Screening for Proteinopathic-related Dementias in Low-resource Clinical Contexts: A Machine Learning Approach

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COMPULSORY DECLARATION

This work has not been previously submitted in whole, or in part, for the award of any degree. It is my own work. Each significant contribution to, and quotation in, this dissertation from the work, or works, of other people has been attributed, and has been cited and referenced.

I confirm that I have been granted permission by the University of Cape Town's Senate to include publications (Chapter 3) in my MA Thesis and where co-authorships are involved, my co-authors have agreed that I may include the publications.

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List of Abbreviations

AD	Alzheimer's Disease
ADLs	Activities Of Daily Living
Aβ	Amyloid Beta
BADLS-M	Bristol Activities of Daily Living Scale – Modified
BNT-SASF	Boston Naming Test – South African Short Form
CDR	Clinical Dementia Rating
CI	Confidence Interval
COMP	Comparison Group
DLB	Dementia With Lewy Bodies
ESE	Effect Size Estimate
FTD	Frontotemporal Dementia
GSH	Groote Schuur Hospital
HAND	HIV-Associated Dementia
HICs	High-Income Countries
HIV	Human Immunodeficiency Virus
HLOE	Highest Level of Education
IAA	Institute Of Ageing in Africa
LBD	Lewy Body Dementia
LL	Lower Limit
LMICs	Low- And Middle-Income Countries
MCI	Mild Cognitive Impairment
ML	Machine Learning
MMSE	Mini-Mental State Examination
NLR	Negative Likelihood Ratio
NPV	Negative Predictive Value
PCP	Primary Care Practitioner
PDD	Parkinson’s Disease Dementia
PLR	Positive Likelihood Ratio
PPA	Primary Progressive Aphasia
PPV	Positive Predictive Value
PRDs	Proteinopathic-Related Dementias

RBANS	Repeatable Battery for The Assessment of Neuropsychological Status
RBANS-DMI	RBANS – Delayed Memory Index
RBANS-FC	RBANS – Figure Copy
RBANS-IMI	RBANS – Immediate Memory Index
sVAD	Subcortical Vascular Dementia
TBI	Traumatic Brain Injury
Trails A	Trail Making Test Part A
Trails MoCA	MoCA Trails Test
UCT	University Of Cape Town
UL	Upper Limit
VaD	Vascular Dementia
VRFS	Vascular Risk Factor Scale

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Abstract

Background: The prevalence of Alzheimer's disease (AD) and other subtypes of proteinopathic-related dementias (PRDs) is increasing rapidly in low- or middle-income countries (LMICs). The wide-ranging social and economic consequences of PRDs means there is an urgent need for clinical services dedicated to their early and accurate detection, particularly in low-resource contexts. The aim of the present study was to use machine learning techniques to identify a minimum number of clinical variables (neuropsychological test data and vascular risk factor information) required for accurate classification of PRDs in an older adult sample from an LMIC population and to derive a decision tree algorithm that diagnoses these types of dementias. ***Methods:*** The present study used data from a memory clinic sample of 253 South African older adults (130 with PRDs, 123 without). Information from 20 clinical variables were used as features for the analysis. We used C5.0 algorithms to identify the most important features for PRD diagnosis and to derive an algorithm that could accurately diagnose these types of dementia. ***Results:*** The C5.0 algorithm reduced the number of clinical variables for screening PRDs from 20 to 9 (Repeatable Battery for the Assessment of Neuropsychological Status [RBANS] Figure Recall, vascular risk factor, phonemic verbal fluency, RBANS List Recall, RBANS List Recognition, Digit Span Backward, CLOX1, CLOX2, and ΔCLOX2-1), and classified the validation sample with an accuracy exceeding chance performance. Accuracy, sensitivity, and specificity values were all greater than 70%. Performance on tests assessing memory and executive functioning were the features that predominantly distinguished the PRD and comparison groups from one another. ***Conclusions:*** The derived decision tree is a suitable and easy-to-interpret approach for PRD screening in LMICs. Its utility as part of standard clinical practice has the potential to free up strained resources and to allow clinical expertise to be employed more selectively.

Chapter 1:
General Introduction

Dementia is a public health priority due to its increasing prevalence and associated wide-ranging social and economic consequences for individuals, their families, and society as a whole. Global estimates indicate there are currently more than 55 million people living with dementia, a figure that is expected to reach 152 million by the year 2050 (Alzheimer's Association, 2022; GBD 2019 Dementia Forecasting Collaborators, 2022). This growth will be most prominent in low- and middle-income countries (LMICs), where the number of individuals living with dementia is projected to increase by 330% over the next 30 years (GBD 2019 Dementia Forecasting Collaborators, 2022). However, the lack of awareness and preparedness for the cost and detection of this disease is reflected by the lack of specialist services and resources dedicated to assessing dementia in those countries (World Health Organization, 2021a).

