Title

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FEATURED ARTICLE

A blood screening tool for detecting mild cognitive impairment and Alzheimer's disease among community-dwelling Mexican Americans and non-Hispanic Whites: A method for increasing representation of diverse populations in clinical research

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Abstract

Introduction: Representation of Mexican Americans in Alzheimer's disease (AD) clinical research has been extremely poor.

Methods: Data were examined from the ongoing community-based, multi-ethnic Health & Aging Brain among Latino Elders (HABLE) study. Participants underwent functional exams, clinical labs, neuropsychological testing, and 3T magnetic resonance imaging of the brain. Fasting proteomic markers were examined for predicting mild cognitive impairment (MCI) and AD using support vector machine models.

Results: Data were examined from n = 1649 participants (Mexican American n = 866; non-Hispanic White n = 783). Proteomic profiles were highly accurate in detecting MCI (area under the curve [AUC] = 0.91) and dementia (AUC = 0.95). The proteomic profiles varied significantly between ethnic groups and disease state. Negative predictive value was excellent for ruling out MCI and dementia across ethnic groups.

Discussion: A blood-based screening tool can serve as a method for increasing access to state-of-the-art AD clinical research by bridging between community-based and clinic-based settings.

KEYWORDS
Alzheimer's disease, diversity, Hispanic, inclusion, Mexican American, mild cognitive impairment, screening tool

1 | BACKGROUND

There has been a substantial underrepresentation of Hispanic populations in Alzheimer's disease (AD) research[12] despite the rapidly changing demographic characteristics of the United States. In fact, Hispanics make up the largest minority population in the United States[3] with ≈50% of the US population growth from 2010 to 2019 being due to an increase in the Hispanic population.[4] It is anticipated that the percentage of Hispanics aged 65 and older will triple by the year 2050[5] and, as a result, Hispanics are expected to experience the largest increase in AD and AD related dementia (ADRD) diagnoses among any racial/ethnic group by 2060.[6] Approximately 65% of Hispanics in the United States are of Mexican American ethnicity;[7] however, few studies to date have explicitly examined mild cognitive impairment (MCI) and AD among Mexican Americans. Novel tools are needed to increase representation of Mexican Americans in AD observational studies and clinical trials (herein referred to as AD clinical research).

One factor contributing to the lack of inclusion of Mexican Americans in AD clinical research is the access barrier posed due to the location of the research itself. Specifically, most AD research has been conducted in dementia specialty clinics; however, Mexican Americans rarely present to such clinics.[8] Two examples of novel methods having substantial impact on increasing diversity in AD clinical research are the National Institute on Aging Alzheimer's Disease Centers (ADCs)[11] and Alzheimer's Clinical Trials Consortium (ACTC).[10] ADC ACTC sites are located across a broad range of US metropolitan areas; however, only 8% of participants in the National Alzheimer's Coordinating Center (NACC) database are of Hispanic ethnicity.[9] Representation is even lower among clinical trials for AD in which between < 1% and 4% of participants identify as Hispanic.[12,13] Furthermore, few trials to date have examined the potential impact of race/ethnicity on safety or efficacy outcomes.[12] Lopez et al. found that the efficacy and safety for cholinesterase inhibitors were similar for Hispanics and non-Hispanic Whites;[14] however, this assumption cannot be applied to all ethnic groups or interventions and must be explicitly examined. Given the lack of awareness of AD among the Hispanic community,[2] a system that allows a community-based approach to build trust and increase awareness is an ideal option for screening Mexican Americans into AD clinical research.

A significant hurdle for community-based studies is the use of comprehensive AD assessment protocols, which incorporate a medical examination, neuropsychological testing, clinical blood work, and neuroimaging. This barrier is not only due to access owing to the need to bring participants to clinics rather than seeing participants in their natural environment, but also due to distrust and language barriers. Additionally, the recent shift to the 2018 AT(N) research framework calls for incorporation of confirmatory biomarkers of disease pathology,[15] which are rarely accessible outside of academic institutions. While these advanced technologies are integrated into some AD observational studies (e.g., Alzheimer's Disease Neuroimaging Initiative [ADNI][16]) and clinical trials (e.g., Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease [A4][17]), implementation of these methods in community-based studies is limited. This gap between the "state-of-the-art" assessment and "real-life" community-based settings is stark when one examines the availability of data on AT(N)–based biomarkers among diverse populations.[1] It is our hypothesis that blood-based tools can serve as a bridge between community-based and clinic-based research settings by serving as the first step in a multi-tiered screening process to increase representation of Mexican Americans in state-of-the-art AD clinical research. In alignment with the AT(N) terminology, we distinguish clinically defined AD[18,19] (i.e., standard clinical practice, referred to as dementia in the AT[N] research framework) and AD dementia (i.e., biomarker-confirmed dementia due to AD pathology).[15]

We previously discovered[20] and cross-validated[21,22] a proteomic profile specifically designed to screen out clinically defined AD dementia among primary care settings, which is currently being prospectively studied explicitly within the proposed context of use (COU). The Food and Drug Administration defines COU as "a statement that fully and clearly describes the way the medical product development tool is to be used and the medical product development-related purpose of the use."[23] Here, we sought to examine a proteomic profile approach for the COU of a blood-based tool for screening out MCI and dementia within community-based settings. As part of this COU, the blood-based screening tool is seen as the first step in a multi-tiered neurodiagnostic system rather than seeking a "magic bullet" biomarker to serve all needs. Within this COU, the goal of the first screening step is to rule *out* disease (i.e., high negative predictive value [NPV]) with the intent that screen-positive cases will be referred for a second level assessment (Figure 1). NPV is the probability of a participant not having dementia based on a negative test result. NPV is impacted by sensitivity (SN) and specificity (SP), as well as the prevalence of the disease state (dementia or MCI in this case) within the population of intended use. It is likely that SN and SP estimates will vary between clinic-based

