Predicting Risk for Dementia: Is It Ready for the Clinic?

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Dementia is one of the most dreaded diagnoses, with devastating clinical and socioeconomic impact, but without any effective treatments or prevention strategies. The majority of dementias affect older adults and typically involve a progressive course with asymptomatic and prodromal stages. Risk assessment methods that could be used in both primary care and specialty settings may be helpful in identifying people who are at risk for dementia and are appropriate for prevention efforts, including enrollment in disease-modifying clinical trials. However, most dementia risk algorithms are heavily weighted by comorbidities, and the metrics commonly available to clinicians may not have sufficient precision for accurate prediction. Given the aging imperative and the projected increase in the number of people afflicted by dementia, there is an urgent need for early diagnosis and reliable risk prediction to identify individuals who would benefit from new treatments and prevention strategies as they become available.

The study by Licher et al. in this issue (1) describes a basic and an extended dementia risk model in predicting 10-year risk for all-cause dementia. The basic risk model includes variables that could be easily collected in a primary care setting, and the extended model evaluates the added value of *APOE4* status, quantitative MRI imaging characteristics, and cognitive test scores in predicting risk for all-cause dementia. The models were developed and validated in the Rotterdam epidemiological longitudinal data set, followed by external validation in the Epidemiological Prevention Study of Zoetermeer and the Alzheimer's Disease Neuroimaging Initiative data sets. This multi-data-set study design is exemplary and raises confidence in the robustness, reproducibility, and generalizability of the findings.

The results of the study suggest that adding *APOE4* genetic status, a major risk factor for Alzheimer's disease specifically, quantitative MRI imaging characteristics, including indicators of atrophy and neurovascular disease, and cognitive test scores significantly improved the precision of 10-year risk estimates of all-cause dementia. The authors suggest, and we agree, that more complete models with relevant predictors will improve identification of people at high risk for dementia. Such knowledge can be used both to improve clinical trials by enrolling, or at least enriching samples with, participants who are among the most likely to convert to dementia and to facilitate clinical and personal decision making. As such, these results and others like it demonstrate the added value of relevant metrics such as neuroimaging to algorithms that can predict, with some degree of certainty in selected contexts, whether a person will decline to dementia. However, many ambiguities persist that somewhat limit the impact and usefulness of the approach of Licher et al.

The outcome in this study was dementia. Dementia itself is an umbrella syndrome with several possible etiologies that may occur singly or in various combinations to produce the syndrome. The added predictors that confer an advantage for predicting dementia were *APOE4* status, MRI estimates of whole brain volume, hippocampal volume and white matter ischemic lesion volume, and cognitive test scores. *APOE4* confers risk for amyloid, one of the proteins involved in Alzheimer's disease, the most common cause of dementia. MRI is adequate for visualizing and quantifying cerebral atrophy and other morphological characteristics suggestive of neurodegeneration, and it is reasonably good at identifying one possible etiology of dementia—macro-level cerebrovascular disease—but there is nothing intrinsic to MRI that provides a *direct* molecular biomarker of Alzheimer's disease, Lewy body disease, Pick's disease, frontotemporal lobar degeneration, or limbic predominant age-related TDP-43 encephalopathy (although patterns of atrophy may be supportive in specific contexts). Finally, cognitive performance at a prior time point may be highly predictive of future cognitive outcomes including dementia, but like MRI, it lacks specificity to the varying etiologies of dementia, although patterns of neuropsychological performance may be supportive in specific contexts.

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The field of dementia now needs more intentional deployment of disease-specific biomarker methods, such as molecular positron emission tomography (PET). For example, specific imaging and fluid biomarkers of amyloid and tau, the defining features of Alzheimer's disease, are available in research contexts (2–4), and their deployment in population-based and convenience sample cohorts have brought an increased level of clarity for predicting decline (5–9) for the purposes of early identification and enriching clinical trial samples with specific disease types. The "ATN" (amyloid, tau, and neurodegeneration) research framework for Alzheimer's disease (10) clearly lays out the rationale and utility of a disease-biomarker based approach that will improve the

construct validity and precision of Alzheimer's disease research. This is sorely needed, since a diagnosis of Alzheimer's clinical syndrome may be wrong 17%–25% of the time when made by dementia specialists (11, 12), and more frequently in primary care settings. While imaging and fluid biomarkers for Alzheimer's disease are maturing and advancing the field, biomarkers for the other major causes of dementia are still lacking and are urgently needed.

Licher et al. are cognizant of the pragmatic clinical realities of needing easily obtainable biomarker predictors. Sophisticated molecular PET imaging, genetics, and cognitive assessment are not yet feasible outside specialized care and research settings. Blood tests (2) for one or more of the neurodegenerative diseases may be a possibility in the near future, although much work remains to be done (13–15). Likewise, although reliable dementia risk prediction could potentially identify asymptomatic persons for enrollment in clinical trials, its utility is limited, given that the majority of treatment trials focus on persons with a specific neurodegenerative disease and not the dementia syndrome.

The Licher et al. study provides a robust demonstration that all-cause dementia can be predicted with some degree of certainty 10 years before conversion using advanced MRI quantification, a genetic test, and cognitive assessment. Since effective prevention and therapy will require target engagement of specific disease processes, disease-specific biomarkers and prediction algorithms are urgently needed to identify people at specific risk for the several neurodegenerative diseases.

Until such precision can be accomplished, approaches such as the one described by Licher et al., although not ideal, nevertheless will help refine the population of interest for risk reduction. Such approaches will have utility in understanding general predictors of dementia and for implementing and assessing general health and lifestyle interventions for improving general brain health, such as exercise, diet, and cognitively stimulating activities.

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