Will precision medicine still require neuropsychiatric phenotypes?

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Precision medicine depends on objective and accurate biomarkers, which are increasingly central to dementia diagnosis for monitoring disease progression and evaluating new disease-modifying treatments. The ATN classification[1] and the 2024 NIA-AA Revised Framework[2] provide systematic examples, while the advent of plasma-based biomarkers[3] further expands the available toolkit. Novel biomarkers continue to be proposed.[4] However, those markers grounded in specific etiological and neuropathological models fail to address the heterogeneity of clinical dementia, particularly when co-pathology–specific biomarkers are not employed simultaneously.

More generally, precision medicine retains clusters of uncertainty at several levels that can be divided into (a) ontological 'world-sided', (b) conceptual, (c) evidence-related, and (d) practical. Ontological uncertainty stems from the inherent complexity of biological systems and human variability; conceptual uncertainty arises from ambiguous definitions and frameworks; evidence-related uncertainty is due to challenges in producing and interpreting evidence and practical uncertainty is related to implementation, measurement, or workflow constraints. As a consequence of such complexity, levels of uncertainty will thus paradoxically not always be reduced by more research in this field.[5] Accepting that uncertainty is inherent, understanding its interactions, and managing it appropriately are key to advancing precision medicine.

Subjective and behavioural measures, such as neuropsychiatric symptoms, feature in all the above clusters of uncertainty and are generally not regarded as useful biomarkers. To explore their potential relevance from first principles and anchored to gold-standard postmortem neuropathological standards, Ross et al. in this issue of *Neurology* report a study of 919 patients from the National Alzheimer's Coordinating Center (NACC) database. They describe how Alzheimer's disease neuropathologic changes (ADNC), frontotemporal lobar degeneration (FTLD), or combination of both are linked to their last pre-mortem clinical assessment.[6] In brief and as expected, they found typical symptom profiles in the 'pure' pathological groups, and that mixed pathology was associated with intermediate symptom patterns. The ADNC-only group had less personality change, disinhibition and apathy and more visual hallucinations,

delusions, and anxiety compared with the FTLD-only group, and vice versa. As predicted, comorbid ADNC/FTLD showed more anxiety, delusions, and irritability relative to the FTLD-only group, while they had more personality change and disinhibition than the ADNC-only group.

What conclusions can be drawn from these observations? In the most conservative formulation, the results underline the clinical importance of considering co-pathology whenever neuropsychiatric features appear atypical of a presumed diagnosis.[6] However, there is a substantial overlap of symptoms, suggesting that such profiles are not necessarily accurate tools to *separate* diagnostic and mixed groups. A statistically and clinically significant difference does not always signify a separation of diagnostic groups by such symptom measures. To establish this, receiver operator analyses of prospective studies, resulting in adequate predictive values, would be necessary.[7]

The strength of this study is that there is no doubt about neuropathological outcomes and diagnostic group membership. Although large, the National Alzheimer's Coordinating Center (NACC) database has a bias towards White, non-Hispanic, and relatively highly educated volunteers, is themed towards Alzheimer's disease, and is thus possibly not generalisable to the whole US population.[6] Important dementia diagnoses, such as vascular and Lewy body dementia, were excluded from the study and could thus interfere with any real world application of the results.[6] Finally, the interval between last clinical observation with measurement of neuropsychiatric symptoms and death was almost three years. As the authors observe, symptoms are only captured on one occasion and relatively late in the natural history of the disease. There is the possibility that pre-terminal non-specific changes or acute ante-mortem delirium confounded the patients' mental state. On the other hand, 30% of patients were not (yet) demented, thus emphasising that pathological brain changes are observable well before the onset of dementia.[8, 9]

In summary, this important large study with gold standard diagnoses allows to estimate the importance of the neuropsychiatric syndromes presenting with ADNC and FTLD in giving an early warning of comorbidity that may be missed if the only focus were on established ADNC biomarkers. Whether symptom patterns will have a positive or even decisive diagnostic use as hoped by the authors remains in doubt.

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