medicine Foundation. We need data gathering before hypothesis testing so it's unfair to only fund grants for specific hypothesis testing, need to fund data collection and analysis especially for the most severe patients. At least 100 million $ yearly budget for ME/CFS, which is still under what's justified by disease burden.
1. Testing and clear diagnosis 2. long term analysis and investigation 3. ME/CFS relation to other illnesses for example: MS, cancer, Lupus etc, does cfs become cancer? or parkinson, if no action is taken? is cfs /ME jsut a slow developing alarmbell for a later illness? 4. HOW MANY PEOPLE ARE DYING OF CFS?ME? !!!!!!!!
FUNDING! MONEY! ATTENTION!
1.To study the course of post-exertional malaise as it resolves over a 7 day period by every blood test possible. 2. To study orthostatic intolerance.
Better understanding of the viral damage caused by viral trigger. Potentially Work with viral meningitis charities to observe patients over time see who develops it. Test treatments improving blood flow to brain including cranial osteopathy and hypobaric oxygen and POTS medicines. Also test anti inflammatoires. Longtitudinal studies to catch the disease progressing. Study people who say they've recovered. Why? Is it remission (I appeared to recover in my 20s but am now disabled) , a wrong diagnosis and some other disease or some biological magic we can possibly tap into? A clear solid sub segmentation to target research. We could have found a cure for 1 group and discarded it due to inconsistent results from sample test group composition. A objective diagnostic tool. Clinician Scepticism is my biggest hurdle at the moment. Having something I could point at would help my sanity while I wait for research. A clear differentiation from depressive illness to finally kill the "its psychological" excuse to not take it seriously, research or treat it and move the discussion beyond "Pacegate" firmly into biomedical. Take healthy, solely depressed, ME not depressed, ME depressed, find the differences.
A blood test identifying ME Possible use of existing drugs to treat ME, like suramine or dextromathorphan
At this point in the exploding global ME epidemic, the priority should be to save lives as in a triage situation...then study those patients who are willing, in their homes.

Bases biologicas.
It is really important to find biomarkers which can be used easily in frontline clinical practice (i.e. tests that can be performed or easily ordered by family doctors) to ensure accurate diagnosis. Many patients have the reality of their illness dismissed, so a clinical diagnostic test is really important in overcoming this problem which has gone on for decades, and which has caused many ME patients to have medical care denied, welfare denied, and to be erroneously referred for inappropriate psychiatric treatment. The next most important thing is to understand the mechanisms of pathophysiology so that we know where to target drug development. Then finally, drug development is urgently needed because there are currently no FDA approved medicines for ME/CFS.
Appropriate levels of funding Biomedical research looking into fundamental causes of ME/CFS - i.e., metabolic, immunological, neurological Having numerous clinical centers of excellence because this disease is too complex to expect PCPs to have an adequate understanding of ME/CFS to treat it properly Research that focuses on ME/CFS patients who are on the severe end of the spectrum (i.e., homebound, bedbound etc.) and adequate accommodations should be made to gather data from inside the patients' homes (because they can't readily leave their homes to go to research sites)
XMRV virus
Biomarker Any approved treatment
Identification of biological cause of ME/ CFS and any sub types
[…] has been achieving durable remissions since 1988 in 90% of his patients. His diagnosis and treatment methods should be subjected to a study against other options. The basic strategy is 'immune reconstitution'. If NK cell activity (or other measure of immune effectiveness) is low, improve it and this ailment (as well as others) will fade away. The ability to improve immune function is almost unknown to most medical practitioners. This is where Stoff has taken a leadership role, although an obscure one. He wrote a book on CFS. More pertinent perhaps is his book on Prostate Cancer which details his more up to date methods.
Repurposing existing drugs for various common symptoms. Particularly the neuroimmune - PENE issues. This focused approach may yield immediate results in lieu of long exhaustive NEW drug trials.

There needs to be research on how to address the most commonly reported symptoms in an attempt to return some level of functionality to patients. While this might just be a band aid, band aids are useful. Other teams would be capable of conducting the search for underlying causes and patients wouldn't be forced to suffer.

1. Include some investigations about how people with ME/CFS "recovered".
2. Include nutritional testing and supplementing based on testing like Genova lab's NutriEval.
3. Study very low dose (2.5 -5mg) prednisone treatment.
4. Study incidence and treatment of chlamydia p. and mycoplasma pneumoniae..
5. Study long term effects and outcomes of ME/CFS with no effective treatment and the evolution of comorbidities that occur and potentially are the cause of death.

1) Identifying prevalence of disease by instituting a tracking/reporting system nationwide.
2) Identifying suicide risk and testing suicide prevention/intervention strategies.
3) Identifying environmental triggers including mold and other sick building pathogens, as well as chemicals and VOCs.
3) Identifying brain, cranial nerve and spinal cord pathology in ME.

Biomarkers

A full understanding of the multiple disease mechanisms and systems effected: Neurology, Gastroenterology, cardiology, hematology, dermatology, endocrinology, etc

This disease effects multiple systems and the brain is just one.

A full understanding of the several subsets and onsets

A full understanding of the genetic components

A full understanding of the multiple comorbidities

Treatments

To keep hope alive for millions who are suffering

Preventative care

A cure

Someone needs to collate all the research, publish a summary online of what's been explored, how large the study was, on going/finished, results. Should include supplements and diagnosis tests. It should be easy to use and understand. There's so much to read for people with fatigue and brain fog. Websites, scams, social media like Reddit has loads of stories of supplements helping but it's impossible to understand it all or know what's genuine and what's just masking symptoms, resulting in worse long-term CFS progression.

1. funding commensurate with similar diseases like MS. $250,000,000/yr.
2. technology is so advanced, fund search research like Ron Davis' instead of denying it, wanting a hypothesis
3. boost funding for Centers of Excellence - as Lipkin said $5M/yr doesn't even break even. And get more centers across the country.
4. We need much more research on severe and long-term patients

5. searches for the cause 6. treatment trials 7. set up autopsy studies + a prtocol that local medical examiners can do + a format the data. Also a way to donate brains, tissues, blood....both along with autopsies and independently 9. Use objective data to measure results and make sure no psychobable, UK-style CBT and GET- like nonsense gets funded
To be SMART and get away from relying on subjective information
- marker for proper diagnosis - more accurate diagnostic criteria for studies (ICC) - why does antiviral treatment help some and some not - trial with IVIG (not low dose) - what about Ampligen? - stem cell therapy - immunoadsorption - other ideas for treatment
Cure as the symptoms are suicidal especially the post exertion malaise.Huge investment needed to fund multi subject investigations so that biomarkers and treatment can be
Clearly, causes and effective tx.
ME international consensus criteria to be used in every study - to identify differences Breen SEID, CFS and ME Biomedical research Energy envelope theory and pacing clinical trials Neurological Symptom investigation especially in severe ME Biobanks and gene analysis for severe and very severe ME
Treatment strategies for people with Chronic Fatigue including Testosterone Replacement Therapy, Aeronic and Resistance Exercise and other Nutritional and/or Pharmacological Therapies such as Beta Two Agonist Administration.
Finding BIOMARKERS or other relatively non-invasive diagnostic tests is my first priority. This is our best hope of receiving adequate, respectful treatment for our comorbid issues at the medical practices and hospitals we visit when we find ourselves desperate for help. We tend not to go for help except when in dire straits. Most medical and social service professionals still roll their eyes and assume we are de-conditioned hypochondriacs when they see ME or CFS or ME/CFS, CFIDS or worse, SEID, in our medical records. My second (but equal) priority is adequate education about our illness in all medical, therapeutic, dental and social service fields. Both must happen if the most severely ill and alone of us are to survive. My previous response appears on pages 240-242 of the Trans-National Institutes of Health (NIH) ME/CFS Working Group of 2016 NOT-NS-16-024; Request for Information: Soliciting Input for New Research Strategies for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). I am now 71 years old and have been ill with relapsing/remitting M.E. for 53 years (since Epstein-Barr

while in college) and am now mostly bed-bound. I believe my son, who lives with us under my care, has it too. I haven't been willing to subject my increasingly disabled 37 year old son, who has been ill for 27 years (following a bi-lateral intra-ventricular cerebral hemorrhage at age 10, then Epilepsy beginning at age 26, each episode followed by Rhabdomyolysis which I believe is set off by unusually intense muscle contractions during his tonic-clonic seizures), to the serial humiliation I experienced before and after my ME/CFS diagnosis until a) definitive relatively non-invasive biomarkers, b) adequate treatment with minimal side effects, and c) appropriate education of all practitioners in all medical specialties are in place. Please read about 'neuropsychiatric' (pain) comorbidities of Epilepsy on the second page of my 2016 response.
We know that the 2 day CPET can measure the level of impairment and disability and we know whilst this test is onerous on the patient it does produce valuable information for managing the disease. We know that people strictly keeping their HR under their anaerobic threshold and doing anaerobic/strength building exercises (if and when able) are stabilising/improving. We know that heart rate based pacing and the use of heart rate and heart rate variability data is helping patients self manage the disease much much better ie reduce symptoms and increase physical functional capacity. Yet, there is a dearth of research backing up what patients and a few clinicians (Workwell Foundation, Nancy Klimas) are saying. We need long term trials (ie years) on how these strategies work . It nominally takes 4 months of strict HR pacing to see any results and the results can be miniscual but they are both real and sustainable.
To clarify case definitions. Research cannot progress while including different patient groups with different diseases. Myalgic Encephalomyelitis must be distinct from the later created CFS as defined by the WHO. The ICC is probably the best we have currently. The blinkers must come off in seeing fatigue as a defining symptom. ME encompasses over 60 extremely debilitating symptoms as published by www.hfme.org
Biomakers and/or reliable diagnostic tests that have been thoroughly proven (debunking the stress, attitude connection) - this would give researchers a valid place to start. For more clarity, first work with subsets that have a known connection with CFS/ME (such as mononucleosis or outbreaks).
The multiple chemical sensitivity and food intolerance aspects of the disease have not been researched or quantified. Exposure to chemicals and foods that cause an intolerance show up in a raised heart rate . Dr. Coca's Cardiac Pulse Testing protocol and apps such as Food Detective can be used to help identify intolerances. Common food intolerances are sugar, alcohol, high salicylate food, amines, soy, diary, preservatives, and grains. Common chemical intolerances are perfumes, cleaning products perfumes, laundry/cleaning products, gas, latex, paints, vinyl, air freshener, fabric softeners and cigarette smoke. Two handbooks that may be helpful are the Royal Prince Alfred Hospital (RPAH) Elimination Diet (food and chemicals) (University of New South Wales Australia and the FODMAPS Diet (food) Monash University Australia. I am not aware of any USA University publications. Plus the video After Unrest - explains the MCS and food intolerance aspects of the disease . Knowledge about these preventable and avoidable ME/CFS triggers will reduce suffering and improve persons health easily ie it is the low hanging fruit that easily yields a positive impact. After Unrest: https://drive.google.com/file/d/1RDBbXcG4tg0WEzlH8xq-Fe69pwDhB2QV/view?usp=sharing

1. Post-Exertional Malaise, as this is a hallmark of ME/CFS 2. ME/CFS among youths 3. People from Indigenous/non-Caucasian/diverse ethnic backgrounds, particularly since the USA is increasingly ethnically diverse as is the rest of the world.
There is a serious need to collect medical data records from those of us who have been ill with ME/CFS more than ten years. I personally have been ill since 1957, when I was six. I have a lot of my records in digital form and have a personal narrative that I added to over more than ten years. Other patients have the similar information. Someone needs to collect it and then review it for patterns. Waiting for the current patients in the NIH study of those ill for five years of less to live as long with the illness as we have means a delay of 50 years or more. Half a century is a long time to ask current children with ME/CFS to wait until enough info is collected to be helpful. You need to collect info NOW, before we die off, ignored in death as we have been in life. I would like my 62 years of suffering to be worth something--not just wasted. In 1994 I was a co-author of the 10+ study which included about 200 patients ill ten to more than 40 years. 25 years later some of them are still alive and still suffering. Most of them were diagnosed by well-known ME/CFS physicians at the time. They had ME/CFS. They have important things to tell. You need to stop neglecting this resource. You need to know the various complications that develop over time and the change in the characteristics of the illness that occur over decades. We found that there was significant variation, but it was important to get an idea of what kinds of variation exist.
Look more into the HPA axis and role of adrenal glands in the syndrome, role of tyrosine and N-acetyl-L-cysteine to support glutathione production, antioxidant activity, and neuronal protection. Look into liver's detox 2 pathways.
Missing obvious controlled studies for Vk, also HBOT Hyperbaric Oxygen treatment that may have helped some patients. Tens of thousands of single patient studies done but need controlled studies
-Finding effective treatments -Creating clear and widely accessible diagnostics -Finding a cause -Identifying subtypes within CFS
Genetic research. My ancestors come from the orkney islands in a Scotland, which has the highest rates of multiple sclerosis in the world. I live in canada and it also has one of the highest rates of ms in the world, especially the province of saskatchewan where I live. This is likely due to heavy settlement of people From Scotland here. In m own research I notice that there are many paralllels in triggers and symptoms for ms and cfids. I believe that cfids is a milder variant of ms. Another area of research should be how educated MD's are on the diagnosis and management of cfids. There also needs to be a real census to get real numbers on people with his disease and a public education campaign especially for the medical community to finally recognize cfids.
Post-exertional malaise

In addition to prior suggestions:

However, hard to prpose:

A key resource would be the collection of a series of 20 sequential autopsy brains on moderate to severe patients commiting suicide. A central consistent processing facility with controls should be used and blinded tissue samples sent to three independent neuropathologists. An important aim would be to exclude any so far missed patterns of pathology but positive findings would be of geat help.

Such a proposal should be set up prospectively with government funding making use of something like the UK Queen Square RNHND brain bank facility . I think Nacul and colleagues have raised this in 2014.

Using cutting edge technologies to study the biological underpinnings of ME/CFS. Establishing for once and for all what the diagnostic definition of the disease is and fund only those studies that conform to that definition.

For us, research on childhood chronic fatigue and ways to treat it as well as ways to work with schools or employees based on research findings (I.e. suggested approaches to educate others on limitations and possible strategies for success)

1. Identify the biomarkers to aid diagnosis and make those tests available so that GP's can use them.
2. Figure out what turns the symptoms on (and off). Is there a way to prevent the symptoms in the first place when one is acutley ill, to prevent ME/CFS from taking over after the acute illness?
3. Best ways to overcome the limitations, such as the fatigue and brain fog that prevent education and work.
4. Cure!!

A priority need in ME/CFS research is the development of rigorously testable hypotheses on potential causes of ME/CFS supported by prior research. THE Vk-CHITINASE DEFICIENCY GENETIC MUTATION HYPOTHESIS is offered in that regard. The zoonotic nematode Varestrongylus klapowi (Vk) discovered in 1994 was found to infect the majority of ME/CFS patients in highly significant blinded diagnostic trials. The Department of Genetics of a top tier university has expressed an interest in investigating the hypothesis. It is based on the observation of extensive biofilms composed of millions of bacteria sized, chitin covered Vk mini-larvae in the nose and sinuses, lying close to the brain. The likely origin of the mini-larvae are large larvae which growth up in the lymphatics, migrate through the brain and olfactory nerves into the nasal cavity and asexually bud thousands of chitinous mini-larvae each. A test case has shown that the Vk biofilms can be reduced with chitinase administration which improved symptoms. Approximately a billion people worldwide cannot produce a working chitinase due to a common mutation in the CHIT1 gene. The mutation is most common in East Asia, at about 30% compared to 3% in the US population. A recent study (Wong and Fielding, 2010) reported that CDC defined ME/CFS in Hong Kong exceeded ten times the US rate, mirroring the difference in genetic chitinase deficiencies. A study proposal has been prepared to test the association between genetic chitinase deficiencies and Vk infection. Another proposal has been made to assay CSF leakage into the nasal cavity through possible parasite borings. If positive, histology sectioning of autopsied brains for Vk tissue identification would be a logical next step.

Vk background information exists in the form of:

1. Video's of live moving Vk larvae. Mini-larvae are most active, moving on biofilms and "battling" engulfing neutrophils.

2. A 44 page presentation of the anatomy, growth, lifecycle, and responses to treatment of the Vk parasite, researched over the past 25 years.

3. A chitinase treatment study case which gave rise to the hypothesis.

4. A Vk Identification Manual sent to possible academic collaboration.

The mathematical statistics prove that ME/CFS is underfunded, neglected and the patients deserve to be clinically treated at the onset of illness, not shuffled around the United States to see a handful of clinicians who treat this illness, yet do not have a cure for over 5 years obtaining an accurate diagnosis.

More biol=market=rs, more doctor education and belief, Most of my docs won't even talk to me about it.It is obvious they have little belief or care about it.They do not understand w=that I am vulnerable, sensitive and my immune system is not as strong as it should be. Of course they also do not understand that my pain levels are off the chart compared to someone else for the same procedure or illness/injury. With the whole pain med issue, it is absolutely crazy.The Gaba's and the cymbalta, etc DO NOT WORK. And all the antidepressants don't work, we are sick not depressed. They don't get this yet. I take one, and they wanted me to be on 3. Really??

