| Relevant considerations and strategies for clinical ME/CFS research, including the development and validation of data standards and outcome measures |
| --- |
| It would be useful to develop a questionnaire for detecting postexertional malaise that yields results that closely align with the objective 2-day CPET protocol.<br><br>If overexertion in the early stage of the illness does worsen the prognosis as many patients suspect, then it would be important to develop a tool to identify patients early on. |
| sample size is an issue but again joined up work may help overcome this |
| More clinical trials. More funding. |
| Open Medicine Foundation has a great model foe this. In the studies I participated in at Stanford, the guidelines were very strict and included healthy controls as well as affected study participants. I beleive Open Medicine Foundation has a good handle on this aspect of research. |
| Ditto |
| A rigorous protocol for assessing patients AND healthy age matched controls, before and after exercise or minimal exertion (depending on health status of the subject) using devices such as the JAMAR hydraulic hand dynamometer. |
| Low hanging fruit. Physiological management of the disease is unlikely to ever be the whole answer but it is a cheap, readily available management tool with objective outcomes that are easily measured and quantified. Recovery should be determined via a 2 day CPET test and not recovery does not appear to ever happen instead it appears that people learn to live within their energy envelope. To date we don't even have a workable disability scale the mild/moderate/severe is misleading and at odds with other diseases in which mild means mild NOT unable to do 50% of previous activity. The Bell scale doesn't work as it confuses symptoms and activity. A person well managing their disease load may only have the cardinal symptoms of PEM, OI and cognitive issues yet be extremely incapacitated. Whilst a relatively healthy person may have more of the flu like symptoms etc but be much more able and active. Outcome measures need to be objective and ideally baseline measures should always be collected. Time on feet seems an easy outcome measure or steps per day without provoking PEM. Everything needs to be tied back to NOT provoking PEM other than the CPET tests which promote PEM by default. |
| Using objective measures for replication and discouraging the use of subjective complaints. |
| Do not use patient diagnosed data or CFS incorrectly diagnosed as the ICC |
| Symptoms wax and wane, depending on a number of factors including activity, stress, and natural course. It is important to compare potential biomarkers with symptoms, exertion, perceived stress, hormone levels and other factors over time. |
| Finding a biomarker for this disease, and how to treat and cure<br><br>Testing family subjects for genetics. For example my cousin was diagnosed with this as well. My father is very healthy. We need collections of family members blood, etc to put in banks to test now and at a later date |

| |
|---|
| Limit the Commonalities, enough to stay stable in the studies and research.<br><br>BDNF gene research, we know so little.<br><br>Neurons, pathways, signals, breakdowns, data, data, data |
| Not my area of expertise. |
| It might help to first grade the severity of illness per sufferers and perform studies within these units as well. ME literate individuals would best be utilized to administer patient intake information/survey. |
| Learn from PACE. Recovered doesn't mean no improvement. Measuring functional ability accurately should be a goal and lessening of symptoms if there is a treatment strategy involved. |
| Again, NIH could help in the recruitment and performance of clinical trials based on enhancing the ACE pathway. These should include the use of KELEA activated water. |
| Unknown |
| Start with large scale data gathering, but do it with the ICC criteria. Broader criteria are what have prevented replication of many findings. Broader criteria okay for clinical purposes but not research. Find ways to study the most severe patients. Offering treatments that may help with recovery may be good to get patients to do invasive exercise testing and offset the risk-like iv saline after a test , among other thing.s consult with doctors on this last point. |
| #NAME? |
| ATTENTION! FUNDING! MONEY! ATTENTION! |
| When I began having hot flashes with perimenopause, I "lost" my adrenaline. If something startles me, my heart rate doesn't spike; I haven't had an adrenaline rush in 7 years! A plasma catacholamine test and two 24 hour urine catacholamine tests show that I am not making or releasing adequate epinephrine. However my cortisol runs high. My fatigue has greatly increased with my loss of adrenaline. I believe there is a researcher(s) who might be able to pinpoint the connection. of CFS leading to loss of adrenaline .Understanding this connection could help in discovering what CFS is. |
| CDC should collect data on how many are ill with ME and where they live |
| Science & western medicine are moving too slow to save the existing 20 million global patients & more viral epidemics will no doubt explode with climate change. Vaccinations are exacerbating the disease by creating retroviruses. |
| Agilidad y perseverancia |

| |
|---|
| Researchers need to work to standard case definitions so that results can be accurately compared across studies. These must include post-exertional malaise as a necessity for diagnosis, to exclude other fatiguing conditions that could confuse results. The SEID diagnostic criteria don't include a lot of the neurological symptoms of ME. The Canadian Consensus Criteria or International Consensus Criteria might be better for excluding other diseases. But it's best to ask the leading researchers in the field at Stanford, Harvard etc. As a minimum, all study participants must have post-exertional malaise. The Oxford Criteria should NOT be used because it can include people with depression or other fatiguing issues that are not ME/CFS, and it doesn't require post-exertional malaise, so the results of Oxford Criteria studies are not relevant for most ME/CFS patients. |
| - Recently, Lucinda Bateman has hosted meetings where expert clinician-researchers explored their strategies for treating ME/CFS; there was a lot of dialogue about their experiences of what has been helpful and what has not. A lot of interesting data emerged from this. Having summaries from this meeting available to researchers and clinicians as well making opportunities available to have more of these types of meetings - and inviting key researchers from the NIH to be a part of these meetings.<br><br>- Create venues where the same thing (in the above bullet point) can be done with patients (with opportunities to participate via phone or online) |
| Kick out anyone receiving anything from big pharma along with proven villains who are move concerned with their careers than helping sick people. |
| Simplify the data standards, publish them and make them requisite for funded research. One can not possibly cover all the anomalies, so pick the data points that have been proven to have commonality in the published research, and pursue those. Also expand and fund OMF strategies of comprehensive discipline approaches, and their unique methodologies in identifying what may change disease course, AND continue to support and duplicate Dr. Klimas computational models in other clinics. |
| Work with both patients and experienced providers to develop a series of both quantitative and qualitative measures; input from both groups is essential, and many aspects of this illness can only be judged through the lens of patient experience. |
| Talk to Ron Davis at OMF |
| Encourage more research around the physiological responses to exertion using heart rate monitoring etc. Encourage exercise physiologists to look at patients with ME using lessons learnt from athletes etc |
| - using only ICC<br>- be aware of subgroups<br>- use objective outcome measures (e.g. heart rate, heart rate variability, temperature, V02 max, counting steps/walking distance, employment)<br>- develop new objective outcome measures<br>- when using subjective outcome measures refrain from scales that are highly susceptible for researcher bias (e.g. Chalder fatigue scale) |

