Disclosing Risk Factors to Individuals Without Cognitive Impairment

Negative consequences of risk factor disclosure are likely to be most severe among people who are inadequately prepared to receive the information.

By Joshua D. Grill, PhD

Introduction

Sporadic Alzheimer's disease (AD), among the most feared conditions for adults over age 55, is a prevalent, fatal, age-related neurodegenerative disorder. In AD, progressive loss of cognitive and functional abilities eventually render people completely dependent on others for activities of daily life. This article outlines contemporary issues related to the disclosure of genetic and biomarker risk factors to people at risk for AD who are without symptoms.

Researchers have identified numerous risk factors for AD. The strongest is age; others include head trauma, lifestyle choices, and family history. Although family history is associated with increased AD risk, the pattern of inheritance is complex. More than 20 genes are implicated in AD risk, most of which are rare and/or have small effects on relative risk.1 The first discovered genetic risk factor for AD, apolipoprotein E (APOE), remains the strongest known. There are 3 alleles for APOE—ε2, ε3, and ε4—yielding 6 potential genotypes. The ε4 allele increases AD risk; the ε2 allele decreases it. The APOE ε4-associated risk for AD is among the most well replicated findings in AD research. People with APOE ε4 alleles are at 2 to 12 times more risk for AD and generally develop disease at younger ages, compared with those without APOE ε4 alleles. People who are homozygotic for APOE ε4 are at substantially higher risk than those who are heterozygotes.

Research has also identified several markers of AD biology, or biomarkers. These include cerebrospinal fluid (CSF) protein levels, structural neuroimaging of brain volume, and molecular imaging for in vivo assessment of brain pathologies. Biomarkers can be used to derive theoretical trajectories of the biological course of AD.2 Markers of the amyloid β (Aβ) protein, which accumulates in the neuritic brain plaques that are required for a definitive diagnosis of AD, appear to represent one of the earliest changes in AD. Changes in Aβ precede clinical symptoms by decades. The Food and Drug Administration (FDA) has approved 3 amyloid positron emission tomography (PET) ligands to estimate amyloid plaque burden in individuals with cognitive impairment. About 25% of people over age 55 without cognitive impairment also have amyloid burden on these scans. Compared with those with no amyloid, individuals without cognitive impairment but with biomarker evidence of Aβ are at substantially higher risk for progression to AD dementia. This discovery has led to creation of research diagnostic criteria for preclinical AD.3 Importantly, 25% of older people die with no cognitive impairment and postmortem evidence of AD pathology, and the lifetime risk of dementia among individuals with positive biomarker findings is an area of active study.4 Amyloid biomarker information for individuals without cognitive impairment is conceptualized as a biologic AD risk factor.

Several studies have found that many people over age 55 without cognitive impairments want to learn their personal AD risk information. No group recommends testing persons without impairments for genetic or biomarker status, because the implications to clinical care and lifestyle recommendations are limited and medicolegal implications are uncertain. Guidelines are unlikely to change until disease-modifying therapies become available for people with AD risk factors. Ongoing clinical trials aim to develop such therapies by specifically enrolling individuals without cognitive impairment based on genetic and biomarker enrollment criteria. These trials frequently inform participants of their personal results and collect critical data related to the effects of risk factor disclosure. Ultimately, these data will instruct a new clinical practice in AD: risk factor testing for initiating disease-delaying therapies. The FDA approval of amyloid PET imaging and the availability of direct-to-consumer (DTC) genetic testing for APOE necessitate understanding AD risk factor disclosure.
Pearls and Pitfalls
When To Disclose Genetic and Amyloid Information?

Neither APOE nor amyloid PET testing are in widespread clinical practice. Professional guidelines from the American College of Medical Genetics and the National Society of Genetic Counselors do not recommend APOE testing for any group. Similarly, in January 2018, the American Academy of Neurology advised that “there are no accepted biomarkers available at this time” for individuals who do not meet diagnostic criteria for dementia. Expert guidelines and commentaries for APOE and amyloid PET testing agree that predictive testing in individuals without cognitive impairments is not recommended. The rationale against testing is that the information is neither diagnostic nor predictive, and results have no impact on lifestyle recommendations for lowering future risk.

