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Featured Article

# A randomized noninferiority trial of condensed protocols for genetic risk disclosure of Alzheimer's disease

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**Abstract**

**Introduction:** Conventional multisession genetic counseling is currently recommended when disclosing apolipoprotein E (*APOE*) genotype for the risk of Alzheimer's disease (AD) in cognitively normal individuals. The objective of this study was to evaluate the safety of brief disclosure protocols for disclosing *APOE* genotype for the risk of AD.

**Methods:** A randomized, multicenter noninferiority trial was conducted at four sites. Participants were asymptomatic adults having a first-degree relative with AD. A standard disclosure protocol by genetic counselors (SP-GC) was compared with condensed protocols, with disclosures by genetic counselors (CP-GC) and by physicians (CP-MD). Preplanned co-primary outcomes were anxiety and depression scales 12 months after disclosure.

**Results:** Three hundred and forty-three adults (mean age 58.3, range 33–86 years, 71% female, 23% African American) were randomly assigned to the SP-GC protocol (n = 115), CP-GC protocol (n = 116), or CP-MD protocol (n = 112). Mean postdisclosure scores on all outcomes were well below cut-offs for clinical concern across protocols. Comparing CP-GC with SP-GC, the 97.5% upper confidence limits at 12 months after disclosure on co-primary outcomes of anxiety and depression ranged from a difference of 1.2 to 2.0 in means (all $P < .001$ on noninferiority tests), establishing noninferiority for condensed protocols. Results were similar between European Americans and African Americans.

**Conclusions:** These data support the safety of condensed protocols for *APOE* disclosure for those free of severe anxiety or depression who are actively seeking such information.



*Keywords:* Alzheimer; *APOE*; Genetics; Genomics; Risk assessment; Personalized medicine

[1]Additional members of the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study Group are listed at the end of the manuscript.

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## 1. Introduction

The ε4 allele of apolipoprotein E (*APOE*) is a common and robust risk factor for Alzheimer's disease (AD), carried by approximately 25% of the population. In the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study, we have utilized the model of disclosing *APOE* genotype for the risk of AD to explore translational questions associated with genetic risk disclosure. In a previous randomized controlled trial, we demonstrated that disclosing *APOE* genotypes with an extended counseling protocol was not associated with increased anxiety, depression, or distress [1]. The predisclosure counseling in that trial followed what were later published as official recommendations for the genetic risk assessment of AD, and that were based on Huntington Disease (HD) Society of America's Guidelines for Genetic Testing for Huntington Disease [2], a protocol that the recommendations called the "gold standard for genetic testing for adult onset conditions" [3]. Briefly, this protocol includes two pretest and one or more posttest genetic counseling sessions conducted in person and incorporates both neurologic and psychiatric evaluations. Sessions address the physical, psychological, social, and family history factors that may influence the decision-making process to ensure informed decision making about testing while minimizing the risks of adverse psychological outcomes [3].

In this report, we describe a separate trial in which all subjects received *APOE* disclosure, but were randomized into one protocol that followed the gold standard above, or into one of two protocols with highly condensed pretesting education and counseling. We hypothesized that subjects receiving the condensed protocols with disclosure from a genetic counselor (CP-GC) would show no greater anxiety or depression than subjects receiving the standard protocol 1 year after disclosure.

## 2. Methods

### 2.1. Study population and instruments

We recruited cognitively normal adult first-degree relatives (FDRs) of patients with AD through mailings to research registries, referrals from collaborating physicians, advertisements in local newspapers, and community outreach at senior centers and nursing homes. We excluded individuals with two or more affected FDRs and individuals from families where the average AD onset age was under 60 years. We screened out individuals who demonstrated potential memory problems by scoring lower than an education-adjusted 87 on the Modified Mini-Mental State Examination [4] and individuals with very severe anxiety and depression, as defined below. We selected European Americans or African Americans for enrollment because we had sufficient data to create ethnicity-specific risk models for these groups that incorporated *APOE* genotype [5]. Given ambiguous data about the relationship between *APOE* and AD for other ethnicities [6,7], however, we excluded other populations.

The co-primary outcomes were validated self-report scales of anxiety and depression at 12 months after disclosure. We measured anxiety using the 21-item Beck Anxiety Inventory (BAI) [8] and depression using the 20-item Center for Epidemiological Studies-Depression Scale (CES-D) [9]. BAI scores can range from 0 to 63, with scores greater than 15 indicating moderate anxiety and scores greater than 25 indicating severe anxiety. CES-D scores can range from 0 to 60, with scores 16 or greater indicating moderate depression and scores greater than 26 indicating severe depression [10]. Test-related distress at 12 months after disclosure served as a secondary outcome, measured using the Impact of Event Scale (IES) [11], a 15-item self-report instrument commonly used in genetic disclosure research [12]. The IES assessed the frequency of intrusive and avoidance thoughts related to the genetic risk assessment over the past week, with scores of 0–5 on individual items summed to create an overall score (range 0–75, scores 20 or above indicating significant distress). Because the IES measures distress specific to genetic risk disclosure, it was administered only after testing. We also evaluated secondary outcomes of BAI, CES-D, and IES scores at 6 weeks and 6 months after the disclosure of genetic risk information.

### 2.2. Study design

As described more fully in prior publications [1,13], the multidisciplinary REVEAL Study group designed the study protocol and risk disclosure procedures, including, for this trial, specific risk curves for African American subjects [5]. The study was designed as a noninferiority trial, despite inherent limitations of this approach [14], because the goal of the study was to develop a protocol that markedly reduced clinical service demands rather than one that improved outcomes that had already been shown to be safe [1]. The study was conducted at sites in academic medical centers in Boston, Cleveland, New York, and Washington, DC. An independent external Ethics and Safety Board (ESB), and institutional review boards at each study site, oversaw the protocol and consent development. Subjects provided informed consent by telephone at the time of study enrollment, then again in writing before the blood draw for genotyping. The overall design of the study is shown in Fig. 1.

Following an initial phone interview, subjects were block randomized equally into one of three treatment arms, within strata defined by site, age ($<60$ vs $\geq 60$), race, and gender. In the reference protocol, pretest education and counseling took place with a genetic counselor (the SP-GC arm) [2]. Participants attended a semistructured 35 minute in-person education session with a genetic