Comprehension of an Elevated Amyloid Positron Emission Tomography Biomarker Result by Cognitively Normal Older Adults

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IMPORTANCE The goal of Alzheimer disease (AD) prevention together with advances in understanding the pathophysiology of AD have led to clinical trials testing drugs in cognitively unimpaired persons who show evidence of AD biomarkers. Data are needed to inform the processes of describing AD biomarkers to cognitively normal adults and assessing their understanding of this knowledge.

OBJECTIVE To determine the comprehension of an elevated amyloid positron emission tomographic (PET) biomarker result by cognitively unimpaired adults.

DESIGN, SETTING, AND PARTICIPANTS The Study of Knowledge and Reactions to Amyloid Testing, a substudy of an AD prevention trial, involved 2 semistructured telephone interviews with 80 participants recruited from 9 study sites: 50 received elevated and 30 received not elevated amyloid PET scan results. Interviews were conducted 4 to 12 weeks after result disclosure and again 1 year later. Data presented here were collected from November 5, 2014, through December 10, 2015. The 50 participants included in this study were cognitively normal, aged 65 to 85 years, evenly distributed by gender, and had elevated amyloid PET results. Subsequent reports will examine persons with “not elevated” results and compare the influence of the different results.

MAIN OUTCOMES AND MEASURES Participant comprehension of an elevated amyloid result was assessed by analyzing their responses to the following questions: “What was the result of your amyloid PET scan?” (followed by “Can you tell me in your own words what that means?” or “How would you explain it to a friend?”), “Was it the result you expected?” and “Did the result teach you anything or clarify anything for you?”

RESULTS Of the 50 participants aged 65 to 85 years, 49 (98%) were white, 40 (80%) reported a family history of AD, and 30 (60%) had a postgraduate educational level. Most participants (31 [62%]) understood that elevated amyloid conferred an increased but uncertain risk of developing AD. Some desired understanding of the term elevated other than its being a categorical result enabling trial entry eligibility; they wanted information regarding how elevated their amyloid was, how close to the study threshold they were, or percentages, numbers, or a scale to help them make sense of the result.

CONCLUSIONS AND RELEVANCE Including an explanation of how and why a dimensional biomarker is converted to a categorical classification would enhance future AD biomarker clinical trials and educational materials.

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Advances in understanding the pathophysiology of Alzheimer disease (AD), together with a US national plan to discover interventions to prevent AD by 2025, have led to clinical trials examining treatment in people at risk for development of the disease before they have disabling cognitive impairments. These trials enroll cognitively normal persons with evidence of AD biomarkers, including amyloid as measured by positron emission tomography (PET) or cerebrospinal fluid, often necessitating biomarker disclosure to participants. The amyloid imaging appropriate use criteria suggest that clinical disclosure is appropriate to aid the diagnosis of persons with dementia or mild cognitive impairment. However, the criteria do not recommend disclosure to cognitively normal adults, explaining that therapy for this group would change this recommendation. This explanation signals how biomarker disclosure to cognitively normal adults will be translated into clinical practice. There is no consensus, however, about whether and how to return AD biomarker results to cognitively normal adults given the prognostic uncertainty and absence of available treatments.

The Anti-Amyloid Treatment in Asymptomatic Alzheimer Study (A4 study) is an example of a trial testing whether a drug can affect the rate of cognitive decline in cognitively normal persons with “elevated” amyloid. The A4 trial investigates 1 particular AD biomarker, that is, amyloid as measured by PET using the radiotracer florbetapir. Participants with amyloid-β plaques at or above a level deemed elevated are eligible for this double-blind phase 3 trial comparing solanezumab with placebo.

The outcome of trials such as the A4 study will begin to translate AD biomarker testing into clinical practice, but data are limited regarding how cognitively normal adults comprehend AD biomarker results. Clinicians and researchers need to understand how participants comprehend this information, because knowing it may generate clinical and ethical problems, including the potential for misunderstanding, discrimination, stigma, depression, anxiety, and, in the most extreme cases, suicide in the face of a debilitating disease with no treatment. Surveys of cognitively normal adults suggest that many would like to receive the results of AD biomarker tests, and as more individuals enroll in prevention trials, researchers and clinicians will need to prepare for increasing requests from participants to return test results.

