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## FEATURED ARTICLE

# Remote blood collection from older adults in the Brain Health Registry for plasma biomarker and genetic analysis

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**Abstract**

**Introduction:** Use of online registries to efficiently identify older adults with cognitive decline and Alzheimer's disease (AD) is an approach with growing evidence for feasibility and validity. Linked biomarker and registry data can facilitate AD clinical research.

**Methods:** We collected blood for plasma biomarker and genetic analysis from older adult Brain Health Registry (BHR) participants, evaluated feasibility, and estimated associations between demographic variables and study participation.

**Results:** Of 7150 participants invited to the study, 864 (12%) enrolled and 629 (73%) completed remote blood draws. Participants reported high study acceptability. Those from underrepresented ethnocultural and educational groups were less likely to participate.

**Discussion:** This study demonstrates the challenges of remote blood collection from a large representative sample of older adults. Remote blood collection from > 600 participants within a short timeframe demonstrates the feasibility of our approach, which can be expanded for efficient collection of plasma AD biomarker and genetic data.

**KEYWORDS**

acceptability, aging research, Alzheimer's disease, brain health registry, education, engagement, ethnicity, feasibility, genetics, internet, plasma biomarkers, race, research registry

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## 1 | BACKGROUND

Recent studies demonstrate the potential for plasma biomarkers of amyloid beta (A $\beta$ ), phosphorylated tau (p-tau), and neurofilament light (NfL) to identify older adults with dementia due to Alzheimer's disease (AD), as well as those with preclinical (presymptomatic, biomarker positive) and prodromal (early symptomatic) AD.<sup>1</sup> Compared to traditional methods (positron emission tomography, magnetic resonance imaging [MRI], cerebrospinal fluid) to measure A $\beta$ , tau, and neurodegeneration, blood samples for plasma biomarkers are easy to collect and non-invasive, and therefore have the potential to be used broadly for community-based phenotyping.

Online registries can efficiently identify those at increased risk for AD, including those with preclinical and prodromal AD, with the potential to minimize participant and staff burden and reduce cost compared to in-clinic studies.<sup>2-5</sup> The Brain Health Registry (BHR) is an online registry to facilitate recruitment and longitudinally monitor participants for neuroscience research. BHR, with >90,000 participants, collects cognitive, everyday functioning, mood, health history, family history, and lifestyle data remotely using self- and study partner-report questionnaires and online neuropsychological tests.<sup>6-8</sup> However, online registries typically lack biomarker phenotyping. BHR, like many in-clinic studies, trials, and other online registries, lacks diversity of ethn racial, and socioeconomic groups,<sup>7,9-15</sup> which limits the impact and generalizability of research findings.<sup>16</sup> The overall goal of this work was to assess the feasibility of remote blood collection from a representative group of older adults in an online registry for plasma biomarker analysis.

Using the BHR platform, we developed a novel online infrastructure for blood collection from BHR participants through a collaboration with local phlebotomy centers and automated blood sample tracking and participant communication. We assessed the feasibility and acceptability of our approach, and addressed scalability by estimating the amount of individual support participants requested during the study. To identify selection biases, we tested the hypothesis that individuals from ethnocultural and education attainment groups that have historically been under-included from AD and related dementias (ADRD) clinical research are less likely to enroll in and complete the study.<sup>13-15</sup>

## 2 | METHODS

### 2.1 | Brain Health Registry

BHR is a public online research registry and cohort for recruitment, assessment, and longitudinal monitoring with a focus on cognitive aging.<sup>6-8</sup> Participants provide informed consent electronically and are invited to complete unsupervised online self-report questionnaires and online neuropsychological tests every 6 months. Each participant can invite a study partner, who separately enrolls, consents, and answers questions about the participant's cognition and everyday functioning.<sup>6</sup> This study included a sample of BHR participants (n = 7150) who were invited to complete blood draws at local phlebotomy centers.