| |
|---|
| I believe focus should be on post exertion (physical and mental both) symptoms in patients compared to at rest. |
| It is vital that all research subjects meet agreed-upon criteria for ME, and NOT merely "fatigue" or "fatiguing illness," as happened in the now-debunked graduated exercise research. |
| Use of International Consensus Criteria for ME<br><br>No funding of research with only subjective outcomes<br><br>Biomarkers to be developed<br><br>CDC to make clear statement on scientific reasons for dropping GET and CBT treatments and erase the other remaining references as highlighted by ME Action Network |
| Multicenter Trials. |
| Outcome measures need to be objective. Ideally the 2 day CPET test at baseline and exit BUT that is too onerous and so less onerous tests need to be devised. |
| Have universally accepted standards and outcome measures. Minimize questions that have patient rate thier own improvement (unless a specific question - like can you walk around the block?, not How do you feel on a scale of one to five?) |
| Tighten up the Common Data Elements - eg make measuring post exertional exacerbation of symptoms mandatory make overall objective data at baseline and exit mandatory in any study that claims to "treat" the disease e.g. 2 day CPET, 6 minute walk test, STE P test., resting HR. HR response to exercise.... Don't allow researchers to focus on say measuring strength of one body part without also measuring changes in overall physiology. Why? Because strength say in arms can increase whilst overall deterioration is taking place. Improvements/stabilisation take months/years so studies need to be long term. |
| 1. Doctors need a clear diagnosis procedure. Keep the diagnostic separate from a purely psychological diagnosis as that confuses everyone, so include physical symptoms.<br>2. There is not nothing that can be done. Patients should be referred to a specialist according to their needs and more than one if necessary. The symptoms have treatments and they should be applied. A nutritionist, a neurologist, a infectious disease specialist can all be part of the treatment regiment given the patient, maybe according to which symptoms at the time are causing the greatest difficulty.<br>3. Have a database to register these patients either anonymously or otherwise and be able to update and score the patient's state at intervals, maybe yearly. Figure out how to score a patient's well being by some sensible criteria, maybe better than what you have currently.<br>4. Once the diagnosis is accurate, the condition is clearly describable without any mind-body duality hocus-pocus and there is good accounting of how many are afflicted, then maybe more research money will be had, we hope.<br>5. Concentrate on researching how to improve the condition of those seriously impaired and moderately impaired. The rest of us can help ourselves. |

| |
|---|
| 6. Fund some labs to figure out the mechanism of this disease so some smart people can work on the problem, as I've heard you have started to do. |
| Larger studies supported by more grant money provided by NIH commiserate with the economic and personal impact of this diseae on over 1 million Americans |
| Solicit input from all current ME/CFS researchers, such as Ron Davis (Open Medicine Foundation), Jose Montoya, Jarred Younger, Nancy Klimas and others. They should be able to identify gaps in the research and point the way to collaborations that may bear fruit. |
| More clinical, integrative and medical trial studies to expedite a CURE! |
| Larger numbers studies to start off with, so that repeating it isn't needed.Larger database of patients labs.Larger studies. When getting info from patients it has to be in short time spans, surveys are hard to stay with for a long time, start a weekly survey of just a few questions each week, combine this data, and use it to try to focus your research, ask the patients what they have the most trouble with. |
| Please see last response. Data needs to be harvested from larger groups of patients and could also identify doctors that have been successful in diagnosis and treatment to discover new standards and learn from the minority who are making a difference with their patients. |
| No input on this point. |
| National database to track the disease. |
| CFS is not a disease of the periphery. |
| So much research is driven by the pharma industry. Which is helpful in some ways, but has a few problems: profit is the goal, many me/cfs patients are sensitive to medication, and it focuses on symptoms. |
| Consult with clinicians to develop meaningful outcome measures. |
| Increased funding. |

