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SCIENTIFIC COMMENTARIES

Plasma p-tau217: from 'new kid' to most promising candidate for Alzheimer's disease blood test

This scientific commentary refers to 'Longitudinal plasma p-tau217 is increased in early stages of Alzheimer's disease', by Mattsson-Carlgren et al. (doi:10.1093/brain/awaa286).

Alzheimer's disease is characterized by a long presymptomatic phase during which neuropathology gradually accumulates. Detecting this pathology at the earliest possible stage offers the best chance of effective treatment. Clinical trials targeting the key pathological hallmarks of Alzheimer's disease, such as cerebral amyloid-β aggregation and tangle formation, therefore focus on enrolling non-demented individuals with early-stage biomarker-defined disease. A reliable blood test for Alzheimer's disease would have major implications for the selection of clinical trial participants by allowing non-demented individuals to be pre-screened in a minimally invasive and cost-effective manner, reducing the numbers who must undergo further testing with more invasive and expensive measures such as CSF analyses or PET scans.

Studies analysing plasma amyloid have shown that pre-screening with a blood test can significantly reduce further testing with more invasive measures (Verberk et al., 2018), while more recent evidence suggests that measures of plasma phosphorylated tau (p-tau) may have greater diagnostic power than plasma amyloid measures

(Janelidze et al., 2020; Thijssen et al., 2020). Cross-sectional studies covering the complete clinical Alzheimer's disease continuum have shown that plasma isoforms p-tau181 and p-tau217 can differentiate amyloid-PET or tau-PET positive cases from amyloid-PET or tau-PET negative cases (Janelidze et al., 2020; Karikari et al., 2020; Palmqvist et al., 2020; Thijssen et al., 2020). These cross-sectional studies have also shown that plasma p-tau measures can distinguish patients with Alzheimer's disease dementia from those with frontotemporal lobar degeneration (Janelidze et al., 2020; Karikari et al., 2020; Palmqvist et al., 2020; Thijssen et al., 2020). In this issue of Brain, a timely longitudinal study by Mattsson-Carlgren and co-workers extends this work to the preclinical stages of Alzheimer's disease, and shows the value of using p-tau217 for participant selection in clinical trials as well as for disease monitoring (Mattsson-Carlgren et al., 2020).

Mattsson-Carlgren et al. included 250 non-demented individuals from the Swedish BioFINDER study, and measured p-tau217 levels at baseline and during follow-up using the 'Meso Scale Discovery' (MSD) Eli Lilly immunoassay. The results showed that p-tau217 was increased in individuals in the preclinical and early clinical stages of Alzheimer's disease when compared to cognitively healthy controls. In addition, higher p-tau217

levels were associated with a greater risk of converting to Alzheimer's disease dementia and with steeper rates of cognitive decline and thinning of the temporal cortex and hippocampus. As well as showing that p-tau217 could be used to identify participants for inclusion in clinical trials, the results also suggest that p-tau217 could be used to monitor treatment responses over time. The authors showed that p-tau217 levels increased more steeply in non-demented individuals with Alzheimer's disease pathology (amyloid positivity) than in those with no evidence of such pathology (Fig. 1). p-Tau217 levels also rose more steeply in non-demented individuals who developed Alzheimer's disease dementia compared to those who remained non-demented during follow-up (Fig. 1). The logical next step would therefore be to analyse p-tau217 in blood samples obtained during trials that show reduction or even complete clearance of amyloid in the brain (Sevigny et al., 2016) to determine whether p-tau217 could help monitor treatment response.