### RESEARCH IN CONTEXT

- 1. Systematic review:** Using PubMed, authors reviewed past literature on remote saliva and blood collection, and associations between demographic variables and Alzheimer's disease (AD) clinical study participation. Novel analyses included: (a) feasibility and acceptability of remote blood collection in older adults enrolled in an online study; and (b) participation of underrepresented ethnocultural and education groups in the study. We also describe novel, online infrastructure for collecting and tracking remote blood draw.
- 2. Interpretation:** We demonstrate feasibility and acceptability of remote blood collection for AD plasma biomarker and genetic analysis from a large cohort of older adults with longitudinal online data. Similar to past studies in other settings, we failed to enroll underrepresented populations and engage them adequately for study completion.
- 3. Future directions:** Future studies will determine the associations between AD plasma biomarkers and online cognitive and functional variables. We also plan to expand and deploy culturally tailored strategies to improve diversity.

### HIGHLIGHTS

- Six hundred twenty-nine Brain Health Registry participants completed the study in 8 weeks.
- Blood was obtained remotely using local phlebotomy centers.
- We failed to adequately enroll underrepresented ethnocultural populations.
- We failed to adequately enroll those with low education levels.
- Future studies will process blood samples for Alzheimer's disease plasma biomarkers.

### 2.2 | Enrollment

Inclusion criteria included existing BHR participants age 55 and over with no clinical or self-reported diagnosis of dementia. Dementia diagnosis was assessed by: (1) self-report of the question, "Please indicate whether you currently have or have had any of the following conditions in the past: Alzheimer's Disease, Dementia, Frontotemporal Dementia (FTD), or Lewy Body Disease (LBD)" or (2) had a clinically confirmed diagnosis of dementia from another study.<sup>17</sup> Participants were required to have completed two BHR online cognitive assessments:

Cogstate Brief Battery (CBB)<sup>18-22</sup> and study partner-report Everyday Cognition Scale (ECog).<sup>23</sup> Additionally, participants were required to reside in California around the metropolitan areas of San Francisco, Palo Alto, or Los Angeles. To maximize recruitment of individuals from underrepresented populations (URPs), which we define herein as those who did not self-identify as White and those with less than a bachelor's degree educational attainment, the maximum geographical radius around sites was 100 miles for URPs and 50 miles for all others. Due to future goals of obtaining imaging data in the same cohort, participants deemed unsafe for MRI were also excluded. MRI safety was assessed with the questions, "Do you currently have: A cardiac pacemaker/defibrillator; Any surgical metal or any foreign objects in your body; Any stents, filter, or intravascular coils; Internal pacing wires; Sternum wires; or Claustrophobia?" and "Have you worked extensively with metal (grinding, welding, etc.)?"

Participants meeting inclusion criteria were sent an e-mail invitation describing the study and providing instructions for enrollment. Participants were recruited between February 24 and March 10, 2020 and May 28 and June 30, 2020. (Due to the COVID-19 pandemic, the University of California San Francisco [UCSF] stopped all non-essential research, which resulted in a pause in recruitment and enrollment from March 10 to May 28.)

### 2.3 | Electronic informed consent

This study was approved by the University of California, San Francisco Institutional Review Board and conducted in accordance with all regulations regarding the ethical use of research participants. All participants completed an online, electronic informed consent document.<sup>24</sup> Potential participants received a study invitation e-mail. Those who selected a "Tell me more" link were taken to a longer description of the study after they logged into the BHR participant portal. The potential participant was then given the option to select "I am interested" or "I am not interested." If they selected "I am interested," they were taken to the electronic consent. Of the 864 participants that enrolled, 12 (1.4%) ultimately withdrew consent.

## 2.4 | Online measures

### 2.4.1 | Sociodemographics

Participants self-reported sociodemographic variables including: age, sex (male, female), race (Asian, Black/African American, Caucasian/White, Native American, Pacific Islander, Other, decline to state), ethnicity (Latino, non-Latino, decline to state), and educational attainment. Throughout the article, we refer to those who selected "White/Caucasian" as "White," following current guidance on the reporting of ethnocultural identity.<sup>25</sup> For our analyses, multiple categories of race and ethnicity were collapsed into two categories (White, non-White) due to the low overall number of non-White individuals. Further, the categorical education variable was converted into a

continuous variable, years of education, ranging from 6 to 20 years. Throughout the article, we use the term URPs to define ethnocultural and educational attainment groups who ADRD clinical researchers have historically failed to adequately recruit, retain, and engage in their research.<sup>25</sup> Due to this failure, these groups are under-included and underrepresented in the vast majority in ADRD clinical research studies, including BHR. For our analyses, URP specifically refers to those who self-identify as non-White and those with lower levels of educational attainment.