Dementia is not a single disease, but rather a syndrome of symptoms caused by a range of different diseases and conditions. Most dementias are considered to be proteinopathies; that is to say, the clinical deficits that characterise them are associated with the accumulation of abnormal protein aggregates in the brain (Ganguly et al., 2017; Kovacs, 2019). Examples of proteinopathic-related dementias (PRDs) include Alzheimer's disease (AD), frontotemporal dementia (FTD), and Lewy body dementia (including dementia with Lewy Bodies [DLB] and Parkinson's disease dementia [PDD]; Allegri, 2020; Dash et al., 2021).

Epidemiological data regarding the prevalence of AD and other subtypes of PRDs in LMICs is limited. However, the increasing number of dementia cases in those countries means there is an urgent need for services that are dedicated to its early and accurate detection (Whittington et al., 2019). Because healthcare systems in LMICs have limited resources, patients typically do not undergo the routine neuroimaging or biomarker examinations recommended for the differentiation of PRDs from dementias with other aetiologies (e.g., vascular dementia [VaD]; Kerwin et al., 2022; Magklara et al., 2019; Parra et al., 2022). Instead, clinicians tend to rely on time-intensive neuropsychological testing to identify patterns of cognitive impairment that might support fine-grained differential diagnoses – but typically they do so without first determining whether the patient is a candidate for the broader category of PRD to begin with (Akinyemi et al., 2022). However, no research has explored whether there is a common neuropsychological profile that can differentiate patients with dementia due to abnormal protein accumulation from those without

such neuropathology. In addition to identifying a common neuropsychological profile, a pivotal step in alleviating the burden of dementia in LMICs would be to optimise neuropsychological test batteries so as to reduce their length while still ensuring diagnostic accuracy for PRDs.

Of relevance here, then, is machine learning (ML), a branch of artificial intelligence that is able to pick out information from various sources and produce an integrated system that can aid decision-making in various contexts (Sidey-Gibbons & Sidey-Gibbons, 2019; Tariq et al., 2020).

In this thesis, I investigate whether ML techniques can identify a minimum number of clinical variables (neuropsychological test data and vascular risk factor information) required for accurate classification of PRDs in an older adult sample from an LMIC population. Moreover, the study seeks to derive an ML-based algorithm that diagnoses these types of dementias efficiently.

Chapter 2:
Extended Literature Review

Dementia is an umbrella term for a host of neurocognitive disorders that primarily occur later in life and that are caused by abnormal neurodegeneration (World Health Organization, 2017). This pathological degeneration of brain tissue is correlated to progressive cognitive impairment (e.g., memory loss, executive dysfunction, language difficulties), behavioural disturbance, and functional disabilities (e.g., disruption in activities of daily living; ADLs). Together, these cognitive, behavioural, and functional declines have a significant impact on quality of life and have wide-ranging consequences for patients, their families, and society as a whole (Cipriani et al., 2020; Prince et al., 2015).

Dementia is a leading cause of disability and dependency globally and is currently the seventh-leading cause of death among all diseases (World Health Organization, 2021a). Estimates suggest there are currently over 50 million people living with dementia worldwide (most of whom are aged 65 or older), a figure that is expected to rise to 152 million by the year 2050 (Alzheimer's Association, 2022). The increasing rates of dementia within the population are not uniform across countries, however. Recent estimates indicate that over the next 30 years dementia prevalence will increase by up to 330% in low- and middle-income countries (LMICs) compared to only 140% in high-income countries (HICs; GBD 2019 Dementia Forecasting Collaborators, 2022).

This disparity is largely due to the fact that population ageing is occurring at unprecedentedly rapid rates in LMICs. Demographic estimates suggest that the growth rate of the over-60 population is three times faster in LMICs than in HICs (Kämpfen et al., 2018; Solanki et al., 2021).

In addition to demographic changes in ageing, increased rates of dementia in LMICs may be a consequence of disproportionate exposure to risk factors and a greater lack of preventative measures in those settings. For example, low average educational attainment, as well as the high prevalence of cardiovascular disease, alcohol abuse, and tobacco use in LMICs may worsen risk profiles in those countries (Li et al., 2022; Livingston et al., 2020; Rosengren et al., 2019; World Health Organization, 2021b).