Results to date suggest that p-tau217 could also play a major role in a clinical diagnostic setting. For a biomarker to be used in the clinic, three phases of development must be completed (Fig. 2). The first phase, which focuses on assay development and validation plus initial clinical validation, has almost been completed for p-tau217. The Eli Lilly assay has shown robust
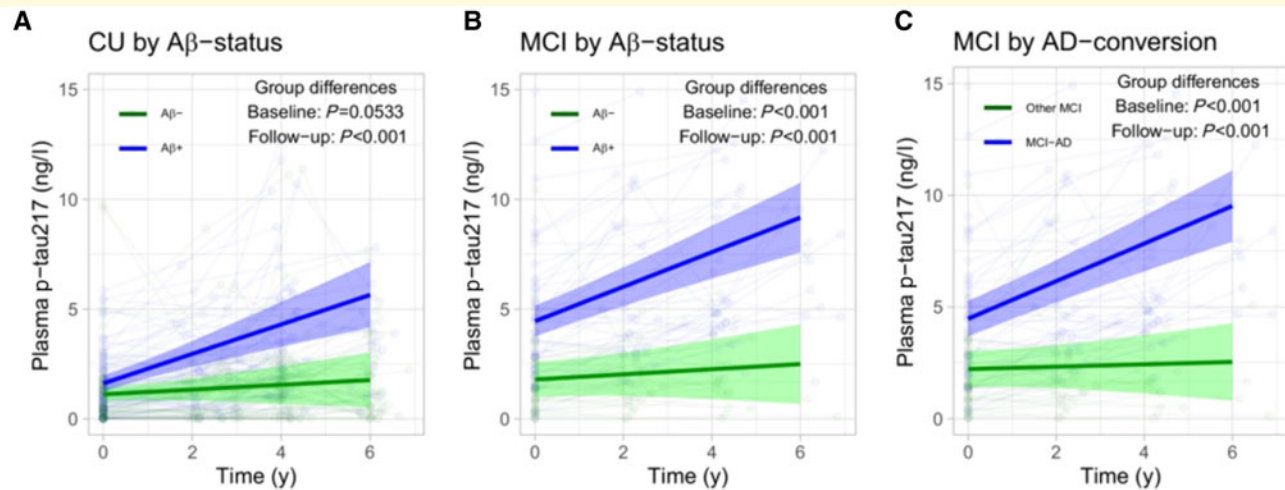
Figure 1 Longitudinal plasma p-tau217 data from Mattsson-Carlgren et al. (2020). Subject-specific biomarker data are shown together with main effects from linear mixed effects models, adjusted for age and sex, for p-tau217 in (**A**) amyloid-β-negative (Aβ–) cognitively unimpaired (CU) versus amyloid-β-positive (Aβ+) cognitively unimpaired; (**B**) amyloid-β-negative mild cognitive impairment (MCI) versus amyloid-β-positive MCI; and (**C**) MCI to Alzheimer's disease (AD) dementia converters versus the remaining MCI population (i.e. stable MCI or 'MCI to other dementia' converters).
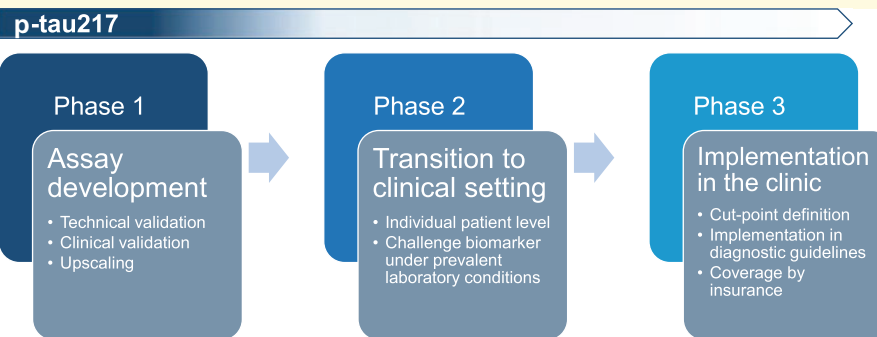
Figure 2 Three-phase trajectory of biomarker development.

