Brain health registry GenePool study: A novel approach to online genetics research

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Abstract

Introduction: Remote data collection, including the establishment of online registries, is a novel approach to efficiently identify risk for cognitive decline and Alzheimer’s disease (AD) in older adults, with growing evidence for feasibility and validity. Addition of genetic data to online registries has the potential to facilitate identification of older adults at risk and to advance the understanding of genetic contributions to AD.

Methods: 573 older adult participants with longitudinal online Brain Health Registry (BHR) data underwent apolipoprotein E (APOE) genotyping using remotely collected saliva samples and a novel, automated Biofluid Collection Management Portal. We evaluated acceptability of genetic sample collection and estimated associations between (1) sociodemographic variables and willingness to participate in genetics research and (2) APOE results and online cognitive and functional assessments. We also assessed acceptance of hypothetical genetics research participation by surveying a larger sample of 25,888 BHR participants.

Results: 51% of invited participants enrolled in the BHR genetics study, BHR-GenePool Study (BHR-GPS); 27% of participants had at least one APOE ε4 allele. Older participants and those with higher educational attainment were more likely to participate. In the remotely administered Cogstate Brief Battery, APOE ε4/ε4 homozygotes (HM) had worse online learning scores, and greater decline in processing speed and attention, compared to ε3/ε4 heterozygotes (HT) and ε4 non-carriers (NC).

Discussion: APOE genotyping of more than 500 older adults enrolled in BHR supports the feasibility and validity of a novel, remote biofluids collection approach from a large cohort of older adults, with data linkage to longitudinal online cognitive data. This approach can be expanded for efficient collection of genetic data and other information from biofluids in the future.

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1 | BACKGROUND

New methods to identify older adults at risk for cognitive decline and dementia due to Alzheimer’s disease (AD) have the potential to improve recruitment and screening for clinical research studies and aid diagnosis of age-related cognitive impairments in various healthcare settings. Online registries can efficiently help identify those at risk using information collected remotely, thus minimizing participant and staff burden and cost compared to in-clinic studies.1–4 Addition of genetic data to online registries has the potential to facilitate identification of older adults at risk and to advance the understanding of genetic contributions to AD.

While there are a number of genes associated with AD, apolipoprotein E (APOE) ε4 is widely known as a major genetic risk factor for AD.5–7 Compared to non-carriers (NC), those with the APOE ε4 allele have a higher prevalence of amyloid positivity,8 show an accelerated rate of cognitive decline at an older age,7 and have 3 to 12 times the increased risk of developing AD.5,6 Saliva-based DNA collection kits are a non-invasive, convenient, and resource- and cost-efficient method for remote APOE genotyping. Multiple commercial services have remotely collected DNA using saliva kits or cheek swabs9–11 from many individuals. Feasibility of remote APOE genotyping in an academic clinical research setting was previously demonstrated by Genematch, a part of the Banner Alzheimer’s Prevention Initiative recruitment registry to match individuals to AD prevention studies.12 However, remote APOE genotyping, in combination with the collection of longitudinal cognitive, health, and lifestyle data online, has not previously been reported.

Brain Health Registry (BHR) is an online website and registry of more than 70,000 participants with the goal of recruitment, assessment, and longitudinal monitoring of participants for neuroscience research.13–15 The BHR platform includes a comprehensive battery of self- and study partner–report questionnaires and online neuropsychological tests. The Brain Health Registry-GenePool Study (BHR-GPS) is a novel approach to combining cognitive and health data with remote genotyping in a cohort of older adults who are already engaged in longitudinal online evaluation. As part of this study, the BHR Biofluid Collection Management Portal was developed to support remote biofluids collection by automating saliva kit tracking and participant communication. We tested the hypothesis that remote APOE genotyping in BHR-GPS, without providing APOE results to participants, is feasible and acceptable. In the context of inconsistent past literature exploring the relationship between APOE and cognition in clinically normal older adults,16 we explored whether APOE ε4 gene dose is associated with worse cognition and everyday functioning in a sample of 529 older adults in BHR, as measured by (1) cross-sectional and longitudinal change in scores from an online, unsupervised version of the Cogstate Brief Battery (CBB);17,18 (2) subjective memory concerns (SMCs); and (3) self- and study partner–reported versions of the Everyday Cognition Scale (ECog), a measure of functional decline.13,19 We also explored sociodemographic and cognitive variables that were associated with willingness to participate in genetics research and actual participation in BHR-GPS.

