



# ‘That would be dreadful’: The ethical, legal, and social challenges of sharing your Alzheimer’s disease biomarker and genetic testing results with others

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## ABSTRACT

Several large clinical trials are underway to discover therapies to delay or prevent the onset of dementia caused by Alzheimer’s disease (AD). A common feature of these trials is that they are testing therapies in people who do not yet have changes in memory or thinking—that is, who are cognitively unimpaired—but who have a biologically defined risk of developing dementia caused by AD. When these trials eventually succeed, it is reasonable to expect the widespread adoption of biomarker and genetic testing of cognitively unimpaired individuals into clinical practice, as well as treatment prescribed to individuals at heightened risk. Here, we report results from two qualitative studies that sought to understand with whom, why, and how individuals share their AD biomarker and genetic testing results, respectively. We found that sharing is common within the confines of close relationships. However, when sharing outside such relationships, people have multiple concerns, including stigma and discrimination. These concerns highlight the need for additional legal protections and policy changes in anticipation of the coming transformation of AD clinical care.

**KEYWORDS:** Alzheimer’s disease, genetic testing, biomarker testing, return of results, research ethics, long-term care

## I. INTRODUCTION

Dementia—the progressive loss of cognitive and behavioral abilities that interferes with daily life—is the most feared condition of old age.<sup>1</sup> What ignites such fear? It is not merely the prospect of losing physical capabilities such as dressing and eating. It is the social consequences of the disease. Our society places significant emphasis on independence, and rational thinking and memory are needed to engage in daily tasks independently.<sup>2</sup> Yet, dementia robs people of exactly these skills. Losing them therefore threatens a person's place in society. This is seen when, after people disclose a dementia diagnosis, they can experience distancing and even shunning by family, friends, and others, experiences that have been described as a sort of social death.

Numerous diseases cause dementia. The most common of these is late-onset Alzheimer's disease (AD). AD is a progressive, irreversible neurodegenerative disease that, early on, impairs cognition and therefore may impair decision-making.<sup>3</sup> Later, AD erodes physical capabilities and ultimately results in death. Presently, there are no therapies that can slow or prevent the progression of AD or cure dementia caused by AD. Identification of such disease-modifying treatments is the first goal of the United States' National Plan to Address Alzheimer's Disease.<sup>4</sup> To achieve this goal, the National Institutes of Health (NIH) has received dramatic annual increases in research funding. Using a novel 'bypass budget' mechanism, the NIH has requested more than \$2.8 billion for research on AD and related dementias in FY 2021 alone.<sup>5</sup> The term 'bypass' describes a process that avoids congressional review and earmarking. Instead, the relevant leadership at NIH requests the funds needed to achieve the National Plan. NIH has similar budgetary authority for only two other conditions: cancer and HIV/AIDS.<sup>6</sup> This authority shows how AD is, like cancer and HIV/AIDS, a distinctly dreaded disease and a national priority.

With this infusion of resources to support AD research, several large clinical trials are underway to discover disease-modifying therapies. A common feature of these trials is that they test interventions in people who do not yet have changes in memory or thinking (that is, people who are 'cognitively unimpaired') but who have a biologically defined risk of developing dementia caused by AD. These individuals are enrolled because earlier, rather than later, intervention in the disease course is more likely to succeed in preventing or delaying cognitive and functional declines.<sup>7</sup> One such

1 Rubin E, Buehler A, Halpern S. *States worse than death among hospitalized patients with serious illnesses*. 176(10) JAMA INTERNAL MEDICINE 1557–9 (2016).

2 POST SG. *THE MORAL CHALLENGE OF ALZHEIMER DISEASE: ETHICAL ISSUES FROM DIAGNOSIS TO DYING*. (2nd ed. 2000).

3 Lai JM, Karlawish J. Assessing the capacity to make everyday decisions: A guide for clinicians and an agenda for future research. *The American Journal of Geriatric Psychiatry*, 15(2):101–11 (2007).

4 ASPE. *National Plans to Address Alzheimer's Disease*. (2015). <https://aspe.hhs.gov/national-plans-address-alzheimers-disease> (accessed Apr 25, 2018).

5 NIH. *Together We Succeed: Accelerating Research on Alzheimer's Disease & Related Dementias – NIH Bypass Budget Proposal for Fiscal Year 2021*. (2019). [https://www.nia.nih.gov/sites/default/files/2019-07/FY21-NIA-bypass-executive-summary-508\\_1.pdf](https://www.nia.nih.gov/sites/default/files/2019-07/FY21-NIA-bypass-executive-summary-508_1.pdf)

6 Kaiser J. *The Alzheimer's gamble: NIH tries to turn billions in new funding into treatment for deadly brain disease* | Science | AAAS. *Science*. (2018). <https://www.sciencemag.org/news/2018/08/alzheimer-s-gamble-nih-tries-turn-billions-new-funding-treatment-deadly-brain-disease> (accessed Aug 5, 2019)

7 Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. *Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's association*

trial is the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Study (A4 Study). Participants in the A4 Study know they are at heightened risk of dementia because, in order to enroll, they learned the results of a test for brain amyloid, a biological sign of disease pathology or 'biomarker'. Another example is the (now-terminated) Alzheimer's Prevention Initiative (API) Generation Program that enrolled participants who learned they had genetic variants that conveyed a heightened risk of developing dementia caused by late-onset AD. These studies are contributing to a seismic shift in how we think about AD diagnosis and treatment.

Historically, AD has been a clinical diagnosis. This meant that it was diagnosed based on the detection of dementia with a characteristic onset and pattern of cognitive and functional impairments, as well as a comprehensive evaluation that excluded alternative causes of dementia. This diagnosis was qualified as 'probable' AD until confirmed post-mortem via autopsy. This approach to diagnosis interweaves the person's experience of disabling cognitive and functional impairments—that is, dementia—with the label of AD. A person is diagnosed with AD because she displays the relevant cognitive and functional impairments.

Now, however, clinical research with participants selected based on the presence of AD biomarkers is disrupting this conceptual model. The threads of AD and dementia are being pulled apart. Clinical trials testing drugs to treat AD in cognitively unimpaired persons who have AD biomarkers or genes that describe a heightened risk of AD—studies including the A4 Study and the API Generation Program—will, if successful, extend the diagnosis of AD into persons who are cognitively unimpaired—individuals who have AD without dementia. This novel stage of AD, characterized by AD pathology in the absence of cognitive impairments, is known to researchers as 'preclinical AD'.<sup>8</sup>

If a disease-modifying treatment for AD is found, it is reasonable to expect that the preclinical AD construct—and with it, biomarker testing of cognitively unimpaired individuals—will be widely adopted into clinical practice. Those who receive a preclinical AD diagnosis will also receive a prescription to reduce their risk of cognitive and functional decline. Genetic testing may also be necessary, as there is emerging evidence that one's Apolipoprotein E (APOE) genotype may affect the safety and efficacy of AD therapies.<sup>9</sup>

This testing and treating regimen will have a broad social impact. An estimated 46.7 million Americans have preclinical AD (defined by amyloidosis, neurodegeneration, or both), though not all will progress to a dementia level of impairment.<sup>10,11</sup> Looking to the future, people who receive a preclinical AD diagnosis will have insight into their risk

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*workgroups on diagnostic guidelines for Alzheimer's disease.* ALZHEIMER'S & DEMENTIA: THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION, 7(3):280–92 (2011).

8 Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, Andrieu S, et al. *Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria.* ALZHEIMER'S & DEMENTIA: THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION, 12(3):292–323 (2016).

9 Sperling R, Salloway S, Brooks DJ, Tampieri D, Barakos J, Fox NC, et al. *Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: A retrospective analysis.* THE LANCET NEUROLOGY, 11(3):241–9 (2012).

10 Brookmeyer R, Abdalla N. *Estimation of lifetime risks of Alzheimer's disease dementia using biomarkers for preclinical disease.* ALZHEIMER'S & DEMENTIA, 14(8):981–8 (2018).

11 Brookmeyer R, Abdalla N, Kawas CH, Corrada MM. *Forecasting the prevalence of preclinical and clinical Alzheimer's disease in the United States.* ALZHEIMER'S & DEMENTIA, 14(2):121–9 (2018).

of dementia years or even decades before the onset of disabling impairments.<sup>12</sup> When they receive this news, they will likely still be engaged in their families, workplaces (both paid and volunteer), and communities.

This future of diagnosis and treatment, though promising, presents ethical, legal, and social challenges to people who learn their gene or biomarker result. One challenge for them will be deciding whether to disclose this information to other people or, instead, to conceal it. In general, disclosing private or non-visible health information involves balancing the perceived risks and rewards of telling others.<sup>13</sup> Rewards include social support and adoption of the sick role, allowing a person to cope.<sup>14</sup> Risks include stigma and discrimination—for example, in the context of insurance, employment, or even housing.<sup>15–17</sup> Further complicating this calculus, results that communicate a heightened risk of dementia caused by AD are often perceived as more sensitive than other kinds of medical information because they speak uniquely to identity. One A4 participant's explanation of the significance of an AD biomarker illustrates this impact on identity: '[A] colonoscopy isn't going to change who I am . . . [but] this is my brain involved'.<sup>18</sup>

There is an urgent need to understand the decision to disclose AD biomarker or genetic test results with attention to whom people disclose them to and why. One way to discover this is to study participants in the clinical trials—such as the A4 Study and API Generation Program—designed to test disease-modifying therapies in cognitively unimpaired adults. The more we understand their decisions to disclose or not, the better we can prepare for the future of clinical practice, for example, to inform consent processes and offer guidance on sharing. Moreover, by understanding the hopes and worries that underlie sharing decisions, we can guide policy makers to design laws that protect and promote the well-being of persons diagnosed with and treated for AD at a stage before dementia.