The increasing number of dementia cases in LMICs corresponds to an increased demand for clinical services that might help alleviate the personal, familial, and societal burden of that neurocognitive disorder in those countries. However, a signal lack of awareness and preparedness for the cost and detection of this disease is reflected by there

being limited financial resources and few services in LMICs that are specifically oriented towards people with dementia.

The global cost of dementia was estimated to be 1.3 trillion USD in 2019, with that statistic expecting to more than double by 2030 (World Health Organization, 2021a). Although most people (61%) diagnosed with dementia in 2019 lived in LMICs, 74% of the total dementia costs were occurring in HICs (World Health Organization, 2021a). The lower costs occurring in LMICs are largely a result of differences in access to diagnostic services, clinical care, and dementia medications (Mattap et al., 2022). For example, currently, 56% of costs in HICs are dedicated to direct medical and social care (e.g., hospital services, diagnostic tests, medicine, and paid long-term care) compared to only 35% in LMICs. The remaining 65% of dementia costs in LMICs is accounted for by informal caregiving (i.e., productivity loss among family members and other informal carers who support people with dementia; World Health Organization, 2021a). Further differences between LMICs and HICs exist in terms of hours of informal dementia care, with estimates suggesting that, in 2019, informal carers in LMICs worked more than twice as many hours (89339 million hours) than those in HICs (43916 million hours; World Health Organization, 2021a).

Informal caregivers include family members, partners, friends, or neighbours who offer a variety of unpaid services to those with chronic or disabling conditions (Lindeza et al., 2020). Of note here is that caregiving for people with dementia is reportedly more stressful than caring for people with other diseases (Del-Pino-Casado et al., 2019; Magaña et al., 2020; Pinquart & Sörensen, 2003; Riffin et al., 2019). This phenomenon is likely related to the large amount of time required to care for a person with dementia, resulting in the caregiver being isolated from social circles, reducing time at work, or even giving up formal employment altogether (Lindeza et al., 2020). A large number of studies have therefore reported on the extensive practical, psychological, and economic strain that informal caregivers of dementia patients experience (for a review, see Chiao et al., 2015). A major predictor of caregiver distress is the severity of the disease, and this may be related to the association between severity of disease and the cost of dementia (Wang et al., 2022).

In LMICs, the estimated annual per-person cost of dementia ranges from about US$7400 for mild dementia to US$15600 for severe dementia (World Health Organization, 2021a). While the current costs of dementia in LMICs are likely underestimated due to unstandardised measurement methods, these estimates, in addition to the relationship between severity of disease and caregiver burden, highlight the importance of a timely diagnosis (a

fact especially important in LMICs, which are characterized by high burdens of medical diseases and relatively poorly resourced clinical infrastructure).

In addition to reducing economic costs, a timely diagnosis also has the potential to improve quality of life for both the patient and their family. For example, it allows people to prioritise modifiable risk factors and to plan ahead while they still have the capacity to make important decisions about their future care. At the same time, the individual and their family will be able to receive practical information, support, and advice early in the disease progression. Additionally, receiving a timely diagnosis will allow the patient to access evidence-based pharmacological treatments (e.g., donepezil, memantine) that have been found to improve cognition, behaviour, and functional abilities especially if initiated earlier in the disease process (Byun et al., 2022; Ju et al., 2021). Further, literature indicates that there is an association between earlier diagnosis and mortality. For instance, using a French sample of 663 individuals with Alzheimer's disease (AD), 141 with vascular dementia (VaD), and 116 with mixed AD + VaD, Bruandet et al. (2009) found that the shorter the delay between first symptom onset and first visit to a memory clinic, the longer the patients survived (see also Black et al., 2018; Lehmann et al., 2018). Overall, then, a timely diagnosis has the potential to not only minimise the distress for the individual patient, their family, and their caregivers, but it can also delay institutionalisation and prolong survival (for a review, see Rasmussen & Langerman, 2019).

Given the wide-ranging social and economic consequences of dementia, as well as the importance of a timely diagnosis, there is an urgent need for services dedicated to the early and accurate detection of dementia in LMICs. However, given the lack of healthcare practitioners equipped for detecting dementia in LMICs, as well as the limited healthcare resources available in those countries, an unacceptably large number of people living with dementia remain undetected, with estimates suggesting that the median diagnostic rate of dementia in LMICs is 21% (World Health Organization, 2021a).

