

Strategies for overcoming scientific challenges or barriers to progress in ME/CFS research

Since most physicians and public at large do not believe the illness is crippling and "real", the illness must be taught at medical schools and more ways to get the information out to the public is needed. Only then, will researchers possibly be interested in using their research skills and time on ME/CFS. I think if researchers knew the extent of the suffering of severely affected patients they would be interested.

NIH needs to take the lead and undo 30+ years of negligence by issuing RFAs for ME/CFS. The amount of funding ME should be getting annually, to be commensurate with disease burden, is \$200 million. Currently, we're getting a drop in the bucket. Please see the following study:
<https://www.oatext.com/Estimating-the-disease-burden-of-MECFS-in-the-United-States-and-its-relation-to-research-funding.php> #Article

ME/CFS could be one label for several different illnesses with similar symptoms. Many of the existing studies could then be severely underpowered. Large studies that attempt to identify any such subgroups could overcome this problem.

Better defining. Things need to be more clearly defined. WHO codes need to be used more. Currently the CDC website is a mess.

Loads of conditions lead to Chronic Fatigue.

That is not the same as an enterovirus attacking the central nervous system leading to brainstem encephalitis or encephalomyelitis.

The biggest barrier is the paradigm of it being a psychological illness that prevails - the research needs to provide more EVIDENCE based biomedical research that is more compelling than the (often discredited) psychological/behavioural studies.

The research needs to be joined up - not carried out in isolation. Researchers are finding some similar things and these should then inform the future direction of research - rather than individual studies getting lost along the way.

Increasing pharmaceutical interest in the illness.

NIH being a leader for taking this serious. I see Francis Collins posting on Twitter frequently about ALS/MS/auto-immune diseases/cancer, yet I never see mentioning of ME/CFS. Public perception is power. I'm of the belief that it can only help researchers apply when they feel there is NIH support and backing.

Funding. Funding for clinical trials and research.

There needs to be more collaboration between ME researchers and other specialty disease research. There is symptom overlap with those who suffer from Ehlers-Danlos Syndrome, POTS, disautonomia, and other diseases. Maybe there is a connection? We need more collaboration to find out. We also need to stop describing every complicated illness as a mental health issue. This is not helpful and actively causes harm.

Create one or more ME/CFS clinics at major medical school/research institution. The Harvard system already conducts NIH sponsored research and has been designated a Center for Excellence. Columbia Presbyterian Medical Center in New York City conducts NIH sponsored research, for example. . Epidemiologic studies predict about 90,000 individuals with ME/CFS in NYC and double that number in the metro area but there is less than a handful of evidence-based clinicians who understand ME here. At Stanford University an impressive privately financed research center is beginning to change the basic understanding of ME. A clinic at a major academic research center guarantees access to a pool of talented researchers with the opportunity to recruit young researchers to the field through jobs and campus based lectures, and Grand Rounds. The clinics would provide volunteer patient recruits for any research and eventually a data base of tissue or blood samples for researchers anywhere.

An ME/CFS clinic would be financially self sustaining and quickly recover any start-up capital costs. Patients would begin to sing the praises of the NIH and have improved quality of life due to skilled medical care. The Bateman Clinic in Utah provides a model and can show the way. [...]

1. Set aside \$\$ and targeted RFA
2. Accessible database
3. Names of people at NIH with whom to connect.

A major challenge is the lack of recognition that many/most patients are doing too much and need to rest more to stabilise/improve. The physiological data is needed to quantify the inordinate amount of rest needed and to make the disease visible. Once visible and measurable research money is more likely to follow. Exercise intolerance is the cardinal symptom of ME/CFS and research into this aspect is woeful as it is within a silo it needs to be carried out in conjunction with experts in abnormal physiological responses to exertion as seen in over training syndrome. However, it is more complicated as cognitive, emotional and exposure to chemicals also affect the physiology .

Stop the stigma that ME/CFS is psychosomatic. Educate doctors that it's a neuro-immune disease with dysfunction in the immune, neuro, endocrine, metabolic systems. Educate doctors on the primary symptom, post-exertional malaise, and stress early intervention of rest and to never push beyond energy capacity.

The first bacterial discovery in bacterial infectious diseases and antibiotics were developed and treated. CFS / ME / ADHD / Mental disorder, etc. Appear to be caused by the interruption of electrical commands that control our body. In other words, it can not be solved by the treatment of existing diseases or researchers.

Just as a microscope has found a new machine and discovered bacteria, CFS / ME can now be found by superpowers because of the interruption of electrical commands flowing through our bodies. Causes of CFS / ME include electromagnetic waves, static electricity, negative charges, bacterial metabolites, viral metabolites, inorganic ions, accident induce molecules, stress induced molecules, toxic braids, toxic underwear and toxic glass

Mixing CFS & ME together and/or accepting MUS or SEID

It is important to be honest about psychological factors and stress affecting ME/CFS, rather than downplaying it. Most patients are open to psychological factors and stress affecting their illness, and downplaying it (as some advocates are trying to do) will just hurt patients. As long as the science is presented in an open and honest manner, there should be no reason for anyone to disagree.

Meeting with doctors and learning from them, Above who treat similiar/coexisting illnesses such as Lyme Literate MDs (Post treatment Lyme Disease), Tick Born Diseases. Integrative Medicine doctors who are more knowledgable about this illness, and specialize in it. They have a different battery of tests. Mast Cell Activation doctors such as Dr. Afrin.

Dr. Shoemaker and mold toxins, and how it relates to this disease.(Shoemaker Protocol) Physicians who specialize in CIRS.*Chronic Inflammatory Response Syndrome. Along with mainstream docs such as genetecists, neurologists, immunologists, etc

- 1) Lack of understanding that this needs funded and studied.
- 2) The numbers of us are growing.
- 3) Please grow the number of physicians that can track the data, good data.

Educate every medical practitioner about ME/CFS.

The NIH MUST take this disease seriously and put up dedicated funding. The community can not continue to have the funding given based on donations from the different institutes with in NIH. That is not sustainable. The NIH must collaborate with our scientists in the field---are you reaching out to HIV scientists to see if they have ideas on how to tackle this, PANS scientists, etc. We should not be working in silos. This is a multi-system disease and many people with ME have severely damaged immune systems that could benefit from other immune system related diseases.

Convincing of the need for funding to research various aspects of the whole body illness.

Need a PSA dispelling myths about ME to medical community and incentivize continuing medical education credits to get patients diagnosed so that they can participate in studies and so that medical students will be taught and go into researching ME.

The biggest barrier to progress in this disease is the medical community's refusal to accept it as a disease at all. Education of PCPs and the greater medical community to recognize this devastating disease as something other than a psychological disorder would be key to establishing the will to find relief for these patients.

Public health authorities should be open to discussion on monkey cytomegalovirus contamination of some of the licensed polio vaccines. They should be willing to confirm the published findings by culturing viruses from at least a few patients and/or study the SCMV-derived stealth adapted virus, which is deposited with the American Type Culture Collection (ATCC). They should also acknowledge the bigger issue of stealth adaptation as an immune evasion mechanism. Acknowledging the existence of stealth adapted viruses will raise national interest in the ACE pathway as a non-immunological anti-virus defense mechanism, applicable to both conventional and stealth adapted viruses. Acknowledging the existence of stealth adapted viruses will also lead to progress in other neuropsychiatric illnesses

Appropriately adjust the pay line for ME/CFS proposals to increase funded projects.

Disseminate as much research and facts of ME to both doctors and patients, to increase the patient's support systems. Friends and family unfortunately believe a doctor over their own family member - so when the doctor is wrong - the suffering of ME is made 10 times worse.

(1) share research both nationally and internationally; (2) talk to current researchers and those actively seeing ME/CFS patients (Dr. Klimas, others)

Funding is key. The other thing besides more funding, is specifically drawing from related fields that are developing drugs for related conditions -like for example drugs being developed for mitochondrial myopathy like ss-31, and testing them in ME/CFS patients, fast tracking any drugs that look promising because we have no drugs. Efficacy has to be weighed against risk, for example and weighed against the difficulty of selecting a subset of people that the drug will work for but most importantly weighed against the fact that there are no drugs for this devastating disease. So approving amplitgen on a non-experimental basis, since it has a lot of benefit for some, and little risk, is a huge priority.

-Collaborate with the community, and the general public who have been touched by these illnesses, ask them for ideas, visit ill people in their homes....otherwise how can you access the full picture? not everyone seeks doctors, not everyone is on the computer, not everyone can be bothered to reach out.

-use more creative people not just scientists!, this illness requires a wider approach and more creativity (I am an artist who was awarded a NASA grant and performed and flew on the KC135), I could see how scientific research is clumsy, is failing and could do a lot better if they just let more artists/creative thinkers into the pot. We are no longer painters and sculptors, we have gone way beyond that now.

-get into the streets of the communities that you are serving, talk to everyone, not just medical people.

-the main barriers to furthering this research are the GPs, it took me 2/3 years to get a diagnosis, I had seen about 10 GP doctors and 10 specialists, how can this problem be seen in its real light if most of the people who are in fact ill are told that to go home and that its all in their heads? If the real number of ill people can come out in the open (meaning that GPs assess how many of their patients have ME/CFS, it would be taken more seriously because it will show that it is an epidemic.

TRAIN GPS!

ATTENTION! FUNDING! MONEY! ATTENTION!

I have had CFS for 36 years. I am financially able to donate to research that has the possibility of applying to me. Let's say a researcher is working on the prevalence of certain cytokine patterns or metabolomic patterns in people with CFS. I would like to pay to have testing done on myself and if in fact my lab work is consistent with what the researchers are finding, I would want to donate money toward that research because there is a chance that it will help me. I believe there are many other people who have money to donate, and would be more likely to do so if they believe the research has a possibility of helping them. And with people paying to have their own testing done, you would have larger sample sizes and research could be trashed sooner if it appears to not be on the right track, or it could be given the go ahead.

1. NIH to keep an up to date list of all worldwide research projects, and make all universities aware of a yearly Thinking the Future event.

Better communication of biomedical basis evidence to combat scepticism and stimulate interest

Move the discussion past the psychosocial model by definitive differentiation from depressive illness

International standardisation of case definitions and sub styles.

Work with viral meningitis charities to observe patients over time see who develops it who doesn't.

Get past reductionism and Create a new consultant specialist disciplinary home that champions ME that isn't neurology as they are so horribly sceptical. Perhaps neuro-immune or virology after effects?

Better interdisciplinary collaborative research eg I just read about a research for a biomarker for fibromyalgia, but they did not involve a M. E. CFS group just other rheumatic conditions.

A new name when the time is right to remove the toxic history and make it be an attractive area to research

Unify the various agencies within the government who are researching ME.

If that isn't possible, than improve communication between the various agencies researching ME.

Collaborate with skilled Chinese acupuncturists especially those trained abroad - they can diagnose it in 1 session & often start treatment of this chronic disease with a strong brew of herbs (if those cannot be tolerated, weekly long term acupuncture is next). [...] in Seattle WA was my diagnostician. Weekly targeted treatment was done on Vashon Island WA by [...] as I was too weak to commute to Seattle (bedridden 23 hours a day, barely able to swallow, digest or rest when I staggered into her office).

Escucha y líneas biológicas claras

A proactive, accurate and concerted effort to educate researchers, the public and doctors about the realities of the illness, it's prevalence, it's debilitating impact and the lack of effective treatments would encourage more to enter the field.

It needs to be led proactively by the NIH, not just waiting for grant applications to come forward. You need to actively reach out, advertise, educate and incentives people to enter this field. Tell them it's a fascinating field with potential for groundbreaking scientific advances, multidisciplinary work, international collaboration, the opportunity to make a really important difference to the world, and most importantly that the NIH will be generous in finding research grant applications - at least on an equal basis to other diseases of similar prevalence and burden. Many researchers and clinicians don't know about ME/CFS or what they think they know is incorrect (myths) that put them off being interested in the field. So the NIH needs to reach out and educate research to get them interested.

- Researchers addressing ME/CFS from different perspectives sharing information - open data.

Because ME/CFS is so complex and affects so many body systems, it is important for researchers and clinicians to have multiple opportunities for open exchanges regarding the most recent research findings

- Increasing general awareness about ME/CFS and opportunities for new researchers go get involved. Although this a highly complex disease, precisely because so little is known about the etiology and treatment of ME/CFS, research in this area is ripe for huge discoveries

- Continuing the NIH ME/CFS conference each year and having it be available online

- Creating a taskforce that oversees issues related to this question and that can make recommendations and oversee accountability

Honestly after 37 years of the misery of this illness I don't have any hope that the NIH or CDC will ever do anything honest.

Educating medical providers, researchers and the general public on the biomedical origins of ME

Negative medical impression that ME/ CFS is psychosomatic needs to change; negative medical establishment impression that sufferers are ' fat, hysterical females' also needs to change - the age of paternalistic medicine should have ended and so should misogynistic medicine

Encourage global uniform data collection and analysis- then develop and pursue hypothesis from that data. But the biggest obstacle for patients and progress in research is the lack of a sustained and profound effort towards clinician education. Like the saying "If you build it they will come." I believe there are thousands of primary care doctors, specialists, and nurses who would participate in organized data gathering and provide anecdotal patient stories for researchers - if they were MADE to understand the prolific nature and enormous burden of this disease and it's various pathophysiologies.

- Entice researchers from an array of backgrounds during their educational training; for example, include medical sociology students as well as medical students. Circular thinking by a group of likeminded, similarly trained individuals limits the creativity and problem -solving abilities of a group.
- Create outreach programs similar to those already in place for illnesses such as Tourette Syndrome. Education of patients and doctors leads to an increase in advocacy; increased advocacy will lead to increased awareness, which in turn will propel funding.

Finalize the one set of criteria that all researchers must use: IOM/NAM, or ICC.

The research teams need more money to hire and retain scientists, to invent, to experiment, to study the patient population.

There needs to be more monetary incentive to get more researchers involved, new talent and there is a need for cross collaboration among specialties

There needs to be less stigma surrounding the disease.

We need hope so need more transparency. We want to see the research as it unfolds

There needs to be more government interest and support in finding the cure. There needs to be a bigger and better campaign to get the public involved

This needs to be seen as a health crisis just like AIDS was and given emergency attention. The government needs to invest big now, also increase funding through philanthropy

More neurologists and radiologists need to get involved since the brain is obviously affected

More hematologists need to get involved because mast cell disorders are a comorbidity: this also affected the brain and blood and organs

More doctors who look at the vein networks need to get involved because we all have flare ups and awful orthostatic intolerance. We can't walk upright or even sit upright at times because we have an enormous amount of pressure and pain that builds up in our heads. We get trapped in our beds for long periods of time, sometimes indefinitely

All GPs need a diagnostic flow chart. Every single GP has been clueless or worse. I've had to discover test after test I should have had. With more people diagnosed comes more awareness and funding.

- .1 provide incentives to bring new researchers into the field
2. fund research at at least \$250 million/yr - it's been 50 yrs of neglect. Too many have died. Too many lives wasted.
3. Fund center like Ron Davis significantly over at least 5 yrs so that he can hire permanent staff
4. Include travel/accomodation/ etc pay to safely get patients to research studies in research funding

Involve patients more in planning research there are many scientists and doctors with ME who would be able to offer relevant observations about potential research avenues

- more funding
- overcoming psychosomatic lobbyism
- look out for subgroups for more accurate results
- better education in med schools. Young scientists now, take serious and have an interest in the disease.
- more accurate diagnostic criteria for studies (ICC)
- a way for severe patients to get in touch to provide research samples and participate in clinical studies.
- An international network of medical professionals assisting the collection of (blood?) samples.

Coalition, multi-focal (especially post exertion genetic-immuno-metabolic studies) collaboration with best Researchers, Doctors, Labs, technology and patients. Listen to patients and their symptoms. Each and every symptom needs to be noted properly and acted upon.

Overcoming the long-held view that the disease is psychogenic and/or imagined. Understandably, researchers do not want to be associated with hocus-pocus.

Greater biomedical funding

Better access to biomedical research facilities

Use of strict ME criteria to avoid researching those with fatigue from other unidentified illnesses and idiopathic chronic fatigue

CDC to make clear statement on scientific reasons for dropping GET & CBT instead of pretending to be "misunderstood"

Autopsy-based research for those who die of the illness or die with the illness

Money for training in Chronic Fatigue such as K01 awards, R01 Awards, and R21 Awards.

EDUCATION, EDUCATION, EDUCATION.

Re-read ALL our suggestions from your 2016 RFI - many, if not most, were excellent.

We are stuck on the whole GET/CBT debate and biopsychosocial views due to a lack of physiological research into pacing and how to do it right.

Growing the open collaborative efforts that are emerging & marketing the area as the exciting opportunity to solve ME & likely discover the keys to many other illnesses in the process. The Emerging medicine has high potential. Awareness campaigns of the true impact of this illness & economic impact. Endeavour to find realistic numbers for patients suffering from ME and CFS to determine economic impact. Prevalence is likely much higher than current figures suggest.

Reproduce results of valid clinical trials - the trials are often so small that they are not taken seriously.

Work with findings already thoroughly established to have a connection - like orthostatic intolerance and low blood volume - and follow these to the metabolic and cellular level, hoping to find the root cause.

Focus on making the disease "visible" by quantifying and measuring level of disability. Focus on the low hanging fruit and lifestyle changes that yield immediate benefits. Heart rate pacing etc... that is known to be effective by clinicians and patients using it

<https://www.youtube.com/watch?v=yKoheNZlqXg> .

Be open to why alternative treatments help patients.

NIH fair funding for ME based on DALYs, disease burden is about \$200M/yr. NIH need to end decades of gross discrimination against women and M.E.