### 2.4.2 | Self-reported memory concerns and cognitive impairment

Subjective memory complaints (SMC) 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: Mild Cognitive Impairment."

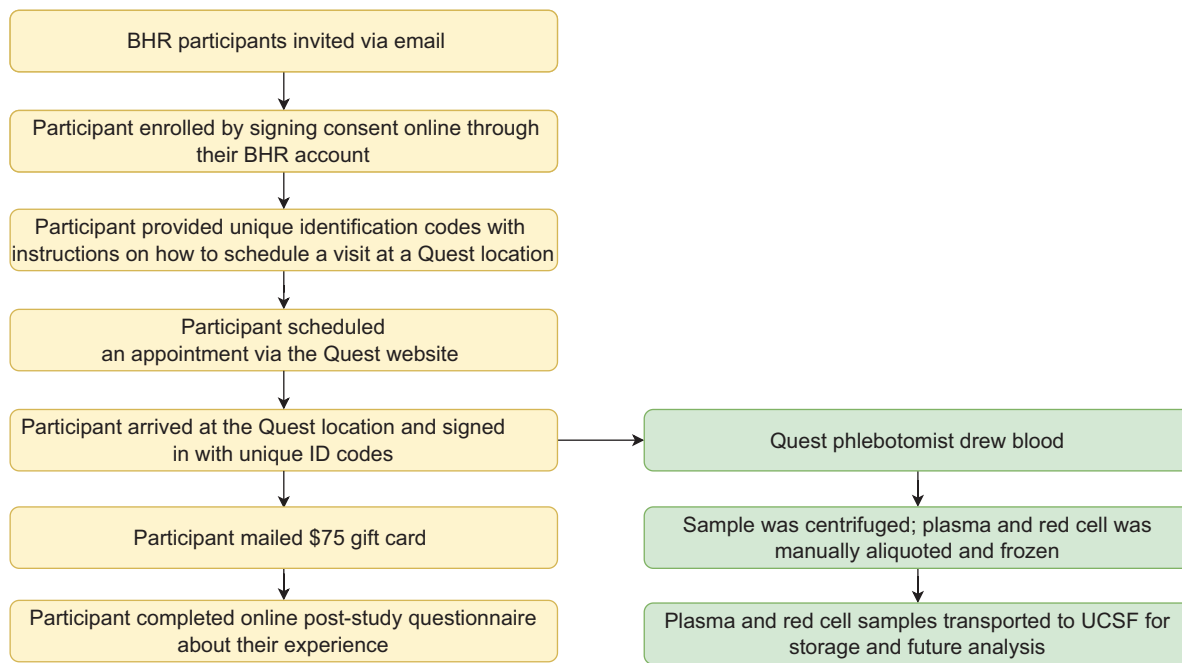
### 2.4.3 | Post-study questionnaire

After the blood sample was successfully collected, participants received an e-mail asking them to complete an online questionnaire about their experience. The post-study questionnaire included questions about difficulty of scheduling an appointment at a Quest Diagnostics phlebotomy center, expectation of time to complete the blood draw, and willingness to participate in a similar study in the future.

### 2.4.4 | Decline survey

Participants who were invited to enroll could actively decline participation by marking "not interested" from their invitation e-mail, clicking the "decline" button at the end of the consent form, or by e-mailing the study team to withdraw consent after enrolling. Participants who actively declined participation could complete an optional Decline Survey, in which they could indicate their reason(s) for decline, including "This study takes too much time," "This study does not interest me," "I have concerns about privacy or sharing information," and "Other [open text]."