Diagnosing Dementia in Low- and Middle-Income Countries

The diagnosis of dementia is a complex process and typically involves both primary and secondary health services. The initial point of contact for patients suspected of having dementia is a primary care practitioner (PCP). The role of the PCP is to identify the presence of cognitive impairment (thereby excluding potentially reversible or treatable conditions such as depression), assess the severity of impairment, and refer the patient to appropriate secondary care specialists for further diagnostic testing (Robinson et al., 2015). The main goal of a specialist is to reach a possible / probable differential diagnosis of dementia to

ensure that patients receive the correct prognosis and appropriate management plans (Drabo et al., 2019). Although definitive differential diagnosis cannot be made until autopsy, dementias can be classified into syndromic groups, with varying degrees of certainty, based on distinctive clinical traits, symptomatic progression, and other supporting diagnostic information (Elahi & Miller, 2017).

Most dementias are considered to be proteinopathies; that is to say, the clinical deficits that characterise them are associated with the accumulation of abnormal protein aggregates intracellularly (e.g., tau, α-synuclein, TDP-43) or extracellularly (amyloid beta [Aβ] peptide; cellular prion protein; Allegri, 2020; Dash et al., 2021). These aggregates disturb cellular functions, molecular processes, and, ultimately, cell survival, thereby disrupting large-scale neural networks involved in cognitive, behaviour, personality, and sensorimotor functioning (Elahi & Miller, 2017; Ochneva et al., 2022).

Epidemiologically, proteinopathic-related dementias (PRDs) account for most cases of neurodegenerative disorders (Rahimi & Kovacs, 2014). For instance, the most common PRD, AD, by itself accounts for more than 60% of dementia cases globally (Alzheimer's Association, 2022). Although limited data exists regarding the current prevalence of both AD and other subtypes of PRDs in LMICs, extent data from memory clinics in LMICs suggest that AD is the most prevalent PRD in LMICs, followed by mixed dementia, frontotemporal dementia (FTD), and Lewy body dementia (LBD), while the most common non-PRD is VaD (Alladi et al., 2011; Kalaria et al., 2008; Kalula et al., 2010; Liu et al., 2020). Other non-proteinopathic dementias also exist and may develop after a stroke, in the context of infections such as HIV, or as a consequence of long-term harmful use of alcohol, of repetitive traumatic brain injuries (TBI), or of nutritional deficiencies (Bevins et al., 2021; LoBue et al., 2020; Rosca et al., 2021).

Neuropathology and Patterns of Impairment in PRDs

Clinically, AD is characterised by an insidious onset of cognitive impairment and a progressive decline in cognitive and behavioural functioning. The neuropathological process underlying AD involves the presence of intracellular neurofibrillary tangles and extracellular Aβ plaques that build up in the brain causing neuronal atrophy and synapse loss to the point that they disrupt normal cognitive functioning (Alzheimer's Association, 2019; DeTure & Dickson, 2019). It is well-documented that the most prominent and earliest symptom of AD is episodic memory impairment. As the disease progresses, deficits in attention (e.g., poor performance on dual processing tasks), working memory, language (e.g., word-finding difficulties), visuospatial abilities (e.g., compromised spatial cognition), executive functions

(e.g., impaired judgement, reasoning, and problem-solving) usually become increasingly prominent (Begali, 2020; Ho & Nation, 2018; McKhann et al., 2011).

FTD refers to a group of progressive PRDs associated with severe neurodegeneration of cortical and subcortical structures within the frontotemporal regions of the brain (Boeve et al., 2022). These areas of the brain are known to control personality, reasoning, social graces, language, and some aspects of memory (Piguet et al., 2017). Neuropathologically, FTD is frequently associated with intracellular aggregates of tau or TDP-43, and, less frequently, with intracellular FUS inclusions (for a review, see Elahi & Miller, 2017).

Taxonomic work in this area suggests there are three types of FTD: (a) behavioural variant FTD (bvFTD), which is the most commonly encountered FTD and which is characterised by progressive changes in personality, behaviour, and emotion; (b) primary progressive aphasia (PPA), which involves a range of language problems that can be categorised as either semantic PPA, agrammatic PPA, and logopenic PPA; (c) motor FTDs, which involve pyramidal and/or extrapyramidal impairments (for a review, see DeRight, 2022). Although each of these variants has a unique neuropsychological profile, they all present with executive function impairment and with relative sparing of visuospatial function and episodic memory (Bang et al., 2015).