There are multiple ways in which this approach can potentially impact the clinical AD research field in the future. It can be used to facilitate clinical AD and dementia research by helping to screen for clinical trials. It allows investigation of participant characteristics, including sociodemographic factors, that are associated with participation in genetics research, which can inform future, novel efforts to recruit and engage older adults. Furthermore, remote saliva collection has the potential to more broadly facilitate AD genetics research beyond APOE genotype, and to facilitate other clinical research using saliva, such as research focused on effects of hormones and cytokines on health and disease.

2 | METHODS

2.1 | BHR overview

BHR is a public online research registry for recruitment, assessment, and longitudinal monitoring focusing on cognitive aging.13–15 Participants provide informed consent electronically and are invited to complete a series of online and unsupervised self-report questionnaires (e.g., demographics, medical history, memory complaints and family history of AD) and online cognitive assessments every 6 months. BHR also includes a Caregiver and Study Partner Portal (CASPP)12 allowing each participant to have a study partner who separately answers questions about the participant’s cognitive and functional status. This study focused on two BHR samples. The first sample included BHR participants who completed a “Genetic study interest questionnaire” (N = 25,888). The second sample included BHR participants who were referred (N = 1117) and completed participation (N = 533) in BHR-GPS.

2.2 | Genetic study interest questionnaire

BHR participants were asked to complete a survey about their interest in participating in a study that collects and stores genetic data. Questions included willingness to provide a saliva sample at home and interest level in providing a sample when results are not shared with the participant. Additional questions about the willingness to provide a blood sample for genetic testing either at home or by visiting a local medical clinic are also included; 268 participants who completed...
the questionnaire twice due to technical issues were excluded from analyses.

2.3 BHR-GPS enrollment

BHR-GPS inclusion criteria included currently enrolled BHR participants who were age 60 and over and had completed: at least three longitudinal CBB sessions, and a medical history questionnaire and self-report Everyday Cognition (ECog) within the past 2 years. All participants had a study partner enrolled in BHR who completed the informant version of ECog at least once. BHR-GPS participants were required to have existing, longitudinal online BHR data to create a cohort of older adults with known APOE genotype, who were also well characterized in terms of their cognitive and functional status to facilitate future analyses aimed at validating online data. Participants meeting inclusion criteria were sent a referral e-mail describing the study and providing instructions for enrollment. Nineteen BHR participants who declined participation in BHR-GPS completed a survey about why they declined. The most common reason was privacy/data sharing concerns (n = 13, 68%). Fifteen participants were accidentally referred twice and excluded from these analyses. The referral/enrollment metrics evaluated were whether invited participants (1) responded to the referral e-mail by clicking the embedded link, (2) indicated interest in enrollment on the BHR website, and (3) successfully enrolled in the study.

2.4 BHR-GPS measures

BHR-GPS participants completed the following online questionnaires and cognitive assessment before enrollment.

2.4.1 Sociodemographic

BHR participants complete a profile questionnaire that asks them to self-report sociodemographic variables, including: age, sex (male, female), race (White, African American, Asian, Native American, Pacific Islander, multiple, other), ethnicity (Latino, non-Latino), and educational attainment. For analyses of sociodemographic variables, multiple categories of race were collapsed into two categories (White, non-White). Further, the categorical variable education was converted into a continuous variable called years of education, ranging from 6 to 20 years.

2.4.2 Everyday Cognition (ECog)

BHR participants and study partners completed an online adaptation of the ECog, consisting of 39 items assessing the participant’s or study partner–reported capability to perform everyday tasks compared to activity levels 10 years prior, including functional activities that map to cognitive abilities across six domains.