Diagnostic process to allow patients a streamlined set of criteria and medical standards to correctly and quickly diagnose ME/CFS. Too many patients go through countless doctors and lab tests to be told they show high levels of inflammation with no immediate cause. The past diagnosis process is a collection of symptoms being diagnosed that confuse and obstruct validation for patients already suffering. Too often patients are put through a process of elimination approach which only serves the medical community by lining their pockets. Awareness and validation is the first step and the most critical need. The medical community needs to come together and create a standard test to be employed by all physicians as part of their medical training. I cannot express enough how just having a valid name and recognition would offer support to all patients regardless of where they are in their journey of living with this disease. Logic demands that you cannot research and cure something that is unidentifiable by current medical standards. A patient should not be limited to their means and access to high cost specialists to determine the cause of their illness and options for treatment.

As a scientist with ME/CFS, my perspective below is formed from personal experience with this illness's acute onset, chronic development and physiological change over the years, and historical research as to the cause. Here is where I feel research needs to be most pressingly directed:

The nexus of Virology, Immunology, Genetics, Toxicology, and Neurology to identify why some bodies crash after a period of psychological anxiety while others do not given the same stress factors. The work of the HHV6 Foundation, Lerner, Montoya, Mikovits, and Alter in this arena continues to be highly debated but survives due to cycles of proof and debunking. Because it is at least established that viruses, genes, and stress are implicated in ME/CFS somehow...it is a metabolic process problem not a causation problem; I was generally a healthy, active youth until work-related stress left a serious infection in my 20s (hospitalization for measles despite having been immunized for MMR as a child, to which I then had an anaphylatic reaction) left me with post-viral malaise that rapidly increased to full-blown ME/CFS. Whenever I undergo treatments for Me/CFS, I experience Herxheimer-Jarisch symptoms consistent with reactivations of an influenza infection, and even when not having treatment my experience lifelong has been feeling like I have the flu all the time, but I am not PIDD

and immunoglobulin has not helped. Viruses like CMV, HHV6, EBV appeared for me in sero at one point in my life then became undetectable load. Furthermore, review of my case history and records led to a poorly synthesized run of the particular MMR vaccine I had in infancy, a batch from a specific manufacturer I will not name at the time in the late 1970's that did not have "bulletproof"quality control in terms of human/animal diploid DNA fetus (which did in the 1960's carry SV40 when monkey kidney was used) or quantity of aluminum adjuvant used. While XMRV-CFS causality has been disproven, we need more research into diagnostics of viruses in the nerve endings that can be done in a clinical setting instead of in the realm of research through treatments for While I am **pro-vaccine** as a matter of public policy at large , and I need to emphasize that to not associate myself with the anti-vaccination movement, more independent research is merited in the effects of inoculation ingredients on early developing immune systems that is free from the politicized stigma of the anti-vaccination movement to turn the tide of regulatory oversight on production methods and better self-policing by manufacturers. I have had my genome sequenced twice, ten years ago when it was still in the realm of academic research and again recently via 23andMe then my imputed genome imported into tools such as Promethease, and there is a marked difference that 10 years progression in my ME/CFS has made coinciding with various other genetic disorders in connective tissue, autoimmunity without systemic ANA, immunodeficiency, that were not congenital, but acquired. Leading to a viral etiology being suspect in the triggering of change in DNA, due to damaged fragments of mRNA released by damaged cells en masse. This is supported by findings that ME/CFS is of an exosomal and not cytokine nature. Ultimately I believe that ME/CFS will eventually be relegated to history as a set of symptoms of a persistent Viral infection of the CNS, with the treatments for that in the short term being antiviral, gene therapy, blood filtration, nerve repair ...and preventatively in the long term changes to vaccine manufacturing practices, reduction in neurotoxic and immunotoxic chemicals in the human environment, and gene editing in the womb to remove implicated germ line viruses like has been done in China with the HIV couple.
In listening to the "Accelerating Research on ME CFS" Thursday and Friday, I learned that the majority of individuals with ME-CFS appear to have antibodies for Epstein Barr and Herpes Simplex virus. These viruses appear to be causative or triggers for ME-CFS. Epstein Barr research points to viral tropism including B cells leading to autoimmune pathology and points to genetic mutations via Epstein Barr. Further work on Vaccine development for Epstein Barr and Herpes Simplex could possibly eliminate causative factors for the majority of people with ME-CFS.
Immunological, microbiome and molecular basis.
Division into post-viral fatigue syndrome and CFS NOS
Information should be captured on what modalities of treatment outside the mainstream have been utilized and have proven effective in symptom relief. . Examples might be acupuncture, acupressure, Myofacial release massage, meditation, etc. This should be done along with mainstream medical research that is being done and appreciated.
Finding out what it is and how it is caused. Then, figuring out how to test patients for ME/CFS.
As patients with ME experience a suicide rate 7 times higher than the average the most pressing need is research into effective treatments. Understanding the intricacies of the disease is much less important than finding effective treatments.

Investigate and identify which chronic pathogens are keeping us ill. AB neutralization test for Cocksackie B1-B6 viruses for all patients would be an interesting one.
Increased funding.
Replication of promising results that have come from small scale studies, which pretty much describes all of the existing ME/CFS literature. Exploration of what is measurably different between patients with ME/CFS, healthy controls and controls with other well-defined illnesses.
I am in the UK and I would say the pressing need is to show NIH is going to increase funding in whatever it sees as the most promising areas of bio-medical research.In the UK bio medical research is often dismissed as small studies with inconsistent results nearly all funded without public money.This is contrasted with the amount of public money put into social/psychology studies,many millions which are often claimed to be definitive because they are large studies.Something very similar happened with a study into gulf war illness and it was deemed to be the definitive study with no need for future research.Even stating CBT and GET is not the answer and making progress on countering the idea ME is perpetuated by false illness beliefs and deconditioning model might help in attracting new researchers
Funding, Advertising, Education, Understanding and Compassion of ME/CFS. A passion to find effective treatments and make ME/CFS research trials so that those inflicted, that want to participate, whether homebound, bedbound, or mobile all can participate. Creating knowledge and understanding in medical schools for research and ME/CFS. Re-educating scientist, researchers, all medical professionals of ME/CFS.
Researching the connection between gut bacteria/ "leaky gut" and Myalgic Encephlalomyelitis, as well non pharmaceutical ways to treat the symptoms of ME. There must be natural, homeoparhic treatments for treating our symptoms. I currently use some for some of the symptoms, but more research needs to be done for solutions to the actual "fatigue" symptom of ME.
Clinical trials on existing drugs.
1) Finding a non-invasive bio-marker so that the breadth of our population is known. We are woefully underdiagnosed. 2) Clinical Care for those most severely impacted by this illness must be included in any future plans. 3) Education of med students and Professionals in all Specialties to reduce the stigma we face: We no longer go to doctors or ERs unless we are in dire straits. Doing so almost always exacerbates our condition. 4) Education is essential.
Money. Considering the economic burden caused by ME/CFS the amount of dollars per patient is far below what would be expected. I have no idea how the bureaucracy works or what mechanism would work best to increase the funding. But please do whatever is possible to eliminate the red tape and ramp up the funding every year.

We need ring fenced funding urgently so that new researchers will enter the field and know that they will have a career.

Money.

Support from gouvernements.

The common knowledge that the PACE trial is a disgrace for science.

Educating the whole medical world about ME.

Collaboration of scientists.

Clinicians with expertise in ME/CFS

The diagnosis of ME/CFS requires specific expertise. Studies have shown that approximately 40% of patients expected to have ME/CFS in primary care have other conditions after examination in a specialist center. [1-4] Because there is no biomarker for ME/CFS, clinicians need to recognize the symptom pattern and exclude other conditions that might cause these symptoms.

For research to obtain reliable results it is vital that participants have ME/CFS and not a related but overlooked condition. A reliable diagnosis of ME/CFS forms the foundation of each study and an expert clinician is at the heart of each ME/CFS research team. The use of questionnaires is rarely a viable alternative as less than 20% [5,6] of patients who meet ME/CFS symptom criteria, turn out to have ME/CFS after clinical examination.

Unfortunately, very few physicians have expertise in ME/CFS. This makes it difficult for research to enlist large and representative samples of ME/CFS patients. Furthermore, many of the expert clinicians who have spurred ME/CFS research, such as Daniel Peterson, Anthony Komaroff, and Nancy Klimas, are reaching retirement age. This indicates an urgent need for clinicians trained in the diagnosis, management, and care of ME/CFS.

To further research in the field of ME/CFS, I would therefore recommend training expert clinicians, specialized in ME/CFS.

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Understanding the dauer or exhaustion state so that treatments and risk avoidance methods can be developed and applied.

Dear Working Group,
I would like to draw your attention to an ME/CFS research breakthrough in Germany. ME/CFS patients in Germany have been symptom-free after undergoing plasmapheresis (like dialysis) in the course of a small preliminary study carried out by Prof. Carmen Scheibenbogen, CharitÃ© University Hospital, Berlin, Germany. According to their research, presumably in a subset of about one third of ME/CFS patients, an autoimmune mechanism is the key.

Please see the publication “Immunoadsorption to remove ÃŸ2 adrenergic receptor antibodies in Chronic Fatigue Syndrome CFS/ME”on plasmapheresis in ME/CFS via:

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0193672

You might consider a research cooperation together with CharitÃ© Immune Defect Ambulance (Prof. Scheibenbogen)

https://immunologie.charite.de/metas/person/person/address_detail/scheibenbogen-2/

You might wish to do research on immunosuppressant medication (like prednisone, methotrexate, biologica) and cholineesterase inhibitors in ME/CFS.

In my view, the field needs research that address underlying causes, specifically what causes the failure to produce energy as well as the failure to restore with sleep. This means extensive research into the krebs cycle, ATP, etc. and extensive research into sleep and why patients' sleep is disturbed, what is actually disturbed. Currently the research is focused on identifying biomarkers related to symptoms of the disease but none is directed to identifying underling cause/s. Research should address what epigenetic factor/s cause immune system dysregulation after a virus (EBV, HHH6, other), how that event causes energy production failures- even subtle ones that go undetected for years, as well as what goes on in the brain to disrupt the sleep cycle.

I forgot to include this in my submission. At least for me there is a fascinating connection between my gut and my brain- which we know exists. In this case, when my sleep is better, my gut works better and i can easily have bowel movements despite having delayed emptying of the stomach. Since i've been seriously ill- over the past 3 years- medicines that don't work- regardless of their class or indication- such as mestinon, fluronif, gabapentin, immunivir and some others ALL give me identical side effects- incredible insomnia and constipation. I do not know how common this is but

there may well be something in the microbiome that affects sleep and that should be researched enough to see if its a promising research area.
Obviously, the most compelling research need involves allocating the appropriate level of funding for research to take place (and for researchers to be motivated to apply for grants); and by appropriate level of funding I mean funding that is commensurate with the disease burden. The NIH leadership has a sacred responsibility to address this problem fully, especially given the fact that it has taken over 30 years for government organizations to acknowledge the seriousness of the disease. After the funding issue has been resolved, other key areas regarding research needs include: a focus on biomedical research looking into fundamental causes of ME (perhaps emphasizing areas such as metabolic, immunological, and neurological abnormalities); creating numerous clinical centers of excellence across the US that combine clinical care with research because this disease is too complex to expect PCPs to have an adequate understanding of ME to treat it properly; and to include research opportunities that focus on ME patients who are on the severe end of the spectrum (i.e., homebound, bedbound etc.); lastly, adequate accommodations should be made to gather data from inside the severe patients' homes (because they can't readily leave their homes to go to research sites).
1. Seed funding to explore new approaches to ME. Why expect patients, most of whom are unable to work, to fund the early stages of research? 2. Reliable continuing funding to enable researchers to assemble top quality teams with tenure.
New Retrovirus or maybe Enterovirus. Tenofovir (Viread) works! In Germany are more and more Remissions following this regime: https://drmyhill.co.uk/wiki/A_Regime_for_Antiretroviral_Treatment_of_Myalgic_Encephalomyelitis
Cause and cure.
FUNDING! Research on MOLD in ME/CFS and the several diagnostic tools that Ron Davis figures out need to hurry and be researched and given out to all clinics etc all over!!! This is URGEN! And I don't understand WHY you keep denying all projects proposed to NIH! WE NEED HELP!!! We need funding so bad!!! It's ridiculous that ME/CFS isn't given the amount that AIDS gets!!! This needs fixed ASAP
Educating doctors- they still have no idea and blame patients' mental health issues. This occurs for patients who have given up high-powered careers and now lie in bed every day- having had to close down their labs, give up their tenure-track positions, and are unable to take care of any of their family needs. They have switched from being investors in society to being kept alive by the support of others. If only doctors could understand this.
I admittedly don't know a lot about the current research, but it seems like the most urgent need is a method to lesson the symptoms enough for patients to be able to function while researchers look for a more permanent cure.
How to monitor and live with ME/CFS. If a druggable target with off label safe medication is not found rapidly, hundreds of thousands will get Ill and have their lives destroyed between now and perhaps 2035. What activities cause PEM.

What strategies (noninvasive biomonitoring) can be taken to alert people with poorly controlled CFS that they are over exerting themselves. When does PEM risk longterm worsening.
Fund research which destroys the lingering misconceptions around ME/CFS that stop researcher interest in this field such as the idea that ME/CFS is caused by deconditioning or malingering and promote research which highlights the effect exercise has on the ability of people with ME/CFS to produce energy. Do this in part by funding large two-day exercise study which a) settles the deconditioning issue once and for all and a) highlights the perhaps unique depletion of energy during exercise in ME/CFS. Getting this information out is a potential game-changer because it strikes at the core misconceptions regarding ME/CFS and it dramatically presents ME/CFS as a unique, energy-depleting disorder Firmly establish that neuroinflammation is present Explore the neuro-immune-energy interface Further explore the effects of exercise more using one-day, and invasive CPET tests Fund burden of illness studies. If possible include fibromyalgia, migraine, IBS, POTS and other "invisible" diseases which mainly effect women, produce large amounts of fatigue and pain, and are prevalent - and get very little funding from the NIH - as a way to highlight an entire realm of common diseases that the NIH is essentially ignoring.
Varifying previous research
1. The need for a bio-marker to indicate ME/CFS. 2. Finding the mechanism that causes ME/CFS symptoms. 3. Finding a cure or treatment regimen.
Fund research which destroys the lingering misconceptions around ME/CFS that stop researcher interest in this field such as the idea that ME/CFS is caused by deconditioning or malingering and promote research which highlights the effect exercise has on the ability of people with ME/CFS to produce energy. Do this in part by funding large two-day exercise study which a) settles the deconditioning issue once and for all and a) highlights the perhaps unique depletion of energy during exercise in ME/CFS. Getting this information out is a potential game-changer because it strikes at the core misconceptions regarding ME/CFS and it dramatically presents ME/CFS as a unique, energy-depleting disorder Firmly establish that neuroinflammation is present Explore the neuro-immune-energy interface Further explore the effects of exercise more using one-day, and invasive CPET tests Fund burden of illness studies. If possible include fibromyalgia, migraine, IBS, POTS and other “invisible”diseases which mainly effect women, produce large amounts of fatigue and pain, and are

prevalent - and get very little funding from the NIH - as a way to highlight an entire realm of common diseases that the NIH is essentially ignoring.
Defining bio markers for the disease as a whole and for subsets within it. These should be tests that are readily available across the country and would not require insurance company “rule out first” mandates.
Bio marker test to identify disease early on and prevent worsening of symptoms also preventing the horrible feeling of knowing something is wrong when your bloodwork and doctors disagree. We need studies to fully understand the connections among brain inflammation, circulatory issues (red blood cell deformation and reduced blood volume) and mitochondrion issues so that treatment can be developed.
To not allow people to keep on suffering because of the stigma and doubt surrounding the validity of this and other similar illnesses. To treat women as equals and not as hysterical, “abused”or psychologically damaged individuals because of their gender. Not continue to allow years and decades to pass while millions of individuals (men and women) suffering excruciating and devastating pain, debilitation and disability because people cannot understand or comprehend how or why these types of disorders and diseases are caused and automatically assuming that the complaints of said sufferers are not valid. Disallow needless suffering due to will not be treated or are unable to be diagnosed due to stigma, ignorance, intolerance of things unknown and refusal to investigate because some people are not affected therefore they do not believe these conditions are real or valid. Stop further stigmatization of sick individuals as drug use and abuse will not cease to exist in this world or in our lifetime and that has absolutely nothing to do with these diagnosis and further research and development to help people cope with these debilitating and life altering conditions, diseases and disorders - through no fault of our own. Stop treating us like drug addicts. We simply want relief we simply want to end our extreme and unnecessary suffering. It is nearly impossible to “live”in these conditions.
Finding effective treatments, including serious research on novel treatments that have been reported to be helpful. It seems like much of the research is focused on finding the cause of ME/CFS, and this is certainly worthwhile; however, all of us suffering with this disease need help now! It honestly doesn't matter to me if or when you find out what's causing it or not, but rather that we find an effective way to treat it and alleviate some of the more bothersome symptoms.
Finding even 1 common denominator in all cases & drug therapy that might derive from that, eg. If a patient’s energy level can be improved by 50% or better
Finding a cure. Which probably is based on finding the cause.
We need a panel of biomarkers.
Allowance for doctors to use off-label prescribing if patients are willing and eager to experiment with different treatments and reporting those results. For example Ketamine or psilocybin for treatment resistant depression in FM.

