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Using Direct-to-Consumer Genetic Testing Results to Accelerate Alzheimer's Disease Clinical Trial Recruitment

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Abstract

Introduction—The apolipoprotein E (APOE) gene is the strongest known genetic risk factor for sporadic Alzheimer's disease (AD). APOE can be used as an enrichment strategy or inclusion criterion for AD prevention trials. Personal genomics companies market direct-to-consumer (DTC) genetic tests, including APOE. We assessed DTC APOE testing usage among enrollees of the UC Irvine Consent-to-Contact Registry, an online recruitment registry, and attitudes toward using this information in clinical trial recruitment.

Methods—We emailed links to an electronic survey to registry enrollees age 50 years or older. We assessed participants' use of DTC services, willingness to learn APOE status, and willingness to share genetic information. Logistic regression models assessed relationships between DTC testing usage and demographic characteristics, as well as with willingness to share results to assist trial recruitment.

Results—Among 1,312 responders (57% response rate), few (7%) had used DTC testing for APOE. Non-Hispanic Asian enrollees were 93% less likely to have used DTC testing, compared to non-Hispanic whites (95% CI: [0.01, 0.67]). Willingness to share APOE information for study recruitment was >90% for both users and non-users.

Conclusions—Matching participants to trials based on DTC APOE information may be an effective way to streamline AD prevention trial recruitment.

Keywords

Alzheimer's disease; APOE; genetic testing; recruitment registry; preclinical

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INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease and the most common cause of dementia[1]. It has been more than 15 years since the Food and Drug Administration (FDA) last approved a new molecular entity as a treatment for AD, and no treatment has been demonstrated to curb disease progression[2]. Disease slowing treatments, if initiated in advance of symptom onset, could dramatically reduce the public health burden of AD[1]. Thus, developing therapies that delay or prevent AD onset is a research priority[3].

Clinical trials to test potentially preventative therapies are made more efficient by enrolling individuals who are at increased risk of developing AD. Varying approaches can be used to enrich AD prevention trials, including enrollment criteria that incorporate age[4], family history of disease[5], biomarkers[6], genetics[7], and composite risk factor scoring systems[8]. In all cases, the goal of enrichment is to increase the proportion of participants who demonstrate progression on the primary outcome of the trial (for example, cognitive decline or new onset dementia).

The apolipoprotein E (APOE) gene is currently the best-described and strongest known genetic risk factor for sporadic AD[9,10]. Three common alleles of the APOE gene are known – ε2, ε3, and ε4. Carrying one or two ε4 alleles may increase the odds of developing AD as much as three- and 12-fold, respectively[9,10], though estimated relative risks vary among differing study populations[11]. Cognitively unimpaired carriers of APOE ε4 are also at increased risk to demonstrate AD-related brain changes[12], such as evidence of fibrillar amyloid beta (Aβ) on positron emission tomography (PET) scans with amyloid-specific ligands[13].

APOE ε4 carriage has been used as an inclusion criterion for AD prevention trials. For example, the Alzheimer's Prevention Initiative (API) Generation Program enrolled participants ages 60 to 75 with one or two ε4 alleles to participate in two phase 2/3 trials of amyloid-targeting therapies[7,14]. Alternatively, prescreening for APOE may help investigators identify participants for preclinical AD trials that enroll based on amyloid PET criteria[15]. These practices may require Clinical Laboratory Improvement Amendments (CLIA) certification[16] and systematic methods of disclosing APOE genotypes[17], producing added burden for trial investigators. But many potential participants may already know their APOE gene status.

Personal genomics companies, such as 23andMe, now market direct-to-consumer (DTC) health-related genetic tests, including APOE. For a fee, consumers can register online to receive testing kits and learn their APOE results (as well as seven other disease-related risk genes through 23andMe) through electronic disclosure. DTC providers first began offering APOE testing in 2013. Although U.S. regulators mandated a hiatus in DTC APOE testing, the FDA approved 23andMe and other DTC companies that demonstrated the clinical validity of genetic testing platforms in 2017[18,19].