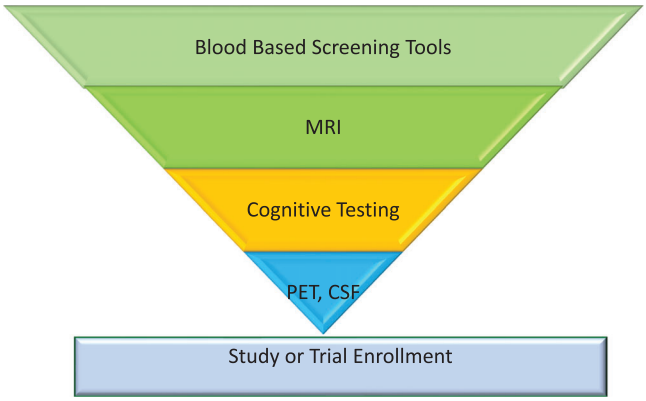


FIGURE 1 Multi-tiered screening process for research study and/or clinical trials enrollment. CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PET, positron emission tomography

and community-based settings due to a broad range of factors, including the more heterogeneous participants (e.g., characteristics, co-morbidities) enrolled into community research. Additionally, recent literature documents the need to examine the impact of race and ethnicity on biomarkers of AD.[1,24–26] Therefore, all aspects of the diagnostic accuracy of the biomarker must be examined within the specific COU rather than making assumptions of applicability across settings.

Based on our prior work demonstrating the importance of metabolic markers in AD among Mexican Americans,[24] we expanded the previously validated proteomic profile[27–30] to include additional metabolic markers (i.e., GLP-1, glucagon, peptide YY, insulin). We also added blood-based proteins of the AT(N) framework to the proteomic profile.

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using traditional sources (e.g., PubMed). Despite the fact that Hispanics are the largest ethnic minority population in the United States, and Mexican Americans are the largest Hispanic population in the United States, this ethnic group remains severely underrepresented in Alzheimer's disease (AD) clinical research. No current methods are available to bridge community-based and clinic-based AD clinical research settings, which could drastically increase representation in these studies.
2. Interpretation: Our findings demonstrate that a blood-based screening tool can rule out mild cognitive impairment (MCI) and clinically defined AD among both Mexican Americans and non-Hispanic Whites with more than 95% accuracy. Additionally, the proteomic profiles vary according to diagnostic classification as well as ethnicity. Therefore, diagnosis and ethnic-specific screening tools may be required.
3. Future directions: This article provides the foundation and justification to prospectively test blood-based screening tools for increasing inclusion of minority populations in AD clinical research. Additionally, the current screening tool will soon be tested among African Americans.

2 | METHODS

The Health & Aging Brain among Latino Elders (HABLE) study[31] is a community-based multi-ethnic, study of MCI and clinically defined AD[18,19] (or dementia) among Mexican Americans and non-Hispanic Whites. Ethnicity in the HABLE study is based on self-report by the participant. Our study uses the terms Hispanic and Mexican American based on participant-reported preferences obtained through feedback. Visits include a functional exam, clinical labs, interview, 3T magnetic resonance imaging (MRI; per ADNI3 protocols), neuropsychological testing, and a blood draw for storage of blood into the HABLE Biorepository. Beginning with Visit 2, all participants undergo amyloid (florbetaben) and tau (PI-2620) positron emission tomography (PET) scans for assignment of AT(N)–defined research classification.[15] All methods are administered in English or Spanish. The neuropsychological testing battery is reported in Table 1. Informant interviews are completed using structured questionnaires to complete the Clinical Dementia Rating (CDR)[32,33] scale and physician's estimate of duration (PED)[34] by clinicians with expertise in dementia. A method was implemented within the electronic data capture (EDC) system to assign cognitive diagnoses based on the following criteria, which were confirmed at consensus review: (1) MCI: complaint of cognitive change (self or other), CDR scale sum of boxes (CDR-SB) score of 0.5 to 2.0,[35] and performance at or below 1.5 standard deviations below the mean on age, education, and primary language adjusted z-score scores on at least one cognitive test; (2) Dementia: CDR-SB > = 2.5, cognitive test score at or below two standard deviations below the mean on adjusted z-scores on two or more neuropsychological tests; (3) Normal cognition: no complaints of cognitive change (self or other), CDR-SB = 0, cognitive test scores considered broadly within normal testing limits. The HABLE protocol is conducted under institutional review board–approved protocols and all participants and/or caregivers sign written informed consent. All participants are evaluated at the Institute for Translational Research (ITR) at the University of North Texas Health Science Center, Fort Worth, Texas. The HABLE database is available the through the ITR webpage data portal.[36]

2.1 | Blood collection and processing procedures

Fasting blood samples were collected according to the international guidelines for AD biomarker studies.[37] Our previously validated proteomic profile was assayed using electrochemiluminescence (ECL) per our published methods on the following biomarkers: fatty acid binding protein 3 (FABP3); beta 2 microglobulin (B2M); C-reactive