I'm hoping for more research on glial cell activation and neuroinflammation.
Understanding the cause of PEM.
Clearinghouse for sharing research and study findings
I have had ME/CFS for 28 years. I see that a lot of the researchers are trying to look at subsets. My worry in looking at subsets is that things get chaotic, and then the illness is not really seen as one illness. I have a suggestion...yes..look at subsets...but also look at how these are all related to find a core issue. If you look at core issues, this may then lead to finding how everything is connected. What would most likely cause the core issues? For example, I saw Dr. **[…]** for ten years..and he connected a lot of the issues to inability to use oxygen, and the idea that the illness is an adaption to something. I feel if more core issues were identified, it would be easier to focus the little money we have on the illness rather than getting off on too many side issues. Lets look at the main part of the elephant, not its toenails or its trunk.
The most compelling ME/CFS research is comprehensive examination of ME/CFS from neurologic perspective, including brain, spine and nerve biopsies. What little is known of ME/CFS seems to indicate a neurologic pathology. Two of the key symptoms, fatigue and brain fog, would seem to have a strongly neurologic origin. This is particularly true in the absence of metabolic failure or immune mechanisms that typically explain fatigue in those conditions. Less common but still frequently seen symptoms, such as sensory sensitivities, would seem to further this hypothesis. Researching a disease that has evaded understanding requires looking in areas less frequently or easily looked at. ME/CFS is not a disease of the foot. But it may be a disease of the nerves, spine and brain. Biopsies of these tissue and metobolomics of the CFS would seem important to this patient. To my knowledge no study has been conducted on morphology of ME/CFS patients. E.g. recessed jaws, long arms, small heads etc.. Distinguishing physical features. Although this may not provide immediate results, it may inform future inquiries.
We need to know exactly what M.E is so that doctor's can have a better way of diagnosing it. This needs to be done quicker and with more certainty
To look at the immune response to activity, why at the end of a day my glands are swollen
A drive for a gathering to get to a treatment/cure. It needs doctors actually getting together to recognize just how much ME/CFS patients suffer and how horribly their quality of life is that having nothing to turn to or having such limited doctors who even understand their disease is tormenting.
To be centred around ME and Post Activity Increase in New or Severity of Symptoms (PAINSS) aka PEM. All those with ME will have a cycle that can be monitored. A delayed response to any activity to 48 hours can show how severe a patient is. Watching how long symptoms take to come out and which

ones are normal and those that are new can show the progression of ME. Looking for the shortest time from convalescence of PAINSS/PEM state shows you a upward turn of ability/recovery Things like spontaneous wake up time and how long they can go with sitting in an upright position also shows how deep they have fallen into a PAINSS/PEM state.
1) Further explore the effects of exercise more using one-day, and invasive CPET tests 2) Firmly establish that neuroinflammation is present 3) Explore Auto-immunity and ME/CFS 4) Further explore mitochondrial defects
I don't know about how any of the specifics should work. All I know is that I've had this disease for 16 years, and I've tried countless therapies and treatments, none of which have worked. I'm steadily getting worse and worse, and the only thing that keeps me hanging on is the hope that some scientific breakthrough will come, hopefully before I'm completely confined to my bed in a dark room. There are *millions* of people suffering with this, and we need help.
biomarker. symptom relief.
Figuring out PEM. It's the most debilitating and unique aspect of this disease. Figuring out how to unstick a stuck stress response. Lots of research and my own experience indicate that this is the problem.
Construct a test to authenticate the pathology.
debilitating brain fog / inflammation / pressure and / or identify a biomarker - to advance the research and quiet the negative ME illness image
Determining the underlying cause(s) of the onset of the disease, and the factors that perpetuate it
Finding the facts about what ME is, what causes it.
We need a better understanding of both the underlying causes of ME/CFS and its impact on patients' lives. We need a better view of how commonly comorbid conditions are actually related to ME/CFS (contributing to its onset? symptomatic of the condition? part of a similar or related pathology? spuriously correlated?).
Connectivity between various research groups and better dissemination of finding to physicians. I am a patient who was lucky enough to find a doctor who could provide a diagnosis after only four year! I find that I am often forwarding information to him on the latest research findings. He is an internal medicine guy who has had a few ME/CFS over the years. And LUCKY ME - he tells me I'm the most severe case he has ever seen. If there was a single pipeline he could access that would keep him up to speed on the latest findings, I think it would improve his already good understanding of the disease and what may be coming up through the latest research
Establish bio-markers for the disease Establish guidelines for determining neuroinflammation

Establish relationship and prevalence rates of comorbidities such as Ehlers Danlos Syndromes, Mast Cell Activation Syndrome, and Cranio-Cervical Instability
How to live with the pain of fibromyalgia How to get disability approval since this is not really recognized as a legit disease yet by mainstream Herbs that work to improve immune function and inflammation, as I have had much better success with herbs than with drugs Med. profs STILL have a long way to go in offering compassionate and empathetic care to ones who suffer from CFS. It's a disease that destroys your life but doesn't have the decency to kill you.
What differences there are in patients vs healthy? Cause of this?
fund research that continues to prove that ME/CFS is not a result of deconditioning or a mental illness fund research into the cell danger response (& the mitochondria, hypometabolism, etc) & its effects on the body as a whole fund research into ways to improve the sleep in ME/CFS patients (the lack of refreshing sleep, the frequently disrupted circadian rhythm) fund research that further explores the immune issues common to ME/CFS patients fund research into orthostatic intolerance that commonly occurs in this illness (& is not always associated with POTS or NMH) fund research into the mast cell issues and chemical sensitivities common to ME/CFS patients fund research into the cognitive difficulties common to ME/CFS and ways to show those other than standard neuropsych testing that has already been shown to fail to truly demonstrate real-world ways in which this affects patients fund research into the thyroid/adrenals/hormones/endocrine system and into the autonomic nervous system dysfunctions that occur with this illness fund research into the many ways that all of the above interact with one another (& with other aspects of the body & brain) - research so far has mostly been in very specific & separate areas of the body& brain, & this illness affects the entire body & brain & each aspect of these also affects other aspects....truly understanding ME/CFS will require studying multi-systemic causes, affects, & interactions fund research to improve all of the above fund research into the connections between mold exposures and ME/CFS

A diagnostic tool which uses biological markers. This would help remove the biopsychosocial approach - it seems it is exists solely due to the void of actual diagnostic measures. When there are indisputable markers of biological disfunction, research funds can be directed away from useless studies that look at aspects such as deconditioning and treatments aimed at using physical and psychological means of improving patients health.
I believe that a person's home must be healing sanctuary free of environmental stressors, with ADA protections that encompass protection from wireless devices and infrastructure. I am, unable to sleep due to data dumps from wireless water and electricity meters and I am unable to heal in my own home. It should be very easy to prove that the frequencies are affecting my heart rate and brain function making my unable to sleep in my own home. Sending a patient to a sleep center for a study is not useful.
Difference in ability to function meaningfully in an environment that is challenging, versus an environment free of toxins, microwaves, or whatever is triggering the illness.
All of the research that I have seen suggests that the illness contains subsets. It is very difficult to elucidate etiology, biomarkers and treatment options when the subsets have not been clearly defined based on known parameters - symptomology, blood pressure, HRV, exercise testing, metabolomics, etc. I believe the most pressing ME/CFS challenge is to define potential subsets. For example, in most respects I appear to suffer from typical ME/CFS - PEM, brain fog, lactic acid build up and body aches, poor immunity, gastro-intestinal issues, etc but I do not experience the low blood pressure that is so common with this illness. Instead my blood pressure often shoots high prior to a crash. This appears to make me an anomaly even though I have been diagnosed with ME/CFS by two doctors. I have a good friend with ME/CFS and despite many similarities (particularly low resistance to viruses and relapse following infection), there are notable differences between us. She experiences nerve issues, trigeminal neuralgia, low blood pressure and appears more narcoleptic when she crashes and visibly fades out. I do not experience nerve issues, never lose consciousness and the ability to talk, but can become almost catatonic and experience strong resistance to movement. We have the same diagnosis. It is hard to make meaningful conclusions from science if a heterogeneous group of patients is being studied.
Test all of the adult patients for the genetic abnormalities currently screened for at birth. Some patients may be dealing with late-onset versions of known but rare genetic conditions.
There is an urgent need to find bio markers that can be used to differentiate ME from other similar illnesses. Those markers could then be used as diagnostic tests, which is another urgent need. The tests would have to be easily administered and inexpensive. Once there is a clear way to diagnose patients based on scientific data and not just symptoms, ME will be taken more seriously in the scientific and medical community.
Vaccination causing me/cfs. How to help people with ME/CFS. We are suffering terribly.

Research dollars.
1)biomarker research 2) treatments even if minimal and niche 3) multiple studies to determine both 4) winning over the scientific community that cfs is not a psychosomatic illness
FMT (fecal microbiota transplant) clinical trial with HIGH QUALITY donors. "High quality" cannot be stressed enough. I'm a patient who's been following the microbiome literature daily for 4+ years while cataloging it into this wiki: https://old.reddit.com/r/HumanMicrobiome/wiki/intro - there's a CFS section there, and more supporting evidence for the gut microbiome in CFS in other parts of the wiki, and stuff that's not in the wiki, such as: Mitochondria Play an Unexpected Role in Killing Bacteria. The energy-producing organelles also send out parcels with antimicrobial compounds to help destroy pathogen invaders in macrophages. (2018): https://www.the-scientist.com/the-literature/mitochondria-play-an-unexpected-role-in-killing-bacteria-65246 - since the mitochondria is the main site of energy production, it's plausible that chronic infection could reduce its energy production since it's spending its resources fighting infections. This link contains a lot of info, including many links to more info, nearly all of which is relevant and important: https://archive.fo/8s91R I've done DIY FMTs from 9 different donors, and based on my own experiences, the experiences of other people doing DIY FMT, and from the literature, I'm absolutely convinced that FMT is a CURRENTLY AVAILABLE TREATMENT/CURE. The primary roadblock/caveat is donor quality. It's looking like fewer than 0.4% of the population qualifies to be a high quality donor. There is various info/links in the previous link elaborating on this, but here's an additional one to help explain why this is the case: https://archive.fo/QRxuU I've written to hundreds of researchers, passing on information, trying to get them to raise their FMT donor quality, and trying to get someone to run an FMT clinical trial with high quality donors, but haven't had much luck so far. The knowledgeable ones don't seem able to run an FMT clinical trial, and the ones able to run clinical trials don't seem knowledgeable/willing. I believe I have the knowledge and insight to serve as a consultant/advisor/director for an FMT clinical trial for CFS. I believe we could provide a cure as soon as we're able to procure a high quality FMT donor.
Viral load testing Mould testing

Developing a reliable test to quickly (and safely) identify ME/CFS patients and to identify any sub-groups that may respond differently to treatments. Without a reliable test patients, doctors and the media in general have doubt on the validity of any diagnosis.
Biomarkers -- If there were biomarkers all doctors could diagnose and begin treatment for all patients. Then it seems like there is research in so many areas, it's great.
Although all patients ultimately wish for treatments / cures for ME/CFS, I feel that the immediate and urgent priority is to establish a valid (high specificity and sensitivity) diagnostic test(s) which would: i) Validate the illness, particularly if the test is closely related to the pathogenesis of ME/CFS e.g. a mitochondrial assay; neuroimaging (showing neuroinflammation); an immune system-related test. Validation of ME/CFS as a biomedical illness would not only improve the lives of patients (by reducing the need to continually having to justify being ill...which I can ensure you is exhausting in itself!) but should attract more researchers and clinicians to the field. ii) Allow for better definition of patient cohorts for research studies. The current situation of using subjective clinical criteria means that (and especially in studies using only Fukuda or Oxford Dx criteria) there is such a large diagnostic error rate that the results of such studies are, in my view, essentially worthless. I am aware that Prof Ron Davis (Stanford) is currently conducting a 'bake-off' between an number of potential candidates for a Dx test and I feel that significant funds should be given to his pursuit of such, so that tests can be quickly and accurately assessed for sensitivity and specificity. It would also be useful if other groups / research centres (e.g. Dr Jarred Younger, etc) were given funds to pursue this goal also as a matter of urgency.
A biomarker or test to confirm illness and medications to control symptoms - especially pain and inflammation.
1. Ways to diagnose CFS/ME. 2. Ways to validate CFS/ME sufferers. 3. Ways to support them physically, financially, socially. 4. Education to doctors and public about this very challenging illnes
Funding! What causes it. How to treat it. How to best educate physicians to diagnose the disease and its severity, and to treat it effectively.
Diagnostic tests to distinguish CFS and it's different subsets. Medications aimed at reducing fatigue, PEM, and cognitive fog.
1. Studies to establish that problems with exercise are NOT due to malingering or deconditioning. 2. More research into neuroinflammation and how vagus nerve may be involved. 3. Serious drug trials for existing drugs that might work for ME, as Jarred Younger is doing. 4. More work to get Ampligen FDA approval.

5. More research into how energy production is so impaired in ME.
6. A LOT MORE MONEY FOR RESEARCH, PERIOD!

Sustainable funding to keep the progress moving

The following suggestion addresses several of the survey questions.

Establish a well-funded Center of Excellence for "expanded replication" research.

We have a back catalogue full of under-powered studies using loose diagnostic criteria with interesting findings. However, many have not been replicated, leaving a field strewn with potentially promising leads of unknown significance.

The sooner we replicate - or fail to replicate - those findings the sooner we can target the most promising lines of inquiry.

Replication studies, however, should not replicate the original studies' shortcomings. Instead they should use large and well-defined cohorts as well as updated technology if available ("expanded replication").

The Center could be partially a "virtual campus" to increase collaboration across a wide geographical area and benefit from the use of existing technology and expertise located in various research centers. Ideally it should have international reach.

The Center would allow young researchers to cut their teeth learning good methodology on "expanded replication" studies in an attractive, secure job environment. They would be exposed to a wide range of ME research from the beginning, encouraging cross-disciplinary thinking, and they would be able to establish contacts with the leading researchers in the field creating opportunities to later join one of those teams.

How it works and how to treat it

Primary: Develop clear diagnostic criteria, tools, tests or methodologies that enable a firm diagnosis.

Secondary: Develop a clear set of strategies for how various individuals with the disease can proactively address or avoid Post-Exertional Malaise early on, and thereby mitigate the worst symptoms of ME/CFS with the goal of not inadvertently worsening them.

People with autoimmune disease or chemically sensitivities are the canaries in the coal mine. We are also adversely affected by EMF & EMR generated by current wireless technology. ME/CFS are common diagnoses that are used to explain away our illness.

Regardless of what acronyms you use, ubiquitous poisons in our water, air, food and medicine is killing us.

MCAS - Mast cell activation syndrome

MCAD - Mast cell activation disease

CIRS - Chronic inflammatory response syndrome (24% predisposed or highly susceptible to toxins) ASIA - Autoimmune/inflammatory syndrome induced by adjuvants TILT - Toxicant Induced Loss of Tolerance (20%) MCS - Multiple Chemical Sensitivities (15%)
- a diagnostic tool; will help researchers, medical community, patients alike. - a variety of researchers with different backgrounds; ME is complex and will require multi-disciplinary researcher interaction - good burden of illness studies - creative, passionate researchers intrigued by ME/CFS
Both basic science and clinical trials of treatment applications that are already anecdotally known to help some subsets - simultaneously, please. We've been waiting far too long. Research on the cardiac complications is critical, and seems to be under-represented so far.
Figure it out
Should include genetic sequencing, epigenetic sequencing, and deep learning aspects to create as accurate a picture of the disease population as possible and the potential to allow this model to inform what course of care would be best for the individual patient. Every MECFS research study should have these relatively cheap aspects to them.
There is some indication that a correct body voltage, rather than a body emitting static electricity for example, is a factor in health. There needs to be decent research to investigate whether this is true and how it can be accomplished if so. Such solutions need to be cheap rather than patented products for Big Pharma. Also helpful: including multiple electromagnetic parameters in research; expanding on research identifying the effects of a combination of (non-ionizing) electromagnetic and chemical in causing harm, as in recent Ramazzini research, and how much removal of such exposures assists.
CFS is associated with lot's of sensitivities, drugs, chemicals, food, mold. Some people think we have a leaky gut which apparently isn't a thing unless you have celiac or some such disease. So you might want to investigate this. We feel like we have flue and are being poisoned so you might want to try to figure out ways to quantify this. Some people think we have encephalitis. So you might want to look for signs of nervous system inflammation. It seems stupid to try drugs like retixusibab unless you have some type of idea of what it is you are treating. I realize there was a lot of hype and enthusiasm about it's possibly being able to eliminate CFS symptoms but that turned out not to be the case. My personal opinion after 22 years of this living death is mold is probably the single most gigantic clue you have to look at. Try to quantitate the phenomenon and then try to figure out what drives the condition instead of looking for ways to deny it.
Any research into this area will be incomplete if it does not investigate in depth effects of non-ionizing radiofrequency radiation (RFR) and adverse power quality or dirty electricity (DE). Both RFR air pollution and DE can cause and or exacerbate auto-immune and other health issues and due to the extraordinary increase in and near-ubiquitous nature of wireless proliferation, we consider low level RFR emission pollution the most significant toxics threat of our time.