Participants who consented but did not complete their blood draw were sent an automated e-mail either 7 or 13 days after consent asking to provide a status update. Reminder e-mails were sent if the participant did not respond. Participants could select multiple reasons: (1) "I already visited a Quest Diagnostics Center and completed my blood draw"; (2) "I have already scheduled an appointment at a Quest Diagnostics Center and will be completing my blood draw shortly"; (3) "I have not scheduled an appointment, but I still wish to participate in the study by completing a blood draw"; and (4) "I no longer want to complete a blood draw." Participants who selected option 4 were asked to provide the reason for declined participation by selecting from a list that included: (1) "I am no longer interested in participating"; (2) "I am no longer interested in participating at this time, due to concerns about



**FIGURE 1** Participant flow. BHR, Brain Health Registry; UCSF, University of California, San Francisco

the coronavirus (COVID-19) pandemic”; (3) “I have concerns about privacy or sharing information”; (4) “The blood draw was too time consuming to complete”; (5) “There is no Quest Diagnostics location near my home”; (6) “I tried to complete the blood draw but was unable to complete it for another reason”; and (7) “Other [open text].”

## 2.5 | Participant communication and support

A study-specific phone number and e-mail address were provided for participants to contact BHR staff with questions about the study. Additionally, participants could generate inquiries to BHR via multiple channels including social media and web-based forms on the BHR website. Participant communication is managed by BHR staff using Zendesk®, a third-party support tool that uses an e-mail/message ticketing system to support and communicate with participants. Each ticket is investigated, sorted, and solved by BHR staff.

## 2.6 | Phlebotomy

Blood samples were collected remotely using an existing network of phlebotomy centers managed by Quest Diagnostics.

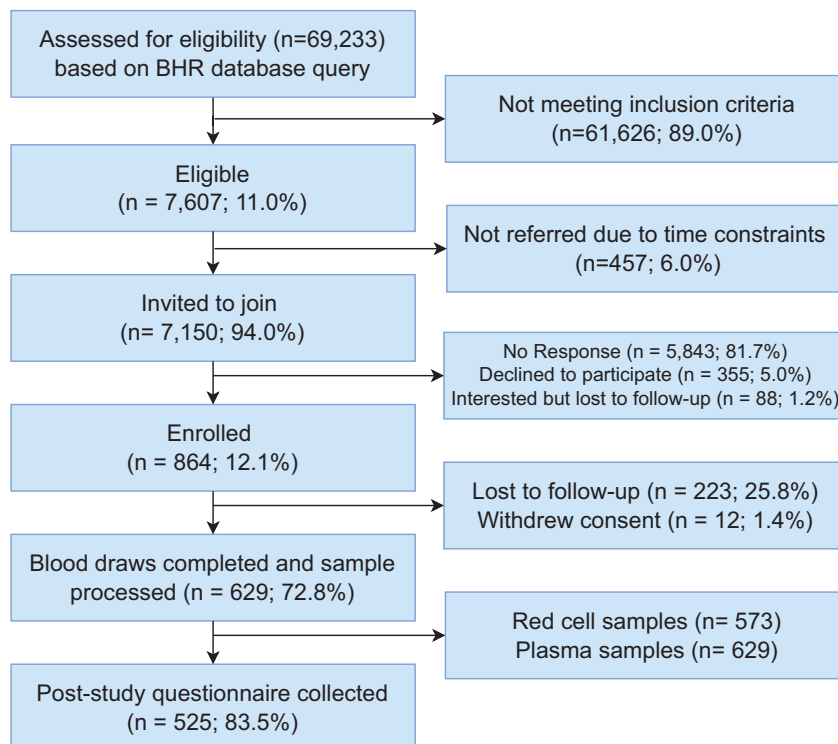
### 2.6.1 | Phlebotomy scheduling

Participants who consented were assigned three unique identification codes for the sample collection (randomly generated dummy codes for the participant’s first name, last name, and date of birth required to complete Quest Diagnostics online scheduling forms) and sent instructions on how to schedule a visit at a Quest Diagnostics Patient Service

Center (PSC) of their choosing (Figure 1). Participants could select from any of the 440 PSCs in California. Participants scheduled an appointment via the Quest Diagnostics website by: (1) selecting a local PSC; (2) entering dummy codes in “First Name,” “Last Name,” and “Date of Birth” fields; and (3) completing any other required fields. Quest Diagnostics sent e-mails with appointment details and confirmation numbers. Participants arrived at their chosen Quest Diagnostics PSC and signed in either using their dummy codes or confirmation number. Participants were called in by the PSC phlebotomist and asked to verify their codes.

