JAMA Neurology | Original Investigation

Digital Delivery of Apolipoprotein E Genotype and Phosphorylated Tau 217 Results
The eSMARTER Randomized Clinical Trial

Jessica B. Langbaum, PhD; Claire M. Erickson, PhD; Carolyn M. Langlois, MA; Elisabeth M. Wood, MS; Brian L. Egleston, PhD; Kristin Harkins, MPH; Rajia Mim, MS; Samantha John, BS; Camille Brown, MS; Sarah Brown, MS; Sarah Howe, MS; Cara Cacioppo, MS; Laura Eppelmann, MS; Jessica Enos, BS; Hayley Salata, BS; Diana De Santiago, BS; Emily A. Largent, PhD, JD, RN; Eric M. Reiman, MD; Marisa N. Denkinger, PhD; Nicholas J. Ashton, PhD; J. Scott Roberts, PhD; Jason Karlawish, MD; Angela R. Bradbury, MD

IMPORTANCE Patients are increasingly learning Alzheimer disease (AD) genetic and biomarker results through electronic health portals. Evaluation of alternative scalable delivery models for return of AD risk information is needed to best support patient knowledge and psychological well-being.

OBJECTIVE To determine whether a digital platform is comparable to clinician-mediated telehealth sessions for returning apolipoprotein E (*APOE*) genotype and plasma phosphorylated tau 217 (p-tau217) results on outcomes of knowledge and psychological well-being.

DESIGN, SETTING, AND PARTICIPANTS The Evaluation of Self-Mediated Alternatives for Risk Testing Education and Return of Results (eSMARTER) study was a noninferiority trial of a digital platform compared to clinician-mediated return of *APOE* genotype and optional p-tau217 results. Enrollment was conducted October 2024 through February 2025. Follow-up was completed November 2025. This was a decentralized, fully remote trial taking place across the contiguous US. Eligible participants were aged 60 to 80 years and had previously undergone *APOE* genotyping (without disclosure) via GeneMatch, passed psychological screening, had internet access, and could speak English. Of the 13 033 people invited by GeneMatch, 2052 accepted, and 813 were assessed for eligibility. Of 666 randomized, 651 were ultimately included.

INTERVENTIONS Participants were randomized, 2:1, to the eSMARTER digital platform or study clinician-mediated return of *APOE* genotype. Following the 6-month post-*APOE* assessment, participants were offered optional p-tau217 disclosure via the same randomized modality.

MAIN OUTCOMES AND MEASURES Primary outcomes at 1 to 7 days following *APOE* disclosure included changes in anxiety, disease-specific distress, and AD-related knowledge within a priori noninferiority margins.

RESULTS A total of 674 persons were eligible and provided demographic information. Of these, 651 participants had been randomized to study clinician–mediated (n = 216) or digital disclosure (n = 435) and completed *APOE* disclosure (mean [SD] age, 68 [4.7] years; 439 [67%] female; mean [SD] telephone Montreal Cognitive Assessment score, 19 [2]; 66 [10%] APOE4 homozygotes, 377 [58%] heterozygotes, and 208 [32%] noncarriers) A total of 604 participants completed the study; 500 completed optional p-tau217 disclosure. Baseline characteristics were balanced across groups. At 1 to 7 days following *APOE* disclosure, scores on AD-related knowledge, Patient-Reported Outcomes Measurement Information System Anxiety T-score, and disease-specific distress measures met noninferiority.

CONCLUSIONS AND RELEVANCE Return of *APOE* genotype by the eSMARTER digital platform is noninferior to study clinician-mediated telehealth disclosure. No significant between-group differences were found following return of p-tau217 results. Together, these results suggest that this digital platform may provide an evidence-based scalable approach for returning AD genetic and biomarker results.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT06459583

JAMA Neurol. doi:10.1001/jamaneurol.2026.4279
Published online November 18, 2026.

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Jessica B. Langbaum, PhD, Banner Alzheimer's Institute, 901 E Willetta St, Phoenix, AZ 85006 (jessica.langbaum@bannerhealth.com).

Downloaded from jamanetwork.com by guest on 11/21/2026

The 21st Century Cures Act mandates the immediate return of most medical test results to patients in the US, including Alzheimer disease (AD) genetic and biomarker results.[1] Consequently, patients can view test results in their electronic health portal before speaking with their health care professional. Although prior studies demonstrate that returning apolipoprotein E (*APOE*) genotype and brain amyloid neuroimaging results can be conducted in a generally safe and well-tolerated manner,[2-13] these all relied on clinicians to conduct the disclosure visits, either in person or via telehealth.[14] This limits the clinical translatability of these prior findings, as patients now often first learn results independently and without explanation via electronic health portals. Due to ongoing shortages of clinicians equipped to return and discuss AD-related results, opportunities for clarification and support may be limited and difficult to access. Additionally, current standard-of-care return of result protocols require considerable clinician time, further limiting the broader translatability of prior research investigating the impact of returning AD-related results. Scalable, evidence-based approaches to returning AD-related information are therefore needed. Yet, it remains unknown whether return of results via digital platforms, such as one that could be integrated into an electronic health care portal, is comparable to a clinician-mediated telehealth session in terms of safety, well-being, and knowledge regarding the information.

Digital health technologies offer an innovative and scalable pathway for returning AD genetic and biomarker results. Such results can be helpful in identifying individuals at elevated disease risk and/or in informing early detection of AD. Given the anticipated shift in AD screening and testing from specialty memory clinics to primary care, safe and effective self-mediated digital platforms that can be scaled for widespread use are needed.[15] These digital platforms can be developed to include structured education and personalized communication of results, allowing the patient and care partners to review the information as needed. They have the potential to reduce clinician burden and patient misinterpretation of results.[16]

Based on previous findings from the Alzheimer's Prevention Initiative Generation Program's *APOE* disclosure program[14] and its ancillary Remote Communication of Genetic Test Results for *APOE* (CONNECT4) randomized trial of telephone vs telehealth videoconference disclosure of *APOE* results,[17] we designed the subsequent Evaluation of Self-Mediated Alternatives for Risk Testing Education and Return of Results (eSMARTER) clinical trial. eSMARTER was a randomized, noninferiority trial comparing returning *APOE* results to participants via digital platforms or a study clinician telehealth session, with optional phosphorylated tau 217 (p-tau217) disclosure, a biomarker of AD pathology, 6 months after returning *APOE* results, by assessing changes in measures of anxiety, disease-specific distress, and AD-related knowledge following disclosure.[18]

Key Points

Question Is learning Alzheimer disease (AD) genetic and biomarker results via self-mediated, patient-centered digital platforms noninferior to learning via a clinician-mediated telehealth session, as assessed by changes in symptoms of anxiety, disease-specific distress, and AD-related knowledge?

Findings In this randomized clinical trial of 651 adults, noninferiority of digital vs clinician-delivered apolipoprotein E disclosure was demonstrated at the prespecified time points, meeting the primary end point; no clinically significant differences were observed between treatment arms following optional phosphorylated tau 217 disclosure.

Meaning The digital platform used in this study for returning AD genetic and biomarker results to adults was found to be no less efficacious than learning this information from a clinician.

Methods

Trial Design and Conduct

The eSMARTER trial was a decentralized and fully remote trial to assess the comparability of returning AD genetic and biomarker results via a self-mediated, patient-informed digital platform or via clinician telehealth (genetic counselor for *APOE* results, study physician for p-tau217 results). The study design was published previously.[18] Enrollment occurred between October 2024 and February 2025; data collection was completed in November 2025. The eSMARTER protocol was approved by an Advarra institutional review board, and all participants provided written informed consent. Participants received gift cards for survey completions and blood draws. An independent, blinded safety officer reviewed and oversaw study safety. Reporting followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.[19]

Participants

Participants were recruited from GeneMatch, a trial-independent research enrollment program that performs *APOE* genotyping in laboratories accredited by the College of American Pathologists and certified through Clinical Laboratory Improvement Amendments.[20] Prior to enrolling in GeneMatch, individuals complete an online education module about *APOE* and AD. GeneMatch sent participation invitation emails and mailed letters to eligible members.

Inclusion criteria were being age 60 to 80 years at screening, having undergone prior *APOE* genetic testing via GeneMatch without having received results, having access to the internet and an internet-enabled device, being able to speak English, and being willing to undergo a blood draw. Exclusion criteria were prior knowledge of *APOE* genotype, lack of psychological readiness to receive *APOE* and p-tau217 results as indicated by a score of 10 or higher on the 9-item Patient Health Questionnaire (PHQ-9)[21] or responding yes to any question from the abbreviated Columbia Suicide Severity Scale or AD Specific Suicidality Questions, presence of a current untreated or unstable major psychiatric illness, and communication difficulties (Protocol in Supplement 1). Eligible participants completed the Telephone Montreal Cognitive Assessment (T-MoCA)[22] and provided additional demographic information.

