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Blood-Based Biomarkers

A blood screening test for Alzheimer's disease

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Abstract

Introduction: This study combined data across four independent cohorts to examine the positive and negative predictive values of an Alzheimer's disease (AD) blood test if implemented in primary care.
Methods: Blood samples from 1329 subjects from multiple independent, multiethnic, community-based, and clinic-based cohorts were analyzed. A "locked-down" referent group of 1128 samples was generated with 201 samples randomly selected for validation purposes. Random forest analyses were used to create the AD blood screen. Positive (PPV) and negative (NPV) predictive values were calculated.
Results: In detecting AD, PPV was 0.81, and NPV was 0.95 while using the full AD blood test. When detecting mild cognitive impairment, PPV and NPV were 0.74 and 0.93, respectively. Preliminary analyses were conducted to detect any "neurodegenerative disease". The full 21-protein AD blood test yielded a PPV of 0.85 and NPV of 0.94.
Discussion: The present study creates the first-ever multiethnic referent sample that spans community-based and clinic-based populations for implementation of an AD blood screen.

Keywords: Alzheimer's disease; Primary care; Blood test; Screening; Diagnosis; Predictive power

1. Introduction

Alzheimer's disease (AD) is the most common dementia and is the fifth leading cause of death for those over 65 years [1]. Currently, over 5 million Americans suffer from AD [2], and it is estimated that those numbers will grow exponentially by 2050. AD has an annual health care cost similar to that of cardiovascular disease and more than cancer [3]. As a result of these rapidly increasing numbers, there is a growing need for the identification of a time-effective and cost-effective screening tool for use in primary care settings.

The Centers for Medicare and Medicaid Services recently implemented the annual wellness visit (AWV) that includes a cognitive examination (CMS.gov); however, the 2015 American Gerontological Society working group reported that "older adults are inadequately assessed for cognitive impairment during routine visits with their primary care providers" [4]. This limited access to early diagnostics has been associated with delayed treatment initiation, delays in provision of services to family members, overall decreased quality of life, and increased family burden [5]. Given the limited time available in primary care visits (average of 18 minutes), primary care providers are left with a significant dilemma of how to meet the AWV requirements.

In our prior work, we have proposed that an AD blood test could serve as the first stage in a multi-stage diagnostic

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workup [6] as is the case in infectious disease, cancer, and cardiovascular disease. A blood test can fit into the current infrastructure and be used to rule out patients who do not need further workup. We hypothesize that a blood-based screening tool for AD [7–10] can serve as the first step in a multistage detection process [11] within community-based clinics. Obtaining an early diagnosis within primary care settings can increase access to current therapies, reduce overall health care costs [12], delay nursing home placement [13], facilitate a connection with community resources, and reduce caregiver stress [13] as well as assist in future planning [13]. This model follows the evolution of breast cancer screening in primary care [13].

When designing a biomarker (blood based or otherwise), it is crucial to first define the context of use and outline the methods for development per that fit-for-purpose [14–16] as well as outline the minimum performance requirements of the biomarker itself. In this case, what is the overall purpose of the AD blood screener when applied to a primary care setting? Is it to "diagnose" AD or to determine who needs follow-up examination? In primary care settings (and other settings), a key context of use for nearly all screening tests is to rule out those who do not have the disease to decrease the numbers of patients that undergo more invasive and costly procedures. For example, mammography does not rule in breast cancer as the positive predictive values (PPV) are below 30% [17,18]. Additionally, screening of depression in primary care has low PPVs (e.g., 0.15–0.27) [19], but negative predictive power is excellent (>0.96) [19]. In both cases, the screening test ensures that only those who need the follow-up examination (biopsy, psychiatric referral) undergo such procedures, which serves as cost containment and reduces unnecessary medical services to patients. This strategy also provides a streamlined, step-wise process for physicians to make decisions regarding which tests are used in what order.

Therefore, it is our proposal that a primary care AD blood screen can be used to rule out 85% or more of elderly patients seen in primary care who do not need to undergo more expensive procedures. Therefore, a screen positive on the AD blood test would trigger a multistage neurodiagnostic process of (1) neurology specialty exam for differential purposes, (2) cognitive testing, and finally, (3) cerebrospinal fluid analysis and/or PET amyloid imaging.

When moving from discovery to clinical consideration of biomarkers, there are a series of steps for validation purposes [20]. Once the biomarker has been identified and initial validation studies have been conducted (independent of the discovery set), the methods must be "locked down" for additional prospective studies (e.g., clinical trials) [20]. This "lock-down" procedure is where all steps in the process are solidified and no longer available for further manipulation. With regard to multimarker algorithm applications, such as our AD blood test, this includes the generation of a locked-down referent sample to which all future blood samples are compared. To date, no work globally has created

Table 1
Demographic characteristics across cohorts

	Total			HABLE			UTSW-ADC			PARI			Mayo		
	Mean (SD)			Mean (SD)			Mean (SD)			Mean (SD)			Mean (SD)		
	Range			Range			Range			Range			Range		
Characteristic	AD	MCI	NC	AD	MCI	NC	AD	MCI	NC	AD	MCI	NC	AD	MCI	NC
Age (y)	75.8 (8.6)	69.4 (8.6)	65.8 (9.8)	74.2 (9.0)	66.3 (8.0)	59.2 (6.7)	72.6 (8.1)	69.0 (7.2)	67.6 (7.3)	82.3 (9.1)	81.7 (7.8)	76.9 (6.7)	76.8 (5.7)		76.7 (5.7)
	51–103	50–102	50–95	58–91	50–86	50–85	51–103	52–94	50–84	66–97	69–102	65–95	64–88		56–88
Gender female %	52.6	54.4	65.7	60.7	63.9	80.6	37.1	47.5	37.6	82.1	64.5	64.9	64.1		72.9
Education	13.1 (4.3)	11.4 (5.2)	11.8 (4.9)	5.6 (4.6)	6.9 (4.6)	8.8 (4.6)	14.6 (2.8)	14.6 (2.9)	15.5 (2.4)	6.8 (3.4)	6.8 (2.9)	9.2 (3.9)	13.7 (3.0)		14.6 (2.9)
	0–22	0–22	0–23	0–16	0–20	0–20	8–20	7–22	10–22	0–14	1–12	1–16	6–20		7–20
Ethnicity %															
Non-Hispanic White	61.8	41.7	31.9		3.1	6.5	66.8	69.8	49.6						
Hispanic/Latino	14.4	41.7	49.5	100.0	96.9	93.3	0.5	1.7	0.4	100.0	100.0	100.0			
African American	3.1	11.4	3.1				6.8	19.6	11.9						
Choctaw	0.4	3.9	2.8				1.0	6.7	10.6						
Other		1.3						2.2							