Disclosing Amyloid Status to a Person Without Cognitive Impairments

Anticipating a novel clinical practice.

By Kristin Harkins, MPH and Jason Karlawish, MD

Neurology is on the edge of a revolution. It may become possible, because of advances in imaging and other technologies, to diagnose Alzheimer's disease (AD) years before the onset of clinical symptoms. Amyloid plaques, for example, may represent the earliest detectable evidence of AD pathology,[1] and buildup can begin 10 to 15 years before symptoms appear.[2] Technologies such as positron emission tomography (PET) can show these plaques accumulating in the brain. This state of biomarker positivity is recognized in updated diagnostic criteria as *asymptomatic at risk for AD*[3] or *preclinical AD*[2] or *AD pathologic change* as part of the AD continuum.[4]

These diagnostic labels are currently framed solely as research designations. As such, these are used to facilitate study of the natural history of AD and to identify individuals eligible to participate in clinical trials. PET amyloid imaging is Food and Drug Administration–approved only for the diagnostic workup of patients with symptoms of progressive cognitive impairment. Appropriate use criteria recommend it for individuals with mild cognitive impairment (MCI) or dementia with an unclear or atypical cause. It is not recommended for those who are cognitively unimpaired in the clinical setting.[5]

It is expected though, that eventually we will have the ability to diagnose AD years before the onset of clinical symptoms. When this happens, AD biomarker testing will move from research into routine clinical practice. Clinicians will use biomarkers to diagnose AD in people who are cognitively unimpaired and prescribe interventions to prevent or delay the onset of symptoms. As preclinical AD—or whatever term the field settles on—is translated from research into a likely common clinical diagnosis, clinicians, patients, and families will face novel challenges.[6] Current research provides insights into these challenges and highlights other unanswered questions.

How to Deliver a Diagnosis of Preclinical Alzheimer's Disease

Best practices for disclosure of amyloid imaging results to adults who are cognitively unimpaired and individuals with MCI in a research setting provide a template (Figure) for clinical practice[7,8] that begins with education using standardized text to emphasize the probabilistic nature of the result. Subsequent steps include assessing understanding, mood, and stressors. This process recommends separate visits for education, scanning, and result disclosure. It is also suggested that a family member or loved one participate in the disclosure session and that there is follow-up to assess well-being and the impact of disclosure on day-to-day life.

Availability of an effective treatment—an essential feature of the preclinical AD construct—will undoubtedly simplify the process by reducing concerns about patient distress and adverse psychologic reactions to disclosure. This has been seen with the translation from research to clinical practice for diagnosing and treating emotionally fraught diseases, such as HIV. In the early years of HIV, testing for the infectious disease required a similar stepped process. As treatment and clinical practice improved, testing became simpler and more efficient and progressed to self-testing in the home. In this article, we discuss 6 considerations that will inform the novel clinical practice of diagnosing AD in a person without cognitive impairment.

