Risk Evaluation and Education for Alzheimer's Disease – the Study of Communicating Amyloid Neuroimaging (the REVEAL-SCAN Study)

Detailed Protocol

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PRINCIPAL/OVERALL INVESTIGATOR(S)

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I. Background and Significance

Alzheimer's disease (AD) clinical trials have traditionally tested potential treatments for individuals with symptoms of dementia, but the discovery of AD biomarkers has dramatically altered this approach. Trials such as the Anti-Amyloid in Asymptomatic Alzheimer's Study, or A4 Study, are now focusing on enrolling cognitively normal participants who have biomarkers suggestive of "preclinical AD" in order to delay the onset of cognitive impairments. This goal presents two questions of critical importance to both the validity and safety of these trials, and the successful translation of their results into clinical practice: (1) Will individuals' knowledge of their biomarker status bias cognitive outcomes? (2) Will such knowledge prompt beneficial behavior changes or cause adverse psychological and social consequences? The goal of *this* study is to answer these questions.

The A4 Study is the first large-scale AD prevention trial to enroll cognitively normal persons who learn that they have elevated levels of brain amyloid. This trial is already underway, yet critical knowledge gaps exist: no studies describe the neuropsychological or behavioral effects of disclosing PET amyloid imaging results to cognitively normal individuals. If simply learning that one is biomarker positive causes a person to perform worse on cognitive testing, then primary outcomes data of AD trials may not be valid. Moreover, since amyloid imaging received FDA approval for use in cognitively impaired individuals, our preliminary studies show that clinical investigators want guidance on whether and how to disclose amyloid imaging results, not only to these individuals, but also to cognitively normal older individuals.

Our randomized clinical trial aims to examine the impact of learning amyloid imaging results in cognitively normal individuals. Our sample will be drawn from a racially diverse population, allowing us to address the generalizability of results. The core team that will conduct this project

has worked together for over ten years on the NIH-funded REVEAL (Risk Evaluation and Education of Alzheimer's Disease) Study trials that have studied risk estimation, risk communication and the disclosure of apolipoprotein E (*APOE*) genotype for risk of AD. For this project, this core team is strengthened by additional collaborators with expertise in amyloid imaging, neuroethics, neuropsychological assessment, minority outreach and recruitment, and the impact of psychological expectations and cultural biases (stereotype threat) on cognitive performance, and a close integration with the A4 Study, including the use of the same primary endpoint, amyloid PET scan reading protocol, and disclosure process.

Alzheimer's disease (AD) is a continuum of cognitive decline caused by progressive neurodegeneration associated with accrual of amyloid plaque and tau tangle pathologies. New diagnostic guidelines prepared by the NIA and the Alzheimer's Association recognize: a preclinical or asymptomatic stage, a mild cognitive impairment stage, and a dementia stage.[1,2] Across these stages, biomarkers are increasingly recognized as core diagnostic features critical to understanding the pathophysiology and ultimately, the treatment of AD.[3] Perhaps the most advanced of the *in vivo* biomarkers is amyloid imaging.[4-11] The 2012 FDA approval of florbetapir PET amyloid imaging for the detection of neuritic amyloid plaques (Aβ+ when present) paved the way for clinical use of this technology.[12]

Converging data show that asymptomatic Aβ+ individuals already have "AD-like" changes in brain structure and function.[13-16] When followed, persons who are Aβ+ decline cognitively and show accelerated brain atrophy in comparison to Aβ- persons.[9,17-19] These data, along with similar data based on cerebrospinal fluid (CSF) biomarkers of AD pathology, have led to the concept of "preclinical AD" in which Aβ+ deposition is an early event in a pathophysiological cascade that includes neurofibrillary pathology, inflammation, synaptic dysfunction, neuronal loss, and, ultimately, cognitive decline and dementia. In most studies, 20%-40% of cognitively normal older individuals show high tracer binding.[20] The prevalence of amyloid-positivity in cognitively normal individuals is age-dependent and correlates highly with the presence of apolipoprotein (*APOE*) ε4, the major genetic risk factor for sporadic AD.[21-23]

Secondary prevention trials planned or underway will enroll participants who are cognitively normal and have positive or "elevated" amyloid. Prospective cohort studies suggest that Aβ deposition takes place over decades, and that it may precede even mild clinical symptoms by 15 years or more.[24,25] The long preclinical phase of AD is seen as a potential therapeutic window in which anti-amyloid therapies might be initiated before irreversible brain damage has occurred.[26] Secondary prevention clinical trials of amyloid-focused therapies in asymptomatic individuals are being launched, two in familial AD and one (the A4 Study) in cognitively normal individuals who are Aβ+ by PET imaging.[27-29] As a condition of enrollment, A4 Study participants are informed that they have elevated amyloid. "Elevated amyloid" is a term developed by the A4 Study to describe a result that combines a visual and quantitative read. It is conceptually analogous to a "positive amyloid PET scan," and "not elevated" is analogous to a "negative scan."

The impact of disclosing amyloid status itself may affect key clinical trial outcomes. Learning that one has a neurocognitive diagnosis,[30] or even that one is at risk for AD dementia[31] can have a deleterious effect neurocognitive performance. We do not know whether participants

who learn that they have elevated amyloid will exhibit diminished neuropsychological performance, biasing cognitive outcomes in trials. There is also concern that these test results may cause psychological distress. For example, the Alzheimer's Association and Society of Nuclear Medicine and Molecular Imaging report on *Appropriate Use Criteria for Amyloid PET* states that the clinical use of amyloid PET in asymptomatic individuals is "not appropriate…the potential harms outweigh the minimal benefits."[8] Yet, there has never been a careful assessment of the likelihood and extent of these potential harms. Although amyloid imaging has only been approved by the FDA for those with cognitive impairment, it will likely be used "off-label." For example, in a recent survey of dementia specialists, 24% reported that they planned to use amyloid imaging to screen asymptomatic individuals,[32] and in a separate survey of ADNI researchers that we conducted, over half of ADNI investigators supported the return of amyloid imaging to cognitively normal ADNI research participants.[33]

African Americans (AAs) are historically underrepresented in clinical trials, including AD clinical trials. A significant challenge in conducting research has been in obtaining sufficient participation and retention among AAs in order to better understand health disparities and their impact.[34-36] AD research studies typically do not include large numbers of AAs, a group that is at high risk for AD[37] but also historically reluctant to participate in medical research.[38] As clinical trials for AD are implemented, it is critically important to make sure that underrepresented minorities, particularly AAs, are included and that questions of potential bias in outcomes and risk-benefit balance be understood so that trial results in this population are equally valid. In this study, through a partnership with Duke,[39] we will include at least 25% AAs.

The team proposing this study has worked for many years on how to disclose the risk of AD. The organizing principle of this proposal is that amyloid burden is a risk factor similar to *APOE* genotype, but we recognize that we are studying a distinct and novel research question. REVEAL Study data are used in this proposal to demonstrate our capability to perform this type of research. Our prior experiences with the REVEAL Study are highly relevant to the methodology needed to conduct this research, and to the outcomes to be measured.