LBD refers to either of two related diagnoses: dementia with Lewy Bodies (DLB) and Parkinson's disease dementia (PDD). The fundamental neuropathology of both disorders is the accumulation of α-synuclein aggregates (Lewy bodies) in the brain (Budson & Solomon, 2022). Over time, persons with either diagnosis experience similar cognitive, behavioural, and motor symptoms such as visuospatial/constructional deficits, REM sleep behaviour disorder, and parkinsonism, respectively (Jellinger & Korczyn, 2018; Sanford, 2018). The difference between the diseases largely revolves around the timing of symptom onset, with cognitive symptoms appearing before motor symptoms in DLB and motor symptoms occurring before cognitive symptoms in PDD (DeRight, 2022).

Neuropsychologically, LBDs typically present similarly to AD but with more severe visuospatial/visuoconstructional deficits and fewer word-finding difficulties (Li et al., 2014; Smirnov et al., 2020). Unique neuropsychiatric features of LBDs include recurring visual hallucinations and fluctuating attention and alertness (Gauthier et al., 2021).

Neuropathology and Patterns of Impairment in Non-PRDs

Vascular dementia (VaD) is a non-PRD that occurs as a result of cerebrovascular disease and whose characteristics vary depending on the location and type of disease (Bir et al., 2021). There are two widely accepted syndromes of VaD: (a) post-stroke VaD, in which

stepwise cognitive decline across one or more domains is temporally linked to a series of strokes or a single strategic brain infarct, and (b) subcortical VaD (sVaD), in which insidious cognitive decline occurs as a consequence of small vessel disease (Smith, 2017).

Neuropsychologically, post-stroke VaD syndromes are characterised by hetero-modal cortical symptoms, such as visuospatial deficits, apraxia, aphasia, and agnosia, as well as executive dysfunction and focal neurological signs. In contrast, sVaD neuropsychological syndromes are primarily characterised by impaired information processing speed and executive functioning (Hamilton et al., 2021).

Other less common non-PRDs include infection-associated dementia (e.g., HIV-associated dementia; HAND), toxin-associated dementia (e.g., alcohol-related encephalopathy), and TBI-related dementia (e.g., chronic traumatic encephalopathy; Brosch & Farlow, 2021). These dementias often manifest similarly to subcortical dementia, with executive dysfunction being prominent (DeRight, 2022; Winston & Spudich, 2020).

The Use of Neuropsychological Tests for Differential Diagnosis of PRDs and Non-PRDs

Given that types of dementia differ in neuropathology, brain scans, basic blood tests, and lumbar punctures to assess proteins in the cerebrospinal fluid are recommended in order to reach a differential diagnosis. However, because healthcare systems in LMICs have limited resources, patients typically do not undergo the routine neuroimaging or biomarker examinations recommended for the differentiation of PRDs from dementias with non-PRDs (Kerwin et al., 2022; Magklara et al., 2019; Parra et al., 2022). Instead, clinicians tend to rely on time-intensive neuropsychological testing to identify patterns of cognitive impairment that might support fine-grained differential diagnoses without first determining whether the patient is a candidate for the broader category of PRD to begin with (Akinyemi et al., 2022; Gauthier et al., 2021).

Although some studies have identified neuropsychological characteristics that distinguish different subtypes of PRDs, the cognitive impairment observed in these patients overlaps in many ways; hence, it is difficult to discern precisely which neuropsychological tests are important for differential diagnoses (see, e.g., Burrell & Piguet, 2015; Foguem & Manckoundia, 2018). For instance, whereas some studies have identified unique patterns of memory and executive function impairment among PRDs, several others report that no differences exist along those dimensions (for a review, see Musa et al., 2020). In a longitudinal study of 111 participants (33 AD, 31 bvFTD, and 47 controls), Ramanan et al. (2017) found that, with the exception of marked disinhibition by the bvFTD participants, performance on standard episodic memory and executive function measures (Addenbrooke's

Cognitive Examination – Revised, and backwards digit span and Trail Making Test-B, respectively; Lezak et al., 2012; Mioshi et al., 2006; Reitan, 1955) did not distinguish one patient group from the other—both scored poorly at baseline and at a 1-year follow-up. Additionally, although limited research exists comparing FTD and DLB, Johns et al. (2009) found markedly similar patterns of executive dysfunction (i.e., poor performance on tests of working memory, verbal fluency, and planning) in patients presenting with these types of dementia. Similarly, research demonstrates that the neuropsychological profile of DLB and PDD overlap in many ways. For instance, using a sample of 47 participants (22 DLB, 25 PDD) and a neuropsychological test battery assessing memory, language, processing speed, visuospatial/construction, and executive function, Aldridge et al. (2018) found no detectable between-group differences.