| |
|---|
| Re: validation of data standards and outcome measures. Again, communication via patient forums. |
| Barriers are that many questionnaires such as SF-36 are challenging to fill out for severe patients, so creating a simple tool to gather data information will help for both patients and caregivers. The less time consuming and complicated the better. Keep it simple as cognitively and physically these patients have very little to give, especially the severe. |
| I am not a researcher or clinician, but may I suggest that more resrarch be done that includes patients who have had ME for longer than 20 years. I do not find many research studies that study this "group". |
| Definition of PEM and Pene (post exertional neuro immune exhaustion)<br><br>Also, a mechanism in place for ME clinical trials. Researchers such as Nancy Klimas are ready for clinical trial but there is nowhere for her to go at NIH. |
| - |
| Case definitions of ME/CFS should require the presence of post-exertional malaise<br><br>Post-exertional malaise (PEM) or a marked symptom exacerbation after minimal exertion is considered to be the hallmark symptom of ME/CFS and should therefore be a mandatory requirement in diagnostic criteria for this illness.<br><br>For several decades, PEM has been described as the characteristic symptom of ME/CFS. In 1985, Behan et al. emphasized that all of the 50 postviral fatigue syndrome patients in their study had “the same primary symptom that of gross fatigue made worse by exercise.” [1] Thirty years later, an influential report by the National Academy of Medicine described ME/CFS as a systemic exertion intolerance disease, noting there to be “sufficient evidence that PEM is a primary feature that helps distinguish ME/CFS from other conditions.” [2] PEM helps to differentiate ME/CFS from related conditions such as depression [3], multiple sclerosis [4] or chronic idiopathic fatigue [5] and is predictive of a poor prognosis [6].<br><br>Some of the characteristics of PEM may be unique to the ME/CFS patient population. An in-depth investigation of PEM by researchers at Stanford University concluded: “There exists no medical condition the authors are familiar with where exertion or emotional distress causes immune/ inflammatory-related symptoms like sore throat, tender lymph nodes, or flu-like feelings, yet 60% and 36% of our subjects, respectively, reported these symptoms with either stimuli and about a quarter experienced all 3 with exertion.” [7]<br><br>I would, therefore, recommend that diagnostic criteria for ME/CFS require the presence of PEM. The most commonly used case definition, the so-called Fukuda-criteria [8], do not meet these standards and should, therefore, be amended or retired.<br><br>References:<br><br>[1] Behan PO, Behan WM, Bell EJ. The postviral fatigue syndrome--an analysis of the findings in 50 cases. J Infect. 1985 May;10(3):211-22. |

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

[3] Hawk C, Jason LA, Torres-Harding S. Differential diagnosis of chronic fatigue syndrome and major depressive disorder. Int J Behav Med. 2006;13(3):244-51.

[4] Cotler J, Holtzman C, Dudun C, Jason LA. A Brief Questionnaire to Assess Post-Exertional Malaise. Diagnostics (Basel). 2018 Sep 11;8(3). pii: E66.

[5] Maes M, Twisk FN, Johnson C. Myalgic Encephalomyelitis (ME), Chronic Fatigue Syndrome (CFS), and Chronic Fatigue (CF) are distinguished accurately: results of supervised learning techniques applied on clinical and inflammatory data. Psychiatry Res. 2012 Dec 30;200(2-3):754-60.

[6] Taylor RR, Jason LA, Curie CJ. Prognosis of chronic fatigue in a community-based sample. Psychosom Med. 2002 Mar-Apr;64(2):319-27

[7] Chu L, Valencia IJ, Garvert DW, Montoya JG. Deconstructing post-exertional malaise in myalgic encephalomyelitis/ chronic fatigue syndrome: A patient-centered, cross- sectional survey. PLoS One. 2018 Jun 1;13(6):e0197811.

[8] Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med. 1994 Dec 15;121(12):953-9.

Consider specifying outcome measures as fuzzy multivariable sets instead of a single measure. For example, if I want to avoid the exhaustion state and speed recovery - I need to have an measures regarding activity, weather, stressors, diet, showering, sleep, and then further characterization of my level of exhaustion such as ranges of BP, amount of voice fatigue, suddenness of heart rate changes, etc.

Comments above address this question informally. I am not an expert in methodology

All data to be openly available.

All outcomes to be objective. No subjective measures such as questionnaires.

All trials to be double blinded placebo controlled.

No amendments to be allowed to pre-stated trial objectives.

If researchers do not comply the funding should be clawed back and prosecution for fraud should be considered.

Again, this is very difficult. As a person with CFS, I'm at a point now where just going somewhere causes a crash. So the possibility of participating in something like this is daunting.

| |
|---|
| Get ALL doctors educated and treating this disease and we will get answers to that! |
| Well-matched control groups are missing. No study should be conducted without a bedridden control group. |
| When exercise tests are included require the use of maximal exercise tests. |
| Creating preclinical trial methods for trying new treatments |
| N/A |
| When exercise tests are included require the use of maximal exercise tests. |
| We need objective measures and a consistent set of data so results can be compared accurately. Is there a group that is respected in the medical community and can review trials and testing to ensure it meets common standards? |
| Length of treatment , history of patient and believing our physical limitations and symptoms are not “made up”, malingering or “drug seeking” |
| Find MDs who have been afflicted so they can speak the medical lingo to researchers & be part of a) changing mindsets and b) collaborating on a solution |
| Use only objective outcome measures. |
| Apples to apples |
| One strategy would be to allow metabolome studies to be used to try treatments for patients..one of the problem with Dr. Naviaux's research is that his university does not allow treatment based on the results of individual testing. This to me is limiting what can be done with that research..there should be a change in those policies..where the testing can lead to trying a new drug or treatment for patients. |
| Even as a patient, I appreciate the difficulties in dealing with a diverse range of subjective symptoms as I myself am frustrated by the same. Even, e.g. steps walked, has been suggested but seems vulnerable to bias in short term follow-ups.<br><br>One possibility would be tracking blood or csf levels of metabolites within the normal range, but which correspond with one or more symptom in a sub-group. I believe Jarred Younger has considered this approach and found sub-groups that may track with things like CRP, etc.. That is, the variable measuring change may not be the variable causing the symptoms. One particular metabolite was brought up, but never followed up on to my knowledge - leptin.<br><br>One possible objective marker could be a change in vision. I often claim to have worse vision when worse - this is something like worsening myopia. Although the change is not a huge scale, it may be true for other people with ME/CFS. REM have been shown to be abnormal in MS patients performing |

