

Reviewer #1: The authors reviewed plasma or urine composition of patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) or fibromyalgia (FM). The focus of the manuscript was search for clues to differential diagnosis between FM and ME/CFS. As the authors stated, causes of FM and ME/CFS were not known. One interesting result was that choline was decreased in patients with FM and ME/CFS. Choline is related with acetylcholine, a neurotransmitter. These results suggested that FM was related with dysfunction of neurotransmitter. It would make this review more attractive to spend discussion focusing on the relation between decreased levels of choline and cause of the diseases.

**RESPONSE:** We appreciate the comments and agree with the reviewer that further elaborating the connections of the decompensated choline and disease-symptoms may be interesting. However, as the manuscript main aim is to detect metabolite differences that could be “sensed” by the proposed stem-cell based assay, we feel that the connections between choline altered levels and the symptoms of the evaluated disease, such as in the established relation to ME/CFS blood pressure symptoms (lines 210, 211); to uncompensated lipid metabolism (lines 291,292); and ME/CFS brain fog and cognitive problems (lines 474-479) should already meet the demands set by this opinion article.

The indicated sentences have been highlighted in yellow to facilitate their localization in the manuscript.

Data were interesting obtained from conditioned medium from cultured cells. Induced pluripotent (iPS) cells were another useful methods because they could be established from the patients and differentiate to fibroblast or the other cells.

**RESPONSE:** Thank you.

Are there any data on conditioned medium from cultured cells differentiated from iPS cells established from the patients with FM or ME/CFS?

**RESPONSE:** We appreciate the interesting comment. To the best of our knowledge no study has yet reported reprogramming of cells from either FM or ME/CFS, much less differentiation of disease-iPSCs with conditioned medium. It is something, however, worth pursuing in the future towards disease modeling.