2.4.3 Cogstate Brief Battery (CBB)

The CBB is a computerized cognitive assessment battery consisting of four subtests comprised of playing card stimuli, which measure psychomotor function (Detection), visual attention (Identification), visual learning (OneCard Learning), and working memory (OneBack). CBB has been validated in supervised and unsupervised settings in a variety of populations. Participants self-administered the CBB through BHR, completing a practice session before each subtest. Outcome variables for the CBB subtests include speed (reaction time for correct responses in milliseconds normalized using a log 10 transformation) for the Detection, Identification, and OneBack tests; and accuracy (proportion of correct responses, normalized using an arcsine transformation) for the OneCard Learning test. Higher scores reflect worse performance for Detection, Identification, and OneBack; lower scores are worse for OneCard Learning.

2.4.4 Self-reported cognitive impairment

SMCs were assessed with the question, “Are you concerned that you have a memory problem?” Self-reported mild cognitive impairment (MCI) was assessed with the question, “Please indicate whether you currently have or have had any of the following conditions in the past: MCI.”
2.4.5 | Feedback questionnaire

After the saliva kit was successfully returned, participants received an e-mail to complete an online questionnaire about their experience. The feedback questionnaire included questions about expectation of time to complete the saliva kit, clarity of instructions, difficulty using the saliva kit, and if they would like to participate in a similar study.

2.5 | BHR Biofluid Collection Management Portal

Participants provided consent online, which included language stating that participants would not receive results of APOE testing. They were then mailed salivary DNA self-collection kits with detailed instructions and return mailing supplies. The participants collected and mailed back their saliva samples. Saliva kit tracking and participant communication were automated using a novel BHR Biofluid Collection Management Portal, which allows staff to collect, store, maintain, and organize data related to remote biofluids collection. An application programming interface was set up in the portal to provide real-time status updates. E-mails were automatically sent to participants to notify them when their kits were shipped, when their sample was received by study staff, and to request a status update if a kit was not returned within a specified period of time. Once samples were processed, APOE results were uploaded into the Portal and APOE data was linked to other BHR data.

2.6 | APOE genotyping

Saliva was collected using the Oragene kit (DNA Genotek, Inc. Ottawa, Ontario, Canada), and DNA was extracted using the protocol specified by the manufacturer from 0.5 mL saliva. DNA extracted was split into several tubes with only one of the tubes used for genotyping. DNA yields ranges between 10 and 25 ug, sufficient for a wide variety of genetic analyses. DNA extracted from saliva has been successfully used for whole genome single nucleotide polymorphisms and sequencing (1 ug being sufficient). APOE genotyping was performed according to the restriction isotyping protocol of Hixson and Vernier. APOE restriction isotyping relies on cleavage at polymorphic HhaI sites to distinguish E2, E3, E4 sequences, followed by gel electrophoresis. The genotyping results were subsequently incorporated into an algorithm, resulting in designation of ε2, ε3, or ε4 genotypes. In addition to inclusion of positive and negative controls, 10% of samples (randomly selected) were double genotyped. From all samples, original saliva was kept, and DNA extracted can be used for comparison. The remaining saliva was stored for future use and quality control.