Research to identify informational needs and reactions, such as the influence on self-perception, relationships, behaviors, and future plans, will inform the recruitment, education, and informed consent of participants of future clinical trials that will require disclosure as well as inform subsequent clinical translation. The more these informational needs and reactions are understood, the better the clinical and ethical challenges of disclosing biomarker results to cognitively normal older adults will be addressed.

Based on the results of interviews with 50 A4 study participants who learned they had elevated amyloid, we report their understanding of this result. Subsequent reports will examine participants in the Longitudinal Evaluation of Amyloid Risk and Neurodegeneration natural history observational arm of the A4 study with not elevated amyloid PET results and compare the impact of these different results. Our intention in reporting on those who learned of their elevated amyloid results is to inform the design and conduct of future clinical trials and clinical practice in the prevention of AD, an entirely novel area requiring data to advise investigators what they should tell participants and how they should assess participant understanding of this knowledge. Our results, although derived from amyloid PET imaging, have implications for returning other AD biomarker results to patients.

### Methods

#### Design and Recruitment

The data used in this study were obtained as part of the Study of Knowledge and Reactions to Amyloid Testing (SOKRATES), an A4 substudy that involved baseline and 1-year follow-up semi-structured telephone interviews with 80 participants recruited through A4 study sites, 50 of whom received elevated and 30 of whom received not elevated amyloid PET scan results. Interviews were conducted 4 to 12 weeks after disclosure, although the interval between disclosure and interview for 10 participants with elevated amyloid was either longer (16-20 weeks) or shorter (1-3 weeks). The present study was approved by the University of Pennsylvania Institutional Review Board, and participants provided verbal informed consent. The participants received $20 each for completing each interview.

All A4 study participants were educated and informed of their amyloid PET scan result through a multiphase amyloid disclosure process designed to maximize safety and effectiveness. The amyloid disclosure process included a depression and anxiety prescreen, an educational session, a teach-back exercise to check comprehension, an in-person disclosure by a trained clinician on a separate day from imaging, and a telephone follow-up to assess mood. The A4 study protocol specified that, as part of this process, participants received a study guide with detailed information about study procedures, with an emphasis on the amyloid PET scan, its purpose, possible results, and limitations (brief version available online).

The study guide describes “preclinical” or “asymptomatic” AD as a new concept in development and explains that elevated amyloid “does not
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Coding and Data Analysis

Interviews were audio recorded, transcribed, and deidentified before being entered into NVivo qualitative analysis software, version 11.0 (QSR International). The research team reviewed all transcripts and developed a coding scheme to reflect the 4 aforementioned topics and to capture themes that emerged during coding and analysis. In the first coding phase, 3 of us (J.M., K.H., and S.H.) triple coded all interviews until the Cohen $\kappa$ coefficient for intercoder reliability was consistently 0.8 or above. The remaining interviews were individually coded by the same 3 team members. After 15 interviews were independently coded, all 3 members coded an additional interview to ensure that the $\kappa$ coefficients remained above 0.8. This process, with regular checks on the $\kappa$ coefficient, continued until all 50 interviews were coded. Coding, including adjustments to the codebook, was an iterative process involving multiple consensus meetings with the study team to discuss and resolve coding discrepancies and included an audit trail of coding rules and decisions made.

The data reported here examining the comprehension by 50 participants of an elevated amyloid PET scan result were derived from analyses of the baseline interview responses to the following questions asked at the start of the interview: “What was the result of your amyloid PET scan?” (followed by either “Can you tell me in your own words what that means?” or “How would you explain it to a friend?”), “Was it the result you expected?” and “Did the result teach you anything or clarify anything for you?” Where relevant, we report the frequencies of participants within the primary themes identified.

Results

Table 1 provides participant demographic characteristics. Participants were oversampled to achieve a greater representation among 65- to 74-year-olds (35 participants [70%]) because of the potentially greater influence of an elevated amyloid PET scan result on the relatively younger participants, who, compared with persons 75 years or older, are likely to have more life expectancy and to still be employed. Participants were evenly distributed by gender and included 49 white individuals (98%), with 40 (80%) reporting family histories of AD, and 30 (60%) having postgraduate education. This reflected the A4 study population of 782 participants, randomized as of November 9, 2016, which included 753 white participants (96%), with a mean (SD) of 16.6 (2.8) years of education and 457 women (58%).