### 2.6.2 | Blood sample handling

The PSC phlebotomist drew two 4 milliliter (mL) ethylenediaminetetraacetic acid tubes of blood labeled with a Quest Diagnostics test code and the participant’s de-identified codes. Immediately after collection, the sample was centrifuged at  $1680 \pm 90$  g for 10 minutes. Plasma and blood cells were manually aliquoted. Aliquoted samples were stored at  $-20^{\circ}\text{C}$  and transported on dry ice via courier to the Quest Diagnostics Core Lab. Specimens drawn that day were sent by late evening or early morning the next day and shipped overnight. Plasma and cell aliquots were stored at  $-80^{\circ}\text{C}$  at the Quest Diagnostics Core Lab. Frozen samples were then shipped to the UCSF AIDS Specimen Bank (ASB), part of the Center for AIDS Research. Due to these constraints, participants were only allowed to schedule their appointments Monday through Wednesday before 1 pm. Participants that showed up outside of the time window were asked to reschedule. BHR was notified by ASB when sample collection was complete. Participants were then mailed a \$75 gift card and asked to complete the online post-study questionnaire about their experience.

**FIGURE 2** Study enrollment. BHR, Brain Health Registry

## 2.7 | BHR biofluid collection management portal

Sample tracking and participant communication were automated using an adapted, expanded version of the BHR Biofluid Collection Management Portal,<sup>26</sup> which allows the study team to collect, store, maintain, and organize data related to remote blood and saliva collection. The application sent e-mails automatically to provide participants with their unique codes and instructions on how to schedule an appointment, to alert participants when their sample was received by study staff, and to request a status update from participants if a sample was not collected after a specified time. The portal included a “code generator” that allowed study staff to specify criteria and generate unique participant identification codes. The portal also supported automated import of reports from ASB that automatically updated the database with collection date and status, and a participant payment management system.

## 2.8 | Statistical analysis

Logistic regression was used to test for associations between demographic variables and four levels of study involvement: response to invitation, indication of interest, enrollment, and blood draw completion. As SMCs have previously been found to be associated with higher registry participation<sup>27</sup> and willingness with to participate in genetic studies,<sup>26</sup> we tested the hypotheses that SMC would be associated with increased odds of interest in the study and increased rate of enrollment and completion. We also hypothesized that ethnocultural and educational URP status is associated with lower odds of

study participation. Predictors included: sex (male = 0, female = 1), age, education (years), ethnocultural status (non-Latinx White = 0, URP = 1), and SMC (no = 0, yes = 1). The study involvement outcomes included the following categorical variables with “yes/no” responses: responded to invitation (among all invited), indicated interest (among total responded), enrolled (among total responded), and completed blood draw (among total enrolled). We included an additional, binary “yes/no” outcome variable of whether participants engaged in additional e-mail communication with BHR (see section 2.5). Adjusted odds ratios (aOR), 95% confidence intervals (CI), and *P*-values from the likelihood ratio test are reported for all logistic regression models. False discovery rate analyses were used to correct for multiple comparisons (four different outcome variables related to study participation and requested support). All analyses were done in R<sup>28</sup> and using four R packages (psych,<sup>29</sup> gmodels,<sup>30</sup> epiDisplay,<sup>31</sup> pROC<sup>32</sup>).

