Pathways to Prevention: Advancing the research on ME/CFS

Public Comment on the Draft Statement

By Catherine H. Balestra, MD

As an Medical Doctor with a father who suffered through 12 years of ME/CFS and having followed the ME/CFS field for many years, I would like to thank the authors of the Draft Report for appropriately recognizing and highlighting a number of issues which are important for moving the field of ME/CFS forward.

However, I would like to draw your attention to two important issues where I find significant changes need to be made. :

1. PEM, not fatigue, is the cardinal symptom of ME/CFS
2. "New money" needed – NIH must issue RFAs for biomedical ME/CFS research

1. PEM, not fatigue, is the cardinal symptom of ME/CFS:

The Draft Report understandably repeats a common misunderstanding: that fatigue is the key symptom of ME/CFS. (Referring to the lines 2-4, 58-59, 96-97, and to the section 'Conclusions')

Many experts in the ME/CFS field, including some who were a part of the panel at the time, have come to deeply regret the focus on fatigue which was created by the CDC Fukuda criteria in 1994. Before 1994, Myalgic Encephalomyelitis (ME) was known as a disease entity which symptoms were considered neurological in nature. The Fukuda criteria changed the scope and view of the disorder, introduced a focus on fatigue and created the misleading term Chronic Fatigue Syndrome.

Rather quickly, clinical experience made it clear that when focusing on the typical ME/CFS patient group (majority of cases triggered by an infection, high symptom severity and frequency), the hallmark symptom was not fatigue, but post-exertional malaise (PEM). PEM is defined by the professional organization IACFS/ME as "the exacerbation of symptoms following minimal physical or mental activity, which can persist for hours, days or even weeks."

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Incorporating this knowledge, ME/CFS experts participated in the creation of the Canadian Consensus Criteria (CCC), where PEM was made a mandatory symptom. Research has shown that CCC identifies a more homogenous and more severely ill patient group, with higher prevalence and severity of symptoms.

50 of the leading clinicians and researchers have requested that DHHS discontinue the use of the CDC Fukuda criteria, where PEM is not a required symptom, and instead endorse the use of the CCC
LINK:
https://dl.dropboxusercontent.com/u/89158245/Case%20Definition%20Letter%20final%2010-25-13.pdf
https://dl.dropboxusercontent.com/u/89158245/Case%20Definition%20Letter%20final%2010-25-13.pdf)

I call for changes in the text so that the Final Report reflects the fact that PEM, not fatigue, is the cardinal symptom of ME/CFS.

2. "New money" needed – NIH must issue RFAs for biomedical ME/CFS research

I endorse many of the recommendations made in the Draft Report (for example lines 178-276). However, I find that the basic problem is not addressed–the minuscule levels of funding available for biomedical research, and the fundamental role of NIH in amending this.

Referring to the sections 'Future Directions and Recommendations' (beginning on line 178) and 'Conclusions' (beginning on line 367), I call for an inclusion of a very strong recommendation that NIH set aside dedicated funds to rectify the disproportionately low levels of funding for ME/CFS, which have been hindering any advancement in the field for several decades. This should be done through the creation of multiple RFAs for biomedical research into ME/CFS, issued over several years.

The CFS Advisory Committee (CFSAC), which provides advice and recommendations to the Secretary of Health and Human Services (HHS) on issues related to ME/CFS, has made this recommendation on numerous occasions, including:

- Nov 2011: "CFSAC recommends to the Secretary that the NIH or other appropriate agency issue a Request for Applications (RFA) for clinical trials research on chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME)."
LINKS
"https://wayback.archiveit.org/3919/20140324192811/http://www.hhs.gov/advcomcfs/recommendations/11092011.html"
https://wayback.archiveit.org/3919/20140324192811/http://www.hhs.gov/advcomcfs/recommendations/11092011.html

- October 2012:
"CFSAC recommends: […] - Instructing the NIH to issue an RFA (funded at the $7-10 million range) for projects to establish outcomes measures for ME/CFS diagnosis, prognosis and treatment which would include but not be limited to biomarker discovery and validation in patients with ME/CFS."
LINK: "http://www.hhs.gov/advcomcfs/recommendations/10032012.html"
http://www.hhs.gov/advcomcfs/recommendations/10032012.html