I think the most important thing is to seek cooperation within this field, to in this way combine all the data and get clearer pictures. I also think that a diagnostic tool is one of the most important things right now, because without it, it's still very hard to do research and pick the right patient groups. Apart from this, it will also be a great step forward regarding stigmatization.
Severe ME Neuroimaging Validation the CPET exercise abnormalities All the areas current research is showing issues with. It's systemoc therefore needs many areas explored simultaneously
Role of environmental variables, especially wireless radiation, should be the number one research priority. This directly harms mitochondria. Diet should be second. This includes chemicals in the food. The Wahls protocol had eliminated my fatigue and I was skiing and iceskating (even picking up 10 year olds off the ice) Previously I was struggling to haul myself up and down steps. Wahls and reducing my exposure to wireless made a huge difference in my physical abilities and eliminated my fatigue completely. Then, against my doctors medical advice, the utilities forced a smart meter on us, causing an immediate relapse. I am doing better after $20,000 in shielding, tightening the Wahls protocol to the strictest level and am back on a ton of supplements. There is an urgent health need, for myself and many others to apply the precautionary principal, update FFC guidelines to reflect the biological effects of wireless radiation (radio frequency radiation, microwave radiation) and apply protective measures such as accommodations for those with electromagnetic sensitivity (contributes to CFS) such as creating "white spaces" People with this condition are increasingly denied the ability to live in their own homes due to smart meter radiation and now 5G will add to that. It is very difficult, sometimes impossible for people with these conditions to find housing, and this needs to be urgently addressed. We have several people in our state right now, with mandatory smart meters, who are moving out of state. (I will send in documentation from an advocacy group I represent as well)
Identify a diagnostic marker/markers that can easily be tested for by primary care physician. Find out what's in the serum of ME/CFS patients that, when the serum is added to healthy cells, those cells become unhealthy. Provide the funds for follow-up studies on promising research on exercise intolerance, general inflammation/neuroinflammation, gut microbiome abnormalities, etc. Fund repurposed drug trials.
Focusing on developing a diagnostic test and finding the root cause of the disease.
Finding a biomarker, finding subgroups, finding treatments and a cure.
Epidemiology studies are needed to determine if autoimmune illness onset coincided with wireless microwave radiofrequency radiation emitting devices, and symptom severity should be tracked when the EMF (electromagnetic fields) of the environment are mitigated and reduced.

Research is needed on the recovery rate when exposed to a high EMF environment as opposed to low EMF environment.

Research is needed on the recovery rate when exposed to a high dirty electricity environment as opposed to a low dirty electricity environment.

Research is needed on the recover rate when exposed to a high EMF and high dirty electricity environment as opposed to a low EMF and low dirty electricity environment.

Does exposure to high EMFs and/or high amounts of dirty electricity reduce a patients ability to recover?

Request for Information ME CFS by **[…]**

The most compelling research needs are adequately funded clinical care and biomedical research into the causes of ME. The recent NIH Conference (April 2019) provided promising directions for both biomedical research and clinical care. The role of metabolomics, neuroinflammation, and immunological dysfunction needs further exploration coupled with clinical efforts to improve the health of individuals with ME. The NIH conference proceedings provided preliminary findings that will stimulate further research and care. The high rate of dysautonomia in ME patients calls for clinical interventions to keep the disease from progressing further. For the field to move forward, funding needs to be made available as it was for the HIV pandemic through Ryan White Funding. ME has been underfunded and under researched for too long, resulting in people becoming sicker and more costly to care for.

There is a pressing need for ME Centers of Excellence to provide clinical research and leadership. A collaborative model that is funds Centers to lend treatment expertise to primary care providers (PCPs) from diverse professions is critically needed. At this time, the majority of patients are not diagnosed because most PCPs providers do not have the necessary training to diagnose and treat this complicated condition. It is important to note that African American and Latino patients are significantly under-represented in the current data.

The absolutely essential first thing to advance research at the NIH and elsewhere is to stop mixing the distinct disease myalgic encephalomyelitis, ME, with various fatigue-based conditions that are not ME under the obfuscatory term "ME/CFS." Use of the hybrid name "ME/CFS" makes explicit the main impediment to productive research in the field-combining the differentiable neurological disease ME with ill-defined fatigue-based conditions as a single heterogeneous group.

Using the existing ICC to select research subjects with ME by far would have the greatest impact on the productivity, reproducibility, and usefulness of research for people with ME. The logical way to research a disease is to use subjects who unequivocally have the disease being studied. This common-sense approach has worked with other diseases, but is yet to be tried significantly with ME.

Combining subjects with ME and subjects without ME into a single group of research subjects adds an unnecessary confounding factor to " ME/CFS" research. Only the ME-ICC were developed by international experts with extensive clinical experience diagnosing the disease in over 50,000 patients. There can be no substitute for the firsthand knowledge of skilled clinicians in defining a disease.
Thirty years of research on mixed groups of subjects labelled CFS or ME/CFS based on varying

combinations of self-reported symptoms has been largely fruitless. ME is an actual disease identified from epidemic outbreaks that can be differentiated from other diseases and disorders presenting with similar symptoms by using the ICC and IC Primer. It is inexplicable why any research group would continue to use the same failed approach studying constantly varying mixed groups of ill-defined subjects reporting chronic fatigue rather than researching an actual identifiable disease permanently disabling thousands. The results of specific ME-ICC research could be reproduced and built upon leading to progress in recognizing, diagnosing, and treating ME for the first time.
Please read ME Action's well-constructed ideas. The most compelling research need in ME/CFS is to deliver tangible outcomes for patients -- diagnostics and treatments -- as quickly as possible. Doing so will require greater political leadership and commitment from NIH, NIH funding commensurate with disease-burden, and a comprehensive creative program of parallel initiatives to deliver those outcomes while simultaneously unraveling the essence of this disease and resolving the barriers and challenges. We need to have the following: a strategic response plan; a rapid expansion of pool of ME/CFS Expert Clinicians; a Case Definition with instrumentation and diagnostic biomarkers, a data repository and biobank. Sufficient funding poured into research by the NIH, and an increase in educating doctors and medical students about the disease.
The most important piece of research needed for these conditions is in relation to EMF's (electromagnetic fields) and how they contribute to the pathology. How many people suffered from ME/CFS before electrification? How does the oxidative stress from EMF's contribute to symptoms, and is there recovery when the EMF's are mitigated?
Adapt and use ICC definition.
Money for more research - worldwide. More exception among the Doctors
Adopt the Myalgic Encephalomyelitis International Consensus Criteria (ME-ICC 2011) for all research. This is the best definition of ME created by 50 ME experts. Everything in research stems from using a well defined patient population, which is not the case now. Fund ME research at a value commensurate with its impact - that would be $250 million per year.
- A variety of research topics, many of which are underway, including brain chemistry, mitochondria, vagus and other nerve signal transmission, and impacts of diet and nutrient absorption. - I would love to see more done on viral causes and viral loads (especially Epstein Barr) and how best to combat them.

It needs to end. ME and CFS are not related in any way. Consider genuine research needs: ME research needs are treatment and prevention. A lot is already known about both. CFS needs are how to stop attaching this label to patients and properly examine all patients instead.
Biomarker, pathomechanism, treatments; diagnostic criteria; cohorts of proper numbers; iCPET, 2-day-CPET, exercise intolerance, PEM; dysautonomia (e.g. POTS); role of vagus nerve; neuroimmaging; metabolism; signaling pathways (e.g. calcium signaling); genome research; connective tissue diseases and its consequences; role of mast cells; invest in the development of new technologies. Very important: keep to scientific standards.
1. Prevent suicides 2. Educate all medical disciplines enough to overcome the "I'll send you to a psychiatrist" continuing response to pts with probable CFS/ME 3.Co-ordinate & share world-wide quality research among all researchers, pts, and publications of all types. 4.Prevent suicides 5. Prevent suicides
A distinctive biomarker that would enable easy diagnosis.
Literally just one effective treatment option. A cure seems unrealistic, but it is unfathomable that an illness as severe and debilitating that causes patients to endure actual indefinite torture is not prioritized when it comes to developing any remotely effective drug or treatment. The definition of effective is NOT "may help reduce pain in 30% of patients." That is not effective, that is false hope and a waste of time. A real treatment option would be effective in up to 85% of ME/CFS patients and address all or most of the symptoms rather than just the physical pain aspect, which, quite frankly, is not even the worst symptom. What is most desperately needed is a treatment or different treatments that increases ATP synthesis, decreases overall inflammation especially in the cranial region, and addresses the unbelievably massive cognitive dysfunction ME/CFS patients suffer from. The cognitive dysfunction is to many, the most challenging aspect because we are mostly housebound and therefore would rely on our cognition for any source or enrichment such as reading or watching a movie, and the cognitive dysfunction often prevents us from being able to do anything sedentary or even maintain conversations with others. It is often overlooked as a symptom while all emphasis is placed on fatigue and pain, but I feel strongly that the majority of the patient community would prefer to focus on the fatigue and the cognitive dysfunction instead of the pain aspect which is over-promoted a lot in relation to how severe the fatigue and cognitive dysfunction are. It doesn't matter if it takes 80 injections or one pill, but effective treatment is the single most necessary and prioritized need within our community. Many have been waiting decades, others for years, and it is beyond time for any bit of appropriate and effective respite from this torture. We know that research regarding biomarkers and etiology are certainly necessary to get there, but those studies ultimately do not meet our immediate need of yielding or quickly developing any type of treatment(s), making it is difficult to emotionally invest a lot into those studies which, honestly, should have already been conducted years ago.
Diagnostic marker, viable treatments.

Ideally, a means to regain normal energy levels, but at least treatment options that provide an increase in energy enough to at least manage other symptoms.
An understanding that this illness is very complex and may have many causes working together
ME/CFS badly needs a diagnostic test. In the absence of supportive diagnostic tests, physicians are insecure in making the diagnosis. Some treat it as a psychogenic illness, and are reluctant to sign disability paperwork Because ME/CFS falls under no medical specialty, primary care physicians are expected to diagnose and treat patients. Some patents have reported being unable to find a primary care physician because of refusal to treat patients with the diagnosis. I have been turned away once, myself. Primary care physicians are constrained to the 15 minute appointment and are unsuited to deal with patients who have complex needs. ME/CFS also needs more up to date longitudinal data. I have been sick for 23 years, and I have no idea what this illness is doing to my body, or my prognosis.
Development of a diagnostic test; possibly based on the measurement of mitochondrial energy production, or morphology (shape of mitochondria), or other (e.g. measurement of phenylalanine by RAMAN spectroscopy) and the effect of filtering out exosomes from the plasma - cells returning to normal. Development of treatments e.g. drugs which appear to work (test tube experiments - data presented by Ron Davis at NIH Conference)
Patient identification and diagnosis Physician and health care provider education Epidemiologists
1. Hereditary disposition, locating gene discrepancies based on viral mutation, and gene therapy cure 2. locate and validate 1990-99 or early 2000's research study finding 7 Substs of CFIDS/CFS. Each subset had a compilation of symptoms based on severity. Proving up the relationship between CFS, ME, Fibromyalgia, MS, Lupus, MD, and one other I can't remember. 3. Approval of Armour and NP Thyroid which unlike levothyroxine and Synthroid have more than one thyroid in them. They've been proven to work on patients with CFS, ME, Fibromyalgia whereas levothyroxine and Synthroid do not
Addressing both the cognitive dysfunction as well as the chronic fatigue that those with this illness experience.
Research on symptom reduction or relief

1.Strategic Research Plan
2. Rapid Expansion of Pool of ME/CFS Expert Clinicians
3. Case Definition, Instrumentation and Research Tools
4. Intrinsic Complexity and Heterogeneity of the Disease
5. Targeted Clinical Intervention Initiatives
6. Insufficient knowledge about the disease
7. Insufficient NIH funding)
8. NIH Administrative Structure
9. Bold Leadership
10. Stakeholder Engagement and Transparency
11. Development of disease-specific instrumentation, subjective and objective characterization methods
12. Blood omics: cytokines, metabolomics, transcriptomic/methylation/proteomic/exosome profiles, cellular integrity & function (e.g. NK cytotoxicity, RBC deformability, B cell maturity, etc.)
13. Measures of functional impairment: CPET alternatives, NASA lean, activity meters, survey instrumentation, etc.
14. Identification of objective sensitive and specific biomarker(s)
15. Diagnostic instrument development & validation (for clinical & research use)
16. Disease-modifying treatment, symptomatic treatment, and exploratory intervention clinical trials
17. Cross-sectional studies to understand subgroups, breadth of symptoms, spectrum of severity
18. Cross-sectional studies to define spectrum & prevalence of onset types, triggers
19. Prospective longitudinal studies following triggering events (infectious and non-infectious)
20. Retro- & 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
21. Prospective study of impact hormonal change (e.g. pregnancy, menopause, HRT) on disease status
22. HHS ME/CFS TASK FORCE

In order to bring in more researchers and gain the attention of doctors/hospitals, we need the full commitment of the NIH toward finding a cure for ME/cfs by investing $200 million a year in research funding through RFA's. This is similar to what is spent on Parkinson's and MS. When the NIH sends this signal to the research/medical community such as they have done with AIDS, the medical community will surely respond. Recently, my friend asked her niece who graduated with a PHD in medical research what area she would focus on, the niece responded: Alzheimer's! My friend asked why, the niece responded... well that is where the funding is!!!

Note: I apologize in advance for the lack of coherence and detail in these suggestions; I am having significant cognitive problems and this is the best I can do.

1) The current number one priority has to be biomarkers and diagnostic tests. I think that'll help unjam a lot of other problems (such as researcher interest and public and medical misperceptions of this disease).
2) Is the perpetuating factor in this disease infectious/environmental or not? (I.e., is this entirely the body's response to a trigger that is now gone, or is it still actively reacting to a pathogen or to

continuing chemical/mold/allergen exposure?) It obviously has very profound treatment implications if the body is simply stuck in a response to a problem that is now resolved vs. actively attempting to manage a response to an ongoing insult.
3) Is this disease transmissible by blood? I think there's enough evidence now (I'm aware of five studies by four different labs) that indicate that something in our blood is actively affecting our cells (and, in some studies, healthy cells exposed to our blood). In any event, it seems that someone should look seriously at preventing ME/CFS patients from donating blood until it's known for sure one way or the other.
3b) For that matter, organ and tissue donations are probably not wise until the question is cleared up, either.
3c) And, of course, studying our blood to figure out what, exactly, is wrong with it (and is that a cause of ME/CFS or a result of it?) is an obvious and very important research priority.
4) What subgroups are there, and how should they be sorted (for example, by symptoms, by probable trigger, by current test results such as cytokine or hormone profiles, etc.)?
4b) Is gradual onset a different subgroup from acute onset?
4c) I've read accounts from several patients who say they had minor symptoms years ahead of actually developing ME/CFS. This leads me to wonder if there is a substantial 'incubation' (or equivalent) period where major symptoms are not present but the disease itself is silently or mostly-silently progressing. So, is there an incubation or silent period in the development of this disease?
4d) While not strictly a subgroup matter, it would be very helpful to figure out if and how this disease changes long-term (over years and decades). Do those changes lead to their own subgroups?
4e) Are adults who had pediatric onset different from adults who had adult onset? (Also, is the long-term effect of teen onset different from young childhood onset? Does this affect development in subtle ways?)
5) Instead of studying the effect of diet on the microbiome, flip it: what is the effect of the microbiome on a person's diet? (For example, does it make certain foods easier to digest, or cause intolerance of certain foods, or affect whether some nutrients are easier to absorb in certain forms or from certain foods or foods prepared a certain way, etc.)
5b) Related to this, instead of the effect of diet on this disease, what is the effect of this disease on patient diets? I've noticed that my health drives my diet, *not* the other way around- when I'm sicker, I eat less 'healthy' foods, because when I'm sicker things like vegetables seem a lot harder for my system to cope with (they give me nausea, stomach pain, loss of appetite, etc.) But when I'm doing better, I crave a much healthier diet and eat large amounts of vegetables with no problem.
5c) Given this, and given how many patients have severe gastrointestinal issues, is it even safe for us to ignore what our bodies are telling us about what to eat at a given illness level and try to force ourselves to eat a 'healthy' diet? Is it likely to cause people to end up being tube fed if our bodies just can't cope with a healthier but harder to digest diet? Is it possible diet itself could be an ongoing insult to our systems if it isn't tailored to what each person's body specifically can and cannot handle?
5d) Considering the above, are treatments that attempt to alter the microbiome safe? Instead of the microbiome affecting or perpetuating this disease, what if it's the other way around- this disease affects our microbiome, and the changes are the microbiome's (and the body's) way of attempting to cope?
5e) Could cravings be an indication of what is happening in this disease? Assuming cravings are the body's way of requesting things it desperately needs, finding out if patients tend to have specific cravings might be helpful. For example, my most constant cravings are salt, protein, garlic, hot peppers, and (when I'm more ill) fats or (when I'm doing better) carbs. These are so specific and unusual I can't help but think they're probably pointing to something underlying, and it could be useful to know if other patients have similar experiences.

