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ABSTRACT

Research suggests that Alzheimer disease (AD) pathophysiology begins prior to the clinical expression of the disease and that biomarker measures may provide direct evidence of this process. As a result, it may be possible to uncouple the diagnosis of AD from the clinical expression of the disease. The shifting boundaries between normal brain aging and disease present 3 challenges: 1) establishing guidelines for researchers and clinicians to safely and effectively communicate the diagnosis of preclinical AD, 2) setting up a process that effectively translates this diagnosis into practice and policy, and 3) adapting laws, regulations, and professional practices to the diagnosis of preclinical AD. The field of genetic testing for AD suggests how to balance a patient’s desire to know his or her risk of developing dementia with a clinician’s desire to mitigate the potential harms of that information. The development of diagnostic and treatment guidelines for other diseases of aging, such as cardiovascular disease, suggests the need for a National Alzheimer’s Education Program to develop policies and procedures to translate preclinical AD into both clinical practice and policy. Revisions are needed to laws, regulations, and professional practices governing driving, financial management and planning, and privacy and confidentiality.

GLOSSARY

- AD — Alzheimer disease
- LDL — low-density lipoprotein
- NCEP — National Cholesterol Education Program
- NIA — National Institute on Aging
- REVEAL — Risk Evaluation and Education for Alzheimer’s Disease project

The diagnosis of Alzheimer disease (AD) is a clinical diagnosis. A clinician judges that a person’s history, examination, and studies show progressive cognitive changes that impair social function and activities of daily living—that is, dementia—and that the cause of this dementia is the neurodegenerative disease called AD.1 And yet, a substantial and growing body of research suggests that AD pathophysiology (hereafter referred to as “pathology” for simplicity) begins prior to the clinical expression of the disease and that biomarker measures, such as PET imaging and spinal fluid assays, may provide direct evidence of this pathology.2,3 As a result, it may be possible to uncouple the diagnosis of AD from the clinical expression of the disease.

In response to this research, the scientific community has proposed diagnostic criteria that encompass persons who do not have clinical signs and symptoms, what this essay calls “preclinical AD.”4,5 The ability to diagnose AD prior to the onset of disabling cognitive impairments is a key step to potentially reduce the burdens of suffering and costs for both patients and society that are estimated to be as much as $604 billion worldwide and $316 billion in the United States.6,7 Many nations, including the United States, have, or are developing, national plans and bureaucratic infrastructures to organize and track the progress of research to translate these criteria into practice.8

As they do this, they need to recognize how preclinical AD will change the boundaries between what is “normal cognitive aging” or “healthy brain aging” vs what is disease. This change must respect that among all the common diseases affecting older adults, AD is the one disease that definitively impairs a person’s capacity to act autonomously and is among the most feared diseases of aging. Preclinical AD will arguably alter the foundation of our selves.
The shifting boundaries between normal brain aging and disease present 3 challenges to researchers, clinicians, patients, and health care policy makers: 1) establishing guidelines for researchers and clinicians to safely and effectively communicate the diagnosis, 2) setting up a process that effectively translates the diagnosis into practice and policy, and 3) adapting laws, regulations, and professional practices to the diagnosis of preclinical AD.

To address these challenges, the field of genetic testing for AD suggests how to balance a patient’s desire to know his or her risk of developing dementia with a clinician’s desire to mitigate the potential harms of that information. The experiences of developing diagnostic and treatment guidelines for other preclinical diseases of aging, such as cardiovascular disease, suggest policies and procedures to translate preclinical AD into both clinical practice and policy. Revisions to laws, regulations, and professional practices governing driving, financial management and planning, and privacy and confidentiality will allow medical, legal, and financial professionals to effectively monitor patients with preclinical AD for losses in their capacities to perform higher level activities of daily living, while at the same time minimizing stigma, preserving privacy, and maximizing respect for autonomy.