Ref: <https://oatext.com/Estimating-the-disease-burden-of-MECFS-in-the-United-States-and-its-relation-to-research-funding.php>

-Funding

- Accesses to monetary resources

-\$

-moolah

-the big bucks

-greenbacks

-m o n e y

-really though, funding so scientists can generate and execute these strategies

<p>Getting cfids validated as a real biological disorder by the medical community</p> <p>May open acceptance and funding for studies.</p>
<p>Educationing doctors about the difference between Post-exertional malaise and the ICD code for “general malaise”; doctors understanding how to validate patients with ME/CFS given the stigma associated with it and it’s trivializing name of CFS</p>
<p>Universal diagnostic criteria: get consensus from all researchers currently in the field. Recognize the results of small studies that have already been done. Let all concerned know about this recognition.</p>
<p>I think a full marketing plan of ways to reach various audiences would be helpful to expand research pool and results sharing.</p>
<p>"Funding and collaboration among the scientists."</p>
<p>Education, you are doing good. Educating doctors in medical school about it and also it be made a course that existing docs have to take for certification.</p>
<p>The medical community and applicable government agencies need to work together to define a plan. That requires transparent communication and access to research and studies by all. The fastest way to incite a united fight for answers is public awareness. I don’t have anyone in my network of family & friends that understand what ME/CFS is and I have been living with it since 2014. If people living with ME/CFS had a platform to share their stories (to put it in perspective, I am not just a 44 year old female with ME/CFS but am a wife, daughter, mother, sister, aunt, coworker etc...) in a relatable way that can help bring awareness then the voice of the people demanding answers may finally grow loud enough to bring change.</p>
<p>The biggest barriers are :</p> <ol style="list-style-type: none"> 1. Ignorance within clinical practice due to a generation of physicians trained on egregiously outdated textbooks by uninformed professors in medical universities when it comes to ME/CFS, which continues to dismiss the disease as being a Psychosomatic one therefore closing the door to curiosity and pursuit of the bona fide issues. 2. Understandable, yet concerted resistance from vaccine makers, insurance underwriters, and other partisan-influenced government agencies that inadvertently impedes impartial inquiry that may implicate current immunization methods and therefore create a public health hazard, but is nonetheless the onus to surmount by venerable agencies like NIH 3. Ethical regulatory barriers to more controversial but necessary research in the West <p>The best strategies are therefore :</p> <ul style="list-style-type: none"> A- advocacy with core curriculum and CME publishers and events on medical campuses B- open private funding of research from non-industry sources C- the stimulus and outsourcing of research to places like Japan, Korea, the United Arab Emirates, etc that have more relaxed regulations on cutting-edge research away from the politicized debates in the

US/Europe allowing research to thrive there if invested in - but that are friendly to the U.S. and share data openly in the spirit of human progress

Severe lack of funding, lack of NIH to direct new scientists to the field and for making ME/CFS a priority target.

Stop funding peripheral cytokines studies

Treatment with activated T-cells against herpesviruses

It is understandable that the medical professionals doing research contribute information that stems from their understanding of the field they specialize in. More effort should go into working in groups with diverse specialties to test their various hypotheses. Databases that capture information are helpful, but face to face group discussions are also necessary.

I firmly believe that without identifying the source of the illness, it will be impossible to truly overcome barriers.

A massive increase in funding for research and drug trials is required. Drug or treatment trials should be the priority for research funding.

Increased funding.

Money, and public education. Strikingly at the recent NIH "Accelerating Research in ME/CFS" meeting, researchers attending were either in the later stage of the career, or in the early stage - this indicates that for the period of time when ME/CFS was psychologised, biomedical researchers were deterred from entering the field, as they could see that there were easier routes to earn a living, routes where research funding was available and they would be welcomed into the field. This resulted in inertia in the field, this has started to move again, mainly due to the patients, now NIH need to add considerably to the momentum.

Training and retraining physicians, healthcare providers, scientists, psychologists, psychiatrists, school personnel, and the general public about ME/CFS so this disease can be taken more seriously, and more people inflicted help. Creating clinical trials that can include bedbound and the homebound with ME/CFS, may include much needed help from the caregivers.

THINK OUTSIDE THE BOX AND DO NOT CONDUCT RESEARCH WITH THE INTENT OF DEVELOPING A PHARMACEUTICAL DRUG AS A SOLUTION.

Data sharing between research centers.

We need many more Centers of Excellence funded, each comprised of experts in all medical specialties under which we might be categorized. We may need our own dedicated well-funded Home at the NIH - a Specialty that encompasses all other known Specialties.

More funding

Strict entry criteria for studies, PEM is an absolute must. The ICC is the most accurate diagnostic criteria for M. E.

Share the questions and knowledge.

Robust findings: replication, larger samples, and better controls

In 2015, a review report by the National Academy of Medicine identified more than 9000 scientific publications on ME/CFS. [1] Few of these, however, have produced robust findings. With the exception of psychosocial research, sample sizes rarely exceed 100 ME/CFS patients. Additionally, there is a lack of independent replication. Most findings in ME/CFS have not been replicated by other research teams, which makes the status and implication of such results uncertain. Intriguing findings such as an elevation of lactate levels in the brain [2], beneficial effects of carnitine on ME/CFS symptoms [3] or defunct endogenous pain inhibition after exercise [4] have received few attempts of independent replication with larger sample sizes.

Thirdly, ME/CFS research has mostly used healthy controls. This makes it easier to find significant results but cast doubt on the relevance of the findings. Ill persons differ in multiple ways from healthy persons, so that any biological difference might be due to a generic deterioration in health such as deconditioning, rather than ME/CFS. Differentiating ME/CFS from sedentary but healthy controls is usually not an issue in clinical or research settings, as it merely requires to ask the patient a few questions. There is however a pressing need for findings that are unique or characteristic of ME/CFS and help to differentiate it from related conditions such as fibromyalgia, multiple sclerosis or post-treatment Lyme disease syndrome. Such results would help to refine diagnostic criteria of ME/CFS and make patient samples less heterogeneous. Using controls with related conditions to ME/CFS instead of healthy controls might thus be another way to make research findings more robust.

I would, therefore, recommend a strategy to obtain more robust research findings by focusing on replication, larger sample sizes and the use of better controls.

References

[1] Institute of Medicine. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington, D.C.: The National Academies Press, 2015.

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[3] Plioplys AV, Plioplys S. Amantadine and L-carnitine treatment of Chronic Fatigue Syndrome. *Neuropsychobiology*. 1997;35(1):16-23.

[4] Van Oosterwijck J, Nijs J, Meeus M, Lefever I, Huybrechts L, Lambrecht L, et al. Pain inhibition and postexertional malaise in myalgic encephalomyelitis/chronic fatigue syndrome: an experimental study. *J Intern Med*. 2010 Sep;268(3):265-78.

1. Using analytical modeling and digital simulation approaches and to further characterize cellular behavior based on what is already know about biological behavior.

2. Focus more on current state of patient over what lead to the current state. The subsetting of patient groups based on prior data - e.g post infectious onset is important especially for statistical analysis. Illness and disability is based on the current state of the individual so a patient may have come to this state as a result of multiple causes such as viral infections, bacterial exposures, cancer treatments, etc.

The primary barriers as I see it are 1) lack of adequate collaboration amongst the funded researchers, 2) a reluctance to share preliminary data, as well as the lack of sharing results with patients, 2) in the case of the Bateman/JAX study, the study that I am participating in, has shockingly little phenotyping inquiry going on in between yearly visits. Nothing is being asked of us. We can contact Dr. B and inform her of what's going on if/when we need help but short of volunteering info they aren't requiring anything from us. I think this is a huge gap. I also think asking patients who are really sick to document symptoms with apps is way too much to ask them to do given their very low energy levels, 3) lack of \$ is a huge problem, 4) study design is preventing many patients from participating- that as well as their illness which can prevent them from traveling. I know someone who randomly went into a 12 year remission- all symptoms gone- he returned to normal-and wasn't pushing through. He got sick in the 80's and is reaching the age of exclusion for most studies, 60, but studying him would be fascinating, 5) studies that are focused on finding root causes- lack of energy and lack of restoration, 6) NIH should look seriously at results coming out of other countries and arguably propose collaborations or at least have Co-PIs in the US collecting US data as well as say Australian data. A coordinated international effort would be informative. Were all countries to offer their data into one repository so that computational biologist could data mine- we might thereby identify some leads or information to inform a solid strategy going forward. Finally, it is important to study the people who are bedridden and a strategy to go to them should be developed, despite the laboriousness required.

1. Researchers addressing ME from different perspectives should share information - open data.
2. Because ME is so complex and affects so many body systems, it is important for researchers and clinicians to have multiple opportunities for open exchanges regarding the most recent research findings. Formal and informal opportunities to allow for this should be provided. The recent conference at NIH was a good start and hopefully will be continued on a yearly basis. Incorporating clinical care into research centers of excellence, and allowing for a range of specialists from different areas of medicine, would be helpful.
3. Increasing general awareness about ME as well as funding opportunities for new researchers to get involved. Although this a highly complex disease, precisely because so little is known about the etiology and treatment of ME, research in this area is ripe for huge discoveries.
4. Continuing the NIH ME/CFS conference each year and continuing to make it available online
5. Creating a taskforce that specifically oversees issues related to this question and that can make recommendations and oversee accountability

Define the disease. Research into Myalgic encephalomyelitis should use the International Clinical Criteria 2011 which do not require a symptom of fatigue. They do require post-exertional exacerbation/crash/relapse. This is the distinguishing feature of ME and any research which does not require it is useless to ME sufferers.

Is research into cancer directed at cancer/CFS? Or MS at MS/CFS? etc. This is nonsense.

CFS is a separate disease. The CDC found that the Lake Tahoe epidemic was not ME, and it should therefore be researched separately.

Teaching more doctors and nurses that this disease is real. Our daughter was told many untrue things about herself on our journey to a diagnosis.

Educating of doctors and other health-care providers so that they will understand that this is real. It's horrible when a doctor tells a CFS patient that they need to exercise more and eat more broccoli (yes, this actually happened to me).

FUNDING!!! That way more researchers will come over to ME/CFS, right now nobody will because they need to be paid and have job stability for more than one research project!

More money is needed; more identification of sub-types; more collaboration between doctors who do try different treatments with patients.

Create a 10-year strategic plan which includes performance metrics. This will provide a sense that ME/CFS is not the Wild West, that field is organized, is populated by credible, serious researchers, has a direction and will be supported by the NIH.

Produce an RFA targeting the neuro-immune-energy production matrix in ME/CFS

Update the IOM report

Produce a new "IOM" report targeting gaps in research

Retire the most ineffective idea ever in ME/CFS - Trans-NIH Working Group - and move ME/CFS into NINDS

Continuing to highlight ME/CFS in Directors blogs and other publications that NIH researchers read

Emphasize that people with ME/CFS are burning to participate, are very thankful for research done on their behalf, and, instead of being problems, are probably the most appreciative study participants one could find - and have researchers attest to those facts. They simply want biological research done.

Offer financial incentives for new researchers to enter the field

It seems like we are still trying to overcome the stigma that ME/CFS is a psychological issue, rather than a medical issue. Finding a bio-marker would certainly help that.

Create a 10-year strategic plan which includes performance metrics. This will provide a sense that ME/CFS is not the Wild West, that field is organized, is populated by credible, serious researchers, has a direction and will be supported by the NIH.

Produce an RFA targeting the neuro-immune-energy production matrix in ME/CFS

Get over the diagnosis hump by producing an RFA or other funding mechanism that focuses on new diagnostics for ME/CFS such as the nanoneedle, microbiome, metabolomics, etc.

Update the IOM report

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Retire the most ineffective idea ever in ME/CFS -" Trans-NIH Working Group -" and move ME/CFS into NINDS

Continue to highlight ME/CFS in Directors blogs and other publications that NIH researchers read

Emphasize that people with ME/CFS are burning to participate, are very thankful for research done on their behalf, and, instead of being problems, are probably the most appreciative study participants one could find - and have researchers attest to those facts. They simply want biological research done.

More money has held back progress for the entire time I've been sick-well over a decade. Teach medical, dental and nursing students about ME so people can make an informed decision about research in the field.

We need dedicated and stable funding so that researchers feel safe committing to research.

Please do not give up on us !

More doctor interest. There are way too few doctors focused on treating this disease, and most of the patient base is being treated by physicians who have very little knowledge about, well, much of anything regarding ME/CFS. We are effectively being swept under the carpet, with very, very few treatment options and doctors who have no idea how to treat us because they don't know anything about our disease.

Just as an example, I'm a breast cancer survivor. I must have participated in at least five studies, because there always seems to be one going on, and I was always asked to be a part of them by my oncologists (and I always said yes!). ME/CFS patients would be more than happy to participate in any study available, but where are they? I feel that even one or two good studies that involved lots of doctors gathering information from their patients would help a lot. It seems like most of the reports I see about studies being done for this disease have a very small focus and small patient bases. There are so many variables to this disease that it seems studies with lots of patients would be more beneficial.

The fact that how people get it differs, and how symptoms can present across such a vast range of severity

Barrier: a lot of people incl doctors think it's a made-up and/or psychological disorder

Investing more money in the field
Use a symptom list that does not include the word "malaise." My daughter is bedbound and desperately ill. She has been sick for 25 years, since college. She does not have malaise, and never did have malaise.
Use the strong and accurate phrase "exertion-induced" instead of the weak phrase "post-exertional."
Making FM more visible everywhere. Social media, magazines, television, email, advertising, etc. People still seem to think it's laziness or all in our mind. People think that we can and should "get used to the pain" and they don't realise how debilitating this disease can be. The public as well as physicians have to be reminded constantly that this is a serious disease and that research needs to be funded.
More funding! There seems to be talented researchers wanting to do this work.
Raise public awareness
I think the new metabolome research is promising. I think some of the barriers are still the name, and lack of visibility. I think more has to be done to increase visibility of the illness...and then research funding will improve. I think one barrier is Lyme has become visible while now a lot of doctors know more about chronic Lyme, and think we have that. I think if we got a test to show we had CFS, and more people were truly diagnosed, we would become more visible. I think every time there is a breakthrough there needs to be a lot of publicity on the news over, and over and over...until people are more aware. Education will help the illness be more visible, and that will help bring in funding. See....even alternative doctors still think we have candida or heavy metal toxicity. That simplistic thinking has got to change.
More research with people who actually suffer with M.E from a wider catchment
Spend the same amount of money that you do on M.S
The community recognizing how prevalent and how horrible this disease is. Medical professionals listening to their patients. More widespread education to the general public on what this disease actually entails so the general populace is more aware this disease even exists and just how bad it is so more research money can start building from them and doctors will start to group together to work toward figuring out a treatment for these patients. If people even understood what this actually is and saw just how poorly their quality of life is then I don't think anyone would turn away from trying to do something to help.
Give money to those who have been talking about PEM and understand its relevance to ME. Give ME the respect it deserves.
<ol style="list-style-type: none"> 1) Produce an RFA targeting the neuro-immune-energy production matrix in ME/CFS 2) Create a 10-year strategic plan which includes performance metrics

A major barrier to progress is that there is a double standard where claims of biological mechanisms and drugs are held to a high standard, while claims concerning CBT, mind-body interventions, exercise and similar are held to a low standard. So low that claims of efficacy concerning the latter are accepted even if based on unblinded clinical trials with primary subjective outcomes and inadequate control groups. Such a design make it a trivially easy to obtain positive results for almost any intervention, even if that intervention is in reality ineffective. These claims about successfully treating ME/CFS with psychotherapy and exercise have created misunderstanding and convinced society that ME/CFS is not really a disease. It is therefore unsurprising that there is a lack of researchers investigating ME/CFS. Society needs to be told clearly that this view of ME/CFS was an error and harmful to patients. The double standard also needs to be eliminated.

i am a patient, not an expert on the research field, so hard for me to respond.

My own experience and that of other patients indicates, at least for less ill patients, that some sort of mind-body technique may be very helpful. I am thinking along the lines of a treatment for phantom limb pain that involves mirrors and tricking the brain into thinking the phantom limb is actually there (resulting, for some patients, in their pain going away). I have several times been made substantially better, in a lasting way, by a life event that makes it imperative that my body function better, such as dealing with a badly injured spouse. The big question is, how to create this kind of thing in normal life? (For the record, I have had the illness for 25 years, have a Master's degree in biomedical research (an almost PhD derailed by ME/CFS) and have been diagnosed by both [...].)

Also, since we are now supposed to think not about mind or body, but rather that's it's all both, get doctors and researchers to actually do this. This is an important paradigm shift for all of biomedicine, but PARTICULARLY for ME/CFS and fibromyalgia. Most researchers and clinicians seem stuck in the past on this important topic.

Make it clear that this is a physical illness, rather than a mental illness.

possibly partner with other similar brain health illnesses / research (at least for a portion of the effort / budget)

Money, money, money, money, money. Destigmatize, destigmatize, destigmatize

Get the CDC off its outdated conclusions and pejorative behaviors towards ME, the must admit what politics have driven this negative campaign and then move forward.

I believe that larger, more long-term studies are needed in order to help narrow down the potential culprits of ME/CFS. Most studies I've seen have been relatively small in participants and relatively short in scope of time. A broader view of the impact of ME/CFS on patients' lifestyles and mental health is crucial to attracting more research and attention, and long-term studies can more easily demonstrate whether patients' health tends to deteriorate over time (and the contributing factors to that). I find it baffling that an illness with so many sufferers, many of whom are desperate to help contribute to a solution or cure, is regularly studied in trials and other research with sample sizes of under 200.

I spent four years patronizing a large group of doctors in Austin, TX. They sent me around and around from this specialist to that specialist, none of whom could diagnose me, even though I showed EVERY symptom of ME/CFS. When I finally found a doctor in Houston, he looked at all the testing that had been done at the Austin clinic, and after a 45 minute interview, he knew precisely what was wrong. I even took the energy to confront one of the doctors at the Austin clinic, and it seemed like they didn't WANT to know about it. It was as if they were working at the medical equivalent of McDonalds, and there was no button on their computer that they could press for ME/CFS. I feel like there are so many practicing physicians who have NO knowledge of the disease and are lost in the 70's thinking that my disease is still the Yuppie Flu.

Establish guidelines for diagnosis
Eliminate the idea that this is a mental disease or conversion disorder
Create access to specialists who are knowledgeable and willing to treat the disease
Create a mandatory continuing ed module for all PCPs

Ha, that's a good one! Sure wish I had a clue.