When asked, “What was your result?” participants used a variety of expressions and language to describe their result and convey their understanding of the meaning of elevated. Most participants (32, 64%) used the word amyloid or amyloids. The remaining participants primarily referred to the presence of “plaques” or to their being “positive.” A few participants used expressions such as “some cloudy something” or “abnormali-
ties in the brain.” Two individuals provided answers that suggested misunderstanding. One referred to amyloid as a “gene present or whatever you would call it,” and another described the result as having amyloid protein that had not yet “organized itself into plaques and tangles.”

A small number of participants (6 of 50) used the word elevated to describe their amyloid result. Most participants instead used words such as increased, higher levels, excessive, sufficient amount, or enough, or said they were an “amyloid collector.” Some participants (19 of 50) described the result in terms of qualifying for the A4 study, saying, “enough amyloid buildup to qualify for the study” or “high enough to put into the A4 study.” Some participants did not refer to an amount or level but rather described a static result, such as “amyloids in my brain” or “plaque was present.”

The following 3 themes were identified from the coded responses to questions regarding participant comprehension of elevated amyloid. Analyses included searching for differences among groups based on demographic variables, including gender, age, and family history. No major demographic differences were found among the subgroups, which reflected the homogeneous composition of the sample as a whole.

1. **Participant expectation of their result:** A little over half of the participants expected their result (27 of 50 [54%]). They explained their expectation as being due to a family history of AD or to their experiencing memory problems, which often stimulated a visit to a memory center or clinic where participants were recruited to the A4 study. Other participants (15 [30%]) were unsure what they had expected, describing mixed expectations or being prepared for either result. The third and smallest group expected to not have elevated amyloid (8 [16%]) because they led a healthy lifestyle and had no family history of AD or no subjective memory concerns (Table 2).

2. **Perceived risk of developing AD based on elevated amyloid result:** When asked questions regarding the meaning of the result, nearly every participant (47 of 50 [94%]) responded with their understanding of the risk of developing AD conferred by elevated amyloid. The majority of participants (31 [62%]) interpreted the result as signaling an increased risk of developing AD. However, participant understanding and uncertainty regarding the degree of increased risk varied considerably. A small number of participants (10 [20%]) perceived the risk conferred by elevated amyloid to be equivocal, stating that the result was open to more than 1 interpretation, which suggested that developing or not developing AD were equally plausible outcomes. Participants in both the increased risk and equivocal categories described uncertainty regarding the risk of developing AD. The smallest number of participants (6 [12%]) perceived elevated amyloid to mean either that they were at an imminent risk of developing AD or that it was diagnostic of AD (Table 3).

3. **Ambiguity of elevated amyloid PET scan result:** Dissatisfaction with the lack of specificity regarding the meaning of elevated was found among a subset of participants (20 of 50 [40%]), most often in response to the question “What was your result?” Those participants explained that the absence of a scale or baseline associated with the result limited their ability to interpret it. Some of these 20 participants desired clarification or more information to make sense of their result. In particular, they wanted to move from the categorical result of elevated vs not elevated to a granular result describing the degree of amyloid elevation. Participants desired percentages, numbers, or a scale to contextualize the meaning and degree of elevation as compared with a known reference. Some wanted to know how close they were to the threshold for study entry. A small number specifically expressed frustration at the lack of detail about their results (Table 4).

### Table 2. Participant Responses to the Question “Was It the Result You Expected?”

<table>
<thead>
<tr>
<th>Code for “Was It the Result You Expected?”</th>
<th>No. of Participants</th>
<th>Illustrative Quote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>27</td>
<td>Yeah, I expected they would find amyloid in my brain because of my family background, so it confirmed my suspicions. (75-y-old woman)</td>
</tr>
<tr>
<td>No</td>
<td>8</td>
<td>Because my memory is completely normal. (69-y-old woman)</td>
</tr>
<tr>
<td>Not sure/mixed</td>
<td>15</td>
<td>I had no expectations one way or the other. (82-y-old woman)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>You know, 50/50. Is it going to be heads or is it going to be tails? I was not super alarmed or surprised. (65-y-old man)</td>
</tr>
</tbody>
</table>

