Disclosing genetic risk for Alzheimer's dementia to individuals with mild cognitive impairment

Kurt D. Christensen, PhD,[1,2] Jason Karlawish, MD,[3] J. Scott Roberts, PhD,[4] Wendy R. Uhlmann, MS, CGC,[5] Kristin Harkins, MPH,[3] Elisabeth M. Wood, MS, CGC,[3] Thomas O. Obisesan, MD, MPH,[6] Lan Q. Le, MPH,[4] L. Adrienne Cupples, PhD,[7] Emilie S. Zoltick, ScD, MPH,[1] Megan S. Johnson,[6] Margaret K. Bradbury, MS, CGC, MSHS,[8] Leo B. Waterston, MA,[9] Clara A. Chen, MHS,[10] Sara Feldman, MPH,[4] Denise L. Perry, MS, CGC,[1] and Robert C. Green, MD, MPH[1,2,11], for the REVEAL Study Group*

1 Division of Genetics, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA
2 Department of Medicine, Harvard Medical School, Boston, MA, USA
3 Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA
4 Department of Health Behavior and Health Education, University of Michigan School of Public Health, Ann Arbor, MI, USA
5 Departments of Internal Medicine and Human Genetics, University of Michigan, Ann Arbor, Michigan, USA
6 Department of Medicine, Howard University College of Medicine, Washington, DC, USA
7 Departments of Biostatistics and Epidemiology, Boston University School of Public Health, Boston, MA, USA
8 Department of Research, Hemophilia Federation of America, Washington DC, USA
9 Center for Outcomes Research & Evaluation (CORE), Maine Medical Center Research Institute, Portland, ME, USA
10 Biostatistics and Epidemiology Data Analytics Center, Boston University School of Public Health, Boston, MA, USA
11 Broad Institute of Harvard and MIT, Cambridge, MA; Partners Personalized Medicine, Boston, MA, USA

* A list of additional members of the REVEAL Study Group is presented in Appendix 1.

Address correspondence to:

Kurt D. Christensen, PhD

Brigham and Women's Hospital and Harvard Medical School

EC Alumnae Building, Suite 301

41 Avenue Louis Pasteur, Boston, MA 02115

Phone: 1-617-264-5883

Fax: 1-617-264-8795

Email: kchristensen@bwh.harvard.edu

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/trc2.12002.

ABSTRACT

INTRODUCTION

The safety of predicting conversion from mild cognitive impairment (MCI) to Alzheimer's disease (AD) dementia using *APOE* genotyping is unknown.

METHODS

We randomized 114 individuals with MCI to receive estimates of 3-year risk of conversion to AD dementia informed by *APOE* genotyping (disclosure arm) or not (nondisclosure arm) in a noninferiority clinical trial. Primary outcomes were anxiety and depression scores. Secondary outcomes included other psychological measures.

RESULTS

Upper confidence limits for randomization arm differences were 2.3 on the State Trait Anxiety Index and 0.5 on the Geriatric Depression Scale, below noninferiority margins of 3.3 and 1.0. Moreover, mean scores were lower in the disclosure arm than nondisclosure arm for test-related positive impact (difference: -1.9, indicating more positive feelings) and AD concern (difference: -0.3).

DISCUSSION

Providing genetic information to individuals with MCI about imminent risk for AD does not increase risks of anxiety or depression and may provide psychological benefits.

Keywords: Alzheimer's disease, Apolipoprotein E4, Genetic Testing, Cognitive Dysfunction, Risk Assessment, Emotions, Health Behavior, Humans, Depression, Dementia, Anxiety, Risk, Random Allocation

1. INTRODUCTION

Genomic testing is increasingly used to diagnose and treat disease [1, 2], but its use to estimate risks for developing dementia remains controversial [3-6], particularly for conditions such as Alzheimer's disease (AD) where proven strategies to prevent or delay disease onset are lacking. Consensus statements discourage genetic susceptibility testing for AD when individuals are asymptomatic for reasons that include its potential to cause psychological harm [7, 8]. People with symptoms that may suggest subclinical levels of disease may be especially vulnerable to anxiety, depression, or even suicidality [9].

Prior research has shown that disclosing *APOE* genotypes and communicating AD risk to asymptomatic individuals in clinical settings does not cause psychological harm for most individuals [10-12], although questions remain about direct-to-consumer contexts [13]. But these studies enrolled participants who, if they were to develop AD, were often decades away from developing symptoms. Questions remain about whether genetic risk disclosure is safe for individuals who have memory problems and may progress to AD dementia in the near future.

To address this gap in knowledge, we conducted a randomized trial of individuals with amnestic mild cognitive impairment (MCI), a clinical syndrome characterized by memory problems without significant impairment in social or occupational functioning [14]. Approximately 10%-15% of MCI patients progress to AD dementia annually [15], depending on factors that include *APOE* genotype [16]. We compared participant outcomes when risk assessments for progressing to AD dementia within three years included or omitted disclosure of *APOE* genotypes. We hypothesized that participants who learned their *APOE* genotype would experience no greater anxiety or depression than participants who did not receive genotype disclosure. We hypothesized secondarily that participants who learned they were *APOE* ε4-positive would experience no greater anxiety or depression than participants who learned they were *APOE* ε4-negative.

2. METHODS

2.1 Design Overview

As described in prior reports [10-12], the multidisciplinary Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study group designed the protocol and risk disclosure procedures. Institutional review boards at each study site approved the protocol. *APOE* was genotyped at a Clinical Laboratory Improvement Amendments-certified facility (Athena Diagnostics). Methods for risk disclosure were reported previously [17].