## 3 | RESULTS

### 3.1 | Study participants

A total of 7150 BHR participants were invited to the study between February/March and May/June 2020 (Figure 2). Of invited participants, 864 (12.1%) enrolled, and 629 (72.8% of enrolled) completed a blood draw. Before joining the study, participants had been enrolled in BHR for an average of 4.8 years ( $\pm 1.3$  years; range: 53 days–6.9 years). Participants who completed a blood draw and had demographic information available ( $n = 624$ ) had an average age of 67.1 (standard deviation [SD]  $\pm 7.4$ ) years, 438 (70.2%) were female, 547 (87.7%) identified

**TABLE 1** Participant characteristics

	Invited (n = 7150)	Enrolled (n = 864)	Blood draw completed (n = 629)	Contacted BHR support (n = 264)
Age, mean ± SD (range)	70 ± 8.5 (55.9, 110.3)	68 ± 7.5 (55.9, 95.4)	68 ± 7.5 (55.9, 95.4)	71 ± 8.4 (56, 96.2)
Female, n (% of total)	4967 (69%)	606 (70%)	438 (70%)	188 (74%)
White, n (% of total)	4926 (68%)	739 (85%)	552 (88%)	222 (84%)
Years education, mean ± SD (Range)	16 ± 2.4 (6, 20)	16 ± 2.4 (6, 20)	16 ± 2.3 (6, 20)	16 ± 2.5 (6, 20)
Subjective memory complaints, n (% of total)	3273 (46%)	364 (42%)	244 (39%)	114 (43%)
Self-report MCI, n (% of total)	231 (3%)	35 (4%)	22 (3%)	12 (0.05%)

Abbreviations: BHR, Brain Health Registry; MCI, mild cognitive impairment; SD, standard deviation.

as White, had an average of 16 (SD ± 2.3) years of education, and 12 (0.6%) self-reported MCI (Table 1). All 629 samples were collected over 8 weeks, with 614 samples collected in the final 33 days.

### 3.2 | Factors associated with study involvement

We considered whether sociodemographic factors or memory concerns were associated with the study involvement metrics—those who responded to the e-mail invitation, indicated interest in the study, enrolled, and completed a blood draw (Table 2). Higher education levels were associated with higher probability of responding to the invitation, study enrollment, and completion. Identifying as non-White was associated with lower probability of responding to the invitation and blood draw completion. Older participants had lower odds of responding to the invitation, indicating interest, and enrolling in this study. SMCs were associated with a lower probability of responding to the invitation and enrollment.

### 3.3 | Acceptability

Of the 629 participants who completed a blood draw, 525 (83.5%) also completed a post-study questionnaire. Of those, 486 (92.6%) rated blood draw scheduling as easy (1 or 2 based on a scale of 1 = least difficult to 5 = most difficult); 200 (38.1%) reported that it took “a lot less time” or “a little less time” than expected to complete the study; 238 (45.3%) reported that the time was “about what I expected”; and 510 (97.1%) reported that they would agree to participate in a similar, future study.

### 3.4 | Reasons for declining participation

Of the 355 participants who actively declined participation and the 12 participants that withdrew consent, 18 (4.9%) completed a Decline Survey. The most common decline reason was concerns due to COVID-19 (n = 6, 33.3%). Out of 327 consented participants who did not complete their blood draw and were asked by e-mail about their blood draw status, 34 indicated that they no longer wanted to complete a blood

draw. From the provided list of reasons participants most commonly selected “Other” (n = 12), describing issues with the phlebotomy center (n = 6), and “COVID-19 concerns” (n = 9).

### 3.5 | Volume and content of participant communication

Study staff received a total of 376 e-mails from participants and potential participants. The five most common themes of the participant e-mails were: confirming study interest (n = 61), participant payment (n = 47), phlebotomy center issues (n = 47), assistance with scheduling (n = 45), and residing outside of California (n = 37; Table 3). In addition, ≈176 participants called the study support telephone line. Of the participants who completed the blood draw (n = 629), 20% contacted BHR via e-mail (n = 127). Of the total number of participants we identified as contacting BHR via Zendesk (n = 263), 48% completed the blood draw (n = 127). Those with higher education levels were more likely to request support, and URP individuals were less likely to request support (Table 2).