Downloaded from jamanetwork.com by guest on 11/21/2026

Digital Interventions for Predisclosure Education and Return of Results

The trial compared 2 methods (patient-informed digital platform or study clinician telehealth) of returning *APOE* genotype and associated risk of mild cognitive impairment or dementia by age 85 years using risk estimates calculated for the Alzheimer's Prevention Initiative Generation Program.[23,24] These methods were used to disclose categorical p-tau217 results (negative, intermediate, positive).[18] The eSMARTER scalable digital platforms (*APOE*, p-tau217) were informed by a modified tiered-binned model and tested by age-matched participants and hence described as patient informed.[18,25] Content and modules have been previously described[18] and were designed to cover what a genetic counselor or clinician would address in pretest education and return of results. Tier 1 information included indispensable information presented to all users; Tier 2 contained optional, more in-depth content. Print and electronic materials containing all content were developed for the study clinicians who were trained prior to conducting telehealth sessions. To better understand differences in user preferences for different platforms, we developed web-based and short message service–based chat platforms for *APOE* and p-tau217 disclosure. Participants in the digital arm selected their preference between a web-based platform, in which users were provided with a link to a secure website, or an SMS-based platform (hereafter referred to as *chat*). Unlike the web portal, the chat platform allowed users to text individual questions to the team through SMS and access information through a weblink. All participants randomized to the digital arm could request to speak with a study clinician before, after, or instead of using the digital platform. All participants were offered optional digital educational materials about *APOE* and p-tau217 to review prior to the disclosure sessions. Procedures for both arms are previously described.[18]

Randomization

After screening assessments, participants were randomized 2:1 to digital platform or study clinician telehealth disclosure. Randomization was by permuted block design and performed centrally using FlexAdvantage with stratification factors of sex (male, female) and *APOE4* carrier group (noncarrier, heterozygote, homozygote). Study personnel did not have access to the allocation sequence. *APOE* genotypes used for disclosure were provided by GeneMatch.[20]

Outcomes

Outcomes to evaluate cognitive, affective, and behavioral outcomes of digital vs telehealth return of results were collected at baseline, 1 to 7 days, 6 weeks, and 6 months after *APOE* disclosure, and 1 to 7 days and 4 weeks after optional p-tau217 disclosure (eTable 1 in Supplement 2). Remote phlebotomy services were used to collect blood between 6-week and 6-month visits; p-tau217 concentrations were measured on the Roche cobas e801 platform using a Research Use Only assay to provide categorical results.[18]

The primary outcomes of return of *APOE* results included (1) AD-related knowledge (with a focus on *APOE*), assessed by 8 items adapted from the Cancer Genetics and ClinSeq Knowledge Scales (Cronbach α = .83)[26-28]; (2) anxiety, assessed by the 7-item Patient-Reported Outcomes Measurement Information System Anxiety measure (Cronbach α = .79)[29,30]; and (3) disease-specific distress measured by 8 items adapted from the Impact of Events Scale.[31,32]

Secondary outcomes of return of *APOE* results included PHQ-9 score,[21] satisfaction with digital vs clinician-provided genetic disclosure services (measured on a scale from 1 [not at all satisfied] to 5 [very satisfied]),[33-35] Psychological Well-Being Scale score,[36] perceived risk of AD,[37,38] Impact of Genetic Testing–AD (IGT-AD) score,[39] recall of results (%), Cognitive Function Instrument score,[40,41] and modified Stigma Impact Scale score.[42] These outcomes were also assessed for return of p-tau217 results and considered secondary.

Covariates

Age, sex, race (available choices from which participants could select included American Indian or Alaska Native, Asian, Black or African American, Hawaiian or Other Pacific Islander, White, other, unknown; more than 1 race could be selected), ethnicity (Hispanic or Latino, not Hispanic or Latino), highest degree or level of school completed, family history of AD, marital status, employment status, and household income were collected via self-report. Collection of race and ethnicity was required by the funding agency. Other covariates included Area Deprivation Index score and rurality, calculated using 2019 National Center for Education Statistics.[43]

Statistical Analysis

We used *t* tests and χ^2 tests to compare demographic differences between arms. We hypothesized that digital platform disclosure of *APOE* would result in noninferior outcomes compared to study clinician-mediated (telehealth) usual care. For primary analyses, we concludes noninferiority if the upper bound of the randomization effect 96.7% CI for each behavioral change variable did not cross the noninferiority threshold in a direction that favors usual care. The noninferiority margins were 2 points for genetic knowledge, 3.5 points for anxiety, and 0.35 baseline standard deviations for disease-specific distress. We used clinical judgment to set the margin for AD-related knowledge. We used the midpoint between a small (0.2 SD) and large (0.5 SD) effect for disease-specific distress (0.35 SD is the midpoint). We set the margin for Patient-Reported Outcomes Measurement Information System Anxiety T-score 0.5 points below the value of 4 that has been reported as clinically relevant.[44] Based on preliminary data, we had 85% noninferiority power and 1.67% type I error (1-sided). We chose 1.67% type I error by applying a Bonferroni correction to 5%. We used multiple imputation methods for the outcome analyses.[45] In secondary analyses, we tested for differences among arms using *t* tests, including for *APOE4* carrier subgroups (homozygotes and heterozygotes combined vs noncarriers). For secondary analyses, we set the threshold for statistical significance at $P < .01$.

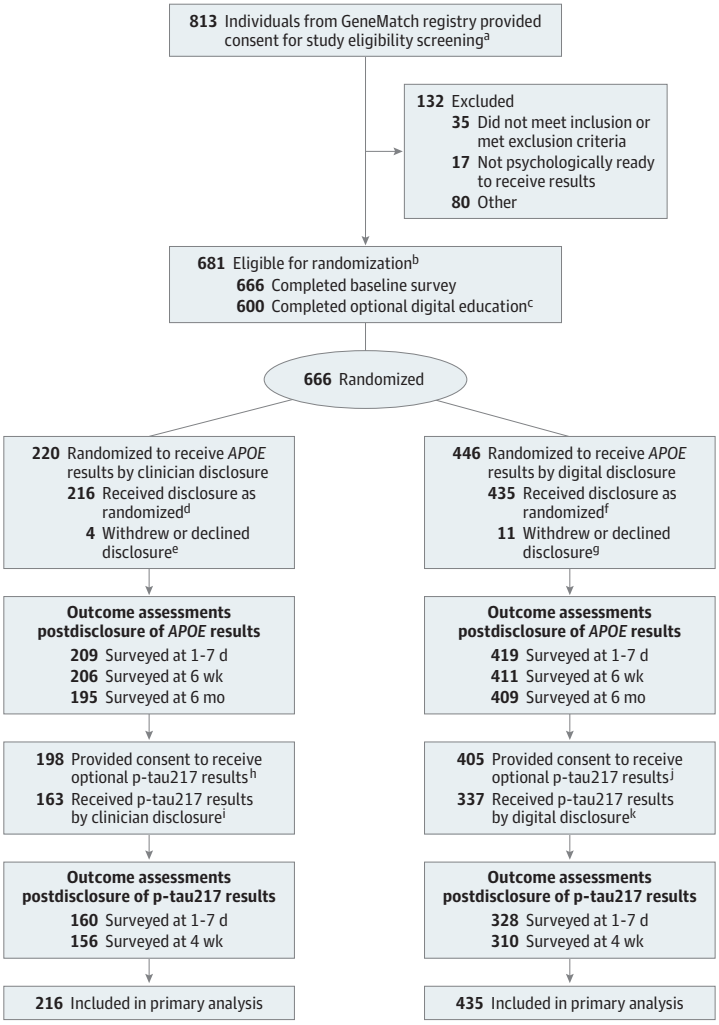
Results

Participants

Enrollment, randomization, and survey completion are shown in **Figure 1**. Of the 813 participants who consented,

Downloaded from jamanetwork.com by guest on 11/21/2026

Figure 1. CONSORT Diagram



eSMARTER study profile illustrating eligibility screening before the baseline survey, after completion of the baseline survey, and after randomization. Randomization was performed for 666 participants selected for the trial who completed the baseline survey and was stratified by sex (male, female) and *APOE4* carrier group (noncarrier, heterozygote, homozygote).

[a]Of 13 033 GeneMatch members who were invited to the study, 2052 accepted their invitation and agreed to have their contact information shared with the central coordinators. Of these, 1204 were marked as not eligible (reasons unknown, not reported) and 7 as not interested; 28 were lost to follow-up.

[b]Of those randomized who did not proceed to *APOE* disclosure, 7 did not provide demographic information, 8 provided demographic information but did not complete baseline surveys, and 15 provided demographic information and completed baseline surveys. eTable 2 compares the demographic characteristics of those who received *APOE* disclosure (n = 651) to those who did not (n = 23).

[c]A total of 600 (90.0%) completed predisclosure education: 290 by web (48.3%) and 251 by chat (41.8%), and 59 by both web and chat (9.8%). Among those who received *APOE* results, 593 (91.1%) completed predisclosure education: 289 by web, 246 by chat, and 58 by both.