5f) In a similar vein, a rheumatologist did extensive testing and advised me to start supplementing with folic acid. I then started taking a supplement (NeuroSur, by GardaVita) that has (among other things) a more easily absorbable form of folic acid. It has helped tremendously with the quality of my sleep (which, over the years, is slowly helping my other symptoms as well). Should ME/CFS patients be routinely screened for different nutritional requirements this disease might impose (and any nutritional deficiencies as well, of course) and counseled on getting more easily-absorbed forms of various nutrients?
There are three equally compelling ME research needs: 1) Finding an inexpensive biotechnical diagnostical tool that can diagnose ME with 100% certainty. Ideally via a blood sample. 2) Developing a healing cure. 3) Figuring out whether ME can be prevented, and if so - how.
Cause and treatment
- Identify a biomarker. - Identify the underlying physiological cause(s) of ME/CFS symptoms. - Identify treatments for ME/CFS.
Research using the ICC Criteria. No more research with Fukuda subjects. They do not have ME.
Significant education of physicians about the symptoms, needs and challenges of those with CFS, Until they know and believe that it is "real" there will be minimal progress.
1) Meaningful patient inclusion in study design processes, as well as patient guiding of research priorities. Nothing about us, without us. 2) Biomarkers. Finding and validating biomarkers, and making them clinically useful. Whether one, or a set that could be used with signs and symptoms. Making a diagnosis and being able to track clinical status through assessing physiological conditions are extremely important. This cannot be emphasized enough. This would help with getting more patients diagnosed, which would in turn help with getting more clinicians and researchers interested. It would also improve the stigma and discrimination issue with the diagnostic label. There are a number which have been historically proposed and some have come up repeatedly (for example, NK cell function, which is not specific but could be used in combination with other things to help support a diagnosis, and has been suggested to correlate with clinical status) although possibly without a useful clinical protocol (even some of the research studies have different results and this is potentially from different handling, such as freezing the samples). A lot of us notice that there are spots on our MRIs and this is mentioned in the literature as well. Our doctors say it's nothing due to not being MS nor a brain tumor. Maybe there's an imaging technique that could show what's going on better. 3) Large longitudinal studies. This will help with building and formalizing knowledge about the prognosis, symptoms, severity, course, comorbidities, and so forth. It's essential that all severities are included. Be sure to be inclusive generally as well. So far studies have mostly studied affluent white women near middle age, but everyone gets this disease. There may be a gender bias in the disease itself (or there may be a diagnosis bias, or both), but it's important to not have any artificial bias in the selection. 4) Inclusion of those with moderate-to-severe and very severe ME. 5) Replications (whether positive or negative; publish them all). Bigger studies are needed. Some

particular things I can think of that could be replicated or expanded:
Neuropsychological testing (including checking for slowed information processing and trouble multitasking; a clinical screening PRO for this would be nice, too)
NK cell function
T cell clonal expansion and other T cell findings
the factor in the serum or plasma that affects the mitochondria
ion channel dysfunction
dysautonomia and getting validated treatments specifically for that, and also an investigation into what particularly is causing the low blood volume (possibly a form of a renin-angiotensin-aldosterone disorder?)
different ways of checking for inflammation
enteroviruses
epidemiology and follow up from various outbreaks, including ones that are named differently (post-SARS, post-Ebola, post-polio, post-H1N1, post-Guillain-Barre, and so on)
sleep and wake wave intrusions
glial cells
mast cells
metabolic acid/base imbalance
how well the heart is working
"sticky" blood
lack of deformability of RBCs
6) Study specific signs and symptoms such as post-exertional malaise, "brain fog," muscle weakness, visual symptoms, food and environmental sensitivities, GI disturbances and weight loss, dysautonomia, muscle fatiguability, sensitivity to light/noise/commotion/vibration/people, aphasia, sore throat, executive dysfunction, problems with swallowing, sweating more or less than usual, getting more or less infections or fewer infectious symptoms than usual, pains, sleep dysfunctions, gait changes, etc.
7) Study specific groups, like separating into early and late stage disease, with or without Ehlers-Danlos or fibromyalgia; study those who had encephalitis at onset, and the very severe.
8) Study social and practical supports. Examples:
What kinds of housing accommodations are needed? What kinds are available?
What kinds of adaptive equipment are needed? What kinds are available?
For the (quarter?) of patients able to continue in work or school, what kinds of occupational barriers exist? What kinds of medical and practical supports are needed? What kinds are available?
For the (three quarters?) of patients who have trouble leaving their homes, what kinds of home-based medical and practical supports are needed? What kinds are available?
For the (quarter?) of patients who cannot leave their beds, what kinds of home-based medical and practical supports are needed? What kinds are available?
What kinds of barriers do patients face at hospitals, immediate care centers, and clinics? What would be needed in a design for a patient-centered area for people with ME at a hospital? (Conversely, what would make it fail? We do not want to continue repeating the story of inappropriate and damaging inpatient care such as occurred with Sophia Mirza, Karina Hansen, Robert Courtney; if we think that would not happen here, all the further we have to look for a publicized case is Boston. Although Justina Pelletier had a different diagnosis, the impulse to deny patients' agency and self-reports is the same.)
What kinds of community barriers exist?
For the patients who have trouble with shopping and food preparation, and also with multiple food allergies and/or intolerances (1-9) what kinds of medical and practical support are needed? What

kinds are available? How many have inadequate nutrition due to food avoidance while attempting to manage symptoms (10,11) ? Since home care aids are in short supply and rarely know anything about cooking from scratch or food and food surface safety anyway, how about a Medicaid pilot program to match patients with personal chefs? Patients with other relevant diseases (such as muscular dystrophy, 12) could be included. Success could be measured by any of A) Reduced GI symptoms, asthma, rashes and eczema, oral allergy syndrome, or other problems attributed to food allergy and/or intolerance B) Increased quality of life C) Increased measure of health on some other factor, such as no longer being underweight, or an improved electrolyte or vitamin count. This would free up care workers to focus on bathing and such things that they're good at, while also helping patients access safe food. If needed, add to the team a dietician knowledgeable about various food allergies and intolerances and supportive of dietary solutions to symptom management. Bonus, add a specialist who can diagnose and treat both things like IgE allergy and mastocytosis and things like MCAD, SIBO, and salicylate intolerance.
A patient friend of mine suggested a wearable device that would track symptom patterns and warn the patient about neutrally mediated hypotension, PEM, or other pending disruptions so the patient could lie down or take other preventative measures. Hopefully, the device could be good enough to help with completing activities of daily living, such as a notification that it was currently a good time to make a phone call (based on symptom profile), for example.

1) Neuro-endocrine-immune-energy deficit connection
2) Documenting exercise intolerance - build a more substantial base of information on exercise testing and invasive exercise testing
3) Understanding exercise intolerance - what happens in the brain during exercise and post-exercise - what areas of the brain are activated/deactivated vs. healthy controls? What is the cellular response? What is the neurotransmitter/molecular response?
4) Investigate neuroinflammation together with neuro-endocrine-immune-energy deficit connection
5) What triggers the metabolic changes?
6) What are ways to determine parameters for the mitochondrial activity in the brain and how they are changed with exercise and PEM - including over days, until return to "normal"
7) Define oxygen transport deficiencies and mechanisms at the cellular level - particularly within the brain

Stringent patient cohorts. (Using patients who meet the ICC would help tremendously)

Clinical Trials using medications that are already FDA approved and available.

ME should not be combined with CFS. A main reason is that CFS is often a wastebasket diagnosis and the name is extraordinarily demeaning and carries an incredible amount of stigma with it. Patients who meet ME per ICC should be studied separately from those who don't.

ME research needs to focus on the patient population that fits the International Consensus Criteria. By focusing on the specific distinct patient population, studies can be replicated properly.

Funding commensurate with the disease burden of this illness. In 2015 Francis Collins said funding for ME/CFS would be substantially ramped up. It went from $6 million in 2015 to $15 million in 2019 and is scheduled to be even less next year. MS funding went from $94 million in 2015 to $117 million in 2019. The INCREASE ALONE in MS funding is greater than TOTAL ME/CFS funding for 2019. Words fail me here. MS funding is over $117 per patient, compared to $7.50 per ME/CFS patient. Dr. Nancy

Klimas has said she would rather have AIDS than ME/CFS, but AIDS funding is in the stratosphere, whereas ME/CFS is in the gutter, and barely that.

Stability is needed to grow a field of research. Young researchers need to know that there is a future in this field, that funding will not be pulled away arbitrarily, as has been the case in the past (and, unfortunately, present, barring change). This is entirely a matter of will and leadership, both of which have been thoroughly lacking in handling this disease, not just at NIH but in the whole of medicine.

Historically, most research in ME has been hit-and-run, researchers working on individual grants then moving to another subject of study because more funding was never available. The usual approach will not work, stable long-term funding has to be set aside so researchers can feel comfortable establishing themselves in the long term.

One large obstacle is attitude. Most ME researchers say they were told by colleagues that they were wasting their career, that it is a dead-end, not a problem worth solving. This is an attitude and cultural problem. Science is about solving hard problems, an attitude that discourages going onto unbeaten paths is completely at odds with that goal.

There are decades of willful neglect to catch up to. Starting slow is not an option, the field has already aimlessly coasted on minimal speed/funding/will for decades. The field needs a long-term commitment with resources to match, anything else will fail, as the last half-century has demonstrated, with millions of lives left to rot in the process.

Additionally, supply-side medicine does not work in such a complex disease. The current status quo of behavioral adjustment is an elaborate fiction that was created with complete disregard for patient experience and objective reality by ideologues who deny the reality of this disease. How this could ever happen, a disease model that contradicts the experience of patients, needs a through examination, in addition to a complete reversal of those egregious mistakes.

An approach that not only finally includes patients in the process but also actually relies on their experience is necessary because of the (so far) untestable nature of the disease and reliance on symptom self-reporting.

Basically: a plan is needed, and the proper resources to achieve that plan need to be provided long-term in ways that cannot arbitrarily be ended.

Biomarkers, treatment trials, more funding

Actively and openly refute the fallacious, harmful and fatally flawed PACE Trial out of Great Britain.

(https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(11)60096-2/fulltext)

PACE has caused incalculable harm to patients around the world. Doctors still think it is valid and routinely tell their patients to exercise (the one thing we can't do without harm!) and get counseling. The CDC relatively recently retracted its recommendations re graded exercise therapy and CBT, but it did so in a halfhearted manner, without directly addressing the real concerns with PACE, which has

been thoroughly discredited. And yet it still holds sway.

Following the PACE trial recommendations are the equivalent of telling your diabetic patients that they need to eat more sugar.
David Tuller has done a stellar job of chronicling the fall of PACE: http://www.virology.ws/mecfs/

See October 21, 22 and 23, 2015: Trial by Error, The Troubling Case of the Chronic Fatigue Syndrome Study (and he has several follow-ups to this in the above link)

You might also look at Tuller's article about the CDC and ME/CFS:
http://www.virology.ws/2011/11/23/chronic-fatigue-syndrome-and-the-cdc-a-long-tangled-tale/

To go forward with this illness, you have to know where we have been and what we are up against.

Why has it taken 35 years to just begin to take this illness seriously? You'll find some of the answers above. And this can help plot the way forward.

The autonomic dysfunction. The mitochondrial dearth of energy production. The neuroinflammation. The sensory hypersensitivities. THE PARALYSIS that many of the severe get. The muteness of the severe. The inability to eat of the severe. The POLYURIA that Dr. Bell says all these patients have 6-7 liters output on average at beginning of illness. The IMMUNOLOGIC abnormalities. The microbiome.

TREATMENTS need research. Repeating IVIG studies. antiviral, LDN, hyperbaric oxygen (small studies showing benefit), OI treatments, over the counter supplements;

Funding to carry out research. Even investigators who are established in the ME/CFS field have difficulty obtaining funding, and new investigators can be discouraged by repeated rejections. The suggestions below cost money but they are worthwhile investments. There seems to be a fallacious concept at NIH that adding funds to this field is a waste of money that will have no effect. But more funds would have a major effect.

Treatment.

Legitimate treatment options that are specific to ME/CFS. There aren't any available therapies or any available medications to help make living with these illnesses somewhat tolerable.

Compelling Needs

I feel that a very compelling area of ME/CFS research need is affording people with ME/CFS, who are able, the opportunity to engage in meaningful work. With the advances in technology and many job opportunities available that are fully virtual, I believe this is more achievable than ever. I think this would require job skills education and placement. I also think it would be beneficial to the people with ME/CFS, their families and caretakers, as well as society as a whole.

Better care nationwide in diagnostics and treatment. Emily Taylor and her team at SMCI are working passionately on extending advocacy from the federal level through to each state; however, it seems a great burden for one organization to accomplish Advocacy, Research and Medical Care for the entire nation.

1. A valid, inexpensive, easily accessible diagnostic test with minimal risk for people suspected to be affected by ME/CFS. A gold standard test would simplify the recruitment process for all studies and pave the way for a more homogenous subject sample.
2. Effective disease-modifying treatments with minimal/ acceptable risk profiles
3. Effective palliative treatments for post-exertional malaise, sleep, cognitive dysfunction, orthostatic intolerance and sleep. For example, clinicians use trial-and-error mostly to select sleep medications for individuals but it is not known which medications are most likely to work for ME/CFS patients as a group or which subgroups of ME/CFS patients would benefit the most from a particular treatment.
4. There are several promising results from studies which need replication, preferably conducted by different research groups, in many patients, recruited from and located in different geographic areas. For example, cardiometabolic issues with 2-day CPET; decreased natural killer cell function; autoantibodies to muscarinic and adrenergic receptors, small fiber neuropathy on skin biopsy, increased nocturnal sympathetic activity, how/ why certain herpes viruses often trigger or are reactivated in ME/CFS Results of these studies might lead to the underlying pathophysiology of ME/CFS, serve as diagnostic/ prognostic/ treatment biomarkers, and function as outcome measures for clinical trials. Traditionally academic advancement and even the NIH grant review process rewards novelty but ultimately diagnostic tests, valid biomarkers, treatments, and healthcare decisions are not based one new, exciting study but based on multiple studies showing the same/ similar results. (In fact, Dr. John Ioannides has argued that up to 95% of study findings may be false.) A better balance between novelty and replication when reviewing grants would be helpful.
5. Delineate the biological mechanisms underlying post-exertional malaise.
6. Longitudinal studies. Most ME/CFS patients have been sick for years to decades yet most studies only last a few months or less than 3 years. Consequently, we do not have good data on the course of ME/CFS nor, for example, how biomarkers change with time. Also, if any clinical trials are conducted, follow-up needs to be long-term: ME/CFS symptoms often fluctuate and temporary remissions are not uncommon. Short-term positive results may merely reflect fluctuations or temporary improvement, not long-term success.
7. Recruitment of groups which have been traditionally underrepresented in ME/CFS research. As brought up twice, once during the Think the Future Workshop and once during the meetings following, in most studies, 95%+ of research subjects have been middle-aged, well-educated, middle/ upper class, Caucasian women who are able to visit a research site and have been sick for many years. Yet we know from practice and from community-based studies that ME/CFS also affects children, the elderly, poor people, men, ethnic minorities (Blacks, Native Americans, etc.). Some severely affected people cannot attend clinic at all. Also, most studies have focused on long-term ME/CFS but capturing the recently ill is also valuable, especially in figuring out questions of etiology and early diagnosis/ treatment. For results to be applicable to as many patients as possible, study populations need to reflect those who are sick.
8. Explore symptoms of ME/CFS that have not been investigated much or at all. For example, thermoregulation issues (e.g. low body temperature, heat/ cold intolerance) have been noted by clinicians and by more than 50% of patients yet few studies have looked at this symptom. A second example are gut symptoms, cited by at least 40%-50% of patients yet even gut microbiome studies have not elaborated on them. For many patients, these are very troublesome symptoms and investigation may uncover as yet unknown aspects of pathophysiology.
9. Pediatric ME/CFS is even more under-researched than adult ME/CFS. We recognize there are unique barriers to pediatric research (e.g. proper consent, dosing of medications, etc.). Nevertheless, with the teen years shown to be the 2nd most common age of onset for ME/CFS and at least in the United Kingdom, ME/CFS being the top cause of long-term health-related school absence for K-12

grades, more work needs to be done. Some of the abnormal findings in adults need to be tested to see if they occur in children and children also deserve effective treatments.

For over three decades, scientific progress into the disease ME has been strangled because of inappropriately dismal levels of NIH funding and funneling of most of that funding toward psychosomatic and psychological research while denying funding for biomedical researchers. This NIH neglect has resulted in scarce, small biomedical studies without funding of large scale replications.

Additionally, NIH helped develop and support poor disease criteria due to systemic bias which misrepresented the disease with a heterogeneous mix of patients with varying symptom clusters and unrelated causes.

One major hurdle, which can be easily fixed going forward, is the fact that most studies on the disease have not used appropriate research criteria.

HHS and all HHS agencies need to first implement and require use of the International Consensus Criteria (ICC) in order to select the right cohort of people actually suffering from the disease ME. The ME-ICC were uniquely developed by international experts with extensive clinical experience diagnosing the disease in over 50,000 patients. There can be no substitute for the firsthand knowledge of skilled clinicians and researchers in defining a disease.

Thirty years of research on mixed groups of subjects labelled CFS or ME/CFS based on varying combinations of self-reported symptoms has been largely fruitless. ME is an actual disease identified from epidemic outbreaks that can be differentiated from other diseases and disorders presenting with similar symptoms by using the ICC and IC Primer. NIH needs to study the 50+ worldwide outbreaks of the disease - instead of burying the facts that these outbreaks took place.

Only with proper true biological features and the correct criteria (ICC) can any research result in meaningful findings. The results of specific ME-ICC research could be reproduced and built upon leading to progress in recognizing, diagnosing, and treating ME for the first time. Large scale biomarker research must be top priority in order to legitimize the disease in the eyes of the medical community and the public.

The most compelling needs at present are identification of biomarkers, development of a clinical diagnostic test, research towards a disease mechanism and drug treatments.