Relevance to future decision-making in both clinical trials and clinical practice. The major relevance of this work will be to the design of future clinical trials that use AD biomarkers such as amyloid as part of the inclusion criteria and the translation of their results into clinical practice. If we demonstrate substantive cognitive bias, the sample size of future trials may need to be increased, and sub-analyses of our data (not described in this proposal) could guide us to select tests or batteries of tests that are less vulnerable to stereotype bias. If we demonstrate that there are individuals who become anxious or severely distressed in response to learning their amyloid status, future trials may require processes for recognition and treatment of such symptoms. While our recruitment procedures will not result in a subject pool that is representative of clinical practice, these insights will also be relevant to guide clinicians in ordering and communicating results of amyloid imaging to cognitively normal individuals. Our study is not designed to formally measure costs or resource utilization, but will measure the degree to which subjects seek consultation and order additional diagnostic tests after obtaining amyloid imaging. This information will help researchers and clinicians begin to understand the downstream implications of amyloid imaging as it becomes increasingly utilized.

II. Specific Aims

We will enroll 370 cognitively normal individuals, aged 65-80, using *APOE* genotyping with oversampling of ε4+ individuals to enrich the enrollment sample such that roughly 30% of those scanned will be amyloid elevated (A+) and the remainder amyloid not elevated (A-). From this enriched sample, 370 participants (approximately 25% African American) will all receive their Alzheimer's Disease Dementia Risk Disclosure and be randomized (50/50) to either receive their amyloid scan results (Disclosure or D+) at the disclosure visit or not at the disclosure visit (D-). Those in the D- group will receive their amyloid scan results at an additional visit at the end of the study. The primary cognitive outcome will be the A4 Study's Preclinical Alzheimer Cognitive Composite and the primary outcome for psychological distress will be the Impact of Events Scale (IES). We plan the following analyses:

Specific Aim #1: To determine whether disclosure of elevated brain amyloid will bias ADCS-Preclinical Alzheimer Cognitive Composite (ADCS-PACC) test results.

At 6 months after disclosure…

Primary Hypothesis 1.1: ADCS-PACC scores will be lower among A+D+ participants than A+D- participants.

Exploratory Hypothesis 1:2: African-Americans will demonstrate a higher level of neuropsychological bias in response to amyloid imaging results than other racial groups due to complex sociocultural reasons which can negatively influence cognitive testing outcomes.

Specific Aim #2: To determine whether disclosure of elevated brain amyloid will cause psychological distress.

At 6 months after disclosure…

Secondary Hypothesis 2.1: A+D+ participants will have greater IES scores than A-D+ or D- participants.

Exploratory Hypothesis 2.2: A+D+ participants will have higher scores on scales of subjective memory complaints than A+D- participants.

Exploratory Hypothesis 2.3: Comparison of outcomes at 6 weeks and 6 months after disclosure will show African-Americans to be equally vulnerable to psychological distress after amyloid imaging as other racial and ethnic groups.

Specific Aim #3: To explore how learning amyloid imaging disclosure will impact preventative health behaviors, advance planning for health (e.g. long-term care insurance decisions) and well-being (e.g. stigma, quality of life and relationships).

Specific Aim #4: To examine whether disclosure of amyloid levels affects performance by inducing
stereotype threat.

At 6 months after disclosure…

Quaternary Hypothesis 4.1: The effects of disclosure on task performance will depend upon whether or not the
test is described as assessing cognition.

Quaternary Hypothesis 4.2: The effects of disclosure on pupil dilation (a measure of effort and

arousal that is
assumed to index stereotype threat) will depend upon whether or not the test is described as assessing cognition.

III. Subject Selection

Eligible participants will be cognitively and neuropsychiatrically normal, fluent English speakers, between the ages of 65-80, who have at least one first-degree relative with AD, are willing to undergo blinded (undisclosed) *APOE* genotyping, and are willing to participate in the randomized trial of amyloid imaging disclosure. Participants will be excluded if they have suffered a stroke or head trauma, have active medical or psychiatric illness that is unstable or progressive, or are taking acetylcholinesterase inhibitors or memantine. Participants with a history of anxiety or depression that has resolved or that has been treated and is stable will be enrolled. Formal documentation of AD family history will not be required as our previous REVEAL studies have demonstrated the reliability of self-reported family history of AD.

The inclusion and exclusion criteria for this study include assessment of participants' mood, especially symptoms of depression and anxiety, and persons who score above cut-off scores will be excluded. In addition, measures of depression and anxiety are endpoints of the study as well as measures of safety. We will decide participants' eligibility based on conversations between the study staff (clinician judgment) and participant, as well as pre-specified cut-off scores in screening measures to identify persons in need of additional monitoring:

-Geriatric Depression Scale (GDS) (range 0 to 15): > 10 exclude. 6-10 additional monitoring/use discretion on whether to enroll

-State-Trait Anxiety Inventory (STAI) (range 6-24): $\geq$ 19 exclude. 17-18 increased monitoring.

-Columbia Suicide Severity Rating Scale (CSSRS): Exclude any serious suicidal risk (investigator judgment)

To have a sufficient number of elevated amyloid participants for the planned analyses, we will enrich the participant pool with additional AD dementia risk factors. Age and having the *APOE* ε4 genotype are robustly associated with amyloid positivity and approximately 24% of unselected individuals will be ε4+. Our experience in the REVEAL Study has indicated that among persons who self-identify as having a first-degree family member with AD, the percentage of individuals who are ε4+ increases to about 47%. Thus, we will restrict participation to those who have such a family history.

In addition to enrichment with family history, we will perform *APOE* genotyping on potential participants. Although the REVEAL Study has focused on the disclosure of *APOE*, in this research project we do not want to conflate disclosure of an AD risk gene variant with the disclosure of an AD biomarker, so the results of *APOE* genotyping will not be returned to the

participants. Instead, *APOE* genotyping will be used to increase the mix of participants who are ε4+ to at least 50%.

"We will not be sharing the results of subjects' *APOE* genotyping because we, and each clinical study site, will be blinded to these results. *APOE* results will be only used to enrich our study sample to ensure we are effectively randomizing 50% elevated amyloid scans vs. not-elevated amyloid scans into each intervention arm. These *APOE* results will only be reported to the centralized data site, Boston University, but not the other clinical sites (Brigham and Women's Hospital, University of Pennsylvania, University of Michigan, and Duke University."

Recruitment

All four sites have extensive experience in recruiting participants for AD clinical trials, with access to research registries of cognitively normal older individuals willing to participate in AD-related studies. Participants will be recruited using a variety of methods including interactions with family members of patients in memory clinics; review of research registries; clinical trials websites; direct referral from neurologists, geriatricians and local Alzheimer's Association chapters; and talks in the community. We will post information about this study on our website, and on social media. We will use trifold brochures in clinician offices and at appropriate forums. The study will be mentioned in grand rounds, local clinic presentations on AD, and media interviews.