Prognostic Uncertainty

In preclinical AD, testing for amyloid (or some other biomarker) will be tied to a prescription for a treatment. The test will lead to treatment and the treatment will
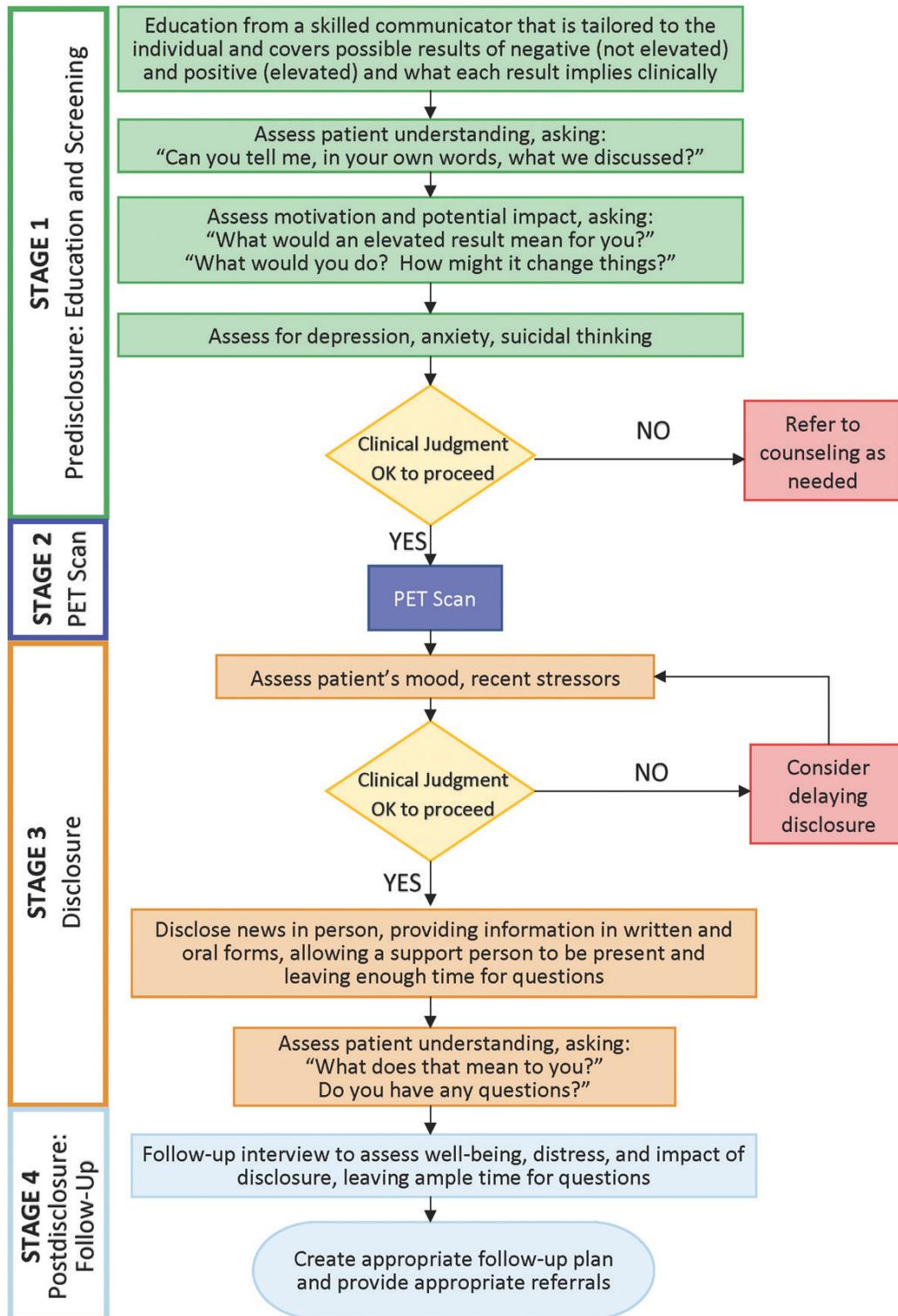
Figure. Best practices for disclosing amyloid imaging results to people without cognitive impairment. It is recommended that at least 24 hours pass between stages.

offer the promise of preventing or delaying a common but uncertain future outcome. Up to 30% of adults over age 65 without cognitive impairment have amyloid deposits[9] and have a higher risk of developing AD.[10] Many will not develop clinically significant cognitive impairments during their lifetimes, however, and we do not yet have the ability to determine who will remain asymptomatic and who will develop clinical AD. Some patients receiving treatment will experience discomfort grappling with this uncertainty. Interviews with individuals who learned an amyloid result through a clinical trial found that these individuals wanted data showing how elevated their amyloid was in the form of percentages, numbers, or a scale to help them make sense of the result and, therefore, their risk.[11] Unfortunately, such data are not available as they are for other common diseases of aging, such as osteoporosis or hypertension, where risk calculators allow patients to foretell their likelihood of, respectively, a fracture or death from heart disease. This is challenging in the clinical setting, where patients are encouraged to know their numbers and instead are given the 1 of 2 categorical descriptions (negative/not elevated or positive/elevated), which are all we have available at present.

Even when risk estimates are finally available and communicated, patients' perceptions of risk may be influenced by their previous experiences and beliefs.[12] Clinicians will need to be skilled in conveying what is known and unknown about the meaning and implications of an amyloid PET scan or other biomarker result, and how it fits into the larger picture of risk for clinical AD. Because biomarker data from large longitudinal population studies and treatment studies will redefine so-called normal states, neurologists should anticipate a future of shifting language and cutoff criteria.