The identification of biomarkers would give ME/CFS legitimacy and help fight the CBT/GET brigade.

Development of a clinical diagnostic test would help in diagnosing patients especially at early stages where rest and preventing PEM episodes is most likely to lead to slower disease progression (as well as help fight the CBT/GET brigade).

A disease mechanism again helps fight the CBT/GET brigade as well as helps provide research direction, more investigators will come into a field with a delineated mechanism they can train their talents on solving.

Drug treatments obviously help patients regain their lives and get back to gainful employment and of course alleviates suffering from this disease.

-- research that proves some of the most destructive misconceptions about ME/CFS; e.g. that it "is not a real disease" because the shortcomings of current medical research and practice prevent finding the true causes. Once and for all disprove the misguided and very harmful "PACE" theory.

--clarify the role of neuro-inflammation in the symptomatology of ME/CFS

--clarify the interaction of neuro-inflammation and immune system and immune system dysfunction

--support and further the kind of invasive CPET tests that David Systrom has been doing up at Harvard

--fund burden of illness studies including ME/CFS, FMS, POTS

--further work in metabolomics and how it relates to ME/CFS

Begin with the international consensus criteria as a definition for M.E. There is no way we can communicate concisely about this disease without clear definitions developed already, by medical professionals that have experience with this disease and its treatment.

An accepted definition will also open the door for researchers to be clear about what they are studying and decrease the misconceptions and historically incorrect information. This clear and specific research is our quickest path to solutions with the very limited funding that is being invested.

Start funding the research fairly by basing it on the disease burden based on population that is estimated to be 200 million. There is no research without money and researchers will come to study the disease if money is available.

Create a screening committee that actually believes in and treats this disease!!

Firmly establish that neuroinflammation is present.

Explore the neuro-immune-energy interface.

Most compelling research needs

A strategic plan is urgently needed - it must be a strategic cross-agency research plan that demonstrates urgency and commitment , including timelines, necessary funding, stakeholder involvement at every level, outcome measures etc, as well as the dedication and drive to get it done. NIH is well -positioned to sponsor the development of this place.

Research Case Definition - Meeting after meeting, report after report have stated that there is a lack of consensus on the research case definition for ME as well as lack of operationalization of research definitions. To ensure proper selection of study participants and strengthen the science, this issue must be resolved as soon as possible.

To do so, NIH must sponsor a meeting of expert clinicians and researchers of ME to reach consensus

on this issue as well as to specify methods to be used to select ME patients for participation. Note - see also the MEAction submission.

Post-exertional malaise - PEM is a hallmark of ME and according to some people in the field also occurs in other illnesses though it manifests differently. It seems that in ME , the triggers, onset, severity, frequency and duration are different than in other diseases/conditions. However, there doesn't seem a thorough scientific characterization of PEM which means that health care professionals and researchers may be missing patients with it or mislabeling patients without it. Therefore PEM needs to be carefully characterized in order to facilitate diagnosis, educate healthcare professionals (and stakeholders) and to elucidate what is same/different about PEM in all conditions in which it occurs. A thorough understanding of the physiology of PEM, the cognitive and physical impact of PEM in ME and of the cognitive and physical triggers of PEM is essential. This characterization should also be done by an NIH sponsored project of ME expert clinicians and researchers as well as researchers in the other conditions said to have PEM. This should be done immediately so as to ensure that the research definition and methods decided upon by ME expert clinicians and researchers will incorporate this characterization of PEM to accurately adjudicate ME patients.

Longitudinal studies are needed - we don't know much about the progression of this disease and for people like me (the caregiver for two young adult patients), that makes it very difficult for plan for the future (theirs and mine). Note - see also the MEAction submission.

Large scale replication studies are needed - with larger, clearly defined cohorts and with other illness groups as well as healthy controls so as to determine if results are an indication of illness in general (across several illnesses) or specific to ME

Cognitive issues are significant for many patients and the inability to engage in cognitive exertion without repercussions (PEM for instance), severely limits the ability of patients to feel meaningfully engaged in life. Research is urgently needed to find ways of enabling patients to (paraphrasing my sons) 'access their brain at will, without repercussions.' Being able to do so would be a huge improvement in quality of life for many patients - possibly enabling them to resume their education, return to work and/or otherwise feeling meaningfully engaged in life.

Inclusion in studies of severely ill people with ME - not studying the severely ill is like studying consumer spending patterns but not including those below the poverty limit. In other words, not an accurate representation of the disease. Provisions must be made to study people severely ill with ME.

People with ME of all ages and races must also be included.

Reminder - oftentimes caregivers observe things patients don't notice and or can more accurately describe what happens to patients. Therefore, whenever possible caregiver input should also be used.

The publication of the null results of the Rituxan study are notable. Publication of other null results should be strongly encouraged. This will help sort out what does and does not work and may also help with subsetting.

Work strategically to significantly increase the number or researchers and clinicians in the field. Increasing the number of clinicians who can accurately diagnose ME, will increase the number of

accurately diagnosed patients which will increase the number of accurately diagnosed people available to take part in studies which will in turn lead to clearer signals in studies.

Pair researchers/clinicians with patients/advocates as mentors to help people new to the field learn how pervasively ME impacts lives.

Workforce training should include presentations by patients/advocate (live, video conferencing, etc) about real life with ME (school, work, SSDI, encounters with HCP, housing, food access, social, etc) to help them better understand the range of difficulties encountered by PwME and as a reminder of why the work they are doing is so important.

Conferences, healthcare education, working group meetings, etc should include presentations by patients/advocates (live, video conferencing, etc) about real life with ME (school, work, SSDI, encounters with researchers/ HCP(healthcare professionals), housing, food access, social, etc) to help them better understand the range of difficulties encountered by PwME and as a reminder of why the work they are doing is so important. (In 2014 at the IACFS/ME conference, a long-time researcher from a Federal agency was shocked to learn that patients had trouble accessing food and/or had trouble preparing it (for instance could prepare it but then not be able to eat it). The researcher had been in the field for years but hadn't been "hit with" this detail about the limitations imposed by ME. How many other researchers who purportedly study ME are similarly unaware of the pervasive impact of ME?)

Ensure that (stakeholders patients, advocates, caregivers, etc) are part of all projects (from inception to completion to publication of results to follow-up) related to ME.

Reminder - oftentimes caregivers observe things patients don't notice and or can more accurately describe what happens to patients, so whenever possible caregiver input should also be used.

Note - see also the MEAction submission:

Scientific Opportunities

- #13 additionally -iCPET, cerebral blood flow,

- #21 also look at puberty

Epidemiologic Knowledge

- inclusion of pediatric patients

Pathobiologiy Discovery

- include other illness groups as well as healthy controls to ensure that results are ME related and not simply an indicator of illness

Workforce Development

with stakeholder participation as an integral component of the education process - Reminder -

oftentimes caregivers observe things patients don't notice and or can more accurately describe what happens to patients, so whenever possible caregiver input should also be used.

Case Definition

Stakeholder Engagement

- must also include caregivers- Reminder - oftentimes caregivers observe things patients don't notice and or can more accurately describe what happens to patients, so whenever possible caregiver input should also be used.

Diagnostic - simple, scalable validated biomarker diagnostic method for primary care doctors to diagnose and pharma to use in clinical trials.

Mechanism of action - a better understanding of the biological/neurophysiological pathways and interactions

Treatments to manage the priority symptoms e.g. dysautonomia, OI, heartrate, vision problems, cognitive problems

Understanding of Heterogeneity - identify clusters, phenotypes, severity levels, biomarkers for each

Disease triggers - pathways, prevention

Increase research capacity.

Unless a large amount of funding is allocated on a regular basis (Invest in ME Research suggested investing $50 million per year for the next five years in biomedical research into ME initially) then the existing capacity needs to be used effectively, and that means international collaboration with genuine organisations/individuals and creating a strategy to avoid unnecessary competition/duplication (duplication is not the same as replication).

The research capacity has to be increased (in facilities and definitely people). The Thinking the Future initiative will hopefully help with young investigators as it begins to be accepted.

The young investigators network needs to be connected with universities and medical students need to be engaged early, also in relation to altering their medical curriculi.

Sub grouping determination is likely to be useful.

Also the key strategy needs to be aimed at finding biomarkers, pathophysiology and causality.

Consistent standards for diagnosis and research - internationally.

Funding provided (or not) will decide how much of a strategy can be formed and turned into action.

a. Develop a consensus, overarching strategy that will drive cross-disciplinary research

b. Address institutional and process barriers that persist at NIH Â

c. Create a global, openly-available, centralized resource of well characterized ME/CFS patient, healthy control and disease control data and bio specimens

d. Establish rigorous, standardized research practices; including the application of case definitions, methodological approaches, utilization of data collection instruments,

and expansion in replication and studies that interrogate or build on previous findings

e. Develop an infrastructure for researchers to easily share data (positive and negative findings) and methodologies to allow them to build on each other's discovery

f. Promote a massive increase in the number of researchers working on the disease; particularly, early-career stage investigators and skilled scientists from relevant

scientific domains or related disease fields who can newly apply their expertise to ME/CFS

g. Redouble existing efforts and expand approaches to educate clinicians, encouraging better clinical care, partnerships in research, and a pipeline of study participants

h. Increase opportunities for collaboration and tools for communication among scientists, clinicians, people living with ME/CFS, and other stakeholders

i. Ensure that people living with ME/CFS are more meaningfully incorporated into research discussions, acknowledged as experts in their own right, and elevated to the

level of partner in research studies

MEICC criteria

1) Identify and validate treatments, including currently-approved FDA drugs and oral and IV nutrients that are useful in the treatment of ME/CFS and/or symptoms related to ME/CFS, and determine who they work for, under what conditions, and how they fit into a comprehensive treatment plan and timeline, as well as newer treatments such as fecal microbiome transplants and hyperbaric oxygen therapy. Currently, there are no official treatments for patients, so patients are left to languish, waiting for the research to offer answers. Cancer patients would die in similar circumstances. ME/CFS patients die as well, while most others may as well be dead as they are isolated and unable to contribute to society.

2) Identify tests that are useful in:

a) Identifying subsets of patients to match treatments that will work - for example, patients with immunodeficiencies may need immune support if they are to make progress, while those who are hypothyroid or have adrenal insufficiency may not be able to function if hormones are not brought to

normal levels, and those with active viruses need antiviral treatments.

b) Determining the stage of the disease - for example, cytokine patterns may differ between the newly diagnosed and patients that have been sick for a long time. Depletion of nutrients, derangement of the micribiome, and damage to mitochondrial and cell membranes by oxidative and nitrosative stress may be increased in some patients.

c) Determining what factors are contributing to the disease course or progression, as well as risk factors for acquiring ME/CFS. These may include genetics, infections, environmental exposures, hormone and nutrient deficiencies or imbalances, comorbidities such as mast cell activation syndrome, postural orthostatic intolerance, and various autoimmune conditions.

d) Identification of diagnostic tools for ME/CFS beyond clinical symptoms and self-report measures.

e) Identification of monitoring tools (i.e. heart rate monitors, blood pressure monitors) to assist patients in preventing PEM.

f) Determining progress in/success of treatments over time.

3) Continue the basic research and increase funding. Over the past 40 years, progression answering the mysteries of this complex, multi organ system disease has been slow. Research findings have been accelerating, and scientists across the world are collaborating generously, trying to fit the pieces in to this detailed and complex multi-faceted study. But, we are years from solid answers that will help explain what exactly has gone wrong to provoke this disease state. Time and patients' lives are wasted as they are struck down as children, teens, and young adults, then languish for years in a twilight state, waiting for this puzzle to be cracked and for light to be shone on the mysteries that elude them, their doctors, and caregivers. We need both basic research AND trials of treatments, informed by both anecdotal information from clinicians AND big data.

The most urgent ME/CFS research need is for funding. There is currently a futile cycle of "there is not enough quality research, so there cannot be more funding allotted to it,"and so no more quality research is done due to lack of funding. There is a need for investment on the part of the NIH in order to break this cycle.

Patient selection criteria and Using the ICC for all research.

Using the ICC for patient selection and marked increase in funding!

These are listed in order of importance on http://www.me-ireland.com/structure.htm#8 and http://www.me-ireland.com/research2.htm

I am a patient and too sick to participate in much research. Multiple research sites or the ability to participate remotely could allow more severe patients be included.

What kills ME/CFS patients?

How do most ME/CFS people die? My money is on heart failure, from repeated muscle injury from

tachycardias combined with the mitochondrial energy deficiency during flares. Heart attack, heart failure, deterioration from gut failure, drugs dangerous to mitochondria but common at hospitalizations, opioids prescribed for pain, no medical care, problems from disease-induced poverty, suicide. Do you know? I imagine you need to identify the patient cohort to find out.

Post-exertional malaise prevention beyond pacing. Addressing the underlying mitochondrial energy deficit. PEM happens partly because it's so difficult to identify if you've done too much at the time, hence the pacing. Developing a test that indicates early on that you are pushing too far would be ideal. A blood test with a finger-prick or better, a test that looks at the blood through the skin. Perhaps a breath test. So I think there needs to be a experiments to determine early biomarkers for progression towards PEM and then a real time test. Pacing is only marginally effective from what I can tell. However there is this fatigue and tingling feeling in my skin and muscles and a faintness that I have to pay close attention to feel. This is an indication that it is starting. So if I'm paying attention I drop everything at that point which takes huge self-discipline for just a whisper of a feeling. However if there was a breathalyzer test or a test similar to a blood oxygen test for my finger, it would confirm the feeling and train me better to sense it. Or I could set a timer to do the test multiple times a day like you might with blood sugar. I love the tests Dr. Ron Davis is developing at Stanford.

Develop an Emergency Protocol Letter for ME/CFS

Right now ME/CFS patients avoid the ER like the plague because they are afraid the doctors there will kill them, by giving them the wrong drugs, eliciting POTS tachycardias, sending them into a severe flare, or simply injuring their muscles by not supporting them carefully like you would with other neuromuscular patients. We REALLY need an emergency letter like doctors give to their mitochondrial disease patients. Because of the variety of mitochondrial diseases the letters are different depending on the gene defect, but I think a more general one could be designed for ME/CFS that would prevent the most harms.

Strength vs stamina in ME/CS. Progressive weakness, tissue models, and the need for a refined strength test.

I hope that there is a better way that comes out of the new biomarker research to measure muscle weakness. Each flare makes my muscles weaker. Yes they have less stamina, but there is also a weakness that may correspond to damage to the muscle fibers. I would really like to see that teased out better at the muscle fiber level. Is there structural damage happening in other muscle proteins? Is it only mitochondrial? Or are the mitochondrial damages creating other structural problems too in the cell? Will those heal with repair of the mitochondria behavior? Because I get a severe strength loss during a flare, it isn't a deconditioning issue. But the strength loss often doesn't recover fully whereas the stamina part may recover more or less than the strength. Perhaps this strength reduction is really a permanent damage to neurons from the brain inflammation and peripheral nerve inflammation, and the stamina damage is more resulting from an increased mitochondrial energy production derangement. But there is also the possibility of structural damage to the muscle fiber. Each component suggests different types of drug and treatment approaches. Strength tests at the neuromuscular doctor are way too coarse to be able to measure the incremental strength loss, and also a patient puts themselves in danger to go visit a doctor while they are in the midst of the flare, when they would see the biggest difference. The doctor would not normally see them at this point and doing a typical strength test will make the symptoms worse, possibly adding permanent damage. So it seems like there needs to be really careful work done on tissue biopsies to tease these things

out, with a nerve + mitochondria + muscle cell + signaling systems-biology model to work from. I think Harvard is working toward a tissue model from the recent Australian talks? The unraveling of mitochondria with application of ME/CFS serum was a really cool result from the NIH conference,. My mind is giving out on me now so it is hard to remember.

and of course, treatments and cures

-Moving towards mechanistic understanding as opposed to simply reporting differences from controls

-Currently, studies are largely focused on middle-to-upper-class, middle-aged white women with moderate symptoms; deliberate outreach beyond that cohort is important

-Support for studies of more severe patients - e.g., specific funding for medical transport

-Collaborations in which the same patients are studied with different methods

-Funds to follow up with Nevada outbreak patients, including EWAS (epigenome)

Correct selection criteria differentiating ME from CFS & respecting the individual WHO codes for each condition. Research is wasted on comparing apples with pears & we are desperate for fast, effective action.

For the last 30 years the most compelling ME/CFS research needs have been and continue to be:
1. Discovery of the disease trigger(s)
2. Discovery of disease perpetuating factor(s), i.e., what causes the chronic state and blocks the body's reset to its pre-illness normal state?
3. Development of diagnostic tests
4. Discovery of treatments and a cure
5. Discovery of preventative measures

CFS and ME/CFS are melting pots for *fatigue*.

Myalgic Encephalomyelitis is a disease and not a symptom of fatigue.

The experts defined using CCC--Canadian Consensus Criteria -- and later further refined with ICC--International Consensus Criteria and the ICPrimer -- International Consensus Primer. ICC eliminated the combo ME/CFS -- to define M.E. more stringently, and to better define the disease Myalgic Encephalomyelitis. The six-month waiting period for M.E. diagnosis was eliminated with the ICC. This is extremely beneficial to persons with M.E. because continuing to push serves to further exacerbate our health.

The identification of the disease in individuals-a way in which doctors can easily and cheaply ascertain whether or not a patient has ME. Dr. Ron Davis is the point scientist here; he needs all the support we can give to him.

