The clinical value of fluid biomarkers for dementia diagnosis - Authors' reply.

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We would like to thank Suzanne Dyer and colleagues for their comments on our Article.[1] We would like to clarify that the Cochrane Review excluded most of the studies that were included in our Article in which a highly consistent pattern of AD-related biomarker changes (increased total-tau, phospho-tau and neurofilament light and decreased Aβ42 concentrations in CSF) emerged, not only in manifest Alzheimer's disease but also in patients with mild cognitive impairment. These biomarkers are backed by a solid literature regarding what types of pathologies they reflect;[2,3] they were not derived from random screens (eg, proteomics or multiplex protein panels) and have been validated with both neuropathology[4] and amyloid PET findings.[5] Thus, there is, in our view, no risk that the consistent findings in the literature are spurious to some kind of meta-phenomenon that would be present in some patients seeking medical advice at memory clinics.

However, we agree with Dyer and colleagues that in the clinical setting, the CSF biomarkers have to be interpreted together with data from a full medical evaluation of the patient. It is clear from the results of our meta-analysis that there are biomarker-negative Alzheimer's disease patients and biomarker-positive patients and controls that do not have Alzheimer's disease. The overlap in pathology between Alzheimer's disease and other neurodegenerative disorders and the high proportion of cognitively normal elderly with Alzheimer's disease-like changes (ie, plaques, tangles and neurodegeneration) preclude the CSF biomarkers from achieving a specificity of close to 100%. The context of the clinical biomarker use we advocate is identical to what is recommended in the International Working Group-2 (IWG2) research diagnostic criteria.[6]

The performance of the CSF biomarkers in a clinical setting has been evaluated in several studies.[7-10] At present, each laboratory has to establish their own reference limits and cut-points, and ascertain longitudinal stability and minimise random variation in their measurements, which is (or should be) standard practice at this stage of clinical laboratory testing and results in high performance over time.[11] An external global quality control programme to assist in this process is in place and is supported by Alzheimer's Association.[12]

Finally, what ultimately determines the true value of a diagnostic test is whether clinicians request it or not. CSF Alzheimer's disease biomarkers have been used in clinical practice, and reimbursed by the health authorities, in several countries (eg, Sweden and Germany) for more than 10 years, and the demand from the clinicians for these tests is steadily increasing, despite that only symptomatic treatment for Alzheimer's disease being available at present. We have

to be prepared for the advent of disease-modifying drugs for the treatment of Alzheimer's disease. We foresee a high demand from patients (and their relatives) to undergo a clinical evaluation to learn if their cognitive problems are due to Alzheimer's disease pathology and, if so, to start treatment with disease-modifying drugs. However, since these drugs may have side-effects, and will most likely be expensive, it will be required by clinicians to determine whether Alzheimer's disease-like phenotypes in the clinic are likely to be due to the pathology against which the drug candidate is directed. It is our duty as clinicians and clinical researchers to do everything we can to meet this need.

References

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