No "cold calls" will be made directly to any potential participant, whether identified from a patient database or medical record, without the consent of the patient and the patient's primary physician or specialist.

We will include all ethnic groups and men and women equally as part of this study. The study population will include both male and female healthy participants, 65 to 80 years of age. There is an increased ratio of women to men in AD, and it is anticipated that our recruited sample will reflect this ratio. Since AD affects individuals from all ethnic and racial backgrounds, every effort will be made to ensure a representative sample of preclinical AD participants. African Americans are historically underrepresented in clinical trials, including AD clinical trials. For this study of amyloid imaging disclosure, we will aim to recruit at least 25% African Americans through a partnership with Duke University. We expect that half of the participants at the Duke site will be African Americans.

IV. Subject Enrollment

All individuals who contact our study coordinator will be given a brief overview of the study, including all potential risks and discomforts, and will be asked if they would like to participate. At this initial contact, they will be given the opportunity to ask any questions and to consider whether they wish to participate. They will be informed that refusal to participate will not interfere with their future medical care. Whenever possible, the consent form will be given to them or mailed to the potential participant and study partner prior to the screening visit to allow the participant and study partner, as well as their family, to review the consent form in the privacy of their own home.

Should the participant be interested in participating, the study coordinator will set up a time to complete a phone interview (Phone Call #1). During the phone interview, subjects will provide verbal consent by expressing their interest in participating in the study. The phone interview will also explain that our participants will be randomized to one of two groups (initial disclosure of amyloid status; or delayed disclosure of amyloid status) and both groups will receive education and risk information for developing Alzheimer's disease dementia by age 85 based on age, gender, race, and family history of Alzheimer's disease dementia.

At the beginning of the participant's first in-person appointment (Visit #1), he/she will undergo an informed consent process and the consent form will be reviewed and signed by each participant and the study coordinator.

We will take great care in the informed consent process of all participants. To ensure that the participants understand what is being requested and the implications of participation, the impact of an elevated amyloid PET scan will be discussed at great length during the consenting process. We will review the consent forms with the participants and they will be allowed to ask for clarification or questions at any point.

Consent of participants will be a requirement for participation in the research. Participants will have normal cognition and will have capacity to provide consent. No surrogates will be used.

At the beginning of the second in-person appointment, the study partner will be consented to participate in his/her specific responsibilities, specifically participating in the CDR scale in Visit #2. The study partner’s consent form will include language for him/her to be re-contacted by the study coordinators to collect additional information from the study partner’s perspective.

Should the participant want his/her study partner present at any visit, and the study partner is unable to accompany him/her, then a substitute study partner (a family member or a paid caregiver) can be sent.

V. Study Procedures

This clinical trial will randomize 370 cognitively normal participants enriched for their odds of having elevated amyloid by age, family history and *APOE* genotype. Written informed consent for the study will be sought from all participants. The site-PI or appropriate study staff at each site will obtain written consent through a standard informed consent document approved by their site’s Institutional Review Board. Informed consent processes are detailed in “Subject Enrollment” above. Participants who pass screening will undergo amyloid imaging and then be randomized to either (1) learn the results of their amyloid scans at the fourth visit, or (2) not learn their result at the fourth visit, though will receive a delayed scan result disclosure within approximately four weeks after their 6-month follow-up visit. All participants will receive an AD Dementia Risk Assessment based on individual risk factors including age, gender, family history and race/ethnicity, with intervention arm participants additionally receiving their amyloid imaging results. Follow-up after disclosure will occur via a phone call and up to three in-person

visits.

Step 1 – Recruitment:

Recruitment will take place through many modalities, such as interactions with family members of patients in memory clinics; review of research registries; clinical trials websites; direct referral from neurologists, geriatricians and local Alzheimer's Association chapters; news media coverage and talks in the community. Additionally, recruitment will rely on self-referral by interested individuals who learn of our study from our brochure or community outreach program. We will also be posting a description of our study on the Clinicaltrials.gov website.

Step 2 – Phone Call #1: Initial Screening for Family, Medical, Medication History + Collect Demographic information + optional Telephone Interview of Cognitive Status (TICS)

During this telephone interview, the study will be described, and a self-reported family history, and self-reported medical history will be obtained from the participant. Family history questions will include asking if the participant had or has a first degree relative with a known diagnosis of amyotrophic lateral sclerosis (ALS), Parkinson's or Parkinsonian disease, Lewy Body disease, or known diagnosis beyond dementia. Formal documentation of having a positive family history of Alzheimer's disease (AD) will not be required as past REVEAL trials have previously demonstrated the reliability of a self-reported family history of AD. If the participant is unsure of his/her family history at the time of this phone call, the participant will be able to update the family history at the first in-person visit. Medical history questions include past history of stroke or head trauma, no active medical or psychiatric illness that is unstable or progressive. Medication history questions include taking acetycholinesterase (ACE) inhibitors or memantine. Formal documentation of medical and medication history is not needed.

Demographic information will be elicited via a brief survey administered to the participant. In addition, information will be collected about previous outside scans, *APOE* testing, testing related to Alzheimer's disease, and genetic counseling services the participant may have received prior to this study. If a participant seems eligible based on screening criteria and expresses interest in participating in this study, the study coordinator will mail or email the study guide and written consent form for the participant to review, and will schedule the in-person screening visit.

If the participant has cognitive complaints, the participant will complete the TICS (telephone interview of cognitive status) assessment during this phone call in order to initially confirm normal cognitive function. If the participant does not express cognitive complaints, the TICS will be administered at the first in-person visit. Participants will be excluded on this phone call based on these initial screening criteria (see "Inclusion/Exclusion Criteria" section).

Potential participants are asked to identify a study partner for support at this time. The participant is required to bring his/her study partner to the second in-person visit to obtain official written informed consent and to participate in an interview, and will have the option to bring his/her study partner to other study visits. The study coordinator will schedule a time for Step 3 – Visit #1 with the participant within approximately one month of this initial phone call.

Step 3 – Visit #1: Informed Consent (participant) + TICS (if not done at Phone Call #1) or MMSE (if TICS done at Phone Call #1) + Measure Blood Pressure + Review eligibility criteria + Mood Scales + Buccal sample collection

At the first in-person visit (Visit 1), written informed consent is obtained from the participant. The consent form includes information about Alzheimer's disease dementia risk factors and amyloid imaging, how this information pertains to this study, and covers all procedures in Steps 4-12 detailed below. The informed consent will be signed by the participant, as well as the study coordinator performing the consent.

If the TICS was not performed at Phone Call #1, the participant will complete the TICS at this visit. If the TICS was performed at Phone Call #1, the participant will complete the Mini-Mental State Exam (MMSE) for the study coordinator to confirm normal cognitive function.

The participant's family, medical, and medication history collected from Phone Call #1 will be reviewed at this visit, in addition to the study's eligibility criteria.