Only about one-third of consumers share their personal DTC genetic testing results with their healthcare provider[20]. Less is known about consumers' attitudes toward disclosing their APOE results to researchers. One setting in which this information might be particularly

informative, as well as easy to capture, is in the setting of large online recruitment registries[14,21]. Using DTC APOE results in registries may aid as an enrichment tactic for recruiting to preclinical trials, even in the instances where CLIA certified testing is still required to verify self-reported results. A critical consideration in such practices, however, is the potential to perpetuate disparities in participation rates. African Americans and Hispanic/Latinos are dramatically underrepresented in AD clinical trials[22] and, if use of DTC services is lower in these groups[23], then such enrichment could further limit their representation in trials.

In this study, we assessed use of DTC APOE genetic testing among enrollees in a local online recruitment registry. We sought to quantify the relationship between enrollee characteristics and DTC APOE genetic testing use. We hypothesized that non-white participants would be less likely to have used DTC testing for learning APOE status than their non-Hispanic (NH) white counterparts. We also sought to characterize DTC users' and non-users' attitudes toward the utilization of APOE genetic testing results for clinical trial recruitment.

METHODS

Participants and Study Design

We sent links to an online survey via email to 2,306 enrollees in the University of California, Irvine Consent-to-Contact (UCI C2C) Registry, a local online recruitment registry[24]. To mirror current preclinical AD trial enrollment criteria, we invited all C2C enrollees age 50 years and older to participate. No exclusion criteria were applied. All invited participants were entered into a drawing for a $100 gift card, regardless of survey completion. Participants were then asked to watch a 5-minute video (https://www.youtube.com/watch?v=mVIYVx3ZvCc&feature=youtu.be) of a researcher and/or read an educational primer on DTC genetic testing, AD, and APOE. The primer outlined the role of APOE in AD risk and the potential risks and benefits of DTC APOE testing. After the primer, the online survey was administered and subsequent data were managed using Research Electronic Data Capture (REDCap)[25].

Ethics Statement

All participants in this survey had previously consented to enroll in the C2C Registry. Participants were emailed an invitation to enroll in the survey, which also served as a unique study information sheet. No additional signed informed consent was collected. Instead, completion of the survey was deemed demonstration of consent to participate. This study was approved by the UCI Institutional Review Board (IRB).

Measurements/Outcomes

The survey used branching logic to adjust participant queries based on preliminary responses (see Figure 1). We asked whether participants were aware of DTC genetic testing companies prior to taking the survey and if they knew their APOE status. If participants knew their status, we asked how they learned it (*23andMe*; *Another direct-to-consumer genetic testing company*; *Healthcare provider*; *Other*; *Unsure*); whether they were an APOE ε4 carrier (*Yes*;

No; *Rather not answer*); whether they would be willing to include that information in their C2C Registry profile; and whether they would want the operators of the C2C Registry to use that information to invite them to future studies. If participants answered “no” or “unsure” to sharing APOE status in their registry profile, we asked why.

If participants reported not knowing their APOE status, we asked their level of interest in learning it (*Not interested*; *Somewhat interested*; *Very interested*; *Unsure*); whether they would be willing to include that information in their C2C Registry profile were they to know it; and whether they would want the operators of the C2C Registry to use that information to invite them to future studies. If participants answered “no” or “unsure” to sharing the information in their registry profile, we asked why. If participants indicated that they would not be interested in learning their APOE status, we also asked why.

When we asked participants why they would not want to learn their APOE status or have their status included in their registry profile, we presented a range of pre-determined responses of which participants could select multiple responses (*It is a private matter*; *I have concerns about confidentiality/implications to my career*; *I have concerns about confidentiality/implications to my insurance*; *I have concerns about confidentiality/implications to my healthcare*; *Other*). If participants selected “Other”, we asked them to describe their concerns in their own words.

