Amyloid imaging

The court of public opinion

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Human amyloid imaging is one of the great recent translational medicine stories. Beginning with the recognition that Thioflavin T derivatives could be used as PET tracers, through development of Pittsburgh compound B, to US Food and Drug Administration (FDA) approval of Florbetapir in 2012, human amyloid imaging has held great promise to allow in vivo inclusive diagnosis of Alzheimer disease (AD), even though the first principle of amyloid PET is that it functions as a surrogate for β-amyloid pathology, and not necessarily as a surrogate for the diagnosis of AD.[1,2]

Concurrent with the development of amyloid imaging is the recognition of mild cognitive impairment (MCI) as a frequent prodromal phase to AD dementia. Persons with MCI who have high levels of β-amyloid are more likely to progress to dementia.[3] Furthermore, cerebral amyloidosis is now recognized as an early finding in asymptomatic individuals, years before the development of memory loss or dementia.[4,5]

Along with the tantalizingly attractive concept of early intervention in dementia, we are now defining new patient populations, such as "cognitively normal—amyloid positive," whose cognitive trajectories are unclear. Research studies, including the Alzheimer's Disease Neuroimaging Initiative (ADNI), either discourage or even forbid communicating such potentially important prognostic information, because we lack firm guidelines for counseling and because longitudinal data are lacking.

These discussions mirror larger societal conversations about access to information, especially genetic polymorphisms conferring disease risk. In the Internet age, access to information has been democratized through disintermediation. Patients often research their medical conditions; patients are empowered and participate in clinical decisions; and life planning adjusts to disclosure of information such as AD genetic risk, exemplified by the Risk Evaluation & Education for Alzheimer's Disease (REVEAL) study.[6]

In this issue of *Neurology*®, Shulman et al.[7] report on an Internet-based survey of ADNI investigators regarding the return of information to research participants, with special emphasis on amyloid imaging, performed before FDA approval of Florbetapir. The results indicate a disconnect among research policies, patient desire for information, and investigator preferences. Sixteen percent of investigators reported that more than 75% of cognitively normal participants requested their amyloid imaging results (with similar percentages for MCI). Fifty-eight percent of ADNI researchers supported disclosure of amyloid imaging results to cognitively normal persons and 82% to individuals with MCI. This discordance between investigator preference and common research practice may reflect the ADNI study in particular, where real-time access to research data for researchers (data available through loni.ucla.edu) is being considered for extension to participants.

The importance of amyloid imaging in making diagnostic decisions is reflected in the percentage of investigators who reported whether a test is clinically meaningful. For people with normal cognition, 50% of respondents believed that the Mini-Mental State Examination (MMSE) was "clinically meaningful," compared to 63% for amyloid imaging. Clinical "meaning" is subjective, but Shulman et al. conclude that ADNI investigators, representing many influential clinical AD researchers, consider amyloid imaging on a path to becoming a well-validated biomarker measure, whose positivity likely presages AD, and also represents our best opportunity for very early interventions.

Many important issues are raised by the findings of Shulman et al. Revision of research disclosure policies in an age of expanded information access has to be considered, but should be weighed against protecting participants from harm from worrisome but incomplete prognostic information. The REVEAL study disclosed *APOE* genotype to those at genetic risk for AD, but the study excluded individuals with high anxiety or depression rating scores.[6] Lay people often do not understand the meaning or context of disclosed information, so simple disclosure of data needs to be fashioned into usable information. Disclosing results of amyloid imaging may require skills that current clinicians lack. Another model for disclosure is informed consent, which is a process, not a document.

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Extrapolating the results to a clinical setting suggests major challenges and problems. If clinicians believe that amyloid imaging is more clinically relevant than the MMSE for normal elders, then access and cost issues become especially acute. PET scan access is limited by the availability of technology, the half-life of F18, and trained readers. Clinical access has been slowed by lack of Medicare reimbursement; payers consider clinical utility of amyloid imaging an unresolved issue. The added cost burden and lack of long-term prognostic information, coupled with the lack of effective interventions,[8] may create considerable anxiety while failing to create better outcomes.

We cannot ignore the possibility that the demand for amyloid imaging will be driven by patients rather than clinicians. Surveys identify AD as the second most feared illness behind only cancer,[9] and the ballooning aging population will intensify the need for early diagnostic information and identification of AD prevention strategies. The United States has been one of only 2 countries that allow direct-to-consumer advertising, and few clinicians could probably withstand repeated requests for amyloid imaging from anxious patients and families without ordering tests, or referring to specialists more likely to utilize PET imaging.

The current study found fluorodeoxyglucose (FDG)-PET to be equally clinically meaningful in cognitively normal persons and those with MCI. FDG gives information about synaptic function reflecting neurodegeneration; use of both FDG and amyloid PET potentially increases radiation exposure and costs.

Ethical issues raised by biomarker positivity in asymptomatic individuals can be considered generic to the field, and we need some societal consensus beyond individual study policies. The AD biomarker field is in its infancy and equally valid and perhaps more clinically useful biomarkers may be found in serum, plasma, CSF, or MRI, where the cost, invasiveness, and radiation exposure issues will differ considerably from PET technology.[10]

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