Mood scales of the Geriatric Depression Scale (GDS),[40] Mini-State Trait Anxiety Inventory (Mini-STAI),[41] and Columbia Suicide Severity Rating Scale (CSSRS)[42] are then administered to the participant to assess for signs of baseline depression and anxiety (see "Inclusion/Exclusion Criteria" section for cut-off scores).

If the participant is not screened out due to deficiencies on the mood scales, he/she is eligible to continue with study participation.

The study participant will have his/her blood pressure measured by a clinical nurse or trained clinical personnel. Participants with blood pressure greater than 140/90 will not be excluded from the study, but will be recommended to speak to their physician.

Participants with blood pressure greater than 180/110 may be excluded and will be recommended to speak to their physician. The participant may choose return to have his/her blood pressure re-measured after seeking care from his/her physician. If his/her blood pressure is under 180/110 at this return visit, he/she may participate in the study at the discretion of the study team. If the participant chooses not to return or if his/her blood pressure still exceeds 180/110 at this return visit, the participant will be excluded.

The study participant will have a buccal swab sample collected for genetic testing. Buccal swab samples will be sent to the designated CLIA-approved laboratory for genotyping, and results will be available in approximately 2 weeks. The consent obtained at the beginning of this visit explains that *APOE* results will not be disclosed as part of the study.

If genotyping of the buccal swab sample fails, the study participant will be asked to return for a brief in-person visit to collect a new buccal swab sample. If the study participant is unable or unwilling to return to complete a second buccal swab sample, the study team may offer to mail a buccal swab collection kit, complete with sample collection and shipping directions, to their home.

APOE genotyping will be used as part of our screening procedures to enrich our study sample with *APOE* ε4+ participants. *APOE* statuses (labeled with study ID and de-identified personal health information) will be reported to the centralized data site, Boston University.

Step 4 – Phone Call #2: Confirm eligibility/ineligibility

The study coordinator will call the participant after the respective site receives the participant's eligibility status, which is based on both *APOE* status and the prior visit's screening measure scores. Participants will not be told their specific reasons for being eligible or ineligible, but those found to be cognitively or emotionally impaired on their screening visit (based on the TICS, MMSE and other questionnaires) will be offered appropriate referral. If the participant is not screened out, he/she is eligible to continue with study participation and the coordinator will schedule Visit 2 within approximately six weeks of this phone call.

Step 5 – Visit #2: Informed Consent (study partner) + Review Medical History + Collect vitals + Clinical Dementia Rating (CDR) Scale with Study Partner + Full Education + Pre-/Post-Education Checklists + Neuropsychiatric battery + Mood scales + Health Behavior Surveys

The participant will have the option of having his/her study partner accompany him/her to any visit. The study partner is encouraged to attend Visit 2 to obtain his/her informed consent to be a study partner and to be interviewed for the Clinical Dementia Rating (CDR) scale.[43] If the study partner is unable to attend in-person, the study team will ask the study partner to complete the informed consent process and interview over the phone or video call (via use of site-specific approved applications) during the visit.

After informed consent of the study partner is obtained, the participant and study partner will be interviewed at this visit using a guided interview and worksheets for the CDR scale. The results of this brief assessment are intended to provide objective information to

verify cognitive normal status at study start.

Participants who score >0 on the CDR scale will be notified at this visit, excluded from the study at this point in time, and will be offered appropriate referral.

For participants who do not screen out based on their CDR scores, medical history (medication and concurrent conditions) will be reviewed at this visit.

The first neuropsychological test battery will be performed at this Visit #2. Baseline cognitive status will be ascertained using the Alzheimer's Disease Cooperative Study Preclinical Alzheimer Cognitive Composite (ADCS-PACC) to ensure the participant is cognitively normal.[44] The ADCS-PACC is comprised of measures of episodic memory (Buschke Selective Reminding Test, Logical Memory I, II), timed sensorimotor function (Digit Symbol Subtest from the WMS), and a global test of cognition (MMSE). Pre-specified cut-off scores of safety screening measures are listed under the "Safety of Participants" section below.

In addition to the ADCS-PACC, the neuropsychological test battery is also comprised of 1) a test of effort: Test of Memory Malingering (TOMM)[45], 2) a measure of attention and short-term memory capacity: Digit Span forward span test[46] and 3) a test of premorbid function (TOPF)[47]

After the neuropsychological battery is the full education session. To assess participants' knowledge prior to the education session, we will ask the participant a list of questions on a "Pre-Education" checklist. Participants will then receive a full educational session about Alzheimer's disease dementia risk factors, amyloid imaging, and the meaning of an elevated and not elevated result in an older adult with normal cognition. The content of this written description was generated using a modified Delphi consensus process that involved experts in human amyloid imaging and informed consent for genetic testing. It includes sections that describe what is amyloid, what is Alzheimer's disease, how do we know whether someone has brain amyloid, what does having a brain amyloid scan involve, what does a positive brain amyloid scan mean, is a positive amyloid scan like other medical risks, and what a negative brain amyloid scan means. The participant is allowed to ask questions regarding the information just learned. After the educational session, the participant will complete a "Post-Education" checklist.

The NEO personality index,[48] Geriatric Depression Scale (GDS),[40] Mini-State Trait Anxiety Inventory (Mini-STAI),[41] and Columbia Suicide Severity Rating Scale (CSSRS),[42] are then administered to the participant to assess for signs of depression and anxiety (see "Inclusion/Exclusion Criteria" section for cut-off scores).

Subjective cognitive measures of the Metamemory in Adulthood (MIA),[49] and Memory Function Questionnaire (MFQ),[50] will be administered. The MIA 108-item test is used to describe memory issues and changes relevant to healthy aging, and assess impact of disclosure of perceived cognitive symptoms and abilities.[49] The MFQ 64-item test reflects subjective appraisals of frequency of forgetting in different situations, the

seriousness of the consequences of forgetting in these situations, comparison of present and past memory functioning, and frequency of memory strategy use; and assesses the impact of disclosure of perceived cognitive symptoms and abilities.[50]

Behavioral health measures obtained at baseline also include: 1) a measure for quality of life, the SF-12 Physical and Mental Health Summary Scale – a 12-item multi-purpose short form (SF) generic measures of health status, and self-rated overall physical and mental health[51]; and 2) a measure of how individuals view their future with the Future Time Perspective Scale – a 10-item scale to assess future time perspective as a developmental construct in adults.[52]

Measures of recall and comprehension, behavioral changes, information sharing and interpersonal relationships, willingness and effort to participate, and cognitive symptoms will be created for this study. Participants will take these created health behavior surveys at baseline and at the 6-week and 6-month follow-up visits (Visits #5 and Visits #6, respectively) to determine the type and frequency of behavior changes in response to learning risk information. Information collected will include assessing health behavior changes, advanced planning, insurance changes (i.e. purchasing or altering long-term care policies), medication changes, willingness to enroll in clinical research, stigma, and tolerance of research risk.