2.7 | Statistical analysis

For the purpose of this study, APOE genotype was analyzed as a categorical variable with three levels: APOE homozygous (HM, ε4/ε4), APOE heterozygous (HT, ε3/ε4), and non-carrier (NC, ε3/ε3 or ε2/ε3). Those with APOE ε2/ε4 genotype were excluded from analyses due to their previously described variable AD risk profile. For a subset of analyses, we also considered APOE as a dichotomous variable of APOE+ (ε4/ε4 or ε3/ε4) or APOE− (ε3/ε3 or ε2/ε3) due to the small number (n = 12) of participants in the HM group. Variables of interest were compared among the different APOE groups (HM, HT, and NC) using one-way analysis of variance with post hoc Tukey’s test for continuous variables; chi square test of proportions with post hoc pairwise analysis for categorical variables. We conducted exploratory analyses to determine whether APOE ε4 gene dose was associated with worse cognition and everyday functioning. We also identified sociodemographic and cognitive variables that were associated with willingness to participate in genetics research and actual participation in BHR-GPS. Ordinary least squares linear regression was used to test for associations between APOE gene dose and cross-sectional scores on the four CBB subtests, self-report ECog, study partner–report ECog, and SMCs. Linear mixed effects models were used to assess associations between longitudinal change in CBB subtests and APOE gene dose. We fit separate linear mixed effects models to each CBB score. Each model included random intercepts and time effects, main effect terms for predictors, and interactions of each predictor with time. The time by predictor interaction terms were used to assess the magnitude of the association of each predictor with change in CBB score. Covariates included age, sex, and education. Logistic regression was used to estimate associations between demographic variables (predictors and covariates) and participation in genetic studies. Participation metrics included (1) self-reported willingness to participate in genetics research assessed by responses to a Genetic Study Interest questionnaire. The outcomes, with yes or no response options, included willingness to provide an at-home saliva sample for genetic testing. (2) For all participants invited to enroll in BHR-GPS, the investigated outcomes, with yes or no response options, were whether the participant responded to the referral e-mail, indicated interest, and enrolled in the study. Predictors included sex (male = 0, female = 1), Latino ethnicity (non-Latino = 0, Latino = 1), racial category (White only = 0, non-White = 1), and years education (6 to 20). Covariates were age at baseline and SMC. Adjusted odds ratios (aOR) and 95% confidence intervals (CI) are reported for all logistic regression models. False discovery rate analysis was used to correct for multiple comparisons (multiple referral outcomes). All analyses were performed in R using R packages psych, gmodels, epiDisplay, and pROC.

3 | RESULTS

3.1 | Interest in genetics studies among BHR participants

BHR participants were invited to complete a questionnaire about general interest in genetic studies. Of the 25,888 participants who completed the questionnaire, 88% expressed willingness to participate in a genetics study involving remote saliva collection, 83% said they would
TABLE 1  Responses to genetic study interest questionnaire

| Question                                                                 | Total | Yes   | No    | I do not know |
|--------------------------------------------------------------------------|-------|-------|-------|---------------|
| Would you participate/volunteer for a study in which you are asked to provide a saliva sample for genetic testing using an at-home self-collection kit? | 25,877 | 22,829 (88%) | 995 (4%) | 2053 (8%)      |
| Would you be interested in knowing whether you are a carrier of a gene that affects your risk of developing Alzheimer’s disease? | 25,859 | 21,520 (83%) | 1647 (6%) | 2692 (10%)   |
| If you knew the results of your sample would not be shared with you, would that change your interest in participating? | 25,858 | 6386 (25%) | 14,088 (54%) | 5384 (21%) |

TABLE 2  Associations between sociodemographic characteristics and willingness to participate in genetics studies

|                                                                 | Adjusted odds ratio | 95% confidence interval | p.fdr (LR-test) |
|-----------------------------------------------------------------|---------------------|-------------------------|-----------------|
| Willing to undergo in-clinic blood draws for genetic testing (N=12,377) |                     |                         |                 |
| Latino                                                          | 1.23                | 0.75,2.04               | .93             |
| Female                                                          | 1.18                | 1.02,1.37               | .15             |
| Years education                                                 | 0.97                | 0.95,1                  | .15             |
| Non-White                                                       | 0.81                | 0.63,1.05               | .58             |
| Age                                                             | 0.99                | 0.98,1.00               | .38             |
| Reported subjective memory concern                              | 1.59                | 1.39,1.82               | .003†           |
| Willing to provide saliva samples for genetic testing (N=13,123) |                     |                         |                 |
| Latino                                                          | 0.93                | 0.49,1.78               | .93             |
| Female                                                          | 1.17                | 0.94,1.46               | .27             |
| Years education                                                 | 0.99                | 0.96,1.042              | .93             |
| Non-White                                                       | 0.87                | 0.61,1.25               | .75             |
| Age                                                             | 1.01                | 0.99,1.02               | .46             |
| Reported subjective memory concern                              | 1.66                | 1.37,2.03               | .003†           |