Secondly, treatment for pain, no matter what form, should be top of the list on issues. I can work (barely) due to good pain management and careful monitoring of my activities throughout the day. And I have a variable hour job and sympathetic employer. I should be on disability, but I have fought long and hard with the progression of this disease to remain at least somewhat of a contributor to the world. This disease has cost me personally thousands of dollars; we must find a way for people to feel well enough to work if they want to. This disease is costing the US millions of dollars too!

From a systems science point of view, I believe the epidemiology of ME/CFS needs a major update. ME/CFS research will not likely be fully funded until the general public become worried about the growth rate of the condition. This is really a big deal in my opinion because nobody is talking about the role of epidemiology in the sequence of power in getting funding. Here is the model:

Competent Epidemiology => Public Worries => Medical Engagement (calls for action, etc) => Pressure on Elected Officials => Congressional Funding Response => NIH and related agency cooperation => Increased Funding => Increased Research Activity => Better Clinical Management => Solutions

Currently the missing link is 'public worries'. We are a worried patient community, but patient worries do not lead to significant medical engagement or pressure on public officials. We are just another special interest group to them. That is not adequate. Think of the AIDS response, how the public fear was a critical factor, that response was not just a few worried patients or patient associations. We are missing the big splash in public awareness, and I believe a competent epidemiological study could trigger that. Yes, this is a long game and I know people want quick studies and answers, I want those too, but for the major funding we need, we have to play the long game well, not just the short game.

On the medical side, cross-over conditions, epigenetics and metabolomics seem to be likely candidates for immediate research to be productive. Given that these are rapidly maturing fields, we should get some quick pay-back.

Molecular studies seem early-stage, there is a need for a lot of basic research, so this seems like a slower pay-back area. I believe we should be funding basic research, but only within a strategy of cost-sharing with other disease interest groups. Basic research funding organizations like the NIH should be interested in the molecular issues. But I think it is not fair for ME/CFS, as a poorly funded illness, to bear the burden alone of figuring out how biology works when cells are unwell.

MOST COMPELLING RESEARCH NEEDS

The overarching and most compelling research need in ME is to deliver diagnostics and treatments as quickly as possible. It is clear from conference reports and literature that opportunities exist today to deliver on this need within 3-5 years. For instance, with the right plan and political will, it should be possible to deliver one or more clinically viable ME biomarkers within 3 years and at least one FDA-approved symptomatic or disease-modifying treatment within 5 years.

However, NIH's current approach is too narrowly focused on basic disease pathology, planting seeds and hoping they grow. This approach is not only slow but also fails to seize on the present opportunities to quickly deliver patient-focused outcomes and proactively resolve the range of barriers, challenges, and misunderstandings that have stymied ME research for nearly 35 years.

These long-standing barriers and challenges have been extensively documented in NIH's 2011 State of Knowledge Workshop report, the FDA's 2013 PDUFA Drug Development Workshop, NIH's 2015 Pathways to Prevention report, the 2015 National Academy of Medicine report, CFS Advisory Committee recommendations since 2003, and numerous reports and recommendations by patient

advocacy organizations over decades. #MEAction submitted a survey-based, patient-led RFI response in 2016; a letter to Director Collins signed by over 7,000 people; and met with and presented recommendations to Francis Collins in December 2018. We have solicited direct input from the community to develop this response, particularly for questions 8 and 9. However, the NIH has failed to act on the majority of recommendations in the past, demanding repeated intellectual labor from a patient community that continues to have the same unmet needs.

Change won't come through watchful waiting. Change can only come through decisive action. Delivering on patient-focused outcomes as quickly as possible will require greater political leadership and commitment from NIH, NIH funding commensurate with disease-burden, and a comprehensive, focused, creative program of parallel initiatives as detailed below. The following components must be included in this program:

Strategic Research Plan: We must have an outcomes-focused, strategic plan with the necessary funding, coordination, cross-institute commitment, stakeholder engagement, and NIH political leadership needed to make rapid progress. This plan must include parallel components to a) deliver diagnostics and treatments as quickly as possible, b) understand basic disease pathology, and c) address barriers and challenges as further detailed below.

One challenge in developing this strategic plan is that some of the most critical barriers and challenges to be resolved are the remit of other Health and Human Services agencies. For this reason, a Health and Human Services-wide strategy is needed. Director Collins had told President Obama in 2012 that Health and Human Services was "working to develop a Department-wide strategy to address the disease"but that never happened. As NIH develops a strategic research plan, it will need to partner with other agencies in the Department to ensure those agencies are actively addressing these issues.

Rapid Expansion of Pool of ME Expert Clinicians: One of the most significant research needs, especially given the definitional issues discussed in responses to other questions, is for rapid expansion of the pool of expert clinicians who can accurately diagnose people with ME . While developing the workforce of ME expert clinicians may not appear to be within NIH's remit, NIH will be unable to ramp up research with proper ME cohorts until this issue is addressed. NIH must provide the political leadership with its partner agencies within Health and Human Services and with the leadership of medical organizations to resolve this issue swiftly before these disease experts retire. NIH needs to creatively use every lever at its disposal to support the rapid expansion of the pool of disease experts.

In addition to expanding the ranks of expert clinicians, it is essential that we capture ME expert clinicians' knowledge to expedite and inform research, including but not limited to knowledge about diagnosis, subtypes, outcome assessment, intervention effectiveness, and symptomology. NIH needs to provide tangible financial and structural support for current efforts targeted at capturing, organizing and disseminating this information before it is lost.

Case Definition, Instrumentation and Research Tools

Case Definition and Methods: The 2011 NIH State of Knowledge report indicated that lack of consensus on the research case definition and methods to operationalize the application of the case definition threatens "the entire scientific enterprise."This issue has never been resolved and study

participant selection criteria and methods still lack the necessary rigor to ensure the selected research cohorts all have ME. In fact, the NAM report stated that the Fukuda Criteria, one of the most commonly used research criteria, includes patients who do not have ME. The artificial heterogeneity resulting from non-specific case definitions has complicated the task of understanding the disease and hampered progress toward biomarker discovery and effective clinical trials. This has created confusion as to whether the observed heterogeneity is intrinsic to the disease or purely an artefact of mischaracterization. This circular problem of selection criteria impacting research and research needed to inform selection criteria will not resolve itself organically; proactive interruption of this cycle is necessary to progress the field.

While NINDS' Common Data Elements Initiative established common data elements for research, it did not explicitly address this issue. Given the current crisis with knowledgeable clinicians, it is essential that NIH sponsor a meeting as soon as possible for expert ME clinicians and researchers to reach consensus on the core criteria and methods used to accurately assess whether a given study participant has ME. Until this is completed, patient selection in NIH-funded research must use the 2003 Canadian Consensus Criteria (CCC) and/or the 2011 ME-International Consensus Criteria (ICC-ME) and must use the NIH CDE approved DSQ to assess symptom profiles. Post-exertional exacerbation is a hallmark of the disease and required for diagnosis according to the NAM report, CCC and ICC-ME; therefore it is essential that NIH-funded researchers ensure that all patients in cohorts labelled with ME exhibit this clinical feature.

Instrumentation: In addition to selection criteria and assessment methods, the field needs further evolution of basic instrumentation for assessing symptoms and outcomes. Numerous needs have been identified in NINDS' ME/CFS Common Data Elements initiative. These needs should be prioritized and funding made available to address them.

Diagnostic Biomarkers: To improve diagnostic accuracy of ME, we need at least one diagnostic biomarker, even if it's not unique to this disease. This has to be one of the highest priorities for the field. To make this happen quickly, NIH will need to issue a targeted funding opportunity with set-aside funding.

Data Repository and Biobank: Finalize a clearly articulated plan to establish and maintain NIH-funded centralized data and biospecimen repositories, which can store anonymized clinical and research data, including imaging data and biospecimens collected from well-characterized patients in past, current, and future research studies. These repositories should be fully operational within two years and accessible by outside researchers. The repositories can be extensions of existing repositories that are storing ME data and biospecimens or built from scratch. The current efforts focused on just the data generated by the NIH supported CRCs must be expanded to include institutions not funded in the CRC grant, provided they share their inclusion criteria and specifics regarding the manner in which the specimens were gathered and stored.

Intrinsic Complexity and Heterogeneity of the Disease: In addition to the issue of artificial heterogeneity, this disease, by its very nature, is heterogeneous in presentation, history, and response to treatment. This complexity impedes progress in research. To make progress in understanding this level of complexity, a plan must advance the following:

Richer subtyping strategies and standards for recording and reporting those subtypes in databases and published literature. Key dimensions of subtyping include but are not limited to duration,

severity, nature of onset, comorbidities, and concomitant medications

Study designs and outcome measures that account for the impact of post-exertional malaise and the waxing and waning of the disease

Biomarkers associated with those various subtypes to improve subtype identification

Study designs that include more study participants and are multi-disciplinary in nature in order to understand the interactions across systems that may be driving the disease and its heterogeneous presentation

Targeted Clinical Intervention Initiatives: ME expert clinicians have identified opportunities for clinical trials of drugs already being used off-label in clinical practice to relieve symptoms and improve patients' quality of life. In March 2019, attendees at the ME/CFS Clinician Summit called for action on this front, stating:

"The field of ME/CFS needs evidence-based treatments. The combined clinical experience of ME/CFS clinicians supports efficacy of several treatments that have potential and warrant testing. Appropriate funding mechanisms are warranted. In addition, funding should support a clinical trials consortium."

Advancing such trials has the potential to not only improve patients' quality of life and insurance reimbursement for clinical care but could also advance our understanding of disease mechanisms and improve trial enrichment strategies and outcome assessment methods. NIH should also leverage all funding opportunities including both clinical efficacy trials for interventions already being used off-label and for exploratory trials to identify responder/non-responder subgroups and investigate underlying biological variables driving disparate outcomes.

To best leverage this opportunity, we recommend NIH issue a targeted funding announcement with set-aside funds to support the establishment of a Clinical Trials and Interventions Consortium to develop the network of clinical sites who participate in trials and to further develop the instrumentation, methods, and trial design to ensure success of these trials. We also recommend NIH institutes prioritize and provide funding for intervention trials already being used off-label in clinical practice.

Insufficient knowledge about the disease: The National Academy of Medicine was pointed in its conclusion that there's a remarkable lack of knowledge about the epidemiology and pathophysiology of ME. Efforts such as the NIH intramural study are important but have a narrowly-focused patient population and have been slow to recruit patients and yield results. The Collaborative Research Centers are too few, underfunded, and narrowly focused. Most studies focus on adults and are lacking in diversity, leaving children and minorities underrepresented. CDC has reported plans to undertake epidemiological research using surveys of patient reports of receiving a clinical diagnosis of "CFS."This method is unlikely to deliver the quality and range of data needed, particularly given the rates of clinical underdiagnosis and misdiagnosis seen in this disease. As outlined in our responses to other questions, additional efforts must be undertaken to understand the multi-system breadth of disease pathology and lay an accurate foundation of knowledge about prevalence, demographics, risk factors, natural progression and prognosis and ultimately prevention.

Insufficient NIH funding: The disparity between NIH's ME funding and the burden of disease, estimated at about $200M, is well-known. NIH has stated that funding will increase when more researchers submit meritorious applications. In response to the low number of submissions, NIH has called on the patient community to recruit researchers.. But without a substantial year-on-year funding commitment from NIH, researchers are unlikely to leave existing funded research programs and risk their careers on such a challenging and uncertain area. This is a point that researchers and CFSAC have made on numerous occasions: researchers are hesitant to enter the field because of challenges securing funding for ME studies and NIH's lack of substantial, sustained and dedicated financial commitment to ME. To overcome this barrier, CFSAC had repeatedly recommended that NIH issue disease-specific RFAs.

The NIH funded 3 centers in the late 1990s, issued one RFA in 2006 and another in 2017 for the collaborative research centers. But these grants have been miniscule compared to the magnitude of the disease burden and research needs, and they have been too sporadic. The number and frequency of RFAs and the level of funding provided have not been sufficient to attract the number of researchers and the breadth of expertise needed to accelerate research.

If NIH is serious about increasing the number of researchers, ramping up the level of funding, and accelerating growth in this field, then NIH must issue multiple, disease-specific, multi-year funding opportunities with set-aside funding. As listed below, there are numerous opportunities for RFAs that could address key issues in the field and rapidly generate breakthroughs that will produce impactful outcomes for patients.

Beyond RFAs, NIH must issue disease-specific funding announcements for investigator-initiated studies and leverage all other funding options, including supplemental grants, to grow the field and attract senior researchers with expertise in adjacent areas. The argument that this would not be fair to other diseases is not an acceptable rationale, given the unique challenges that the field needs to overcome and the debility of ME patients.

NIH Administrative Structure and Review Processes: In spite of assurances to the contrary, it is not clear that any NIH institute has taken strategic accountability for ME. While NIH has reinvigorated the Trans-NIH Working Group, NIH is ultimately an institute-driven organization and it seems unlikely that the Trans-NIH structure can compensate for lack of strategic accountability for ME by one of the institutes. For instance, it is unclear how Trans-NIH Working Group recommendations translate into institute-specific strategies, goals, resource commitments, and actions. Even NINDS, which leads the Trans-NIH Working Group, does not list ME in the list of diseases it studies and its financial commitment is less than that of NIAID. Further, as has been reported by NIH staff, the number of Center grants awarded was throttled by the low level of financial commitment that NIH institutes were willing to offer.

NIH has said it has chosen the Trans-NIH approach because ME is a multi-system disease. To our knowledge, the use of the Trans-NIH structure for ME is unique situation in that while such Working Groups do exist for other diseases, those diseases are primarily housed in a given institute even when they are multi-system.

To ensure that ME is not at a disadvantage in strategic planning and funding decisions, NIH should maintain the Trans-NIH Working Group but also formally house ME in the National Institute of Neurological Disorders and Stroke and formally include ME in the strategic goals of the National

Institute of Allergy and Infectious Diseases.

If NIH continues not to house ME in NINDS, then NIH must implement the necessary organizational structures to ensure progress is effectively achieved within its institute-driven organization. One approach is to establish and fund an Office of ME Research within the Office of the Director to drive the strategic planning, coordination, resource commitment, stakeholder engagement, and monitoring across institutes and with other key stakeholders that are required to get this field moving. Continuing to use part-time staff and the Trans-NIH structure to implement our country's response to this disease is inadequate and must be urgently revised.

Grant Review Processes: Given the challenges that researchers have reported in getting grant applications approved for ME, it is important to assess in what ways these processes may be impeding access to funds. Specific concerns with the review processes include:

What is NIH doing to address the dearth of reviewers on the SEP who both:

thoroughly understand ME as a disease and

have sufficient knowledge and expertise about the given area of science being studied (e.g. immunology, metabolomics, genomics, etc.) and the type of technology being used (e.g. imaging technology, computational modeling)?

Is the ad hoc nature of the SEP reviewers resulting in challenges with getting grants approved because the grantee is faced with new reviewers and new concerns if he or she has to resubmit the application?

Are applications being scored poorly by SEP reviewers and reviewers of clinical trials because:

The reviewer has a personal opinion that the research is unimportant but that personal opinion does not reflect the actual priorities of the field?

The reviewer has an expectation for preliminary data, size of supporting studies, etc. that is not realistic given the state of ME research?

Are experienced researchers with broad success in getting grants in other fields still having their ME applications scored poorly and if so, why?

Why are researchers having difficulty getting applications approved for clinical trials, even following multiple applications? Given that these are institute-specific processes, it is unclear whether the issue is lack of strategic commitment to the disease by that institute, or whether one of the issues above might be at play.

Do the program offices in each involved institute have the time, expertise, and interest to support applications that intersect with their institute and thus come their way? Have their institutes made this disease a priority in their strategic planning and goal setting?

NIH should formally evaluate the effectiveness of the review processes and whether they are creating an unnecessary impediment to the goal of accelerating research.

Bold Leadership to Drive Rapid Change: Two of the key barriers to forward progress are:

the widespread stigma and misunderstanding about the disease and

the critical lack of engagement by major academic centers, researchers, the pharmaceutical community, and the medical community and its leadership, as well as relevant federal agencies and NIH institutes.

As noted above, making progress on research is further complicated by the fact that some of the most critical barriers are within the remit of other agencies.

The ME patient community has done its part but does not have the political power, physical capacity, or financial resources to change the research landscape. It is the NIH that has the unique organizational position and political capital to influence the other Health and Human Services agencies and the research, industry, and medical communities to do what is needed to advance research. NIH must leverage its position and capital in an aggressive and creative outreach plan to these agencies and organizations to accelerate research.

Stakeholder Engagement and Transparency: NIH has implemented the Trans-NIH Working Group as a structure for coordinating ME initiatives. However, the activities of this group lack transparency and accountability to the community. With little buy-in as shown by the small financial commitments from relevant NIH institutes in recent years (resulting in funding of only 3 CRCs), this mechanism is insufficient to drive the needed scale of participation and commitment from across NIH. Finally, this group's work is not informed by the vital perspectives of those living with and studying ME.

With the recent dissolution of CFSAC, no formal venue exists for engagement of ME stakeholders with federal agencies responsible for addressing needs of patient community, research groups and other institutions. In a field where agency-interdependent issues have long been critical bottlenecks to advancement, it is unacceptable that a venue does not exist for the communication and coordination of actions to address interrelated needs.