This overlap, in combination with the fact that PRDs are neuropathologically distinguishable from other types of dementia, provides reason to suggest that PRDs may share a common differential neuropsychological profile. However, no research has explored whether there is a common neuropsychological profile that can differentiate patients with dementia due to abnormal protein accumulation from those without such neuropathology. The identification of such a profile might ensure that patients be referred for the appropriate resource-heavy diagnostic tests, and, thereby, receive the correct prognosis and efficient, appropriate management plans (Jolley et al., 2006; Ramirez-Gomez et al., 2017).

In addition to identifying a common neuropsychological profile, a pivotal step in alleviating the burden of dementia in LMICs would be to optimise neuropsychological test batteries so as to reduce their length while still ensuring diagnostic accuracy for PRDs. The time-intensive nature of neuropsychological assessments, as well as the lack of specialist services dedicated to assessing dementia in LMICs, means that such optimization is indeed crucial in ensuring better patient care in those countries (Gauthier et al., 2021; Seeher et al., 2022).

Furthermore, using neuropsychological tests to distinguish between PRDs and non-PRDs can be an efficient and important step early in the diagnostic process. Specifically, this step can help inform treatment approaches and, if done early enough, can provide sufficient time to acquire particular treatments (e.g., cholinesterase inhibitors, memantine) that may not be readily available in LMICs (Cooper et al., 2016; Ellis, 2005; Giebel et al., 2023; Noufi et al., 2019).

The Use of Machine Learning to Aid Dementia Diagnosis

Of relevance here, then, is machine learning (ML), a branch of artificial intelligence that is able to identify complex patterns implicit in various sources of data and produce models that can aid decision-making in various situations (Sidey-Gibbons & Sidey-Gibbons, 2019). In the context of healthcare, this advanced computational technique uses medical records from previously solved cases as the training set to learn patterns in the data that map input variables (e.g., high cholesterol, diabetes, hypertension) and response variables (e.g., the presence or absence of cerebrovascular disease). Additionally, during the learning process, input variables that are not important for classification can be eliminated, thereby ensuring the model is efficient while still maintaining accuracy rates. Once relationships between input and response variables have been learned and important variables have been selected, an algorithm is produced that predicts a way to classify individuals based on the input variables. This algorithm is then applied to an independent set of data (the test set) to determine the reliability and validity of the learned model (Weakley et al., 2015). The ability of a predictive tool that can automatically generate predictions from unstructured data is exceptionally useful in healthcare settings where diagnostic decisions are complex and involve the consideration of an enormous number of diagnostic variables (Sidey-Gibbons & Sidey-Gibbons, 2019). Numerous studies indicate that ML techniques improve the accuracy of medical diagnosis decisions while reducing errors and excessive medical costs (for a review, see Bhavsar et al., 2021).

In dementia research, several previously published studies confirm that ML can be used successfully to derive algorithms that can detect dementia using neuropsychological tests (Guest et al., 2020; Miah et al., 2021). However, the majority of these studies have focused on creating algorithms that accurately classify the *presence* and *severity* of dementia, rather than the *type* of dementia (see, e.g., Battista et al., 2017; Datta et al., 1996; Er et al., 2017; Joshi et al., 2009; Williams et al., 2013).

For instance, using a sample of 2528 individuals aged 60 years or older living in India, Jin et al. (2021) developed a machine learning model (support vector machine) that uses cognitive tests and informant reports to classify the presence of dementia with an accuracy above 90%. Additionally, using the Oxford Project to Investigate Memory and Ageing dataset, Vyas et al. (2022) presented automated prediction models for detecting the presence and severity of dementia using both neuropsychological tests and demographic variables with an f1 score (i.e. the harmonic mean of precision and recall) greater than 0.81.

Their findings further suggest that decision tree models can be used to enhance the interpretability of the models.

Several previously published studies have also validated the use of ML techniques in optimising neuropsychological test batteries for identifying the presence and severity of dementia. For instance, using machine learning techniques and a sample of 1354 individuals recruited from healthcare centres in Taiwan, Chiu et al. (2019) developed a screening tool that could discriminate normal cognition, mild cognitive impairment (MCI), very mild dementia, and dementia (as measured by scores on the Clinical Dementia Rating [CDR]; Morris, 1993) with an 87% sensitivity and 92% specificity. While building their model, they were able to reduce the number of items needed for accurate classification from 42 to 12. The final questionnaire assessed the following domains: orientation, memory, judgement, home hobbies, and community affairs. Similarly, using a cohort of 272 participants from the United States and various ML techniques (e.g., decision tree, naïve Bayes, and logistic regression models), Weakley et al. (2015) evaluated the contribution of 27 neuropsychological tests in classifying older adults as having either no cognitive impairment, mild cognitive impairment (MCI), or dementia (as measured by scores on the CDR). Their findings showed that only 6 of the 27 tests were needed to classify dementia-related cognitive impairment with an accuracy rate above 80%. Results consistent with those were reported by Bhagyashree et al. (2018), who indicated that machine learning may be helpful when identifying older adults with a 10/66 criterion diagnosis of dementia (Prince et al., 2008) in LMICs such as India.