| |
|---|
| a fatiguing task (Ferreira M., 2017).<br><br>A massive priority must be the measurement of “brain fog”. Though this is an subjective experience, I firmly believe it can be objectively measured. Brain fog, above all other symptoms, is the one the most closely matches my overall worsening or not. The features of this brain fog include slurred speech and memory. |
| Conduct bigger trails that jarred younger and Ron Davies have already done |
| An app that records HE/BP, sitting up time, feet on the floor time, PAINSS/PEM duration. ME is all about PAINSS/PEM measuring this with an app will give validation, data and set standards |
| 1) When exercise tests are included require the use of maximal exercise tests. |
| find biomarkers. |
| Require that exercise tests be 2-day, using the Workwell protocol. |
| Copy whatever was successful for Parkinsons, HIV, MS |
| With so many many areas of research finding abnormalities in patients, it is important to have a strategy that can consolidate all the diverse data so the right hand can know what the left hand just discovered. |
| This seems obvious. |
| Conform to AllTrials-style study/trial reporting to bypass publication bias. Make data and methodologies, as well as results, accessible. Make it easy for researchers, doctors, and patients to access extant and ongoing research. Make it easier for patients to volunteer their time, bodies, and experiences for research trials and studies. |
| Sure wish more herbs could be studied here like in Europe and standardized so you know what you are getting. I am not sure Big Pharma has any answers, they are too entwined with profit to spend $$$ on an enigmatic disease no one really cares about. |
| not sure |
| Don't know. |
| using the biomarkers already identified by Dr. Bel;pomme in France and the AAEM |
| Environment must be controlled. That is no testing for EMF tolerance in a space that has multiple sources of EMF. Basic Science. |
| Sorry, I don't have enough expertise in this area to comment. |
| Would it be possible for local GPs, internists and family medicine physicians to be given the tools and instructions to do blood draws and collect other relevant data to be used in research? As a patient I wouldn’t mind taking the responsibility of sending data and blood to researchers. I just need to know |

| |
|---|
| how, especially sending bodily fluids and feces. Do you overnight it; pack in dry ice; freeze it? Let me know and I will send you anything you want, as many times as you want! |
| Turn to your clinical healthcare providers and teach them how to look for these patients so they don't continue suffering year after year. Teach well. Teach them that it is not in our heads. Saying that is a lie. Francis Collins should have welcomed the hypothesis of XMRV and done more untainted research rather than get up and say Judy was wrong, in so many words. I may not have much of a body, but I have a mind! |
| Study ALL age groups |
| Crowd sourcing the different centers, symposiums such as with omf |
| Make sure the PACE trail researchers aren't allowed to touch ANYTHING. Sorry but it's needed. It's like letting a homeopathy 'doctor' play with your patients.<br><br>Have an external group check the methodology BEFORE the trails take place. If the independent group sees flaws in the research it would be nice to find that out before it takes place and not years after.<br><br>Allow other groups to access the data in an anonymized form, both to re-analyze the data and to perform larger meta-analysis. |
| Over my head..... |
| Consensus on the Dx criteria to be used e.g. CCC, IOM criteria. I feel that all studies using only Fukuda or Oxford should not be funded by the NIH. Ideally, a Dx test (as described above) would help to confirm the patient cohorts are valid.<br><br>All studies should involve patients who are not just at rest i.e. stress-tests, to bring out the main feature of ME i.e. PEM.<br><br>Outcome measures in all studies should be primarily OBJECTIVE only e.g. return to work data; need for state benefits; actigraphy. Subjective measures (e.g. fatigue questionnaires) should only ever be secondary, if recorded at all (we've seen the significant problems in using subjective measures in studies such as the PACE trial which have led to considerable levels of patient harm and set the field back many years). |
| These would be important to gain more widespread scientific acceptance. |

| |
|---|
| See above |
| I really think that if the med records from the patients entire health history, not just from onset, would begin to show a commonality |
| Any data collection must include PEM (which needs to be much better defined, currently it is frequently confounded with the more common exercise intolerance for example).<br><br>Many of the commonly used instruments such as fatigue or mental health scales were developed and validated for other conditions. In ME they give uninterpretable results and need to be replaced by more valid instruments developed specifically for ME. |
| Given that so much of this community is medically neglected, direct data submission and database participation by patients in an open database promoted by means of advocacy organizations is going to be the fastest and best way to get the widest degree of information sharing. Data quality will not be up to clinical research data collection standards, but it will a) engage the relevant communities b) connect individuals and communities together as part of a wider effort, which is extremely important for morale c) provide an immediate source of patient information that can then be used as the springboard to build an official, measured clinical research effort (in a closed medical-research database). |
| - strict definitions of ME/CFS in research literature to ensure research relevance, quality; ability to access research funding should be dependent on this in the future |
| Need to incorporate detailed data from both subjective client outcomes and objective biological measures. People with ME/CFS should always be consulted in the development of data collection methods and outcome measures, because we WILL be aware of flaws in the protocols designed by people without ME/CFS. So much of this illness is counter-intuitive, that real input from real people with the illness MUST be included and incorporated in development. |
| Complete blood transfusions:<br><br>Blood is 'donated by someone' with me/cfs, then a similar amount of healthy donor blood is transfused into them. This process repeats over and over again, taking out large amounts of 'CFS blood' and transfusing in large amounts of healthy blood until the proportion of transfused-in blood to original blood is calculated to be heavily skewed towards the healthy transfused in blood. This may prompt a 'reset', one suggested means by which those cured become so. This therapy is also informed by the fact that healthy ME/CFS cells have been shown to when separated from MECFS blood serum and surrounded with healthy patient blood serum behave healthy, and when rexposed to MECFS blood serum resume behaving 'sick'/abnormally.<br><br>Rats ( including the African giant pouched rat) have been shown to be trainable to identify specimens from individuals with specific diseases, employing such a method of diagnosis may spare much time for patients chasing differential diagnosis and more importantly enable the classification of mecfs into those subclasses of the disease which it has long been suspected to have.<br><br>The lymph nodes of the brain and those around the skull should be studied, and the lymphatic system |