TABLE 1 Cohort characteristics

	Total cohort N = 1649	Mexican American N = 866	Non-Hispanic White N = 783
Age	66.47 (8.78)	63.87 (7.99)	69.26 (8.75)
Sex (% female)	61%	67%	55%
Education	12.38 (4.81)	9.49 (4.59)	15.50 (2.57)
Diabetes (% yes)	25%	36%	13%
Dyslipidemia (% yes)	62%	64%	61%
Hypertension (% yes)	59%	63%	55%
Control	80%	76%	83%
MCI	14%	17%	11%
Dementia	6%	7%	6%
MMSE	27 (3.32)	26.05 (3.75)	28.75 (1.96)
Trails A	44.72 (28.05)	52.01 (32.61)	36.77 (19.12)
Trails B	121.69 (79.75)	151.41 (88.70)	91.94 (55.49)
WMS-III digit span	13.68 (4.27)	11.42 (3.52)	16.13 (3.63)
Digit Symbol Substitution Test (DSST)	39.78 (13.65)	34.70 (13.43)	45.32 (11.60)
Verbal fluency (FAS)	31.85 (12.25)	27.13 (10.99)	37.00 (11.44)
Category naming (animals)	17.47 (5.16)	16.28 (4.83)	18.77 (5.21)
WMS-LM 1	35.16 (11.99)	30.71 (10.60)	39.98 (11.54)
WMS-LM 2	21.24 (8.95)	18.50 (8.07)	24.20 (8.92)
SEVLT trials 1–5	30.69 (9.08)	28.90 (8.29)	32.68 (9.49)
SEVLT 30-minute delay	7.60 (3.45)	6.97 (3.31)	8.29 (3.47)
AMNART (errors)	16.09 (9.86)	23.92 (9.69)N = 318	13.05 (8.09)
WAT (correct)	14.38 (6.37)	14.38 (6.37)	N/A

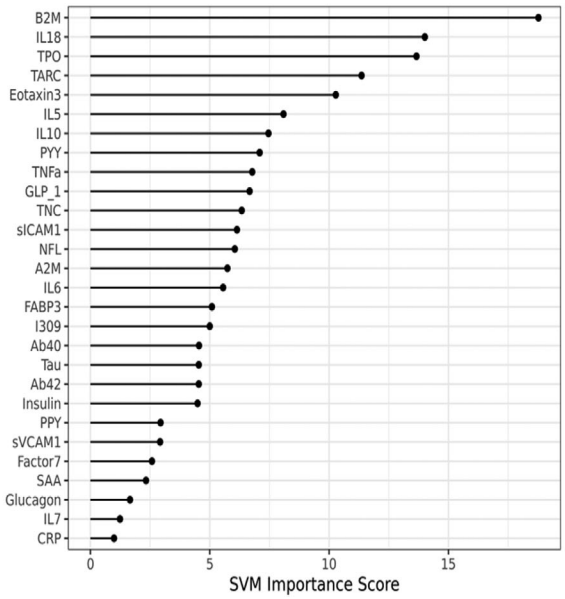
NOTE: cognitive test scores reflect raw scores. For consensus diagnoses, all scores were z-scored correcting for age (< = 65 vs. 66 and older), education ranges (0 to 7 years of education, 8 to 12 years of education, 13+ years of education) and language (English vs. Spanish).
Abbreviations: AMNART, American version National Adult Reading Test; DSST, Digit Symbol Substitution Test; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; SEVLT, Spanish English Verbal Learning Test; WAT, Word Accentuation Test; WMS-LM, Weschler Memory Scale Logical Memory.

protein (CRP); thrombopoietin (TPO); alpha 2 macroglobulin (A2M) eotaxin 3; tumor necrosis factor alpha (TNFa); tenascin C (TNC); interleukin (IL)-5, IL-6, IL-7, IL-10, IL-18; I-309; factor VII (factor 7); soluble intercellular adhesion molecule 1 (sICAM1); circulating vascular cell adhesion molecule 1 (sVCAM1); pancreatic polypeptide (PPY); thymus activation regulated chemokine (TARC); and serum amyloid A (SAA).[27,28,30] Glucagon-like peptide 1 (GLP-1), insulin, glucagon, and peptide YY (PYY) were also assayed weekly via ECL multiplex kit. The ITR Biomarker Core has conducted > 20,000 assays using these specifications and the platform performs excellently (coefficient of variation [CV] < = 10%). The Quanterix Simoa HD-1 platform was used for assay of plasma amyloid beta $(A\beta)_{40}$, $A\beta_{42}$, total tau (3-plex plate), and neurofilament light (NfL). The ITR Biomarker Core has conducted n > 5000 assays with CVs < = 5%.

2.2 | Statistical methods

Statistical analyses were completed using R (V 3.3.3). Support vector machine (SVM) analyses were conducted. SVM is based on the concept of decision planes that define decision boundaries and is primarily a classifier method that performs classification tasks by constructing hyperplanes in a multidimensional space that separates cases of different class labels. Ten times repeated 5-fold cross-validation was used to directly perform SVM parameter tuning and an optimal cutoff was determined using grid search, which is a traditional way of performing hyperparameter optimization.[38] In the 5-fold cross-validation, the data are divided into five folds. The model is trained on four folds with one fold held back for testing. This process gets repeated to ensure each fold of the dataset gets the chance to be the held-back set. When the process is completed, the evaluation metrics are summarized using the mean. This method provides a more reliable estimate of out-of-sample performance by reducing the variance associated with a single trial of cross-validation. All proteomics were entered into a single algorithm based on our prior methods.[27–30] Diagnostic accuracy was calculated via receiver operating characteristic (ROC) curves with positivity based on clinical diagnosis of normal cognition versus MCI and normal cognition versus dementia. Analyses were conducted as follows: (1) detecting MCI versus cognitively unimpaired in the entire cohort,