After verbal consent and a phone interview to assess eligibility (Figure 1), participants met with a study clinician (typically a genetic counselor) for screening and to provide written consent. Participants also learned more about MCI and AD, and reviewed the benefits, risks, and limitations of genetic risk assessment for AD. Risks and limitations included potential difficulties coping with test results and the lack of "proven ways to prevent Alzheimer's disease." If participants met inclusion criteria and wished to proceed, blood was drawn for *APOE* genotyping. Participants were randomized 2:1 in blocks of 6 to groups that received *APOE* genotype disclosure (disclosure arm) or

did not receive genotype disclosure (nondisclosure arm). Randomization strata were defined by site and age.

Approximately one month after the blood draw, participants returned to the clinic to receive results in person. Participants in both randomization arms received education about MCI and AD and personalized estimates from a study clinician about the likelihood they would progress to AD dementia within 3 years. These estimates, provided as part of a semi-scripted protocol, ranged from 8% to 57% (see Appendix 2) and were created using data from the Memory Impairment Study [18]. Personalized estimates for progressing to AD dementia were based on participants' age stratum and their MCI diagnoses [17]. For participants in the disclosure arm, personalized estimates of conversion to AD were additionally based on the presence or absence of a copy of the *APOE* ε4 allele (i.e., *APOE* ε4 heterozygotes and homozygotes were provided the same AD risk estimates). All personalized risk estimates included written information, a pictogram, and a line graph (see Appendix 3). Participants were followed for six months following disclosure sessions, with assessments conducted in person at 6 weeks and via telephone and mail at 6 months.

A one year follow-up visit was originally planned, but was shortened to 6 months to reduce demands on participants and because prior studies [10] and anecdotal descriptions had suggested that there were no additional changes in psychosocial outcomes after 6 months. Participants in the genotype nondisclosure arm had the option to learn their *APOE* genotypes after completing their final follow-up survey.

2.2 Study Population

We recruited individuals with amnestic mild cognitive impairment (MCI) who were aged 55-90 years from memory clinics, neurology and medicine departments, and AD centers. MCI was defined as having (1) a memory complaint, corroborated by an informant; (2) abnormal memory function, as documented by delayed recall on the Logical Memory II subtest of the Wechsler Memory Scale-Revised; and (3) adequate general cognitive function (Mini-Mental State Examination (MMSE) score ≥24 [19] or approval from a clinician for scores below 24). To ensure participants' safety, we required participants to enroll and attend sessions with a companion. Exclusion criteria included severe anxiety or depression per a clinician's judgment and informed by scores on mood scales. Additional details about the recruitment and safety monitoring protocols are provided in Appendix 4.

2.3 Outcome Measures

Co-primary outcomes were time-averaged scores of anxiety, as assessed with a six-item version of the State-Trait Anxiety Inventory (STAI) [20]; and depression, assessed with the 15-item version of the Geriatric Depression Scale (GDS) [21, 22]. STAI scores were scaled to range from 20-80, and scores above 40 may warrant clinical concern [29, 30]. GDS scores ranged from 0-15, with higher scores indicating greater depression and scores of 5 or above indicate clinical concern [23, 24]. Secondary psychological measures included test-related distress, as measured by the Impact of Event Scale (IES) [25] (range: 0-75; higher scores indicate greater distress), and the individual subscales that comprised the Impact of Genetic Testing for Alzheimer's Disease scale (IGT-AD) [26]: test-specific distress (range: 0-60; higher scores indicate greater distress) and positive test impact (range: 0-20; lower scores indicate greater positive feelings). We also assessed hopelessness with the four-item Beck Hopelessness Scale (BHS; range: 0-4, higher scores indicate greater hopelessness)

[27], and a 4-item AD concern scale (range: 1-5, higher scores indicate greater concern about AD) [28]. Participants who scored above 8 on the 15-item GDS, above 56 on the 6-item STAI, or endorsed at least 2 out of 4 statements on the BHS received additional follow-up and monitoring. Test-related distress and positive impact scales were administered only after AD risk assessments. All other measures were assessed at baseline and again at 6 weeks and 6 months after AD risk assessments. As in prior REVEAL Study trials [28-30], we also assessed participants' risk perceptions at all time points by asking them to estimate their chances of AD conversion within the next three years on a scale of 0-100%.

2.4 Statistical Analysis

We planned to enroll 180 participants and provide 151 risk assessments. We used a noninferiority framework to test the primary hypothesis that participants in the genotype disclosure arm would report no greater anxiety or depression than participants in the nondisclosure arm [31]. We also used a noninferiority framework to test the secondary hypothesis that, within the genotype disclosure arm, participants who received *APOE* ε4-positive results would report no greater symptoms of anxiety or depression than participants who received *APOE* ε4-negative results. In this paper therefore, the phrase "noninferiority of genotype disclosure" means the comparison of scores of one group to another showed that genetic risk disclosure did not increase scores of psychological harm more than a margin of error from that of the nondisclosure group.

We used t-tests and chi-squared tests to compare demographics of the randomization arms and to analyze who dropped out after randomization. We used chi-squared tests to compare dropout of study arms after randomization, but before results were communicated to participants. For all other analyses, we used generalized linear models fit with generalized estimating equations to compare time-averaged and time-specific outcomes by randomization arm or by *APOE* status. Analyses of STAI, GDS, IES, test-related distress with the IGT-AD, and BHS used a log link and gamma distribution because the distributions of these outcomes were highly skewed. A value of one was added to each of these scales, except the STAI, to shift their distributions away from zero. Analyses of positive impact, AD concern, and perceived risk for AD conversion used an identity link and normal distribution. Models included interaction terms between time and randomization status because prior work has shown that, when observed, the psychological impact of genetic information typically fades over time [32]. All models included terms for randomization status, time as a categorical variable, and interaction between time and randomization arm. We included age, gender, race, education, and, given imbalances by randomization status, marital status as covariates in analyses of continuous outcomes. The analytic approach followed our initial statistical analysis plans (these covariates were omitted from analyses of dichotomous outcomes because statistical models that included them were unstable). We also included the clinician who disclosed results as a covariate in the analyses of continuous outcomes to account for potential confounding [33]. We included baseline scores where available (STAI, GDS, BHS, and AD concern) given their strong associations with scores at follow-up and best practices [10, 34]. Analyses of STAI, GDS, BHS, and AD concern compared changes in scores from baseline. Analyses that compared participants by *APOE* status included a dichotomous variable to distinguish participants with no copies of the ε4 allele and participants with at least one copy, as well as terms for interaction between *APOE* status and randomization status, *APOE* status and time, and *APOE* status, randomization status, and time.