outcomes (Palmqvist *et al.*, 2020), although the results of assay validation studies have yet to be published. The second phase focuses on the transition from a research setting to a clinical setting, with the aim of ensuring that the results are consistent at the level of individual patients in different settings and to define the context of use. Here, clinical evaluation should focus on establishing large databases containing information on the plasma p-tau217 concentrations of individual patients alongside their clinical and biomarker characteristics. During this phase, work on the assay includes assessing its robustness, developing reference material, and testing biomarker stability under prevalent

conditions. This may include testing the variation introduced by delays in processing samples or by the need to cool samples and transport them to the laboratory. The third phase focuses on the final definition of cut-points based on the data obtained in phase 2, and on evaluation of the assay results in real-life clinical settings in unselected patients. In parallel, insurance coverage of plasma testing for diagnostic purposes needs to be arranged where required, and the biomarker positioned in clinical diagnostic guidelines. Currently, we are close to reaching the end of phase one for p-tau217. It is thus time to transition to phases two and three, aiming for a swift implementation of

the plasma p-tau217 biomarker in both trials and clinical practice, to accelerate drug development and improve clinical care for Alzheimer's disease.

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Competing interests

The authors report no competing interests.

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Is bad brain worse than no brain? Salvaging the cerebral cortex in epilepsy

This scientific commentary refers to 'Resective surgery prevents progressive cortical thinning in temporal lobe epilepsy', by Galovic et al. (doi:10.1093/brain/awaa284).

The human cerebral cortex, whose thickness ranges from 1 to 4 mm depending on the region, has one of the highest neuronal densities of all species. This highly folded sheet of cells is responsible for many of the higher cognitive functions that characterize humans. Cortical thickness, a proxy for cortical structural integrity, is dynamic; it changes with growth, maturation and ageing. However, our increasing ability to assess the cortex *in vivo* has also revealed associations between cortical thickness and factors such as sex, genetic background, cognitive function and disease states. Cortical thinning that progresses at a rate higher than expected for age has been demonstrated in a number of neurological and psychiatric conditions, including schizophrenia, depression, dementia and neurodegenerative disorders, multiple sclerosis and, not least, epilepsy. In this issue of *Brain*, Galovic and co-workers shed new light on this important area of epilepsy research (Galovic et al., 2020).

That loss of brain tissue occurs in chronic epilepsy has been known for many years, as a result of structural brain imaging and the analysis of pathological specimens. What has been less well studied until more recently is the relative contribution of cortical thinning to overall brain tissue loss in epilepsy. Other unanswered questions include the histopathological and pathophysiological underpinnings of cortical thinning, its rate of progression and topography, its association with specific clinical aspects of epilepsy, and importantly, its response to effective epilepsy surgery.

One concept that is closely related to cortical thinning in epilepsy—a process that occurs over time—is that of epilepsy as a progressive disorder. Progressive structural brain changes in epilepsy include neuronal damage and loss, dendritic and synaptic reorganization, axonal loss and thinning, neurodegenerative changes, and gliosis and microgliosis. Progressive functional brain changes in epilepsy include the emergence of the abnormal connectivity and synaptic circuitry that sustains epileptogenesis and that gives rise to abnormal cognitive function. The severity of epilepsy can also increase over time, with the extent of the increase depending on the type of epilepsy or epilepsy syndrome, and the patient's age and genetic background (Pitkänen and Sutula, 2002).

The notion that seizures themselves contribute to the observed progressive worsening of epilepsy and cognitive function is supported by observations from basic research (Pitkänen and Sutula, 2002). As early as the 19th century, Gowers proposed that 'seizures beget seizures', and in the 1950s, Penfield and Jasper introduced the concept of 'nociferous cortex' in patients with epilepsy (Penfield and Jasper, 1954). This term was applied to cerebral cortex that does not function normally, is the origin of epilepsy, impairs the function of other brain areas, and whose resection results in dramatic improvement of function, behaviour and seizures. Clinical observations, however, have yielded less consistent results with regard to the progressive nature of epilepsy and cognitive decline, and regarding the role of the epileptic process and the nociferous cortex.

Recent advances in quantitative MRI have produced objective imaging biomarkers of disease progression that allow us to measure the rate of age-adjusted cortical thinning in a variety of