	Actual	
Predicted	MCI	NC
MCI	148	40
NC	32	1008
Sensitivity	82.22%	
Specificity	96.18%	
NPV	96.92%	
AUC	90.67%	



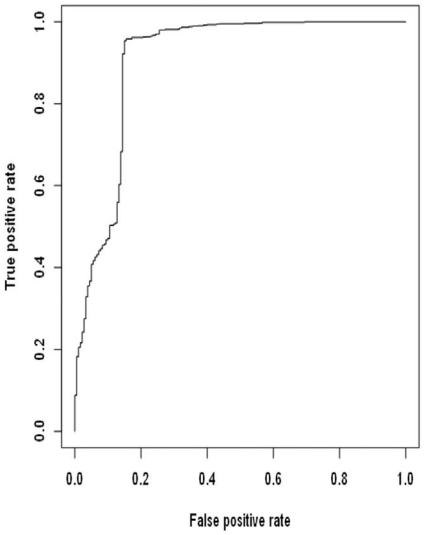


FIGURE 2 Classifying mild cognitive impairment (MCI) in the entire cohort. A2M, alpha 2 macroglobulin eotaxin 3; AUC, area under the curve; B2M, beta 2 microglobulin (B2M); CRP, C-reactive protein; GLP-1, glucagon-like peptide 1; FABP3, fatty acid binding protein 3; IL, interleukin; NC, normal control, non-cognitively impaired; NfL, neurofilament light; NPV, negative predictive value; PPY, pancreatic polypeptide; PYY, peptide YY; SAA, serum amyloid A; factor VII (factor 7); sICAM1, soluble intercellular adhesion molecule 1; sVCAM1, circulating vascular cell adhesion molecule 1; SVM, support vector machine; TARC, thymus activation regulated chemokine; TNFa, tumor necrosis factor alpha; TNC, tenascin C; TPO, thrombopoietin

(2) detecting MCI versus cognitively unimpaired split by ethnicity, (3) detecting dementia versus cognitively unimpaired in the entire cohort, and (4) detecting dementia versus cognitively unimpaired split by ethnicity. Analyses were conducted using proteomics alone and then proteomics + demographic factors (age, sex, education) per our prior methods.[27,28]

3 | RESULTS

A total of n = 1649 participants (n = 106 dementia; n = 234 MCI; n = 1309 cognitively unimpaired) had the requisite data and were included in this study. When separated by ethnicity: Mexican American: normal control n = 659, MCI n = 147, dementia n = 60; non-Hispanic White: normal control n = 650, MCI n = 87, dementia n = 46. To estimate NPV (to examine the COU as a rule-out screening tool), we used the prevalence of diagnosis in the cohort. In HABLE, the prevalence (or base rate for use in Bayesian calculations of predictive accuracy[39]) of MCI was 14% and dementia was 6%. Among Mexican Americans, the prevalence of MCI was 17% and dementia was 7%. Among non-Hispanic Whites, the prevalence of MCI was 11% and dementia was 6%. Table 1 provides the demographic characteristics of the cohort.

3.1 | MCI

In the entire cohort, the proteomic profile (optimized cut-score = 0.995) yielded an area under the curve (AUC) of 0.91, SN of 0.82, and SP of 0.96. Based on an MCI prevalence of 14%, the NPV was 97%. See Figure 2 for classification accuracy, variable importance plot, and receiver operating characteristic (ROC) curve. Inclusion of demographic factors, using an optimized cut-score of 0.988, yielded an AUC of 0.94, SN of 0.83, SP of 0.98, and NPV 97%.

When examining the Mexican American cohort, the proteomic profile (optimized cut-score = 0.809) yielded an AUC of 0.91, SN of 0.76, and SP of 0.99. Based on an MCI prevalence of 17%, the NPV was 95%. See Figure 3A for classification accuracy, variable importance plot, and ROC curve. When demographic factors were added to the model (optimized cut-score = 0.773), the AUC was 0.99, SN was 0.95, and SP was 0.99; NPV was 99%.

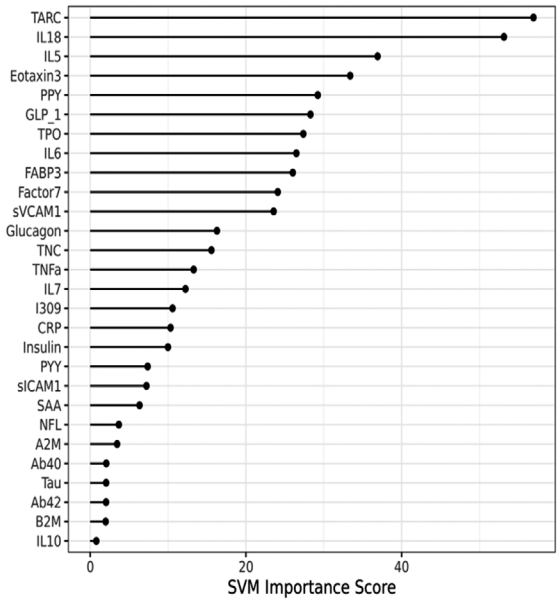
When examining the non-Hispanic White cohort (optimized cut-score of 0.991), the proteomic profile alone yielded an AUC of 0.94, SN of 0.87, and SP of 0.99. Based on an MCI prevalence of 11%, the NPV was 98%. See Figure 3B for classification accuracy, variable importance plot, and ROC curve. Inclusion of demographic factors (optimized cut-score of 0.985) yielded an AUC of 0.99, SN of 0.90, and SP of 0.99; NPV was 99%.

