Currently, however, there are no rapid or cost-effective tools for primary care providers to use in daily practice to screen patients with possible PD symptoms. Within primary care settings, the purpose of screening tests is to rule out patients who do not require additional medical procedures or diagnostic follow-up, thereby resulting in stress reduction and cost containment.

Our team has proposed a multi-tiered neurodiagnostic process for neurodegenerative diseases including Alzheimer's disease, Parkinson's disease and Dementia with Lewy Bodies (DLB) [5-7].

Over the last several decades, the search for biomarkers that have diagnostic and prognostic utility in neurodegenerative diseases has grown exponentially with the majority of work focusing on neuroimaging and cerebrospinal (CSF) methodologies. In fact, the dopamine transporter single photon emission CT [DaT-SPECT] has been approved as a tool for diagnosing PD. Research suggests that CSF markers may also hold utility in the differential diagnosis of neurodegenerative diseases [8-15]. While advanced neuroimaging and CSF methods have tremendous potential as biomarkers of PD, invasiveness, accessibility and cost barriers preclude these from being utilized as an initial step in detection procedures. Therefore, it has been proposed that blood-based biomarker methods may serve as the optimal first step in a multi-tier detection process [17,18] and requires additional investigation, similar to their application in the field of oncology [16-21]. Our team has conducted a series of studies demonstrating the utility of blood-based biomarkers for detecting PD as well as discriminating PD from other neurodegenerative diseases [22]. Here we completed a large-scale cross-validation of our PD Blood Test (PDBT) for use in primary care settings.

Materials and Methods

Participants and reference database

Parkinson's disease data: Our team recently completed baseline and longitudinal assays on serum samples from the previously conducted DATATOP trial. DATATOP methods regarding participant recruitment, study design, enrollment, consent procedures, and funding sources have all been previously published. Briefly, DATATOP was a multi-site placebo- controlled clinical trial designed to test the impact of deprenyl 10 mg/d and/or tocopherol (vitamin E) 2000 IU/d on PD progression (in combination with levodopa) [23]. A total of 656 baseline PD serum samples had requisite data in our database, and were used in the current study. An additional n=190 serum samples from PD cases were already included in our research database from PD specialty evaluations. Therefore, there was a total number of n=846 PD cases. No cases included in this study had a diagnosis of PD-dementia.

Neurodegenerative Disease Blood Test Reference Database (NDRD): Complex diseases, such as neurodegenerative diseases, require that multiple factors (or biological pathways) be considered when making a diagnosis rather than just a single factor. In m

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.

Diagnostic accuracy was calculated via Receiver Operating Characteristic (ROC) curves. The sample was randomly split (70/30) into training and test samples with diagnostic accuracy derived from the test sample. Finally, to provide estimates of the overall utility of the PDBT in ruling out PD in primary care settings, negative predictive values (NPVs; the probability that subjects with a negative screening test truly do not have disease) were calculated using a range of base rates including 2%, 5%, 10% and 15%.

Results

Descriptive statistics of the sample are provided in Table 1. The average age of the sample 63.8 (SD=13.4). The PD group was younger, more likely to be male, and reported higher levels of education (p-values<0.001) as compared to the normal control group.

	PD	**Normal control**	**p-value**
	Mean(SD)	**Mean(SD)**	
N	846	2291	
Age	59.5(12.6)	65.4(13.4)	4.16E-29
Education	13.76(4.65)	12.74(6.62)	1.59E-06
Gender (%M)	62.8	40.1	5.65E-30

Table 1: Demographic characteristics of the cohort.

In the training sample, there were a total 592 PD samples and 1604 control samples. The SVM was applied with a 5-fold internal cross-

as well as for general neurology clinics when receiving referrals to determine the most appropriate clinician to receive the new patient.

There are limitations to the current study. First, it is possible that additional proteomic markers, not examined in this study, will increase the overall accuracy of the PDBT. AD specific markers such as Amyloid Beta (Aβ) 40, Aβ 40, tau and neurofilament light chain (NfL) have been increasingly explored both in blood and CSF for their utility in detecting AD and PD as well as distinguishing between neurodegenerative conditions [29–35]. Karikari and colleagues examined phosphorylated tau 181 (ptau181) and found that this one marker alone reached an AUC of 0.81 in distinguishing AD from PD [36]. In addition to AD specific biomarkers, PD specific biomarkers such as a-synuclein have also shown promise particularly when applied to distinguishing PD from other related conditions such as DLB [30,37]. While increased accuracy is not needed for the current screening Context of Use (COU), increased accuracy would be needed for the generation of a blood-based diagnostic test and therefore the addition of other such markers should be considered in future work. Second, it is possible that novel or known genetic markers will improve the diagnostic accuracy. It is of importance to note that the COU for the PDBT is not diagnostic, but rather as a screening tool to rule out PD within primary care settings. It will be important for this work to be replicated to ensure reproducibility.

Conclusion

The availability of the PDBT for primary care holds tremendous benefit. First, this is a rapidly scalable technology that can be implemented globally as a Laboratory Developed Test (LDT). The PDBT would provide primary care providers with action]ip thatuff}
'glot

16. Henchcliffe C, Dodel R, Beal MF (2011) Biomarkers of Parkinson's disease and Dementia with Lewy bodies. Prog Neurobiol 95: 601–613.
17. Schneider P, Hampel H, Buerger K (2009) Biological marker candidates of alzheimer's disease in blood, plasma, and serum. CNS Neurosci Ther 15: 358–374.
18. Eller M, Williams DR (2011) α-Synuclein in Parkinson disease and other neurodegenerative disorders. Clin Chem Lab Med 49: 403–408.
19. Shtilbans A, Henchcliffe C (2012) Biomarkers in Parkinson's disease: An update. Curr Opin Neurol 25: 460–465.
20. Henriksen K, O'Bryant SE, Hampel H, Trojanowski JQ, Montine TJ, et al. (2014) The future of blood-based biomarkers for Alzheimer's disease. Alzheimers Dement 10: 115–131.
21. Gold LS, Klein G, Carr L, Kessler L, Sullivan SD (2012) The emergence of diagnostic imaging technologies in breast cancer: Discovery, regulatory approval, reimbursement, and adoption in clinical guidelines. Cancer Imaging 12: 13–24.
22. O'Bryant SE, Xiao G, Zhang F, Edwards M, German DC, et al. (2014) Validation of a serum screen for Alzheimer's disease across assay platforms, species, and tissues. J Alzheimer's Dis 42: 1325–1335.
23. No authors listed (1989) Datatop: A multicenter controlled clinical trial in early parkinson's disease: Parkinson study group. Arch Neurol 46: 1052–1060.
24. O'Bryant SE, Lista S, Rissman RA, Edwards M, Zhang F, et al. (2016) Comparing biological markers of Alzheimer's disease across blood fraction and platforms: Comparing apples to oranges. Alzheimers Dement (Amst) 3: 27–34.
25. O'Bryant SE, Xiao G, Barber R, Reisch J, Doody R, et al. (2010) A serum protein-based algorithm for the detection of Alzheimer disease. Arch Neurol 67: 1077–1081.
26. Software as a Medical Device (SAMD): Clinical Evaluation - Guidance Aaeiríg group