*p.fdr = P-value adjusted for multiple comparisons using false discovery rate analysis.
†P-values < .05

be interested in knowing if they are a carrier of a gene that affects their risk of developing AD, and 54% said their interest in participating in a genetics study would not depend on disclosure of results (Table 1). SMCs were associated with greater probability of willingness to participate in a genetic study requiring in-clinic blood draw, as well as a higher willingness to participate in a genetic study requiring remote saliva collection (Table 2).

3.2  Participants enrolled in BHR-GPS

A total of 1117 BHR participants were invited to join BHR-GPS. Of those, 573 (51%) consented to enroll in the study, and 529 had successful APOE genotyping (Figure 1 and Table 3). There was no statistical difference between the participants who completed the BHR-GPS study (N = 533) and BHR-GPS participants who dropped out after enrollment (N = 40) in regard to age, sex, years of education, race, or ethnicity. Of those with completed APOE genotyping, 143 (27%) had at least one APOE ε4 allele (APOE ε3/ε4: n = 120, 23%; APOE ε4/ε4: n = 12, 2%; APOE ε2/ε4: n = 11, 2%; 386 (73%) had no APOE ε4 alleles (APOE ε2/ε3: n = 77, 15%; APOE ε3/ε3: n = 309, 58%). Compared to APOE NC,  

FIGURE 1  Flow diagram of the progress through eligibility, enrollment, sample collection, and processing
Factors associated with BHR-GPS enrollment

Acceptability

We considered whether sociodemographic factors or memory concerns were associated with the BHR-GPS recruitment metrics. Higher educational attainment was associated with higher probability of interest in, and enrollment in, BHR-GPS. No other predictors were significantly associated with any outcome (Table 4).

3.4 Acceptability

Of the 533 BHR-GPS participants who completed saliva kits, 458 (86%) completed a post-study feedback questionnaire. Of those, 397 (87%) respondents rated the difficulty of using the saliva collection kit as 1 or 2 based on a scale of 1 to 5 (1 = least difficult and 5 = most difficult); 417 (91%) reported the instructions were either “extremely clear” or “very clear”; and 446 (97%) reported that if given the opportunity, they would agree to participate in a similar study.

3.5 APOE associations with online cognitive and functional measures

In multivariable regression models accounting for demographics, APOE HM genotype was associated with worse CBB visual learning (OneCard Learning) scores compared to NC (Table 5). APOE HM genotype was also associated with greater longitudinal decline in psychomotor function (Detection) and attention (Identification) CBB subtest scores (Table 5). There were no significant associations between APOE gene dose and any other online measures considered, including the other CBB subtests, subjective functional decline measured by the

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### TABLE 3  Demographic and cognitive profile of BHR-GPS participants with APOE results