| |
|---|
| inspected for signs of an infection isolated to this system alone.<br><br>If lymphatic flow studies can be done they should be, if not they should be developed.<br><br>Genetic engineering to create mouse models of mecfs so those genes correlated with mecfs in human populations are in the mice. Then the gene editing out of those genes associated with mecfs to see if the symptomologies resolve. Some gene editing tools to help achieve this may be CAS9 and SLENDR, the latter being purposed specifically for gene editing in the brain.<br><br>Gene editing research in embryos to remove those genes associated with mecfs as to allow those potential parents who have had the disease, do, or have family members who do to be secure in that they will not pass on a predisposition for mecfs down to their children.<br><br>Use those tools to map inflammation in the brain used by and or developed by Jared Younger at the university of Birmingham to test inflammation in the brain over time when exposed to a control environment and all number of variables, from specific mold species, to multiple mold species at a time, to antivirals, to antibiotics. Analyze these models with deep learning.<br><br>If possible, FMRIs or OpenWater lightbased imaging tech used to charecterize inflammation in the gut, analyzed by deep learning A.I. |
| See above, on considering electromagnetic aspects |
| Huh? |
| Disability related outcomes. I am in pediatrics so unfamiliar with adult strategies.<br><br>I'd think balance assessments, functional assessments, TUG (Timed up and Go test), Disability Scales.<br><br>Functionally I struggled to walk up and down steps until I started a full Functional Medicine program at the Cleveland - then I did things I never imagined, like skiing for the first time in 35 years. Iceskating with my kids, picking kids up off the ice. |
| 1. Get Ampligen moving, tested, approved<br>2. NASA lean test, check for Orthostatic Intolerance and the new kinds that are being found and find treatments<br>3. reverse T3 and T3 blood tests examined to see if current normal ranges aren't really normal and if there is new medication that can help with that<br>4. What are the blood tests that are commonly off in ME/CFS patients (vit D3, CoQ10, B12, etc) test for those and treat<br>5. What helps the gut? Digestive enzymes (how much, papaya, something else)? Probiotics (freeze dried or refrigerated)? Aloe Vera juice? Cabbage Juice?<br>6. Do diets play a role to in the gut healing process? Blood tests (international companies do them to see what foods a person is intolerant to) and then removal from diet of those highly intolerant to. Does a paleo, keto, vegetarian, or celiac diet, etc make any difference or for some subgroups? |
| There are too few clinicians with ME expertise and many of the current pool are approaching retirement. Efforts need to be made to consolidate their expertise and to disseminate their collective wisdom. In the past year, Cindy Bateman has convened ME clinician-researchers twice to capture their collective wisdom and to foster clinical research. Information from these meetings is advancing care and should help lead to clinical trials. |

| |
|---|
| The collaborative efforts noted at the meeting need to be fiscally supported and a clinical model for developing expertise in local ME providers developed. For example, The Bateman Horne Center, Stanford and Nova Southeastern University support PCPs who are learning to manage ME patients. The complex, multisystem involvement of ME require clinicians to spend more time with ME patients. There need to be efforts to disseminate what tests/treatments<br><br>are and equally important, what tests are not informative and cost effective.<br><br>Again, drawing on some of the successful approaches to the HIV pandemic is worth applying to the ME field. Patients as care partners will strengthen the care of people with ME. Future clinician-researchers meetings including participation by NIH funded biomedical researchers and incorporating a venue for patients to contribute- perhaps livestreaming or in specific sessions summarizing discussions with an opportunity to contribute could advance our understanding. |
| See the ME-ICC and IC Primer. Significant findings in CFS research need to replicated and expanded using subjects unequivocally with ME and not labeled as an undefined subset of Fukuda CFS. Much Fukuda CFS research may have used mislabeled subjects actually with ME. As further objective laboratory tests are developed using ME-ICC subjects, these objective tests should be used to confirm future ME research subjects. |
| - Produce a Cross Institute Multidisciplinary multi-year Fatigue Initiative including RFA's and Conferences to create interest and facilitate collaboration.<br><br>- Emphasize how fatigue is a core symptom in many diseases, how little is known about it, the great need to learn more about it, and how ME/CFS - one of the most functionally disabling diseases on the planet - provides a unique opportunity to unlock much that is unknown about fatigue.<br><br>- At minimum, fund a Fatigue Conference to bring researchers from across the spectrum to learn from and interact with and form collaborations with each other.<br><br>- Give VIcky Whittemore more funding and assistance to carry out her job. |
| Adapt and use ICC definition. |
| Clinical 'ME/CFS' research is not possible. No such disease exists and while ME is clinical, CFS is not.<br><br>Instead, do clinical research into ME.<br><br>Prevent enteroviral infections.<br><br>Take measures to prevent enteroviruses from entering the central nervous system. |
| Use good diagnostic criteria (Canadian Consensus Criteria or International Cknsensus Criteria); cohorts with higher numbers; use objective primary outcome measures, which can be combined with subjective outcomes. Be sure to exclude other diseases that present with comparable symptoms (this is especially relevant if the diagnosis was made with Fukuda or Oxford criteria or any criteria that use "tiredness" or "fatigue" as a defining symptom) - this happens regularly. Close communication with patients who are experts about their illness. |

