Abstract: β-amyloid (Aβ) and tau are the neuropathological hallmarks of Alzheimer’s disease (AD). PET radiotracers for the in vivo assessment of Aβ burden have transformed the evaluation of AD pathology, extending our insight into Aβ deposition in aging and AD by providing highly accurate, reliable, and reproducible quantitative statements of regional and global Aβ burden in the brain, essential for therapeutic trial recruitment and for the evaluation of anti-Aβ therapies. While this progress has already resulted in the approval of an Aβ radiotracer for clinical use, it is only in recent years that there has been significant progress in the development of tau imaging tracers.

As new treatment strategies to prevent or slow disease progression through early-intervention are being developed and implemented, there is an urgent need for early disease recognition, which is reflected in the necessity of developing sensitive and specific biomarkers as adjuncts to clinical and neuropsychological tests. Antecedent, diagnostic and prognostic biomarkers include the examination of disease specific traits such as Aβ, tau or α-synuclein in blood and cerebrospinal fluid, as well as the application of neuroimaging techniques such as PET for the characterization and quantification of metabolic and neurochemical alterations that lead to neurodegeneration and cognitive impairment. Because the molecular changes occur well before the phenotypical manifestation of the disease, a change in the diagnostic paradigm is needed, where diagnosis moves away from the identification of signs and symptoms of neuronal failure to the early and non-invasive detection of a particular trait or traits underlying the pathological process, that will also allow evaluation of efficacy and monitoring of the molecular effects of disease-modifying therapies. Furthermore, given the complexity and sometimes overlapping characteristics of these disorders, it is unlikely that a single biomarker will be able to provide the diagnostic certainty required, especially for the identification of at-risk individuals before the development of the typical phenotype. Consequently, a multimodality approach for the accurate and early diagnosis, monitoring disease progression, and better treatment follow-up of AD is warranted.