[d]One individual completed digital disclosure due to assignment error.

[e]Two withdrew, 1 actively declined *APOE* results, and 1 passively declined *APOE* results (ie, never opened the module or scheduled their disclosure session).

[f]A total of 370 individuals (85.1%) completed by web and 64 (14.7%) by chat; 1 (0.2%) had results disclosed by genetic counselor given assignment error.

[g]Five withdrew, 2 actively declined *APOE* results, and 4 passively declined *APOE* results (ie, never opened the module or scheduled their disclosure session).

[h]Eighteen did not consent to p-tau217 disclosure, 12 withdrew from the study, 3 were lost to follow-up, and 3 opted out of disclosure.

[i]Six completed by web, given time constraints at study end; 1 completed by web due to assignment error. Of those who consented but did not receive p-tau disclosure, 5 failed the psychological screening, 11 were not able to have blood collected, 7 were not offered disclosure due to insufficient study time for follow-up, 7 were lost to follow-up, and 5 withdrew.

[j]Thirty did not consent to p-tau217 disclosure; 16 withdrew from the study, 7 were lost to follow-up, 1 opted out of the blood draw, and 6 opted out of disclosure.

[k]A total of 298 completed by web and 38 by chat; 1 completed by clinician due to assignment error. Of those who consented but did not receive p-tau disclosure, 6 failed the psychological screening, 22 were not able to have blood collected, 13 were not offered disclosure due to insufficient study time for follow-up, 23 were lost to follow-up, and 4 withdrew.

681 were eligible for randomization, 666 completed the baseline survey, 651 were randomized and received *APOE* disclosure. Of the 666, 600 (90%) completed optional digital education prior to disclosure. The mean (SD) age of

Downloaded from jamanetwork.com by guest on 11/21/2026

Table 1. Sample Characteristics by Randomization Arm

Characteristic	Population, No. (%)			
	Telehealth (n = 216)	Digital (n = 435)	Total (N = 651)	*P* value
Age, mean (SD), y	68.1 (4.8)	67.8 (4.7)	67.9 (4.7)	.39
Sex				
Female	147 (68)	292 (67)	439 (67)	.81
Male	69 (32)	143 (33)	212 (33)	
Race[a]				
American Indian or Alaska Native	1 (1)	3 (1)	4 (1)	.35
Asian	3 (1)	10 (2)	13 (2)	
Black or African American	8 (4)	13 (3)	21 (3)	
White	198 (92)	387 (89)	585 (90)	
Other (unspecified)	6 (3)	13 (3)	19 (3)	
Not known	0 (0)	9 (2)	9 (1)	
Ethnicity[a]				
Hispanic	13 (6)	25 (6)	38 (6)	.89
Not Hispanic	203 (94)	410 (94)	613 (94)	
Marital status				
Currently married or partnered	156 (72)	312 (72)	468 (72)	.92
Widowed	17 (8)	40 (9)	57 (9)	
Divorced or separated	32 (15)	63 (15)	95 (15)	
Never married	11 (5)	19 (4)	30 (5)	
Unknown	0 (0)	1 (0)	1 (0)	
Education level				
≤High school	8 (4)	16 (4)	24 (4)	.85
Some college or trade school	37 (17)	82 (19)	119 (18)	
≥College	171 (79)	336 (77)	507 (78)	
Unknown	0 (0)	1 (0)	1 (0)	
Family history of Alzheimer disease				
No	46 (21)	83 (19)	129 (20)	.20
Yes	148 (69)	286 (66)	434 (67)	
Not sure	22 (10)	66 (15)	88 (14)	
T-MoCA total score, mean (SD)	19.1 (1.9)	19.0 (2.1)	19.0 (2.0)	.70
Health literacy at baseline, mean (SD)[b]	7.06 (1.02)	6.93 (1.07)	6.97 (1.05)	.13
ADI score, mean (SD)	36.7 (24.0)	39.4 (23.7)	38.5 (23.8)	.17

(continued)

participants was 67.9 (4.7) years; 439 (67%) were women and 212 (33%) were men; 4 (1%) were American Indian or Alaska Native, 12 (2%) were Asian, 21 (3%) were Black or African American, 585 (90%) were White, and 19 (3%) were another race (unspecified); and 38 (6%) were Hispanic and 613 (94%) non-Hispanic (**Table 1**[46]). Participants were enrolled from the contiguous US; 336 (52%) were from rural areas. The mean (SD) T-MoCA score was 19.0 (2.0) and 232 participants (36%) had scores less than 19, a cutoff commonly used for cognitive impairment. Of 651 participants who were randomized and received *APOE* results, 434 (67%) had a family history of AD; 66 (10%) were *APOE4* homozygotes, 377 (58%) heterozygotes, and 208 (32%) noncarriers. Of the 565 participants with blood samples, 126 (22%) had a positive p-tau217 result, 175 (31%) had an intermediate result, and 264 (47%) had a negative result. There were no significant differences in baseline characteristics between arms.

Failure to have *APOE* disclosure, and hence exclusion from intention-to-treat analyses, did not differ between arms (8/224 [4%] initially randomized to telehealth; 15/450 [3%] initially randomized to digital) (eTable 2 in Supplement 2). Participants who did not receive results had a higher mean (SD) age (69.9 [4.7] years, not disclosed, vs 67.9 [4.7] years disclosed; $P = .05$) and were more likely to be Hispanic (4 [17%] of those not disclosed vs 38 [6%] disclosed; $P = .02$).

Primary Noninferiority Analyses for *APOE* Disclosure

In the primary intention-to-treat analyses, we met the noninferiority thresholds for all primary outcomes (**Figure 2**). We also met the noninferiority thresholds for the primary end points at later time points. Two participants (0.5%) randomized to the digital arm requested a genetic counselor. Per-protocol noninferiority analyses yielded similar results

Downloaded from jamanetwork.com by guest on 11/21/2026

Table 1. Sample Characteristics by Randomization Arm (continued)

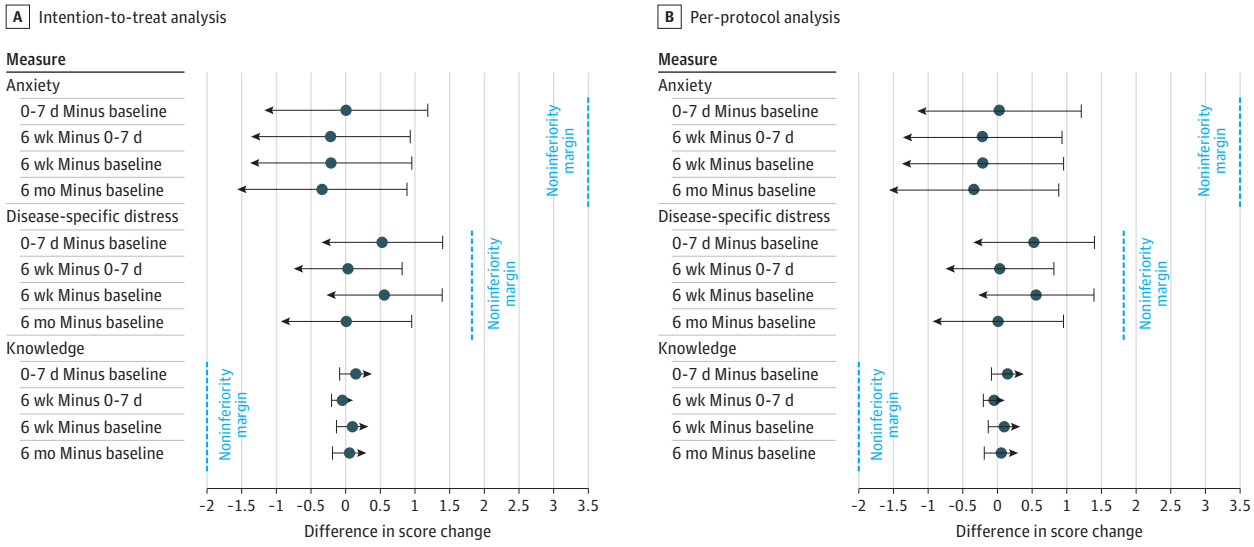
Characteristic	Population, No. (%)			*P* value
	Telehealth (n = 216)	Digital (n = 435)	Total (N = 651)	
Rurality				
City/suburb/town	101 (47)	207 (48)	308 (47)	.94
Rural	113 (52)	223 (51)	336 (52)	
Unknown	2 (1)	5 (1)	7 (1)	
Income, $				
<100 000	107 (50)	222 (51)	329 (50)	.19
≥100 000	99 (46)	178 (41)	277 (43)	
Prefer not to answer	10 (5)	35 (8)	45 (7)	
Employment status				
Employed/homemaker	68 (32)	139 (32)	207 (32)	.16
Not working	12 (6)	10 (2)	22 (3)	
Retired	136 (63)	285 (66)	421 (65)	
Unknown	0 (0)	1 (0)	1 (0)	
APOE genotype				
Homozygote	22 (10)	44 (10)	66 (10)	.98
Heterozygote	124 (57)	253 (58)	377 (58)	
Noncarrier	70 (32)	138 (32)	208 (32)	
P-tau217 results by *APOE* carriership				
Positive p-tau217				.16
Carrier	41 (19)	68 (16)	109 (17)	
Noncarrier	10 (5)	7 (2)	17 (3)	
Intermediate p-tau217				
Carrier	41 (19)	89 (21)	130 (20)	
Noncarrier	10 (5)	35 (8)	45 (7)	
Negative p-tau217				
Carrier	46 (21)	102 (23)	148 (23)	
Noncarrier	37 (17)	79 (18)	116 (18)	
Unknown (ie, not tested)	31 (14)	55 (13)	86 (13)	

Abbreviations: ADI, Area Deprivation Index (scale, 0-100; higher scores indicate more disadvantaged neighborhood); *APOE*, apolipoprotein E genotype; p-tau217, phosphorylated tau 217; T-MoCA, Telephone Montreal Cognitive Assessment (scale, 0-22; higher scores indicate more intact cognition).