### Discussion

In this sample of SO cognitively normal older adults enrolled in a clinical trial who learned they had elevated amyloid, more than half had expected the result of elevated amyloid. Most explained that this expectation was based on their family history of AD. This explanation makes sense because 80% of the sample reported a family history of AD, and family history is among the motivators for learning biomarker results. Participants also reported subjective memory concerns as a reason for expecting their elevated amyloid result. This suggests that some people who are cognitively normal but symptomatic will use an AD biomarker test to explain their memory concerns, potentially pathologizing normal and nondisease-related cognitive aging. This result also suggests the need to determine whether persons with subjective memory problems who learn their AD biomarker status will experience an exacerbation of their preexisting memory concerns, which could then affect cognitive performance.

These results also indicated that if AD biomarker testing expands to include individuals in a population without family history or subjective memory concerns, such individuals...
may be unprepared to receive their biomarker results. Research is needed to discover how such individuals understand and react to learning AD biomarker test results.

Most participants interpreted their result to mean they faced a heightened risk of developing AD, but their understanding was variable, from imminent and highly increased to uncertain and equivocal. Regardless of where participants fell on this spectrum of understanding, most qualified their statements about their risk of developing AD with uncertainty, emphasizing the possibility of not developing the disease. This result indicates that the amyloid disclosure process and informational materials accurately conveyed the prognostic uncertainty of elevated amyloid. Nonetheless, participants still grappled with how to make sense of the result in terms of their individual risk of developing AD, suggesting that the risk of developing AD may be the most pertinent information for cognitively normal adults.

The disclosure process and A4 study guide describe elevated amyloid as necessary for trial entry while reiterating that the result is not diagnostic of AD nor of developing AD. The materials also state that individual risk estimates are not available. It is therefore understandable that participants were uncertain how to make sense of the meaning of “elevated amyloid” beyond a categorical result that made them eligible for trial entry. Their desire for clarification regarding how elevated their amyloid was, a description of how close to the trial acceptance threshold their PET scan result was, or a presentation of percentages, numbers, or a scale to make sense of the result should be interpreted in light of this ambiguity in the A4 trial materials and the limitations of current scientific knowledge.

This desire for more specific, dimensional, and quantitative information, such as how “elevated” the amyloid was, may be especially important to cognitively normal adults who are not yet symptomatic. Such specific information is likely less relevant for symptomatic individuals who receive a binary result that either confirms or rules out a diagnosis that explains their history of cognitive decline. Individuals with mild cognitive impairment who underwent simulated sessions involving fictitious amyloid imaging information (but did not undergo imaging) were satisfied with the information they received. These cognitively impaired individuals likely have different informational needs than cognitively unimpaired individuals. The limited data available in cognitively unimpaired adults who learn amyloid results indicate that disclosure is not associated with depression, anxiety, or stress, although a small increase in anxiety has been observed among those with elevated amyloid. Consistent with our results, the findings of Lim et al indicate that cognitively normal adults want more information regarding the sensitivity and reliability of amyloid PET scan results for predicting disease burden and progression.

Most participants interpreted their result not as a diagnosis of “preclinical” or “asymptomatic” AD but rather as a risk factor for developing AD. This message was conveyed in A4 trial materials that described amyloid as a risk factor alongside age, genetics, family history, and comorbidities. Framing amyloid as a risk factor, not a diagnostic test that confirms the presence of AD or its development in the future, is especially important among cognitively normal adults.