THE CONCEPTUAL MODEL OF PRECLINICAL AD

The two proposed criteria—one from the National Institute on Aging (NIA)/Alzheimer’s Association and the other from the International Working Group for New Research Criteria for the Diagnosis of AD—emphasize that sufficient evidence does not support clinicians using the criteria. Instead, they are research criteria that should be applied in the context of studies. Of particular value are longitudinal studies that correlate changes in biomarkers with declines in cognitive and functional measures, and experiments that test drugs that may slow cognitive decline that herald the transition from preclinical to clinical AD. If this research succeeds, the criteria will begin to move into clinical practice.

Although differences exist between the NIA/Alzheimer’s Association and International Working Group criteria, they have a common conceptual model. The scientific community is converging on a concept of AD as an “at-risk state” defined by biomarkers and other risk factors, and uncoupled from clinical symptoms of the disease.

This model reflects a general shift in concepts of disease from a category defined by pathology in a person that causes symptoms or signs to disease as a risk defined by factors. The goal of the NIA-AA criteria for preclinical AD is, for example, “to better define the factors which best predict cognitive decline in biomarker positive individuals, so as to move toward an accurate profile of preclinical AD.” The diagnostic exercise is moving from clinical-pathologic correlation (fitting symptoms and signs to a pathology) to clinical-actuarial correlation (assessing factors that define health risks in need of risk reducing interventions). As a result, clinical practice is not so much about confirming the presence of pathology as using markers of the presence of pathology, as well as other risk factors, that predict the likelihood of decline.

The authors of the preclinical AD guidelines cite cardiovascular disease as a model for their preclinical concept. Cardiovascular disease is defined as the probability of a cardiovascular event that is sufficiently high that a clinician ought to recommend interventions to reduce that risk. The National Heart, Lung, and Blood Institute’s National Cholesterol Education Program has, since 1985, supported and disseminated the Adult Treatment Panel’s “10 Year Heart Attack Risk Calculator.” A clinician enters into the Calculator a patient’s biomarkers of lipid levels and systolic blood pressure as well as other relevant risk factors such as age, gender, and smoking status. The Risk Calculator’s results guide whether to recommend to a patient interventions, such as a statin, to reduce the risk.

As AD transforms to this desktop model, researchers, clinicians, and professionals who interact with patients will face challenges related to communicating the diagnosis and translating it into policy, clinical practice, and daily life. Below, I address each of these challenges.

Safely and effectively communicating a diagnosis of preclinical AD. When clinicians and researchers are faced with patients who are considering whether to undergo testing to diagnose preclinical AD, how should they decide whether the patient should undergo testing?

The ethical challenge is that the results of Alzheimer biomarker testing are potentially harmful knowledge; that is, a patient can develop anxiety or depression or even become suicidal. Americans fear AD more than heart disease, diabetes, and stroke, and those 55 and older fear AD more than any other disease, such as, for example, cancer, a finding that
lends credence to the popular phrase that "the Big A [Alzheimer's] has replaced the Big C [cancer]."13

Given these intense emotions, people are likely to strongly differ both in their desire to know whether they are at risk to develop Alzheimer dementia and, if they do learn the diagnosis, how they react to it. When the psychologist Steven Pinker decided to have his whole genome sequenced, he followed James Watson's decision. Watson, one of the first two humans to have his genome sequenced, chose not to learn his APOE genotype. Pinker explained he found his "current burden of existential dread just about right."14

While the scientific community differs over whether APOE is a "biomarker of AD,"15 testing for APOE provides a similar result as testing for biomarkers such as amyloid imaging with a PET scan: persons who have APOE4 or brain amyloid, compared to persons who do not have them, are at greater risk to develop cognitive impairment.

