Throughout the last 3 decades, researchers have investigated a wide variety of biomarkers concerned with etiology, pathophysiology, diagnosis, treatment, and prognosis. Rather than duplicate the work of other subgroups involved in this project, the Biomarker subgroup decided to focus on 5 areas of research that may not be covered by others: microbiome/microorganisms, proteome/proteins, metabolome/metabolism, genome/epigenome, and gene expression/transcriptome. There are no biomarkers in these categories that we can recommend. Consequently, we reviewed and selected resources which would be generally useful for biomarker research as well as specific guidelines for the 5 areas we concentrated on. Future work will likely involve areas beyond the biomarkers we examined; researchers should still heed the general guidelines suggested here which are relevant to their study.

In their 2012 paper, Jason et al. included, for additional, optional elements that should be considered for ME/CFS studies, proteomic, genomic, and transcriptomic aspects. We have examined and made recommendations in these areas.

Not enough research has been conducted on subgroups of ME/CFS patients for us to make recommendations. It should be noted most biomarker research has been performed in adults: even as there are challenging ethical and logistical issues involved in pediatric research, there is an urgent need for more studies in children.

Other than ethical considerations, obtaining informed consent and logistical issues/difficulties in obtaining samples from pediatric cases, the considerations taken in designing a biomarker related study (sample procurement, processing, storage and analysis) are equivalent for pediatrics or other target populations with ME/CFS.

**Summary of Recommendations**

Please see the Biomarkers Guidelines and Reference Table for general recommendations concerning factors that should be considered or included when designing, analyzing and reporting studies.

The Subgroup discussed the following issues unique to ME/CFS:

a. **Patient samples:** Power calculations should be made and reported corresponding to the study’s purpose. This is especially relevant given that some types of biomarkers studies, like genetic association studies, may require a large sample size to make valid conclusions. We recognize that recruitment of study participants may be challenging due to the high rate of under-diagnosis of ME/CFS.

b. **Diagnostic criteria** – Researchers often use various and different criteria and inclusion/exclusion criteria. At the minimum, they should be clear about which case definition is used and how potential study participants were assessed during enrollment.

c. **Selection of control study participants** – The proper comparative group for a ME/CFS study will depend on the goal of the study. For some purposes, comparing to healthy controls will suffice, others will require sedentary or mobility-impaired controls, other studies may wish to compare to individuals with other types of fatiguing illness or who have illnesses that are...
often co-morbid with ME/CFS. Researchers should explain the rational for their selection of a particular control group or groups.

d. Confounding factors -- These will vary for any individual study but should be accounted for as much as possible. Some examples include study participant characteristics (e.g. duration of illness, disease severity), medication use, and factors specific to a biomarker assay (e.g. time sample taken, method of storage/processing, etc.). This information needs to be reported so that comparisons between studies are possible.

Overall, more support and funding for biomarker research is urgently needed. Lack of an objective diagnostic biomarker contributes both to the heterogeneity of studies, as study participants are recruited based primarily on symptoms, and to the skepticism towards ME/CFS that remains in many scientific/medical circles. Funding should support not only novel projects but also projects focused on replicating published studies. The history of ME/CFS is replete with fascinating studies based on a small sample of patients without follow-up in larger samples or in multiple study sites.

**Patient Advocate Considerations**

The subgroup examined biomarkers which are usually available via relatively non-invasive, low-risk means, e.g. blood, urine, and stool samples. Such samples are likely to be adequate for many ME/CFS studies, but after more is known about the disease, more invasive samples may be needed.

*THE IRB IS RESPONSIBLE FOR CONSIDERING THESE ISSUES.*

For studies, which may require multiple clinic visits for sample collection (e.g., longitudinal studies), the possible benefits and risks from such studies will need to be clearly communicated to potential study participants. Commuting to clinics can lead to severe or prolonged post-exertional malaise for some patients and even for moderately affected patients, careful planning is needed in order for many to be outside the home.

We also recommended general resources for data management and sharing. Since for this field, these aspects are early in development, we did not make ME/CFS-specific suggestions. For the future, researchers and funders will need to consider how study participants feel regarding sharing of biomarker information across research groups and studies. Aside from confidentiality and privacy concerns associated with any chronic illness, ME/CFS, as shown in multiple studies, carries additional stigma*: sufferers are often viewed, incorrectly, as being depressed, lazy, or malingerers.


The subgroup strived to examine promising biomarkers covering a variety of physiological areas.

The subgroup did not make recommendations specific to homebound or severely ill ME/CFS patients. This is a group that merits study but is often difficult to incorporate into studies. Current (e.g. mobile blood drawing units) and future technological advances may make studying these populations easier, safer and less costly.

As with all ME/CFS studies, inclusion of men, children, and people of different ethnic or socio-economic backgrounds must be considered.