|                          | Homozygous (HM) (APOE ε4/ε4) | Heterozygous (HT) (APOE ε3/ε4) | Non-carrier (NC) (APOE ε2/ε3/ε3) | Total |
|--------------------------|-------------------------------|-------------------------------|----------------------------------|-------|
| Total number enrolled    | 12                            | 120                           | 386                              | 518   |
| Age                      | 65.92 ± 4.29* (61–77)         | 69.59 ± 5.87* (60–88)         | 70.94 ± 6.97* (60–95)            | 70.51 ± 6.73 (60–95) |
| Years education          | 17.0 ± 2 (14–20)              | 17.1 ± 2.25 (12–20)           | 17.2 ± 2.16 (12–20)              | 17.1 ± 2.18 (12–20) |
| White                    | 11 (91.7%)                    | 118 (98.3%)*                  | 357 (92.5%)                      | 486 (93.8%) |
| Female                   | 6 (50.0%)*                    | 77 (64.2%)                    | 252 (65.3%)                      | 335 (64.7%) |
| Family history of AD     | 6 (50.0%)*                    | 43 (35.8%)*                   | 97 (25.1%)                       | 146 (28.2%) |
| Self-report SMC          | 6 (50.0%)*                    | 45 (37.5%)                    | 148 (38.3%)                      | 199 (38.4%) |
| Study partner-report SMC | 2 (16.7%)                     | 18 (15.0%)                    | 73 (18.9%)                       | 93 (18.0%) |
| Self-report MCI          | 0 (0.0%)                      | 13 (10.8%)                    | 48 (12.6%)                       | 61 (11.8%) |
| Self-report ECog score   | 1.48 ± 0.56 (1–2.62)          | 1.40 ± 0.44 (1–3.33)          | 1.40 ± 0.42 (1–3.55)             | 1.4 ± 0.42 (1–3.55) |
| N=514                    |                               |                               |                                  |       |
| Study partner-report ECog score | 1.23 ± 0.32 (1–2.03)          | 1.26 ± 0.35 (1–3.08)          | 1.28 ± 0.41 (1–3.82)             | 1.28 ± 0.39 (1–3.82) |
| N=501                    |                               |                               |                                  |       |
| Cogstate Detection       | 2.53 ± 0.06 (2.39–2.62)       | 2.54 ± 0.08 (2.38–2.78)       | 2.55 ± 0.08 (2.37–2.82)          | 2.54 ± 0.08 (2.37–2.82) |
| (Psychomotor Speed)      |                               |                               |                                  |       |
| Cogstate Identification  | 2.70 ± 0.07 (2.6–p2.82)       | 2.70 ± 0.06 (2.57–2.95)       | 2.70 ± 0.05 (2.54–p2.87)         | 2.70 ± 0.06 (2.54–p2.95) |
| (Attention)              |                               |                               |                                  |       |
| Cogstate One Back        | 2.85 ± 0.058 (2.78–2.94)      | 2.86 ± 0.08 (2.71–3.14)       | 2.86 ± 0.08 (2.66–3.09)          | 2.86 ± 0.08 (2.66–3.14)|
| (Working Memory)         |                               |                               |                                  |       |
| Cogstate OneCard learning | 1.00 ± 0.10 (0.63–1.23)       | 1.07 ± 0.11 (0.804–1.35)      | 1.05 ± 0.13 (0.47–1.41)          | 1.05 ± 0.13 (0.47–1.41) |
| (Visual Learning)        |                               |                               |                                  |       |

Notes: For continuous variables, values shown are mean ± SD (range). For categorical variables, values shown are number of participants (% of total). Participants with APOE ε2/ε4 genotype (n=11), not included in the table, had an average age 70.36 ± 8.03 (range: 61 to 87), 72.7% female, 81.8% White, and average years of education 17.36 ± 2.84 (range 12 to 20).

*P < .01 compared to NC, †P < .05 compared to HT, using chi square test of proportions with post hoc pairwise analysis for categorical variables; one-way ANOVA with post hoc Tukey’s test for continuous variables.

Abbreviations: AD, Alzheimer’s disease; ANOVA, analysis of variance; APOE, apolipoprotein E; BHR, Brain Health Registry; ECog, Everyday Cognition; GPS, GenePool Study; HM, ε4/ε4 homozygotes; HT, ε3/ε4 heterozygotes; MCI, mild cognitive impairment; NC, ε4 non-carriers; SD, standard deviation; SMC, subjective memory concerns.