Unlike James Watson, the other of the first two humans to have their genomes sequenced, Craig Venter, elected to learn his APOE status, and, upon discovering he was an APOE4 carrier, started taking simvastatin in an effort to reduce his risk.16 The evidence supporting the value of this risk assessment and intervention is uncertain, but what is certain is that some people are like Craig Venter. They desire to know if they are at risk for AD and, if they are, will take even unproven interventions to reduce this risk, and there are physicians willing to fulfill this desire. Anecdotal evidence suggests that some clinicians already are using AD biomarkers in their clinical practice with persons who are asymptomatic or at most mildly symptomatic.17 The possible Food and Drug Administration approval of flurbetapir to image amyloid plaques and the direct to consumer sale of APOE results will undoubtedly promote this practice.18,19

For researchers studying the proposed criteria for preclinical AD, as long as consensus exists that the criteria do not provide meaningful clinical information, researchers have no obligation to disclose to participants their biomarker results. The informed consent form for the US AD Neuroimaging Initiative offers a model to explain why participants will not learn their biomarker results. The form discloses to participants that the results of biomarkers are not yet able to provide meaningful information for care so they will not be shared with participants, their families, or their physicians.

When biomarkers do begin to provide meaningful information for care, a per-protocol specified plan not to disclose results will be less and less feasible as some participants will want to know their results and they arguably should receive them. Of more immediate concern are proposed studies that will follow exclusively persons who meet criteria for preclinical AD, such as a clinical trial to test a potential intervention. Even if the researchers agree that the results of biomarkers are not yet able to provide meaningful information for care, these studies will, by design, effectively disclose to enrolled participants that they are "biomarker positive." Researchers will need a plan to decide whether a person can enroll in such a study, and if they do, how to manage the risks and burdens of disclosure.

The informed consent form should disclose the risks, burdens, and uncertainties of biomarkers that may indicate preclinical AD. The protocol should describe steps to minimize risks and burdens. Studies of AD genetic risk disclosure provide researchers and clinicians the most relevant evidence base to develop a method to decide who to test and how to disclose that someone has biomarkers that may indicate a diagnosis of preclinical AD. The Risk Evaluation and Education for Alzheimer's Disease project (REVEAL) used a randomized and controlled design to compare the effects of disclosing a genotype that describes an increased risk of developing AD (the APOE4 allele) to not disclosing that information.

After first-degree relatives of persons with AD learned they were APOE4 carriers, they were no more likely than persons who either did not learn their APOE status or persons who were told they were APOE4 negative to suffer a negative impact upon their health and psychological well-being.20 A follow-up study showed that following the review of an educational brochure sent by mail, this genetic information can be safely delivered at a single face-to-face session with a genetic counselor.21,22

These findings suggest that the REVEAL methods are a useful approach to safely disclose being at risk to develop AD dementia. To be eligible for REVEAL, persons needed to score within an acceptable range of scores on measures of anxiety and depression.20 The researchers separated the education about risks and benefits of disclosure from the actual disclosure of APOE result, disclosed the information using written and oral formats, monitored mood and anxiety postdisclosure, required an emergency contact, and provided study participants as-needed access to mental health professionals.

The REVEAL methods provide a starting point for researchers and clinicians to disclose biomarker results to asymptomatic persons. Their generalizability is limited as persons who enrolled had to be willing to potentially not learn their APOE result. Hence, a deeply motivated and curious person such as Craig Venter might have chosen not to enroll. Still, the study procedures present a model so that just as the field of oncology developed methods to
break bad news to asymptomatic patients,23 AD researchers and clinicians can develop an evidence base on the impact of the diagnosis of preclinical AD and best practices on how to disclose it. Key features should address identifying symptoms of affective impairment and resources to treat them, assessing the adequacy of psychological and social resources such as a trusted friend or family member; and providing time for reflection prior to disclosing results. As advances are made in AD therapeutics, this practice will likely become less intensive, as for example, progress in HIV treatments has led to more relaxed HIV testing guidelines and practices, such as home HIV testing.