For noninferiority testing, we calculated 97.5% confidence limits (CL), using upper bounds of two-sided CIs of (1 - 2α) × 100%, with α equal to 2.5% (0.05/2) to account for multiple testing across 2 primary outcomes [35]. We asserted noninferiority (e.g., no greater anxiety or depression) if 97.5% confidence limits for the differences between randomization arms or *APOE* genotypes were below noninferiority margins (because all scales indicated worse scores with higher values, we were able to focus on upper bounds). The same approach was used to examine all outcomes at specific time points and all secondary psychological outcomes. More details about the margins that defined noninferiority and the statistical models are provided in Appendix 4.

Analyses included all randomized participants. Analyses were conducted using R version 3.5.1 or SAS, version 9.4 (SAS Institute). We assumed that data were missing at random (up to 19 participants were missing data on primary and secondary outcomes), and imputed missing data with fully conditional specification, running 100 iterations to create each of 20 imputed data sets.

3. RESULTS

We enrolled 146 of the 386 participants that we recruited (37.8%), and ultimately provided results to 114 participants (Figure 1). Characteristics of participants who were provided risk assessments are summarized in Table 1. Participants were 74 years old, on average, and 75 (65.8%) had at least a bachelor's degree. MMSE scores ranged from 21 to 30, with most participants (91.7%) scoring 24 or higher. A greater percentage of participants in the genotype disclosure arm were married compared to the nondisclosure arm (76.0% vs 51.3%, respectively, P value=.007). No other differences were observed by randomization status. Clinicians communicated results to between 4 and 47 participants each and did not differ in their likelihood of disclosing results to participants in either randomization arm (P value=.819).

3.1 Randomization Arm Comparisons

Mean anxiety and depression scores in both randomization arms were below cutoffs for concern at all time points (Table 2), and noninferiority of genotype disclosure was demonstrated in time-averaged analyses (Figure 2). Mean adjusted time-averaged anxiety scores were 1.4 points lower in the disclosure arm than the nondisclosure arm, and the 97.5% confidence limit (2.3) was below the noninferiority margin (3.3). Mean adjusted time-averaged depression scores were the same in the disclosure and nondisclosure arms, and the 97.5% confidence limit (0.5) was below noninferiority margin (1.0). Noninferiority of genotype disclosure was also supported on time-averaged analyses of all secondary psychological outcomes. Similar patterns were observed at 6 weeks. Noninferiority of genotype disclosure at 6 months was observed only for positive impact and AD concern. Notably, participants were more likely to score above our pre-established cutoffs for increased monitoring on scales of anxiety, depression and hopelessness if they were randomized to genotype nondisclosure compared to genotype disclosure (28.9% vs 13.5%, respectively, P value=.050).

3.2 Comparisons by APOE status

Mean anxiety and depression scores were still below cutoffs for concern regardless of *APOE* ε4 status (Table 3). Preplanned secondary analyses of participants in the disclosure arm that compared disclosure of *APOE* ε4-positive status against disclosure of *APOE* ε4-negative status were inconclusive (Figure 3), as upper bounds of the 97.5% confidence limits for both anxiety and

depression (4.1 and 1.0, respectively) were equal to or above margins for noninferiority (3.3 and 1.0, respectively). Furthermore, participants who received *APOE* ε4-positive results scored higher than those who received *APOE* ε4-negative results on time-averaged scales of test-related distress as measured by the IGT-AD (diff= 6.8, 95% confidence interval: 2.7 to 10.9), as well as all time point specific analyses of the same scale.

3.2 Comparisons of Randomization Arms by APOE Status

We conducted exploratory analyses that compared genotype disclosure to genotype nondisclosure for participants with specific *APOE* genotypes (Appendix 5). Among individuals who were *APOE* ε4-negative, genotype disclosure was noninferior on time-averaged analyses of all psychological outcomes except anxiety and hopelessness. Moreover, scores were lower in the genotype disclosure arm on time-averaged scores of test-related distress as measured by the IGT-AD (diff=-7.4, 97.5% confidence limit (CL): -2.1), positive impact (diff= -3.1, 97.5% CL: -0.7), and AD concern (diff= -0.6, 97.5% CL: -0.2). Similarly, analyses of 6-week outcomes among *APOE* ε4-negative participants showed noninferiority of genotype disclosure on all measures except hopelessness, and lower scores in the genotype disclosure arm on measures of test-related distress, as measured by the IGT-AD, and AD concern. At 6 months, noninferiority of genotype disclosure was observed only for test-related distress (both measures), positive impact, and AD concern.

Among individuals who were *APOE* ε4-positive, genotype disclosure was noninferior to genotype nondisclosure on time-averaged measures of anxiety (diff= -2.3, 97.5% CL: 3.0 vs margin of 3.3), depression (diff= 0.8, 97.5% CL: .9 vs margin of 1.0), positive impact (diff= -0.6, 97.5% CL: 2.3 vs margin of 5.0), and hopelessness (diff= -0.1, 97.5% CL: 0.2 vs margin of 0.3). In time point-specific analyses of *APOE* ε4-positive participants, disclosure was demonstrated to be noninferior to nondisclosure at 6 weeks only for depression, positive impact, hopelessness, and AD concern, and for no psychological outcomes at 6 months except positive impact.