This study was not designed to evaluate the amyloid disclosure process itself, which was conducted by local study investigators. All investigators completed training on how to disclose amyloid results and were provided with a detailed protocol, including key messages to convey to participants at each stage of the process. We did not collect data from investigators or record disclosure sessions. Rather, this study reports on the subjective understanding

Table 3. Participant Perceived Risk of Alzheimer Disease Based on Elevated Amyloid Result

<table>
<thead>
<tr>
<th>Code for Perceived Risk of AD</th>
<th>No. of Participants</th>
<th>Illustrative Quote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imminent risk/diagnostic</td>
<td>6</td>
<td>I have, should we say, some positive findings of early Alzheimer’s. (67-y-old man)</td>
</tr>
<tr>
<td>Increased risk of various degrees</td>
<td>31</td>
<td>It means that it’s likely that you will wind up with Alzheimer’s. (72-y-old man)</td>
</tr>
<tr>
<td>Equivocal/ open to more than 1 interpretation</td>
<td>10</td>
<td>That I have a higher risk of most people to get Alzheimer’s, but that doesn’t mean I will get it. (78-y-old man)</td>
</tr>
</tbody>
</table>

* Data derived from participant responses to the following 3 questions: “What does the result mean to you?” Did it teach you anything or clarify anything for you?” and “How would you explain it to a friend?”

Table 4. Participant Responses to the Ambiguity of the Elevated Amyloid Result

<table>
<thead>
<tr>
<th>Code for Ambiguity of Result</th>
<th>Illustrative Quote</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficult to interpret due to absence of scale or baseline</td>
<td>Oh, they said that you have elevated amyloids in other words and whatever that means. I know that it means you have more amyloids than I, guess, the norm, but I don’t know to what extent. I didn’t know if it was twice as many, 3 times as many what the norm should be. I can’t tell you that, but I know they said they were elevated. (83-y-old man)</td>
</tr>
<tr>
<td>Clarification or more information desired</td>
<td>I don’t know how elevated the result is. It could be like right over the edge, and other people are right under the edge. I don’t know that. (71-y-old man)</td>
</tr>
<tr>
<td>Frustration at lack of information</td>
<td>I asked the doctor, I said, “Okay, how many amyloids? Are we talking 9 amyloids or 9000 amyloids? Can you see the results of what’s on my brain? Can I see a picture of it?” (68-y-old man)</td>
</tr>
</tbody>
</table>

* Subset of responses (20 of 50 [40%]) to the following questions: “What was the result?” “What did the result mean to you?” “Did it teach you anything or clarify anything for you?” and “How would you explain it to a friend?”
by participants of the meaning of elevated amyloid. Participant comprehension should therefore be taken in the context of time (interviews occurred 4-12 weeks after participants received their results) and other factors that contribute to how participants make sense of their results, such as concerns about the future, their children, current responsibilities (such as employment or caretaking), and relationships.

Our results have implications for disclosure to participants of other AD biomarker results. The variations in interpretation and the desire for clarification about the meaning of elevated amyloid should inform the development and enhancement of future AD biomarker research and educational materials as disclosure to cognitively normal adults is translated into clinical practice. Our results suggest that an explanation of how and why a dimensional biomarker is converted to a categorical classification would help individuals comprehend their results.

Limitations
Our results must be interpreted in the context of the following limitations. Participants were a racially/ethnically homogeneous sample that reflected the overall A4 study population, which as of November 9, 2016, was approximately 96% white (3% African American, <1% Asian, and 1% American Indian/Alaskan). The reasons for low representation of African American and Hispanic individuals in the A4 trial are multifactorial. One factor is comorbidity, such as an autoimmune disease, that excludes some individuals from eligibility (Reisa Sperling, MD, email communication, November 10, 2016). Additional factors related to engagement, access, and interest in AD research will require further study. The SOKRATES participants are highly educated (60% have postgraduate education), and 80% have a family history of AD, limiting the applicability of these results to populations with different characteristics and supporting the need to recruit diverse study populations. We did not incorporate quantitative measures or a mixed methods design to supplement the qualitative findings.

We will report the influence on sense of self, social relationships, and behaviors undertaken among cognitively normal adults who receive an elevated compared with not elevated result when baseline and follow-up interview data collections have been completed.

Conclusions
To slow the onset of cognitive decline caused by Alzheimer disease, researchers and clinicians will have to adopt a novel practice: telling a cognitively unimpaired older adult an Alzheimer biomarker result. This study of cognitively unimpaired adults who learned of an amyloid PET result shows that clinicians should be prepared to explain how and why a dimensional biomarker, in this case amyloid-β as measured using PET, is converted to a categorical state, in this case “elevated” and “not elevated,” and what the result means in terms of a person’s risk for developing Alzheimer disease dementia.