the APOE HM (ε4/ε4) group was younger, included a lower percentage of females, and higher percentages of those who reported a first degree relative with AD and those with SMCs (Table 3).
TABLE 4  Associations between sociodemographic characteristics and BHR-GPS referral/enrollment

|                               | Adjusted odds ratio | 95% confidence interval | p.fdr (LR-test) |
|-------------------------------|---------------------|--------------------------|-----------------|
| Responded to referral e-mail  |                     |                          |                 |
| Latino                        | 1.12                | 0.37, 3.40               | .94             |
| Female                        | 1.9                 | 0.90, 1.56               | .28             |
| Years education               | 1.04                | 0.98, 1.1                | .31             |
| Non-White                     | 1.00                | 0.57, 1.77               | .99             |
| Age                           | 1.03                | 1.01, 1.05               | .065            |
| Reported subjective memory concern | 0.94             | 0.72, 1.23               | .68             |
| Interested in referral        |                     |                          |                 |
| Latino                        | 0.92                | 0.11, 7.77               | .94             |
| Female                        | 1.45                | 0.85, 2.48               | .28             |
| Years education               | 1.19                | 1.07, 1.33               | .01             |
| Non-White                     | 2.01                | 0.46, 8.87               | .75             |
| Age                           | 0.97                | 0.93, 1.01               | .33             |
| Reported subjective memory concern | 0.71             | 0.40, 1.23               | .35             |
| Enrolled in referral          |                     |                          |                 |
| Latino                        | 0.67                | 0.13, 3.34               | .94             |
| Female                        | 1.26                | 0.79, 1.99               | .33             |
| Years education               | 1.13                | 1.02, 1.24               | .04             |
| Non-White                     | 0.84                | 0.33, 2.14               | .90             |
| Age                           | 0.99                | 0.95, 1.02               | .73             |
| Reported subjective memory concern | 0.92             | 0.58, 1.46               | .55             |

*p.fdr = P-value adjusted for multiple comparisons using false discovery rate analysis.

Abbreviations: BHR, Brain Health Registry; GPS, GenePool Study.

ECog, or SMCs (P values > .15 for all). There were no significant differences between the NC versus HT, or HT versus HM groups for any cognitive or functional measures. There were no significant associations between APOE and any cognitive or functional measure when considering APOE as a dichotomous variable of APOE+ (including ε4/ε4 and ε3/ε4 genotypes) versus APOE− (including ε3/ε3 and ε3/ε2 genotypes).

4 | DISCUSSION

The major findings of this study were (1) remote DNA collection and APOE genotyping from a large cohort of older adults, who have been previously characterized remotely in an online registry, without disclosure of results, is feasible and has high acceptability to enrolled participants. This was supported by enrollment of more than 500 participants without requiring the burden and cost of in-clinic visits, the high completion rate (93% of those enrolled), and positive participant feedback about their experience. (2) The results from a novel survey assessing interest in genetics studies, completed by more than 25,000 BHR participants, show a high rate of willingness to participate in genetics research, and high levels of interest in genetic results disclosure, although the lack of disclosure was not indicated as a barrier to participation for most participants. SMCs were associated with greater willingness to participate, suggesting that concern about developing dementia may be a motivating factor. (3) In a cohort of 529 older adults, the vast majority of whom were likely to be cognitively unimpaired (CU), APOE ε4/ε4 HM had significantly worse online learning test scores, and showed greater decline in processing speed and attention reaction time tasks compared to ε4 NC. (3) APOE ε4/ε4 participants were more likely to report a first-degree relative with AD and SMCs.

An important component of this study, with potential to broadly impact the clinical research field, was the development of a novel data infrastructure, the BHR Biofluid Collection Management Portal, to manage remote collection of saliva. Features included automated participant communications and saliva kit tracking. BHR-GPS participants were tracked and e-mailed using this infrastructure, which provided a streamlined and automated approach to remote biological sample collection, reducing staff burden. Moreover, the infrastructure allowed for the questionnaire and cognitive test data collected online to be
linked to genetic data collected remotely, leading to ease of future analysis, further reducing staff burden. This infrastructure will be used to expand APOE genotyping and other genetic testing to more BHR participants, as well as to manage the collection of blood and other biomarker data in future studies. In future studies, the remote saliva collection methods we developed can be used to more extensively explore the genetics of AD and other diseases (DNA samples from current BHR-GPS participants are being stored for future genetic analysis), and to facilitate clinical research investigating effects of hormones and cytokines on health and disease. Thus, the BHR Biofluid Collection Management Portal has the potential to broadly facilitate clinical research.

