

Challenges in communicating and understanding predictive biomarker imaging for Alzheimer's disease

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There is accumulating evidence that the pathophysiological process underlying Alzheimer's disease—including protein aggregation, synaptic dysfunction and neuronal loss—begins years if not decades prior to the onset of clinical symptoms and functional limitation. This long prodromal period represents our greatest hope for effective therapeutic intervention as well as a domain of serious ethical concern. Interventions to arrest or even to delay the neurodegenerative process could profoundly reduce the anticipated societal burden of Alzheimer's disease in an aging global population,<sup>1</sup> especially if initiated prior to the development of functional impairment. However, successfully implementing such a strategy will likely require the identification and targeting of people who are cognitively normal but have evidence for underlying neurodegeneration—initially only for recruitment into clinical trials to test the utility of preventive strategies, but eventually (it is hoped) for the broad delivery of such interventions if they are proven effective. New molecular diagnostic techniques now allow for *in vivo* detection of abnormal levels of the disease biomarkers amyloid- $\beta$  and tau, using positron emission tomography or cerebrospinal fluid analysis. But given remaining uncertainties about the clinical meaning and predictive power of these techniques, it remains controversial whether or how test results can be responsibly disclosed to cognitively normal individuals.<sup>2,3</sup>

In this issue of *JAMA Neurology*, Mozersky and colleagues present early work addressing how cognitively normal adults interpret a finding of elevated brain amyloid- $\beta$  in the context of enrollment for the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) clinical trial.<sup>4</sup> The design of the A4 study itself illustrates the ethical challenges at play. This clinical trial addresses whether administration of solanezumab (a humanized monoclonal antibody targeting amyloid- $\beta$  aggregation) can prevent cognitive decline among cognitively normal adults with elevated brain amyloid- $\beta$ , as measured using positron emission tomography (PET) with the radiotracer florbetapir.<sup>5</sup> Prevailing appropriate use criteria advise against clinical use of amyloid imaging in asymptomatic individuals,

citing “a significant potential for patients and families to make inaccurate assumptions about risk and future outcomes on the basis of amyloid PET results.”<sup>6</sup> However, in the A4 study, prospective participants are screened using amyloid PET and evidence of amyloid accumulation is an inclusion criterion for enrollment. Thus, the trial design not only requires that amyloid imaging be performed, but also effectively requires that the results of such imaging be disclosed to participants (as well as to prospective participants who are excluded as having negative imaging results). Recognizing these challenges, the A4 investigators have implemented a rigorous process for disclosure of imaging results, appropriately emphasizing the ambiguity and limitations of amyloid imaging as an individual predictor of future clinical disease.<sup>7</sup>

The current paper presents findings from a sub-study of A4, using semi-structured telephone interviews with research participants who have elevated amyloid- $\beta$  on PET to elicit participants’ own understandings of the significance of findings. A slight majority (27/50) of participants anticipated their finding of elevated amyloid- $\beta$ , perhaps unsurprising in a group volunteering for a study of Alzheimer’s disease prevention in which elevated amyloid- $\beta$  is a condition for enrollment. Likely more important given ethical concerns over biomarker disclosure, participant responses indicate that the A4 investigators did successfully communicate the prognostic uncertainty associated with imaging results.

A strength of qualitative research is its ability to elicit stakeholder beliefs or concerns that may not have been initially anticipated. In this case, a sizable proportion of participants (20/50) expressed dissatisfaction with the categorical characterization of results as “elevated” or “not elevated,” in some cases desiring more specific information about how elevated their own results were relative to the threshold for inclusion in the A4 study. The authors speculate that concern for more fine-grained interpretation of results may be more salient for cognitively normal individuals undergoing predictive testing than for symptomatic patients seeking an explanation for current

symptoms. However, their finding is echoed in another recent study of clinical amyloid imaging in symptomatic patients with dementia and mild cognitive impairment.<sup>8</sup> In this work by Grill and colleagues, several caregivers expressed an expectation that PET images could be used as a measure of disease severity—a similar wish for granularity that is considered an inappropriate application of amyloid imaging given the absence of data to support such inferences.<sup>6</sup> These findings together suggest that, in addition to counseling regarding prognostic uncertainties with amyloid imaging, closer attention must be paid to advising prospective participants about the presently limited, categorical interpretation of these tests.

Overall, the findings of Mozersky and colleagues are broadly reassuring regarding research participants' ability to understand the prognostic uncertainty of amyloid imaging. But as they note, caution is needed in generalizing from their results. For instance, all but one participant was white/non-Hispanic, 30 of 50 had undergone postgraduate education, and 40 of 50 had a family history of Alzheimer's disease. In addition to these demographic markers, these participants represent a selected subpopulation of an already rarified group: prospective participants in the A4 study were provided with study materials for this sub-study, and interested participants themselves contacted the study investigators. These participants are thus likely to be particularly supportive of the Alzheimer's disease research enterprise, and given their family histories and high educational attainment may be better positioned to interpret information about the limitations and ambiguities of testing than other groups.

Also, while Mozersky and colleagues address one source of ethical concern about imaging biomarker disclosure to cognitively normal individuals (the possibility of faulty assumptions about the risk for clinical disease), the present paper does not address other potential concerns such as potential adverse psychological effects,<sup>9,10</sup> or participants' perspectives on the possibility of

employment or insurance discrimination.<sup>11</sup> Fortunately, further work from these authors as well as by other groups is currently underway to examine these issues empirically.

Moving forward, how should we think about predictive uses of such biomarkers, both in research and in clinical practice? First, the present study and the A4 study more generally provide helpful examples of how biomarker information can be disclosed to cognitively normal people, while also suggesting how participant education could be improved in future studies (e.g., further educating prospective participants about the categorical interpretation of findings). Targeted preventive strategies for Alzheimer's disease and related dementias are at high priority for future research, so this is particularly valuable in considering the design of future work.

Second, might these and other findings lead us to reconsider prevailing appropriate use criteria and the judgment that in this population, “the potential harms outweigh the minimal benefits”?<sup>6</sup> While these findings are reassuring about some of the potential harms, work remains to be done on the benefit side of this equation before these techniques can be clinically adopted in cognitively normal persons. Of course, success in preventive strategies such as the intervention being tested in the A4 study would drastically change any assessment of the benefits of predictive testing. But it is also possible to imagine that technical and diagnostic improvements, such as perhaps from the paired application of PET markers for amyloid- $\beta$  and tau, could sufficiently improve individual estimates of risk to provide prognostic information that would be useful to some cognitively normal individuals—just as we presently offer genetic testing even in the absence of preventive intervention.

What is clear is that, with the advance of molecular diagnostic tools in neurology, clinicians and investigators will increasingly be faced with the challenge of presenting patients with information of uncertain prognostic significance. The investigators of the A4 study are to be commended for developing a thoughtful process of disclosure for predictive biomarker findings,

and Mozersky and colleagues have performed valuable work in subjecting this disclosure process to further critical scrutiny. As our understanding of the mechanisms of Alzheimer's disease and other dementias grows more complex, the task of communicating to research participants and patients what they need to know grows more challenging while also more urgent.

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<sup>5</sup> Clinical Trial of Solanezumab for Older Individuals Who May be at Risk for Memory Loss - Full Text View - ClinicalTrials.gov. 2017; <https://clinicaltrials.gov/ct2/show/NCT02008357>. Accessed August 15 2017.

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