Statistical Analyses

Survey responses were linked to demographic information available in the C2C Registry. For analysis purposes, participants who selected their race as Native American/Alaska Native, Native Hawaiian/Pacific Islander, Other, a combination of three or more races, or selected “refused to answer” for either the race or ethnicity were categorized as Other. Specific ethnoracial categories (NH white, NH Black, NH Asian, Hispanic white, Other) were created by combining race and ethnicity information. In the primary analysis, we used a logistic regression model to assess the relationship between previous use of DTC APOE genetic testing with ethnoracial group, using NH white as the reference group. Participant age, years of education, and sex were adjusted for as potential confounding variables, where age and education were treated as continuous. In the secondary analysis, we used logistic regression to model the relationship between previous use of DTC APOE testing with the willingness to share APOE results for clinical research recruitment. Potential confounding variables similar to those in the primary analysis were adjusted for in the secondary model, as well as APOE carrier status and ethnoracial group, using NH white as the reference group. No multiple testing corrections were performed. We quantified uncertainty in all analyses with 95% confidence intervals. Statistical analyses were conducted using R version 3.4.1[26]. Two investigators independently reviewed open-ended responses for themes and a third examined responses for which there was disagreement. No formal statistics were used in qualitative analyses.

RESULTS

Participants

Table 1. describes the demographics of the survey participants, stratified by DTC APOE genetic testing use. From the 2,306 registrants contacted, 1,312 valid responses were recorded (response rate 57%). Overall, the sample was mostly female (64%; n=840) and NH white (89%; n=1,055). Survey participants' demographics did not appear to differ from those of survey non-responders. Though not statistically significant, users of DTC APOE genetic testing were observed to be more often NH white (90% vs. 87%), slightly younger, and more often had a family history of AD, compared to non-users.

Knowledge and Use of DTC Genetic Testing

Most survey participants were aware of DTC genetic testing (77%; n=1,015) but few had used it to learn their APOE genotype (7%; n=91). Fewer still had learned their APOE genotype through a healthcare provider (0.8%; n=10) or some other means (0.3%; n=4). Of those who did not know or were unsure of their APOE status (n=1,198), 81% were "Somewhat interested" or "Very interested" in learning their status (n=969; Figure 2).

A logistic regression model assessing the relationship of participant characteristics with previous DTC APOE testing use found that C2C enrollees who identified as NH Asian had estimated odds of being users of DTC APOE genetic tests that were 93% lower than NH whites (OR: 0.07; 95% CI: [0.01, 0.67]). The only other characteristic that demonstrated a significant association was age, where an additional year of age was associated with 8% decrease in the odds of being a DTC APOE user (OR: 0.92; 95% CI: [0.85, 1.00]; Figure 3).

Willingness to Allow Researchers to Use Genetic Information

Among actual DTC testing users, 97% (n=84) were willing to include their APOE information in the C2C Registry and 92% (n=77/84) of those willing to include the information in the Registry were willing to have their information used by operators of the registry to match them to studies. More than 86% of those who had not used DTC APOE genetic testing were hypothetically willing to include their APOE information in the C2C Registry (n=852) and 96% of those willing to include the information in the Registry would be willing to allow researchers to use that information to match them to studies (n=822/852).

We observed no difference in willingness to allow researchers to use APOE status to match participants to studies between those who had and had not used DTC genetic testing (OR: 1.15; 95% CI: [0.10, 13.54]; Figure 4). Similarly, no difference was observed between DTC users who were and were not APOE ε4 carriers (OR: 3.36; 95% CI: [0.34, 32.85]).

Reluctance to Share Genetic Information

One hundred thirty-four (10%) participants indicated that they would be unwilling to share their APOE results in their registry profile, of which 3 (2%) had used DTC genetic testing to learn their APOE status and 10 (8%) identified as NH Asian. Among these participants, approximately half were concerned about implications to their insurance (48%; n=64) and implications to their healthcare (46%; n=62). One-third indicated they considered APOE

genotype results a private matter (34%; n=45). Fewer participants were concerned about career implications (14%; n=19), or specified their own reason (10%; n=14; see Table, Supplemental Digital Content 1).