An Emergency Contact Information sheet will be completed by the participant, including two personal emergency contacts and one physician contact. In the event that the participant experiences significant study-related distress, the study team may disclose to an emergency contact that the participant is enrolled in the study. Amyloid status will not be disclosed by the study team.

In addition, Dynamic Experiments for Estimating Preference (DEEP)[61] behavioral assessments will measure participant risk and time preference as presented electronically through various decision-making scenarios.

Finally, the Everyday Discrimination Scale[62] has been developed and will be used to assess perceived discrimination.

Step 6 – Phone call #3: Confirm eligibility/ineligibility + Schedule Scan

The study coordinator will call the participant within two weeks of Visit #2. If the participant is not screened out, he/she is eligible to continue with study participation. If eligible, the study coordinator will schedule the participant's PET scan at their site's imaging center, This visit should happen within approximately one month of Visit #2. A study coordinator will also call to schedule the disclosure session (Visit #4) within approximately two weeks from when the scan results are returned to Boston University.

Step 7 – Visit #3: Amyloid Neuroimaging Scan + Randomization

At this third in-person visit, participants who pass the above listed screening measures will undergo amyloid imaging via a scheduled PET scan at each site's respective imaging center. Participants will receive a single intravenous administration of approximately 370 MBq (10 mCi) of florbetapir F 18 amyloid imaging agent. Participants will be positioned in the PET scanner and at 50 ± minutes after injection.

Imaging data from this scan visit will be sent to Molecular NeuroImaging (MNI) electronically through a secure, already existing Web upload process. The imaging data will undergo a comprehensive quality control process consisting of both a technical and scientific quality control. MNI has already worked with, and received images from, all of the imaging centers in this study and has experience with all study site cameras. Imaging interpretations from MNI will be sent directly to our centralized data site, Boston University, labeled with study ID and de-identified personal health information.

Boston University will randomize the participants into either (1) Comparison/non-disclosure arm (D+): participants will learn the results of their amyloid scans at Visit #4 or (2) Intervention/disclosure arm (D-): participants will not learn their scan results at Visit #4, but will return for another in-person visit (Visit #7) after the completion of their 6-month follow-up (Visit #6) for a delayed disclosure visit. Participants are randomized with a 1:1 randomization for non-disclosure arm: disclosure arm. For participants who are randomized in the disclosure arm, their amyloid imaging results of "elevated" or "not elevated" amyloid will be returned to their respective sites.

Step 8 – Visit #4: Alzheimer's Disease Dementia Risk Disclosure with (D+)/without (D-) Amyloid Scan results (in-person)

All participants will return to the study site for their fourth in-person visit to receive their Alzheimer's Disease Dementia Risk Assessment either with or without their amyloid imaging result, as determined by random assignment. At each site, a trained disclosure provider will present the participant with generalized reference curves of Alzheimer's disease risk based on age, gender, family history, and race/ethnicity. If the participant is randomized to receive their amyloid imaging result, the disclosure provider will communicate whether they have elevated or not elevated amyloid and present his/her AD dementia risk estimate compared to the general population.

If the participant is randomized to not receive their amyloid imaging result at this visit, but will receive their scan result at the end of the study, the disclosure provider will only present the participant's AD dementia risk estimate based on age, gender, family history, and race/ethnicity.

The participant will have the opportunity to ask questions.

Step 9 – Phone Call #4: 1-3 Day Safety Check

The study coordinator will call the participant in 1-3 days to assess the participant's status as a safety check to assess any psychological impact of the disclosure visit, regardless if they are in the immediate scan disclosure group or delayed scan disclosure group. Psychological impact of the disclosure visit will be measured by using the Impact of NeuroImaging for Alzheimer's Disease (INI-AD) scale adapted to this study to measure the impact of amyloid imaging for AD[53] and using the intrusion subscale of the Impact of Event Scale (IES). The INI-AD scale is a 16-item multi-dimensional assessment of risk disclosure across distress, uncertainty, and positive experience.

The INI-AD was developed and validated in our prior REVEAL trials, and will be adapted for this safety check by phone to allow for differentiation of the emotional effects of risk disclosure from more general distress or worry.

The IES-intrusion subscale, a 7-item self-reported measure,[54] assesses response related to a specific stressful life event, and has been specifically anchored to test-related distress in studies of the impact of health risk information, including all previous REVEAL Study trials.

Pre-specified cut-off scores of safety screening measures are listed under the "Safety of Participants" section below. Those found to be cognitively or emotionally impaired will be offered appropriate referral. Should safety be a concern, the disclosure provider or study coordinator will schedule additional in-person visits or phone calls as needed or make a referral to a mental health professional as indicated.

Step 10– Visit #5: 6-Week Follow-Up + Neuropsychological test battery + Secondary Outcome Measures + Cognitive Measures + Health Behavior Surveys

Participants will return in-person six weeks (Visit 5) post-disclosure. The neuropsychological battery, consisting of the 1) ADCS-PACC as our primary outcome measure to assess neuropsychological status,[44] 2) TOMM,[55] 3) Digit span forward test [46] TOPF[47] will be administered.

The secondary outcomes measures at six weeks will measure anxiety and depression with the GDS,[40] mini-STAI,[41] and CSSRS measures[42]; test-specific distress with the Impact of Events Scale (IES)[54]; psychological impact of risk disclosure with the adapted INI-AD; quality of life with the SF-12 measure[51]; and perceived time with the Future Time Perspective scale.[52]

Subjective cognitive measures of the Metamemory in Adulthood (MIA),[49] Memory Function Questionnaire (MFQ),[50] and Cognitive Function Instrument (CFI)[56] will be administered.

Participants will also take the follow-up health behavior surveys to determine the type and frequency of behavior changes in response to learning risk information. Information

collected will include assessing health behavior changes, advanced planning, insurance changes (i.e. purchasing or altering long-term care policies), medication changes, willingness to enroll in clinical research, stigma, and tolerance of research risk.

In addition, Dynamic Experiments for Estimating Preference (DEEP)[61] behavioral assessments will measure participant risk and time preference as presented electronically through various decision-making scenarios.

Step 11 – Visit #6: 6-Month Follow-Up + Neuropsychological test battery + Secondary Outcome Measures + Cognitive Measures + Health Behavior Surveys + Additional Stereotype Threat Measures

Participants will return in person six months (Visit 6) post-disclosure. The neuropsychological battery, consisting of the 1) ADCS-PACC as our primary outcome measure to assess neuropsychological status,[44] 2) TOMM,[55] 3) TOPF[47] (4) a non-standard Digit span forward test[46] under low and high threat will be performed. Pupil dilation, which indexes arousal and effort, will be measured by a portable eye-tracking device while participants complete the two digit span task sequences.