3.3 Perceptions of Risk for Converting to AD

Exploratory analyses also showed differences between randomization arms in perceived risk of progressing to AD within three years, contingent upon *APOE* status (Appendix 6). Among participants who were *APOE* ε4-negative, individuals in the genotype disclosure arm provided time-averaged estimates of their risk of progressing to AD that were an average of 11.3% lower in the disclosure arm than the nondisclosure arm (24.6% vs 36.0%, respectively, P value=.010), although differences were not significant at 6 weeks. No differences between randomization arms were observed at any time point or in time-averaged analyses among participants who were *APOE* ε4-positive (all P values ≥ .165). Among participants in the disclosure arm, participants who were ε4-positive provided risk estimates for AD conversion that were 19.7% higher in time-averaged analyses than participants who were ε4-negative (44.3% vs 24.6%, respectively, P value<.001). Differences were also significant in time point-specific analyses.

4. DISCUSSION

This study showed that among individuals with MCI, disclosing genetic risk about progressing to AD dementia does not increase risks for clinically significant depression or anxiety, and overall reduced

concern about AD. It also resulted in more positive feelings about the risk assessment experience. These findings are consistent with results from prior trials that demonstrated the safety of disclosing genetic risk information about AD when provided to volunteer populations by clinicians in a well-designed education and disclosure protocol [10-12, 36] and that showed psychological benefits for participants who learned that they were *APOE* ε4-negative. In this trial, it is likely that psychological benefits accrued, in part, because participants were expecting bad news given their mild memory problems. Similar responses have been observed in studies of genetic testing for conditions such as Huntington disease and Lynch syndrome, where identification of genetic risk factors have not caused clinically significant distress but negative results have provided emotional relief [37, 38]. Further supporting this rationale, we found participants estimated their likelihood of progressing to AD lower when their *APOE* ε4-negative status was disclosed rather than withheld, while no differences were observed when participants were *APOE* ε4-positive.

Findings from our study have grown in importance as *APOE* genotyping has become more available. Trials of investigational medications, such as the A4 Trial [44] and the bapineuzumab trial [39] have used *APOE* genotyping to enrich or stratify their study populations. In the Generation Program [40], disclosure of APOE genotype is a mandatory part of determining trial eligibility. The design of these trials provide access to *APOE* genotyping results to their participants. In addition, some healthy individuals have obtained genetic risk information about AD through studies of precision medicine, physicians or direct-to-consumer options [13, 41, 42]. Most notably, 23andMe has FDA approval to include *APOE* results in their direct-to-consumer personal genome service [43]. Given the strong public interest in genetic susceptibility testing about AD [44, 45] it is likely that the number of individuals with mild memory problems – and healthy individuals – who pursue *APOE*-based risk information about AD will only continue to increase.

In this trial, participants' distress responses to risk disclosure appeared to be greater than in prior studies of asymptomatic, at-risk adults. Mean scores on both test-related distress scales were higher at all time points than previously observed [10-12, 36]. Differences in responses between trials may be the result of differences by trial in eligibility criteria (e.g., MCI in this trial, no MCI in prior trials), the magnitude of numeric risk estimates, or the proximity of AD conversion (i.e., risk was conveyed for the next three years in this trial, as opposed to by age 85 in prior trials) [46]. These findings highlight the heightened risk for distress in disclosing AD risk information to individuals with MCI, regardless of whether *APOE* genotypes are disclosed [47], and the need for carefully designed education, communication, and follow-up protocols when providing dementia information to individuals with MCI.

Strengths of this study include an ethnically diverse study population, with 18% of participants self-identifying as black or African American. Limitations include enrollment of a volunteer population of individuals who were generally more educated and may be better prepared to cope with higher-risk results than the population at-large [13]. Our study also mandated that participants enroll with a study partner who provided social support and responded to risk disclosure in ways that may have influenced study outcomes [17, 48], so the findings may not be generalizable to individuals lacking such social support. The wait for disclosure in the nondisclosure arm may have induced anticipatory anxiety. Lastly, we did not achieve our study enrollment targets, and provided risk assessments to fewer participants than planned (151 planned vs 114 actual). Moreover, loss to follow-up and missing data at each time point also increased the width of confidence intervals. Nonetheless,

sample sizes were sufficient to confirm noninferiority of genetic risk disclosure in analyses that compared randomization arms on primary outcome measures. Tests of hypotheses that compared *APOE* ε4-positive and ε4-negative participants within the disclosure arm were inconclusive, however, possibly because these analyses were underpowered.

Importantly, our data suggest that including genetic information to estimate the likelihood that individuals with MCI will progress to AD dementia may reassure people who are ε4-negative. Although short-term test-related distress was clearly higher among participants who learned they were ε4-positive rather than ε4-negative, no differences were noted on general measures of anxiety or depression. Given the ever-increasing accessibility of genetic information, our findings provide encouraging data about the safety and personal utility of genetic risk disclosure via standardized education and counseling protocols among populations who are often considered to be most vulnerable to potential harms. These results provide reassurance that *APOE* genotypes, as well as common genotypes for other neurodegenerative diseases (such as *LRRK2* for Parkinson disease), may be disclosed safely even in persons who have already begun to show clinical symptoms of the condition itself. Since enrollment for new experimental treatments may be increasingly genotype-specific in the future, our work suggests that even participants with MCI can receive information about their *APOE* status without increasing risks for depression or anxiety.

ACKNOWLEDGMENTS

Funding: Work was supported by the National Institutes of Health [grant numbers R01HG002213, K01HG009173, RF1AG047866, U01AG010483, P30AG013846, P30AG053760, M01RR000533, M01RR010284, UL1TR001102, U01AG24904 and T32HL125232]. We also thank Lauren Galbraith for her assistance preparing the manuscript.