Here, we report results from an analysis of whether and why individuals in the A4 Study and the API Generation Program shared their amyloid or APOE results with others. While some research has examined how cognitively unimpaired adults share

12 Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. *NIA-AA research framework: Toward a biological definition of Alzheimer's disease*. *ALZHEIMER'S & DEMENTIA: THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION*, 14(4):535–62 (2018).

13 Checton MG, Greene K. *Beyond initial disclosure: The role of prognosis and symptom uncertainty in patterns of disclosure in relationships*. *HEALTH COMMUNICATION*, 27(2):145–57 (2012).

14 Parsons T. *Illness and the role of the physician: A sociological perspective*. *THE AMERICAN JOURNAL OF ORTHOPSYCHIATRY*, 21(3):452–60 (1951).

15 Arias JJ, Tyler AM, Oster BJ, Karlawish J. *The proactive patient: Long-term care insurance discrimination risks of Alzheimer's disease biomarkers*. *THE JOURNAL OF LAW, MEDICINE & ETHICS*, 46(2):485–98 (2018).

16 Chapman CR, Mehta KS, Parent B, Caplan AL. *Genetic discrimination: Emerging ethical challenges in the context of advancing technology*. 7(1) *JOURNAL OF LAW AND THE BIOSCIENCES* lsz016 (2019), doi: <https://doi.org/10.1093/jlb/lsz016>.

17 Rothstein MA, Rothstein L. *How genetics might affect real property rights: Currents in contemporary bioethics*. *THE JOURNAL OF LAW, MEDICINE & ETHICS* 44(1):216–21 (2016).

18 Largent EA, Harkins K, Dyck CH van, Hachey S, Sankar P, Karlawish J. *Cognitively unimpaired adults' reactions to disclosure of amyloid PET scan results*. *PLOS ONE*, 15(2):e0229137 (2020).

their APOE results with others,<sup>19,20</sup> this is the first study to report on patterns of sharing AD biomarker results as well as the first to compare sharing of AD biomarker results to sharing of APOE results. We conclude by identifying gaps in social supports and legal protections that must be addressed now for research participants, as well as before the preclinical AD construct is widely adopted into clinical practice.

## II. ALZHEIMER'S DISEASE BIOMARKERS AND GENETIC TESTING

AD biomarker tests—most commonly, tests for accumulations of amyloid and tau proteins and neurodegeneration—give cognitively unimpaired individuals information about their risk of developing dementia.<sup>21</sup> Lifetime risk of dementia varies considerably by age, gender, and the combination of biomarkers present; moreover, with age and other diseases presenting competing risks, many cognitively unimpaired people with AD biomarkers never develop dementia. For instance, the lifetime risks for a 90-year-old versus a 65-year-old female with only amyloid plaques are 8.4 and 29.3%, respectively.<sup>22</sup> In contrast, a 65-year-old woman with both amyloid plaques and neurodegeneration has a lifetime risk of 40.8%.<sup>23</sup>

In contrast to AD biomarker tests, which measure underlying AD pathology, genetic tests measure chromosome structure. Researchers have not found a single, deterministic gene that directly causes late-onset AD. APOE is a susceptibility gene linked to AD. There are at least three alleles, or variants, of the APOE gene:  $\epsilon 2$ ,  $\epsilon 3$ , and  $\epsilon 4$ . Whereas  $\epsilon 2$  and  $\epsilon 3$  alleles are protective or neutral, respectively,  $\epsilon 4$  alleles increase the carrier's risk of developing AD.<sup>24</sup> For the 10–15 % of the general population who are APOE  $\epsilon 4$  heterozygotes, lifetime risk for mild cognitive impairment (MCI) or dementia caused by AD is 20–25%.<sup>25</sup> For the one to 2% of individuals who are APOE  $\epsilon 4$  homozygotes, lifetime risk for AD may exceed 50%.<sup>26</sup> It bears emphasizing that carrying an APOE  $\epsilon 4$  allele is neither necessary nor sufficient to cause AD: not all people with AD have an APOE  $\epsilon 4$  allele, and not all people with an APOE  $\epsilon 4$  allele develop AD.<sup>27</sup>

19 Ashida S, Koehly LM, Roberts JS, Chen CA, Hiraki S, Green RC. *Disclosing the disclosure: Factors associated with communicating the results of genetic susceptibility testing for Alzheimer's disease.* JOURNAL OF HEALTH COMMUNICATION, 14(8):768–84 (2009).

20 Ashida S, Koehly LM, Roberts JS, Chen CA, Hiraki S, Green RC. *The role of disease perceptions and results sharing in psychological adaptation after genetic susceptibility testing: the REVEAL study.* EUROPEAN JOURNAL OF HUMAN GENETICS, 18(12):1296–301 (2010).

21 See *supra* note 12.

22 See *supra* note 10.

23 See *supra* note 10.

24 Kim J, Basak JM, Holtzman DM. *The role of apolipoprotein E in Alzheimer's disease.* NEURON, 63(3):287–303 (2009).

25 Qian J, Wolters FJ, Beiser A, Haan M, Ikram MA, Karlawish J, et al. *APOE-related risk of mild cognitive impairment and dementia for prevention trials: An analysis of four cohorts.* PLOS MED, 14(3):e1002254 (2017).

26 *Id.*

27 Mayeux R, Saunders AM, Shea S, Mirra S, Evans D, Roses AD, et al. *Utility of the apolipoprotein E genotype in the diagnosis of Alzheimer's disease.* THE NEW ENGLAND JOURNAL OF MEDICINE, 338(8):506–11 (1998).

Clinical practice guidelines currently recommend against both AD biomarker testing and APOE genetic testing for cognitively unimpaired adults.<sup>28–30</sup> However, it is acknowledged that guidelines for the appropriate use of these tests will be increasingly important as the sensitivity and specificity of testing improve and also as disease-modifying therapies for AD become available.

The same clinical studies designed to test novel interventions to delay or prevent the onset of dementia in cognitively unimpaired adults are also an opportunity to understand the ethical, legal, and social dimensions of genetic and biomarker testing. These studies typically require prospective participants to undergo AD biomarker testing or APOE genetic testing.<sup>31–33</sup> Because having elevated AD biomarkers or an APOE  $\epsilon 4$  allele is an inclusion criterion and not having elevated amyloid or an APOE  $\epsilon 4$  allele is an exclusion criterion, these testing results are disclosed to participants.<sup>34</sup> Prior work has shown this disclosure is generally safe, and that, though the disclosure is not medically actionable, many people use the information to change their health behaviors as well as to inform their future plans.<sup>35,36–40</sup>

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- 28 Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, 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.* ALZHEIMER'S & DEMENTIA: THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION. 9(1):E1–16 (2013).
  - 29 Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, et al. *Update on appropriate use criteria for amyloid PET imaging: Dementia experts, mild cognitive impairment, and education.* JOURNAL OF NUCLEAR MEDICINE 54(7):1011–3 (2013).
  - 30 Goldman JS, Hahn SE, Catania JW, Larusse-Eckert S, Butson MB, Rumbaugh M, et al. *Genetic counseling and testing for Alzheimer disease: Joint practice guidelines of the American College of Medical Genetics and the National Society of genetic Counselors.* GENETICS IN MEDICINE 13(6):597–605 (2011).
  - 31 Roberts JS, Dunn LB, Rabinovici GD. *Amyloid imaging, risk disclosure and Alzheimer's disease: Ethical and practical issues.* NEURODEGENER DIS MANAG. 3(3):219–29 (2013).
  - 32 Grill JD, Johnson DK, Burns JM. *Should we disclose amyloid imaging results to cognitively normal individuals?* NEURODEGENER DIS MANAG. 3(1):43–51 (2013).
  - 33 Lingler JH, Klunk WE. *Disclosure of amyloid imaging results to research participants: Has the time come?* ScienceDirect. ALZHEIMER'S & DEMENTIA. 9(6):741–744.e2 (2013).
  - 34 Kim SYH, Karlawish J, Berkman BE. *Ethics of genetic and biomarker test disclosures in neurodegenerative disease prevention trials.* NEUROLOGY 84(14):1488–94 (2015).
  - 35 See supra note 18.
  - 36 Bemelmans SASA, Tromp K, Bunnik EM, Milne RJ, Badger S, Brayne C, et al. *Psychological, behavioral and social effects of disclosing Alzheimer's disease biomarkers to research participants: A systematic review.* ALZHEIMER'S RESEARCH & THERAPY 8(1):46 (2016).
  - 37 Burns JM, Johnson DK, Liebmann EP, Bothwell RJ, Morris JK, Vidoni ED. *Safety of disclosing amyloid status in cognitively normal older adults.* ALZHEIMER'S & DEMENTIA: THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION, 13(9):1024–30 (2017).
  - 38 Wake T, Tabuchi H, Funaki K, Ito D, Yamagata B, Yoshizaki T, et al. *Disclosure of amyloid status for risk of Alzheimer disease to cognitively normal research participants with subjective cognitive decline: A longitudinal study.* AMERICAN JOURNAL OF ALZHEIMER'S DISEASE AND OTHER DEMENTIAs 35:153331752090455 (2020).
  - 39 Grill JD, Cox CG, Harkins K, Karlawish J. *Reactions to learning a "not elevated" amyloid PET result in a preclinical Alzheimer's disease trial.* ALZHEIMER'S RESEARCH & THERAPY 10(1):125 (2018).
  - 40 Grill JD, Raman R, Ernstrom K, Sultzer DL, Burns JM, Donohue MC, et al. *Short-term psychological outcomes of disclosing amyloid imaging results to research participants who do not have cognitive impairment.* 77(12) JAMA NEUROL. 1504–1513 (2020), doi: [10.1001/jamaneurol.2020.2734](https://doi.org/10.1001/jamaneurol.2020.2734).



