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The impact of the availability of prevention studies on the desire to undergo predictive testing in persons at risk for autosomal dominant Alzheimer's disease ☆

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ABSTRACT

Persons at risk for autosomal dominant neurodegenerative diseases provide the opportunity to efficiently test preventive interventions. Only a minority of such persons, however, choose to undergo revealing genetic testing, presenting a challenge to enrollment. Thirty-four preclinical Latinos ($n = 26$) and non-Latinos at risk for familial Alzheimer's disease (FAD) unaware of their genetic status were administered a questionnaire exploring their interest in undergoing revealing genetic testing at baseline and in the context of eligibility for four prevention trials of increasing invasiveness. Forty-four percent of subjects expressed a baseline interest in undergoing revealing testing which increased to 85% in order to be eligible for a study of an oral drug "felt to be very safe." If there were a 50% chance of receiving placebo, this number dropped to 62% ($p = 0.02$). Among those not interested in a study involving a 50% chance of receiving placebo, a range of 5% to 40% chance of receiving placebo was given as acceptable. For more invasive studies, living in the United States (as opposed to Mexico) positively influenced the likelihood of participating. Our data suggest that clinical trial designs in which persons must confront their genetic status prior to enrollment are feasible. Study designs to minimize the likelihood of being placed on placebo or provide the eventual administration of the drug through open-label extensions should be considered.

1. Introduction

Dementia affects approximately twenty-four million people worldwide [1], with Alzheimer disease (AD) comprising 60–70% of all cases [2]. The clinical manifestations of AD are preceded by a 15- to 20-year period of silent pathology that includes accumulation of fibrillar beta amyloid and development of neurofibrillary tangles and ultimately results in synaptic and neuronal loss that produce cognitive impairment [3]. Because reversing the neuronal loss caused by AD is difficult and may ultimately prove impossible, there are increased efforts at identifying interventions to prevent the clinical manifestation of AD. Delaying onset of AD dementia by 2 years would lead to 2

Abbreviations: AD, Alzheimer disease; FAD, early-onset familial Alzheimer's disease; HD, Huntington disease; FTD, frontotemporal dementia

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million fewer cases in the United States after 50 years [4]. AD prevention studies, however, present several challenges. For prevention trials to be informative, sufficient numbers of participants must develop dementia to power comparisons of intervention to placebo. Prevention trials may therefore "enrich" the study population for persons more likely to develop AD (e.g., with a family history of the disorder [5,6]), but even so, they must recruit several thousand participants and follow them for many years [7]. Studying a population in whom the disease can be more reliably predicted would greatly augment the performance of prevention studies.

Early-onset familial AD (FAD) is a rare, fully penetrant, autosomal dominant form of AD [8] due to mutations in the *PSEN1*, *APP*, or *PSEN2* genes. The typical age of onset is in the mid-30s to late-50s [5] and can be highly consistent within mutation-carrying kindreds [9]. Although affected individuals or pre-symptomatic individuals at risk for a known familial mutation can undergo genetic testing, such testing is not currently widely offered, at least in part due to the unavailability of effective interventions [10].

One way to perform efficient prevention trials in AD is to enroll presymptomatic FAD mutation carriers. The number of such individuals who decide to undergo predictive, presymptomatic testing, however, is relatively low [11]. In one study, less than 10% of eligible persons from families with known pathogenic mutations for frontotemporal dementia (FTD) or FAD decided to undergo predictive testing [12]. As persons at risk for FAD do not typically desire to undergo genetic testing, one cannot identify appropriate subjects in whom exposure to a potentially toxic treatment is justified [11]. Additionally, the risk of being placed into the placebo arm of a controlled study may be too high for an individual to risk learning that they will develop the disease [11]. The decision to undergo genetic testing prior to such trial participation is therefore a difficult one and performing prevention studies ethically such that subjects are truly informed regarding the scope of risks and benefits presents challenges [11].

The design of prevention trials in FAD will be improved by enhanced understanding of protocol features that affect at-risk persons' desire to undergo genetic testing. We examined what aspects of study design are important to individuals at risk for FAD in determining whether they would be willing to undergo genetic testing, learn the results, and participate in the study. We also explored the effect of potential assignment to placebo and participants' reasoning behind their decisions.

2. Materials and methods

2.1. Participants

Thirty-four participants of a comprehensive study of pre- and symptomatic FAD being performed at UCLA completed a questionnaire exploring their interest in undergoing genetic testing in multiple contexts. All participants were at 50% risk of inheriting FAD due to known mutations in *PSEN1*, *APP*, or *PSEN2* by virtue of being the first-degree relative of someone affected by the illness in a family shown to carry such a mutation. This observational study seeks to characterize cognitive, behavioral, imaging (via positron emission tomography and multi-modal magnetic resonance imaging), and biochemical (plasma and cerebrospinal fluid) changes occurring during the pre- and symptomatic stages of FAD. In this study, participants undergo genetic testing for the mutation for which they are at risk but in the context of the study are not told the results. All participants are offered clinical testing outside the study at no expense to them. Only non-demented participants (Clinical Dementia Rating Scale [13] score less than 1) who were unaware of their mutation status were administered the questionnaire. The population included Mexicans living in Mexico ($n = 10$), Mexican Americans ($n = 9$), other Latinos residing in the United States ($n = 7$), and non-Latino Caucasians residing in the United States ($n = 8$). The questionnaire was created in both English and Spanish, and subjects completed it in the language in which they were most proficient. Questionnaires were completed during a research visit or at home and were returned by mail. All subjects sent the questionnaire by mail ($n = 10$) or asked to complete the questionnaire during the research visit ($n = 24$) completed the questionnaire. No additional incentives were provided to subjects to complete this sub-study. All study procedures were approved by the UCLA Institutional Review Board.

2.2. Questionnaire

A written questionnaire collected background demographic information and explored at-risk persons' baseline attitudes about genetic testing and clinical trial participation. Willingness to undergo genetic testing in the context of eligibility for four hypothetical prevention trials of "promising interventions" of increasing level of invasiveness was then explored. These hypothetical studies were modeled after currently ongoing trials in AD. In each of the four hypothetical scenarios, it was explicitly explained that subjects would have to learn their genetic status and only mutation carriers would be eligible to participate. Subjects read that "In such studies, it may be necessary to assign some subjects to receive placebo (an inert, inactive intervention, or 'sugar pill') in order to demonstrate that persons receiving the active drug develop AD at a lower rate."

The questionnaire was initially written in English and then translated into Spanish by a fluently bilingual person of Puerto Rican origin (author LDM). It was then back-translated to English by a bilingual native of Colombia working as a neuropsychologist in Mexico (author YA-R). Differences in the back-translated version were discussed and edits made to reconcile discrepancies.

2.2.1. Hypothetical study 1

Study 1 was described as follows: "A drug company is looking for participants for a research study for a medication with substantial promise in preventing AD. The medication has been studied extensively in animals and humans and is felt to be very safe. The treatment is a pill, taken twice a day that would most likely be required for the rest of your life."

2.2.2. Hypothetical study 2

Study 2 was described as follows: "A research study is looking at the effects of a vaccination that is given once per year for the rest of your life and hopefully will provide protection from the development of AD. Earlier studies of this vaccination in people have shown a 5% risk of brain