Setting up a process that effectively translates the diagnosis of preclinical AD into practice and policy. Before clinicians are able to use the proposed criteria for preclinical AD, researchers need to validate them. The histories of other diseases of aging such as cardiovascular disease, hypertension, and osteoporosis suggest that one key method to establish validity is the randomized and controlled clinical trial. These experiments can demonstrate whether an intervention such as a drug alters the risk predicted by a biomarker. Of course, a “positive trial” has clinical value too. Persons with preclinical AD have a treatment. But experiments also provide criterion validity that demonstrates what was once a risk factor is now a disease. Trials of drugs that lower blood pressure were, for example, essential to transform the risk factor of elevated systolic pressure into the disease of systolic hypertension in elderly persons.24 The discovery of low-density lipoprotein (LDL) cholesterol as a disease was in large part made possible by clinical trials showing that lovastatin therapy in persons with elevated LDL reduced the risk of heart attack.25 Clinical trials will not simply change how we treat AD, but what we mean when we say “AD.”

As clinical trials show that an intervention reduces the risk of cognitive decline from preclinical to clinical AD—or intermediate states such as mild cognitive impairment due to AD26—a question will animate clinical decision-making and the development of diagnostic and treatment guidelines. Which patients with preclinical AD should receive treatment? The “evidence-based medicine” answer to this question is that clinicians should prescribe treatment to persons that trial results show benefit from the intervention, but both the nature and politics of risk-based diseases suggest experts may recommend treatment for persons in which gold standard clinical trial evidence does not exist to support that they will benefit.

A case study that illustrates this is the National Cholesterol Education Program’s (NCEP) recommendation that women at moderately high risk of cardiovascular disease receive statin therapy despite the absence of supporting data from a randomized and controlled clinical trial.27,28 NCEP argued that the risk-based nature of cardiovascular disease together with the results of animal, genetic, pathologic and epidemiologic studies, and clinical trials was sufficient evidence. In addition, they argued that the urgency of the public health problem supported the recommendation because waiting for data from additional clinical trials of women at moderately high risk would mean more women will die of sudden death.29

The logic of this approach relies on coherently linking 2 distinct kinds of evidence: prognostic evidence that a biomarker validly describes the risk of clinical event with predictive evidence that an intervention targeting the biomarker reduces that risk. When this link can be made, recommending that groups who do not have clinical trial data supporting an intervention should still receive the intervention gains credence. If the population at risk is sufficiently large that the failure to intervene could cause large numbers of people to suffer the clinical event, then the proposal gains political power. That women, compared to men, have been disproportionately underrepresented in cardiac disease research likely further supported the proposal.

The current and projected size of the numbers of persons with AD dementia—an expected increase in the United States from 5 million to 10 to 13 million people by 2050,30 often described as an “epidemic”—and the fear of the disease suggest that statistics describing the population at risk could have similar power and influence on AD diagnostic and treatment guideline writing.

Controversies over how far to extend treatment for risk factor-based diseases are recurrent. They have, in addition to dyslipidemia, occurred in the fields of osteoporosis and diabetes.31-37 These controversies are arguably inherent when medical science and health policy interface to develop treatment guidelines for diseases that are defined along a risk dimension that can potentially encompass millions of persons.

To anticipate and mitigate controversies about whether the diagnosis of preclinical AD is ready to move from research to clinical practice and which persons with the diagnosis should receive treatment, the scientific, clinical, and policy communities should develop the “National Alzheimer’s Education Program.” This national and public program will address how to translate research results into clinical practice for persons with preclinical AD. To assure that it represents the public interest, the Department of Health and Human Services is a sensible institution to support and staff it. The recently authorized
National Alzheimer Project provides a sensible home for this group.4

The structure of this program and its processes to review and weigh evidence need to address the challenge of conflicts of commitment. Not only scientific and clinical expertise shapes how experts interpret evidence. Financial relationships and intellectual commitments do as well. Committee membership and responsibilities should describe what kinds of financial relationships are permissible for what kinds of committee activities.