### III. METHODS

The data presented herein were drawn from two qualitative studies conducted with cognitively unimpaired older adults: the Study of Knowledge and Reactions to Amyloid Testing (SOKRATES I) and the Study of Knowledge and Reactions to APOE Testing (SOKRATES II). SOKRATES I participants learned the result of an amyloid PET scan, and SOKRATES II participants learned an APOE test result, in order to enroll in an AD clinical trial. SOKRATES I and II sought to understand, in part, to whom participants chose to disclose (or not disclose) their test results as well as the reasons underlying their choices.

#### III.A. Participants

SOKRATES I participants were recruited from the pool of individuals screening for the A4 Study (NCT0200835)—a secondary prevention trial testing whether solanezumab can slow cognitive decline in persons with amyloid accumulation.<sup>41</sup> A4 Study inclusion criteria required that participants were aged 65 to 85 and had evidence of amyloid plaque build-up (i.e., an ‘elevated’ amyloid PET scan result) and were cognitively unimpaired. Prospective A4 Study participants underwent a standardized amyloid disclosure educational session that included both verbal and written information about amyloid imaging, possible results, their meaning, and implications for risk of future cognitive decline, and then a comprehension check.<sup>42</sup> The study guide explained that elevated amyloid ‘does not necessarily mean you will develop AD-related memory loss’ but can be associated with an increased risk. Site investigators disclosed the amyloid PET scan results in-person using standardized talking points. Participants received a post-disclosure follow up phone call and regular monitoring of mood and well-being throughout the study. A subset of individuals who screen-failed for the A4 Study solely because they did not have evidence of amyloid plaque build-up (i.e., a ‘not-elevated’ amyloid PET scan result) were recruited into the A4 Study’s companion observational study, Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN, NCT02488720).<sup>43</sup>

SOKRATES II participants were recruited from the pool of individuals screening for the API Generation Program, which consisted of Generation Study 1 (NCT02565511) and Generation Study 2 (NCT03131453), secondary prevention trials testing the safety, efficacy, and tolerability of two investigational drugs, CAD106 and CNP520, respectively.<sup>44</sup> Generation Study 1 inclusion criteria required that participants were APOE  $\epsilon$ 4 homozygotes, cognitively unimpaired, and aged 60–75 at baseline. Generation Study 2 inclusion criteria required that participants were APOE  $\epsilon$ 4 carriers

41 Sperling RA, Rentz DM, Johnson KA, Karlawish J, Donohue M, Salmon DP, et al. *The A4 study: Stopping AD before symptoms begin?* SCIENCE TRANSLATIONAL MEDICINE, 6(228):228fs13–228fs13 (2014).

42 Harkins K, Sankar P, Sperling R, Grill JD, Green RC, Johnson KA, et al. *Development of a process to disclose amyloid imaging results to cognitively normal older adult research participants.* ALZHEIMER'S RESEARCH & THERAPY 7:26 (2015).

43 [ClinicalTrials.gov](https://clinicaltrials.gov), Longitudinal Evaluation of Amyloid Risk and Neurodegeneration – the LEARN Study (LEARN), (2019), <https://clinicaltrials.gov/ct2/show/NCT02488720> (accessed Feb. 7, 2019).

44 Lopez Lopez C, Tariot PN, Caputo A, Langbaum JB, Liu F, Riviere M, et al. *The Alzheimer's prevention initiative generation program: Study design of two randomized controlled trials for individuals at risk for clinical onset of Alzheimer's disease.* ALZHEIMER'S & DEMENTIA: TRANSLATIONAL RESEARCH & CLINICAL INTERVENTIONS. 5(1):216–27 (2019).

(APOE  $\epsilon$ 4 heterozygotes were required to have elevated amyloid), cognitively unimpaired, and aged 60–75 at baseline. API Generation Program participants underwent a standardized gene disclosure process that included an educational session with both verbal and written information about APOE, possible results, their meaning, and their implications for risk of future cognitive decline, including an estimated risk of developing mild cognitive impairment (MCI) or dementia due to AD by age 85, and then a comprehension check. The API Generation Program study guide explains that the APOE  $\epsilon$ 4 allele is a risk factor for AD but cannot predict who will or will not definitely develop cognitive impairments.<sup>45</sup> Genetic counselors disclosed the APOE results in-person, by phone, or by video conference using standardized talking points. Participants received a post-disclosure follow-up phone call and regular monitoring of mood and well-being throughout the study. While individuals who had learned their APOE results previously through other means (e.g., via direct-to-consumer genetic testing site 23andMe) were able to join the API Generation Program, only individuals who first learned their APOE result through the API Generation Program were eligible for SOKRATES II.

A4 Study and API Generation Program study staff at select sites provided materials describing SOKRATES I or II, respectively, to individuals following AD biomarker or APOE status disclosure. Individuals interested in enrolling contacted the research team at the University of Pennsylvania. Data are not available on the number of individuals who were provided these materials by study site staff. In all, 114 individuals contacted the SOKRATES I team and 163 contacted the SOKRATES II team. Of those who did not ultimately participate, several declined after learning more about the study (SOKRATES I: 4; SOKRATES II: 9), some were found ineligible upon screening (SOKRATES I: 13; SOKRATES II: 8), and 89 were not interviewed due to demographic quotas being full or the study having closed enrollment (SOKRATES I: 13; SOKRATES II: 76).

### III.B. Semi-Structured Interview

For SOKRATES I, 50 participants who had received an 'elevated' amyloid PET scan result and 30 who had received a 'not elevated' amyloid PET scan result completed an initial semi-structured interview 4–12 weeks after disclosure of their results; 47 and 30 of these individuals, respectively, completed a 12-month follow-up interview. For SOKRATES II, 50 APOE  $\epsilon$ 4 carriers (i.e., inclusive of homo- and heterozygotes) and 20 non-carriers completed an initial semi-structured interview three months after disclosure of their genetic testing results; 47 and 16 of these individuals, respectively, completed a 12-month follow-up interview. All SOKRATES I interviews occurred between Nov. 5, 2014 and Nov. 30, 2016, and SOKRATES II interviews were conducted between June 20, 2017 and Aug. 23, 2019.

Interviews for SOKRATES I and II were recorded, transcribed, and analyzed in NVivo (QSR International). The research team reviewed all transcripts to develop a

45 Langlois CM, Bradbury A, Wood EM, Roberts JS, Kim SYH, Riviere M, et al. *Alzheimer's prevention initiative generation program: Development of an APOE genetic counseling and disclosure process in the context of clinical trials.* ALZHEIMER'S & DEMENTIA: TRANSLATIONAL RESEARCH & CLINICAL INTERVENTIONS. 5(1):705–16 (2019).



coding scheme. This iterative coding process involved multiple consensus meetings to resolve coding discrepancies, regular checks on agreement using the Cohen coefficient for inter-coder reliability, and adjustments to the codebook with an audit trail of coding rules and decisions made. Other results from SOKRATES I have previously been published.<sup>46,47,48</sup>

The data reported here are derived from the initial interviews of SOKRATES I and II participants. Participants were asked whether—and if so, with whom—they had shared their AD biomarker or APOE result; whether—and if so, from whom—they had withheld their result; and their reasons for sharing or withholding this information.

### III.C. Ethical Approval

The University of Pennsylvania Institutional Review Board (IRB) approved both SOKRATES I and II. Participants gave verbal consent.

## IV. RESULTS

Table 1 reports participant demographics. Due to the differing eligibility criteria of the trials from which they were recruited (i.e., ages 65–85 for the A4 Study and ages 60–75 for the API Generation Program), participants in SOKRATES I were on average older than participants in SOKRATES II, though we oversampled for participants aged 65–74 in SOKRATES I. Other demographic characteristics did not differ statistically between groups. SOKRATES I and II participants are demographically reflective of participants in the parent studies.

In this section, we report data on sharing of results for SOKRATES I participants who have elevated amyloid and SOKRATES II participants who were APOE  $\epsilon 4$  carriers. Then, we report briefly on participants who did not have elevated amyloid or were not APOE  $\epsilon 4$  carriers.

### IV.A. Disclosing Increased Risk for Dementia Caused by AD

SOKRATES I participants who learned they had elevated amyloid and SOKRATES II participants who learned they carried either one or two APOE  $\epsilon 4$  alleles routinely assessed these results as sensitive medical information with implications for their identity. This assessment informed the content of the overarching themes that described the decision to share these results with others. Most participants engaged in a careful decision-making process, weighing whether to share or conceal the information from others in their lives. They often found this process burdensome. Although participants did not necessarily draw these distinctions, the decision-making process had three substantive components: deciding whom to tell, why to tell, and how to tell them.

46 See *supra* note 18.

47 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 NEUROLOGY 75(1):44–50 (2018).

48 Largent EA, Terrasse M, Harkins K, Sisti DA, Sankar P, Karlawish J. *Attitudes toward physician-assisted death from individuals who learn they have an Alzheimer disease biomarker*. JAMA NEUROLOGY 76(7):864–6 (2019).