DISCUSSION

These are among the first findings to examine research participants' use of DTC genetic testing and their attitudes toward disclosing these results with researchers. Our results suggest that enrollees in recruitment registries may be open to sharing APOE genetic test results obtained through DTC services with investigators to accelerate research recruitment, including recruitment to AD prevention trials. Though relatively few (<10%) participants in this study had actually undergone DTC genetic testing, most registry enrollees indicated that they would want to provide their results to investigators for the purpose of better matching them to research studies. These results may be instructive to investigators operating recruitment registries or recruiting from them. Registries may consider systematically asking whether participants have used DTC testing and what results enrollees are willing to share to facilitate future recruitment.

While matching potential participants to studies via DTC genetic test results may hold potential for accelerating AD prevention trial recruitment, it is unclear whether this tactic could enrich study populations in other important ways, such as diversifying the race and ethnicity of participants. We found that among relatively few non-white enrollees in this registry, fewer NH Asians and Hispanic whites had undergone DTC APOE testing. This aligns with previous studies of DTC genetic testing awareness[23,27], though it is also notable that the overall use of DTC APOE services in our registry was lower than that observed previously in a survey of a large healthcare system[28]. Lower rates of DTC use among underrepresented racial and ethnic groups could have ramifications to trial recruitment. Registry enrollees who already know their APOE ε4 carrier status represent motivated, available, and likely to be eligible potential participants for preclinical AD trials[15]. Exclusive or prioritized recruitment of these individuals could exacerbate already troubling disparities in AD trial participation[22]. Trial investigators recruiting from registries that track DTC genetic testing use and results will need to carefully balance overall recruitment rate goals with goals to ensure diverse participation.

The practice of APOE testing and disclosure in the research setting is becoming more frequent[15,29] and many participants indicate that they desire this information[30,31]. A 2011 joint statement by the Society of Genetic Counselors and American College of Medical Genetics recommends developing strict protocols for the disclosure of personal genetic test results[17]. Previous research has shown that disclosing APOE carrier status to cognitively unimpaired individuals with a family history of AD does not cause clinical depression or anxiety when the disclosure process includes in-person education as well as pre-test and post-disclosure counseling[32]. While performing pre-disclosure education via brochure, rather than in-person, did not impact the safety of disclosure in one study[33], telephone disclosure of results failed to demonstrate non-inferiority for APOE ε4 carriers in another study[34]. Given especially that disclosure of APOE results via DTC genetic tests is often conducted via email or links to online health reports, those who disclose their DTC APOE

results in registries may have additional expectations. Some may expect that disclosure will gain them access to answers for questions they still have about the meaning of their results, counseling on their probability of developing AD, or immediate matching into certain types of trials. Registry operators should consider such possibilities and carefully outline the opportunities and risks that accompany disclosure of previous DTC results.

At least some registry enrollees who disclose their DTC APOE genetic test results may misremember or misunderstand the results provided by the DTC genetic test company[35]. Alternatively, the DTC genetic test results themselves may disagree with other CLIA certified lab results. Thus, recruiting from registries based on DTC results may require several operational considerations, including the need for re-testing to validate self-reported results and consideration of potentially difficult communications with participants for whom discordant results are identified. Further research is needed to elucidate the true impact of inquiring about DTC testing on actual trial enrollment rates.

Interestingly, in this study, willingness to share APOE results was not different in those who had undergone actual testing compared to those who answered hypothetically. This observation may support the validity of responses to hypothetical scenarios, as well as previous research that found concerns about healthcare discrimination did not increase after compared to before learning APOE results[36].