[a] Race and ethnicity data were collected via self-report and reported due to funding agency requirements.

[b] Health literacy assessed as per Chew et al[46]; scale, 3-15; higher scores indicate lower health literacy.

Figure 2. Forest Plot Showing Noninferiority Intention-to-Treat and Per-Protocol Analyses



The dots represent the difference between arms by each primary outcome: change in anxiety, change in disease-specific distress, and change in *APOE* knowledge. Failure to cross the margin threshold indicates that digital disclosure was noninferior to telehealth disclosure on the relevant item.

Downloaded from jamanetwork.com by guest on 11/21/2026

to the intention-to-treat results. Results remained consistent after excluding those who did not correctly recall their *APOE* results.

Secondary Analyses for *APOE* Disclosure

As shown in **Table 2**, most primary and secondary outcomes did not differ significantly by arm in the intention-to-treat analyses. There was a slightly higher mean (SD) negative response on the IGT-AD in the digital compared to the telehealth arm immediately after disclosure (14.1 [11.6] vs 11.3 [9.8]; $P = .003$), although there were no differences at later time points and the magnitude of the difference was small, suggesting that it may not have been clinically significant. Mean (SD) satisfaction was high overall, but higher in the telehealth vs digital arm (4.8 [0.7] vs 4.3 [0.9]; $P < .001$). There was slightly lower accuracy in recall of *APOE* result at 6 weeks in the digital compared to the telehealth arm (14% incorrect vs 6% incorrect; $P = .005$), although there were no differences between the 1-7-day vs 6-month time points. These findings were similar in per-protocol analyses. No differences were found when stratifying by baseline T-MoCA score greater than 19 vs 19 or less (eTable 5 in Supplement 2).

Outcomes of *APOE* Disclosure by Arm and by Result

Among *APOE4* carriers, there were 3 significant differences between arms. First, greater reduction in mean (SD) disease-specific distress in the telehealth arm vs digital arm at 1 to 7 days (−0.67 [4.3] vs 0.71 [5.4]; $P = .009$), although these differences did not persist longitudinally. The overall scores were low and likely subclinical, and the differences were small. Thus, these short-term differences were likely not clinically significant. There was also higher mean (SD) negative response to learning *APOE* genetic risk (IGT-AD) at 1 to 7 days in the digital vs telehealth arm (17.3 [12.1] vs 14.2 [10.0]; $P = .008$). The differences were small; overall scores were low and were likely not clinically significant. There was also slightly higher mean (SD) satisfaction at 1 to 7 days in the telehealth vs digital arm (4.7 [0.6] vs 4.3 [0.8]; $P < .001$), although the differences were small and satisfaction was high in both arms (eTable 3 in Supplement 2).

Among noncarriers, there were no significant differences in knowledge or affective outcomes between arms at 1 to 7 days, 6 weeks, or 6 months. Mean (SD) satisfaction was slightly higher in the telehealth vs digital platform arm (4.8 [0.6] vs 4.4 [0.9]; $P < .001$), although the differences were small and satisfaction was high in both arms (eTable 3 in Supplement 2).

Outcomes of P-Tau217 Disclosure

As shown in **Table 3**, outcomes did not differ significantly by arm in the intention-to-treat analyses. Examining differences by categorical p-tau217 result following disclosure, there was slightly higher mean (SD) satisfaction in the telehealth vs digital arm among those who received an intermediate result (4.6 [0.6] vs 4.3 [0.6]; $P = .005$), although the differences are small and satisfaction was high in both arms. While there were some cross-sectional differences, the change scores between groups following disclosure were not significant (eTable 4 in Supplement 2). No differences were found when stratifying by baseline T-MoCA score greater than 19 vs 19 or less (eTable 6 in Supplement 2).

Discussion

To our knowledge, this is the first randomized clinical trial to examine whether learning *APOE* results through digital platforms is noninferior to a telehealth visit with a study clinician. It is also the first to explore if outcomes differ between digital and clinician-mediated return of p-tau217 results. Together, the results can inform a clinical practice in which patients learn genetic and biomarker results via patient-centered digital platforms, ideally integrated into their electronic health portal, as part of their medical workup for anti-amyloid monoclonal antibody treatments to inform them of their treatment-related risks.

No overall differences in AD-related knowledge, symptoms of anxiety, or disease-specific distress were observed between arms following return of *APOE* results. However, there were some differences between arms on secondary outcomes and exploratory subgroup analyses. In almost all instances, satisfaction with disclosure services was higher among those in the telehealth arm, although the differences were small. Although there were no differences in recall of *APOE* result between arms immediately (1-7 days) following disclosure, nor at 6 months, recall was lower in the digital arm at 6 weeks following disclosure (86% vs 94%). Although there were no differences at 6 months, recall was lowest for both groups at this time point (87% telehealth and 83% digital), suggesting that over time, more people may incorrectly recall their *APOE* result, regardless of disclosure modality.

Higher negative response to genetic testing (IGT-AD) was observed in the digital arm immediately after return of *APOE* results, with no differences at 6 weeks or 6 months after disclosure. Among *APOE4* carriers, disease-specific distress increased slightly, and the IGT-AD was higher 1-7 days following disclosure in the digital arm, with no differences observed between arms at 6 weeks and 6 months following disclosure. The observed differences were relatively small, and none of the subgroup mean scores for measures with clinical thresholds were in the range that would be considered clinically significant. No differences in knowledge of p-tau217, symptoms of anxiety, disease-specific distress, or secondary outcomes were observed between arms following p-tau217 disclosure. This pattern persisted when stratified by categorical p-tau217 result. The scores observed in the eSMARTER trial align with previous disclosure studies which reported similar changes in mood and well-being.[3,5,10,14,17,47] Together, the results further support that AD-related genetic and biomarker results along with information about a person's risk of future diagnosis of cognitive impairment due to dementia can be returned remotely in a safe and effective manner.

We met the a priori–defined noninferiority thresholds for outcomes following return of *APOE* results. In addition, we did not observe differences between arms following return of

Downloaded from jamanetwork.com by guest on 11/21/2026

Table 2. Intention-to-Treat Analysis by Delivery Mode for Apolipoprotein E (*APOE*) Genotype Disclosure