| |
|---|
| Using people who all have ME as defined by the ICC as study volunteers, increasing the likelihood that all of them have the same illness. |
| The accepted criteria used diagnostically for ME/CFS is in dire need of updating yet the medical field lacks the ability to do so primarily because few if any biomarkers have been found (due to lack of research, funding, and general interest in patients with this condition). ME/CFS should not have to be a diagnosis of exclusion simply because there is no properly agreed upon diagnostic criteria by 2019 already. An actually appropriate "operational definition" of ME/CFS must be established.<br><br>It has been proposed that there are subsets of ME/CFS yet there has been no properly funded or conducted research allowed to occur to verify or dismiss this notion.<br><br>Every study should begin with a sample size large enough to avoid any need to repeat the same study again simply due to sample size. |
| ? |
| Implementation of a standard research databank for sharing information across studies would allow researchers to access each other's work and patient data, and encourage collaboration. |
| Mitochondrial biomarkers should be used to identify which people have ME i.e. can participate in any NIH research. E.g. the current NIH study should select people who have these reversible mitochondrial problems; those who do not should be assessed separately - do they have another disease?<br><br>The measures of who has ME should be objective (based on molecular data) and the assessment of treatments should use objective criteria - changes to biomarkers - activity monitors (widely used technology). |
| Get young scientist interested in a new set of research with different parameters than what we've been doing. It hasn't been working. Send lecturers or information to medical schools and research facilities to get them interested. It's an expensive process and not all drug companies are interested. They're only interested in mass production for their investors and stockholders. We need to make it where there is some sort of subsidy disease and diligently get the government to start funding again in a higher manner. There are so many on undocumented patients. There needs to be an active effort to get doctors informed through continuing education courses |
| Very important. High standards give a better chance of replication of findings and advancement from there. |
| 1) There are numerous issues related to participant privacy and confidentiality. Of concern is the fact that many patients are enrolling in multiple studies. There is a need to have GUIDs (globally unique identifiers) to allow researchers to match participants across studies and research data repositories without exposing personally identifiable information. This will allow researchers to better understand how much generalizability is being lost and what opportunities for merging datasets may exist.<br>2) Community standards are needed for the documentation of "caseness." Moreover, this definition |

should include multiple sub-types to distinguish between moderate and severe cases (at a minimum) as early investigations which do consider subtypes frequently show distinct biological markers for these patient groups. It would be preferred if studies all used the same definition, but thorough documentation and clean data collection should be a minimum standard for ME/CFS research.
3) Studies should not assume that severe and moderate ME/CFS have the same biological underpinnings. Rather, analysis plans should be designed such that distinct subtype analyses can be performed to test if the different forms of the disorder have distinct etiologies.
4) There are also issues related to the appropriate comparison population. For example, what is a "healthy control?" Some studies have used "sedentary controls," but are most of these individuals actually healthy?
5) How can the field cost-effectively ensure high sensitivity and specificity for studies of individuals with ME/CFS and healthy controls based on the experience of the NIH cross-sectional study that rigorously evaluated and then screened out a significant number of both types of participants?

There should be a focus on investigating any drug that has the potential to alleviate some of the symptoms of ME/CFS. The NIH must issue program announcements for ME/CFS. Of course there also has to be an overall increase in funding for research grants.

We've been talking about these for years and made little progress. Find people who came down with the illness a year prior and study them intensively. People like me who've had this for over 20 years are now hopelessly confounded with other things.

CLINICAL EXPERTISE
CLINICAL INTERVENTION TRIALS
ARTIFICIAL COHORT HETEROGENEITY
BIOLOGICAL HETEROGENEITY
BIOMARKERS
STAKEHOLDER ENGAGEMENT

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!!!

Beyond my competence to make a qualified statement about this.

Stop using questionnaires that primarily assess a single vague symptom, such as fatigue (like the Chalder Fatigue Scale) and questionnaires that make a value judgment about the cause of symptoms, such as the HADS. If questionnaires are needed, try to use questionnaires with specific questions (including questions related to everyday functions) like the PROMIS Physical Function, Cognitive Function, Ability to Participate in Social Roles and Activity questionnaires, or the Short Musculoskeletal Function Assessment.

Be careful with HALYs. (38)

| |
|---|
| Make programs to increase healthcare delivery at home, so the infrastructure for this is already there. |
| See research of Drs. Ron Davis, David Systrom, Robert Naviaux, et. al. |
| Clinical ME research should begin with the International Consensus Primer. it has in depth information that we should be using to improve outcome measures.<br><br>HHS MUST be a vocal leader to undo the damage of decades of misinformation about ME patients. We do not have a "mystery" disease. We know a lot about what is happening that is causing symptoms. |
| More funding. Develop an affordable and doable diagnostic test (see Ron Davis' research). The 2-day CPET which ME/CFS patients fail spectacularly at on the 2nd day and which shows in irrefutable black and white the reality and horror of this illness, unfortunately is very hard on patients and many if not most can't tolerate it. So we need a test that the average doctor can have done. Then they might believe us and if nothing else start treating us with respect and dignity. |
| Current outcome measures are inadequate, often highly misleading. Needless to say future outcome measures should be objective, but recognizing that past (and, sadly, present) measures are simply inadequate and are unfit for purpose is necessary to move forward.<br><br>One crucial problem is a lack of adequate vocabulary. Most of the common labels used in this disease are unrepresentative and unnecessarily vague. It is unfortunate that “I feel sick” is an inadequate description, but nothing of value was gained by arbitrarily preferring instead the even more inadequate obsession with fatigue, a secondary symptom of ME, a term that is used to provide various meanings from sleepiness to the common “subjective sensation of tiredness”, a completely inadequate and misleading definition of ME.<br><br>Vocabulary deficit is a common problem in medicine and in no way unique or particular to ME. But continuing with inadequate vocabulary is a clear obstacle for progress, especially the deliberate use of terms and labels that carry multiple meanings. This would be especially fruitful in the cardinal symptom of ME, which sadly also suffers from being a massive understatement: post-exertional malaise.<br><br>Words matter. Proper definitions matter. A proper and accurate vocabulary is a foundation for how we speak of a disease, a very first step that has not been achieved yet.<br><br>It’s likely that a reliable test will require less reliance on language and more on objective measures, but there are clear advantages to creating a common and accurate idiom that actually relates to the lived experience of the disease while carrying proper meaning to researchers and clinicians, as initial clinical consultations will require the proper use of accurate terms to guide the diagnostic process towards a proper (future) test. |