No professional organization recommends APOE testing for any group of patients[17,37–39]. This consistency among guidelines and recommendations emphasizes the lack of clinical implications for APOE, in either symptomatic or asymptomatic populations at risk for AD. Additionally, though the 2008 U.S. Genetic Information Nondiscrimination Act (GINA) protects individuals from discrimination in health insurance and employment based on genetic testing results, the law is not comprehensive. For example, it does not protect against discrimination by long term care (LTC) insurers. This exemption is notable in the case of APOE genetic testing, as there are several examples of individuals using knowledge of their APOE genotype to inform LTC insurance decisions (e.g., purchasing LTC insurance after learning they are an APOE ε4 carrier[40]). Approximately 10% of participants in this study expressed reservations about sharing their real or hypothetical genetic results, with primary concerns being the potential negative implications to insurance or healthcare. Though our informational video and other materials briefly addressed these concerns, this information was delivered in a unidirectional manner and would not achieve the standards of research informed consent. Thus, it is possible that reservations would have been expressed at higher rates in this study with more thorough education. Similarly, it may be necessary for registries (or investigators recruiting from registries) to provide education about APOE genotypes, its relation to AD risk, and individual rights and coverage under GINA before asking participants to disclose their DTC APOE results.

We note some other limitations to this work. The survey was sent to participants of a local recruitment registry. This population may have more favorable attitudes toward research (and potentially genetic testing) than the general public. Similarly, it is unclear how this sample might compare to participants in larger national recruitment registries, some of which have recruited people specifically interested in learning genetic or other AD risk

information[14,21]. Though we had a moderate sample size overall, specific groups were smaller, limiting precision. This is particularly notable for the racial and ethnic subgroups. Ongoing efforts in this registry, including translation to four non-English languages, aim to address this limitation to generalizability.

CONCLUSIONS

Matching potential participants to trials based on previous APOE genotype knowledge from DTC genetic tests may be an effective strategy to improve AD prevention trial recruitment. Further research is needed to optimize the manner in which this is done, to more fully understand the implications of sharing DTC results, and to assess the validity of self-reported DTC results.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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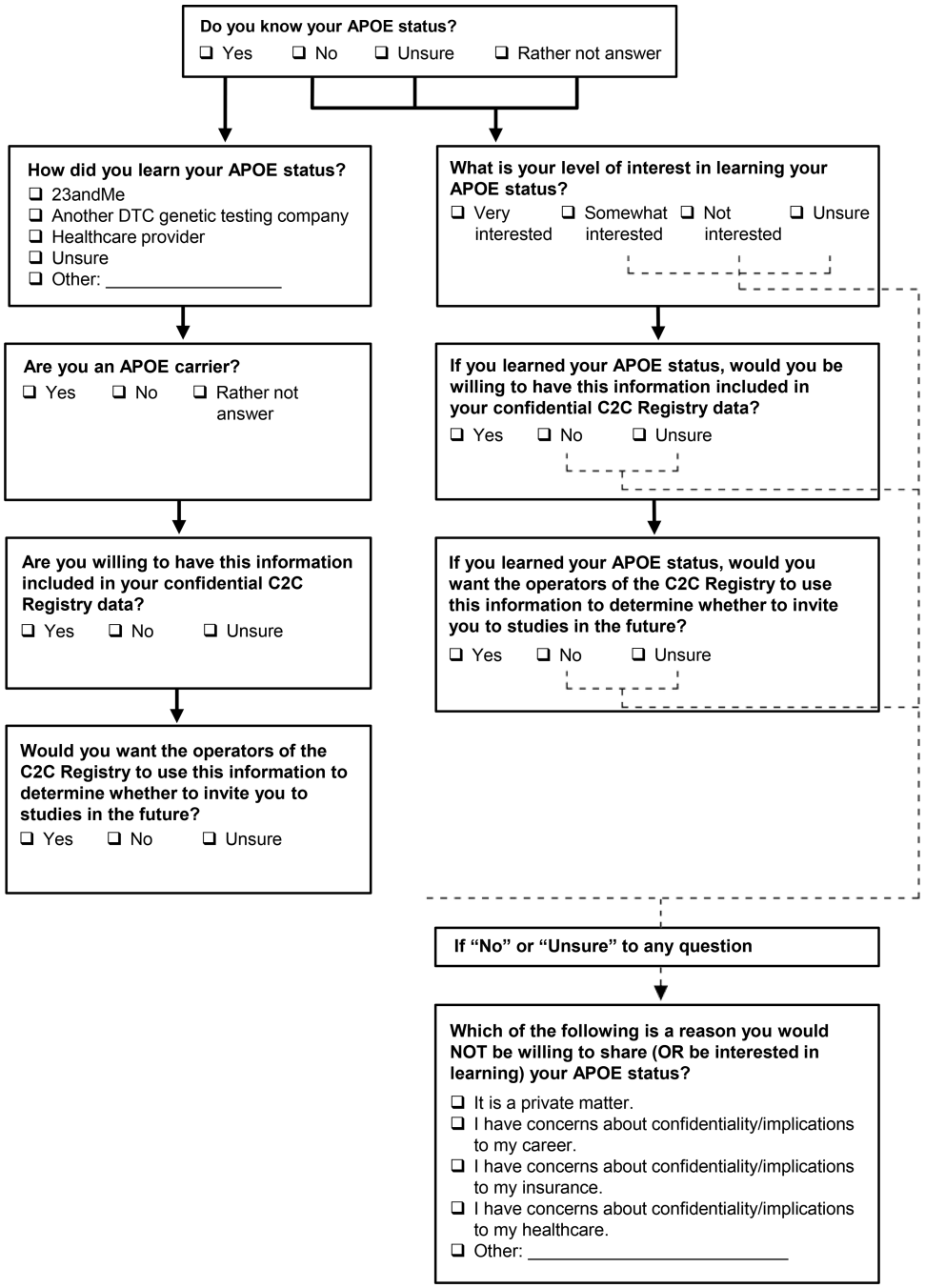