Substantial increase in funding. 200 million. Statements by NIH acknowledging me/cfs and promoting research into the illness.

determine the many gaps that exist in M/CFS research

find ways to overcome the stigma associated with this illness (while this affects patients & needs to be dealt with in that regard, it also prevents many researchers & Drs from learning more or goign into this field)

establish a long-term plan for research

understand that patients really want to be involved in research, advocacy, etc, but may need accommodations in order to be able to physically handle doing so

use the Canadian Consensus Criteria &/or the International Consensus Criteria as the only research definitions of this illness...other variations are not always actually studying this patient grp and they confuse the research

Put up some prize money, induce the competitive nature to drive researchers to be creative and thorough.

Jazz up ME/CFS as an intriguing research field - there are some very interesting developments happening (the nano-needle, brains scans showing widespread inflammation, having trouble remembering others atm). Create intrigue and interest to draw in new researchers.

In this case, the FCC is relying on outdated and inapplicable standards.

The best strategy I know is to keep on writing letters like this one and calling my legislators. I wish there were more effective ways. I wish there was a government agency to protect us and to protect all Americans. In fact there are such agencies...the EPA, for example, but it is now under control of the companies that profit from the toxins.

Fully eliminate medical (and the wider social) prejudice that this illness is "in the head" or in any way arising from malingering or self-serving behaviour by widely disseminating any robust biomedical research.

Create a teaching programme for medical students based on the most up to date body of research available on this illness and make it mandatory for educational facilities to expose students to this common illness and best practice diagnostic criteria. Colleges could consider studying this illness as an ethical case study for how not to treat patients with poorly defined illnesses in the future. Inspire idealistic students with the opportunity to provide meaningful change for millions of people and inspire the ambitious with the rare opportunity to pioneer new territory in an illness (or illnesses) with an unknown etiology.

Researchers have to be assured that they will not only have adequate funding for one round of testing but will have funding for years to come. This has been a problem in ME research. They don't see it as a stable field they can stay in, because funding may or may not come. Or, they get so little funding that they can't do enough testing to make much of an impact. They may see a pattern in the data, but if there aren't enough subjects or samples, the data can't be as iron clad. This has to be frustrating. Our researchers need to know that there is enough money and that it will be there in the long haul. It's sad and shocking what the leading ME researchers have had to do to get their ME research accomplished.

Too much focus on the scientific analysis. We need more on how to help patients. I realize one may need to come before the other but some of us are desperate and dying a slow, painful, pitifully death.

Every medical school needs it to be taught. Public awareness also needs to be improved. Doctors need to take patients and learn. The attitude towards ME/CFS needs to change.

Funding, and sympathizing with us please

One of the most alarming things is how much ignorance and incompetence seems to be in the entire system of researchers and doctors. I've observed many PhDs who specialize in FMT/microbiome being severely deficient in knowledge/insight in this field, not up to date with the literature, etc.. Some of it seems to stem from the fact that much of their knowledge might be too specialized, and they're lacking broad knowledge/insight on human health and the gut microbiome's impact on the entire body.

Another example is a short chat I had with a professor who is/was an advisor for a UK CFS research body. He was not up to date with the literature at all and thus gave extremely harmful recommendations which were completely contrary to the current evidence. And thus steered that UK body away from a possible cure. The professor also mentioned that he had served as an advisor to the NIH (and others) as well.

Ignorance

Invisible disability

Fluctuating symptoms

Good science. Do not fund corrupt scientists with conflicts of interests, or any involved in the PACE trail. Bad science could set back research decades, longer if the bad science is sitting on top of the real solution. Spend a bit of time, google the scientists names and see if they've been involved in bad trials in the past. See if there are ongoing court cases against them and maybe, just maybe, think twice before throwing money at them or promoting them to lead all the research.

Quacks are drawn to unsolved diseases. Think homeopathy and herbal medicine. Do not fund alternative medicine and corrupt scientists trying to profit over the suffering of desperate people.

Solid science. Real science. Fewer random, experimental treatment trails until the causes are understood.

Education of the medical world as well as the general public to increase awareness on ME/CFS.

The stigma surrounding ME/CFS is still all too apparent which, I feel, discourages new researchers and physicians from entering the field; I feel the NIH could really initiate a very positive change here.

As mentioned above, a Dx test would go a long way to ensuring legitimacy for the illness.

Also, the provision of significant levels of funding to research centres, to a level commensurate with illness burden, would be a strong signal from the NIH to the medical community that ME/CFS is an illness that needs to be taken seriously. Although the establishment of 3 research centres was welcome, I feel we need many more, funded by government agencies - 10+ centres, with guaranteed provision of funds for 7-10+ years (to providing visibility of funding) could dramatically change this field and attract many new researchers to study ME/CFS.

It's pleasing to see many more annual conferences / symposia relating to ME/CFS, compared to what there used to be some years ago. An annual (i.e. not just one-off) NIH conference would clearly send out the message that ME/CFS is being taken seriously by government agencies.

Open research to wider groups. i have been denied every time i try to be a part of research. Denial reasons include BMI, drug history (long-term prednisone use), or presence of hypothyroidism. You can control for these factors and still get good data from patients like me.

Funding from the NIH and other governmental research bodies.
We need big-time help. Research on the cheap won't get it done.

Develop a short course on CFS that can be taught to medical students.

Currently researchers tend to use small samples of people with Cfs in their studies. A lot more information could be obtained by allowing people with Cfs to have the same testing done on themselves that the researchers are using. at our own expense. Let's say an individual study has 30 participants and a researcher was able to get 500 people to self finance the same relevant testing. Let's say those 500 people with Cfs don't show the same testing patterns as the researcher is studying. The researcher could move on to the next theory much more quickly! If there is consistency, continued research in that area would be warranted.

<p>MORE FUNDING. Find ways to get current and new researchers interested in ME research. Teach accurate info about ME in medical schools. Place ME under NINDS.</p>
<p>Data collection from All patients</p>
<p>The name Chronic Fatigue Syndrome has to go. It's a barrier. The name is tainted and misleading (stop researching 'fatigue', fatigue is just one symptom, it isn't at the core of anything).</p>
<p>Establish credible engagement with pharmaceutical and biotechnology companies' research leadership.</p>
<p>Access to patients: Increase the number of patients in the medical care system who are diagnosed with ME/CFS, to be able to have their doctors know of and mention potential opportunities for research study participation. Outreach to healthcare providers to reeducate a generation of doctors currently convinced that ME/CFS is primarily a psychological illness, instead of a physical one, when the opposite is true. Also, spread the word to healthcare providers about the importance of a) taking the illness seriously, b) maintaining contact with patients despite their condition being "untreatable," c) locating and discussing with patients the availability of potential research studies for individual participation and d) increasing ways for ME/CFS patients to participate in said studies, despite facing limitations imposed upon them by the disease.</p>
<p>The biggest need is for scientific integrity and professional courage in speaking truth to power.</p>
<ul style="list-style-type: none"> - calls for interdisciplinary research in major researcher-targeted publications and journals - public and vocal affirmation of ME/CFS from the highest levels as a legitimate, complex, biological disease. - creation of more specialist/research centres with access to patient groups. A majority of patients with ME/CFS do not have access to these despite the need. There are simply not enough specialists. - increasing the ability of primary health care practitioners to detect, diagnose, refer to specialty centres and/or research groups patients with ME/CFS. The stigma from primary health care practitioners leads to high rates of patients living without a diagnosis, unavailable to researchers.
<p>Enough funding that samples could be drawn at home so that the more severe homebound and bedbound patients can be studied, too.</p> <p>You need to be willing to fund reasonably promising but high-risk research - negative outcomes at this stage in our understanding are just as important as positive findings. If we can rule out dead ends, that's essential scientific - and clinical - information.</p>
<p>See "relevant considerations..." and see "overcoming challenges..." also Free data intuitively compiled and easily accesses in the same place.</p>
<p>Give attention to ionizing and non-ionizing electromagnetic influences: pulsing, frequency, direction, field type, light, etc. Support research examining how to insure the integrity of research in the face of corruption, financing, and politicization in favor of polluting industries. Also support research investigating corrupting influences on ME/CFS research.</p>

I can't tell you how to overcome a barrier unless you are more specific about what that barrier is. It seems to me the biggest barrier is will. Nobody really cares about the issue but the victims and they are not in any condition to do anything about it. The second biggest barrier is funds. And the biggest barrier to this is the fact that deniers just say it's psychological and that there is nothing to research. So the people doing this need to be ostracized the same way antivaxers are for their pseudoscience. Or homiopathes are for theirs.

Financial and popular conflict of interest and bias against deep digging into health effects of telecommunication devices.

I think the field has shown that it's important to think outside of the box, otherwise we would have already had a solution a long time ago. Open access data could be a great tool to involve many researchers from different fields.

Money

Ring fenced Money incentivises researchers who aren't currently engaged in the field to come into it

Real commitment from NIH not just talk & small gestures

NIH had opportunity to fund 10 centres of excellence, for finance reasons you only funded 3. You haven't put in significant money to stimulate research interest. We know the current way the NIH gives money doesn't work fit MECFS yet you still just blame the system instead of finding ways to overcome barriers. You need to act in a dedicated way as you address any medical situation you deem important.

Education

Obviously with years with a rubbish name and scorn the forked is still misunderstood and dismissed. Education at Medical school and beyond is vital

In states such as ours, it would involved swapping out smart meters for analog meters, which do not emit wireless radiation. This would be necessary on both the subjects home and surrounding homes, and an RF engineer needed to assess RF levels in the home. I cannot emphasize enough how important this is. I was in the best shape ever before they smart metered the neighborhood. Many people get sick from the neighboring meters, they do not even have a meter. The fatigue is unbelievable. My doctor warned me that I would get worse with this, but I never, ever imagined the effect would be sudden and severe. Most people I believe its a slower effect, some of us, like myself are apparently "the canaries."

The IOM should revisit and update its ME/CFS report.

ME/CFS needs to be taught in all medical schools and not just in one third of medical schools. Having it widely accepted as a severe chronic illness well break down some of the other barriers to progress.

Top priority: well-fund the research, so that the researchers can work on ME/CFS full-time!!!!

Other priorities:

1. One specific case definition and criteria. 2. Use specimens that anyone can do at home and send in (i.e. saliva, hair, feces, urine) or provide for mobile blood draw facilities to go to patient's homes for the draw. 3. A registry (that does not require a doctor's diagnosis, as they are so hard to come by, since doctors don't know about or understand this disease). 4: sharing of current research among researchers without waiting for it to be published. 5. Setting up collaborative research centers throughout the country, so they are easier for people to get to.

Repeal Section 704 of the Telecommunications Act of 1996 to allow rejection of placement of cell towers and small cell tower equipment that would be in close proximity to homes, schools, businesses, libraries, and other public places where exposure to excessive amounts of wireless microwave radiofrequency radiation is not necessary and hard-wiring is possible. Note: Hard-wiring is faster, safer, more secure, and more reliable than wireless.

First and foremost, ME stigma must be addressed directly. This stigma adversely affects providers and patients alike. Until stigma is openly addressed, there will continue to be a reluctance to research and treat ME. The physiological devastation of ME is exacerbated by the pervasive stigma and provider ignorance regarding what is known about ME in 2019. NIH leadership could spearhead this effort by directly discussing the stigma through building an aggressive research and care agenda. This is reminiscent of the early days of HIV disease when it was (mis)characterized as gay related immunodeficiency disorder (GRID).

ME is now recognized as a neuroimmune disorder that impacts multiple body systems and is no longer dismissed as a psychological disorder by providers who are aware of the recent developments in the field. Unfortunately, the majority of providers remain largely uninformed, most medical schools and other healthcare professional groups' training do not include ME in their curriculum. Patients must receive competent and compassionate care provided by practitioners informed with accurate ME knowledge.

The recent NIH Conference (April 2019) provided promising directions for both research and clinical care. Research and clinical care must occur simultaneously. It is unacceptable to call for a biomarker for the illness to the exclusion of attempting to ameliorate the declining health of those affected by ME. A preliminary strategy to address this is to have national medical leadership organizations (NIH, CDC, Departments of Health) issue calls for interdisciplinary medical and mental health specialty organizations (neurology, pulmonology, primary care, infectious disease, mental health across professional groups: nursing, physician assistants, psychologists, social workers and physicians) issue statements to their respective members to become informed about ME. A few select references including the ME article summarizing the 2019 NIH ME Conference by Medscape, CDC Factsheet, IOM Summary sheet and NYS Department of Health can serve as a starting point. This information needs to be disseminated to practitioners in training.

The conference provided a forum for collaborative efforts which are a prerequisite to understanding this complex illness. Since current research is examining different body systems, there needs to be information sharing and conferences like the Bateman Horne Clinician Summit or the NIH research conference to stimulate further research. Live streaming and videos will benefit clinicians, researchers and patients. The NIH Conference Planning Committee could serve as a clearinghouse to keep these initiatives moving ahead.

See above. Basically stop combining patients with ME meeting the ICC and those without ME not meeting the ICC into a single mixed group. Using the irrational, mixed term "ME/CFS" makes the differential diagnosis of ME and specific research of ME impossible.

- Conduct exhaustive, comprehensive epidemiologic study, using appropriate patient selection methods, to define: demographics; prevalence; natural history, onset types, triggers/exposures, risk factors; breadth of symptomology; spectrum of severity, establishing foundation to develop grading metric and instrumentation; provocation/PEM triggers; duration, fluctuation, progression, remission/recovery, relapse; comorbidities and overlapping syndromes.

- Create a 10-year strategic plan which includes performance metrics

- Produce an RFA targeting the neuro-immune-energy production matrix in ME/CFS.

Overcoming challenges or barriers to establishing a career in ME/CFS research for early career investigators and those new to the field.

- Include ME/CFS-targeted components in existing broad epidemiological initiatives like the All of Us Research Program and the Environmental Influences on Child Health Outcomes Program

- Establish a large data and biorepository for comprehensive study of disease landscape, implementing exceptional rigor in data collection, construction, and design; and incorporate other large cohorts (e.g. UK Biobank, Klimas, Stanford, etc.) into the DMCC

- Fund establishment of a patient registry portal for data capture

- Fund targeted data aggregation efforts and analyses utilizing pooled existing cohort data

- Fund/initiate prospective longitudinal studies

Move ME/CFS into NINDS.

- Continue to highlight ME/CFS in Directors blogs and other publications that NIH researchers read.

Research must be done from independent scientists, free from any industry bias.

Adapt and use ICC definition.

Bringing the Main Researchers on one table for a week.

keep spreading the word, not only about the condition, but also the huge negative impact it has on patients lives. For me it's been 30 years of compromised life.

'ME/CFS' doesn't exist. This barrier is absolute and cannot be overcome.

Stop funding all 'ME/CFS' research. A disease with this name does not exist. This combination of terms has no medical meaning and makes no sense at all.

Stop funding all research into CFS aimed at cause or treatment. It has neither, a disease named CFS does not exist. It is a research diagnosis only, and a poor one at that.

Start funding ME research. This is a horrible disease which is not rare yet has never received any funding whatsoever.

Make sure selected patients actually have ME. Do the scans.

More money. More money will also attract young researchers.

End the stigma - no researcher will go into a field that is viewed as questionable or a dead end. PR campaign that shows that ME research is a fascinating, promising research field, not a dead end. Real commitment of NIH and comparable research institutes to solving ME. Good/positive media coverage. Define ME as a central research field with high priority where a career can be built upon. This will also address the problem of journals being unwilling to publish ME/CFS research; if ME research gets published in good journals, this will be an attractor, too.

Use the International Consensus Criteria (ICC) to select people being studied.

Increase NIH overall funding for ME/CFS as it has notably declined from 2017 to 2018, and that peak during 2017 still fell short by several million dollars needed and would be deemed appropriate to tackle such a widely debilitating and mysterious systemic disease.

Physicians and healthcare providers MUST be properly educated and informed regarding this illness, as the notion that it is psychosomatic or so rare and misunderstood that it can be easily dismissed still prevails. I have personally been to several professional healthcare providers at Columbia, NYU Langone, and Mt. Sinai that have literally never heard of ME/CFS and I have seen an additional several physicians who informed me I was just depressed and/or a hypochondriac. It is outrageous that in 2019, a disease that results with a QOL score lower than those of end stage AIDS patients and is not even rare as it affects hundreds of millions Americans, can be met with such resounding ignorance and disinterest. The entire medical establishment needs to do better and if seminars and the like cannot be set up as widely as necessary, it should become mandatory for every physician to educate themselves about this illness via an online program or tools. There is a documentary on Netflix called "Unrest" that details the widespread destruction this illness causes, and even with that kind of mainstream accessibility, patients are still being regularly dismissed because the physicians are uneducated or ill prepared. If the majority, or even half at this point, of the medical community knew the truth about this disease, it would help generate research interest and result in better patient care. Perhaps a physician who has never heard of ME/CFS before they were obligated to learn about it will be the one to come up with a new theory that helps lead to a different research approach and actual treatment.

The NIH immediately needs to start accepting more grants with perhaps less straightforward or direct preliminary data for ME/CFS than it would normally want to approve; ME/CFS grant proposals needs to be held to a different standard than those submitted for other, already properly funded and better understood illnesses that are infinitely less severe - this is because so little is known about the etiology and underlying mechanisms of essentially one of the most debilitating illnesses that exists. With so little understanding of ME/CFS, grants that seem more exploratory or have more broadly

defined missions are absolutely essential to even beginning to understand this systemic illness with innumerable symptoms and presentations... the disease ultimately has too many components to be treated the same as others. The NIH cannot reject ME/CFS grant proposals based on the same standards they would for other diseases as there are currently too many theories regarding the ME/CFS and hardly any concrete data or studies to confirm or deny any of the theories experts have been proposing - due to lack of grants being approved and due to overall lack of even remotely sufficient funding needed for fully fledged large scale studies that will produce data and conclusions without the "a larger scale study will be needed to confirm these data" at the end. Start with sufficient sample sizes in the first place so that any research that actually is approved will produce truly meaningful and more importantly, applicable data. This disease needs to be researched and explored from so many different standpoints: neurologically, rheumatically, metabolically, via virology and infectious diseases, through endocrinology and through cardiology. All of the ME/CFS experts currently have slightly different theories as to which field is most appropriately applicable to the etiology or mechanism of ME/CFS and no real new information pertaining to this disease can be acquired unless every approach is given an opportunity to be properly researched or even simply explored more vaguely.