The first Digit span test[46] will be done under low-threat instructions. Participants will be told that the purpose of this test is to calibrate the eye-tracking equipment. This is mild deception. No calibration will be conducted, but this instruction will reduce any evaluative concerns that may be felt by the participants. It will also provide a reasonable explanation for doing the Digit span test twice without revealing the stereotype threat manipulation or hypotheses to the participant. The second Digit span test will be done after giving high-threat instructions, where the participants will be told that the purpose of the test is to assess how memory is affected by levels of amyloid, and that the eye tracker measures how difficult the tasks are for them. Of note, this second set of instructions contains no deception. We will be analyzing the relationship between amyloid levels, memory performance, and pupil responses. Although making clear the purpose of the task may cause participants to feel evaluative pressure, this is precisely the response that we are interested in measuring. It is worth noting that lab studies investigating stereotype threat have often used similar instructional manipulations. In the consent form, we have also noted as a risk that distress could be caused by thinking about how amyloid status might affect cognitive performance. At the end of the study, participants will also be fully debriefed about the full purpose of the experiment. We will explain the full purpose of varying the instructional manipulation.

If a participant's eyes cannot be tracked for some reason, they will complete the test anyway (i.e., they will hear the same instructions and complete the digit span tasks while the eye-tracker is on, even if it is not able to calibrate to their eyes). We will administer a Vision Questionnaire in order to later determine whether we need to exclude any participants from pupil dilation analyses due to vision issues that would impede data quality.

The secondary outcomes measures at six months will measure anxiety and depression

with the GDS,[40] mini-STAI,[41] and CSSRS measures[42]; test-specific distress with the Impact of Events Scale (IES)[54]; psychological impact of risk disclosure with the adapted INI-AD; quality of life with the SF-12 measure[51]; perceived time with the Future Time Perspective scale[52], Essentialist Beliefs about Aging Question[63], and a question about feelings of stereotype threat about Alzheimer's disease risk..

Subjective cognitive measures of the Metamemory in Adulthood (MIA),[49] Memory Function Questionnaire (MFQ),[50] and Cognitive Function Instrument (CFI)[56] will be administered.

Participants will also take the follow-up health behavior surveys to determine the type and frequency of behavior changes in response to learning risk information. Information collected will include assessing health behavior changes, advanced planning, insurance changes (i.e. purchasing or altering long-term care policies), medication changes, willingness to enroll in clinical research, stigma, and tolerance of research risk.

In addition, Dynamic Experiments for Estimating Preference (DEEP)[61] behavioral assessments will measure participant risk and time preference as presented electronically through various decision-making scenarios.

Finally, the Everyday Discrimination Scale[62] has been developed and will be used to assess perceived discrimination at Visit 6.

Step 12 – Visit #7: Delayed Amyloid Scan Disclosure for Initial D- Group

At the end of study data collection, participants in the control arm will return in-person (Visit 7) within approximately four weeks after their 6-month follow-up to learn their amyloid imaging results.

Step 13 – Phone Call #5 for initial D- Group after delayed disclosure: 1-3 Day Safety Check

Participants initially randomized to be in the delayed non-disclosure (D-) group, who later learn their amyloid imaging scan results at Visit #7 will be called by the study coordinator in 1-3 days to assess the participant's status as a safety check. Psychological impact of the disclosure visit will be measured by using the adapted Impact of NeuroImaging for Alzheimer's Disease (INI-AD) scale.[53]

VI. Biostatistical Analysis

Data Collection

Data will be collected by the study coordinator and project manager, and monitored by the PI. The PI will be responsible for monitoring and assuring the validity and integrity of all data and adherence to the IRB approved protocol.

De-identified study data will be collected and managed using REDCap electronic data capture tools hosted at Boston University. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

Data Coordination

De-identified data is coordinated by Boston University (BU). Subjects will be identified only by their assigned randomization number, initials, sex, and year of birth. No names will be used on buccal samples or PET scans that will be sent to diagnostic laboratories to link information to a specific person. If medically necessary to patient care, information or laboratory results of a research participant may be placed in the medical record (i.e., unexpected abnormality found on PET scan). No information will ever be released or published in a way that will identify a specific individual.

Buccal samples collected for this study will be sent directly to the CLIA-approved laboratory for genotyping and will not be shared with research collaborators. Samples sent to the lab will be labeled with the participant's unique study ID, gender and sample collection date. We will not label the buccal samples using names or other identifiers. Buccal samples collected for this study will not be stored. Subjects' *APOE* results will be returned to BU, and BU will report participants eligibility results to each of the clinical sites such that our study sample overall will be enriched for *APOE* ε4+ participants.

Molecular NeuroImaging (MNI) will ensure standardized acquisition of ^{18}F-amyvid (AV-45) PET data at each of the study sites. MNI has developed a comprehensive setup procedure to reduce variance in the imaging outcome among sites that has been used in numerous multicenter amyloid PET imaging studies. MNI has already worked with, and received images from, all of the imaging centers in this study and has experience with all study site cameras. MNI's setup includes review of the imaging protocol with site personnel, set-up of the imaging acquisition protocol on the site camera. Following MNI site approval, each site will acquire ^{18}F-amyvid (AV-45) PET imaging using the protocol currently in use in both ADNI and the A4 study. Imaging data will be sent to MNI electronically through an already existing secure Web upload process. The imaging data will contain the subjects' assigned study number, and will not contain personal identifiable information. The imaging site will send the subjects' PET image to MNI and undergo a comprehensive quality control (QC) process consisting of both a technical (documenting receipt, naming convention, assessing for camera artifacts, etc) and scientific quality control (review by an imaging expert to ensure adequate for analysis). Imaging sites will provide scan transfer data and ongoing camera log information with each scan. Sites will be queried if data does not meet the study standards. Typically data quality control processes are completed within 3-5 days to enable the scans to continue data analysis. MNI will return the scan

results to BU, and BU will randomize and return the results to each of the clinical sites such that 50% are in the initial amyloid scan disclosure group and 50% are in the delayed disclosure group at the end of the study.

To minimize the risk of disclosing amyloid PET results in the EPIC record, scan results will be classified as a "PET research exam entry" that discloses that a research study was conducted and will not include the study name or any interpretable images for incidental findings. Scan orders and results will only be viewable by designated research staff (i.e., study coordinator, site PI and PET imaging center staff).

Eyetracking data and questionnaire data from the 6-month follow-up visit related to stereotype threat and the digit span task will be analyzed by the University of Southern California (USC) team. All data will be de-identified before being sent to USC for analysis. Each site will upload their de-identified, raw pupillometry data (labeled with subject ID#) to the BU secure Web data repository and from there it will be sent to USC.