Measure	Population, mean (SD)[a]		*P* value[b]
	Telehealth (n = 216)	Digital (n = 435)	
APOE knowledge (baseline)	7.03 (1.26)	7.00 (1.28)	.78
Knowledge change (baseline to 1-7 d post *APOE* disclosure)	0.05 (1.29)	0.19 (1.30)	.18
Knowledge change (baseline to 6 wk post *APOE* disclosure)	0.12 (1.29)	0.22 (1.27)	.37
Knowledge change (baseline to 6 mo post *APOE* disclosure)	0.07 (1.33)	0.12 (1.35)	.64
Anxiety T-score (baseline)[c]	47.80 (6.85)	47.56 (7.01)	.69
Anxiety change (baseline to 1-7 d post *APOE* disclosure)	−0.74 (6.08)	−0.73 (6.81)	.99
Anxiety change (baseline to 6 wk post *APOE* disclosure)	−0.95 (6.89)	−1.16 (6.35)	.70
Anxiety change (baseline to 6 mo post *APOE* disclosure)	−0.61 (7.28)	−0.95 (6.60)	.55
DSD (baseline)	4.44 (5.55)	4.46 (5.03)	.96
DSD change (baseline to 1-7 d post *APOE* disclosure)	−0.36 (4.13)	0.17 (5.20)	.20
DSD change (baseline to 6 wk post *APOE* disclosure)	−1.56 (4.32)	−1.01 (4.82)	.16
DSD change (baseline to 6 mo post *APOE* disclosure)	−0.45 (4.88)	−0.44 (5.40)	.99
PHQ-9 (baseline)	1.63 (2.02)	1.48 (1.83)	.34
PHQ-9 change (baseline to 1-7 d post *APOE* disclosure)	0.13 (1.70)	0.15 (1.67)	.90
PHQ-9 change (baseline to 6 wk post *APOE* disclosure)	0.11 (1.87)	0.30 (1.83)	.24
PHQ-9 change (baseline to 6 mo post *APOE* disclosure)	0.51 (2.19)	0.50 (2.47)	.98
IGT-AD total (1-7 d post *APOE* disclosure)	11.34 (9.80)	14.12 (11.55)	.003
IGT-AD total (6 wk post *APOE* disclosure)	12.03 (9.26)	13.53 (10.10)	.07
IGT-AD total (6 mo post *APOE* disclosure)	13.03 (9.15)	14.24 (10.37)	.15
Satisfaction (1-7 d post *APOE* disclosure)[d]	4.77 (0.63)	4.32 (0.85)	<.001
Perceived numeric risk (baseline)[e]	45.58 (24.87)	45.85 (24.34)	.90
Numeric risk change (baseline to 1-7 d post *APOE* disclosure)	−18.32 (23.68)	−13.18 (24.58)	.01
Numeric risk change (baseline to 6 wk post *APOE* disclosure)	−14.89 (24.11)	−9.72 (24.02)	.01
Numeric risk change (baseline to 6 mo post *APOE* disclosure)	−9.12 (24.61)	−7.65 (25.29)	.49
Perceived odds risk (baseline)	3.24 (1.08)	3.23 (1.01)	.92
Odds risk change (baseline to 1-7 d post *APOE* disclosure)	−0.16 (1.13)	−0.13 (1.06)	.75
Odds risk change (baseline to 6 wk post *APOE* disclosure)	−0.14 (1.08)	−0.04 (1.04)	.28
Odds risk change (baseline to 6 mo post *APOE* disclosure)	−0.09 (1.14)	−0.05 (1.05)	.70
Perceived relative risk (baseline)[f]	3.01 (1.05)	3.09 (0.94)	.33
Relative risk change (baseline to 1-7 d post *APOE* disclosure)	−0.32 (1.07)	−0.32 (1.01)	.94
Relative risk change (baseline to 6 wk post *APOE* disclosure)	−0.32 (1.05)	−0.28 (0.97)	.61
Relative risk change (baseline to 6 mo post *APOE* disclosure)	−0.19 (1.13)	−0.24 (1.03)	.64
PWB score (baseline)	74.06 (8.00)	72.85 (9.09)	.10
PWB score change (baseline to 6 mo post *APOE* disclosure)	−2.13 (6.83)	−1.67 (7.55)	.46
Stigma total (1-7 d post *APOE* disclosure)[g]	7.77 (2.34)	8.32 (2.76)	.01
Stigma change (1-7 d post *APOE* disclosure to 6 wk post *APOE* disclosure)	−0.06 (2.01)	−0.31 (2.14)	.16
Stigma change (1-7 d post *APOE* disclosure to 6 mo post *APOE* disclosure)	0.15 (2.29)	−0.07 (2.51)	.29
CFI score (baseline)	1.80 (1.92)	1.78 (1.86)	.93
CFI score change (baseline to 6 mo post *APOE* disclosure)	−0.23 (1.38)	−0.20 (1.38)	.82
Correct recall of result (1-7 d post *APOE* disclosure), %			
Incorrect	5	8	.18
Correct	95	92	
Correct recall of result (6 wk post *APOE* disclosure), %			
Incorrect	6	14	.005
Correct	94	86	
Correct recall of result (6 mo post *APOE* disclosure), %			
Incorrect	13	17	.17
Correct	87	83	

Abbreviations: CFI, Cognitive Function Instrument (scale, 0-15; higher scores indicate greater perceived difficulties or complaints regarding memory and everyday tasks); DSD, disease-specific distress (measured via 8 self-report items adapted from the Impact of Events Scale, scale, 0-40; higher scores indicate more frequent thoughts or feelings about Alzheimer's disease; scale, 0-80); IGT-AD, Impact of Genetic Testing–AD (scale, 0-80; higher scores indicate higher psychological distress in response to learning genetic test results); PHQ-9, 9-item Patient Health Questionnaire (scale, 0-27; higher scores indicate greater depression severity symptoms); PWB, Psychological Well-Being Scale (scale, 0-84; higher scores indicate greater well-being).

[a] Includes multiply imputed data.

[b] *P* values <.01 were considered statistically significant.

[c] Anxiety T-scores are scaled 0-100; higher scores indicate more frequent anxious symptoms during the past 7 days.

[d] Satisfaction was measured with a 15-item self-report scale.[33-35]

[e] Risk refers to participant self-perceived risk of developing Alzheimer disease.

[f] Relative risk means self-perceived risk of developing Alzheimer disease relative to others.

[g] Stigma was measured via 6 self-report questions from the Stigma Impact Scale measuring impact of negative social attitudes toward the patients' health or mental health condition or disorder.

Downloaded from jamanetwork.com by guest on 11/21/2026

Table 3. Intention-to-Treat Analyses by Delivery Mode for Optional Phosphorylated Tau 217 (P-Tau217) Disclosure

Measure	Population, mean (SD)[a]		*P* value[b]
	Telehealth (n = 163)	Digital (n = 337)	
P-tau knowledge (1-7 d post p-tau217 disclosure)	6.67 (0.63)	6.62 (0.66)	.47
P-tau knowledge (4 wk post p-tau217 disclosure)	6.63 (0.66)	6.62 (0.70)	.86
Knowledge change (4 wk post p-tau217 disclosure to 1-7 d post p-tau217 disclosure)	−0.03 (0.77)	0.00 (0.78)	.66
Anxiety T-score (6 mo post *APOE* disclosure [before p-tau disclosure baseline])[c]	46.50 (7.66)	45.90 (7.87)	.42
Anxiety T-score (1-7 d post p-tau217 disclosure)	46.13 (7.90)	45.05 (8.02)	.16
Anxiety T-score (4 wk post p-tau217 disclosure)	46.01 (8.21)	46.28 (7.91)	.74
Anxiety change (6 mo post *APOE* disclosure [before p-tau disclosure baseline]) to 1-7 d post p-tau217 disclosure)	−0.37 (7.20)	−0.84 (6.56)	.46
Anxiety change (6 mo post *APOE* disclosure [before p-tau disclosure baseline]) to 4 wk post p-tau217 disclosure)	−0.49 (6.40)	0.38 (5.73)	.13
DSD (6 mo post *APOE* disclosure [before p-tau disclosure baseline])	3.52 (5.48)	3.93 (5.40)	.43
DSD (1-7 d post p-tau217 disclosure)	3.31 (5.32)	4.45 (6.07)	.04
DSD (4 wk post p-tau217 disclosure)	4.11 (5.74)	4.17 (5.94)	.96
DSD change (6 mo post *APOE* disclosure [before p-tau disclosure baseline]) to 1-7 d post p-tau217 disclosure)	−0.22 (4.96)	0.52 (4.74)	.11
DSD change (6 mo post *APOE* disclosure [before p-tau disclosure baseline]) to 4 wk post p-tau217 disclosure)	0.58 (5.51)	0.24 (4.61)	.46
PHQ-9 (6 mo post *APOE* disclosure [before p-tau disclosure baseline])	1.64 (1.87)	1.58 (1.99)	.71
PHQ-9 (1-7 d post p-tau217 disclosure)	1.44 (1.75)	1.38 (1.76)	.71
PHQ-9 (4 wk post p-tau217 disclosure)	1.49 (1.83)	1.48 (1.78)	.93
PHQ-9 change (6 mo post *APOE* disclosure [before p-tau disclosure baseline]) to 1-7 d post p-tau217 disclosure)	−0.20 (1.60)	−0.20 (1.46)	.97
PHQ-9 change (6 mo post *APOE* disclosure [before p-tau disclosure baseline]) to 4 wk post p-tau217 disclosure)	−0.15 (1.76)	−0.10 (1.64)	.74
IGT-AD total (1-7 d post p-tau217 disclosure)	12.70 (10.52)	14.60 (12.80)	.10
IGT-AD total (4 wk post p-tau217 disclosure)	13.43 (11.30)	14.50 (12.11)	.35
Satisfaction (1-7 d post p-tau217 disclosure)[d]	4.58 (0.68)	4.41 (0.70)	.02
Perceived numeric risk (6 mo post *APOE* disclosure [before p-tau disclosure baseline])[e]	35.60 (22.67)	38.92 (22.58)	.14
Perceived numeric risk (1-7 d post p-tau217 disclosure)	39.96 (25.05)	42.79 (24.69)	.24
Perceived numeric risk (4 wk post p-tau217 disclosure)	39.34 (25.11)	42.23 (23.67)	.22
Numeric risk change (6 mo post *APOE* disclosure [before p-tau disclosure baseline]) to 1-7 d post p-tau217 disclosure)	4.36 (21.47)	3.87 (20.95)	.81
Numeric risk change (6 mo post *APOE* disclosure [before p-tau disclosure baseline]) to 4 wk post p-tau217 disclosure)	3.74 (20.84)	3.31 (19.51)	.83
Perceived odds risk (6 mo post *APOE* disclosure [before p-tau disclosure baseline])	3.17 (1.09)	3.21 (1.05)	.70

(continued)

p-tau217 results. Together, these results suggest that scalable digital platforms are effective methods for communicating these types of sensitive information. This is important as genetic and biomarker testing increases with antiamyloid monoclonal antibody therapies (eg, lecanemab, donanemab) and as interest in using biomarker tests in primary care settings expands. Although these platforms are not the same as viewing a laboratory report in an electronic health portal, there may be opportunities to embed digital platforms into portals as well as for researchers to use these platforms in studies without resources to provide clinician-mediated return of results.