?

The biggest challenges are lack of funding and patient recruitment. Because travel is so difficult or even impossible for patients, it's very tough to get involved with research.

Jason 2016 proposed that the NIH develop a DALY for ME/CFS. They estimated that it should be receiving \$188 million per year. It's frustrating that an illness which causes so much disability has not been evaluated. Developing a DALY is one way the NIH could commit to endorsing the serious nature of ME/CFS and open future pathways of interest and funding among the research community.

Source (Jason 2016): <https://tinyurl.com/y5fk8zkr>

Research grants for the validation of a diagnostic test; since this will allow researchers to test a cohort who have this disease. Also, this will allow increased funding since it will be clear that this is a biomedical not a psychological disease. Also, validating the test using Gulf War veterans; since this would be acceptable to the Government (overcome funding barrier).

Funding for assessment of re-purposing drugs for use in ME. Publication of NIH position regarding the use of drugs, which have approval in another disease, in ME. Also, testing the proposed treatment on Gulf War veterans; since this would be acceptable to the Government (overcome funding barrier).

Patient identification and diagnosis

Physician and health care provider education

Epidemiologists

Stop repeating the same research that's been disproved such as Epstein-Barr virus. Join forces m e CFS fibromyalgia MS research similar parameters. That would bring in more money.

This one is essential. If research is limited by funding or prejudice we'll never get anywhere. I remember when HIV was a death sentence. Wasting away men waited in doctors' offices with little to help them. Millions poured into research. A somewhat normal life is possible for them now. I hope out turn will come.

Supplemental funding is needed specifically for the collection and analysis of data to aid in better understanding which subjective assessment instruments should be used as Common Data Elements (e.g., for psychometric analyses, factor structure, ceiling effects). Without consistent research measures, it is hard to compare results across studies and obtain a coherent understanding of patient experiences, subjective outcomes, and the potential environmental, clinical, and epidemiological factors that may impact disease onset and course.

There must be a comprehensive effort to properly educate physicians and other health care providers about this illness. Funding for ME/CFS research must be significantly increased.

More money for research and for training researchers/ clinicians.

Research Funding

EPIDEMIOLOGIC KNOWLEDGE

NIH ADMINISTRATIVE STRUCTURE, GRANT SUBMISSION & REVIEW

CLINICAL EXPERTISE

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!!!

1. Providing long term funding for research. Some of them should include possibilities for tenured positions for the best researchers in order to ensure ongoing excellent research.
2. Ongoing communication and advocacy particularly aiming at reluctant / hostile target groups e.g. physicians who still insist ME is a functional disorder / psychosomatic disease.
3. Cooperation with politicians and other relevant decision makers at top level is essential.

- Director Francis Collins should immediately issue a strongly worded statement on multiple platforms with national and international visibility that ME/CFS is an organic disease that affects millions in the US and tens of millions worldwide, that medical education needs to be brought up to date with current research, and that past efforts to psychologize ME/CFS were wrong and a disservice to patients. This statement should be published as a letter to the editor in prominent medical journals, issued to all medical schools in the US, and publicized in the national media.

- Assign ME/CFS research to a home institute at NIH. The rationale for a Trans-NIH Working Group is that ME/CFS is a multi-system disease. However, this risks leaving ME/CFS outside the normal NIH budgeting and strategic planning processes which are largely institute-based. In addition, other Trans-NIH working groups focus on interdisciplinary topics like the microbiome, structural birth defects or climate change, not specific diseases, again giving ME/CFS a nonstandard designation. Assigning ME/CFS to NINDS, for example, would make sense due to the clear neurological manifestations and might provide a path for designated funding. Or assigning ME/CFS to NIAID would make sense due to the frequent onset after an infectious illness. Most of the currently funded research projects are administered by NIAID. Being assigned to an institute does not preclude

interdisciplinary research either at NIH or in externally funded projects.

- Fund more clinical trials on biomarkers and treatments for ME/CFS. Many small studies, often funded by limited private funding, have identified promising biomarkers and treatments, but confirmation requires much larger studies. NIH has the resources to fund these larger studies, and does so for other diseases. For example, a search on the NIH website for clinical trials on multiple sclerosis found 11 active and 21 completed or terminated clinical trials, covering different biomarkers and multiple drugs. A search on fibromyalgia, a closely related and often comorbid disease, found 10 active and or recruiting clinical trials. Meanwhile, NIH is funding only 2 treatment clinical trials for CFS, one of which is a behavioral intervention.

- Issue a new Funding Opportunity Announcement (FOA) for collaborative research centers and fund at least three more, preferably in other geographical areas besides the Northeast.

- While NIH cannot directly fund clinical care at the collaborative research centers, NIH leadership should encourage funding for a clinical care component through HHS or private funding sources. Having a clinical care center associated with each research center will enhance the effectiveness of the basic research, and, in addition, provide the community with desperately needed access to medical care. NIH's encouragement will help overcome the stigma and misunderstanding that surround ME/CFS and that have led to a paucity of health care practitioners.

- Issue an FOA for investigator-initiated, hypothesis-generating research on ME/CFS. While many abnormalities have been documented, leading to a variety of hypotheses about the underlying pathology and etiology of ME/CFS, there may be other ideas and researchers that would be stimulated by some unrestricted, exploratory funding.

Use ICC Criteria. Don't bury Myalgic Encephalomyelitis.

Extensive education of physicians that it exists would be a wonderful first start.

Rare (13) and non-rare orphan diseases face significant barriers in research. For picking a career research field, some recommendations are to discuss the issue with those already in the field, and identify funding sources. (14) If mentors and funding sources don't exist or are very scarce, it will be harder to begin, and people who have the interest might actually be told this is a bad career choice because reliable funding doesn't exist. (15) ,

It seems that NIH allocates funding based on number of funding applications received. (16) If people are finding it difficult to start out, this will not generate enough applications to support a robust field. In fact, the evidence shows that this is not working in ME.(17,18)

And seems to be pretty spotty in rare diseases (19-23) . . . , . There are other non-rare diseases which doing especially poorly also, for example, migraine. (24) Also in these categories are diseases like celiac disease, Crohn's disease, women's conditions like endometriosis and vulvodynia, Ehlers-Danlos syndrome (the hypermobile type is common (25-27) while the other types are rare). The US government is the top funder of neglected diseases worldwide (28) (but seems to focus on acute infectious diseases).

In 1993, Congress established a separate budget for HIV/AIDS and designated its amount at 10% of the entire NIH budget. This 10% requirement has lately been dropped (29) (there are now many treatments for HIV/AIDS and most patients who do have access are doing well: this is a great illustration of how well this model works).

There is a strong case to be made that there should be new funding. NIH funding has fallen from a peak in 2003 (30) due to inflation, cuts, and sequestration; recent spending boosts have restored the losses to pre-sequestration levels. (31) As a percentage of GDP, nondefense discretionary spending (which if I understand correctly includes NIH spending), is on a declining trend. (32) Money spent on public research can be shown to stimulate private research. Indeed, economists think every \$1 of NIH funding may produce \$1.70 to \$2.30 in the private economy (in bioscience industries). (33)

However, even if NIH cannot obtain new funding, this does not remove the responsibility NIH has to ensure all patients have equal access to research into diagnostics and treatment for their disease. If the current system isn't working for some patients, the system must be changed so that everyone is included. Allowing a system to stand unrevised when it is known to exclude people from accessing necessary resources, based on their illness label (i.e. with similar symptoms and debility but a different illness label, one would have access to laboratory and/or imaging-based diagnosis and tests to follow one's disease course, specialists in one's city, possibly a treatment or five to pick from, and a Group 3 power wheelchair), would be to participate in institutional discrimination. (34)

It would make sense to have a dedicated funding category for all substantially underfunded diseases and conditions. This would help everyone who is behind get a better start in research, and it could not be criticized as benefitting solely a particular group. There would be a standing fund set at some generous amount tied to a relevant index, perhaps 10% (or even 15% or some other percentage, given that it's for many diseases) of the overall NIH budget. That way there would be a stable funding source that everyone in need could access if for any reason (the disease is too rare; the patients are too ill to advocate for funds; there's a lack of information; etc.) there isn't funding for any particular condition, and this way could be easier and simpler than doing it group by group. A fix for everyone in one go. And any group that does catch up to a reasonable funding level phases out of the category, so it is always relevant.

It should be further noted that knowledge gained from one area will be applicable in others (for example, low NK cell function is related to ME, cancer, autoimmune disease, HIV/AIDS, other infections, and congenital immunodeficiencies (35) ; surely there are many more examples (36,37)). So this would have an overall benefit to humanity, not just to those having or wanting to study conditions that are currently neglected.

As a separate point, the diagnosis should require post-exertional malaise (this is not merely feeling fatigue with/after exercise; this is feeling sick, weak, and a general symptom exacerbation that will include various symptoms such as sore throat, sensitivity to light and/or noise, GI problems, and other symptoms). Although some patients may not receive an early diagnosis, this is not unusual for complex diseases and should not prevent clinical follow-up.

Promote awareness

Increase funding

Direct funding to valid research areas

Larger sample sizes using stringent patient cohorts (ICC)

Scientific challenges in the past have stemmed from using patients who do not have ME. Results from studies are not reproducible when the patients studied do not have the same disease or even the same symptoms.

Adequate funding. It seems the chief barriers to research are lack of belief in the reality of this illness. There's no other explanation for the almost complete lack of interest and funding for 35 years. The CDC's name of Chronic Fatigue Syndrome pretty much guaranteed no one would take it seriously. So education of doctors and researchers and people at the top of the NIH and CDC is crucial to securing research dollars. very few medical schools even teach about ME/CFS. This has to change.

The NIH itself has erected barriers to research. See the following where Ron Davis of the Human Genome Project responds to the NIH's denial of a 2017 Stanford grant application which could have been instrumental in finding a biomarker for this illness. The type of thinking which denied this application needs to be rooted out.

ME/CFS/SEID Biomarker Discovery Grants

Principal Investigators: Ronald W Davis Ronald Tompkins Mike Snyder Mark Davis Catherine Blish Steve Fodor Michael Mindrinos Andreas Kogelnik Wenzhong Xiao

Scientific Advisory Board: Paul Berg, PhD, Nobel Laureate, Molecular Genetics, Stanford University Mario Capecchi, PhD, Nobel Laureate, Genetics & Immunology, University of Utah Mark M. Davis, PhD, Immunology, Stanford University H. Craig Heller, PhD, Biology & Exercise Physiology, Stanford University Andreas M. Kogelnik, MD, PhD, Infectious Disease, Open Medicine Institute Baldomero M. Olivera, PhD, Neurobiology, University of Utah Ronald G. Tompkins, MD, ScD, Trauma & Metabolism, Harvard Medical School James D. Watson, PhD, Nobel Laureate, Molecular Genetics, Human Genome Project Wenzhong Xiao, PhD, Computational Genomics, Harvard University, Stanford University

Response to reasons NIH refused to accept grant applications, Ronald W. Davis, PhD

Two pre-proposals were sent to NINDS. The first pre-proposal was for a P01 grant for \$1,000,000 per year for 5 years. Below are the reasons given for not considering funding and my responses.

1. NIH: It was not clear that the proposal falls within the mission of NINDS since there was no mention of collection of CSF or of analysis of cognitive or other nervous system function of the individuals with ME/CFS/SEID.

Response: The mission of NINDS is to study diseases with a neurological component. CFS is clearly such a disease. The mission is not defined by what data is collected. It is not possible or necessary to

collect either CSF or cognitive data from severely ill patients in their homes. It is very clear in the proposal that we are going to study severely ill (bedbound) patients. We also state, "Although many of the symptoms suggest a neurological basis, molecular biomarkers that reflect the underlying mechanism may be present in the blood, saliva, sweat, urine and/or stool. Identification of biomarkers in these easily assayed fluids can be convenient and inexpensive, and could be conducted on the estimated 25% of patients who are currently house-bound or bed-bound." Also, bedbound patients cannot visit a clinic where an MRI or other imaging can be performed. They are frequently unable to speak, unable to be spoken to and unable to read. Cognitive testing is thus also impossible. It is already clear that there are cognitive impacts in these patients. Cognitive testing will not contribute to anything this study seeks to address. Further, we cannot do a spinal tap (CSF) and the IRB would correctly never approve of taking CSF from a severely ill patient in a home.

2. NIH: Everyone agrees that this research needs to be done for ME/CFS/SEID, but that you would be more successful in review if you narrow the focus of the application to focus on the very ill population and appropriate controls (for example) and submit an R01 with a budget of less than \$500,000 for any year of the application.

Response: This comment is mystifying. The entire proposal is written to study severely ill patients already. This comment made me wonder if they had even read the proposal. The proposal is already very focused, and we do propose to focus on the very ill. Reducing the proposed research budget by half will reduce the number of patients by half and reduce the statistical significance. This will likely cause the R01 proposal to be rejected in review because they will correctly judge that there are too few patients studied to identify the false positive biomarkers. This was clearly articulated in the grant. Further, we cannot "narrow the focus" by reducing the number of tests. The heart of this proposal is to assay a very large number of molecular species all from biological samples collected at the same time. This is essential for reducing variance and for enabling us to correlate the various types of data from one point in time. This is what makes this a groundbreaking study.

3. NIH: There was a lack of clear hypotheses to be tested and many felt there was a lack of detail provided in the proposal.

Response: There is not a clear hypothesis because this is not a hypothesis-testing proposal but a hypothesis-generating proposal in the form of observations. The scientific method starts with observation, then hypothesis. Without first observation you cannot formulate a good hypothesis. I'm extremely surprised that NIH does not know this. Furthermore the Human Genome Project had no hypothesis and was one of the most important projects accomplished by NIH in its history. The lack of detail was intentional. This was a pre-proposal and not a completely detailed grant. I clearly stated what we were proposing to do but not exactly how we were going to do it. The exact details are not for NIH to review because they lack the experience and expertise. That is the job of a peer review study section.

4. NIH: There was agreement that a large biomarker study is needed in ME /CFS/SEID, but that perhaps there needs to be an RFA that spells out what NIH would like to fund, with agreement between several institutes so that appropriately powered studies would be submitted and provided with sufficient funding to accomplish the studies.

Response: Why would NIH not consider an excellent large biomarker study from a very experienced team when they state a "large biomarker study is needed"? Our proposed study could help NIH "spell out what NIH would like to fund". Ill patients have already waited 30 years for NIH to decide what to fund. 30 years is long enough.

The second pre-proposal was for an R01 grant for \$800,000 per year for 5 years. The rejection is given below and is essentially the same as the P01 rejection:

NIH: "I am writing to inform you that the NINDS Extramural Science Committee did not approve your request to submit an R01 application with a budget over \$500,000 to NINDS. The Committee was concerned that the grant does not fall in the NINDS mission since it will measure markers and biomarkers in the peripheral blood from individuals with ME/CFS and there are no neurological outcomes in the grant. They also suggested that the application is more appropriate for NIAID, so I suggest you contact Program staff at NIAID to discuss whether or not the application is appropriate for their Institute."

Response: I believe they don't want to fund either grant and are pushing us to another Institute even though NIAID has publicly stated they will not support research on ME/CFS/SEID. The IOM report has made it clear that there are cognitive issues with this disease. The fact that many of our severe patients cannot talk, listen to spoken words or read should indicate neurological involvement possibly similar to stroke, which they clearly support. Furthermore, there is considerable research looking for blood biomarkers for stroke patients. I am mystified why if they support stroke and other neurological diseases, they refuse to support ME/CFS/SEID research. The IOM and P2P reports both state the urgent need for research support. This research proposal addresses many of the critical needs specified in these reports. This should be viewed as an opportunity for NIH to show leadership and quickly initiate research activity.

The biggest current barrier to progress is a status quo of misinformation. The dominant psychosocial paradigm has warped perception and as a consequence most physicians and researchers do not understand the true impact of the disease, treat it as a minor annoyance or any alternative explanation they personally favor.

This is something that requires little funding. The gap between perception of the illness and its true impact is enormous, especially within the medical profession. Those mistakes should never have happened and were duly warned against. A change in direction cannot occur without acknowledging that the last few decades have been a complete failure and have directly caused harm to millions.

To achieve this, the "controversy", which has essentially always been the obsessive belligerence of ideologues who deny that it exists as it is experienced by sufferers, needs to be taken behind the proverbial shed and buried for good.

The IOM/NAM report established the basis for this change, but leadership has failed to materialize in actually following through on what the report revealed. The current state of published science in this disease is one of two realities: one entirely fictional, the other an incomplete puzzle. This needs to be corrected, as has happened in the past with mistakes like psychosomatic models of peptic ulcers.

The AIDS crisis provides all the strategies that are likely needed to kickstart research on a problem that has not succeeded at grabbing the interest of medicine. The record was corrected, misinformation was countered and an actionable plan was given adequate resources. The blueprints are there, they just need willing leadership and adequate funding relative to disease burden and opportunity cost.

We must first overcome the stigma and ignorance that still exists in mainstream medicine. Getting current research out such as Workwell's 2 day CPET findings to once and for all get rid of the deconditioning and graded exercise therapy recommendations still incorrectly cited by the medical community would hopefully help with this.

An initiative educating researchers about this disease and the urgent need for research along with the FUNDING that it deserves will quickly SOLVE the problem!

CDC and NIH created this crisis in care, and they should BOLDLY correct the decades of neglect and inaction. CDC purposely named the disease to sound "not medical" in 1988 with world experts storming from the meeting i read, and NIH parked this disease in the Office of Woman's Studies. NO stable funding. What career researcher would pursue this stigmatization and dead end funding. You need to Sponsor an INITIATIVE with stable FUNDING of magnitude to the number and severity of the Americans afflicted. Koop was a leader. He did not let politics get in the way of educating Americans on AIDS. We need NIH leaders to be bold and educating the public/researchers on this disease. NIH needs to have a presence at national neurology, immunology, etc organizations and show leadership in educating researchers on this urgent neglected need AND HAVE FUNDING FOR OUTSTANDING RESEARCHERS TO JOIN. CDC/NIH put was in this hole, and they should boldly be the responsible parties to reverse this travesty. Look above at the diverse areas to study with regards to MEcfs, and NIH has been an ostrich with its head in the sand. I can't think of a more complex, exciting disease to unravel for a research, combined with a grateful patient population.