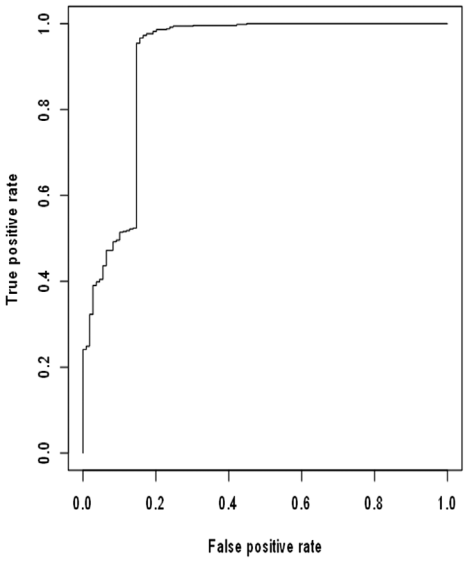
3.2 | Dementia

In the entire cohort, the proteomic profile (optimized cut-score = 0.99) yielded an AUC of 0.95, SN of 0.82, and SP of 0.99. Based on a dementia prevalence of 6%, the NPV was 99%. See Figure 4 for classification accuracy, variable importance plot, and ROC curve. Inclusion of demographic factors in the profile yielded an AUC of 0.98, SN of 0.95, and SP of 0.99; NPV was 99%.

A

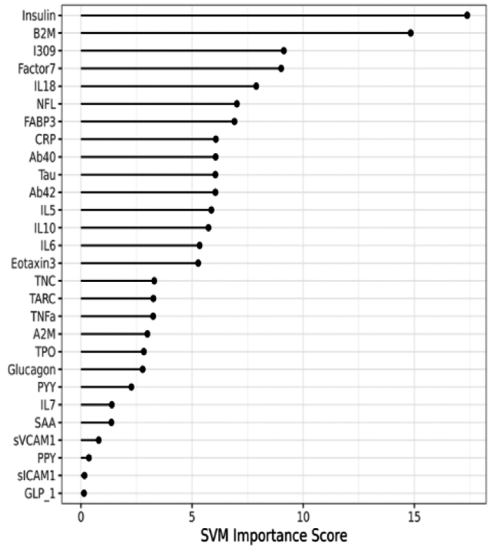
	Actual	
Predicted	MCI	NC
MCI	83	4
NC	26	498
Sensitivity	76.15%	
Specificity	99.20%	
NPV	95.04%	
AUC	91.41%	





B

	Actual	
Predicted	MCI	NC
MCI	62	7
NC	9	539
Sensitivity	87.32%	
Specificity	98.72%	
NPV	98.36%	
AUC	93.96%	



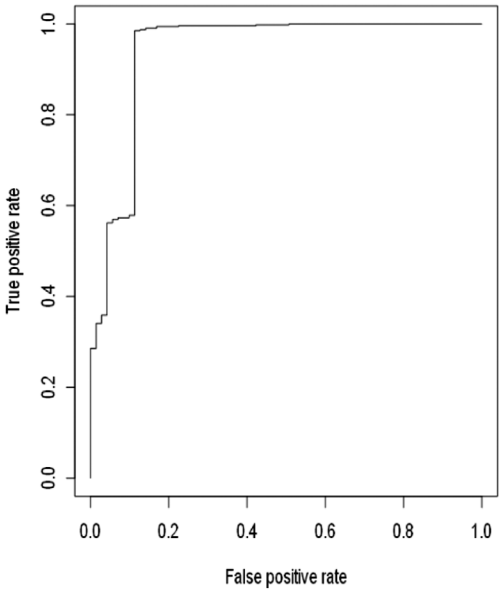
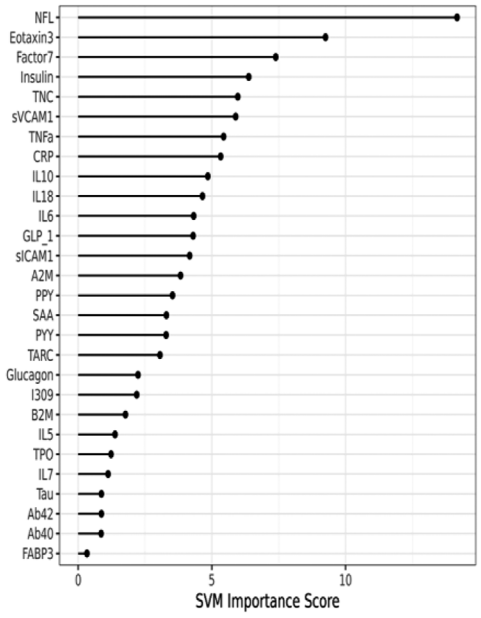