Figure 1:
Flowchart of survey logic.

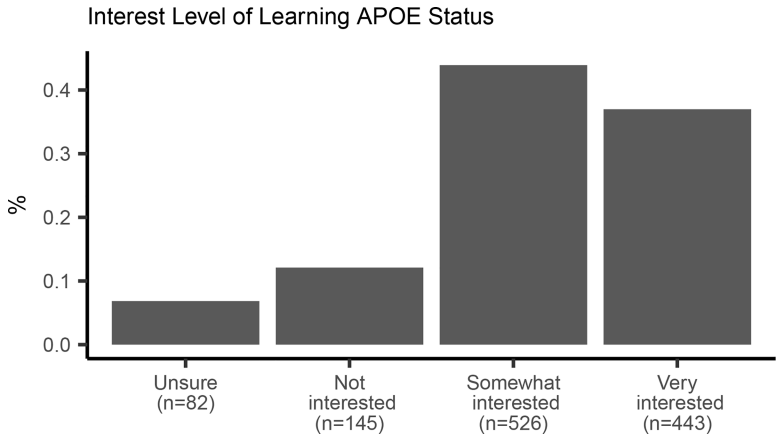

Figure 2:

Level of interest in learning APOE genotype, among those participants who do not know or were unsure about their APOE status.