RFAs are essential so that worthwhile proposals can be funded even if the scores do not place them in the top 20% of proposals. A proposal that is in the top 35% of all proposals submitted to NIH is worthy of being funded on a topic that needs more rapid progress to be made. And whether that proposal belongs in the top 5% or the top 35% can be an arbitrary judgment call largely made by 3 people, some of whom may not understand the serious nature of the disease.

Fund commensurate with disease burden and top researchers will join.

Funding!

1. Provide funding for additional Collaborative Research Centers and consider more equitable geographic distribution. Currently, all 3 CRCs are located within the Northeast. This means that results may not be applicable to patients living in other geographic areas because of different environmental exposures, ethnic makeup, etc.

2. Consider issuing ME/CFS-specific RFAs. A healthy number of groups applied for the CRCs because they knew money had been set aside for ME/CFS and that there would be less competition from groups studying other conditions. Similarly, RFAs would assure dedicated dollars on a smaller scale for ME/CFS researchers. While it is true that researchers can creatively look for NIH grant announcements that fit their work, we do wonder how likely their grant will be approved under non-ME/CFS-specific grants given the paucity of knowledge among scientists and clinicians - who serve as grant reviewers - generally about ME/CFS. It is more likely in such cases, people will pick a grant studying a condition they are familiar with or have at least hear about.

3. Include ME/CFS explicitly in relevant grant program announcements from various institutes, initiatives, and programs. For example, a PA concerning treatment for pain or sleep issues could mention ME/CFS in its description of one area where this work is needed. This might help pique the interest of pain and sleep researchers who currently do not work in the ME/CFS field.

4. Based on the best available knowledge, house ME/CFS under one specific institute. The institute can always be changed if needed as the pathophysiology become clearer. For many years, NIH has stated that since the pathophysiology is not clear, it is uncertain which institute should be responsible

for ME/CFS. What this means in practice is no institute views ME/CFS as a priority and thus few funds have been committed to its research given the numbers of people affected and the burden of disease. This lack of commitment, funds, and prioritization has meant the search for ME/CFS's pathophysiology has been slowed, leading to a vicious cycle of it not being housed under any specific institute.

5. Provide funding for clinical trials and./or a clinical trials network. Some of the treatments used to manage ME/CFS are no longer under patent or are not patentable in the first place (e.g. pacing, low-dose naltrexone). Hence, there is little interest from pharmaceutical companies to sponsor trials yet this is very much needed if progress is to be made in helping patients.

6. Explicitly encourage researchers to address underrepresented groups in ME/CFS research. Currently, subjects in ME/CFS studies consist of mostly middle-aged (around 50), well-educated, middle-class, Caucasian women who have been sick for years and are able to attend clinic. Yet clinicians know and studies show ME/CFS affects a much wider group. Researchers should address how they intend to recruit men, younger and older people, people of color, poor people, people who have sick only briefly, and severely affected people. Pediatric ME/CFS research must be especially encouraged as onset during the teenage years is common.

7. Encourage researchers to take into account comorbidities when recruiting, analyzing, and interpreting data in their grant submissions. For recruitment, a balance, which will vary depending on a study's purpose, will need to be struck between excluding enough comorbid conditions that a clear signal is obtained and excluding too many conditions such as that the remaining study sample no longer represents the average ME/CFS patient. (For example, studies which do not allow any individual with depression (even controlled depression) may mean 50% of potential subjects are excluded since up to 50% of patients may experience co-morbid depression.) For interpretation, novel or unusual findings are often attributed to ME/CFS when in fact they could be due to co-morbid conditions, like fibromyalgia, POTS, or depression. So analyzing data by subgroups via stratification or statistical methods would be helpful.

8. Related to point #6, continue to encourage control groups other than healthy individuals. Selecting an appropriate control group can be challenging and will depend on a study's purpose. However, a control group should help account for factors that could confound the analysis or interpretation. For example, sedentary controls help account for inactivity; controls affected by multiple sclerosis, for a look-alike fatigue condition; controls affected by POTS, for ME/CFS subjects with co-morbid POTS, etc.

9. Provide leadership and support to help grow the network of knowledgeable clinicians. While this is not directly NIH's responsibility, the lack of disease experts is obstructing the ability to accelerate research and ensure that cohorts include appropriately diagnosed trial participants.

10. Continue to convene workgroups of ME/CFS researchers and expert clinicians to reach consensus on the criteria, methods and instrumentation for selection of ME/CFS patients.

11. The lack of consensus on patient selection methods was highlighted as a priority in both the 2011 NIH State of Knowledge meeting and the 2015 NIH Pathways to Prevention report but has not yet been addressed. By design, the NIH Common Data Elements initiative also did not address this issue nor will subtyping strategies defined by inclusion criteria in specific trials.

The sole reliance on the "hallmark" symptom of the disease - post-exertional malaise (PEM) is incorrect because people suffering from other diseases or disorders display similar symptoms.

Using Fukuda or SEID criteria is a barrier to progress which can be easily remedied.

This is why it is imperative that NIH use and demand the ICC be used for all NIH funded research. Relying on false definitions will result in unreliable and even questionable findings and is the reason we currently have no scientifically accepted biomarkers and no FDA approved treatments - after over three decades of looking at the disease!

Funding for researchers is of course a primary necessity. Many scientists currently working in ME/CFS research have tenure so a job but little or no research budget or rely on donations from patients or their families who are already tapped out with many living below the poverty line and unable to get disability benefits since ME/CFS is not a "legitimate" disease. A few private individuals have made large donations, The Pineapple Fund making a one time \$5 million dollar donation comes to mind. This is not enough to cover a lifetime of research in salaries (for young nontenured researchers) or equipment costs for an organization with dozens of researchers.

Historically researchers have been told going into ME/CFS was a career ender and not worth bothering to study. This stigma needs to be eliminated by future NIH actions.

NIH has claimed only a percentage of applications are approved. While the percentage of approvals is unknown this is a poor policy in a field with so few researchers, it ensures the field can never grow because a percent of a small number is an even smaller number. And younger researchers do not want to enter a dwindling field because its a dead end. So to get research off the ground vetted applications need funding at 100% until the funding cap is reached. Once you have a growing field where you have more applications then allocated money then being choosy makes perfect sense since the funds available are certainly not infinite.

Most of the current researchers have tried to get NIH funding but have been denied repeatedly and have come to believe they can't get money so stop trying to apply. Not to mention the time required to make multiple applications that are routinely denied taking away from the work they can do. In one poignant example linked below I quote "The review complained that our institutional environment was "mediocre". The Stanford office that reviews all Stanford grants told me that they had never seen a Stanford rating anywhere close to that low in their entire history. It's absurd to think that Stanford is not an excellent institutional environment."

This is bad faith.

<https://forums.phoenixrising.me/threads/me-cfs-collaborative-research-centers-data-management-center-announcements.54655/page-5#post-912874>

Another example

<http://www.meaction.net/wp-content/uploads/2015/08/ResponseToNIHRejectionsRonDavis.pdf>

More background specifically relating to barriers in NIH funding of ME/CFS research

<https://www.statnews.com/2019/01/10/nih-obstacles-thwart-myalgic-encephalomyelitis-research/>

If Nobel prize winners and world renowned researchers cannot get funding then who can?

Create a 10-15 year strategic plan which includes periodic performance measures. This should help to provide a research environment with some stability, as compared to the way the ME/CFS research field has been until now, attract more qualified and committed researchers. The questions should be fascinating to scientists, provided they can reasonably assume there will be sufficient infrastructure to support them -- on a more continuing basis, with the potential for building on one another's work.

Tackle the diagnosis hurdle by producing an RFA or other funding mechanism to focus on new diagnostic techniques/markers for ME/CFS (e.g. nanoneedle, microbiome, metabolomics)

Situate ME/CFS firmly into NINDS

Continue (and even increase) the highlighting of ME/CFS in Directors' blogs and other publications that NIH researchers read

MONEY!!! MONEY!!! MONEY!!! That equates to the disease burden that is estimated at \$200 million. Answers can be found quickly if money is available.

Clear criteria for research and obtaining the grants! The attitude of the government agencies that do not understand or care about the devastation that this disease is causing.

Create a 10-year strategic plan which includes performance metrics. This will provide a sense that ME/CFS is not the Wild West, that field is organized, is populated by credible, serious researchers has a direction and will be supported by the NIH.

Produce an RFA targeting the neuro-immune-energy production matrix in ME/CFS.

Get over the diagnosis hump by producing an RFA or other funding mechanisms that focuses on new diagnostics for ME/CFS such as the nanoneedle, microbiome, metabolomics, etc.

Open Medicine Foundation should be funded to speed on the nanoneedle bio marker research which would make this disease much more attractive to new researchers and provide a way to quickly find medications that may help the patient population that has suffered for so long. There is no doubt about the expertise and renowned scientists that are part of this group and its criminal not to invest our tax dollars.

Simmaron Rresearch should also be supported with funding and assisted in getting Ampligen so that they can complete important and promising research. Since Ampligen is all ready approved for ME in Argentina this is also criminal to not assist in getting a medication to market.

Overcoming sci challenges/barriers

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.

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 plan.

Also needed are

simultaneous, continuous efforts in parallel (not just sequentially)

committed funding for the Collaborative Research Centers and DMCC as well as additional Collaborative Research Centers

multiple RFAs, PAs, administrative supplements and other funding mechanisms

outreach (reduce stigma associated with being in the field, dx etc)

committed efforts to increase the number of clinicians who can appropriately diagnose patients which in turn increases the number of accurately diagnosed patients which in turn increases the number of appropriately diagnosed patients available to participate in studies

Note - see also the MEAction submission

- More funding

- Create large scale registries of patients with a wide variety of data types (clinical and patient data). Since many patients have no doctor and are not recorded via traditional care pathways use innovative online digital methods to discover and engage with these patients - digital marketing/social media

campaign to reach and recruit possible patients, online workflow to validate diagnosis and gather additional data (blood test data, activity levels, cognitive function etc.).

- Use large scale registries to support phenotyping and endotyping of ME/CFS through segmentation/clustering etc.

- Given the systemic nature of ME/CFS a cross discipline research approach is needed, drive this approach via funding policies/programs that mandate a cross discipline consortium and provide support in how to manage such complex programs (similar to EU Horizon2020).

- Fund more exploratory research i.e. early stage hypothesis generating science that is too early for pharma funding but struggles to meet the criteria for NIH grants.

- Fund research collaborations with early stage pharma/biotech companies on novel treatments that for commercial reasons are being targeted at established diseases but also have potential to help MECFS e.g. Inflazome

- Recruit additional researchers by targeted labs focused on related areas/diseases - create funding awards that will encourage Research Directors to broaden their research agenda to include aspects relevant to ME/CFS. For example, those research centres focused on MS, Parkinson's, Severe Asthma, Inflammation, Neurology. This supports junior/mid-career researchers to get involved in novel research that might then be spun off into dedicated research centres as they grow their careers.

- Support the creation of patient/advocate advisor groups - to encourage patient centric research.

- Progress the evolution of a medical discipline that will "own" MECFS. Does it belong in Neurology, Rheumatology, Haematology, Immunology? Fund the creation of an "American ME Clinician Society" that will acting as a central organisation for researchers/clinicians/educators (similar to what the American Thoracic Society does for Asthma and other lung conditions).

- Include MECFS in all medical textbooks and training. Increase outreach/education to existing healthcare providers at all levels.

Set up RFA call for ME research

Lack of research capacity - increase flow of young researchers (TtF)

Update medical education - by involving medical students in research, changing medical curricula

Campaign for a specialism in ME to be created

Standardise on guidelines to use with a commitment to regular (annual) updates

Common Data Elements usage mandatory

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

- Activate a diverse stakeholder group in a "moonshot" model for ME/CFS to reach an agreed upon disease model that reflects the best current scientific knowledge and how it fits together. The group should be charged to set ambitious, time bound goals to fill gaps in the research pipeline, and meet regularly to monitor progress. Their activities should be communicated regularly to the community.

- Establish "Dream Teams" that consist of researchers organized by area of focus headed by a leading researcher (like this analog model of Standup to Cancer:

<https://standuptocancer.org/research/research-portfolio/dream-teams/>). The Dream Teams communicate on a regular basis, share findings, identify collaborative projects and support each other's work. The heads of the Dream Teams meet regularly to share findings across areas of research.

b. Address institutional and process barriers that persist at NIH

- The decision to organizationally position ME/CFS in a trans-NIH Workgroup and not in an Institute can be detrimental to progress and accountability. House ME/CFS in an Institute (NINDS), but ensure other related institutes are connected.
- Engage in communications efforts that reinforce the validity of the disease and increase awareness of ME/CFS among NIH researchers, scientists external to the field, clinicians, students, and the broader public; including, listing ME/CFS on the NINDS website, authoring blog posts on the impact of the disease Directors blog, placing impactful content in the Director's album, and amplifying the message on NIH social media channels
- Expedite the impact of the consortium approach adopted by NIH's creation of Collaborative Research Centers by marshaling the funds to aggressively expand the number of Centers. Although the three centers are advancing great work, high-quality proposals were left on the table; the centers are too few, too small and too narrow. NIH needs to fund more centers in more diverse domains (e.g. in autonomic nervous system dysfunction)
- Initiate an investigator-initiated research funding stream aimed at hypothesis generation to amplify existing community-driven and privately-funded seed funding mechanisms, like Solve M.E.'s Ramsay Award Program - with the aim to build a robust bench of researchers and pilot data that can be used to apply for R-01 level funding based on defined hypotheses
- Increase the amount of funding available for researchers wishing to better understand this disease
- c. Create a global, openly-available, centralized resource of well characterized ME/CFS patient, healthy control and disease control data and bio specimens.
- Provide directed funding opportunities to support the establishment of a global registry and biobank for ME/CFS that integrates data from existing, disparate sources (e.g. SolveCFS Biobank/You + ME registry, UK's ME/CFS Biobank at London School of Hygiene and Tropical Medicine, Simmaron Research, and other research groups)
- Support methods for longitudinal data collection, including biosample collection at multiple time points and ongoing capture of symptoms and outcomes
- Ensure house- and bed-bound people with ME/CFS are reflected in the global biobank and registry by requiring methods to complete at-home blood draws or facilitate travel to blood draw centers or clinics
- 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
- The lack of a consensus research case definition is a fundamental barrier to progress and quality research and replication. Until a consensus can be agreed upon, or a new research criteria is universally-adopted, NIH should issue guidance that researchers require the presence of post-exertional malaise (PEM) in determining a case of ME/CFS.
- The field lacks the studies and instrumentation to back up a standard for disease severity.
- Utilize open science framework mechanisms to increase transparency and share data (positive and negative findings) and methodologies to ensure researchers are building on and synergizing each other's findings.
- Package up the state of ME/CFS scientific knowledge and most promising areas research, best data collection practices, and optimal research methods (including how to define an ME/CFS case, the use of Common Data Elements and other validated or recommended questionnaires) into a NIH sanctioned toolkit for researchers new to the field. Update it yearly and make it readily available on the NIH website, making a concerted effort to publicize it to potential new researchers (analog from Solve ME's Ramsay Program here: <https://solvecfs.org/wp-content/uploads/2019/04/Toolkit-2019-Final.pdf>).
- e. 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

- Create NIH-sponsored career growth resources, mentorship opportunities, and retention mechanisms that encourage young researchers into the field and reinforces the field of study is a valid, viable career path.
- Repeat the 2019 US-based “Thinking the Future” young investigators conference every year.
- Make use of existing networks of researchers, for example Solve ME’s Ramsay Award Program Investigators, as a vertical structure for mentorship and a resource for idea generation, proposal validation and career advice in the field of ME/CFS
- Issue directed funding to support the development of tools for a ME/CFS researcher network that brings new actors into the field

- Make a research toolkit that readily orients new researchers to the field and reduces the learning curve for best practices

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

- Support and expand the efforts of the Clinical Education Working Group (Bateman Horne)
- Leverage opportunities to educate clinicians about the disease by making them aware of clinical research opportunities (e.g. at NIH, or in the creation of a disease registry/biobank)

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

- Host a yearly conference on the NIH campus
- Fund non-NIH sponsored conferences aimed at building an integrated network of researchers. There is an existing network of researchers funded through Solve ME’s Ramsay Program, consisting of established ME/CFS researchers, young investigators, and scientists new to the field, that can be capitalized on to build out a robust agenda for a conference that is generative and collaborative
- Open up research by establishing a central data sharing platform to allow researchers to share data (both positive and negative findings) and methodologies
- Establish an ME/CFS research communication channel (e.g. Slack) to allow for real-time communication between researchers
- Encourage young researchers to come into and stay in the field through mentorship programs with established ME/CFS researchers

h. 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

- Provide opportunities for people living with ME/CFS to weigh in before decisions are made on priorities, strategy, study design and research approaches
- Promote community-based participatory research approaches in ME/CFS

MEICC criteria

We believe that strategies for overcoming scientific challenges or barriers to progress in ME/CFS research should include :

- 1) Reduce stigma around ME/CFS through NIH’s communications with the scientific community regarding the seriousness of the illness and urgency for research.
- 2) Learn from patients. While it is important to understand the etiology of ME/CFS, the desperate

plight millions of patients are in demands scrutiny of solutions. Today, we know that ME/CFS patients typically have dysfunctional immune, nervous system, and endocrine function, with many having common comorbidities of autoimmune POTS, MCAS, adrenal insufficiency, and sick thyroid. Though a definitive diagnostic test will be useful, patients can be readily diagnosed by expert clinicians today. And, while the odds of recovery are grim, the relatively few patients who get top quality care can and do improve dramatically - moving from being housebound/bed bound to be able to work, exercise, and participate in social functions. Learning from these patients is crucial, for they point the way for greater solutions. Typically, these patients have a team of doctors and a suite of treatments, so the learnings and progress cannot be easily collected from a single EHR system. Attention as to HOW data is collected to ensure it is complete for each patient will yield better results.