FIGURE 3 Classifying mild cognitive impairment (MCI) by ethnicity. A, Classifying MCI among Mexican Americans. B, Classifying MCI among non-Hispanic Whites. A2M, alpha 2 macroglobulin eotaxin 3; AUC, area under the curve; B2M, beta 2 microglobulin (B2M); CRP, C-reactive protein; GLP-1, glucagon-like peptide 1; FABP3, fatty acid binding protein 3; IL, interleukin; NC, normal control, not-cognitively impaired; NfL, neurofilament light; NPV, negative predictive value; PPY, pancreatic polypeptide; PYY, peptide YY; SAA, serum amyloid A; factor VII (factor 7); sICAM1, soluble intercellular adhesion molecule 1; sVCAM1, circulating vascular cell adhesion molecule 1; SVM, support vector machine; TARC, thymus activation regulated chemokine; TNFa, tumor necrosis factor alpha; TNC, tenascin C; TPO, thrombopoietin

Among the Mexican American cohort, the proteomic profile (optimized cut-score = 0.98) yielded an AUC of 0.87, SN of 0.60, and SP of 0.99. Based on a dementia prevalence of 7%, the NPV was 97%. See Figure 5A for classification accuracy, variable importance plot, and ROC curve. The addition of demographic factors (optimal cut-score = 0.96) resulted in an AUC of 0.90, SN of 0.73, and SP of 0.99; NPV was 99%.

Among the non-Hispanic White cohort, the proteomic profile (optimized cut-score = 0.976) resulted in an AUC of 0.97, SN of 0.94, and SP of 1.0. Based on a dementia prevalence of 6%, the NPV was 99%. See Figure 5B for classification accuracy, variable importance plot, and ROC curve. The addition of demographic factors (optimal cut-score = 0.961) yielded an AUC of 0.97, SN of 0.94, and SP of 0.99; NPV was 99%.

	Actual	
Predicted	AD	NC
AD	61	4
NC	13	1044
Sensitivity	82.43%	
Specificity	99.62%	
NPV	98.77%	
AUC	95.19%	



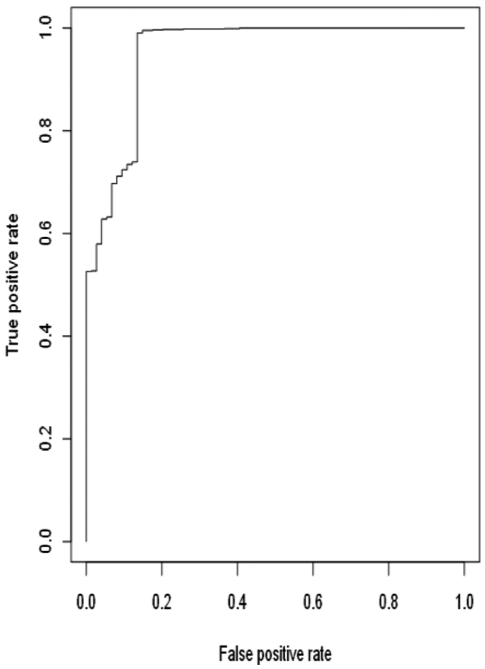


FIGURE 4 Classifying dementia among entire cohort. A2M, alpha 2 macroglobulin eotaxin 3; AUC, area under the curve; B2M, beta 2 microglobulin (B2M); CRP, C-reactive protein; GLP-1, glucagon-like peptide 1; FABP3, fatty acid binding protein 3; IL, interleukin; NC, normal control, non-cognitively impaired; NfL, neurofilament light; NPV, negative predictive value; PPY, pancreatic polypeptide; PYY, peptide YY; SAA, serum amyloid A; factor VII (factor 7); sICAM1, soluble intercellular adhesion molecule 1; sVCAM1, circulating vascular cell adhesion molecule 1; SVM, support vector machine; TARC, thymus activation regulated chemokine; TNFa, tumor necrosis factor alpha; TNC, tenascin C; TPO, thrombopoietin

4 | DISCUSSION

The availability of tools that can be implemented within ethnically diverse, community-based settings can increase representation of the population in research, which is urgently needed in AD clinical research. Community-based methods are more successful in the recruitment of diverse populations; however, implementation of advanced neurodiagnostic methods within these settings is a challenge. Therefore, we tested a blood-based screening tool within a multi-ethnic, community-based setting to determine the accuracy in ruling out MCI and clinically defined AD. Leveraging the community-based methods to build trust within the community and then applying a blood-based screening tool as the bridge to the clinic-based setting can be implemented as outlined in Figure 1. Our results support the potential utility of blood-based biomarkers for this specific COU.

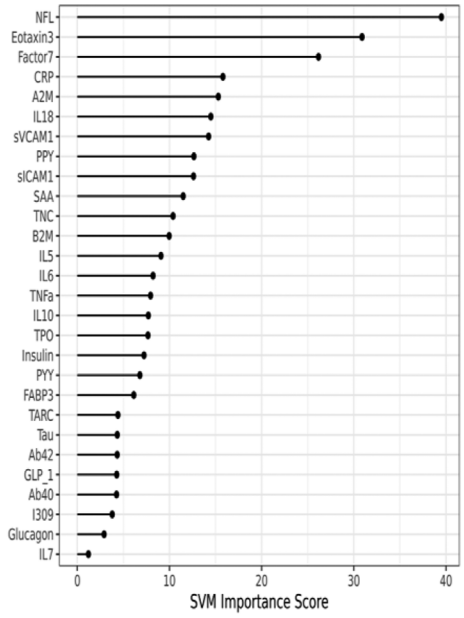
The COU of screening out MCI and dementia among multi-ethnic, community-based settings as a means for increasing inclusion in AD clinical research cannot be tested with clinic-based designs. Clinic-based studies cannot mirror community-based populations due to selection bias, access barriers, as well as differences in disease prevalence, which directly affects diagnostic accuracy estimates. In the present community-based setting, the prevalence of dementia was 6% and MCI was 14% and, therefore, the most important first step is to identify those without disease. What are the potential benefits of a blood-based screening tool for community-based settings, such as provided here? First, access to state-of-the-art AD clinical research has been limited among Mexican American (and other underserved) populations. In contrast, the advanced tools needed for comprehensive dementia (and AD) research studies are largely available among academic specialty clinics. Therefore, a blood-based screening tool can be most feasibility used in community settings (urban and rural) that are in proximity to dementia clinics using community-based protocols. Those who screen negative undergo limited assessments while those who screen positive can then be referred to the specialty clinic setting. This approach can leverage the "best of both worlds" and drastically open access to state-of-the-art research among underserved communities.