To our knowledge, this is the first study to combine remote APOE genotyping with longitudinal online characterization, including subjective measures and cognitive assessments, in a large cohort of older adults. Our results demonstrate the feasibility of the approach. In our study, 51% of those invited successfully enrolled, and 93% of those enrolled completed the study. Although this enrollment rate is lower than more traditional study designs, in which genetic data are collected as part of an in-clinic study,28,35–37 we would like to emphasize the novelty and, most importantly, the scalability of the online approach. Remote methodology allows collection of genetic data from a large number of participants, using few resources, because it precludes the need for associated costs and participant burden of in-clinic collection. Once the infrastructure for remote collection has been set up, the program can be rapidly scaled up to create a large cohort of older adults with genetic data linked to online cognitive assessments.

A total of 23% of BHR-GPS participants were HT (ε3/ε4) and 2% were HM (ε4/ε4). Compared to previous estimates of APOE ε4 prevalence in the population,12,35,38 and in an online registry,12 our sample may slightly underrepresent APOE ε4 carriers, possibly due to a selection bias for CU older adults. However, such a comparison is complicated by the variable APOE allele prevalence across different racial and ethnic groups, and the lack of diversity in our sample.39–41

In our sample of older adults with existing longitudinal cognitive data, APOE HM (ε4/ε4 genotype) was associated with worse online visual learning test performance, as well as greater longitudinal decline in processing speed and attention, compared to NC (ε3/ε3 or ε2/ε3). Conversely, we did not find any associations between APOE gene dose and measures of subjective decline (ECog or SMCs). While evidence that APOE affects cognition42–46 and daily functioning47,48 in CU older adults is inconsistent, our finding supports the validity of our remote assessment approach. Many past studies have found that associations between APOE and cognition are attributable to the presence of preclinical AD in a subset of CU older adults.43,46,49–52 The AD biomarker status of our participants, such as levels of brain amyloid, is unknown. Additional longitudinal data over a longer time period in a larger, more diverse cohort may allow us to more clearly observe cognitive decline associated with APOE ε4 in BHR, and future studies will explore the relationship between longitudinal change in subjective decline and APOE.

A higher percentage of HM participants (50%) endorsed memory concerns compared to NC (38.3%; Table 3). However, when account-
in in-clinic research. 60 we found no associations between sex or any other sociodemographic factors and willingness to participate in genetic studies in our sample. This may be due to an overall selection bias in BHR for those who are interested in research participation. Analysis of a more diverse, generalizable sample is necessary to better understand the role of sociodemographic factors in research participation.

We acknowledge limitations of this study. The BHR cohort in general, and the BHR-GPS subsample specifically, are likely to be affected by multiple selection biases, including for those with computer and internet access and literacy. Participants join BHR from the general public and are not compensated for participation, contributing to high levels of drop-out over time and substantial missing data. Inclusion criteria for BHR-GPS required existing longitudinal BHR data, which may have positively influenced enrollment rates and created a bias for participants indicating higher levels of study acceptability in feedback questionnaires. Because BHR-GPS participation is completed remotely, we have no way to confirm the identity of participants who provided saliva samples. Self-report of MCI may be unreliable. To more accurately address this issue, we are assembling a cohort of participants with clinically confirmed diagnosis. The BHR-GPS sample lacks racial, ethnic, and educational diversity, which effects generalizability of results. Several diversity initiatives are now underway to increase enrollment of underrepresented groups in BHR, including the use of culturally tailored advertising, a Spanish-language website, and plans to make the BHR platform more compatible with mobile devices.

In conclusion, our results support the feasibility and acceptability of remote APOE genotyping of an older population enrolled in an online registry, with linkage between genetic results and longitudinal health and cognitive data. Saliva-based collection kits paired with an automated data collection infrastructure offer the possibility for remote collection of genetics that are non-invasive, convenient, and resource- and cost-efficient.

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CONFLICTS OF INTEREST
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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of the article.

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