2) Fund multi-year studies with multiple stages of research. Patients should be identified for each known subset and the following should be collected, analyzed, and best practices/knowledge should be gleaned and shared with researchers and healthcare organizations:

a) Complete medical history, with attention to history of known viral or bacterial infections, immune system abnormalities, hormonal irregularities (adrenal, thyroid, sex hormones including pregnenolone and DHEA), and autoimmune conditions

b) Family history, with attention to other ME/CFS, MCAS, EDS, and POTS patients, autoimmune conditions, multiple sclerosis, autism, and cancer.

c) Genetic data

d) History of current illness, including timeline, symptoms, lab work and treatments over time

3) Funding new technologies.

4) A database should be built correlating treatments, timing of treatments in relation to other treatments, lab work, symptoms, ICD10 codes, team of doctors and their specialties and institutions, and SF-36 scores, that can be accessed and used by researchers

5) Committees who make decisions on research, which should include patients who have undergone successful treatments (not just sick patients who have not been successful with treatment), functional medicine doctors who look at the body as a system of systems, and scientists from bodies like the Institute for Systems Biology who look at the body as a system of interrelated systems, and not just the usual suspects. And include ME/CFS researchers in NIH the Working Group.

One of the most significant barriers to ME/CFS research and patient care is the need for a clinical standard for diagnosis/evaluation. Without an accepted standard means to stratify a patient population for research, it becomes difficult to compare individual studies and creates confusion that is a barrier to progress. Patients can be subtyped further based not only on age, ethnicity, and disease severity and duration but also on orthostatic intolerance, hormonal differences, autoantibodies, and inflammatory status. Note that each of these variables will need their own standards of classification.

Funding!!!!!!

These are listed on <http://www.me-ireland.com/research2.htm> and www.me-ireland.com

Using the same diagnostic criteria for all research - 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 of symptoms and worsening of the disease 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 as ME/CFS exhibit this clinical feature.

You MUST get the whole medical community involved. You will never be able to educate enough new scientists and doctors to tackle 1,000,000 patients without the whole medical community interested. Patients need access to doctors now. It is very important that the projects I list here come from the NIH and CDC so doctors will take them seriously. You are a most highly trusted source of new medical information.

So first:

Rename PEM to something more accurately descriptive

Chronic fatigue syndrome is a vicious disease with a stupid name, like calling smallpox polka-dots. The name "post-exertional malaise" is not quite as bad of a description for the debilitating flares that result from too much activity and end in permanent progressive muscle weakness, but it's sort of close. It really needs a new, accurate name that includes "flare", and would help grab doctors' attention.

And then:

Establish medical homes for ME/CFS and send an emergency alert to physicians

Please develop an emergency alert that asks physicians to screen for PEM, cease prescribing exercise immediately to prevent harm to their patients, and substitute pacing until an accurate diagnosis can be accomplished.

I am an ME/CFS patient. I exercised myself into being completely disabled and homebound. You have plenty of evidence now from the amazing research that has happened over the past few years to call chronic fatigue syndrome what it is - a severely disabling inflammatory brain and neuromuscular disease, and an acquired mitochondrial disease, with a likely autoimmune component. Now you have to pick a medical home for it. Neuromuscular medicine, neurology, and cardiology come to mind. Exercise is a good recommendation for nearly every disease that has components of chronic fatigue syndrome, with the glaring exception of post-exertional malaise. So there are, what, 800000 + ME/CFS patients out there that are being injured and driven into disability right now because they are either misdiagnosed and told to exercise, or properly diagnosed and mistakenly told to exercise. This is a terrible emergency. An infectious disease with these types of severe outcomes and patient numbers would be treated as an emergency. An infectious disease this bad, with as simple of a remedy as "stop exercising while we figure out what to do next", would be immediately acted on. It is times for NIH and CDC to work together and act on this now.

To clarify, I would like to see NIH and CDC to get together on a letter that is pushed out to all doctors in specialties who are likely to come across this disease. The goal would be to identify patients with post exertional malaise and stop exercise recommendations, substituting pacing.

It would be best if it was one page long with bullet points and links to more information. The letter has to have an accurate description of post exertional malaise right up front because that indicates that a patient is having the flares that cause progressive disability. That is the symptom the doctors will be able to use to sort out chronic fatigue patients. It must emphasize pacing to minimize damage while waiting for more treatments to become available, and would need a link to pacing resources.

After the PEM description, it needs supporting bullet points on: brain inflammation and raised lactate in the spinal fluid, suppressed mitochondrial oxidative energy generation including reduced fatty acid oxidation, viral or other insults pushing cells into a metabolic trap and the mitochondrial cell danger/cell healing response, POTS racing heart and angina (leading to heart failure?) with or without a drop in blood pressure, deranged sleep, proliferation of concurrent autoimmune diseases, other autoimmune indicators like proliferation of certain immune cells, overactive mast cell responses that can be addressed with H1 and H2 antihistamines, T3 problems, deranged microbiome causing a reduction in butyrate-producing microbes that would normally supply SCFA's for energy, and an emphasized bullet that ME/CFS is twice as common but much more disabling than MS with 1 million Americans affected.

Even though medical tests aren't always available yet for what has been discovered so far, the bullet points would indicate the expansiveness of the biological changes to the physicians. Each bullet point needs to link to a physician's guide on what to do about it from current knowledge of chronic fatigue researchers. The last line of the letter should urge physicians to screen their patients for post exertional malaise and to treat them appropriately, and to track down patients they had treated previously and given the wrong advice to and likely injured. Perhaps money or resources could be made available to doctors to assist with this part? This sounds hard but I have some technical ideas listed later. I don't know how you do it with infectious diseases but it seems like there must be good models there for accomplishing it.

Develop a patient questionnaire to discern PEM from other symptoms

The second page of the letter should have a questionnaire/ interview for a patient to determine if they have post exertional malaise. Creating the interview in a way that can do this discernment is critical, and a good short-term research project. I think you need to be really aggressive with the wider medical community now, in light of the new research. It is nice that you are training up new researchers and doctors, but that will only make a small dent in achieving treatment for 1 million ME-CFS patients. The current medical establishment needs to get their head around this disease and start dealing with it effectively. They absolutely have to stop injuring patients with bad exercise advice, or by simply kicking them out of their offices with no help at all.

Be aggressive in pushing the alert into the medical community, to protect patients and open up more avenues to push doctors into acting responsibly.

Most doctors are really happy when they learn new information that updates their understanding of a patient whose symptoms confused and worried them. However, I think you know that some doctors can be pretty thick-headed about changing their views. I ran into a truly terrible neuromuscular doctor, after losing a wonderfully helpful MDA doctor to retirement. I haven't been able to find any neuromuscular doctors in Southern Michigan who treat ME/CFS with current knowledge of the disease - zero - a common problem in the Midwest. So I tried to bring a new doctor online last year and it was a disaster. The head of the neuromuscular clinic at a major university told me he would not treat chronic fatigue syndrome now or in the future, and neither would anybody in the department that he ran. I was in bad shape that day and having trouble talking, so he had me at a big disadvantage, but really, patients shouldn't need to do this work. Because of the maligned reputation of chronic fatigue syndrome, I think you need to be really tough and aggressive with these doctors to get them to pay attention. I had an underlying very mild fatty acid oxidation disorder and was initially diagnosed with mitochondrial disease and ended up with the MDA because of that. But it became

clear later that I was DISABLED by chronic fatigue syndrome, AFTER I exercised my life away. My experience with doctors is that four out of five neuromuscular and neurology doctors are complete blockheads when it comes to ME/CFS. Cardiologists on the other hand welcome this information because they see patients like me with normal blood pressure and POTS and don't really know what to do. They also seem to be less prone to deciding that they are also your psychologist. The advantage of a one-page letter alert is that the doctors are then put on notice that they must address the disease seriously. For a patient, that means if they are injured after being given bad advice, they actually have recourse to demand better medical treatment or compensation through malpractice laws. A couple lawsuits may be what's needed to move the alert faster through the medical community. It certainly will get the attention of doctor-employing institutions and their insurance companies. I imagine a broadly distributed alert would also get the attention of news agencies, informing many more patients about what is actually happening to them. Push the letter to doctors you fund now, first.

I think that my terrible doctor might have had NIH funding for neuromuscular research. It seems critical to me that you get this new information out to all of your neuromuscular, neurology and cardiology fundees ASAP because not screening for PEM could cause significant problems in their research. Patients who have ME/CFS concurrent with the disease they are studying could present confounding results since there would be an additional disease process going on. Since doctors with grants are generally admired at their institutions they are trusted source of information. Since doctors with NIH grants generally pay close attention when NIH talks to them, well that's an added benefit. Please encourage these doctors to take on ME/CFS patients, first because these patients belong in their care, second because the need to be able to identify the symptoms and differentiate them in their study patients, and personal experience with ME/CFS patients will help a lot with that.

-There should be accountability with *replication*, collaboration, methods-sharing, and data sharing. There is too much weight placed in some groups' work and hypotheses. More influential groups should avoid big press releases before something has been replicated. These patients have had to endure too many cycles of hype and bust.
-At the NIH conference, in the "Young Investigators" talk about general grant proposals, emphasis was placed on "innovation." For this condition, that should be de-emphasized and replication should be emphasized.

The most important thing to overcome barriers to research progress in ME/CFS would be for the research community as a whole to be for the Director of NIH to make a clear public statement, distributed broadly, that ME/CFS is a real, physiological illness, stating clearly that it is not psychosocial. I am trying to work with the Cleveland Clinic, and I believe that great research can come from there. But at the Cleveland Clinic, they still believe the CBT/GET treatment protocol, and believe in the psychosocial model. Or, they say to me, "I don't believe in Chronic Fatigue Syndrome." If I could send them to the NIH website, or give them a copy, to view a statement from Dr. Collins that ME/CFS is indeed a real, serious, severe, and physiological illness, with exciting areas of research to pursue, and that the CBT/GET/psychosocial model has been disproven, it could make all the difference in the world. The biggest barrier to progress in research is the stigma. Dr. Collins and NIH can take care of that with mere words, words that don't cost a dime.

Realise that most patients are too disabled to participate fully in these questionnaires. We require advocacy assistance. I would like to say much more but am too unwell. Most patients are intelligent people, we're simply very ill. This is the best I can manage & I will suffer the consequences of PEM for my efforts.

Launched in the past 5-6 years, strategies to bring highly talented researchers into the ME/CFS field, deploy state-of-the-art technology, and foster inter-disciplinary and international collaboration are proving successful evidenced by progress reported at the "Accelerating ME/CFS Research Conference" April 4-5, 2019.

NIH should build on the success of these strategies and act to:

1. Provide additional funding to accelerate and expand research at the existing three CRC's
2. Provide funding to add six or seven additional CRC's, geographically dispersed with one dedicated to Pediatric ME/CFS research
3. Provide funding to advance treatment research
4. Provide funding to advance diagnostic test development
5. Provide funding for large-scale patient data collection for Big Data Projects based on the Common Data Elements work
6. Provide funding for joint projects with Industry namely medical equipment and device manufacturers, diagnostics companies, Pharma, AI companies, etc.

Note: Claudia Clarara has identified sources of additional ME/CFS funding within NIH [ME/CFS Advocacy Call, April 9, 2019]. Furthermore, changes to NINDS portfolio can be made to decrease the Basic/Basic allocation and increase the Basic/Disease, Applied Translational and Applied Clinical allocations to provide ME/CFS funding. [NANDS Advisory Council, September 13, 2018].

Use the ICC -- International Consensus Criteria.

The other defs are about fatigue and / or hold no methods of testing for Myalgic Encephalomyelitis.

Need clearly defined and same disease patient cohorts for M.E. -- use ONLY ICC.

Fatigue is not what any M.E. study ought to be about.

Scientific challenge? I am not qualified to address that, other than it is my personal belief that fibromyalgia is an early symptom of CFS/ME. At least it was with me. How are we going to diagnose patients with so many different responses and levels of pain? As for the barriers to progress, we as a group have found a motley response from our doctors. My doctor ignores the fact that I have orthostatic intolerance to the point that I can't get into my office building from my car some days and have an electric wheelchair. Others have sympathetic doctors, but they have NO TOOLS with which to even diagnose us, let alone treat us.

ME/CFS research is bogged down in complexity. Each patient seems almost to have their own customized disease. Traditional research based on statistical group comparisons is poorly suited to this type of challenge. There are other related conditions in a similar state (EDS/ESD, Lyme Disease, GWI, MCAS, MCS, Mold Illness, etc). The suffering in the patient community due to the inability of research to address individuality in these illnesses is immense. Patients regularly receive treatments that have low probability of helping, often making the patient sicker rather than better.

I believe a systems biology approach to all of these conditions will be essential in finding the best approach to finding effective clinical strategies. We need a way to combine research in stealth microbes, neuroscience, molecular energy pathways, and the genomics of immune response and detoxification, for example.. Putting all those pieces together may require development of new approaches to modeling complex biological responses. Supporting a Systems Biology approach to ME/CFS and all related conditions would be a good strategy, in my opinion.

EPIDEMIOLOGIC KNOWLEDGE

Barriers:

Lack of basic epidemiologic assessments characterizing disease landscape precludes informed construction of subgroup cohorts for exploratory and clinical research

Given that CDC's plan for epidemiologic research is BRFSS, which is self-report phone survey based, there is a need for NIH to lead comprehensive epidemiologic studies that adequately capture this disease population

Lack of patient engagement with medical care/survey capture due to stigma, uninformed practitioners, psychosomatic narrative polluting literature/medical practice

Lack of centralized patient registry portal for engagement with research data capture efforts

DMCC only includes CRC data and omits many large cohorts with extensive phenotyping data

Sex, race, age, socioeconomic biases in existing data and research cohorts, males, minorities, poor, youth underrepresented (and underdiagnosed)

Strategies:

Conduct exhaustive, comprehensive epidemiologic study, using appropriate patient selection methods, to define: demographics; prevalence; natural history, onset types, triggers, environmental exposures, risk factors; breadth of symptomology; spectrum of severity, establishing foundation to develop disease grading metric and instrumentation; exertional and cognitive provocation/PEM triggers; duration, fluctuation, progression, remission/recovery, relapse; comorbidities and overlapping syndromes (e.g. POTS, EDS, FM, MCAS, SFN, endocrine dysfunction, SIBO, MCS); functional and mobility impairment, disability.

Assess and rectify age, sex, race, socioeconomic biases in diagnostic capture and prevalence estimates

Overcome the sex, race, socioeconomic, age biases in existing data and research cohorts; account for males, minorities, poor, youth (underrepresented and underdiagnosed)

Support appropriate community-based epidemiological strategies to help medical practitioners in underserved areas recognize ME in their patient populations

Include ME-targeted components in existing broad epidemiological initiatives like the All of Us

Research Program and the Environmental Influences on Child Health Outcomes Program

Establish a large data and biorepository for comprehensive study of disease landscape, implementing exceptional rigor in data collection, construction, and design; and incorporate other large cohorts (e.g. UK Biobank, Klimas, Stanford) into the DMCC

Fund establishment of a patient registry portal for data capture

Fund targeted data aggregation efforts

Fund retrospective analyses utilizing pooled existing cohort data and clinical histories

Fund/initiate prospective longitudinal studies

ARTIFICIAL COHORT HETERO/HOMOGENEITY

Barriers:

Lack of standardized research case definition, or agreement on core features required in all ME research cohorts

Lack of validated, standardized objective measure(s) and/or biomarker(s) for cohort selection

Lack of clarity, consensus, and transparency in defining and reporting cohort selection methods

Deficiencies in disease-specific instrumentation, methods and guidelines to fully characterize and report disease features

Lack of representation of severely ill in many studies

Sex, race, age, socioeconomic, biases in existing data and research cohorts (males, minorities, youth, poor underrepresented)

Strategies:

Encourage research selection criteria requiring PEM during grant application/review process

Encourage transparency in reporting cohort composition metrics, including: definition(s) met and how this was determined; debility (KPS); severity definition and scale (by future disease-specific scale); duration; onset type; age; and sex

Reach consensus on core inclusion/exclusion criteria and methods used for all ME research cohort selection to facilitate cross-study comparability and reproducibility

Reconvene a methodological working group to identify deficiencies in CDE guidelines, further standardize assessment methods and measures, and recommend areas of need for development of novel tools

Issue RFA for development and validation of disease-specific instrumentation and methodological practices to enable consistency in cohort selection, descriptive cohort reporting, comprehensive disease characterization, phenotype subgroup stratification, and sensitive capture of change in disease status, including: severity instrument, scale and standardized terminology; PEM instrument; fatigue instrument; sleep instrument; orthostatic intolerance instrument; pain instrument

Review and refine CDE recommendations to include: require cohort reporting and data stratification by PEM status; PEM instrument; severity instrument, scale and standardized terminology; disease-specific fatigue, sleep, OI, pain instruments

Develop and disseminate strategies for engaging severely ill and very severely ill in studies

Overcome the sex, race, age, socioeconomic biases in existing data and research cohorts; account for males, minorities, youth, poor underrepresented (and underdiagnosed)

INTRINSIC BIOLOGICAL HETEROGENEITY

Barriers:

Complex disease, multisystem involvement

Multiple triggers/etiologies

Disease provocation, spontaneous fluctuation

Disease progression, remission, relapse

Diversity of severity

Diversity of symptomology

Confounding comorbidities, overlapping syndromes

Lack of validated, standardized objective measure(s) and/or biomarker(s) for cohort selection

Deficiencies in disease-specific instrumentation, methods and guidelines to fully characterize and report disease features

Strategies:

Issue FOA with set-aside funding for diagnostic tests

Develop and disseminate strategies for engaging severely ill and very severely ill in studies

Develop and disseminate strategies, methods and ethical guidelines for capturing baseline versus provoked states