**Table 1.** Demographic Characteristics of SOKRATES I and II Participants

Characteristic	Elevated Amyloid (n = 50)	Not Elevated Amyloid (n = 30)	$\epsilon 4$ Carriers (n = 50)	$\epsilon 4$ Non-Carriers (n = 20)
	N (%)	N (%)	N (%)	N (%)
<b>Sex</b>				
Male	25 (50%)	13 (43%)	21 (42%)	7 (35%)
Female	25 (50%)	17 (57%)	29 (58%)	13 (65%)
<b>Age</b>				
60–64	0	0	19 (38%)	6 (30%)
65–69	15 (30%)	14 (47%)	15 (30%)	7 (35%)
70–74	20 (40%)	11 (37%)	14 (28%)	7 (35%)
≥75	15 (30%)	5 (17%)	2 (4%)	0
<b>Race</b>				
Caucasian	49 (98%)	29 (97%)	49 (98%)	20 (100%)
Asian	1 (2%)	0	0	0
American	0	0	1 (2%)	0
<b>Indian/Native Alaskan</b>				
Multi-racial	0	1 (3%)	0	0
<b>Ethnicity</b>				
Hispanic/Latino	0	1 (3%)	0	1 (5%)
Non-	50 (100%)	29 (97%)	50 (100%)	19 (95%)
<b>Hispanic/Latino</b>				
<b>Education</b>				
High school	1 (2%)	0	2 (4%)	1 (5%)
Some college or college degree	19 (38%)	11 (37%)	18 (36%)	5 (25%)
Post-graduate education	30 (60%)	19 (63%)	30 (60%)	14 (70%)
<b>Family history of Alzheimer's</b>				
Yes	40 (80%)	21 (70%)	41 (82%)	15 (75%)
No	10 (20%)	9 (30%)	9 (18%)	5 (25%)
<b>Marital status</b>				
Married/living with partner	36 (72%)	26 (83%)	40 (80%)	13 (65%)
Divorced/separated	8 (16%)	2 (7%)	4 (8%)	3 (15%)
Widowed	4 (8%)	2 (7%)	3 (6%)	1 (5%)
Single	2 (4%)	1 (3%)	3 (6%)	3 (15%)
<b>Employment status</b>				
Retired	31 (62%)	20 (67%)	29 (58%)	12 (60%)
Part-time	14 (28%)	7 (23%)	12 (24%)	4 (20%)
Full-time	5 (10%)	3 (10%)	9 (18%)	4 (20%)

#### IV.A.1. Burdensomeness of Disclosure Decision-Making

SOKRATES I and II participants who learned they were at heightened risk of developing dementia due either to having elevated amyloid or to carrying APOE  $\epsilon$ 4 alleles described wrestling with whether or not to share this information with others. One participant with elevated amyloid likened disclosure to 'making that decision if you're gay to come out of the closet'. He went on:

[I]t has taken more emotional energy than I ever thought it would when I first got into the study to make these kinds of decisions. I mean, it's been an ongoing decision, as it were . . . . I mean, I never really appreciated how much energy, psychic energy, that process might take and . . . whether there might be unintended consequences . . . . It just has taken much more emotional energy than I ever imagined it would.

This theme of surprise about the burdensomeness of disclosure decision-making was common.

#### IV.A.2. Recipients of Disclosure

All SOKRATES I participants who had elevated amyloid and all SOKRATES II participants who were APOE  $\epsilon$ 4 carriers shared their result with at least one person. This likely reflected the designs of the A4 Study and Generation Program. Each required a participant to designate a study partner who served as a knowledgeable informant and accompanied the participant to some study visits.

Spouses and partners were the most common recipients of elevated amyloid and APOE  $\epsilon$ 4 results. All married individuals with elevated amyloid shared their result with their spouse. With the two exceptions, married APOE  $\epsilon$ 4 carriers also shared with their spouses. Participants often told their results to their adult children and their siblings. Though sharing within the immediate family was common, it was not universal. Some participants declined to share their result with their adult children or siblings, or shared with some but not others. Overall, participants were less likely to report disclosing their result to in-laws, extended family members, or living parents.

Slightly more than half of participants shared their results with friends and neighbors. Some—more often those with elevated amyloid—reported telling their results to assorted other individuals and social groups, such as members of their bible study group or running club. A select few shared their results much more broadly—for instance, making a Facebook post or discussing their result in a televised interview about AD research. One participant wrote about the result in a holiday newsletter, telling readers, '[T]he good news was I was eligible for the [A4] study. The bad news was I have amyloid plaque in my brain.'

Participants who were still employed or actively engaged in volunteer work rarely reported sharing their results with colleagues and, with only one exception, declined to share with their employer or supervisor. Though less than a quarter of respondents overall shared their result with their health care provider, such sharing was nearly three times more common among APOE  $\epsilon$ 4 carriers than among those with elevated amyloid.

#### IV.A.3. Reasons for Disclosing Results

Participants' reasons for telling other people their elevated amyloid PET scan result or APOE  $\epsilon$ 4-carrier status fit into four major themes: a good relationship with the

prospective recipient; anticipation of positive reactions to disclosure from the prospective recipient; relevance of the result to others; a promotion of AD research. See Table 2 for illustrative quotes.

*Good relationship with prospective recipient*—Most participants identified the strong nature of their relationship with the recipient as a fundamental reason for disclosing their result. Participants often indicated that sharing was a norm within some of their relationships, explaining that they ‘share everything’ with certain people in their lives such as a spouse or best friend. In these cases, where sharing was an established expectation of the relationship, the disclosure-decision-making process was often abbreviated.

*Prospective recipient's positive anticipated reactions*—Participants described disclosing their results so as to enable or to encourage the recipient of the information to engage in desirable actions. Often, that action was provision of emotional support to a participant who felt ‘agitated’ or upset after learning his or her heightened risk for dementia caused by AD. Notably, participants shared in an effort to secure near-term emotional support and also to create long-term support structures. Some participants shared their result so that the recipient could monitor the discloser for incipient changes in cognition and function that might affect well-being; such monitoring was also identified as a reason for disclosing AD biomarker and APOE results to a health care provider in the limited instances such sharing occurred. Additionally, many participants disclosed their testing results in order to better prepare the recipients for the possibility of becoming a caregiver or of acting as a surrogate decision-maker should the participant become cognitively or functionally impaired in the future. This was mentioned much more frequently by APOE  $\epsilon 4$  carriers than by individuals with elevated amyloid.

*Relevance to others*—The relevance of the result to the recipient was another commonly cited reason for sharing. Some participants spoke of the recipient’s ‘right to know’ the results. Relevance was often linked to the recipient’s health and—solely in the case of APOE  $\epsilon 4$  results—also to the health of the recipient’s genetic relatives. When participants were genetically related to the recipient of the information, they explained that sharing their APOE  $\epsilon 4$  carrier status was a matter of ‘respect’ and ‘familial responsibility,’ and expressed that it ‘wouldn’t be right’ to withhold the information.

Other reasons for perceived relevance were the recipient’s personal experience with or interest in memory loss as well as the recipient’s explicit or inferred interest in knowing the participant’s test result. Some participants mentioned sharing the result with people they know who have a medical or scientific background. This was often secondary to a close relationship in which the result would likely have been disclosed anyway, although a few described sharing with more casual acquaintances for this reason. One APOE  $\epsilon 4$ -homozygote, for instance, described sharing the result with coworkers ‘just out of a matter of interest in science’.

*Promotion of AD research*—Participants told others their results to raise awareness about and encourage others to participate in AD research. They explained that they wanted the specific studies they were enrolled in—the A4 Study or the API Generation Program—to successfully meet their recruitment targets and also that they wanted their loved ones and friends to have the opportunity to benefit from access to promising investigational therapies.

**Table 2.** Reasons for Disclosing Results

	Elevated Amyloid (n = 50)	Illustrative Quotes	APOE ε4 Carriers (n = 50)	Illustrative Quotes
<b>Theme 1: Good relationship with prospective recipient</b>				
Closeness	36	'Why would not I share it with her? We're husband and wife. We've been married for 55 years.'	38	'Well with my husband, I mean we share everything in our lives. There are no secrets in our house and in our relationship. I would not... I just cannot imagine not sharing something that is as this important to me.'
		'She's my best friend and I'm her best friend. We share everything. We talk about everything... We've been intimately involved in each other's lives.'		'[I told my golf buddies b]ecause we are buddies and we share everything.'
<b>Theme 2: Prospective recipient's positive anticipated reactions</b>				
Future caregiving or surrogate decision-making	10	'She can make intelligent decisions and recommendations, because if anybody I know will end up doing that for me later, it's her.'	32	'[H]e's my designated person for health care decisions... He needed to be aware. He's the one that's going to sign all the papers.'
		'Some day they might have to take care of me.'		'I mean if I did get Alzheimer's, she would probably eventually be involved in making decisions about my care and things like that, and so [I shared so] that we could both better prepare as a couple for financial and medical decisions that might come down the road.'