Conflict of interest notification page

Robert Green receives compensation for advising AIA, Applied Therapeutics, Biggs Institute, Helix, Humanity, Verily and Veritas, and is a cofounder with equity in Genome Medical.

REFERENCES

[1] Biesecker LG, Green RC. Diagnostic clinical genome and exome sequencing. N Engl J Med. 2014;370:2418-25.

[2] Green RC, Rehm HL, Kohane IS. Clinical genome sequencing. In: Ginsberg GS, Willard HF, editors. Genomic and Personalized Medicine, Second Edition. San Diego: Academic Press; 2013. p. 102-22.

[3] Flinter F. Should we sequence everyone's genome? No. BMJ. 2013;346.

[4] Kwon JM, Steiner RD. "I'm fine; I'm just waiting for my disease": the new and growing class of presymptomatic patients. Neurology. 2011;77:522-3.

[5] Keogh LA, Niven H, Rutstein A, Flander L, Gaff C, Jenkins M. Choosing not to undergo predictive genetic testing for hereditary colorectal cancer syndromes: expanding our understanding of decliners and declining. J Behav Med. 2017:1-12.

[6] Offit K. Genomic profiles for disease risk: predictive or premature? JAMA. 2008;299:1353-5.

[7] 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. Genet Med. 2011;13:597-605.

[8] Berg JS, Khoury MJ, Evans JP. Deploying whole genome sequencing in clinical practice and public health: meeting the challenge one bin at a time. Genet Med. 2011;13:499-504.

[9] Vansenne F, Bossuyt PM, de Borgie CA. Evaluating the psychological effects of genetic testing in symptomatic patients: a systematic review. Genet Test Mol Biomarkers. 2009;13:555-63.

[10] Green RC, Roberts JS, Cupples LA, Relkin NR, Whitehouse PJ, Brown T, et al. Disclosure of APOE genotype for risk of Alzheimer's disease. N Engl J Med. 2009;361:245-54.

[11] Green RC, Christensen KD, Cupples LA, Relkin NR, Whitehouse PJ, Royal CDM, et al. A randomized noninferiority trial of condensed protocols for genetic risk disclosure of Alzheimer's disease. Alzheimers Dement. 2015;11:1222-30.

[12] Christensen KD, Roberts JS, Whitehouse PJ, Royal CDM, Obisesan TO, Cupples LA, et al. Disclosing pleiotropic effects during genetic risk assessment for Alzheimer disease. A randomized trial. Ann Intern Med. 2016;164:155-63.

[13] Zallen DT. "Well, good luck with that": reactions to learning of increased genetic risk for Alzheimer disease. Genet Med. 2018;20:1462-7.

[14] Petersen RC, Lopez O, Armstrong MJ, Getchius TSD, Ganguli M, Gloss D, et al. Practice guideline update summary: mild cognitive impairment: report of the Guideline Development, Dissemination,

and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018;90:126-35.

[15] Petersen RC, Roberts RO, Knopman DS, Boeve BF, Geda YE, Ivnik RJ, et al. Mild cognitive impairment: ten years later. Arch Neurol. 2009;66:1447-55.

[16] 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. 2017;14:e1002254.

[17] Guan Y, Roter DL, Erby LH, Wolff JL, Gitlin LN, Roberts JS, et al. Disclosing genetic risk of Alzheimer's disease to cognitively impaired patients and visit companions: Findings from the REVEAL Study. Patient Educ Couns. 2017;100:927-35.

[18] Grundman M, Petersen RC, Ferris SH, Thomas RG, Aisen PS, Bennett DA, et al. Mild cognitive impairment can be distinguished from Alzheimer disease and normal aging for clinical trials. Arch Neurol. 2004;61:59-66.

[19] Creavin ST, Wisniewski S, Noel-Storr AH, Trevelyan CM, Hampton T, Rayment D, et al. Mini-Mental State Examination (MMSE) for the detection of dementia in clinically unevaluated people aged 65 and over in community and primary care populations. Cochrane Database Syst Rev. 2016:Cd011145.

[20] Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). Br J Clin Psychol. 1992;31 (Pt 3):301-6.

[21] Almeida OP, Almeida SA. Short versions of the geriatric depression scale: a study of their validity for the diagnosis of a major depressive episode according to ICD-10 and DSM-IV. Int J Geriatr Psychiatry. 1999;14:858-65.

[22] Sheikh JI, Yesavage JA. Geriatric Depression Scale (GDS). Recent evidence and development of a shorter version. In: Brink TL, editor. Clinical Gerontology: A Guide to Assessment and Intervention. New York: The Haworth Press; 1986. p. 165-73.

[23] Bunevicius A, Staniute M, Brozaitiene J, Pop VJM, Neverauskas J, Bunevicius R. Screening for anxiety disorders in patients with coronary artery disease. Health Qual Life Outcomes. 2013;11:37.

[24] Grant KA, McMahon C, Austin MP. Maternal anxiety during the transition to parenthood: a prospective study. J Affect Disord. 2008;108:101-11.

[25] Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: a measure of subjective stress. Psychosom Med. 1979;41:209-18.

[26] Chung WW, Chen CA, Cupples LA, Roberts JS, Hiraki SC, Nair AK, et al. A new scale measuring psychologic impact of genetic susceptibility testing for Alzheimer disease. Alzheimer Dis Assoc Disord. 2009;23:50-6.

[27] Yip P, Cheung Y. Quick assessment of hopelessness: a cross-sectional study. Health Qual Life Outcomes. 2006;4:13.