- June 2014: “CFSAC recommends that the NIH issue a Request for Applications (RFA) for ME/CFS by November 1st, 2014, or as soon as feasible, to address the gaps in ME/CFS knowledge and research. The RFA should consider current known gaps in knowledge for the following areas:
- Provocation designs where symptoms are triggered through standardized challenges involving exercise, cognitive tasks, and mental stressors. These designs appear to be more likely to identify symptom to biology relationships in comparison to assessments done in resting states.
- Ambulatory monitoring of symptoms, activities, behaviors, and physiological states that identify associations between biological and behavioral measures, e.g., daily fatigue ratings and cytokine fluctuations.
- Network analysis of dysregulation of multiple bodily systems, such as the neuroendocrine system, the central nervous system, the autonomic nervous system and the immune system.
- Natural history studies aimed at identifying the genetic triggers and causal factors of ME/CFS.
- Treatment trials that address both clinical and biologic outcomes.

This RFA may also be informed by the gaps identified in the 2011 NIH State of the Knowledge Workshop, the Pathways to Prevention Program for ME/CFS research panel report or any relevant source, including but not limited to, the IACFS meeting summary.”
LINK: "http://www.hhs.gov/advcomcfs/recommendations/06142014.html"
http://www.hhs.gov/advcomcfs/recommendations/06142014.html

The fact that these repeated recommendations have been rejected has meant that ME/CFS research has moved forward at the same staggeringly slow pace, in spite of the fact that many very promising areas of research have appeared.

The call for RFAs have been echoed by several parties.

In March, 2014, eleven members of Congress wrote NIH Director Dr. Francis Collins, saying: 'We applaud your efforts […] in hosting the ME/CFS Research Workshop in April 2011. The Workshop concluded that there continues to be a need for additional interdisciplinary research, coordination of research, centralized data sharing, and recruitment of additional qualified investigators.' These suggestions are in line with the recommendations of the HHS CFS Advisory Committee, including an NIH RFA in the range of $7-10 million.

We encourage you to act decisively on these recommendations. We also ask that you provide us with the current status of the effort to meet the need in ME/CFS research, as well as plans for moving forward with a strong and fully supported research program.”
LINK: "https://dl.dropboxusercontent.com/u/57025850/Congressional%20letter%20-%20Dr.%20Collins%20-%20March%202014.pdf"
https://dl.dropboxusercontent.com/u/57025850/Congressional%20letter%20-%20Dr.%20Collins%20-%20March%202014.pdf

In April, 2014, the professional organization for clinicians and researchers, International Association of CFS/ME (IACFS/ME) wrote an open letter to Dr. Francis Collins: “We call on you and Directors of key Institutes at NIH to collectively work together to issue a Request for

Applications (RFA) calling for R01 and R21 projects related to ME/CFS. At a level of $7-10 million annually for five years, an RFA would double current funding and bring talented investigators into the field for the first time. The ME/CFS RFA would also dovetail nicely with ongoing NIH initiatives including those related to the brain, big data and transformative research.

We realize the substantial reductions in the NIH budget over the past decade have made it hard to issue RFAs. This is even more reason that we must focus our support on specific targets that are poised to make significant progress in the near future. With ME/CFS related to so many other medical diseases and conditions, support for research on ME/CFS will add to, for instance, our understanding of chronic pain, viral/ bacterial infections, sleep disorders, fatigue, autoimmunity, and cancer. In this regard, ME/CFS research already has aided knowledge of Gulf War Illness, fibromyalgia, retroviruses, and Lyme disease.

The Trans-NIH ME/CFS Research Working Group members have been helpful in coordinating awareness of the disease at the NIH. However, without financial support, their efforts to enhance applications to study ME/CFS are limited to oral encouragement. We all know that is not enough. The State of the Knowledge Workshop on ME/CFS in 2011 concluded that there is a need for interdisciplinary research, coordination of research, centralized data sharing, and recruitment of additional qualified investigators. The ME/CFS RFA could address those needs as well as the longstanding CFS Advisory Committee appeal for such an RFA."
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As you can see, there is agreement across the board that without specific RFAs for biomedical research into ME/CFS, the field will not move forward.

I sincerely hope you will include in the Final Report, a very strong recommendation that NIH issue multiple RFAs over several years for biomedical research into ME/CFS, bringing the funding up to levels on par with comparable diseases.

Thank you for your work.

Kind regards,

Catherine H. Balestra, MD