To the best of my knowledge, only three published studies have attempted to demonstrate the use of ML techniques in aiding differential diagnosis. Using a cohort of 138 Greek patients (DLB: n = 62; PDD: n =78) and various machine learning methods (e.g., K-NNs, SVM, naïve Bayes classifiers), Bougea et al. (2022) were able to accurately differentiate between patients with DLB or PDD using 15 different neuropsychological tests. Similarly, using a sample of 329 Spanish participants (170 AD, 72 bvFTD, 87 healthy control) and neuropsychological tests normed in Spain, Garcia-Gutierrez et al. (2021) developed machine-learning models that could diagnose AD, bvFTD, and the differential diagnosis between them with an accuracy greater than 84% using an algorithm-selected subset of neuropsychological tests. In an effort to replicate these findings in resource-limited settings, Maito et al. (2023) used data from 1794 participants (AD: n = 904; FTD: n = 282; healthy controls: n = 606) recruited from five different Latin American LMICs in Latin America. They developed a Random Forest machine learning model that could differentiate between AD, FTD, and healthy ageing with an accuracy of 91%. However, in addition to

cognitive screening and executive function performance (as measured by the INECO frontal screening; Torralva et al., 2009), their findings suggest that social cognition, neuropsychiatric symptoms, educational attainment, age, and sex are important predictors.

The body of research reviewed above clearly demonstrates that ML techniques can be used to generate algorithms that aid dementia diagnosis using neuropsychological tests. However, the utility of existing models is limited. For example, while the existing models are able to identify broadly-defined dementia and/or subtypes of dementia, they miss a pivotal first step: the determination of whether the patient is a candidate for PRD to begin with. By missing this step, they do not provide insight into appropriate referral pathways and into which resource-heavy diagnostic tests would be useful for differential diagnosis. Instead, they can either be used at either the primary care level to identify dementia and/or at the secondary care level once patients have already undergone resource-heavy diagnostic testing. Additionally, the existing models are difficult to interpret in clinical settings and often involve the use of computer-based algorithms to analyse the data. That is to say, in order to classify patients clinicians must, at the very least, upload the data onto computers containing the requisite analytic software.

Overall Aims and Rationale

Recent estimates suggest that the prevalence of Alzheimer's disease (AD) and other subtypes of proteinopathic-related dementias (PRDs) is increasing rapidly in low- or middle-income countries (LMICs). The wide-ranging social and economic consequences of PRDs mean there is an urgent need for clinical services dedicated to their early and accurate detection. Because LMIC clinics typically do not have access to routine neuroimaging and biomarker screening, clinicians in those settings tend to rely on time-intensive neuropsychological test batteries for screening and detecting PRDs. Under optimal conditions (e.g., using psychometrically acceptable instruments, administering the test in the patient's home language, and ensuring a distraction-free environment), these test batteries provide valid and reliable data supporting the process of differential diagnosis (Begali, 2020). Broadly speaking, however, the test batteries are designed to distinguish between different subtypes of PRDs, and so miss a pivotal first step: the determination of whether the patient is a candidate for PRD to begin with. Therefore, reducing the number of tests used to identify PRDs is a crucial step in enhancing time- and cost-efficiency at LMIC clinics.

Recently, machine learning (ML) techniques have been used to optimise neuropsychological test batteries for the purpose of classifying the presence and severity of

dementia and for the purpose of differentiating between subtypes of dementia (see, e.g., Bougea et al., 2022; Yim et al., 2020; Zhu et al., 2020). However, the utility of existing models is limited in that they (a) generate algorithms that are not easily interpretable in clinical settings, (b) do not classify PRDs specifically (instead, they focus on broadly-defined dementia and/or on subtypes of dementia), and therefore (c) do not provide insight into diagnostic pathways and which resource-heavy diagnostic tests are appropriate for differential diagnosis.