[28] Christensen KD, Roberts JS, Zikmund-Fisher BJ, Kardia SLR, McBride CM, Linnenbringer E, et al. Associations between self-referral and health behavior responses to genetic risk information. Genome Med. 2015;7:10.

[29] Gooding HC, Linnenbringer EL, Burack J, Roberts JS, Green RC, Biesecker BB. Genetic susceptibility testing for Alzheimer disease: motivation to obtain information and control as precursors to coping with increased risk. Patient Educ Couns. 2006;64:259-67.

[30] Linnenbringer E, Roberts JS, Hiraki S, Cupples LA, Green RC. "I know what you told me, but this is what I think:" perceived risk of Alzheimer disease among individuals who accurately recall their genetics-based risk estimate. Genet Med. 2010;12:219-27.

[31] Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SW. Reporting of noninferiority and equivalence randomized trials: an extension of the consort statement. JAMA. 2006;295:1152-60.

[32] Heshka JT, Palleschi C, Howley H, Wilson B, Wells PS. A systematic review of perceived risks, psychological and behavioral impacts of genetic testing. Genet Med. 2008;10:19-32.

[33] Kahan B, Morris T. Assessing potential sources of clustering in individually randomised trials. BMC Med Res Methodol. 2013;13:58.

[34] Fitzmaurice GM. Applied longitudinal analysis. Hoboken, N.J.2004.

[35] Walker E, Nowacki AS. Understanding equivalence and noninferiority testing. J Gen Intern Med. 2011;26:192-6.

[36] Christensen KD, Uhlmann WR, Roberts JS, Linnenbringer E, Whitehouse PJ, Royal CDM, et al. A randomized controlled trial of disclosing genetic risk information for Alzheimer disease via telephone. Genet Med. 2018;20:132-41.

[37] Brodersen NH, Sutton S, Goff S, Hodgson SV, Thomas HJ. Anticipated reactions to genetic testing for hereditary non-polyposis colorectal cancer susceptibility. Clin Genet. 2004;66:437-44.

[38] Wiggins S, Whyte P, Huggins M, Adam S, Theilmann J, Bloch M, et al. The psychological consequences of predictive testing for Huntington's disease. Canadian Collaborative Study of Predictive Testing. N Engl J Med. 1992;327:1401-5.

[39] Vandenberghe R, Rinne JO, Boada M, Katayama S, Scheltens P, Vellas B, et al. Bapineuzumab for mild to moderate Alzheimer's disease in two global, randomized, phase 3 trials. Alzheimers Res Ther. 2016;8:18.

[40] Doostparast Torshizi A, Wang K. Next-generation sequencing in drug development: target identification and genetically stratified clinical trials. Drug Discov Today. 2018;23:1776-83.

[41] Calero O, Garcia-Albert L, Rodriguez-Martin A, Veiga S, Calero M. A fast and cost-effective method for apolipoprotein E isotyping as an alternative to APOE genotyping for patient screening and stratification. Sci Rep. 2018;8:5969.

[42] Perkins BA, Caskey CT, Brar P, Dec E, Karow DS, Kahn AM, et al. Precision medicine screening using whole-genome sequencing and advanced imaging to identify disease risk in adults. Proc Natl Acad Sci U S A. 2018.

[43] Food and Drug Administration. Evaluation of automatic class III designation for the 23andMe Personal Genome Service (PGS) genetic health risk test for hereditary thrombophilia, alpha-1 antitrypsin deficiency, Alzheimer's disease, Parkinson's disease,Gaucher disease type 1, factor XI deficiency, celiac disease, G6PD deficiency, hereditary hemochromatosis and early-onset primary dystonia. Decision summary. 2017.

[44] Roberts JS, Gornick MC, Carere DA, Uhlmann WR, Ruffin MT, Green RC. Direct-to-consumer genetic testing: user motivations, decision making, and perceived utility of results. Public Health Genomics. 2017.

[45] Sherman K, Shaw LK, Champion K, Caldeira F, McCaskill M. The effect of disease risk probability and disease type on interest in clinic-based versus direct-to-consumer genetic testing services. J Behav Med. 2015.

[46] Roberts JS, Christensen KD, Green RC. Using Alzheimer's disease as a model for genetic risk disclosure: implications for personal genomics. Clin Genet. 2011;80:407-14.

[47] Gallagher D, Coen R, Kilroy D, Belinski K, Bruce I, Coakley D, et al. Anxiety and behavioural disturbance as markers of prodromal Alzheimer's disease in patients with mild cognitive impairment. Int J Geriatr Psychiatry. 2011;26:166-72.

[48] Guan Y, Roter DL, Erby LH, Wolff JL, Gitlin LN, Roberts JS, et al. Communication predictors of patient and companion satisfaction with Alzheimer's genetic risk disclosure. J Health Commun. 2018;23:807-14.

Figure 1. Study flow diagram.