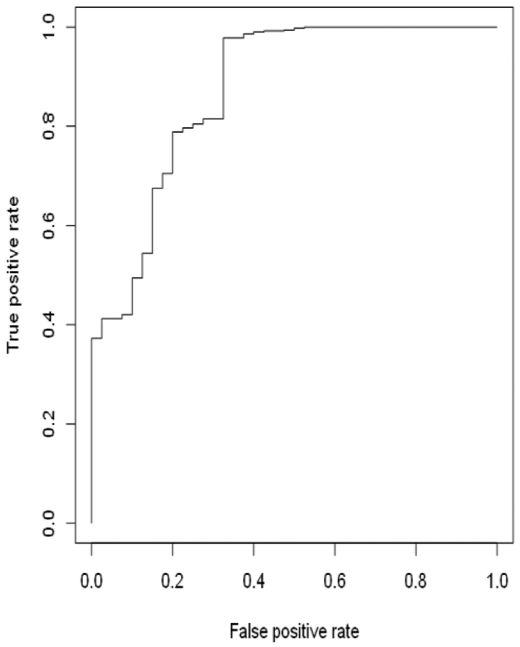
A practical illustrative example of the utility of this approach is as follows. If US NACC– or ACTC–wide projects sought to enroll a population of Mexican Americans with dementia and MCI for clinical research, a total of n = 20,000 participants could be screened from the rural and urban communities near existing ADC or ACTC sites. Estimating the prevalence found in the current study would result in approximately n = 3400 MCI cases (n = 20,000 x 0.17) and approximately n = 1162 dementia cases (n = 16,600 x 0.07). If the blood test cost $300 per person, the total screening costs would be ≈$6 million. However, if screening were conducted via amyloid PET scans, screening cost would be $60 million (estimated $3000 per person).

While the current proteomic profile yielded excellent results, it is possible that additional blood-based biomarkers may add to

A

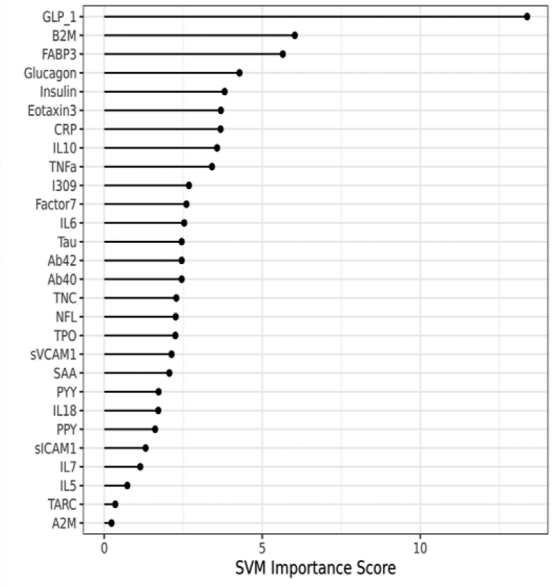
	Actual	
Predicted	AD	NC
AD	24	6
NC	16	496
Sensitivity	60.00%	
Specificity	98.80%	
NPV	96.88%	
AUC	87.41%	





B

	Actual	
Predicted	AD	NC
AD	32	0
NC	2	546
Sensitivity	94.12%	
Specificity	100.00%	
NPV	99.64%	
AUC	96.99%	



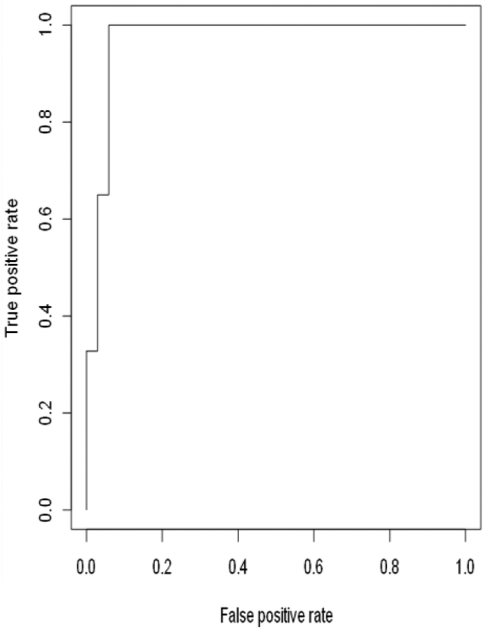


FIGURE 5 Classifying dementia by ethnicity. A, Classifying dementia among Mexican Americans. B, Classifying dementia among non-Hispanic Whites. A2M, alpha 2 macroglobulin eotaxin 3; AUC, area under the curve; B2M, beta 2 microglobulin (B2M); CRP, C-reactive protein; GLP-1, glucagon-like peptide 1; FABP3, fatty acid binding protein 3; IL, interleukin; NC, normal control, non-cognitively impaired; NfL, neurofilament light; NPV, negative predictive value; PPY, pancreatic polypeptide; PYY, peptide YY; SAA, serum amyloid A; factor VII (factor 7); sICAM1, soluble intercellular adhesion molecule 1; sVCAM1, circulating vascular cell adhesion molecule 1; SVM, support vector machine; TARC, thymus activation regulated chemokine; TNFa, tumor necrosis factor alpha; TNC, tenascin C; TPO, thrombopoietin