Continued

**Table 2.** Continued

	Elevated Amyloid (n = 50)	Illustrative Quotes	APOE ε4 Carriers (n = 50)	Illustrative Quotes
Emotional support	15	<p>I had just learned the news and it was really on my mind and making me feel kind of agitated about it. I think that is why [I shared it].</p> <p>'They're good friends . . . I knew they'd be supportive and I knew I needed that.'</p>	11	<p>'She could also be very supportive, you know. We got the results and she made sure I was okay with those, and yeah, checked in with me several times, make sure I was feeling alright.'</p> <p>'[S]he knows my fear of getting the disease. When she learned about my results, she knew that might be a little concerning for me. For her, I think she tried to be comforting.'</p>
Monitoring for cognitive symptoms	6	<p>'At some point, I may need to count on other people to tell me if I'm changing in a way that I'm trying to deny. She's someone I would trust with that.'</p> <p>I did tell some folks that I run with . . . because I'm concerned about telling the same stories to people more than once.'</p>	6	<p>'[W]hen people start seeing symptoms sometimes we are in denial, and I said, "Tell me if you start seeing them. I need to know because I may be rationalizing things."</p> <p>'They're the ones that I see several times a week, you know? So they would notice changes.'</p>
<b>Theme 3: Relevance to others</b>				
Perceived relevance to recipient's health (or recipient's family)	7	<p>I think she ought to know that there is a good possibility that she, too, might have the same mental status.'</p>	33	<p>I felt that they ought to know that I have a potential and they could too. And, like I said, I was hoping that they might want to look into it further themselves and maybe they will at some point.'</p> <p>'It was important for her to know that I have this gene, which means that I passed it on to her.'</p>

Continued



**Table 2.** Continued

	Elevated Amyloid (n = 50)	Illustrative Quotes	APOE ε4 Carriers (n = 50)	Illustrative Quotes
Wanted to know	8	<p>'I probably would not have told them except they point-blank asked me. I did not want to disseminate or put them off. They're very sincere in their concern.'</p> <p>'He knew I was going into the test, and he wanted to know what the results were.'</p>	16	<p>'I had mentioned at some point that I was going to be doing this study, and he was interested so I told him.'</p>
Personal experience with or interest in memory loss	4	<p>'I've told very long term friends, very close friends, told them. They were very interested in the whole issue of Alzheimer's. The wife of the friends is also in the studies, because her mother had Parkinson's and she's enrolled in studies, related more to Lewy Bodies Syndrome and Parkinson's.'</p>	21	<p>'I told him before that I was gonna take this test, and I said... if you want to know when I get the results he said sure, so I shared it with it him.'</p> <p>'[S]he also had some Alzheimer's in her family, so she's familiar with the disease.'</p>
				<p>'Because we are only a year apart, and we were both concerned about the possibility of developing Alzheimer's. I wanted to share with her that I was doing this testing, and share with her the results of it.'</p>

Continued

**Table 2.** Continued

	Elevated Amyloid (n = 50)	Illustrative Quotes	APOE ε4 Carriers (n = 50)	Illustrative Quotes
<b>Theme 4: Promotion of Alzheimer's disease research</b>				
To raise awareness about Alzheimer's disease research	19	I do it because I'm trying to recruit other people to go into the study. These people are about my age. I know from [study staff] that I think they are looking for other people.'	10	'I mean I tell people that are my age that, 'You really ought to look into this. This is a really good thing.' In fact, I have a friend whose father did have Alzheimer's, and I told him definitely to get himself tested and all of that.'
		I thought she could be another one of the 1000 people that's in this test and may not only save her life or her golden years but... make medical history.'		'I wanted to give them the opportunity to enroll in the study, although they live in different parts of the country, so it technically might be a little bit more challenging.'

#### IV.A.4. Reasons for Not Disclosing Results

Participants' reasons for not sharing their amyloid or APOE result fit into three major themes: a poor relationship with the prospective recipient; anticipation of negative reactions to disclosure from the prospective recipient; and the discloser's lack of symptoms. See Table 3 for illustrative quotes.

*Poor relationship with prospective recipient*—Participants explained that they did not disclose their results to individuals with whom they did not feel close—for example, individuals outside their 'inner circle,' individuals with whom they had a difficult relationship, or individuals from whom they were estranged. They explained that it was 'not their business' or expressed doubt that distant connections would have interest in the information.

*Prospective recipient's negative anticipated reactions*—Participants most often described not telling their result to others because they believed the prospective recipient would find the information emotionally distressing. These beliefs were predicated on assessments of the particular prospective recipient and his or her likely responses, rather than on a feeling that the result was too distressing to share with anyone at all. Additionally, participants mentioned not disclosing their results to individuals already dealing with serious health problems or other significant burdens or to those who lacked the capacity to understand, either due to age (e.g., minor grandchildren) or cognitive impairment (e.g., parents or siblings with dementia or adult children with developmental disabilities). Statements about not wanting to 'burden' or 'worry' others were often accompanied by assessments that the result did not require immediate action. Several participants declined to share because the prospective recipient had stated or implied that they did not want to know the result.

In addition to seeking to prevent harms to others, participants sometimes avoided sharing their results to prevent harms to themselves. Participants cited concerns about three types of harms: stigma, discrimination, and gossip.

Concerns about stigma or changes in the way others would perceive or treat them were more common among participants with elevated amyloid than among APOE  $\epsilon$ 4 carriers. Participants described a wide range of negative social consequences that could follow from sharing their results. These included social exclusion such as not being invited to join in card games or share meals, scrutiny of their behavior and interpretation of minor memory lapses as symptoms of dementia onset, and distrust of their ability to perform activities like driving their car or babysitting their grandchildren. Participants used emotionally charged words in these descriptions, saying this would be 'embarrassing' or that others would think they were 'an idiot' or 'goofy'. They also discussed more well-intentioned social consequences that they wished to avoid, such as expressions of sympathy and pity or families being 'overbearing'.

About 1 in 5 participants mentioned concerns about discrimination, particularly discrimination in employment, housing, or insurance, as a reason for not sharing their results. This came up especially in discussion of workplace disclosure. Participants emphasized the need for cognitive skills—such as good judgment, sound decision-making, and intact memory—in their work and expressed fears that they could be forced to retire or would not be considered for new opportunities if their test results were known.

**Table 3.** Reasons for Not Disclosing Results

	Elevated Amyloid ( <i>n</i> = 50)	Illustrative Quotes	APOE $\epsilon$ 4 Carriers ( <i>n</i> = 50)	Illustrative Quotes
<b>Theme 1: Poor relationship with prospective recipient</b>				
Distance	10	I'm definitely not discussing it with people that are friends but not close friends.'  I have one brother that is estranged from the family . . . I did not talk to him.'	13	'She has told me maybe 15 years ago that she has no interest in anybody in our family, so I have not communicated with her at all.'  'I'm not that close to them. It's not their business to know, I guess.'
<b>Theme 2: Prospective recipient's negative anticipated reactions</b>				
Emotional distress	11	I do not want to upset her. There's no need for her to know that I'm going to dwindle and decline before it becomes obvious and necessary.'	15	'I think that they would be worried... and I did not think that was what I needed to burden them with right now.'

Continued

**Table 3.** Continued

	Elevated Amyloid ( <i>n</i> = 50)	Illustrative Quotes	APOE $\epsilon$ 4 Carriers ( <i>n</i> = 50)	Illustrative Quotes
Stigma, being treated differently	13	<p>It involves a stigma and that if people are going to assume I'm an idiot if I tell them that I have this problem then that would not be the right thing to do while I'm still experiencing a normal memory.</p> <p>I guess it would be embarrassing to have your normal senior moment, to have people close to you start to attribute it to that [the amyloid], when everybody... has a few lapses once in a while.'</p>	4	<p>'Well,... I do not want them to treat me and feel like they need to treat me differently.'</p> <p>'[T]hey'd mother me and then they'd be worried and, ah geez. It would be awful . . . my oldest daughter just got this great opportunity for work in [another city]. She would not go. I know she would not. She needs to go. They need to live their own lives and not be worried about their mother.'</p>

Continued

**Table 3.** Continued

Elevated Amyloid (n = 50)	Illustrative Quotes	APOE ε4 Carriers (n = 50)	Illustrative Quotes
Discrimination 9	<p>'I'm a little bit worried that the [continuing care] communities might have an exclusion criteria based on elevated amyloid plaque... I do not want to be ruled out of the place I want to live just because I have an elevated amyloid plaque. That would be dreadful.'</p> <p>'In my job... it's absolutely necessary to me that people have confidence in my memory and my decision-making power. I try to be very, very careful about what I say so that nothing will diminish the confidence that people have in me.'</p>	9	<p>'It would affect their insurability. It could affect their life insurance, ability to get life insurance, knowing that they are sitting there with a chance of having Alzheimer's, that kind of thing.'</p> <p>'So far as employers are concerned or colleagues at work and so forth, I do not want them to know... I do not want to retire and I am concerned that while I am quite liked at work and I do not think retirement is very likely, the idea that I might at some point be asked to retire bothers me.'</p>

Continued



**Table 3.** Continued

	Elevated Amyloid (n = 50)	Illustrative Quotes	APOE ε4 Carriers (n = 50)	Illustrative Quotes
Didn't want to know	7	'I specifically did not tell her because she was very clear about the fact that she did not want to know... I do not want to push it... on anybody else.'	4	'They said they did not want to have genetic studies done, that there's really nothing you can do about it. That was it. They did not want to know anything.'
Gossip	9	'She talks too much. She's also a good friend, but she's just... She's a bit of a real gossip. She's a real gossip, she's not bit of one.'	2	'Well, for one thing, he would not be able to keep his mouth shut, and so everybody else in the world would know.'
<b>Theme 3: Discloser's lack of symptoms</b>				
No symptoms	5	'There's no real need for everybody else to know this at this point... My driving skills are intact and I'm still able to take in new information. My judgment is still pretty good. I keep track of my finances. Nothing has really changed.'	3	'I wasn't sure what benefit there would be to [share]... If I developed dementia, at that time in the early stages or mild cognitive impairment, I would let all of those folks know.'

Participants also described not sharing because they feared loss of control of the information, due to others sharing the result with individuals the participant would not have told. These concerns about control were both broad—‘word gets around’—and specific, such as not sharing with a particular friend known to partake in gossip.