Minimizing Harm With Compassion

Diagnostic tests and treatments have risks and side effects. The field of oncology, for example, is a story of progress at a price. Effective chemotherapy causes disabling and disfiguring side effects. In the diagnosis and treatment of preclinical AD, the potential for adverse psychological effects and catastrophic reactions is an important consideration. Survey research suggests that some individuals may use amyloid PET scan results to plan ending their life.[13-15] Reassuringly, studies of individuals without cognitive impairment who have undergone amyloid PET disclosure have shown that disclosure is generally well-tolerated, with minor increases in anxiety and test-related distress that are mild and improve over a period of 6 months.[16] Although these findings provide reassurance, participants in these studies were well-educated motivated individuals who are voluntarily participating in research

that includes amyloid disclosure. Most importantly, they were carefully screened for psychiatric comorbidities, and went through an extensive education and disclosure process as outlined in the Figure. In a clinical setting with a more diverse population, clinicians will need to balance the benefit of providing a preventive treatment with the risks of disclosure, including the individual's psychologic well-being and potential for a catastrophic reaction.

Treatment Helps the Patient but Changes the Person

Knowledge of having preclinical AD may affect individuals' perceptions of their cognitive abilities and cognitive performance. Adults age 50 or more who knew they had at least 1 copy of the *APOE4* allele (APOE4 carriers) judged their own memory more harshly and performed worse on an objective verbal memory test than APOE4 carriers who did not know their genotype.[17] In contrast, those who knew they were APOE4 noncarriers judged their memory more positively than people without *APOE4* who didn't know their status, although these groups did not differ in objective memory test performance. In focus group discussions, research participants without cognitive impairments worried that learning about their risk of developing AD would lead to hypervigilance and overinterpretation of typical memory lapses.[18]

Treatment Helps Patients but Changes Their Relationships

Disclosing the diagnosis of preclinical AD has implications for people other than the patient. Family members, in particular, may have ideas about what the result means and preferences about knowing it. Although individuals cite preparing their family for a potential future illness as a reason to learn the result,[15] others raise concerns about burdening their family with the knowledge.[18] In one study involving amyloid status disclosure, at least one potential participant declined screening because the individual's spouse did not want to know the result.[16]

In clinical trials, a subject must disclose results to at least one other person, as these studies require a knowledgeable informant to serve as a study partner and provide information about the participant's cognitive and functional abilities. Although this requirement is unique to the needs of research, it suggests a model for clinical practice, as most individuals would plan to share a biomarker result with loved ones.[13] Patients should be counseled to consider the views of and potential impact on their loved ones, and whether they should be involved in the disclosure process. The patient's desire for privacy must be balanced with family members' desires to prepare for the future and protect the patient from potential harm. Clinicians should anticipate questions and concerns from loved ones and

the possibility of family conflict or adverse psychologic reactions in family members.

There are both potential benefits of disclosing amyloid PET scan results to loved ones, including social support and preparing for the future, and potential risks. Dementia is a stigmatized condition that leads to diminished social status, including being discriminated against, patronized, or isolated.[19] Spillover stigma may also lead to diminished social status for caregivers and other loved ones. Stigma increases stress and deters individuals from seeking care, leading to worse health outcomes for both patients and caregivers. The stigma of AD varies across demographics and cultural backgrounds and knowledge of AD; thus, the experience of stigma will depend on the characteristics of an individual's social milieu.[20]

Whether and how these same social reactions will occur for individuals with preclinical AD is currently unknown, although research suggests that AD stigma is a concern for individuals with MCI and those learning about their risk for AD.[21] Stigma associated with AD is partially driven by perceptions of AD as a progressive condition with a poor prognosis.[22] Therefore, an effective treatment might lead to reduced social stigma for individuals with preclinical AD, assuming that knowledge about this development is widely disseminated and understood by the public. Public health efforts including messaging to reduce stigma associated with AD are currently underway.