The management of intellectual commitments is a more recently recognized issue in guideline writing.38 Guideline writing and review needs input from the most informed experts, but these same persons often have strong commitments to one or another competing interpretations of evidence. They may, for example, have discovered the evidence and thus have a personal and passionate attachment to it. Guideline writing organizations have increasingly recognized the value of soliciting input and commentary from these experts while giving nonexpert clinician-methodologists the responsibility for final guideline writing.39 This means that the National Alzheimer Education Program should include persons who are not experts in AD but, instead, in diseases of aging that share the conceptual model of preclinical AD such as cardiovascular disease.

Adapting professional practices, social policies, and laws to the diagnosis of preclinical AD. As the diagnosis of preclinical AD enters clinical practice, professional practices, social policies, and laws will need to adapt to the change in the meaning of the AD label. The label does not necessarily equate to disability. In persons with preclinical AD, who despite treatment have cognitive decline, the earliest disabilities are likely to be in cognitively demanding activities of daily living related to driving, the workplace, and financial management (the latter, aptly dubbed “the canary in the coal mine of impending dementia” and the principal cause of elder abuse and exploitation40). Persons with preclinical AD will require assistance to plan for and monitor emerging disabilities.

In the case of financial management, the professional’s core responsibilities will include how to help patients plan for the loss of financial capacity using mechanisms such as a durable power of attorney for finances and joint accounts, how to identify events that signal the need for a capacity assessment, and how to assess the relevant capacity.41 Physicians are certainly a key profession but not the only profession to do these tasks. The legal, banking, and financial services industries arguably bear some responsibility for assessing financial capacity as they are on the front line of witnessing a patient’s ability to manage their finances. The Financial Industry Regulatory Authority’s training materials for working with senior investors demonstrate how the industry is beginning to recognize this responsibility.42

Laws should be revised to address that persons at risk for cognitive declines may suffer stigma and discrimination, and, if they do suffer disability, exploitation. States should adopt the Uniform Power of Attorney Act as it provides a template for a power of attorney that allows the person with preclinical AD to minimize the hazard of financial abuse and exploitation.43 Privacy and confidentiality laws, regulations, and professional practices should address how to minimize that insurance, pharmacy, and medical records may disclose that a person has preclinical AD. This information could be damaging to patients, especially those who are still in the workplace. Finally, laws should be revised to recognize that the label of AD does not equate to disability. For example, driving laws that require mandatory reporting of a person with a diagnosis of AD will need to be revised to require that reasonable evidence exists of impaired cognition and function that warrants reporting.

DISCUSSION

As research translates the criteria for preclinical AD into clinical practice, our language for talking about AD will likely change. Just as progress in cardiovascular disease changed it into a risk-based diagnosis and simplified the many types of dyslipidemia into simple concepts of “good” and “bad” cholesterol (HDL and LDL, respectively), one or more biomarkers of AD may achieve this status. In the future, we may speak not of AD, but “brain amyloidopathy.” And yet, such terms cannot elide an essential fact. They denote a dreaded risk: developing dementia.

Although medicine and society have successfully integrated an actuarial model to think about how to have healthy hearts, bones, and glucose, the brain that is at risk of dementia presents special challenges. The discovery of preclinical AD may be how we prevent the tsunami of AD dementia, but we must not drown in the challenges created by our own discovery.

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DISCLOSURE

Dr. Karlawish serves on the Professional Advisory Board for and holds stock in SeniorBridge, Inc.; is a co-holder of a license of an Integrated NeuroDegenerative Disease Database developed at the University of Pennsylvania; serves as an Associate Editor of the Journal of the American Geriatrics Society; receives publishing royalties for Treating Dementia: Do We Have a Pill for It? (Johns Hopkins University Press, 2009) and Open Wound: The Tragic Obsession of Dr. William Beaumont (University of Michigan Press, 2011); and receives research support from Pfizer Inc, the NIH (NIA, NINDS, NIMH), and the Robert Wood Johnson Foundation.

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