*Discloser's lack of symptoms*—Several participants chose not to tell others due to the participant's current lack of cognitive symptoms, which they concluded made disclosure unnecessary at this time. Some also noted that, though they were at increased risk for dementia caused by AD, they may not ever experience cognitive decline. There was often an acknowledgement that the decision not to share could be revisited if things changed—that is, if cognitive symptoms developed. Participants who did not share with their health care provider often explained that, in the absence of symptoms, the result is not medically relevant or actionable.

#### *IV.A.5. Disclosure Processes*

Participants put significant thought into the actual process of disclosure, or as one participant phrased it, ‘how to do it’. For instance, one participant with elevated amyloid explained that she ‘didn’t want to talk to [my husband] directly because I knew [the result] would upset him’. Therefore, she chose to tell him ‘in a causal way’ by mentioning it offhandedly while out to dinner with the neighbors. Though this participant’s ‘casual’ approach was not typical, her attention to the mechanics of sharing was.

Several participants identified some individuals whom they wanted to tell or were planning to tell but had not yet told at the time of the interview. This delay often reflected a desire to disclose under the ‘right’ circumstances—typically in-person and without distractions. One participant explained, ‘I’d rather be with them ya know? I don’t really wanna call them up on the phone and say, ‘Hey, guess what?’” Another stated, ‘There hasn’t really been a time when we aren’t just in the middle of a whole social thing with the grandchildren and everything. I would like to sit down quietly and tell [my son]’.

#### **IV.B. Disclosing Decreased Risk for Dementia Caused by AD**

SOKRATES I and II participants experienced relief and other positive emotions after learning that they did not have elevated amyloid or did not carry any APOE  $\epsilon 4$  alleles. For instance, one individual explained that he had been ‘living under this cloud that someday [AD] may get me . . . [The result] took a lot off of my mind’. Given the positive valence of the risk information, these participants did not experience the disclosure decision-making process as burdensome but rather likened sharing their result to sharing good news.

All of these participants disclosed their result to at least one person, most often a spouse, sibling, adult child, or friend. Participants’ reasons for sharing included having a good relationship with the recipient as well as a desire to raise awareness about AD research. Some SOKRATES II participants shared their APOE result with genetic relatives because they felt it was relevant to the recipients’ health. The most common reasons for not sharing were to do with poor relational quality or feeling that the result was unimportant. Participants who did not have elevated amyloid and were not APOE  $\epsilon 4$ -carriers expressed no concerns about gossip, stigma, or discrimination except as a

outcomes that might have resulted in the event they had elevated amyloid or carried APOE  $\epsilon 4$  alleles.

## V. DISCUSSION

We found notable differences between SOKRATES I and II participants who learned they were at increased risk of developing dementia caused by AD and those who learned they were not. Individuals who did not have elevated amyloid or did not carry APOE  $\epsilon 4$  alleles felt they were sharing good news or no news at all and paid relatively little attention to disclosure decision-making. In contrast, individuals with elevated amyloid or APOE  $\epsilon 4$  alleles felt this health information was quite sensitive. As a result, they engaged in a deliberate process, often perceived as unexpectedly burdensome, to determine whether they should share this information with—or conceal it from—others.

Below, we discuss our study results in light of how individuals decided whether or not to share their results with others, potential stigma associated with sharing these results, the threat of discrimination and the inadequacy of legal protections, and 'next friend' risk for dementia care. We conclude by making recommendations for protections that would benefit AD research participants now and preclinical AD patients in the future.

### V.A. Disclosure Decision-Making

The Disclosure Decision-Making Model (DD-MM) is a validated framework for conceptually and empirically assessing disclosure of private or non-visible health information. The DD-MM separates the disclosure process into three assessments.<sup>49</sup> First, the discloser assesses the personal health information, weighing five factors: preparation (i.e., the discloser's expectations prior to receiving the information); prognosis (i.e., the relative probability of various outcomes); symptoms (i.e., whether there are noticeable symptoms); relevance to others (i.e., whether others are directly or indirectly affected by the diagnosis); and stigma (i.e., perceived stigmatization of the health information). If this first assessment suggests the risk is not too great, the discloser will then assess the potential recipient of the information, taking into account both the relational quality and the recipient's anticipated reactions. If disclosure is still favored, then the discloser will assess her disclosure efficacy—that is, her ability to share the information with this particular recipient and produce the desired result. The discloser may choose the timing, setting, and message features to maximize confidence in her disclosure efficacy. If the decision is ultimately made to disclose, the discloser will enact the message. The discloser can exit the disclosure process at any point by not disclosing or, perhaps, by waiting to disclose at some point in the future.

As described above, participants with elevated amyloid or APOE  $\epsilon 4$  alleles described a decision-making process consistent with the three assessments outlined in the DD-MM, though they did not clearly draw this tripartite distinction themselves. First, we found that consideration of the five factors emerged in participant interviews. As reported previously, many participants expected their results even prior to testing,

49 Greene K. *An integrated model of health disclosure decision-making*, in *UNCERTAINTY AND INFORMATION REGULATION IN INTERPERSONAL CONTEXTS: THEORIES AND APPLICATIONS*. (2009).

either due to a family history of AD or to memory concerns.<sup>50,51</sup> Most understood, correctly, that their result placed them at increased risk of dementia caused by AD, but that dementia was not guaranteed.<sup>52,53</sup> Although some participants had subjective cognitive complaints, all were cognitively unimpaired on clinical testing, as this was a requirement for A4 Study and API Generation Program eligibility.<sup>54,55</sup> Carrying an APOE  $\epsilon$ 4 allele was seen as relevant to the health of others, particularly genetically related family members; elevated amyloid was also seen as relevant to recipients, though often because it would influence the recipient's future plans or responsibilities. Stigma, discussed further below, figured prominently in our results.

Next, participants considered both the nature of their relationship with the recipient and the recipient's predicted reactions. Closer relationships and positive expected reactions favored disclosure, while poor relationships and negative expected reactions favored non-disclosure. Finally, participants were mindful when selecting disclosure processes or 'how to do it'. They often, though not always, favored sharing in-person and privately. All participants disclosed their results to at least one other person, but often chose not to disclose to others or indicated that they would disclose at some point in the future.

SOKRATES I and II were both qualitative studies gathering exploratory data about individuals' decisions to disclose AD biomarker and APOE genetic testing results. However, we examined in detail the heuristics that participants used deciding whether or not to share their testing results with others and find that the DD-MM is well-suited to understanding our results. The DD-MM should be the basis of future empirical research identifying population-level factors that influence the likelihood of disclosing AD biomarker and genetic testing results. This information could in turn be examined in future studies to further characterize associations among the factors.

### V.B. Stigmatization

Dementia caused by AD is highly stigmatized.<sup>56–58</sup> The stigma, or negative public attitudes, experienced by people with AD increases with the severity of their

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50 See *supra* note 47.

51 Largent EA, Harkins K, Stites SD, Abera M, Barg F, Karlawish J. 02-06-05: *Preliminary results from the study of knowledge and reactions to apoe testing (SOKRATES 2)*. *ALZHEIMER'S & DEMENTIA*, 15:P550–P550 (2019).

52 See *supra* note 47.

53 See *supra* note 51.

54 See *supra* note 18.

55 See *supra* note 51.

56 Corner L, Bond J. *Being at risk of dementia: Fears and anxieties of older adults*. *JOURNAL OF AGING STUDIES* 18(2):143–55 (2004).

57 Werner P, Giveon SM. *Discriminatory behavior of family physicians toward a person with Alzheimer's disease*. *INTERNATIONAL PSYCHOGERIATRICS*, 20(4):824–39 (2008).

58 *Alzheimer's Association*. 2019 *Alzheimer's disease facts and figures*. *ALZHEIMERS DEMENT*. 15(3):321–87 (2019).

symptoms, as well as with the expectation that symptoms will worsen.<sup>59–61</sup> Participants in SOKRATES I and II were cognitively unimpaired; this was a requirement of participation in both A4 and the API Generation Program, the parent studies from which we recruited our sample. This means participants had no clinically measurable signs of dementia caused by AD. Yet, they learned something about their heightened risk of developing dementia caused by AD. They worried that this risk information would be stigmatizing if disclosed to others.

Worries about stigma were more common among those with elevated amyloid than among  $\epsilon 4$  carriers. Perhaps this is because the presence of elevated amyloid is evidence of a pathologic change that has already occurred in one's brain, whereas one has always been an APOE  $\epsilon 4$  carrier or not, and carrier status does not by itself indicate AD pathology. This finding is an interesting challenge to genetic exceptionalism—that is, the idea that genes are special and therefore demand different treatment than other types of health information. Unfortunately, the hesitancy of individuals with elevated amyloid to disclose is likely sensible. A recent survey experiment showed that, even in the absence of cognitive symptoms, a positive AD biomarker result evokes stronger stigmatizing reactions among members of the general public than a negative result.<sup>62</sup> This suggests cognitively normal individuals with undisclosed elevated amyloid may not be perceived as being a member of a stigmatized group. But disclosure of the result would render the non-visible health information visible and thus open them to stigmatization.<sup>63</sup>

### V.C. Discrimination

Discrimination occurs when stigmatization is enacted via concrete behaviors such as exclusion, rejection, or devaluation. When assessing how recipients would react to the disclosure of an elevated amyloid result or disclosure of APOE  $\epsilon 4$  carrier status, SOKRATES I and II participants anticipated possible discrimination across a variety of contexts—from discrimination in everyday social interactions to discrimination in employment, housing, and insurance. The latter highlight particular legal vulnerabilities, which we consider in turn.