NIH is in a strategic position to rectify this deficiency and should therefore develop a structured, NIH-led venue that engages community, academic, federal agency and industry stakeholders in a holistic and comprehensive approach to advancing research. This structure should also serve as a platform for facilitating movement on shortcomings that are outside NIH's purview but which gravely impact the community and represent critical barriers for growth.

In addition to establishing such a venue, there is a need for NIH to leverage its position and capital in pressing for restoration of CFSAC by HHS in order to reestablish a space for all cross-agency and community partnership, and resume the critical work that was underway in CFSAC subcommittees. This trans-agency mechanism, which included participation by multiple Health and Human Services, the VA, DOD, Social Security Administration, and the Department of Education, is essential to fully informing a broader federal strategy to address ME needs, and NIH is a critical player in this approach.

MOST COMPELLING SCIENTIFIC OPPORTUNITIES

The above issues are primarily focused on the initiatives needed to address the challenges and

barriers. In parallel, there are compelling scientific opportunities that are immediately actionable and could make a big difference for the field if funding and researchers were in place. To seize these scientific opportunities and simultaneously grow the workforce, RFAs could be issued immediately to pursue these domains. We don't need to wait for the CRC and intramural studies to deliver findings to begin pursuing these opportunities. These scientific opportunities include:

Identification of objective sensitive and specific biomarker(s)

Analysis of disease-modifying treatment efficacy, symptomatic treatment efficacy, and exploratory intervention clinical trials

Characterization of spectrum of disease severity and associated features, development of standardized scale and terminology

Cross-sectional studies to understand subgroups, breadth of symptoms, spectrum of severity

Cross-sectional studies to define spectrum and prevalence of onset types, triggers

Exhaustive objective and subjective characterization of the pathophysiology underlying PEM (e.g. metabolites, cytokines, cellular composition, cardiopulmonary and metabolic dysfunction, etc.)

Development of in vitro models (e.g. serum transfer studies)

Characterization of metabolic dysfunction, mitochondrial function in energy metabolism and host defense

Measurement of of neuroinflammation, impaired functional connectivity, hypoperfusion, neurocognitive impairment

Characterization of autonomic, orthostatic and vascular dysfunction

Characterization of immunologic dysfunction (e.g. autoreactivities, immunodeficiencies, chronic inflammation)

WGS, GWAS to identify predisposing and symptom-associated risk variants, subset stratification

Analysis of the mechanisms of central and peripheral asthenia

Blood omics: cytokines, metabolomics, proteomics, transcriptomics, methylation profiles, exosome profiles, cellular integrity and function (e.g. NK cytotoxicity, RBC deformability, B cell maturity, T cell clonal expansion)

Measurement of functional impairment: CPET alternatives, orthostatic intolerance measures (e.g. NASA lean, cerebral hypoperfusion), activity meters, survey instrumentation

Additional CRCs to improve research domain diversity, accelerate progress

Development of disease-specific instrumentation, subjective and objective assessment methods,

outcome measures

Diagnostic instrument development and validation (for clinical and research use)

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 hormonal change (e.g. pregnancy, menopause, HRT, puberty) on disease status

(1) Identification of a trauma/toxin subset
(2) New diagnostic tools commercially available and/or suited for low-resource settings
(3) Documentation of potential for preventive medicine
(4) Groundwork for precision medicine and/or pathogen identification

From the perspective of extensive experience at the federal policy level, including a stint at HHS, I agree with MEAction's many specific concerns about the NIH record on ME/CFS.

The sustained discrepancy between disease burden and federal investment is a powerful indictment. Without conceding any ground on that point, I hope to see NIH spend in ways that create robust enabling conditions for patients to solve niche problems on their own and aggressively innovate, to help stretch scarce resources however possible.

My top priority by far is rich characterization of the Trauma/Toxin Subset, with gradual onset, which appears to be uniformly disqualified by the NIH intramural study and by all pre-screening I have undergone for ME/CFS studies at Stanford.

By "toxin" I mean to include both (a) environmental toxins and (b) weaponized toxins, which are increasingly hazardous for military veterans, foreign service officers, and far more civilians than ME researchers currently assume (explosive growth in nonconsensual experimentation post-9/11 will be reflected in data sets of sufficient heterogeneity and size, possibly presenting an analytical puzzle).

Given the ignoble history of branding ME/CFS "psychosomatic," trauma must be precisely defined. "Trauma" in this usage refers to a physiological disease process induced by psychic trauma that is chronic, severe, and sufficiently complex to require distinction from PTSD in the WHO ICD-11 by the prefix "C-" PTSD. Rooted in mouse studies of "repeated social defeat stress," the symptom cascade is understood to follow from high levels of oxidative stress and neuroinflammation, especially affecting the brain.

Echoing numerous entries in PubMed that describe how bodies respond to severe stress over time, NASA's just-published Twins Study predictably found hyper-activation of the immune system and epigenetic change in the body subjected to the stress of space travel.

To my knowledge, the 2017 Harvard study published in Arthritis and Rheumatology is the first and largest longitudinal study "examining whether trauma exposure and PTSD are associated with increased risk of incident [autoimmune disease – in this study, lupus] in a civilian cohort." If we do not

construe Harvard to be suggesting in this context that lupus is psychosomatic, neither should we construe trauma-induced ME/CFS as anything besides autoimmune disease with a distinct etiology and, perhaps, a unique molecular profile.

Innovations like surveillance technology and outsourcing to security contractors have elevated "plausible deniability" to an art form. As traditional physical evidence of abuse becomes nearly impossible to collect (per no less an authority than the U.S. Senate's senior investigator for Iran-Contra), modern human rights adjudication will hinge critically on our ability to identify distinctive markers of trauma, at the most microscopic level.

As a survivor of treatment meeting the legal definition of torture, I have learned to be thankful for illness because sickness means the body doesn't lie, even when perpetrators and enablers do. The body doesn't lie, but it doesn't exactly cough up all its secrets either. I stand somewhere in the middle, trying to speed along the translation.

More immediately, I worry about the reliability of drug trials that fail to define patient subsets better than we currently do. My greatest fear for Cortene is excessive reliance on the viral cases, disproportionately represented, to prove the efficacy of the drug in the narrow window before capital runs dry.

We need to know as soon as possible whether there is a meaningful difference between viral patients who stay stick after an initial short-term assault because they are somehow biologically primed not to recover … and patients whose bodies slowly break over time because external assaults keep coming, stretched to extremities no human body can withstand indefinitely.

Because we have no adequate data, I can offer only my gut instinct that complex trauma cases are less likely to involve genetic predispositions found in family history, multiple comorbidities (including rare diseases), neuro-structural issues, and the complications of many concomitant medications. Trauma cases, well-chosen, may therefore be better suited to expose an underlying mechanism common to all ME/CFS … or more likely to respond powerfully to drugs (as I do, to high-dose B-12)?

The pressing need to establish biobank holdings unique to Trauma/Toxin ME/CFS was one of my prime motivations for building a new institution in Houston. I am not averse to someday housing our subset within the one master ME/CFS repository MEAction proposes. But I am not willing to wait, and I believe the project requires somewhat arcane know-how.

I would like NIH to support cooperation across the CRC's and other grantees to help us cull trauma-induced cases from existing data, hopefully, with sufficient demographic information to support geographic mapping in search of new patterns (e.g., proximity to military bases or research universities with major DOD funding).

I intend to apply for the Stanford Medicine X ePatient Scholar program this year, to develop more skills and channels for cross-site data-sharing. (In addition to the CRC, Stanford is also home to the new head of the federal Research Advisory Committee on Gulf War Illness, with whom I have already met, and the Nolan Lab, which I am told (?) has historical data to support a longitudinal study of victims exposed to novel weapons that induce disease.)

Based on experience, I believe even the best data sharing will offer limited returns for our subtype

because a large majority of prime trauma cases do not and will not have an ME/CFS diagnosis without our most proactive intervention. (This is a point different, but related to admonitions sounded by […] re. the underrepresentation of African-Americans in existing ME/CFS data.)

To illustrate the paradigm shift underway in human rights adjudication – seismic enough to unleash creative energies affecting multiple fields – I like to explain that Simon Wiesenthal was a Nazi hunter, and we have to be "victim hunters."

I have spent the last few years developing multiple strategies to hunt for victims, including but not limited to unlabeled cases of ME. We have in our reach an embryonic design for a wearable diagnostic tool that continuously monitors relevant indicators (sending data to the cloud, in real time) and is suitable for low-resource settings.

Continuous monitoring is important to capture PEM, but also the strategic deployment and withholding of weapons capable of inducing a natural disease ("withholding" to evade the documentation required for legal penalty, reparations, etc.). This is the type of cross-discipline synergy I would like to exploit more, to wring added value for ME/CFS from funds not typically "in our lane" (though note that this type of money should be administered by major academic institutions only, not a patient-led NGO, to ensure political controversy is sanitized well before it reaches the ME door).

We need more than one new diagnostic tool, and I do imagine that ultimate refinement and perhaps marketability will depend on NIH-sponsored research collaboration.

For me, inadequate diagnostics posed a much more significant barrier than disease stigma. I diagnosed my own CFS and referred myself to Dr. Rey because, in the entire Texas Medical Center, billed as the "world's largest life sciences destination," no expert ever collected a single relevant data point from a wildly expensive battery of diagnostic tests. And I could not make up the difference by doing my own research in PubMed.

The most fascinating revelations to me at the recent NIH conference were the presentations by Dr. Systrom and Dr. Oaklander that explained precisely how the overnight harness, the stress test, and the electrodiagnostics failed. ME is like the medical equivalent of the perfect crime, even in a major hospital system boasting slick machines.

I am interested in working on two distinct parts of the broader challenge: (1) accommodation for indigent patients, as mentioned above, but also (2) diagnostics required to support prevention hypotheses that may be unique to the trauma cohort. Houston is unusually blessed with Global Health leaders at Baylor College of Medicine and Rice University (including a MacArthur Fellow) who create a dazzling parade of budget bioengineering, ripe for adaptation.

Based on personal experience and life shoulder-to-shoulder in a conflict zone, I believe prophylactic use of antioxidants or a product like Cortene could be infinitely more powerful than improved nutrition to reduce "minority health disparities." But it will be difficult to finance the next phase of R&D for a prospective pharmaceutical we have idling in a lab, without better data to predict preventive power and model associated cost savings.

To collect that data, I am nearly certain we require specific diagnostic innovation that will not follow

organically from the master list of recommendations in the MEAction Response.

I also find MEAction silent on the possibilities of precision medicine and exact pathogen identification Dr. Peterson brought to the recent NIH conference. These are issues of possibly unique (legal) importance to the trauma field – by which you should read, "possible triggers for outside investment by large foundations not interested in ME/CFS per se."

Echoing MEAction's call for additional "diversity of research domains," I would like to work collaboratively to lay the groundwork for a new CRC dedicated to the trauma subtype, with a centralized registry portal for qualified patients and specialized strategies to engage community-based clinics in broader studies. This is a partial, but not sufficient, strategy to increase minority representation in clinical data, biobanks, published research studies, etc.

The most compelling ME/CFS research need is a commitment for sustained investment of $200 million annually from NIH.

Surveying the literature on ME/CFS calls to mind the proverbial group of blind men happening on an elephant: one reaches out and touches what feels like a tree trunk. Another, the broad side of a very large cow, somehow already tanned for leather. Two more find dangling snakes but one is more than double the size of the other. A fifth blind man doesn't find an animal at all, but rather a long piece of smoothed rock, like a curved spear.

Colloquially this metaphor is sometimes used as a criticism--since no one person immediately succeeds in grasping the whole--but in the case of a multi-systemic disease like ME/CFS, it's a portrait of highly promising findings that will add up to more than the sum of their parts if only NIH would commit the funding necessary to grow their reach. Each of these blind men learned an essential piece of what makes up the elephant. And as their research has expanded, parts of the elephant begin to connect up. Immune research begins to speak to neuroinflammation begins to speak to brain stem, neck and spine research. How many more pieces would we have already added to the puzzle if we pursued promising research pathways? Too many lay fallow as we are told there is nothing ripe enough to pursue.

This claim that NIH lacks for anything worth investing in is a very strange thing to hear for anyone who has paid attention to NIH's own model of pursuing Collaborative Research Centers (CRCs): it's plain to see how much promising work such focused ME/CFS research hubs can generate. For instance, if one examines activity at Stanford, it's striking how many of Ron Davis's colleagues in adjacent fields have joined the field of ME/CFS research in the span of just a few years: the center is attracting serious scientific interest. Yet the current NIH funding level is so meager, Stanford's growth as an ME/CFS research center has principally depended on grants from small foundations, which in turn are often underwritten by donations from patients themselves--75% of whom are too ill to work. This situation is frankly shameful on a moral level; and a massive research institution like NIH also knows perfectly well that it is no way to drive science forward. A handful of very senior (and self-sacrificing) investigators may personally be able to afford leaving reliably grant-making areas of research to take on projects out of sheer humanitarian urgency, but we all know perfectly well they cannot build the field this way. Mid-career scientists risk their livelihoods if they turn their lab toward a field NIH publicly characterizes in word and deed as undeserving of funding. And even before you consider career prospects, it's simply not possible to bring graduate students into a lab if there's no funding to pay their stipends. These problems have starved science on ME/CFS for more than three decades, while millions of patients' lives have slipped away. And without training subsequent generations of

scientists, the next generation of patients faces the possibility the state of the field will get even worse: the senior researchers in the field, many of whom are also the only ME/CFS clinicians in the nation, will not be with us forever.

But NIH has the power to turn this around for me and millions of other Americans. Increase funding for ME/CFS at least tenfold, including (but not limited to) with significant and sustained increases in funding at existing CRCs, the establishment of new ones (Harvard, Stanford, DePaul, the University of Alabama are all equipped for significant investment), and the creation of an ongoing ME/CFS research base with dedicated hiring lines housed at one of the permanent NIH Institutes or Centers. When the components of the elephant are so diverse and touch so many areas of biomedical science, it is inexplicable that NIH--already home to leading scientists in nearly every imaginable field, as well as the foremost technology--has established no institutional home to bring its breadth of scientific perspectives together to investigate ME/CFS--both to advance the field and take the lessons from it back out to the many other diseases ME/CFS clearly has implications for. With nearby specialists like Peter Rowe at Hopkins and James Baruniak at Georgetown, Bethesda is a natural center for this work. It is also a structurally necessary one. It is clear that as long as NIH does not have an in-house constituency facing the daily realities of the disease and the severe deficits in research support for it, the external ME/CFS field--patients, caregivers and researchers alike--will continue to spend our time and money begging for NIH's time and money, when the energy of all involved should all be focused on health and scientific progress. NIH must stop being a drag on the field and start leading it, with a commitment to fund ME/CFS commensurately with disease burden: aiming for $200 million annually.

[…]

Facilitation of a ME Mapping Project is an urgent need. Recent research findings, as well as the NIH CRS provide new opportunities to bring clarity to the field. However, unless a parallel effort is begun with the aim of systematically and far more precisely mapping the symptoms and symptom presentation dynamics, confounding of cohorts and inefficient testing and survey methods will continue to obstruct both research efforts and optimal clinical care.

I strongly urge a parallel effort which might be termed the “Mapping Project.” A core component would be to create a series of master survey instruments which could be used to compile the databases essential to the more precise delineation of the illness and its etiological and physiopathological attributes. The Mapping Project would necessarily involve a collaborative stakeholder approach involving and facilitating more substantial input by the patient community and those involved in public policy in a systematized way. I stress the word “systemized” because many previous governmental efforts have sought and achieved important and useful broad stakeholder input, but not in a manner that enables contribution to the state of the science with the requisite level of precision. Recent NINDS (and previous CFSAC) invitations for stakeholder input represent examples of strong outreach. However these and other initiatives do not allow for input in a clear, comprehensive and systematized manner.

I am an ME patient and too sick to fill these boxes out, but I am very much interested in good research and believe the NIH can make all the difference!

I wish I knew. The research is all over the place. When I review any research that is happening or reported, I am amazed that there is no focus. Why has research into retroviruses in ME/CFS no longer being done? I just reviewed the XMRV fiasco and the drama that followed and wonder whether Dr. Mikovits was actually on the right path. I tested positive for XMRV; has the lab test been totally

discredited? How were there negative results if there was lab contamination? Would not XMRV be a biomarker for a certain subset of patients? I do not believe the focus should be on one biomarker for all sufferers of ME/CFS. The focus should be on the whole body abnormalities and how to treat the discrete abnormalites. Gene therapy for SNPs. Treatment for high levels of inflammation.
Remission in pregnancy. I had complete pain relief and ME remission throughout both pregnancies. How can we replicate this? Electromagnotherapy and hyperbaric oxygen therapy seem to have helped ME/CFS and Fibromyalgia. More studies need to be done into these treatments in relation to oxygenation and stiff haemoglobin found in patients with ME/CFS etc .
To diagnose with a real diagnosis of exclusion, do a cpet obligation if possible, keep us enough hours and days tosee us compketely and finally received the disability report that you need for decently surviving and be able to rest adequately for have the most benefit of some minute or hours of peace, less pain and enough energy for eat , wash teeth more regular and rest. Its important. We dont received a diagnosis of exclusion and we are in between and lost all. We need to be recognised decently, we are very sick and this illness is not an illnessof 08h00 to 16h00 office hours. We need good doctors . If we have that correctly, we will not need lawyer!