Encourage longitudinal data capture

Large data and biorepository for comprehensive study of disease landscape

Encourage and support identification of subjective-objective correlates

Encourage and support subgroup stratification analyses:

Define prominent clinical phenotypes by: leveraging existing (and imminently expiring) clinical expertise, conducting large-scale data analysis in a comprehensive database

Encourage researcher data stratification analyses and reporting by: definition, severity, debility, onset type, exposure/trigger, duration, progression, recovery/remission, symptoms, age, sex

Encourage transparency in reporting cohort composition metrics, including: definition(s) met and how this was determined, debility (KPS), severity (by future disease-specific scale), duration, onset type, age, sex

Reconvene a methodological working group to identify deficiencies in CDE guidelines, further standardize assessment methods and measures, and recommend areas of need for development of novel tools

Issue RFA for development and validation of disease-specific instrumentation and methodological practices to enable consistency in cohort selection, descriptive cohort reporting, comprehensive disease characterization, phenotype subgroup stratification, and sensitive capture of change in disease status, including: severity instrument, scale and standardized terminology; PEM instrument; fatigue instrument; sleep instrument; orthostatic intolerance instrument; pain instrument

Review and refine CDE recommendations to include: require cohort reporting and data stratification by PEM status; PEM instrument; severity instrument, scale and standardized terminology; disease-specific fatigue, sleep, OI, pain instruments

BIOMARKER(S) DISCOVERY and VALIDATION

Barriers:

Heterogeneous cohort even when properly characterized with case definitions that require core features of the disease such as PEM

Lack of study reproducibility, incongruous findings across cohorts due to: intrinsic biologic heterogeneity, definition/selection criteria, specimen handling, laboratory methods

Lack of replication studies of prior findings in larger cohorts

Lack of comprehensive study of disease landscape to support subgroup analyses

Specimen handling issues (e.g. culture of tissues without donor serum)

Strategies:

Issue FOA with set-aside funding for biomarker discovery and validation

Large data and biorepository for comprehensive study of disease landscape

Expand cohort sizes and define selection criteria for replication of prior findings

Deploy systems biology approaches for aggregate dataset analysis

Support unbiased omics approaches with subgroup stratification analyses

Fund large GWAS to identify risk variants, candidate pathways perturbed

Encourage targeted subgroup stratification analyses defined by clinical phenotype, severity, comorbidities, symptom profiles

Define, disseminate and incorporate into grant review feedback disease-specific specimen handling specifications and encourage adequate methods reporting

PATHOBIOLOGY DISCOVERY

Barriers:

Artificially heterogeneous cohorts due to variable research case definitions not requiring PEM

Lack of validated, standardized objective measure(s) or biomarker(s) for cohort selection

Intrinsically heterogeneous cohorts due to biologic disease variability (diversity of severity, diversity of symptomology, potential diversity of triggers/etiology, confounding comorbidities, overlapping syndromes, multisystem involvement, fluctuation, progression/remission)

Lack of dedicated disease-specific research funding opportunities

Lack of in vitro/in vivo model systems, reliance on primary biospecimens for all experiments

Dearth of clinical research resources: very few expert clinicians to support biospecimen pipeline;

limits to properly diagnosed and characterized patients engaged with medical care (due to stigma,

misperception, psychosomatic narrative, absence in medical education, few expert clinician); lack of centralized registry to channel patients toward qualifying research studies

Paucity of aware, interested, capable, disease-informed researchers

Lack of/failed study replication efforts across multiple/larger cohorts

Spontaneously fluctuating and provoked disease state

Need for appropriate control and illness comparison groups to support specificity

Narrow focus of recent infectious acute-onset intramural study

Strategies:

Issue FOA with set-aside funding for exploratory etiology investigations

Issue FOA to develop in vitro and in vivo models (e.g. serum transfer studies)

Expand cohort sizes and define selection criteria for replication of prior findings

Encourage mitigation of artificial cohort heterogeneity by requiring PEM for all study participants

Clarify methodological definition reporting standards to support study reproducibility

Encourage use of sample sizes adequate to perform subgroup analyses on heterogeneous cohorts

Encourage all researchers to conduct subgroup analyses within their datasets, supply suggested

stratification variables (e.g. definition +/- PEM, clinical phenotype, symptomology, severity,

comorbidities), and establish reporting expectations

Solicit and fund "phase 0" exploratory trials in stringently-selected, enriched cohorts with the goal of pursuing exploratory outcomes, responder/non-responder and subgroup analyses rather than proving efficacy

Encourage systems biology approaches, aggregate dataset analysis

Utilize unbiased exploratory omics approaches with subgroup stratification analysis

Support large GWAS to identify risk variants, candidate pathways perturbed

Encourage accounting for baseline vs. provoked state with provocation studies

Account for spontaneous fluctuation with longitudinal data capture, utilize time interval assessments to capture fluctuations, do not assume static even when unprovoked

Survey and account for use of off-label pharmaceuticals, supplements

Define and utilize appropriate control populations/illness comparison groups (i.e. activity-matched, fatigued, inflamed groups); ensure healthy controls are free of ME symptoms; standardize methods for determining control appropriateness

Large data and biorepository for comprehensive study of disease landscape

Establish disease-specific autopsy tissue biobank

Support multi-disciplinary research studies that look at multi-system interactions

Funding mechanism to support writing up case reports and comparison group studies

Accelerate intramural infectious onset study; see multiple participants in parallel

Initiate design process of comprehensive intramural studies on other subgroups (e.g. long duration, severely ill)

NIH ADMINISTRATIVE STRUCTURE, GRANT SUBMISSION AND REVIEW

Barrier:

No formal institute home, administrative ownership, institutional accountability

ME not listed on NINDS website list of diseases

No dedicated full-time program officer(s) focusing solely on this disease

Insufficient trans-institute coordination, institute participation, inconsistent funding commitments

Insufficient commitment across NIH to making tangible progress on this disease

In being handled exclusively by a Trans-NIH WG process, ME is not prioritized within any one institute; unclear how Trans-NIH WG recommendations translate into institute-specific strategies, goals,

resource commitments, and actions

Lack of transparency and stakeholder engagement with the Trans-NIH Working Group
Ad hoc nature of Special Emphasis Panel not sufficient to ensure consistency in application review
Dearth of qualified, informed grant reviewers, confounded by COI as collaborators in small research community
Multidisciplinary representation required for each SEP review
Not every ME application is captured and channeled through SEP
Clinical trials applications not supported/reviewed by disease-informed reviewers across institutes
Lack of disease-specific FOA to entice new researchers, support career focus
Lack of ME researcher knowledge of availability of relevant RFAs in various institutes
Lack of meritorious applications (rigor, novelty, significance)

Strategy:

Develop a comprehensive outcomes-focused strategic plan that has the necessary funding, coordination, cross-institute commitment, stakeholder engagement, and NIH political leadership to aggressively address the challenges and barriers and truly “accelerate ME research”. This plan must leverage the numerous opportunities to deliver patient-focused outcomes while simultaneously building up foundational knowledge about ME.

Establish an Office of ME Research within the Division of Program Coordination, Planning, and Strategic Initiatives of the Office of the Director staffed with:

A director responsible for developing and coordinating a long term fully-funded strategic plan, integrating ME initiatives into every Institute and Center (including leading/liasing with the Trans-NIH WG), who functions as a trans-institute “czar” (as recommended by CFSAC) driving progress across institutes; and

At least one staff member responsible for outreach and coordination across all research priorities in each of the extramural and intramural grant programs, working with Program Officers in various institutes to facilitate informed review committees and ensure ample support to applicants during grant preparation.

Increase Trans-NIH Working Group transparency and stakeholder engagement

Hire multiple full-time Program Officers within ME’s formal home institute focused exclusively on ME to support grant applicants, career development, study section composition

Periodically re-evaluate Special Emphasis Panel effectiveness, composition, reviewer knowledge of disease-specific issues

Bolster disease-specific grant writing support from Program Officers (e.g. regular grant assistance call-in “office hours” with NINDS and NIAID POs, invite junior/senior investigators as well as outside domain experts, listserv, website covering study design issues)

Engage a Program Officer in each of the Trans-NIH institutes with ME in their portfolio who knows how to navigate their institute

Issue FOAs including those with set-aside funding; RFA and/or Program Announcement would resolve uncertainty about where to send applications and streamline grant application process

Make guidelines and process very explicit and transparent to grant applicants (who to contact and when in considering submitting an application, whom to contact at various institutes and on the SEP)

Ensure grant applicants and reviewers are given disease-specific CDE guidelines, feedback, and guidance

Ensure clinical trials applications are handled by staff knowledgeable of ME issues

Overcome reviewer bias toward significance versus basic questions that are not necessarily novel but are essential for this field at this time; ensure field-informed reviewers know to defend the merit of addressing basic questions in this disease

Ensure grant reviewers understand and acknowledge the value of unbiased exploratory approaches versus standard hypothesis-driven proposals in this disease at this time

RESEARCH FUNDING

Barriers:

Lack of set-aside RFAs, program announcements, administrative supplements

Lack of year-over-year growth trajectory funding

Inconsistent, insufficient contributions from other institutes

Insufficient commitment from Office of the Director

Paucity of investigator-initiated applications, including those from senior researchers at major academic centers

Lack of meritorious applications

Lack of committed, multi-year funding disincentivizing researchers, especially senior researchers from risking their career and entering this field

Strategies:

Issue disease-specific FOAs for investigator-initiated applications

Issue multiple, multi-year, disease-specific RFAs to ensure stability for newcomers (senior and junior investigators) to the field and enable a secure dedicated career path

Supply, at minimum, an initial \$50MM infusion to fund RFAs that will accelerate the field. Thereafter, implement consistent year-over-year growth trajectory funding increases (minimum 40%), including commitments from all trans-NIH WG institutes and a substantial commitment (e.g. 10% of the total NIH ME funds) from the Director's Common Fund, until funding is commensurate with disease burden.

Issue and advertise the availability of interdisciplinary administrative supplements enabling grant recipients to recruit outside expertise, prompting established investigators to find expert collaborators in overlapping fields and construct joint approaches

Solicit and fund high-risk, low-data exploratory and hypothesis-driven R21 applications

Increase the payline for all ME grant applications

Engage in targeted outreach and solicitation of applications from senior investigators at major academic centers whose domain expertise is relevant to ME

CLINICAL EXPERTISE

Barrier:

ALL ME research currently relies on primary patient-derived data and/or biosamples

There are very few expert clinicians with substantial experience diagnosing, monitoring or treating this disease

The pool of diagnosed patients and the pipeline of patient-derived research resources are severely limited by the paucity of expert clinicians

These expert clinicians are overburdened with clinical care obligations and existing research efforts and do not have the bandwidth to participate in new research collaborations with newcomers to the field or young investigators

This small group of clinicians are nearing retirement, which will further diminish research capacity

The collective knowledge of this clinician group is not recorded or disseminated, which is a barrier to new and less experienced clinicians

ME diagnostic and treatment protocols are not incorporated into medical education curricula

Medicare only allows for a 15-minute meeting in ME, meaning this complex illness is financially impossible for clinicians to take on

Lack of objective testing/biomarkers poses an uncomfortable challenge to physicians in making an ME diagnosis by exclusion of other diseases and subjective symptom report

Strategy:

Fund, convene and maintain a clinical network leveraging medical and scientific expertise
Document, operationalize and encourage dissemination of clinical expert knowledge to researchers and the medical and patient communities
Leverage Director Collins' political capital to draw attention to the clinical care crisis and pressure other federal agencies and medical societies to resolve barriers in expert clinician workforce growth, medical education, medicare funding, and accessibility to clinical care
Provide leadership for a cross-agency structure to identify and tackle critical bottlenecks in clinical care and the clinical research pipeline
Utilize existing NIH programs and work with other federal and state agencies to incentivize clinical specialization and research via loan forgiveness programs
Pair researchers/clinicians with patients/advocates as mentors to help people new to the field learn how pervasively ME impacts lives and why work in this field is important

CLINICAL INTERVENTION TRIALS

Barrier:

Paucity of clinical expertise, expert knowledge not widely accessible, limited bandwidth, nearing retirement, few sites that are remote for most patients

Clinical subtypes undefined

Variable selection criteria, lack of objective biomarker

Cohort heterogeneity and complexity of presentation, comorbidities, concomitant medications

Lack of standardized objective and subjective measures, undefined safety and efficacy outcome measures

Historic failed grant applications are a deterrent to reapplication

NIH's stated position that the field is not ready for clinical treatment trials

Complexity of assessing response to intervention(s) (e.g. long term relapsing/remitting pattern, short term fluctuation, potentially high or low placebo effect, comorbidities, concomitant medications)

Disease modifying versus symptomatic treatment approaches

Lack of FDA engagement

Population highly vulnerable to iatrogenic harm (especially severely and very severely ill)

Lack of/failed study replication efforts across multiple/larger cohorts

Spontaneously fluctuating and provoked disease state

Need for appropriate control and illness comparison groups

Strategies:

Fund, convene and maintain a clinical trials network leveraging clinical and scientific expertise

Operationalize clinical expert knowledge

Support standardization of research case definition, terminology, methods, and instrumentation

Solicit and fund phase 1/2/3 efficacy trials in stringently selected, enriched cohorts, i.e. therapies that are already being used in clinical practice to decrease symptom burden, address comorbidities, and improve quality of life; therapies which have demonstrated efficacy in subsets of patients in small preliminary studies; and potentially promising novel interventions implicated in disease-specific and overlapping domain research. Examples of these therapies include: antivirals, immune modulators, drugs for pain, orthostatic intolerance, sleep, and comorbidities such as MCAS that are already being successfully used off-label in expert clinical practice to decrease symptoms and improve quality of life.

Given the absence of understanding of underlying disease mechanism or in vivo models, solicit and fund "phase 0" exploratory clinical trials in stringently-selected, enriched human patient cohorts with the goal of pursuing exploratory biologic and subjective outcomes and utilizing comprehensive responder/non-responder and subgroup analyses rather than targeting efficacy outcomes in order to

generate disease knowledge, parse cohort heterogeneity, and produce enrichment strategies and outcome measures for subsequent efficacy trials

Support development of enrichment strategies:

Clinical subgrouping (e.g. symptoms, comorbidities, severity, duration, sex, medication use)

Objective selection criteria (e.g. 2-day CPET, PEM instrument, nano-needle impedance, cytokines, orthostatic intolerance measures)

Define and utilize appropriate control populations/illness comparison groups (i.e. activity-matched, fatigued, inflamed groups); ensure healthy controls are free of ME symptoms; standardize methods for determining control appropriateness

Define/develop and validate objective and subjective disease-specific measures of disease status for use as outcome measures/endpoints (e.g. CPET, activity meters, hours of upright activity ('feet on the floor'), heart rate variability, symptom assessment instrumentation, disease severity instrument, cognitive measures, and QoL measures)

Include physical and cognitive provocations to measure PEM at baseline and endpoints in study protocols

Account for disease fluctuation, appropriate longitudinal timecourse and data capture

Survey use of off-label pharmaceuticals, supplements

Develop methods for and ensure appropriate study design accounting for complexity of assessing response to intervention(s) (e.g. long term relapsing/remitting pattern, short term fluctuation, potentially high or low placebo effect, comorbidities, concomitant medications)

Large data and biorepository for comprehensive study of disease landscape

Support large-scale, high-throughput profiling studies to identify molecular targets/pathways

Support large-scale, in vitro drug screening to identify candidate repurposed drugs

Facilitate FDA engagement

Engage the severely ill through encouraging studies to budget for e.g. home visits and mobile phlebotomists and engage very severely ill in studies through caregivers

Develop instrumentation to capture a change in disease severity (as well as severity scale, standardized terminology, definitions), ensure usage during trials to capture potential harms due to participation/intervention, ensure vigilant harms assessments and reporting

WORKFORCE DEVELOPMENT

Barrier:

Ignorance about ME in academic community

Stigma/lack of disease validity in academic, medical community

Lack of senior mentorship support to young investigators, discouragement to enter field

Lack of evident funding stream to entice outside expertise, sustain a dedicated young investigator's career

Lack of accessible bioresources (lack of large biorepository, patient registry, paucity of clinical expertise)

Lack of in vitro/in vivo models to entice outside expertise, sustain a dedicated young investigator's career

High threshold of disease knowledge for entry into the field

Paucity of review materials in literature

Publications often relegated to niche/low impact journals

Psychosomatic narrative continues to pollute literature

Strategies:

Heavily leverage NIH intramural and extramural networks to actively promote disease awareness and scientific intrigue; actively bait interest in disease mystery, novel opportunities for discovery

Leverage Director Collins's and Koroshetz's megaphones, utilize every NIH media opportunity available to make the untapped scientific opportunities and plight of patients known within academia and industry

Engage a concerted campaign to rectify medical and scientific stigma

Sponsor NIH conferences annually to endorse validity, disseminate findings, facilitate collaborations; include dedicated day(s) and poster sessions for young investigators

Require publication of whitepapers out of NIH-sponsored events

Disseminate recorded materials out of NIH-sponsored events

Facilitate representation at society conferences, encourage block symposium to elevate disease profile, invite high-profile scientists to leverage star power

Exhaustively publicize new disease findings, CRC results

Targeted outreach soliciting proposals from relevant intramural and extramural domain experts (senior PIs)

Compile and disseminate a disease primer/educational videos for new investigators of biologic knowns, clinical resources, crash-course on disease-specific issues

Facilitate matchmaking between domain experts and clinical expertise/bioresources

POs perform matchmaking between applicants and outside domain experts during grant submission/revision

Issue dedicated disease-specific RFA to entice outside expertise, demonstrate capacity to sustain a dedicated young investigator's career

Improve perception of limited funds by e.g. broadcasting existing funding availability and SEP support across various institutes, via NIH communiques, Director's office

Issue administrative supplements to support interdisciplinary involvement of senior newcomers

Establish career training and mentorship program for young investigators

Develop and disseminate documentation encouraging young investigators to enter the field, ensure a viable career path