Data Analysis

The analytical strategy will focus on comparing A+D+ and A+D- groups on the ADCS-PACC score at 6 months to better identify if non-disclosure itself had an effect on ADCS-PACC performance. Although the primary comparison is not based on the fully randomized groups, it is a comparison of randomized groups in the pre-specified subgroup of A+ subjects, thus controlling for type 1 error. The power calculation is based on the comparison within the subgroup of A+ subjects, so type 2 error is also controlled. Our primary analysis will use a mixed-effects model repeated measures (MMRM)[57] approach to evaluate the three repeated measures over time. This Intention-to-Treat (ITT) analysis will incorporate information from those who drop out over the 6 months, assuming missing at random, and have better control of type 1 error and power. We will model time as a categorical measure, and the primary outcome will be the estimated difference (contrast) between the two groups at 6 months. As randomization may not be fully successful in balancing confounding factors between the groups (subgroups of the randomized groups), the analysis will also adjust for potentially confounding measures such as sex, age and *APOE* genotype. We will also include the baseline measure of the ADCS-PACC score in one regression model (using the two repeated measures at 6 weeks and 6 months) to allow for differences in cognitive functioning at baseline. We will also consider models that examine change from baseline, with and without adjustment for the baseline measure.

Analyses of IES as the main secondary outcome and of other measures, will be conducted in a similar fashion. While our main focus for the IES will be upon the contrast between the A+D+ and A-D+ groups, we will also contrast the A+D+ and the D- groups (as long as the A+D- and A-D- exhibit similar outcomes). The D- group may experience increased distress waiting for the disclosure of their imaging, which could reduce our power to explore comparisons between A+D+ and D- groups, although we did not see this occurring in our prior REVEAL studies when participants in the non-disclosure arms were waiting for their genotype data at the end of the study. It will also be of interest to compare the difference between A+D- and A-D- groups, because this comparison would reveal any differences in cognition due to the amyloid burden

itself among participants who do not learn their amyloid status at the fourth visit. We do not expect to find any difference here in only 6 months of follow-up. For Exploratory Aims 1.2 and 2.3, we will examine regression models or MMRM models with interaction terms for race and group to evaluate whether the differences at 6 months between the groups (e.g. A+D+ vs A+D-) are similar for AAs and non-AAs. Point estimates will be considered in addition to confidence intervals and p-values.

For the 6-month follow-up visit digit-span task, we will examine whether working memory performance and
pupil dilation responses differ when under high than low threat differentially depending on both disclosure
status and amyloid levels.

For the 6-month visit digit-span task, we will examine whether working memory performance and pupil dilation responses differ when under high than low threat differentially depending on both disclosure status and amyloid levels.

Power Calculation

Our objective is to achieve 80% power to detect a difference of moderate effect size (0.4-0.6 SD units) on the primary outcome of ADCS-PACC mean score between the A+D- and A+D+ groups at 6 months.

Assuming a PACC standard deviation of 2.2[44], 50 individuals per group would provide 80% power to detect a difference of 1.25 PACC units (0.52 SD units) between A+D- and A+D+ at 6 months.

Based on this calculation, we have set a target to enroll n=50 in each of the 2 elevated amyloid groups (A+D-, A+D+). Due to a much lower than anticipated rate of amyloid positivity and a dropout rate of approximately 10%, we plan to enroll 370 total participants and achieve 100 completed 6 month visits to reach our group enrollment targets of n=50 for each elevated amyloid group.

VII. Risks and Discomforts

Psychological risks: We recognize that persons with normal cognition who learn they have elevated amyloid and an increased risk of developing AD dementia could experience psychological distress. We will monitor psychological well-being in our participants by pre-screening potential participants for anxiety and depression and administering standardized rating scales with pre-specified cut-off scores for affect and anxiety at scheduled follow-up visits after disclosure of PET amyloid imaging results. Additional monitoring and appropriate actions will be taken based on conversations between the study staff (clinician judgment) and participant.

For the 6-month visit digit-span task, we will examine how memory performance is affected by task instructions. Although the purpose of all the included cognitive measures is to assess the link between amyloid status and performance, during this task we will explicitly state this

relationship. Although we expect this to increase concerns about task performance, we do not expect this to create emotional distress. However, we will monitor responses. This will be done via conversations between the study staff (clinician judgment) and participant.

Deception: Mild deception will be used during the 6-month visit digit-span task. More specifically, during the initial trials of this task participants will be told that the purpose is to calibrate the equipment. No calibration will be conducted, but this instruction will reduce any evaluative concerns that may be felt by the participants. We do not anticipate this mild deception to create any distress. However, participants will be fully debriefed about this at the end of the study and their questions will be answered.

Breach of privacy risks: Violations of confidentiality are unlikely given well-established procedures to protect participant privacy that will be carried out by experienced study investigators. We have disclosed genetic testing results to over 1100 REVEAL Study participants to date, and we have received no reports of insurance or employment bias. Participants have the alternative of refusing the study intervention and can discontinue the study at any time.

PET imaging risks: The primary risk related to PET is that of radiation exposure associated with the CT scan or transmission scan and the injected radiotracers. We use a minimal dose of radiopharmaceuticals to permit high quality images with low exposure. These doses have been approved by the FDA in previous studies, and combined doses will fall within ranges approved by the Radiation Safety Committee or the Radioactive Drug Research Committees (RDRC). This radiation dose is not expected to produce any harmful effects, although there is no known minimum level of radiation exposure considered to be totally free of the risk of causing genetic defects or cancer. The risk associated with the amount of radiation exposure participants receive in this study is considered low and comparable to every day risks.

Current or recent participation in any procedures involving radioactive agents such that the total radiation dose exposure to the participant in any given year would exceed the limits of annual and total dose commitment set forth in the US Code of Federal Regulations (CFR) Title 21 Section 361.1 is an exclusion for amyloid imaging (when amyloid imaging is employed).

There is also minor risk associated with the venipuncture and radioisotope injection (pain and bruising or painful infiltration of a failed injection).

Minimizing Risks

Risks to participants include the possibility of psychological distress, social stigmatization, violations of confidentiality, and insurance or employment bias. In many ways, our study is designed to identify and quantify these risks. Our prior studies show that severe or long-term distress from learning *APOE* genetic risk information has been rare. However, we are prepared

for monitoring psychological well-being in our participants, and each site will be prepared to refer participants to appropriate mental-health professionals in the event that distress reaches clinical levels.

Should a serious adverse event (e.g., self-inflicted physical harm due to receipt of test results, severe acute depression or anxiety attributed to receipt of test results, etc.) occur, the investigator at that site would notify the co-PIs and the multidisciplinary Data Safety and Monitoring Board via email immediately following the event. They would review the case in question and additional study data as needed to make recommendations as to how we can improve the safety of the study, or if the study needs to be halted.

Ensuring Safety of Human Subjects

In previous REVEAL Study clinical trials that have involved disclosure of AD dementia genetic risk information, we have developed the following detailed and documented procedures for reducing risks to participants that we have adapted for this study that will involve the disclosure of amyloid imaging.