In the research setting, specifically in clinical trials that enroll people without cognitive impairment who are at increased risk for AD based on findings of genetic or biomarker tests, the risk of disclosing amyloid or gene findings is balanced by the benefit of knowledge gained and potential therapeutic advances developed.5 Trial inclusion criteria are designed to lower risk for type 2 error and ensure generalizability. This typically restricts trials to participants who are of protocol-defined ages and who demonstrate adequate cognitive performance. In contrast, exclusion criteria are chosen to ensure participant safety and to prevent adverse outcomes during a trial. In preclinical AD trials, this has included careful assessment of participant well-being. Individuals with psychiatric conditions such as major depressive or generalized anxiety disorders are excluded from undergoing AD risk testing and disclosure. Similarly, participants are assessed for suicidality prior to enrollment. About 10% of participants in recent surveys indicate that they wish to attain AD risk information to instruct end-of-life planning.6 Education and referral to social support and mental health services are prioritized for these individuals.

In the research setting, individuals undergoing AD risk factor testing are often required to have a partner who can provide support,7 which may be essential to overcoming distress associated with risk-information disclosure. Ensuring optimal support for individuals considering AD risk factor testing may be a critical topic when preclinical AD is translated into clinical practice. The decision to undergo risk factor testing, regardless of setting, however, should be made freely and without pressure or coercion by family members or other outside sources.

How To Disclose Genetic and Amyloid Information?
The criterion standard process for disclosing health information is that used in genetic counseling for hereditary diseases, such as Huntington’s disease.8 In-person education and counseling are performed prior to and separated in time from actual testing. Disclosure is performed in-person, similarly separated in time from testing, and includes additional in-person counseling. Follow-up monitoring is essential. This model of disclosure has been incorporated into clinical trials examining the safety of disclosing APOE genetic information to individuals without cognitive impairment. Using this model of APOE status disclosure to adults with a family history of AD did not result in clinical depression or anxiety.9 Efforts to streamline the disclosure process without sacrificing quality or safety with a condensed protocol using educational brochures instead of in-person educational sessions had no impact on participant understanding or recall of disclosed information.10 A randomized noninferiority study comparing telephone vs in-person disclosure, however, did not provide statistically significant evidence of noninferiority for people carrying the ε4 allele, although few differences were observed between the 2 groups overall.11 Clinically significant outcomes were rare, but measures of distress and depression were higher 12 months after disclosure in people with ε4 who received information by telephone, compared with those who received it in-person.

The genetic counseling model guided development of a process for disclosing amyloid-PET results to people without cognitive impairment who were participating in the first preclinical AD trial.12 The test (scan) and results disclosure are separated in time so that participants have the opportunity to change their mind between education/counseling and testing, and again between testing and disclosure. Only medical experts with adequate understanding of amyloid imaging and preclinical AD should disclose results to participants.

Disclosure focuses on the limited understanding of long-term outcomes (eg, overall risk for cognitive impairment and timing of onset if impairment begins). Assessments of adverse psychological outcomes and follow-up are recommended. Methods to streamline this disclosure process have not been investigated, although 1 study emphasizes the need for thorough education and counseling because some participants will change their minds (from disclosure to nondisclosure) after education focused on limited understanding of what results imply.13

What Information Should Be Disclosed?
The language used to communicate AD risk factor results is critical to the safety, understanding, and long-term implications of disclosure. Disclosure of APOE results may seem straightforward—a person is told their APOE genotype or ε4 status, but other factors including race, sex, and age should also be considered (Table 1).10 Pictographs can enhance understanding, and written materials can provide answers to frequently asked questions. Several challenges in disclosure of APOE risk information should be considered. First, the exact
relative risk estimated for those with ε4 varies among studies and populations. In particular, data from noncaucasian cohorts are limited, making extrapolation to Asian, Latino, and other ethnoracial groups tenuous. Second, as many as 35% of participants will inaccurately recall disclosed risk information. Last, postdisclosure perception of AD risk may be more strongly tied to personal beliefs than to information received during disclosure. This suggests a need for reiteration of risk information and monitoring of health behaviors and safety.