## 4 | DISCUSSION

There were two major findings of this study. (1) Remote blood sample collection for AD plasma biomarker analysis from a large cohort of previously characterized older adults in an online registry is feasible and has high acceptability among participants. This was supported by enrollment of >600 participants (12% of those invited) within 8 weeks, a high study completion rate (73% of those enrolled), and positive participant feedback about their study experience. (2) Our study failed to refer and engage a representative number of individuals from underrepresented ethnocultural and educational groups. These results demonstrate that our approach has potential as a method to collect blood for plasma AD biomarker analysis in a large group of older adults. Major challenges of this approach include the need for effective, culturally tailored strategies to mitigate the selection bias for highly educated White individuals at multiple levels of study involvement, and to

**TABLE 2** Associations between sociodemographic characteristics and study response, interest, enrollment, and completion

	Adjusted odds ratio	95% confidence interval	p.fdr (LR-test)*
Responded to invitation (n = 7,150)			
Female	1.07	0.93, 1.23	.581
Years education	1.09	1.06, 1.12	.003
Underrepresented race/ethnicity	0.6	0.51, 0.72	.005
Age	0.98	0.98, 0.99	.002
Reported subjective memory complaint	0.82	0.72, 0.93	.007
Indicated interest in blood draw study (n = 1308)			
Female	0.82	0.61, 1.09	.427
Years education	1.04	0.98, 1.09	.173
Underrepresented race/ethnicity	0.9	0.62, 1.3	.567
Age	0.94	0.92, 0.96	.002
Reported subjective memory complaint	0.91	0.70, 1.18	.657
Enrolled in blood draw study (n = 940)			
Female	0.92	0.70, 1.2	.672
Years education	1.07	1.01, 1.12	0.02
Underrepresented race/ethnicity	0.84	0.60, 1.19	.426
Age	0.94	0.93, 0.96	.002
Reported subjective memory complaint	1.0	0.78, 1.28	.999
Completed blood draw (n = 633)			
Female	1.01	0.71, 1.43	.946
Years education	1.07	1.00, 1.14	.055
Underrepresented race/ethnicity	0.57	0.37, 0.86	.013
Age	1.01	0.99, 1.03	.368
Reported subjective memory complaint	0.59	0.43, 0.82	.005
Contacted BHR Support (n = 263)			
Female	1.33	1.00, 1.78	.24
Years education	1.09	1.04, 1.15	.002
Underrepresented race/ethnicity	0.61	0.42, 0.89	.013
Age	1.01	1.00, 1.03	.192
Reported subjective memory complaint	0.92	0.71, 1.19	.657

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

minimize the amount of one-on-one participant interaction needed to complete the study, for scalability.

To our knowledge, this study was the first to demonstrate feasibility and acceptability of remote blood sample collection in a large cohort of older adults engaged in longitudinal online evaluation. The high completion rate supports the feasibility, while the positive experience feedback shows participant acceptability. This adds to emerging evidence for the feasibility of adding biofluids collection to online studies, as was previously shown with remote saliva collection for apolipoprotein E (APOE) genotyping in BHR<sup>26</sup> and the Banner Alzheimer's Prevention Registry GeneMatch study.<sup>33</sup> Blood draws were collected in a relatively short time frame (> 600 blood draws within 8 weeks from February–June 2020), despite constraints on in-person medical visits

and research due to the COVID-19 pandemic. Because blood draws can be performed locally (Quest Diagnostics phlebotomy centers can be found in most major metropolitan areas with ≈2000 patient locations in the United States), this approach has high potential for scalability. A number of factors likely contributed to the high study enrollment rate (12% of those invited). Those who enrolled had been BHR participants for an average of 4.8 years prior to being approached about this new study, and 78% had returned to BHR for longitudinal follow-up prior to joining the study, suggesting a high level of engagement with BHR.

We prioritized recruitment of non-White individuals and those with an education less than a bachelor's degree; 32% of those invited (n = 2224) were non-White and 30% of those invited (n = 2197) had an education less than a bachelor's degree. Thus, the pool of eligible BHR