As a theoretical physicist, my impression was always that data analysis is cheap and does not yield significantly more insight than a well-conducted experiment carried out with high precision. Therefore, method development is the most important strategy for success. However, novel methods usually require novel data formats. The huge advantage of data is that it can be shared most easily. (For instance, thanks to relentless patient efforts, I can now reproduce the PACE trial analysis, too; I have already downloaded the data and already played around a bit.) Tragically, however, curating data and developing new formats is usually a very thankless task for the primary investigator. Thus, I suggest:

* Assemble an independent unit of excellent data scientists whose task is to curate and share existing data; chances are that they will get bored with mere curation and develop new tools for analysing and sharing it. They should be distributed across the and located in the groups of the primary investigators; communication between them is cheap, but the contact to the primary investigator makes or breaks this approach, because the latter are the ones who generate and consume the data.

Again app/computer based pooled data collection from ME/CFS patients via wearables

An RFA could be issued for investigators to develop medical school training for ME/CFS so that the next generation of M.D.s will not be taught it is a psychological illness. Funding also to engage in remedial training for current physicians who have received misinformation in medical school and from other sources.

Outcome measures for many of the symptoms in ME/CFS are needed, including PEM, sleep, cognitive dysfunction, orthostatic/ autonomic issues, function, etc.

During the NIH CDE process, the groups came up with many possible tools and questionnaires which would be used but the majority (especially generic measures which were developed for another condition or for many conditions) had not been validated much less tested in ME/CFS samples. Additionally, no good ME/CFS-specific patient-reported outcome measure exists currently.

Clinicians and researchers need to be educated on proper diagnosis and cohort selection for studies. ME as described by the ICC must be one of the many diseases ruled out before a patient receives a diagnosis of the overly broad syndromes of ME/CFS (SEID) or CFS.

Outcome measures must be based on a group of patients who share the same disease.

Having suffered from decades of under funding and under research ME/CFS is starting from close to scratch. While technology has advanced making up for lost time is extremely difficult. Early attempts at diagnostic criteria such as the Oxford and Fukuda criteria were well intentioned but were not specific enough. The recent Canadian Consensus Criteria and proposed International Consensus Criteria are better but not perfect.

In the end a biomarker/diagnostic test will be ideal at weeding out people who do not have ME/CFS but have another diagnosed condition. This would help validate findings and lead to research and outcome measures that do not end up in sand traps.

It may be a good idea to put together some working groups with ME/CFS experienced clinicians and patients to come up with outcome measures that are objective, measurable and useful in a

clinical/diagnostic and real life scenarios, simple measures like returning to work may seem clear cut but the difference between someone functioning at a pre ME/CFS level and someone only working part time and spending evenings and weekends crashed would be missed by an unnuanced measure.

There has been some research on measures such as grip strength between ME/CFS patients and healthy controls that show clear differencesÂ¹. Also a detailed questionnaire to diagnose ME/CFS and determine its severity with greater precision then the CCC or ICC has been developedÂ²'Â³. These and several others may be viable for clinical deployment but would need validation with larger cohorts and perhaps a testing series integrating them as well as other to be developed measures. A clinical diagnostic tool analogous to the UPDRS used in Parkinson's disease could be developed for ME/CFS.

Â¹https://www.frontiersin.org/articles/10.3389/fneur.2018.00992/full

Â²https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6232226/

Â³https://www.youtube.com/watch?v=AFim2gz5VQI

When exercise tests are included require the use of maximal exercise tests and make sure measurements are taken standing, not prone

Question a whole range of currently accepted diagnostic techniques and tests as to their validity in light of the new knowledge coming out about the functioning of the immune system, the neurological system, the brain, and some of the specific fatigue findings in ME/CFS as highlighted at the April 4-5 conference

When exercise tests are included require the use of maximal exercise tests.

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.

This disease impacts every moment of every day of the lives of patients, caregiver, families, etc.

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

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

Study cohorts must consist of patients with PEM (well-characterized).

Cohorts must also include patients of all ranges of severity, ages, gender, socio-economic status, ethnicities, etc

Outcome measures must be meaningful to patients

Ensuring that pre-study, post-test data/input from patients is captured to show the pre-testing reduction in cognitive/physical activity (in order to be able to take part) and post-test recovery periods and the length of time there is reduced cognitive/physical activity as a result of having taken part.

Work strategically to significantly increase the number or researchers and clinicians in the field. Increasing the number of clinicians who can accurately diagnose ME, will increase the number of accurately diagnosed patients which will increase the number of accurately diagnosed people available to take part in studies which will in turn lead to clearer signals in studies.

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

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

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

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

Note - see also the MEAction submission:

Workforce Development

with stakeholder participation as an integral component of the education process - Reminder - oftentimes caregivers observe things patients don't notice and or can more accurately describe what happens to patients, so whenever possible caregiver input should also be used.