Although FDA-approved labels for amyloid PET ligands indicate results as positive or negative, the first preclinical AD trial disclosed results as elevated or not elevated amyloid levels. Rationale for this decision was based on several factors. First, amyloid-PET results can change over time and there was concern that delivering a negative result, especially to persons with borderline scans, could produce false reassurance. What threshold to use to determine positivity (or eligibility) remains an area of active research, and recent studies indicate that subthreshold amyloid may be associated with increased risk for cognitive decline. Assessments of the effectiveness of amyloid PET disclosure are limited. In a study of 50 individuals who learned they had an elevated amyloid PET scan as part of a larger clinical trial, nearly all (94%) understood that the scan result conferred an increased risk for AD. A notable minority (40%) expressed dissatisfaction with disclosure, resulting from a desire to learn more (eg, a quantitative result or personal AD dementia risk estimate). Such estimates remain preliminary, vary depending upon age, sex, and whether neurodegeneration is present (Table 2), and have not yet been disclosed to research participants. In a smaller interview study focused on participants with a nonelevated scan result, most participants correctly recalled their disclosed result a median 20 months after disclosure, although some incorrectly recalled being told they had “no plaques” or “no amyloid.” Some even recalled being told they had no neurofibrillary tangles.

### Implications of Disclosing Risk Factor Information

Ensuring the safety of individuals receiving AD risk factor information is paramount. Disclosure of APOE status appears safe when the full disclosure process is implemented in a carefully selected population at risk for AD. Issues that may plague the field arise when incomplete disclosure processes are used or risk information is inadequately disclosed to individuals at increased risk for negative consequences. This may include individuals who learn their APOE results through their cardiologist (ε4 is also a risk factor for cardiovascular disease) and later discover the implications for AD risk. It may also include consumers of DTC APOE testing who opt not to pursue pre- or posttest counseling. Anecdotes indicate these individuals may be at substantially increased risk for negative outcomes associated with disclosure. For example, a case known to many AD researchers is the former nurse, Jamie Tyrone, who was informed of her ε4 homozygosity while participating in a study of personal genetics. Ms. Tyrone was interested in learning her genetic risk for multiple sclerosis, but instead unwittingly learned her increased risk for AD. She experienced substantial distress and was diagnosed with post-traumatic stress disorder. Now an AD research advocate, Ms. Tyrone has described publicly the harmful consequences learning her APOE status had on her behavior, personal relationships, and mental health. She is unlikely alone in this experience. Some genetic counselors describe an influx of clients requesting “damage control” services after (but rarely before) undergoing DTC APOE testing. The limited data assessing safety of amyloid disclosure are essentially all from the research setting, where careful exclusion criteria and rigorous disclosure processes are implemented. Burns and colleagues described stable scores on depression measures in 27 individuals without cognitive impairment who learned an elevated amyloid PET result, compared with 70 participants who learned of a nonelevated result. They also observed transient increases in distress in individuals with elevated amyloid. Larger trials are underway and will be critical to understanding the short- and long-term impact of amyloid disclosure on mental health. Compared with the 10% of individuals who