**TABLE 3** Participant e-mail support themes

Support themes	Number of e-mails received (out of a total of 376 e-mails)
Confirming interest	61
Participant payment	47
Phlebotomy center issues	47
Assistance with scheduling	45
Out of state (California)	37
Other	29
Access to results	24
COVID-19	24
Questions about study	22
BHR technical issue	15
No local Quest Diagnostics Center	6
Blood draw concerns	4
Privacy concerns	2
Time burden	2

participants falling into prioritized URP categories was adequate to oversample URP groups in the study. We also expanded the geographical radius from study sites allowed for individuals from URPs, resulting in an additional 544 individuals from URP groups who were eligible to enroll. However, neither “oversampling” at the recruitment stage nor expanded eligibility criteria were successful in recruiting and engaging a representative sample of ethnocultural URPs for remote blood collection. Although only 68% of those invited to the study were White, the final cohort of participants who completed the study included 88% White individuals. Our findings agree with past studies demonstrating failure to engage and retain URPs in clinical AD research, both in BHR,<sup>27</sup> and in clinic settings.<sup>13,15,34,35</sup> Our ability to test the hypotheses that individuals from ethnocultural and education attainment URPs are less likely to enroll in and complete the remote blood collection study is limited by the broader failure to adequately enroll and engage these same URPs in the larger ( $n > 90,000$ ) pool of potential participants in BHR. This limitation warrants caution in interpretation of our results. Nonetheless, our findings suggest that the approach of establishing a large, registry-based cohort to facilitate ADRD biomarker and genetic studies has the potential to amplify under-inclusion of historically under-included populations at each step of the enrollment “funnel.” Our results highlight the urgent need for development and evaluation of strategies that are effective at recruiting and engaging URPs at each step, including at the “top of the funnel” where participants join an online registry like BHR. Related to this, future analyses should include investigation of barriers and facilitators to participation, including the role of barriers (e.g., burden, competing demands, distance from blood draw sites), that are known to unduly burden URPs.<sup>36–40</sup>

We have several new initiatives to address this limitation. These include deployment of surveys around barriers and motivators, and

creation, evaluation, and optimization of culturally tailored recruitment and engagement materials and a Spanish-language website, developed in collaboration with Community Science Partnership Boards within BHR. We hope that these initiatives will help us make evidence-based decisions in redesigning our approach to recruitment, both in BHR and the additional studies to which BHR participants are referred. Further, our efforts failed to engage older participants and those with SMCs (Table 2), which is in agreement with previous studies.<sup>26,27</sup> Therefore, future recruitment and engagement strategies should be developed to appeal to these groups.

For our remote blood draw approach to be deployed for widespread screening in the community, it needs to be highly scalable. Our study identifies logistics that currently require a high level of one-on-one support: blood draw scheduling and instructions, as well as coordination between BHR and the phlebotomy centers. Overall, 20% of those who completed a blood draw contacted BHR via e-mail. Interestingly, ethnocultural and educational URPs were less likely to communicate with and request support from BHR, which may contribute to their lower engagement and participation levels of these groups, because communicating with study staff was positively associated with successful blood draw completion. We plan to use this information to further automate the remote blood draw process and to optimize our novel Biofluids Management Portal, and to better engage URPs using the strategies described above. One limitation of using local phlebotomy centers was the variability of available cold storage (dry ice, etc.). As we learn more about plasma collection and storage requirements for AD biomarkers processing, the need for cold storage may be relaxed, allowing greater efficiency and scalability, and improved accessibility to participants in diverse locations.

The next step in this study is to process plasma to quantify A $\beta$ 42/40, p-tau, and NFL, and to extract DNA for genome-wide association studies. Plasma biomarker and genetic results will be used to investigate the relationship between these variables and online variables in BHR. One impactful line of research will be to identify combinations of online cognitive, everyday functioning, and health data (from questionnaires and cognitive tests) and plasma AD biomarkers (from remote blood collection) that best predict preclinical and prodromal AD, cognitive decline, and future disease progression. To accomplish this, we plan to acquire imaging and clinical data from participants in future studies. This novel approach could then be deployed more broadly in BHR, as well as in-clinic observational studies and clinical trial screening, as an efficient way to identify older adults with preclinical and prodromal AD.

In conclusion, remote blood collection from a non-representative group of older adults in the BHR online research registry is feasible. Major challenges include the need to expand efforts to effectively recruit and engage ethnocultural and educational URPs, older individuals, and those with SMCs; and to improve scalability, so that this approach can be used to facilitate future AD and aging observational research and clinical trials.

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### CONFLICTS OF INTEREST

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