Limitations

Several limitations should be noted. Our study was not designed to assess how return of results via digital platforms compares to learning results from lab reports released to electronic health portals, in which minimal context or education is provided. Further, psychological readiness was assessed at screening due to the novelty of using digital platforms. Such screening may not be possible in all clinical settings, though best practices suggest that pretest counseling or predisclosure confirmation be conducted.[48] The digital platforms used in eSMARTER for *APOE* disclosure include information covered by genetic counselors; we recognize that this information is not necessarily discussed by other medical professionals or in real-world *APOE* testing. The eSMARTER digital platforms did not offer voice-over narration; participants had to read the text on their screen. This contrasts with the telehealth arm, in which clinicians verbally communicated the results. Although we tracked whether participants requested to

Downloaded from jamanetwork.com by guest on 11/21/2026

Table 3. Intention-to-Treat Analyses by Delivery Mode for Optional Phosphorylated Tau 217 (P-Tau217) Disclosure (continued)

Measure	Population, mean (SD)[a]		*P* value[b]
	Telehealth (n = 163)	Digital (n = 337)	
Perceived odds risk (1-7 d post p-tau217 disclosure)	3.23 (1.18)	3.25 (1.16)	.85
Perceived odds risk (4 wk post p-tau217 disclosure)	3.25 (1.16)	3.21 (1.18)	.74
Odds risk change (6 mo post *APOE* disclosure [before p-tau disclosure baseline]) to 1-7 d post p-tau217 disclosure)	0.05 (0.92)	0.04 (0.95)	.85
Odds risk change (6 mo post *APOE* disclosure [before p-tau disclosure baseline]) to 4 wk post p-tau217 disclosure)	0.08 (0.99)	0.00 (0.99)	.44
Perceived relative risk (6 mo post *APOE* disclosure [before p-tau disclosure baseline])[f]	2.85 (0.98)	2.88 (0.95)	.71
Perceived relative risk (1-7 d post p-tau217 disclosure)	2.94 (1.05)	3.00 (1.06)	.55
Perceived relative risk (4 wk post p-tau217 disclosure)	2.96 (1.05)	2.91 (1.09)	.66
Relative risk change (6 mo post *APOE* disclosure [before p-tau disclosure baseline]) to 1-7 d post p-tau217 disclosure)	0.10 (0.86)	0.12 (0.87)	.76
Relative risk change (6 mo post *APOE* disclosure [before p-tau disclosure baseline]) to 4 wk post p-tau217 disclosure)	0.11 (0.84)	0.03 (0.91)	.38
PWB score (6 mo post *APOE* disclosure [before p-tau disclosure baseline])	73.83 (7.93)	72.12 (9.59)	.05
PWB score (4 wk post p-tau217 disclosure)	73.82 (8.29)	72.10 (9.42)	.05
PWB score change (6 mo post *APOE* disclosure [before p-tau disclosure baseline]) to 4 wk post p-tau217 disclosure)	−0.01 (5.69)	−0.02 (6.39)	.99
Stigma (6 mo post *APOE* disclosure [before p-tau disclosure baseline])[g]	7.77 (2.49)	8.11 (2.70)	.19
Stigma (1-7 d post p-tau217 disclosure)	7.95 (2.74)	8.49 (2.97)	.06
Stigma (4 wk post p-tau217 disclosure)	7.98 (2.72)	8.37 (2.94)	.16
Stigma change (6 mo post *APOE* disclosure [before p-tau disclosure baseline]) to 1-7 d post p-tau217 disclosure)	0.20 (2.42)	0.38 (2.30)	.42
Stigma change (6 mo post *APOE* disclosure [before p-tau disclosure baseline]) to 4 wk post p-tau217 disclosure)	0.22 (2.56)	0.26 (2.36)	.87
Correct recall of result (1-7 d post p-tau217 disclosure), %			
Incorrect	3	2	.64
Correct	97	98	
Correct recall of result (4 wk post p-tau217 disclosure), %			
Incorrect	5	9	.20
Correct	95	91	

Abbreviations: *APOE*, apolipoprotein E genotype; DSD, disease-specific distress (measured via 8 self-report items adapted from the Impact of Events Scale, scale, 0-40; higher scores indicate more frequent thoughts or feelings about Alzheimer's disease); IGT-AD, Impact of Genetic Testing–AD (scale, 0-80; higher scores indicate higher psychological distress in response to learning genetic test results); p-tau, phosphorylated tau; PHQ-9, 9-item Patient Health Questionnaire (scale, 0-27; higher scores indicate greater depression severity symptoms); PWB, Psychological Well-Being Scale (scale, 0-84; higher scores indicate greater well-being).

[a] Includes multiply imputed data.

[b] *P* values <.01 were considered statistically significant.

[c] Anxiety T-scores are scaled 0-100; higher scores indicate more frequent anxious symptoms during the past 7 days.

[d] Satisfaction was measured with a 15-item self-report scale.[33-35]

[e] Risk refers to participant self-perceived risk of developing Alzheimer disease.

[f] Relative risk means self-perceived risk of developing Alzheimer disease relative to others.

[g] Stigma was measured via 6 self-report questions from the Stigma Impact Scale measuring impact of negative social attitudes toward the patients' health or mental health condition or disorder.

speak with a clinician following their disclosure session or had general questions, the study was not powered to rule out possible differences among subgroups requiring additional or immediate psychological support following disclosure. The sample was different from a true clinic sample, was racially homogenous, had a high overall level of education, was largely married or partnered, and self-selected to participate in a decentralized trial, limiting the generalizability of results. Future efforts should explore whether outcomes differ if participants received risk discordant results (eg, *APOE4* homozygotes with negative p-tau217). The order of results disclosed (*APOE* followed by p-tau217) and the time between disclosure do not reflect current clinical practice.

eSMARTER was developed within a research infrastructure and is not currently available as a standalone software product. The research version can be made available at nominal cost for research and implementation purposes, interested groups may contact the study team for additional information.

Conclusions

In conclusion, this study provides information about the comparability of patient-centered digital platforms and clinician-telehealth sessions for returning AD genetic and biomarker information to adults. The findings support the use of digital platforms for disclosure when it is preferred by the individual or when speaking with a health care professional (genetic counselor or clinician) is not available or feasible.[49] Moreover, these types of digital platforms offer a scalable approach to address the quickly increasing need for returning results to patients at elevated risk for AD dementia.

ARTICLE INFORMATION

Accepted for Publication: October 2, 2026.

Published Online: November 18, 2026. doi:10.1001/jamaneurol.2026.4279

Open Access: This is an open access article distributed under the terms of the CC-BY-NC-ND License, which does not permit alteration or commercial use, including those for text and data mining, AI training, and similar technologies. © 2026 Langbaum JB et al. *JAMA Neurology*.

Author Affiliations: Banner Alzheimer's Institute, Phoenix, Arizona (Langbaum, Erickson, Langlois, Enos, Salata, De Santiago, Reiman, Ashton); Department of Medicine, Division of Hematology-Oncology, University of Pennsylvania Perelman School of Medicine, Philadelphia (Wood,

Downloaded from jamanetwork.com by guest on 11/21/2026

Mim, John, C. Brown, S. Brown, Howe, Cacioppo, Eppelmann, Bradbury); Fox Chase Cancer Center, Temple University Health System, Philadelphia, Pennsylvania (Egleston); Department of Medicine, Division of Geriatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia (Harkins, Karlawish); Department of Medical Ethics and Health Policy, University of Pennsylvania Perelman School of Medicine, Philadelphia (Largent, Karlawish, Bradbury); Banner Sun Health Research Institute, Sun City, Arizona (Denkinger, Ashton); Department of Health Behavior and Health Equity, University of Michigan School of Public Health, Ann Arbor (Roberts); Dignity Health St Joseph's Hospital and Medical Center, Phoenix, Arizona (C. Brown).