Pathobiologiy Discovery

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

Biomarker(s) Validation and Discovery

Clinical Expertise

Stakeholder Engagement

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

Clinical Intervention Trials

Artificial Cohort Heterogeneity

Intrinsic Biological Heterogeneity

- Ensure outcomes and data models are patient centric and informed by patient advisors

Standardisation of outcome measures - internationally accepted guidelines and protocols

These need to be regularly updated as new data and experience emerges

Minimum datasets agreed

MEICC criteriaMEICC criteria

Implementation of objective measures, such as accelerometers and heart rate monitoring, in conjunction with self-report measures.

There is an outstanding need for clinical trials of FDA approved drugs for ME/CFS. Nutritional studies would also present a low-hanging fruit for treatment.

The use of disability outcome measures such as the Functional Independence Measure (FIM) which is used for conditions such as multiple sclerosis and is the standard in physiatric evaluations in the clinic may apply to ME/CFS patients.

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

-Better medical fatigue scales, the Chalder scale is terrible

-Following up mono patients in large groups. For example, several universities could have shared consent form to give to new mono patients who give samples, and those patients could be tracked longitudinally to see who fails to recover.

Reference Ron Davis's work & nanoneedle Program. He's on the right track with stringent parameters.

1. Develop a disease severity classification system with 4 levels based on a patient's functional capability:

Mild-- able to work full time

Moderate-- able to work part time

Severe-- unable to work

Very severe-- bedridden

2. Develop a Data Base of all of the major ME/CFS symptoms observed and recorded by researchers and clinicians over the past three decades. The sheer number of symptoms experienced by any one patient is a distinguishing feature of the disease. Very severe symptoms such as malignant hypertension are often overlooked. This data base would help future subgrouping efforts, AI projects, and be a clinician's educational tool. "The Clinical and Scientific Basis of ME/CFS" is one important source of symptom data among many others available; there should be one data repository of the information.

Not our field. We are just a group of sufferers, trying to find answers on our own. Pathetic.

Again, defining a Systems Biology clinical approach seems important in a complex multi-system disease like ME/CFS. I believe the clinical failure thus far is in part due to the linear thinking of traditional disease mechanics, the believe in singular factors, single 'broken' elements. But with ME/CFS and similar conditions the disease is literally a pattern of data across multiple systems (Dr Lucinda Bateman recently made that remark in a presentation on her clinical approach). I don't

believe we will have clinical success until we learn how to measure a wide range of metabolites, neural function parameters and cellular signals, then use pattern recognition and simulation methods to identify the most likely complex explanation for the presenting symptoms. In this case the data standards are less important because we are using complex data as an INPUT to the clinical assessment. We are not trying to classify all patients by category, saying who is the 'perfect' ME/CFS patient. But rather taking a complex systems biology approach we start with the assumption of uniqueness and look for patterns that repeat, in unpredictable combinations perhaps, across the patient population. The outcome measure would be to identify whether there are in fact multiple disease patterns at work in the patients, and log the treatment successes and failures addressing each combination. This will certainly require some competent analytical approaches, perhaps some machine learning / AI. But so be it. Those are available tools today, we have the perfect disease here to prove the tools work, let's do it!

Eventually the clinical approach may be to plug the patient's metabolomic profile into an app, this may be a disease where humans are incapable of properly diagnosing differentially due to the complexity of patterns presenting in the metabolic data. But hopefully the human doctor will learn how to treat. Interpreting the patterns and careful trials of treatments may be the future art of treating ME/CFS for the practitioner…

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

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

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 accomodations, 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<br>Disseminate new research findings, funding opportunities, study recruitment opportunities, event notifications via listserv<br>Support a patient registry to facilitate study recruitment and data/sample procurement<br>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.<br>Fund epidemiologic studies<br>Support resolution of clinical expertise bottleneck to facilitate patient/data/sample access<br>Fund, convene and maintain a clinical network leveraging clinical and scientific expertise<br>Document, operationalize and encourage dissemination of clinical expert knowledge to researchers and the medical and patient communities |
| I understand this is more of a long-term goal for ME, compared to better established diseases, but I am amazed and heartened by how effectively the Global Health program at Baylor College of Medicine is using AI to diagnose complex cancers in the field when equipment is sparse and patients who can't travel need on-the-spot answers.<br><br>How soon could this be an innovation to help compensate for the dearth of ME clinical expertise, ferret out more of the unlabeled ME trauma patients hiding beneath other disease labels, increase the quantity and quality of patient matches to future clinical trials, and identify more off-label uses of FDA-approved drugs for the afflicted? Is the work of the DMCC designed to advantage early adoption of AI to maximize return on scarce dollars?<br><br>I look at the CareSet startup based at the TMCx accelerator in Houston and wonder also how more sophisticated crunching of Medicare data might help advance cost-saving arguments to improve reimbursement for ME/CFS care beyond the current pittance and/or find profit centers to help bring more ME drugs to market. Is there anyone in our work-group-ecosystem specifically charged with asking these kinds of questions? |
| Vastly improved survey instruments and data collection is needed to map out the disorder with precision. Without far more questions being asked, and data reliably compiled and maintained, this newly cleared field will just become a slightly reoriented morass. No stakeholder interest is served by that advent.<br><br>Validation of data standards and outcome measures is putting the cart before the horse at this point. There has not even been much comparison between ME patients and those presenting with other chronic illnesses like lupus and MS, so how can we properly identify data standards and outcome measures before these distinctions are better delineated?<br><br>That is why a Mapping Project (see response to first question above) is a prime imperative. |