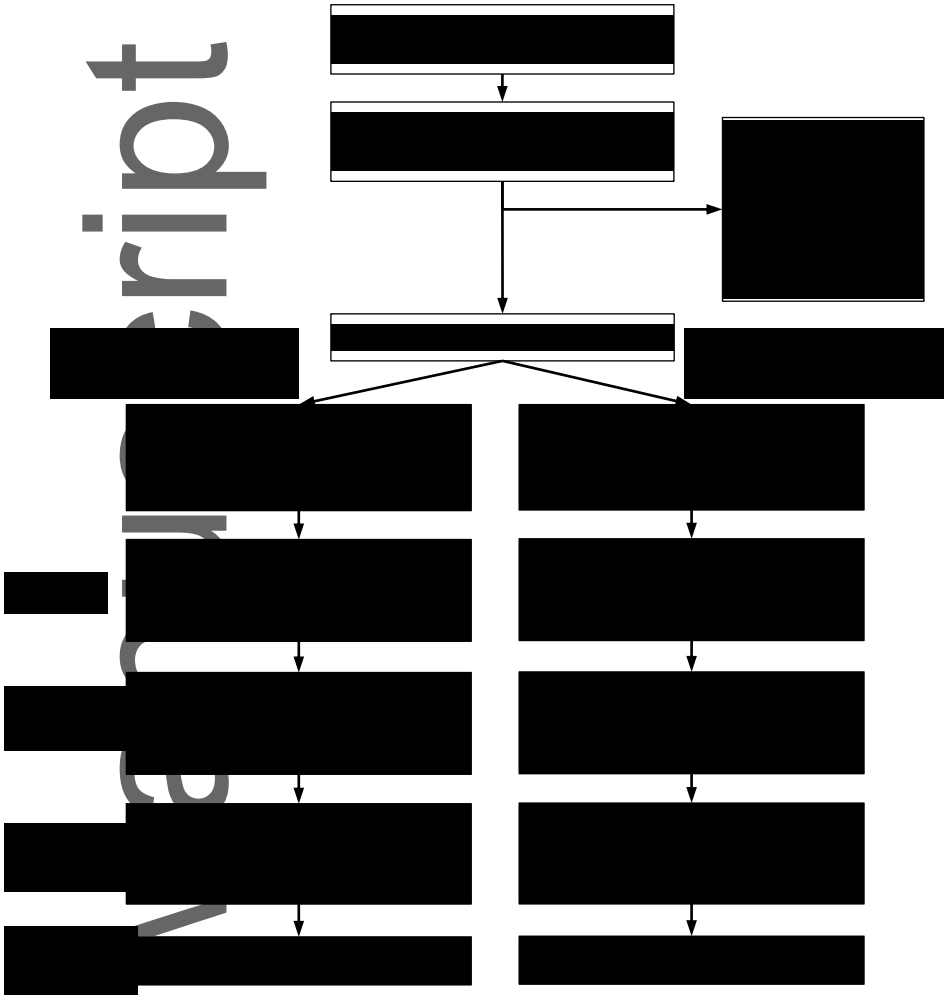

Figure 2

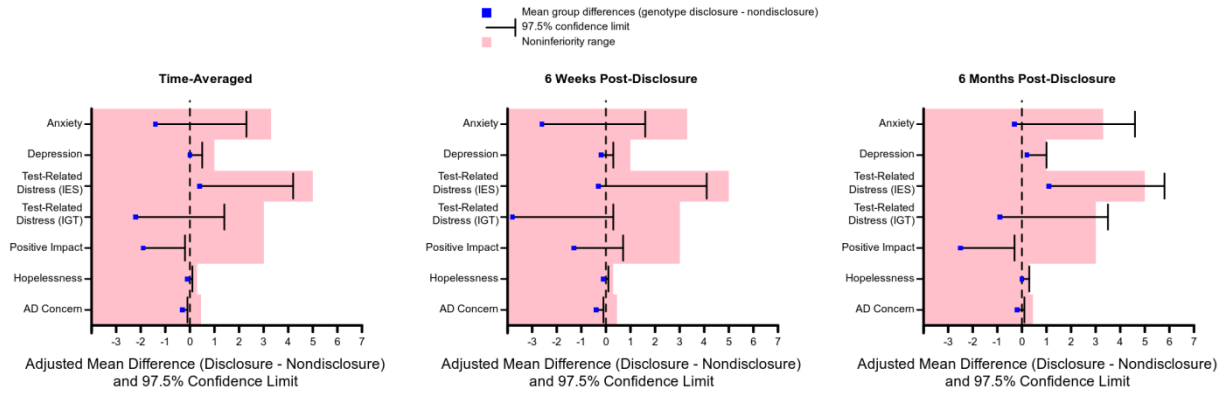

Figure 3

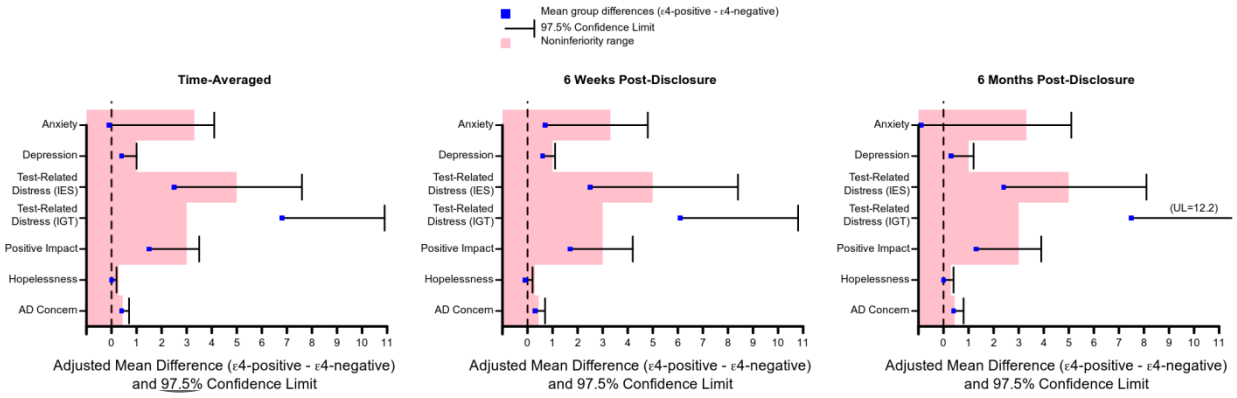

Table 1. Baseline characteristics of the 114 participants who attended risk disclosure sessions.