Author Contributions: Drs Langbaum and Egleston had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Langbaum, Erickson, Langlois, Wood, Egleston, Harkins, S. Brown, Salata, Largent, Ashton, Roberts, Karlawish, Bradbury.
Acquisition, analysis, or interpretation of data: Langbaum, Erickson, Langlois, Wood, Egleston, Harkins, Mim, John, C. Brown, Howe, Cacioppo, Eppelmann, Enos, De Santiago, Largent, Reiman, Denkinger, Ashton, Bradbury.
Drafting of the manuscript: Langbaum, Erickson, Wood, Egleston, John, De Santiago, Ashton, Bradbury.
Critical review of the manuscript for important intellectual content: Erickson, Langlois, Egleston, Harkins, Mim, C. Brown, S. Brown, Howe, Cacioppo, Eppelmann, Enos, Salata, Largent, Reiman, Denkinger, Roberts, Karlawish, Bradbury.
Statistical analysis: Egleston, Bradbury.
Obtained funding: Langbaum, De Santiago, Reiman.
Administrative, technical, or material support: Erickson, Langlois, Wood, Egleston, Harkins, Mim, John, C. Brown, S. Brown, Howe, Cacioppo, Eppelmann, Enos, Salata, De Santiago, Reiman, Ashton, Bradbury.
Supervision: Langbaum, Langlois, Reiman.

Conflict of Interest Disclosures: Dr Langbaum reported receiving grants from the National Institute on Aging and Arizona Department of Health Services via the Arizona Alzheimer's Consortium during the conduct of the study; institutional grants or contracts to Banner Health from Eli Lilly; and personal fees from Premiere outside the submitted work. Ms Langlois and Ms Enos reported receiving grants from the National Institute on Aging during the conduct of the study. Dr Reiman reported receiving grants from the National Institute on Aging and Arizona Department of Health Services via the Arizona Alzheimer's Consortium during the conduct of the study; institutional grants or contracts to Banner Health from Eli Lilly; personal fees from Alzheon, Beren Therapeutics, Cognition Therapeutics, Denali Therapeutics, Enigma Diagnostics, Jocasta Neuroscience, NewAmsterdam Pharma, Retromer Therapeutics, and Vaxxinity; and stock options from Alzheon, Denali Therapeutics, Retromer Therapeutics, and Vaxxinity outside the submitted work. He is a cofounder, advisor, and shareholder of ALZPath, which produces a phosphorylated tau 217 (p-tau217) capture antibody licensed for plasma p-tau217 assays on several immunoassay platforms, including the Roche platform used in this study. Dr Roberts reported receiving grants from the National Institutes of Health and Alzheimer's Association during the conduct of the study. Dr Karlawish reported receiving grants from the National Institute on Aging and Pennsylvania Department of Public Health during the conduct of the study, consulting fees from Darmiyan, and service on the board of directors of the Greenwall Foundation. Dr Largent reported receiving grants from the National Institute on Aging and Greenwall Foundation and personal fees from Novartis outside the submitted work. Dr Ashton reported receiving grants from the National Institute on Aging and Arizona Department of Health Services via the Arizona Alzheimer's Consortium during the conduct of the study; service on scientific advisory boards for Alamar Biosciences (Alzheimer's Drug Discovery Foundation initiative), Biogen, NewAmsterdam Pharma, Bristol Myers Squibb, and Abbott; and consulting or speaking fees from Alamar Biosciences, BioArctic, Biogen, Eli Lilly, Neurogen Biomarking, Roche, Spear Bio, Quanterix, and Vigil Neurosciences. Dr Egleston reported receiving institutional salary support from the National Institutes of Health, including the National Cancer Institute and National Institute on Aging, National Aeronautics and Space Administration, and Department of War, and honoraria from American Journal Experts for journal reviews. Dr Bradbury reported receiving grants from the National Institutes of Health during the conduct of the study, research support from AstraZeneca for a separate trial evaluating digital interventions in cancer genetics (eREACH1), copyrights covering intervention content and related data, and being the founder of Lucidigene, which has no direct relationship with the conduct of the trial. No other disclosures were reported.

Funding/Support: The eSMARTER study was supported by funding from the National Institute on Aging under award numbers R01AG058468 and P30AG072980.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The content of the manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Data Sharing Statement: See Supplement 3.

Meeting Presentation: This paper was presented at the Clinical Trials on Alzheimer's Disease conference; November 18, 2026; Boston, Massachusetts, and in part at the Alzheimer's Association International Conference; July 13, 2026; London, UK.

Additional Contributions: We thank the site principal investigators, staff, and participants for their involvement in the study. We also thank Joshua Grill, PhD, University of California Irvine, for serving as the study's safety officer, as well as Robert Alexander, MD, Banner Alzheimer's Institute; Tainá M. Marques, PhD, Banner Sun Health Research Institute; Kari Dieckhoff, MS, Banner Sun Health Research Institute; Davron Hanley, MS, Banner Sun Health Research Institute; Darlene Ellenor, MSc, ICON Plc; and James Liu, BS, Banner Sun Health Research Institute, for their assistance during the conduct of the study.

REFERENCES

1. Largent EA, Bradbury AR. Bringing Alzheimer disease testing and results disclosure into the 21st Century Cures Act. *JAMA Neurol*. 2022;79(3):219-220. doi:10.1001/jamaneurol.2021.4851

2. Green RC, Christensen KD, Cupples LA, et al; REVEAL Study Group. A randomized noninferiority trial of condensed protocols for genetic risk disclosure of Alzheimer's disease. *Alzheimers Dement*. 2015;11(10):1222-1230. doi:10.1016/j.jalz.2014.10.014

3. Green RC, Roberts JS, Cupples LA, et al; REVEAL Study Group. Disclosure of *APOE* genotype for risk of Alzheimer's disease. *N Engl J Med*. 2009;361(3):245-254. doi:10.1056/NEJMoa0809578

4. Roberts JS, Chen CA, Uhlmann WR, Green RC. Effectiveness of a condensed protocol for disclosing *APOE* genotype and providing risk education for Alzheimer disease. *Genet Med*. 2012;14(8):742-748. doi:10.1038/gim.2012.37

5. Alber J, Popescu D, Thompson LI, et al. Safety and tolerability of *APOE* genotyping and disclosure in cognitively normal volunteers from the Butler Alzheimer's Prevention Registry. *J Geriatr Psychiatry Neurol*. 2022;35(3):293-301. doi:10.1177/0891988721993575

6. Grill JD, Raman R, Ernstrom K, et al; A4 Study Team. Short-term psychological outcomes of disclosing amyloid imaging results to research participants who do not have cognitive impairment. *JAMA Neurol*. 2020;77(12):1504-1513. doi:10.1001/jamaneurol.2020.2734

7. Grill JD, Raman R, Ernstrom K, et al. Immediate reactions to Alzheimer biomarker disclosure in cognitively unimpaired individuals in a global truncated randomized trial. *Neurol Clin Pract*. 2024;14(2):e200265. doi:10.1212/CPJ.0000000000200265

8. Lim YY, Maruff P, Getter C, Snyder PJ. Disclosure of positron emission tomography amyloid imaging results: a preliminary study of safety and tolerability. *Alzheimers Dement*. 2016;12(4):454-458. doi:10.1016/j.jalz.2015.09.005

9. Clark LR, Erickson CM, Basche KE, et al. Health behavior of adults without cognitive impairment after receiving amyloid-β PET results. *JAMA Netw Open*. 2025;8(12):e2545774. doi:10.1001/jamanetworkopen.2025.45774

10. Grill JD, Raman R, Wang S, et al. Amyloid imaging and *APOE* genotype disclosure and short-term psychological distress. *JAMA Netw Open*. 2026;9(3):e263845. doi:10.1001/jamanetworkopen.2026.3845

11. Clark LR, Erickson CM, Chin NA, et al. Psychosocial implications of learning amyloid PET results in an observational cohort. *Alzheimers Dement*. 2024;20(9):6579-6589. doi:10.1002/alz.14153

12. Largent EA, Bhardwaj T, Abera M, et al. Disclosing genetic risk of Alzheimer's disease to cognitively unimpaired older adults: findings from the study of knowledge and reactions to *APOE* testing (SOKRATES II). *J Alzheimers Dis*. 2021;84(3):1015-1028. doi:10.3233/JAD-210675

13. Largent EA, Harkins K, van Dyck CH, Hachey S, Sankar P, Karlawish J. Cognitively unimpaired adults' reactions to disclosure of amyloid PET scan results. *PLoS One*. 2020;15(2):e0229137. doi:10.1371/journal.pone.0229137

Downloaded from jamanetwork.com by guest on 11/21/2026

14. Langbaum JB, Bradbury AR, Egleston BL, et al. Impact of learning APOE genotype on cognitively unimpaired adults: a pre-screening cohort study of the Alzheimer's Prevention Initiative Generation Study 1. *Lancet Healthy Longev*. 2025;6(11):100778. doi:10.1016/j.lanhl.2025.100778