Patients Will Look to the Future and Need to Make Plans

A diagnosis of preclinical AD may affect consideration of and preparation for the future, including living situations, financial and legal planning, and employment and leisure activities. Commonly cited reasons for desiring amyloid status disclosure include arranging personal affairs and changing the timing of planned life events.[15] After disclosure of APOE genotype, individuals who are APOE4 carriers have been shown to purchase or make changes to long-term care insurance at much higher rates than people who are noncarriers.[23]

Surveys of the general population show that people expect individuals with clinical AD to experience discrimination in areas such as employment and insurance.[24] Laws and policies are not currently in place to distinguish preclinical AD from clinical disease or to protect the autonomy of adults who are at risk but competent. These individuals could, therefore, face discrimination in the realms in which they are likely to be adjusting future plans, such as health care, housing, insurance, and employment. They could also potentially lose rights and privileges such as driving a car or making medical and financial decisions.

Prior to obtaining or disclosing biomarker results, patients should be informed that the inclusion of a bio-marker for AD pathology or a diagnosis of preclinical AD in the medical record may affect their ability to obtain or make changes to long-term care or other types of insurance. Clinicians should also encourage patients to consider whether there are financial, legal, or other arrangements they wish to make before learning their biomarker result and reflect on how each of the possible results will influence their plans for the future.

Lifestyle Changes and Risk Reduction

A diagnosis of preclinical AD may influence behaviors patients take to reduce their risk of developing AD dementia. In a study of APOE disclosure to individuals with a family history of AD, those with at least 1 copy of the APOE4 allele were significantly more likely to report the adoption of AD-specific health behavior changes, such as changes in medications. vitamins, diet, or exercise, 1 year after disclosure in comparison with participants who were not APOE4 carriers.[25] Approximately 90% of individuals surveyed from an AD research registry responded that they would make lifestyle changes if they learned they were at risk for or had biomarker evidence of AD.[13] Clinicians will need to be prepared to provide information about known risk factors for AD dementia and recommendations regarding changes patients can make to reduce risk. This may include dissuading patients from engaging in unproven or potentially harmful interventions and encouraging patients without biomarker evidence of AD pathology that risk reduction activities are still beneficial for them.

Conclusion

The translation of preclinical AD from a research designation to a clinical diagnosis will present novel challenges for clinicians, patients, and families. Patients may struggle with the prognostic uncertainty of this diagnosis and experience psychologic and emotional challenges, as well as changes in their relationships and sense of self. They will need to make decisions about their lifestyles, behaviors, and future plans. Clinicians will need to be attuned to these concerns, prepared to provide information and guidance, and able to facilitate connections to support resources for patients and families as needed. ∎

1. Jack CR, Knopman DS, Jagust WJ, et al. Update on hypothetical model of Alzheimer's disease biomarkers. *Lancet Neurol*. 2013;12(2):207-216.

2. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement*. 2011;7(3):280-292.

3. Dubois B, Feldman HH, Jacova C, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol*. 2014;13(6):614-629.

4. Jack CR, Jr., Bennett DA, Blennow K, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-562.

5. Johnson KA, Minoshima S, Bohnen NI, et al. Appropriate use criteria for amyloid PET: A report of the Amyloid Imaging Task Force, the society of nuclear medicine and molecular imaging, and the Alzheimer's association. *J Nucl Med*. 2013;54(3):476-490.

6. Brookmeyer R, Abdalla N, Kawas CH, Corrada MM. Forecasting the prevalence of preclinical and clinical Alzheimer's disease in the United States. *Alzheimers Dement*. 2018;14(2):121-129.

7. Harkins K, Sankar P, Sperling R, et al. Development of a process to disclose amyloid imaging results to cognitively normal older adult research participants. *Alz Res Ther*. 2015;7:26.

8. Lingler JH, Butters MA, Gentry AL, et al. Development of a standardized approach to disclosing amyloid imaging research results in mild cognitive impairment. *J Alzheimers Dis*. 2016;52(1):17-24.

9. Chetelat G, La Joie R, Villain N, et al. Amyloid imaging in cognitively normal individuals, at-risk populations and preclinical Alzheimer's disease. *Neuroimage Clin*. 2013;2:356-365.