Characteristic: n (%), unless noted	Disclosure Arm (n=75)	Nondisclosure Arm (n=39)	
Age in years			
57-70	30 (40%)	14 (36%)	
71-77	19 (25%)	10 (26%)	
78-89	26 (35%)	15 (38%)	
Gender			
Female	39 (52%)	18 (46%)	
Male	36 (48%)	21 (54%)	
Self-identified race			
Black	11 (15%)	9 (23%)	
White	64 (85%)	30 (77%)	
Years of education, mean (SD)	16.2 (2.7)	16.4 (2.9)	
Median household income	$70-$99K	$50-69K	
Currently married	57 (76%)	20 (51%)	*
Has AD-affected family member	43 (59%)	17 (44%)	
ε4-positive	39 (52%)	17 (44%)	
MMSE score, mean (SD)	27.4 (1.9)	27.0 (2.4)	

Mood scale scores, mean (SD)		
Anxiety (range: 20-80)	36.5 (10.9)	36.3 (12.0)
Depression (range: 0-15)	2.1 (2.0)	2.6 (2.6)
Hopelessness (range: 0-4)	0.3 (0.6)	0.5 (0.8)
AD concern (range: 1-5)	3.7 (0.9)	3.6 (0.7)
Perceived risk of AD conversion (range: 0-100%), mean (SD)	34.9% (28.5%)	30.2% (24.2%)

* Difference between randomization arms at P value<.01

Table 2. Mean psychological outcome scores and standard errors, by randomization arm and time after risk disclosure sessions*

	Disclosure Arm (n=75)			Nondisclosure Arm (n=39)		
	Time-Averaged	6 Week	6 Months	Time-Averaged	6 Weeks	6 Months
Anxiety	35.6 (1.0)	35.6 (1.0)	35.6 (1.5)	37.0 (1.6)	38.2 (1.9)	35.8 (2.0)
Depression	1.9 (0.2)	1.8 (0.1)	1.9 (0.2)	1.9 (0.2)	2.0 (0.2)	1.7 (0.3)
Test-related distress (IES)	11.8 (1.3)	11.4 (1.5)	12.1 (1.5)	11.3 (1.4)	11.7 (1.7)	11.0 (1.9)
Test-related distress (IGT-AD)	10.0 (1.0)	10.0 (1.1)	10.1 (1.2)	12.3 (1.6)	13.8 (1.8)	11.0 (1.8)
Positive impact	9.3 (0.5)	9.2 (0.6)	9.4 (0.6)	11.1 (0.7)	10.4 (0.8)	11.9 (0.9)
Hopelessness	0.3 (0.1)	0.3 (0.1)	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)
AD concern	3.3 (0.1)	3.2 (0.1)	3.4 (0.1)	3.6 (0.1)	3.6 (0.1)	3.6 (0.2)

* Scores were estimated using generalized estimating equations, with adjustment for demographic characteristics, disclosing clinician, and baseline values. Models for all outcomes used a log link and gamma distribution.

Table 3. Mean psychological outcome scores, by randomization arm, APOE status and time after risk disclosure sessions*

	Time-Averaged	6 Weeks Post-Discl	6 Months Post-Discl	Time-Averaged	6 Weeks Post-Discl	6 Months Post-Discl
Disclosure Arm	**APOE ε4-Positive (n=39)**			**APOE ε4-Negative (n=36)**		
Anxiety	35.6 (1.4)	36.0 (1.6)	35.1 (1.9)	35.7 (1.6)	35.3 (1.4)	36.1 (2.4)
Depression	2.1 (0.2)	2.1 (0.2)	2.1 (0.3)	1.7 (0.2)	1.5 (0.2)	1.8 (0.3)
Test-related distress (IES)	12.9 (1.8)	12.6 (1.9)	13.2 (2.0)	10.4 (1.9)	10.1 (2.3)	10.8 (2.1)
Test-related distress (IGT-AD)	13.5 (1.7)	13.1 (1.9)	13.8 (2.0)	6.7 (1.2)	7.0 (1.4)	6.4 (1.3)
Positive impact	10.0 (0.7)	10.0 (0.9)	10.0 (0.8)	8.5 (0.8)	8.3 (1.0)	8.7 (1.0)
Hopelessness	0.3 (0.1)	0.2 (0.1)	0.4 (0.1)	0.4 (0.1)	0.3 (0.1)	0.4 (0.1)
AD concern	3.4 (0.1)	3.3 (0.2)	3.6 (0.2)	3.1 (0.1)	3.0 (0.1)	3.1 (0.1)
Nondisclosure Arm	***APOE* ε4-Positive (n=17)**			***APOE* ε4-Negative (n=22)**		
Anxiety	37.9 (2.3)	37.9 (2.3)	37.9 (2.8)	36.1 (2.1)	38.3 (2.9)	34.1 (2.6)
Depression	1.8 (0.2)	1.9 (0.3)	1.7 (0.4)	1.9 (0.3)	2.1 (0.4)	1.7 (0.4)
Test-related distress (IES)	9.2 (1.9)	11.3 (2.4)	7.5 (1.9)	13.0 (2.1)	12.2 (2.4)	13.8 (2.8)

Test-related distress (IGT-AD)	9.7 (2.0)	11.0 (2.2)	8.6 (2.3)	14.1 (2.4)	15.8 (2.8)	12.5 (2.7)
Positive impact	10.6 (1.3)	10.2 (1.4)	11.0 (1.6)	11.6 (1.0)	10.6 (1.1)	12.6 (1.3)
Hopelessness	0.5 (0.1)	0.5 (0.2)	0.4 (0.2)	0.4 (0.2)	0.4 (0.2)	0.5 (0.2)
AD concern	3.4 (0.1)	3.5 (0.2)	3.4 (0.2)	3.7 (0.2)	3.7 (0.2)	3.8 (0.2)

* Scores were estimated using generalized estimating equations, with adjustment for demographic factors, disclosing clinician, and baseline values. Models for all outcomes used a log link and gamma distribution.