### TABLE 1. APOLIPOPROTEIN E-ALLELE-RELATED RISK OF ALZHEIMER’S DISEASE BY AGE 85

<table>
<thead>
<tr>
<th>Sex (Ethnicity)</th>
<th>ε2/ε3</th>
<th>ε3/ε3</th>
<th>ε2/ε4</th>
<th>ε3/ε4</th>
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</thead>
<tbody>
<tr>
<td>Women (African-American)</td>
<td>36%</td>
<td>49%</td>
<td>69%</td>
<td>73%</td>
<td>74%</td>
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<td>Women (white)</td>
<td>19%</td>
<td>29%</td>
<td>49%</td>
<td>52%</td>
<td>57%</td>
</tr>
<tr>
<td>Men (African-American)</td>
<td>33%</td>
<td>41%</td>
<td>48%</td>
<td>56%</td>
<td>77%</td>
</tr>
<tr>
<td>Men (white)</td>
<td>13%</td>
<td>18%</td>
<td>25%</td>
<td>29%</td>
<td>56%</td>
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</tbody>
</table>

### TABLE 2. INFLUENCE OF AMYLOIDOSIS AND NEURODEGENERATION ON LIFETIME RISK OF ALZHEIMER’S DISEASE

<table>
<thead>
<tr>
<th>Age</th>
<th>Women A+ / N-</th>
<th>Women A+ / N+</th>
<th>Men A+ / N-</th>
<th>Men A+ / N+</th>
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<tbody>
<tr>
<td>60</td>
<td>31%</td>
<td>42%</td>
<td>23%</td>
<td>34%</td>
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<td>29%</td>
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<td>8%</td>
<td>17%</td>
<td>5%</td>
<td>12%</td>
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Abbreviations: A, amyloid; N, neurodegeneration.
Indicate in hypothetical surveys that they would use AD risk factor information to instruct suicide planning, approximately 20% of participants with elevated amyloid in an ancillary study to a preclinical AD trial indicated that they have actively considered trying to utilize physician-assisted suicide.21

Beyond medical safety, it is critical to understand other potential implications of AD risk factor disclosure, both negative and positive. For example, there are gaps in legal protections for individuals who undergo genetic testing, and few protections apply to those who undergo biomarker testing.22 Disclosure of risk information may change self-perception. Individuals who learn they are the ε4 allele may experience subjective and even objective declines in memory performance, which does not occur when people with the ε4 allele are not informed of their APOE status.23

A best-case scenario is that learning AD risk factor information spurs improved health behaviors, planning, and preparation. For example, when a well-informed neurologist accidentally discovered he was an ε4 homozygote he was shocked and frightened, but he began a self-described process of “anticipating disease.” For the same individual, a positive amyloid PET result was “reassuring” and launched preparations such as adjusting his advance health directive and family planning.24 People who learned they have the ε4 allele rarely improved their exercise regimens or diets. They did, however, frequently purchase long-term care insurance policies and begin taking dietary supplements (which lack evidence to support risk reduction for dementia and may even be harmful).6 Individuals without cognitive impairment who learn their risk information may be motivated to participate in preclinical AD clinical trials, although this is mostly unstudied.

Most individuals screened for APOE genotype or amyloid status will ultimately prove not to have the ε4 allele or elevated amyloid. In a study of participants without elevated amyloid, no individual reported reduced motivation to exercise or a perceived ability to consume a less healthy diet due to reduced risk for AD.17 A few individuals reported that the experience of screening for a preclinical AD trial resulted in a heightened awareness and increased attention to brain-healthy behaviors. Nearly every participant reported they would have undertaken improved health behaviors (eg, diet, exercise, medicolegal changes), if they had received an elevated amyloid result.

Conclusions
People frequently want to learn their personal AD risk factor information, and there are now pathways to do so. Thoughtful approaches to disclosing AD risk factor information may be key to ensure individual’s safety, since some data indicate that abbreviated processes may not achieve the high standards set by thorough in-person education and counseling. Negative consequences related to learning AD risk information are likely to be most severe among those unwittingly learning their results or doing so with inadequate education and counseling. For well-prepared individuals, risk factor disclosure has the potential to catalyze important planning, including making arrangements of personal affairs and even longer-term plans around familial care. ■

Joshua D. Grill, PhD
Institute for Memory Impairments and Neurological Disorders
Departments of Psychiatry & Human Behavior and Neurobiology & Behavior
University of California Irvine
Irvine, CA

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JG reports no disclosures.