Further support a network of young investigators through the following initiatives: annual NIH young investigators conference; website; Program Officer availability for career growth; grant application support; proactive notification of applicable funding/fellowship opportunities, facilitation of collaboration and mentorship matchmaking dispersal of information on available bioresources; quarterly email updates on new resources/research findings targeted education on applicable funding opportunities; supplement awards to enable young investigator collaborations with established PIs/CRCs; encouragement and sponsorship for society conference attendance; encouraging young investigators to evangelize about ME to their colleagues; and providing materials summarizing research knowns, needs and opportunities

Create a large data and biorepository for comprehensive study of disease landscape

Create a patient registry to support study recruitment and data/sample procurement

Support resolution of clinical expertise bottleneck to facilitate patient/data/sample access

Fund development of in vitro/in vivo disease models

Fund epidemiologic studies

Fund biomarker discovery, disease-specific instrumentation and methods studies

Utilize existing NIH programs and work with other federal and state agencies to incentivize specialization and research via loan forgiveness programs

Pair researchers with patients/advocates as mentors to help people new to the field learn how pervasively ME impacts lives and why work in this field is important

For conferences, working group meetings, e.g., include presentations by patients/advocates (live, video conferencing) about real life with ME (school, work, SSDI, encounters with HCP, housing, food

access, social) to help them better understand the range of difficulties encountered by people with ME and as a reminder of why the work they are doing is so important

INTERDISCIPLINARY COLLABORATIVE APPROACHES

Barriers:

Investigators with expertise in overlapping domains are ignorant about ME

ME research is currently being conducted in silos

Need mechanisms to link clinicians and researchers

Role of comorbidities, overlapping syndromes understudied

Clinical subtypes undefined

Strategies:

Targeted outreach soliciting proposals from relevant domain experts (senior PIs) (e.g. energy metabolism, neuroinflammation, autonomic dysfunction, mechanisms of central/peripheral asthenia)

Issue FOAs for collaborative projects to facilitate engagement of outside expertise with established ME researchers

Issue FOA for collaborative supplements to existing projects (i.e. NIGMS Supplements for Collaborative Science (SCS))

Issue FOA for interdisciplinary collaborative project proposals (i.e. NIGMS Glue Grants)

Sponsor NIH conferences annually to disseminate findings, facilitate collaborations

Facilitate representation at society conferences, encourage block symposium to elevate disease profile, invite high-profile scientists to leverage star power

Engage in targeted outreach soliciting proposals from relevant intramural and extramural domain experts (senior PIs)

Facilitate matchmaking between domain experts and clinical expertise/bioresources

Compile and disseminate a disease primer/educational video(s) for new investigators of biologic knowns, clinical resources, crash-course on disease-specific issues

Program Officers perform matchmaking between applicants and outside domain experts during grant submission/revision

Issue dedicated disease-specific RFA to entice researchers and clinicians with outside expertise

Create a large data and biorepository for comprehensive study of disease landscape. Leverage the integration database created for the current Centers to store research from present and future ME-related projects. Make data integration a requirement for NIH-funded research on ME. This could include structured and unstructured data with all PII masked to safely protect patient data. Solicit data from other agencies to get a baseline sample set for research. Department of Veteran Affairs has a very large health database, for example.

Exhaustively publicize new disease findings, CRC results

Leverage Director Collins's and Koroshetz's megaphones, utilize every NIH media opportunity available to make the untapped scientific opportunities and plight of patients known within academia and industry

Support development of in vitro/in vivo disease models

COLLABORATIVE RESEARCH CENTERS

Barrier:

Not enough CRCs

Existing CRCs are underspending

Ongoing and renewal funding for existing CRCs not secure

Lack of clinical capacity within CRCs, dependent upon sparse, busy, distant outside clinical expertise

Not enough scientific and clinical outreach, lack of clinical education component

Narrow focus of CRC studies (primarily blood omics)

Not enough collaboration, data sharing

Strategy:

Fund existing CRCs adequately; encourage rapid CRC funding utilization by leveraging follow-up RO1 availability to build upon promising findings; and issue renewal funds at expiry

Issue administrative supplements to support educational outreach to the research and medical communities

Issue administrative supplements to facilitate engagement of outside/overlapping domain expertise in CRC projects

Issue FOA to fund a minimum of three more CRCs with expanded domains of focus

Support new CRCs with a diversity of research domains, for example: characterize functional/exertional features (i.e. Cook, Stevens, Keller, Systrom), neurologic aspects (i.e. Younger, VanElzakker, structural, neurocognitive).

Enforce requirements for collaboration, data sharing between CRCs

Accelerate DMCC construction, analyses, and make CRC/DMCC data publicly available to the scientific community

Heavily publicize CRC existence, publications, study recruitment

STAKEHOLDER ENGAGEMENT

Barriers:

Dissolution of CFSAC has left the ME community with no channel through which to communicate needs to NIH or other federal agencies

No specific venue within NIH for community engagement

Lack of transparency and community engagement with the Trans-NIH Working Group

Sparse disease-specific information and resources available online

Lack of venues for researcher engagement with patient/caregivers to understand disease features

Level of patient physical and cognitive impairment, disability and lack of financial resources

Not enough CRCs

Lack of clinical capacity within CRCs, dependent upon sparse, busy, distant outside clinical expertise

Not enough scientific and clinical outreach, lack of clinical education component

Not enough collaboration, data sharing

Strategies:

Leverage Director Collins's political capital to ask HHS to restore CFSAC

Develop a structured, NIH-led venue focused on advancing research that engages: ME patient, caregiver, and advocate communities; clinical communities; research communities; relevant NIH institutes; other federal agencies; academic institutions; medical and scientific societies; and the pharmaceutical industry in order to:

>> undertake a holistic approach to the wide-ranging problems impacting ME research

>> engage cross-agency collaboration in resolving interrelated and interdependent bottlenecks in growing the field

>> provide leadership and structure for a venue which facilitates movement on key issues that fall outside NIH's remit (e.g. HHS, Department of Education, SSA, VA) but impact the community and ultimately the capacity for growth in NIH-led research (such as diagnosis, clinical care, medical education, school accommodations, social security disability, and medicare).

Establish Trans-NIH Working Group transparency and stakeholder engagement

Proactively leverage Director Collins's and NIH Institutes' political capital and networks to increase disease awareness and active engagement among medical and scientific societies, academic institutions, and federal agencies

Leverage NIH intramural and extramural networks to promote disease awareness and scientific intrigue; actively bait interest in disease mystery, novel opportunities for discovery

Initiate a concerted academic awareness campaign to bait scientific interest

Leverage Director Collins's and Koroshetz's digital megaphones, utilize every NIH media opportunity available to make the untapped scientific opportunities and plight of patients known within academia and industry

Initiate a concerted public awareness campaign to rectify medical and scientific stigma

Fund additional CRCs

Encourage/require and support CRC education, clinical training, outreach efforts

Sponsor NIH conferences annually to endorse validity, disseminate findings, and facilitate collaborations; include dedicated day(s) and poster sessions for young investigators, and invite the patient and advocacy communities to attend and participate

Disseminate recorded materials out of NIH-sponsored events

Require publication of whitepapers out of NIH-sponsored events

Facilitate representation at society conferences, encourage block symposium to elevate disease profile, invite high profile scientists to leverage star power

Exhaustively publicize new disease findings, CRC results

Compile and disseminate a disease primer/educational video(s) for new investigators of biologic knowns, clinical resources, crash-course on disease-specific issues

Facilitate matchmaking between domain experts and clinical expertise/bioresources

Initiate and host digital roundtable events between researchers and patients/caregivers to facilitate discussion and brainstorming around key issues in ME research (e.g. barriers to study participation, what PEM feels like, triggers of PEM or long-term relapse)

Include ME in the list of diseases on the NINDS website

Expand the NIH digital space addressing ME research to include recorded materials (conference presentations, links to CDC resources), disease-specific educational materials for researchers and newcomers to the field, links to patient registries and available data/biorepositories, links patient support/advocacy organizations

Disseminate new research findings, funding opportunities, study recruitment opportunities, event notifications via listserv

Support a patient registry to facilitate study recruitment and data/sample procurement

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, including existing repositories. Make accessible to outside researchers.

Fund epidemiologic studies

Support resolution of clinical expertise bottleneck to facilitate patient/data/sample access

Fund, convene and maintain a clinical network leveraging clinical and scientific expertise

Document, operationalize and encourage dissemination of clinical expert knowledge to researchers and the medical and patient communities

The most serious impediment to progress at present seems to be limited funds. By defining the Trauma/Toxin subset, you potentially access (1) new funding sources and mechanisms while providing (2) more bait for interdisciplinary cooperation with experts in related fields and (3) inspiration for the boldly creative strain of young talent we need.

I believe, with clever planning, it is possible to advance significant pieces of the ME/CFS research puzzle under alternate headings, including but not limited to: C-PTSD and MST in military veterans, domestic poverty policy, and global health and human rights.

When I treated the physiological symptoms of ME, most of the “psychological” features that supported my C-PTSD diagnosis either shrank or disappeared. Thank heavens I wasn’t strung out on anti-psychotics that would have hopelessly obscured the underlying character of the mind-body interface, confounding even hypothesis formation. I look at traditional PTSD interventions – funded to the hilt – and know I narrowly escaped permanent hell by the simple quirk of not being a veteran.

One of our key stakeholders in Houston is a veteran R.N. who has endured both Gulf War Illness and Military Sexual Trauma. We want more research ammunition to argue that the VA’s PTSD programs suffer from undetected overlap with trauma ME. My OI was routinely mistaken for “panic attacks,” while the avoidance behavior and sensory overload considered classic hallmarks of PTSD are mediated by brain changes characteristic of ME.

Ironically, my ME breakthroughs have been subsidized by VA dollars, but that doesn’t mean veterans are getting help too, and this feels like a gap we should be able to help close.

My personal preoccupation is, not the millions missing, but the full-on “disappeared” who are nowhere on social media or in scientific journals. They live in my flashbacks. Once I was sick too, I finally had an explanation for the phenomenon of community stalwarts in pre-gentrification D.C. who retreated, preternaturally young, to some deep interior behind a locked door and were never seen again. Many women went that way, in their forties. They were joined by a few of the best men, paying deferred tax on old freedom fights.

I observed enough pattern to inspire my forays in PubMed, hunting for a link between trauma and autoimmune disease, when my big-hospital-system doctors who don’t take Medicaid blinked quizzically from their blind spot. I found my allies in scientific journals, with the earliest clues tending to post from war-torn habitats like Serbia and Uruguay.

As I lay in my own small dark room day after day, utterly dependent on my father to bring me food, I grieved to realize retrospectively that someone literally starved to death behind one of those doors in D.C. Someone too proud to risk the stigma of not working in that neighborhood where non-work is freighted with all kinds of meaning I am spared. Since my own descent was slow and I started catching on, I participated in more than a few elaborate schemes to protect colleagues from degradation they did not deserve.

The most honorable man I knew in those years drank himself to death. He is the reason I can mention a prospective pharmaceutical “idling in a lab,” a few paragraphs above. I understood intuitively at the time there was a catch and, when I became sick myself, the “catch” acquired a name. Today I know he was using alcohol – not to “forget” – but to medicate the symptoms of hyperbolic oxidative stress that make you scream, drop embarrassing body fluids in wrong places, and beg in prayer to pop out of your skin.

He deserved at least to die in dignity, but he did not. He lost his house and, in the final days, was cramped into a tiny apartment where his beloved children saw too much. When I figured out the

problem, I swore I would fight for medication more respectable than cheap Vodka, and I have made a decent start.

In my mind's eye, I see too my brave coworker in the throes of neuroinflammation – the same one who rose from girl gang leader to deputy in the pioneering Office of Neighborhood Self-Help at HUD during the Carter years. In our last years together in N.W. D.C., she would begin crossing the street at the top of the walk light, but never reached the curb without having to hold up her hand to stop the green-lit cars.

Perhaps it was garden-variety arthritis? And maybe all the young men's Parkinson-like tremors were just cannabis side effects or the hallmarks of inadequate health care and poor nutrition? Those were my assumptions at the time, but today I wonder and I hope to design instruments to tell us the underlying science ... both to guide healing and to keep the soft bigotry of the uninformed from labeling them as less than they are.

When my own hands tremble, they take me back to the day every plate in my food line was dancing in the air so much I could hardly serve, and every face attached looked impossibly young. The Gates Foundation is beginning to take on board, in preliminary fashion, the possibility that life stress and stressful environments may be determining variables in health and welfare policy. They strategically added "Brain Science" to their poverty initiative – launched because they were not seeing the desired return on one-dimensional investments in education – but do not use the word "trauma" in publications I have seen.

I confess that, when I was working on welfare reform, I paid little heed to the occasional white papers that crossed my desk on environmental (and other external) hazards in my neighborhoods. From the preconceptions of ideology, I advantaged behavioral health and moral choice far more. Twenty years in the streets and Dr. Rey set me straight.

When I have enough empirical ammunition at hand, I hope to use the power of my story to mobilize former colleagues around trauma ME (mostly, at one major Washington think tank, where a bipartisan poverty initiative continued to track real-world impact long after others moved on – same tank hosts the monthly "Braiding and Blending Working Group" deep-dive to better coordinate multiple funding streams, state and federal, to address social determinants of health and reduce health disparities).

Perhaps counter-intuitively for ME/CFS researchers, we may find Medicaid a more hospitable and productive innovation partner than Medicare. I don't have firsthand exposure at this late date, but I am reliably told we will discover impressive cross-sector work to improve complex disease management in Medicaid, and that seems a likely target to leverage for trauma ME.

Medicaid seeding pilots to improve patient outcomes, dismantle barriers to data exchange, craft new payment strategies, and generally drive the conversation to change culture is one specific application of a general principle I want the ME workforce to internalize – namely, that poverty folk are always asked to craft castles out of Kleenex, have adapted a culture accordingly (if imperfectly), and may therefore present ripe opportunity for a multi-system beast like ME that stumps traditional health providers.

In 1995-1996, I sat on the welfare reform task force for both the House and Senate prior to passage of landmark legislation that included “Personal Responsibility” and “Work Opportunity” in the title. I do not disavow my support for that legislation but, if we muster clear scientific evidence of place-based injuries severe enough to preclude steady work and independent living, we must own up to the challenge of fashioning new urban policy.

I favor a special legislative initiative at the federal level and federal waivers to free state-level experimentation (proprietary details withheld for publication). One role specific to dedicated ME/CFS work groups or program staff at NIH might be spreading knowledge acquired from successful pilots throughout the ecosystem and encouraging long-term sustainability across different political administrations, state or federal.

If I had my way, we would routinely scour the capabilities of start-ups in every prestigious accelerator – learning from cutting-edge ideas, communicating need, scanning for collaboration, and preparing to snatch any licenses or ideas on the cutting-room floor that might be repurposed for ME, with an academic or nonprofit production model (e.g., Rice 360 and Houston Methodist Research Institute’s pioneering nonprofit drug development).

We should publicize tech transfer opportunities as a creative solution to the conundrum of financing expensive R&D for products aimed primarily at indigent care and explore the history of Product Development Partnerships to distribute vaccines for neglected diseases in Global Health. As a lone wolf, I risk irritating or alienating the team developing Cortene, to cite one example; but the underrepresentation of trauma ME patients and the infancy of the disease field in general pose such alarmingly high barriers to the right outcome, when the stakes are life and death for whole neighborhoods of innocent people.

For the subtype I represent, ME/CFS is not just a disease. Well-documented ME is the essential mediator that transmutes abstract claims of abuse or extreme social disadvantage into actionable evidence. It is an early warning of calamities deserving public attention or a draw on the public purse, in a society that values human dignity.

I very much fear that ME in this sense is a way station, on a spectrum that will carry survivors in a painfully slow orbit from first symptoms to neurodegenerative disease and death. My job is to question the inevitability of that orbit – refusing to accept its gravitational pull that will degrade us all, if we sit hands folded on the sidelines.

The number one boost HHS could give the field is to require – within the agency apparatus, and as a mandate for research groups receiving NIH funding – use of the term Myalgic Encephalomyelitis (ME). Corresponding to this effort, should be the gradual phase-out of the name Chronic Fatigue Syndrome (CFS).

Regardless of many positive developments, strong evidence suggests that researcher disinterest, negative provider attitudes and disease stigma will continue to plague the area so long as the CFS name remains embedded.

As has been elaborated upon at length in the literature and in many filings, CFS focuses unduly on one symptom – fatigue – which is vague and a component of virtually every major disease. Perhaps even more problematically, this name is heavily loaded with inappropriate baggage. This reality is noted by Dr. Anthony Komaroff, who was present at the meeting in which the name CFS was chosen: “None of

the participants in creating the 1988 case definition and the illness name ever expressed any concern that the name might appear to trivialize the illness. We simply were insensitive to that possibility, and we were wrong. Since fatigue is a universal human experience, I'm afraid some people have responded to the word fatigue in the name by thinking 'I'm tired now and then, like everyone, Why is this even an illness?'"

ME has the benefit of being widely known by researchers, clinical groups and other stakeholders and it is identified in the title of the primary 21st Century definitions in use: the 2003 Canadian Clinical Working Case Definition (more widely known as the Canadian Consensus Criteria (CCC); the 2011 Myalgic encephalomyelitis: International Consensus Criteria (ICC); and is featured in the title of the 2015 Institute of Medicine of the National Academies Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome report: "Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness" (IOM Report).

The currently prevalent umbrella term ME/CFS is one for which I and others have previously advocated. In the past, there were reasons to retain the broader, more amorphous construct. At this point, however, there is no valid rationale for remaining wedded to terminology that is outmoded and detrimental.

Please brainstorm with other ME/CFS stakeholders ways in which to encourage researchers into the field. I think any type of healthcare and public education/awareness efforts will chip away at the stigma attached.

Media. Statistics. Widespread knowledge of the severity of this condition. I just reviewed the NIH's news items and didn't see one mention of ME/CFS. There are up to 2.5 million of us in the U.S. alone, and the disease is not getting the attention that it deserves. Why? Because the majority of us aren't Hollywood actors or artists? Most of us are you, and you--just prior hardworking American citizens.

Take us for many days consecutively, 24h00 per 24h00 and you will see. Give us some challenge like in our life and you will see all the symptoms!
Its a real disease! And we are so sick !