10. Villemagne VL, Pike KE, Chetelat G, et al. Longitudinal assessment of A-beta and cognition in aging and Alzheimer disease. *Ann Neurol*. 2011;69(1):181-192.

11. Mozersky J, Sankar P, Harkins K, Hachey S, Karlawish J. Comprehension of an elevated amyloid positron emission tomography biomarker result by cognitively normal older adults. *JAMA Neurol*. 2018;75(1):44-50.

12. Linnenbringer E, Roberts JS, Hiraki S, Cupples LA, Green RC. "I know what you told me, but this is what I think:" perceived risk of Alzheimer disease among individuals who accurately recall their genetics-based risk estimate. *Genet Med*. 2010;12(4):219-227.

13. Caselli RJ, Langbaum J, Marchant GE, et al. Public perceptions of presymptomatic testing for Alzheimer's disease. *Mayo Clin Proc*. 2014;89(10):1389-1396.

14. Caselli RJ, Marchant GE, Hunt KS, et al. Predictive testing for Alzheimer's disease: suicidal ideation in healthy participants. *Alzheimer Dis Assoc Disord*. 2015;29(3):252-254.

15. Ott BR, Pelosi MA, Tremont G, Snyder PJ. A survey of knowledge and views concerning genetic and amyloid positron emission tomography status disclosure. *Alzheimers Dement*. 2016;2(1):23-29.

16. Burns JM, Johnson DK, Liebmann EP, et al. Safety of disclosing amyloid status in cognitively normal older adults. *Alzheimers Dement*. 2017;13(9):1024-1030.

17. Lineweaver TT, Bondi MW, Galasko D, Salmon DP. Knowledge of APOE genotype affects subjective and objective memory performance in healthy older adults. *Am J Psychiatry*. 2014;171(2):201-208.

18. Milne R, Bunnik E, Diaz A, et al. Perspectives on communicating biomarker-based assessments of Alzheimer's disease to cognitively healthy individuals. *J Alzheimers Dis*. 2018;62(2):487-498.

19. Stites SD, Milne R, Karlawish J. Advances in Alzheimer's imaging are changing the experience of Alzheimer's disease. *Alzheimer Dement*. 2018;10:285-300.

20. Stites SD, Johnson R, Harkins K, et al. Identifiable characteristics and potentially malleable beliefs predict stigmatizing attributions toward persons with Alzheimer's disease dementia: Results of a survey of the U.S. general public. *Health Commun*. 2018;33(3):264-273.

21. Beard RL, Neary TM. Making sense of nonsense: experiences of mild cognitive impairment. *Sociol Health Iln*. 2013;35(1):130-146.

22. Johnson R, Harkins K, Cary M, Sankar P, Karlawish J. The relative contribution of label and prognosis to Alzheimer's stigma: a vignette-based experiment. *Soc Sci Med*. 2015;143:117-127.

23. Zick CD, Mathews CJ, Roberts JS, Cook-Deegan R, Pokorski RJ, Green RC. Genetic testing for Alzheimer's disease and its impact on insurance purchasing behavior. *Health Aff (Millwood)*. 2005;24(2):483-490.

24. Stites SD, Rubright JD, Karlawish J. What features of stigma do the public most commonly attribute to Alzheimer's disease dementia? Results of a survey of the U.S. general public. *Alzheimers Dement*. 2018:Published online March 27. doi.org/10.1016/j.jalz.2018.01.006

25. Chao S, Roberts JS, Marteau TM, et al. Health behavior changes after genetic risk assessment for Alzheimer disease: The REVEAL Study. *Alzheimer Dis Assoc Disord* 2008;22(1):94-97.

Kristin Harkins, MPH
Penn Memory Center
Department of Medicine
University of Pennsylvania Perelman School of Medicine
Philadelphia, PA

Jason Karlawish, MD
Professor of Medicine, Medical Ethics & Health Policy, and Neurology
Penn Memory Center
University of Pennsylvania Perelman School of Medicine
Philadelphia, PA

Disclosures

Jason Karlawish is a consultant for Squintmetrics and site PI for clinical trials sponsored by Novartis and Lilly. Kristin Harkins, MPH has no financial or other relationships to disclose.