First, concerns about the abilities, particularly the cognitive abilities, of older workers are common. For example, Yale New Haven Hospital, citing such concerns, recently adopted a 'Late Career Practitioner Policy' requiring all clinicians over age 70 seeking reappointment to undergo neuropsychological examination. A substantial portion of

59 Johnson R, Harkins K, Cary M, Sankar P, Karlawish J. *The relative contributions of disease label and disease prognosis to Alzheimer's stigma: A vignette-based experiment*. *SOCIAL SCIENCE & MEDICINE* 143:117–27 (2015).

60 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*. 14(7) *ALZHEIMER'S & DEMENTIA* 925 (2018), doi: <https://doi.org/10.1016/j.jalz.2018.01.006>.

61 Stites SD, Johnson R, Harkins K, Sankar P, Xie D, Karlawish J. *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 COMMUNICATION* 33(3):264–73 (2018).

62 Stites SD, Gill J, Largent EA, Harkins K, Fallon C, Krieger A, et al. *P4-200: Effects of advances in biomarker-based diagnosis and disease-modifying treatment on alzheimer's disease stigma*. *ALZHEIMER'S & DEMENTIA*, 15:P1353–P1353 (2019).

63 Corrigan P, Markowitz FE, Watson A, Rowan D, Kubiak MA. *An attribution model of public discrimination towards persons with mental illness*. *JOURNAL OF HEALTH AND SOCIAL BEHAVIOR* 44(2):162 (2003).

these clinicians (12.7%) were determined to have 'cognitive deficits likely to impair their ability to practice medicine independently.'<sup>64</sup> Late career screening has been adopted—and suggested—in other employment contexts.<sup>65</sup> Such plans are likely to face 'practical, legal, and political barriers.'<sup>66</sup> In Feb. 2020, for instance, the Equal Employment Opportunity Commission (EEOC) sued Yale New Haven Hospital, alleging that the 'Late Career Practitioner Policy' violated both the Age Discrimination in Employment Act (ADEA) and the Americans with Disabilities Act (ADA).<sup>67</sup>

Against this background, it is unsurprising that numerous SOKRATES I and II participants were hesitant to share results that might 'diminish the confidence that people [at work] have in me'. They did not want to be forced out of jobs or fulfilling volunteer positions or to 'be asked to retire'. Our team has previously found that learning an elevated amyloid PET scan result brings into relief tradeoffs between working to save money in anticipation of future memory care expenses and retiring early to enjoy time while still cognitively unimpaired.<sup>68</sup> If keeping paid employment is seen as financial necessity due to current or anticipated future expenses (or even if work is simply meaningful), it is reasonable that people would choose to keep information about biomarkers and APOE  $\epsilon$ 4 to themselves if they thought disclosure could threaten their employment.

Presently, it is unclear if the ADA would cover cognitively unimpaired adults with elevated AD biomarkers—who would likely need to show that they had a perceived disability that caused the employer to discriminate.<sup>69,70</sup> The Genetic Information Nondiscrimination Act (GINA) offers employment protections to cognitively unimpaired APOE  $\epsilon$ 4 carriers, if GINA covers their employer.<sup>71,72</sup> But APOE  $\epsilon$ 4 carriers in SOKRATES II did not mention either GINA or the various state laws that protect against genetic discrimination. We might infer that they do not know about those laws or, if they do, that those laws do not assuage their concerns about workplace discrimination. The ADA might be strengthened to protect both those with elevated AD biomarkers and APOE  $\epsilon$ 4 alleles if, as suggested by others, it is amended to prohibit discrimination against individuals who are not currently disabled but perceived to be

64 Cooney L, Balcezak T. *Cognitive testing of older clinicians prior to Recredentialing*. JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION 323(2):179–80 (2020).

65 Butcher L. *Doctors are suing over age-based screening requirements*. QUARTZ (2020), <https://qz.com/1872984/doctors-are-suing-over-age-based-screening-requirements/> (accessed Sep. 17, 2020).

66 Arias JJ, Stephens ML, Rabinovici GD. *Legal and policy challenges to addressing cognitive impairment in Federal Officials*. JAMA NEUROLOGY 76(4):392 (2019).

67 *EEOC Sues Yale New Haven Hospital for Age and Disability Discrimination*. U.S. EQUAL EMPLOYMENT OPPORTUNITY COMMISSION (2020), <https://www.eeoc.gov/newsroom/eeoc-sues-yale-new-haven-hospital-age-and-disability-discrimination> (accessed Sep. 17, 2020).

68 See *supra* note 18.

69 Arias JJ, Karlawish J. *Confidentiality in preclinical Alzheimer disease studies*. NEUROLOGY 82(8):725–9 (2014).

70 Preston, McTeigue J, Opperman C, Krieg JDS, Brandt-Fontaine M, Yasis A, et al. *The legal implications of detecting Alzheimer's disease earlier*. AMA JOURNAL OF ETHICS 18(12):1207–17 (2016).

71 Rothstein MA. *Currents in contemporary ethics GINA, the ADA, and genetic discrimination in employment*. THE JOURNAL OF LAW, MEDICINE & ETHICS, 36(4):837–40 (200).

72 Clayton EW, Evans BJ, Hazel JW, Rothstein MA. *The law of genetic privacy: Applications, implications, and limitations*. JOURNAL OF LAW AND THE BIOSCIENCES 6(1):1–36 (2019).



at risk for future impairments.<sup>73</sup> Attention should also be paid to the possibility of employer-mandated disclosures of test-results.<sup>74</sup>

Second, though not very common, some participants worried that discrimination would take the form of being 'ruled out of the place I want to live'. Three motivations have been identified for learning about the health of older adults seeking to move to continuing care retirement communities: the high anticipated costs of providing services to people at risk of cognitive or functional decline; a desire to market the 'vibrant lifestyle' of the community; and concern about residents' ability to pay for their housing into the future.<sup>75</sup> The third concern may also be relevant to individuals looking to rent or purchase housing in the community. It has been noted that 'obtaining and using predictive genetic information in residential property transactions is legally uncharted territory'.<sup>76</sup> It is not, for instance, clear that the federal Fair Housing Act would apply to genetic discrimination.<sup>77</sup> California, however, has a law prohibiting genetic discrimination in housing and mortgage lending, amongst other contexts, which would protect APOE  $\epsilon 4$  carriers.<sup>78</sup> Seemingly no protections are available to those who might experience housing discrimination due to AD biomarkers such as elevated amyloid.

Third, cognitively unimpaired individuals might reasonably want to use their knowledge of an AD biomarker result or of their APOE  $\epsilon 4$  carrier status to plan ahead for long-term care services and supports.<sup>79</sup> Such pre-planning could reduce both the personal and societal burdens associated with caring for individuals with dementia caused by AD. Yet, current laws offer limited protections against insurance discrimination, meaning that AD gene and biomarker results can, as one participant explained, 'affect . . . insurability'. GINA does not prevent insurers from denying APOE  $\epsilon 4$  carriers long-term care insurance—the kind of insurance they might most want. Some states, however, restrict the use of genetic information for long-term care insurance.<sup>80</sup> Moreover, GINA provides no protections whatsoever to individuals with AD biomarkers.<sup>81</sup> Providing blanket protections to individuals at increased risk for dementia caused by AD could result in adverse selection, but it would be helpful to think about how to underwrite policies that are neither discriminatory nor cost-prohibitive.

Across SOKRATES I and II, less than a quarter of respondents shared their research results with their health care provider. This lower rate may reflect participants' concerns about potential privacy issues as well as awareness of the lack of medical actionability, given that there is no Food and Drug Administration (FDA)-approved

73 Hoffman S. *Big data and the Americans with disabilities act*. 68(4) HASTINGS LAW JOURNAL 777 (2017).

74 Lawrence MW, Arias JJ. *Alzheimer's disease biomarkers: Another tool for FAA pilot screening?* JOURNAL OF LAW AND THE BIOSCIENCES, 6(1):85–110 (2019).

75 See *supra* note 17.

76 *Id.*

77 See *supra* note 72.

78 See *supra* note 16.

79 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 AFFAIRS, 24(2):483–90 (2005).

80 National Human Genome Research Institute. GENOME STATUTE AND LEGISLATION DATABASE, <https://www.genome.gov/about-genomics/policy-issues/Genome-Statute-Legislation-Database> (accessed Sept. 18, 2020).

81 See *supra* note 15.

disease-modifying treatment for AD. Interestingly, very few participants expressed concern that having an amyloid or APOE result documented in their medical record would affect their eligibility for health insurance. This may be because many—though not all—individuals in our sample are eligible for Medicare, which is generally available to adults 65 years of age and older. Presently, the Patient Protection and Affordable Care Act (ACA) offers important protections to individuals with pre-existing conditions; some protections are also available through GINA and the Health Insurance Protection and Accountability Act (HIPAA). Yet, as partisan efforts to destroy the ACA progress—and if preclinical AD is clinically diagnosed in middle age—use of pre-existing conditions like elevated amyloid in health insurance may become an increasingly salient issue.