15. Liu JL, Baker L, Chen A, Wang J, Girosi F. Modeling early detection and geographic variation in health system capacity for Alzheimer's disease-modifying therapies. Accessed May 11, 2026. https://www.rand.org/pubs/research_reports/RRA2643-1.html

16. Bolton CJ, Rostamzadeh A, Chin N, et al; Advisory Group on Risk Evidence Education in Dementia (AGREEDementia). Disclosure of Alzheimer's disease blood-based biomarker results in a primary care setting: opportunities and challenges. *J Prev Alzheimers Dis*. 2025;12(9):100310. doi:10.1016/j.tjpad.2025.100310

17. Wood EM, Langbaum JB, Egleston BL, et al. CONNECT4 *APOE*: a randomized trial of telephone versus real-time two-way videoconference for disclosure of *APOE* genotype results in cognitively unimpaired adults. *Alzheimers Dement*. 2026;22(7):e71658. doi:10.1002/alz.71658

18. Erickson CM, Langlois CM, Wood EM, et al. Evaluation of self-mediated alternatives for risk testing education and return of results (eSMARTER) study: a randomized study of methods for returning *APOE* and pTau-217 results. *Alzheimers Dement (N Y)*. 2025;11(4):e70177. doi:10.1002/trc2.70177

19. Hopewell S, Chan A, Collins GS, et al. CONSORT 2025 statement: updated guideline for reporting randomized trials. *JAMA*. 2025;333(22):1998-2005. doi:10.1001/jama.2025.4347

20. Langbaum JB, Karlawish J, Roberts JS, et al. GeneMatch: a novel recruitment registry using at-home *APOE* genotyping to enhance referrals to Alzheimer's prevention studies. *Alzheimers Dement*. 2019;15(4):515-524. doi:10.1016/j.jalz.2018.12.007

21. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med*. 2001;16(9):606-613. doi:10.1046/j.1525-1497.2001.016009606.x

22. Katz MJ, Wang C, Nester CO, et al. T-MoCA: a valid phone screen for cognitive impairment in diverse community samples. *Alzheimers Dement (Amst)*. 2021;13(1):e12144. doi:10.1002/dad2.12144

23. Qian J, Wolters FJ, Beiser A, et al. APOE-related risk of mild cognitive impairment and dementia for prevention trials: an analysis of four cohorts. *PLoS Med*. 2017;14(3):e1002254. doi:10.1371/journal.pmed.1002254

24. Langlois CM, Bradbury A, Wood EM, et al. Alzheimer's Prevention Initiative Generation Program: development of an *APOE* genetic counseling and disclosure process in the context of clinical trials. *Alzheimers Dement (N Y)*. 2019;5:705-716. doi:10.1016/j.trci.2019.09.013

25. Bradbury AR, Patrick-Miller L, Long J, et al. Development of a tiered and binned genetic counseling model for informed consent in the era of multiplex testing for cancer susceptibility. *Genet Med*. 2015;17(6):485-492. doi:10.1038/gim.2014.134

26. Kelly K, Leventhal H, Marvin M, Toppmeyer D, Baran J, Schwalb M. Cancer genetics knowledge and beliefs and receipt of results in Ashkenazi Jewish individuals receiving counseling for *BRCA1/2* mutations. *Cancer Control*. 2004;11(4):236-244. doi:10.1177/107327480401100405

27. Kaphingst KA, McBride CM, Wade C, et al. Patients' understanding of and responses to multiplex genetic susceptibility test results. *Genet Med*. 2012;14(7):681-687. doi:10.1038/gim.2012.22

28. Lerman C, Narod S, Schulman K, et al. *BRCA1* testing in families with hereditary breast-ovarian cancer. a prospective study of patient decision making and outcomes. *JAMA*. 1996;275(24):1885-1892. doi:10.1001/jama.1996.03530480027036

29. Cella D, Riley W, Stone A, et al; PROMIS Cooperative Group. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. *J Clin Epidemiol*. 2010;63(11):1179-1194. doi:10.1016/j.jclinepi.2010.04.011

30. Pilkonis PA, Choi SW, Reise SP, Stover AM, Riley WT, Cella D; PROMIS Cooperative Group. Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS): depression, anxiety, and anger. *Assessment*. 2011;18(3):263-283. doi:10.1177/1073191111411667

31. Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: a measure of subjective stress. *Psychosom Med*. 1979;41(3):209-218. doi:10.1097/00006842-197905000-00004

32. Sundin EC, Horowitz MJ. Impact of Event Scale: psychometric properties. *Br J Psychiatry*. 2002;180:205-209. doi:10.1192/bjp.180.3.205

33. Pieterse AH, van Dulmen AM, Beemer FA, Bensing JM, Ausems MG. Cancer genetic counseling: communication and counselees' post-visit satisfaction, cognitions, anxiety, and needs fulfillment. *J Genet Couns*. 2007;16(1):85-96. doi:10.1007/s10897-006-9048-1

34. Cella D, Hughes C, Peterman A, et al. A brief assessment of concerns associated with genetic testing for cancer: the Multidimensional Impact of Cancer Risk Assessment (MICRA) questionnaire. *Health Psychol*. 2002;21(6):564-572. doi:10.1037/0278-6133.21.6.564

35. DeMarco TA, Peshkin BN, Mars BD, Tercyak KP. Patient satisfaction with cancer genetic counseling: a psychometric analysis of the Genetic Counseling Satisfaction Scale. *J Genet Couns*. 2004;13(4):293-304. doi:10.1023/B:JOGC.0000035523.96133.bc

36. Ryff CD, Keyes CL. The structure of psychological well-being revisited. *J Pers Soc Psychol*. 1995;69(4):719-727. doi:10.1037/0022-3514.69.4.719

37. LaRusse S, Roberts JS, Marteau TM, et al. Genetic susceptibility testing versus family history-based risk assessment: impact on perceived risk of Alzheimer disease. *Genet Med*. 2005;7(1):48-53. doi:10.1097/01.GIM.0000151157.13716.6C

38. 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(4):219-227. doi:10.1097/GIM.0b013e3181cef9e1

39. Chung WW, Chen CA, Cupples LA, et al. A new scale measuring psychologic impact of genetic susceptibility testing for Alzheimer disease. *Alzheimer Dis Assoc Disord*. 2009;23(1):50-56. doi:10.1097/WAD.0b013e318188429e

40. Li C, Neugroschl J, Luo X, et al. The utility of the Cognitive Function Instrument (CFI) to detect cognitive decline in non-demented older adults. *J Alzheimers Dis*. 2017;60(2):427-437. doi:10.3233/JAD-161294

41. Walsh SP, Raman R, Jones KB, Aisen PS; Alzheimer's Disease Cooperative Study Group. ADCS Prevention Instrument Project: the Mail-In Cognitive Function Screening Instrument (MCFSI). *Alzheimer Dis Assoc Disord*. 2006;20(4)(suppl 3):S170-S178. doi:10.1097/01.wad.0000213879.55547.57

42. Pan AW, Chung L, Fife BL, Hsiung PC. Evaluation of the psychometrics of the Social Impact Scale: a measure of stigmatization. *Int J Rehabil Res*. 2007;30(3):235-238. doi:10.1097/MRR.0b013e32829fb3db

43. Education Demographic and Geographic Estimates Program (EDGE). ZIP code tabulation area (ZCTA) locale assignments file documentation (NCES 2018-077). National Center for Education Statistics; 2019. Accessed December 14, 2023. https://nces.ed.gov/pubsearch

44. Kroenke K, Baye F, Lourens SG. Comparative responsiveness and minimally important difference of common anxiety measures. *Med Care*. 2019;57(11):890-897. doi:10.1097/MLR.0000000000001185

45. Raghunathan T, Lepkowski J, Hoewyk J, Solenberger P. A multivariate technique for multiply imputing missing values using a sequence of regression models. *Surv Methodol*. 2001;27(1):85-95. Accessed November 1, 2026. https://www150.statcan.gc.ca/n1/pub/12-001-x/2001001/article/5857-eng.pdf

46. Chew LD, Bradley KA, Boyko EJ. Brief questions to identify patients with inadequate health literacy. *Fam Med*. 2004;36(8):588-594.

47. Christensen KD, Uhlmann WR, Roberts JS, et al. A randomized controlled trial of disclosing genetic risk information for Alzheimer disease via telephone. *Genet Med*. 2018;20(1):132-141. doi:10.1038/gim.2017.103

48. Largent EA, Grill JD, O'Brien K, Wolk D, Harkins K, Karlawish J. Testing for Alzheimer disease biomarkers and disclosing results across the disease continuum. *Neurology*. 2023;100(21):1010-1019. doi:10.1212/WNL.0000000000206891

49. Uhlmann WR, Chan AK, Goldman JS. Now is the time: the need to update guidance to expand access to *APOE* genetic testing. *Front Dement*. 2026;5:1808512. doi:10.3389/frdem.2026.1808512

Downloaded from jamanetwork.com by guest on 11/21/2026