this process. In addition to amyloid and total tau, phospho-tau217 and phospho-tau181 have received attention in the recent literature as putative biomarkers for AD;[40–42,43] however, none of this work has been conducted within this specific COU where base rates are far lower than dementia clinic settings. Additionally, it is unknown if race/ethnicity impact these markers. These, and other, novel markers will be examined within this COU leveraging the HABLE biorepository.

When examining the variable importance plots for MCI and dementia across ethnic groups, there were clear differences. Among

Mexican Americans, inflammatory and metabolic markers were in the top half of all markers whereas plasma-based markers associated with AD pathology (i.e., amyloid, tau, and neurodegeneration) were in the bottom of the variable importance plot. Among non-Hispanic Whites, however, the top half of the proteomic profile was largely inflammatory and traditional markers of AD pathology with most metabolic markers (except for insulin) being in the bottom of the variable importance plot. Therefore, metabolic markers are more relevant to MCI among Mexican Americans whereas inflammatory and AD-pathology related biomarkers are more important among non-Hispanic Whites. The profile of dementia among Mexican Americans, however, was inflammatory and neurodegeneration (i.e., NfL) while the non-Hispanic White profile shifted to become largely metabolic, inflammatory, and AD-pathology marker related. Therefore, the current results suggest a shift in biological profiles from MCI to AD that is different among Mexican Americans compared to non-Hispanic Whites. In fact, metabolic factors appear to be more relevant in MCI among Mexican Americans whereas these factors become more relevant to dementia among non-Hispanic Whites. The AD-pathology markers were not major drivers of the profiles for detecting MCI or dementia among Mexican Americans whereas they were significant contributors to diagnostic accuracy of both among non-Hispanic Whites. It is also noteworthy that demographic factors increased the accuracy of the profiles (MCI and AD) more among Mexican Americans than non-Hispanic Whites. Future work will determine whether these profiles vary by sex and ethnic status.

These findings of the inflammatory and metabolic nature of MCI and dementia are of importance. In our prior work, we identified a proinflammatory endophenotype of AD[44] that was later shown to predict treatment response among a specific subset of AD patients to anti-inflammatory medications.[45] We also proposed a metabolic endophenotype[24] and have now demonstrated that this endophenotype can also predict treatment response of a specific subset of AD patients to anti-diabetic medications.[46] Combined, this data suggests that both inflammatory and metabolic factors require additional investigation for precision medicine approaches to novel AD clinical trials, and the efficacy of these interventions may vary not only by disease state, but also by ethnicity.

The cross-sectional nature of the current findings is a limitation. However, the HABLE study is currently collecting Visit 2 examinations so longitudinal assessments will be available. A second limitation is the age of enrollment of 50 and above. Given the younger age of onset of cognitive loss among Mexican Americans, as well as the differential importance of the identified biological mechanisms, it is important to study younger age ranges of these ethnic/racial groups to fully understand the life course nature of MCI and AD, as well as associated biomarkers, if appropriate prevention strategies are to be attempted. A third limitation to the current study is the lack of comparison of AT(N) plasma biomarkers across assay platforms or direct comparison to cerebral amyloid status (PET or cerebrospinal fluid). Recent work suggests that mass spectrometry–based plasma amyloid may result in high classification accuracy for detecting clinical or amyloid positivity status.[47–49] Future studies can assay plasma AT(N) biomarkers across a wide range of platforms by leveraging the HABLE biorepository. Additionally, the HABLE study is currently collecting PET amyloid and tau scans longitudinally and, therefore, future work will directly compare blood-based and PET-based biomarkers of AT(N). A fourth limitation is the lack of inclusion of factors related to social determinants of health (SDOH); however, ongoing work is directly assessing the impact of SDOH on a broad range of biomarkers (including A, T, and N) within this cohort. A final limitation is the lack of inclusion of African Americans, who currently reflect the largest proportion of AD and ADRDs in the United States.[6] No prior studies have simultaneously examined AT(N) biomarkers across the three largest racial/ethnic populations of the United States. Therefore, the HABLE study (now entitled the Health & Aging Brain Study – Health Disparities, HABS-HD, to better reflect the community it serves) is currently enrolling n = 1000 African Americans to undergo comprehensive AT(N) based assessments. Strengths of the current study include sample size, the multi-ethnic nature of the cohort, and the leveraging of both community-based and clinic-based methods. Overall, our findings support the COU of a blood screening tool for increasing representation of diverse communities in AD clinical research.

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CONFLICTS OF INTEREST

SEO has multiple patents on precision medicine for neurodegenerative diseases and is the founding scientists for Cx Precision Medicine, Inc. LAJ has financial interests in Cx Precision Medicine, Inc. MMM has consulted for Biogen and Brain Protection Company and receives funding from NIH.

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