To briefly summarize, there is a relative lack of protections against discrimination for people who are cognitively unimpaired but have AD biomarkers or APOE  $\epsilon 4$  alleles that place them at increased risk of dementia caused by AD. It is also worth noting that participants in SOKRATES I and II learned either an AD biomarker test or APOE genetic test result. Additional legal challenges will arise when these results are learned together. Practically speaking, 'in an era in which traditional clinical tests, biomarkers, and imaging are often used in conjunction with genetic testing to forecast disease, GINA is limited in scope.'<sup>82</sup> A person who is an APOE  $\epsilon 4$  carrier who also has amyloid plaques would likely not be covered by GINA. Further, the patchwork of state laws means that, depending on where they live, some people are more protected than others. Thus, we might conclude that the low frequency with which we saw SOKRATES I and II participants raise concerns about discrimination reflects a concerning under-awareness of these important issues.

#### V.D. Next Friend Risk

An individual who receives an AD biomarker or APOE  $\epsilon 4$  carrier result learns about his or her risk for progressing to a dementia level of impairment. The individual's family members also learn about their own risk of needing to provide care to a loved one with dementia—or 'next friend' risk.<sup>83</sup> The heft of this information cannot be underestimated given our national over-reliance on informal caregiving. As evidenced by the 16.3 million informal caregivers who provide care to the 5.8 million Americans presently living with dementia,<sup>84</sup> US law has repeatedly reinforced a structure of long-term care that relies heavily on informal caregiving, steadily expanding next friend risk.<sup>85</sup> The central role of informal caregiving in the lives of people living with dementia was implicit in responses indicating that sharing occurred because the recipient would 'take care of me' in the future.

Of course, participants in SOKRATES I and II do not yet need a caregiver because they are cognitively and functionally unimpaired. Nevertheless, our results strongly suggest that disclosing an elevated amyloid result or APOE  $\epsilon 4$ -carrier status to

82 See *supra* note 16.

83 Hoffman AK. *Reimagining the risk of long-term care*. YALE JOURNAL OF HEALTH POLICY, LAW, AND ETHICS, 16:147 (2016).

84 2020 *Alzheimer's disease facts and figures*. ALZHEIMER'S & DEMENTIA, 16(3):391–460 (2020).

85 See *supra* note 83.

family and friends may lead those individuals to assume a 'pre-caregiver' role.<sup>86</sup> A pre-caregiver is someone tasked with monitoring the individual's cognitive and functional status and looking out for their welfare in daily life. Across SOKRATES I and II, 12% of participants at increased risk for dementia stated that they disclosed their result so that they could 'count on other people to tell me if I'm changing'. This kind of vigilance can necessitate mental and emotional labor that may impact the individual, the pre-caregiver, and how they relate to one another. Yet, while acknowledging the potential burdens and privacy intrusions accompanying such monitoring, it is also worth considering the potential welfare benefits conferred by the identification of pre-caregivers in clinical practice as well as how identification of pre-caregivers might be encouraged.

### V.E. Recommended Protections for Participants and Patients

Contextualized within the broader ethical, legal, and social context, our research findings make it clear that AD clinical trial participants are contributing to science without adequate protections. And, if one or more of these ongoing clinical trials succeeds in identifying a disease-modifying therapy for AD, the patients who utilize that therapy will also lack adequate protections.

Drawing on our clinical, ethical, and policy experience, we suggest that existing laws like GINA should be amended—or new laws, regulations, or guidance documents should be drafted—to protect them. At a minimum, however, the risks outlined herein need to be explicitly incorporated into the informed consent process for AD clinical trials. In pre- and post-testing education, participants should be educated about what the possible results are and what they mean but also how they might use the results and what they should consider when sharing the results with others in their life. Moreover, research-derived AD biomarker and APOE genetic testing results should be left out of medical records entirely. Looking ahead, we must work to change stigmatizing attitudes as well as improve the social safety net for people with dementia.

Additionally, it is essential to understand how a preclinical AD diagnosis affects not just individuals but family systems. It will be important to consider how best to involve pre-caregivers in clinical disclosure of biomarker and APOE  $\epsilon 4$  results and to determine whether, and if so when, these pre-caregivers would benefit from support. Further research is merited to understand the effect of AD gene and biomarker disclosure on pre-caregivers and their interpersonal relationships.

The United States has recognized the human and financial toll of dementia as a public health crisis. In Jan. 2011, President Obama signed the National Alzheimer's Project Act (PL 111–375). The first National Plan to Address Alzheimer's Disease was issued in 2012. The Plan's top goal is to prevent and effectively treat AD by 2025.<sup>87</sup> Many ongoing clinical trials are aiming to reach this goal, and eventually, one will succeed.<sup>88</sup> The prospect of FDA-approval of AD therapies, which will doubtlessly be

86 Largent EA, Karlawish J. *Preclinical Alzheimer disease and the Dawn of the pre-caregiver*. *JAMA NEUROLOGY*, 76(6):631–632 (2019).

87 See *supra* note 4.

88 Silverman E. *When off-label may mean off-target: How would doctors and insurers navigate demand for a new, narrow Alzheimer's drug?* *STAT+* (2020), <https://www.statnews.com/pharmalot/2020/10/13/biogen-a-lzheimers-aducanumab-off-label-prescribing/> (accessed Oct. 22, 2020).

coupled with biomarker and likely also genetic testing to determine who should receive them, adds urgency to the project of understanding and addressing the ethical, legal, and social risks of sharing information about AD biomarkers and APOE status with others.

#### V.F. Limitations

SOKRATES I and II were relatively small samples, and participants—though reflective of participants in the parent studies, the A4 Study<sup>89</sup> and API Generation Program—are demographically homogeneous and not reflective of AD patients generally. This is indicative of a broader challenge for AD research: AD is disproportionately prevalent among African American and Hispanic older adults, but minority participation in research remains low.<sup>90</sup> We suggest additional research to examine decision-making around disclosure of AD biomarker and APOE genetic testing results across a larger, more representative sample to more fully understand upside/downside analyses and how, if at all, disclosure decision-making varies across groups.

Because SOKRATES participants had received either an amyloid PET scan or an APOE genetic testing result at the time of their initial interviews, which are the source of the data presented here, we cannot speak to the effects of learning both an amyloid PET scan and APOE genetic testing result on individuals' disclosure decision-making. Seventeen APOE  $\epsilon 4$  carriers from SOKRATES II eventually received an amyloid PET scan result through their participation in the API Generation Program; of these, seven had elevated amyloid. Overall, they described the amyloid PET scan as 'more definitive' than the genetic test. Studying the experiences of individuals who learn both amyloid and APOE results is a path for future research, as we expect joint testing to be the norm in clinical practice. APOE  $\epsilon 4$ -carrier status may increase the risks of certain amyloid-modifying therapies.<sup>91,92</sup>

All SOKRATES I and II participants underwent standardized education and disclosure processes, tailored for amyloid or APOE, as a result of their participation in the parent studies. While that is a strength of the present study, we note that our findings may be contingent on the education and disclosure process. If there is more heterogeneity in how education and disclosure are handled, sharing of results may differ. Additionally, there were minor differences in interview guide and research procedures between SOKRATES I and II that preclude direct comparisons of the frequency of reasons for not sharing, though we expect these resulted in a relative undercounting of reasons for not-sharing amyloid.

Here, we have reported on the experience of sharing an amyloid PET scan result, but there are other AD biomarkers, such as tangles of tau protein and neurodegeneration.<sup>93</sup> Amyloid may not be the biomarker ultimately used to diagnose preclinical AD in practice or the biomarker that is eventually targeted by successful disease-modifying

89 See *supra* note 40.

90 Wilkins CH, Schindler SE, Morris JC. *Addressing health disparities among minority populations: Why clinical trial recruitment is not enough.* JAMA NEUROLOGY, 77(9):1063 (2020).

91 See *supra* note 9.

92 Sperling RA, Jack CR, Black SE, Frosch MP, Greenberg SM, Hyman BT, et al. *Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: Recommendations from the Alzheimer's association research roundtable workgroup.* ALZHEIMER'S & DEMENTIA 7(4):367–85 (2011).

93 See *supra* note 12.

therapies. It is reasonable, however, to assume that our findings will remain relevant. Participants in SOKRATES I were not focused on amyloid per se but rather on their risk of dementia caused by AD; insofar as other biomarkers also communicate dementia risk, we would expect similar findings around disclosure decision-making. However, as tau might be even more useful than amyloid at predicting an individual's disease progression, concerns regarding sharing tau results may be heightened or somewhat different.<sup>94</sup> Moreover, as there is a move to use of blood-based biomarkers; it will be worth examining if the testing modality changes sharing-related concerns. Further, even if a disease-modifying treatment for AD is identified, absent a treatment that entirely prevents or cures dementia, the ethical and legal implications of biomarker-based diagnosis of Alzheimer's disease will remain relevant to both policy and practice.

## VI. CONCLUSION

SOKRATES I and II empirically evaluated the extent to which—and why—cognitively unimpaired individuals who receive AD biomarker and APOE genetic testing results share these results with others, whether family, friends, health care providers, or others. When the news is good, relatively little thought is given to sharing. When, however, the test results communicate an increased risk of dementia caused by AD, the disclosure decision-making process is complicated, particularly by considerations of stigma, discrimination, and our national reliance on informal caregivers for persons living with dementia. Attention to these issues can inform research—but they should also inform the future clinical practice as our understanding of Alzheimer's disease continues to evolve biomarker and genetic testing are incorporated into clinical care. The utility of these results is not, however, limited to the clinical encounter. They should inform our response to AD as a society so that receiving a diagnosis of AD is neither so risky nor so devastating.

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94 La Joie R, Visani AV, Baker SL, Brown JA, Bourakova V, Cha J, et al. *Prospective longitudinal atrophy in Alzheimer's disease correlates with the intensity and topography of baseline tau-PET*. *SCIENCE TRANSLATIONAL MEDICINE* 12(524):eaau5732 (2020).