In addition to careful and thorough communication with potential participants around the consent process, we have several layers of protection built into this protocol that have adequately guarded against any adverse consequences to date. These include:

A. Pre-screening of all participants for clinically significant depression and anxiety.

B. Careful education defining amyloid imaging and the meaning of amyloid imaging results.

C. Scheduled follow-up visits after disclosure of PET amyloid imaging result with standardized rating scales for affect and anxiety. Additional monitoring and appropriate actions will be taken based on conversations between the study staff (clinician judgment) and participant, as well as pre-specified cut-off scores in screening measures:

-Impact of Events Scale (IES): >25 increase monitoring

-Geriatric Depression Scale (GDS) (range 0 to 15): >10 exclude. 6-10: Increase monitoring at investigator discretion and look at change from previous score

-State-Trait Anxiety Inventory (STAI) (range 6-24): $\geq$ 19 exclude. 17-18 Increase monitoring at investigator discretion and look at change from previous score

-Columbia Suicide Severity Rating Scale (CSSRS): Exclude any serious suicidal risk, based on investigator's judgment, can be followed up by site designated mental health professional and increase monitoring

D. On-going phone contact and follow-up as needed with the participant through study staff, with referral to the site clinician who has experience in dealing with older adults who have cognitive impairment and mood disorders (a neurologist, geriatrician or psychiatrist). We have identified clinicians at each site who will rapidly respond to distress in any participant if referred by the study team.

E. Secure maintenance of participant research records: All written records are kept in locked files within locked offices, separate in every sense from the medical records of the participants. Whenever possible, electronic documents that are used to store important information related to research projects are password-protected so that a password must be entered before the document can be opened and before it can be modified. To minimize the risk of disclosing amyloid PET results in the EPIC record, scan results will be classified as a "PET research exam entry" that discloses that a research study was conducted and will not include the study name or any interpretable images for incidental findings. Scan orders and results will only be viewable by designated research staff (i.e., study coordinator, site PI and PET imaging center staff).

F. Obtaining an NIH Certificate of Confidentiality: We are applying for a Certificate of Confidentiality and have included appropriate language in the informed consent form.

G. Oversight of the entire project by an independent Data Safety and Monitoring Board (see below)

H. We will require participants to have a study partner and require emergency contacts. Participants will be asked if they would like to have a close friend or family member (such as an adult child, spouse or partner) accompany them to study visits. We will also collect the name and contact information for two participant-designated emergency contacts described as "(1) a person who we can contact in the event you experience a problem that in our judgment requires the assistance of a close friend or family member (such as an adult child, spouse or partner), and (2) a physician such as an internist, neurologist or family practitioner who we can contact in the event you experience a problem that in our judgment requires medical assistance." Participants will be told that this contact may require disclosure of their amyloid imaging result to this provider contact.

VIII. Potential Benefits

There is no direct benefit from participating in this study. This is not a treatment study, and participants will not receive any medication. By participating REVEAL-SCAN, participants may be eligible to participate in other research studies.

Trials that require disclosing AD biomarker results to cognitively normal older adults may present the prospect of empowering people to action beyond research participation, such as adopting healthy behaviors and lifestyle changes, but they may also cause harm to both perceived and actual cognitive performance, mood, and social and personal well-being. Prior

data from the REVEAL Study suggests that the information that subjects learn may decrease their anxiety about developing AD (or about their close friend, relative or spouse' chance of developing AD) or may allow individuals to make long-term decisions for the future.[53,58-60]

The results of our study will be first-of-their kind data to measure whether such harms are real, and, if they are, their magnitude and severity. This knowledge will be of substantial importance to AD investigators, clinicians and healthcare policy makers, and, therefore, we believe the risks to the participants are reasonable and justified.

IX. Monitoring and Quality Assurance

The risks of the study are outlined above. The study clinician/project manager will be responsible for the monitoring of participant outcomes, under the supervision of the PI. Frequent contact with the study clinician, both by phone and in person at the designated follow-up sessions, will be our primary source of clinical participant monitoring. Participants will be contacted by phone within 1-3 days of receiving their AD risk assessment in order to check in on their emotional state and answer any questions regarding the information or the study itself. At minimum, the study clinician will also meet with each participant for in-person follow-ups 6 weeks and 6 months after receiving their risk assessment. At each of these follow-up appointments, the study clinician will also review participants' mood screening measures and other survey responses in real time in order to help look for possible adverse psychological reactions.

Additionally, at minimum, the study clinician will monitor safety through the completion of mood scales, review participants' mood screening measures and other responses in real time in order to help look for possible adverse psychological reactions.

Quality control for standardized ADCS-PACC administration via audio recordings will be shared with Duke University via secure file sharing. Sites will only provide the study personnel's name performing the ADCS-PACC, and label the recording with subject ID numbers, not with names or any other identifiable information.

Non-serious Adverse Events will mostly include events in which participants exceed thresholds on the anxiety or depression scales (GDS $\geq$ 12; Mini-STAI $\geq$ 19), and will be recorded and reported within 1 week to the PI for review and appropriate follow-up, and reported to the IRB and Data Safety and Monitoring Board annually.

An interim analysis may be conducted by the Data Safety Monitoring Board (DSMB). They will review the study on an annual basis.

Review of Adverse Events

Study site personnel must report immediately to the principal investigator any adverse events from this study. Should a serious adverse event (e.g., self-inflicted physical harm due to receipt of test results, severe acute depression or anxiety attributed to receipt of test results, etc.) occur, the investigator at that site would notify the co-PIs and the multidisciplinary DSMB via email immediately following the event. They would review the case in question and additional study data as needed to make recommendations as to how we can improve the safety of the study, or if the study needs to be halted.

If, for some reason, a participant withdraws or is unable to complete cognitive assessments, the Investigators will discontinue him or her undergoing detailed cognitive batteries. Where possible, safety monitoring procedures will be conducted until the end of the study.

During all portions of this research study, the privacy and confidentiality of all participants will be maintained at all times. All hard copies of research data will be kept in the study clinician's locked office. Data will be stored in locked filing cabinets, in binders, and on the study staff members' computers. Digital files of audio recordings will be labeled only with subject ID numbers, not with names or any other identifiable information. This data is accessible only by research staff, primarily the PI and study staff. The code linking the study ID with the identifiers will be stored on the study clinician's computer in a password protected computer file. Only the password protected file will contain the link between the identifiers and the study ID.

Any information obtained from a potential participant who chooses not to participate in the study will be destroyed unless they choose to participate in another study, in which case the information will be stored as part of the other study. All research and imaging data will be assigned a code with the participants' initials and study number. The data will be blinded in all data analyses.

No one other than the PI and the study staff will have access to identifiable research data. De-identified data may be shared with collaborating institutions (University of Pennsylvania, University of Michigan, Duke University) and investigators, as well as with the NIH and public data repositories upon request.

Confidentiality will be ensured by keeping all subject records in a locked file cabinet in a locked office and by using subject identification numbers (as opposed to names) in all databases created during this research. If any data are used for publication, it will be done so without any identifying information. Audio tapes will treated with the same level of protections by using subject identification numbers and storing all tapes in a locked file cabinet.

A certificate of confidentiality has been obtained for this study.

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