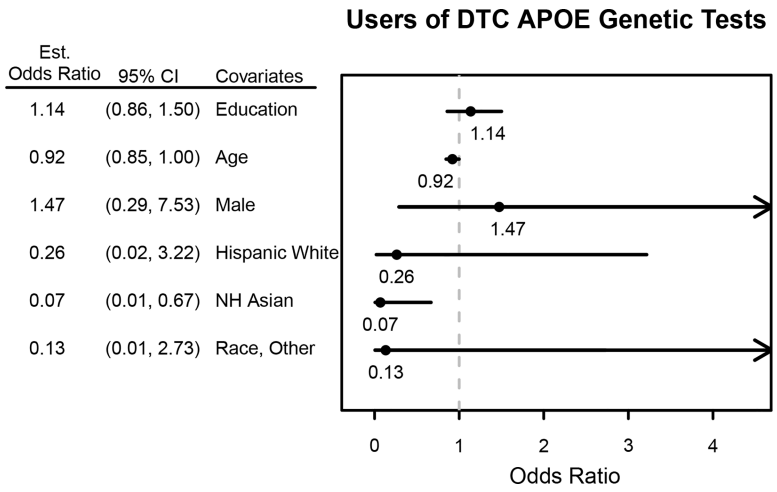

Figure 3: Estimated odds ratios for logistic regression model assessing the relationship of participant characteristics with previous DTC APOE testing use.

Solid points represent estimated odds ratios, solid lines represent estimated 95% confidence interval, and the dashed line represents an odds ratio of 1.

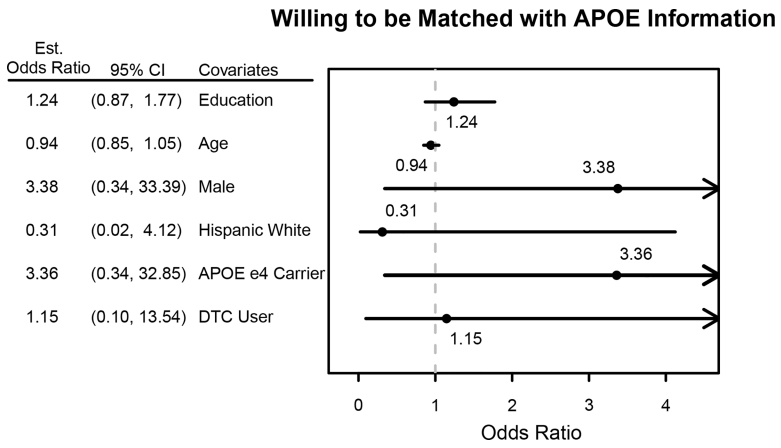

Figure 4: Estimated odds ratios for logistic regression model assessing the relationship between previous DTC APOE testing use and willingness to use APOE results for invitation to clinical studies.

Solid points represent estimated odds ratios, solid lines represent estimated 95% confidence interval, and the dashed line represents an odds ratio of 1.

Table 1.

Characteristics of survey participants. Continuous variables are summarized as means (sd), while discrete variables are summarized as counts (%).

	Survey Responders			Survey Non-responders (n=994)
	DTC APOE Genetic Testing Use		Total (n=1,312)	
	User (n=91)	Non-User (n=1,221)		
Sex				
Male	25 (27.5%)	447 (36.6%)	472 (36.0%)	405 (40.7%)
Female	66 (72.5%)	774 (63.4%)	840 (64.0%)	589 (59.3%)
Family History of AD	9 (9.9%)	53 (4.3%)	62 (4.7%)	49 (4.9%)
Age	63.54 (8.27)	66.78 (9.07)	66.56 (9.05)	66.02 (9.63)
Years of Education	17.45 (2.77)	16.54 (2.55)	16.60 (2.58)	16.30 (2.73)
Ethnoracial Group				
NH white	72 (90.0%)	983 (86.7%)	1,055 (86.9%)	723 (83.1%)
NH Black	0	12 (1.1%)	12 (1.0%)	11 (1.3%)
NH Asian	2 (2.5%)	50 (4.4%)	52 (4.3%)	50 (5.7%)
Hispanic White	3 (3.8%)	32 (2.8%)	35 (2.9%)	26 (3.0%)
Other	3 (3.8%)	57 (5.0%)	60 (4.9%)	60 (6.9%)
Missing	11 (12.1%)	87 (7.1%)	98 (7.5%)	124 (12.5%)
APOE4 Status				
Carrier	27 (31.0%)	5 (35.7%)	32 (34.8%)	-
Non-Carrier	60 (69.0%)	9 (64.3%)	69 (75.0%)	-