Given the literature reviewed above, as well as the fact that PRDs have several overlapping cognitive features, one might assume that ML techniques can be used to aid the classification of these categories of dementia. However, no published study has explored the use of ML to optimise neuropsychological test batteries for the specific diagnosis of PRDs. In light of this gap in the literature, and of the potential benefits (particularly for LMIC clinicians) of such exploration, the aim of this study was to use ML techniques to (a) identify the minimum number of neuropsychological tests and other relevant clinical variables (e.g., vascular risk factors, functional abilities) required to diagnose PRDs in an older adult sample from an LMIC population, and (b) derive a decision tree algorithm that accurately diagnoses these types of dementias.

Chapter 3:
STUDY: Screening for Proteinopathic-related Dementias in Low-resource Clinical Contexts: A Machine Learning Approach

This chapter has been submitted to, and is under review at a peer-reviewed journal:
Lewis, R, Steenkamp, N.S., Thomas, K.G.F (under review). Screening for Proteinopathic-related Dementias in Low-resource Clinical Contexts: A Machine Learning Approach. *Journal of Experimental and Clinical Neuropsychology*

The measures used in this study can be found in:

Appendix A: Mini-Mental State Examination

Appendix B: Repeatable Battery for the Assessment of Neuropsychological Status – Immediate Memory Index

Appendix C: Repeatable Battery for the Assessment of Neuropsychological Status – Figure Copy

Appendix D: Repeatable Battery for the Assessment of Neuropsychological Status – Delayed Memory Index

Appendix E: Boston Naming Test – South African Short Form

Appendix F: Digit Span Test

Appendix G: CLOX Task

Appendix H: Trail Making Test

Appendix I: Luria Hand Sequences

Appendix J: Luria Recursive Figures

Appendix K: Bristol Activities of Daily Living Scale - Modified

Appendix L: Vascular Risk Factor Scale

Abstract

Background. The prevalence of Alzheimer's disease (AD) and other subtypes of proteinopathic-related dementias (PRDs) is increasing rapidly in low- or middle-income countries (LMICs). The wide-ranging social and economic consequences of PRDs means there is an urgent need for clinical services dedicated to their early and accurate detection, particularly in low-resource contexts. The aim of the present study was to use machine learning techniques to identify a minimum number of clinical variables (neuropsychological test data and vascular risk factor information) required for accurate classification of PRDs in an older adult sample from an LMIC population and to derive a decision tree algorithm that diagnoses these types of dementias.

Methods. The present study used data from a memory clinic sample of 253 South African older adults (130 with PRDs, 123 without). Information from 20 clinical variables were used as features for the analysis. We used C5.0 algorithms to identify the most important features for PRD diagnosis and to derive an algorithm that could accurately diagnose these types of dementia.

Results. The C5.0 algorithm reduced the number of clinical variables for screening PRDs from 20 to 9 (Repeatable Battery for the Assessment of Neuropsychological Status [RBANS] Figure Recall, vascular risk factor, phonemic verbal fluency, RBANS List Recall, RBANS List Recognition, Digit Span Backward, CLOX1, CLOX2, and ΔCLOX2-1), and classified the validation sample with an accuracy exceeding chance performance. Accuracy, sensitivity, and specificity values were all greater than 70%. Performance on tests assessing memory and executive functioning were the features that predominantly distinguished the PRD and comparison groups from one another.

Conclusions. The derived decision tree is a suitable and easy-to-interpret approach for PRD screening in LMICs. Its utility as part of standard clinical practice has the potential to free up strained resources and to allow clinical expertise to be employed more selectively.

Keywords: dementia; developing countries; machine learning; decision trees; classification model; neuropsychological tests

Introduction

Dementia is an umbrella term for a host of neurocognitive disorders that result in progressive cognitive impairment, functional disabilities, and behavioural disturbance (World Health Organization, 2017). Global estimates indicate there are currently more than 55 million people living with dementia; most live in low- and middle-income countries (LMICs) and are over the age of 65 (Alzheimer's Association, 2022; GBD 2019 Dementia Forecasting Collaborators, 2022). These estimates further suggest that the number of people living with dementia will more than triple by 2050 and that this increasing prevalence is driven by population ageing, a process that is occurring at an unprecedentedly rapid pace in LMICs (United Nations Department of Economic and Social Affairs, 2017).

Most dementias are considered to be proteinopathies; that is to say, the clinical deficits that characterise them are associated with the accumulation of abnormal protein aggregates either intracellularly (e.g., tau, α-synuclein, TDP-43) or extracellularly (amyloid beta [Aβ] peptide; Ganguly et al., 2017; Kovacs, 2019). For instance, Alzheimer's disease (AD) is characterised by neurofibrillary tangles (aggregates of tau proteins) and Aβ plaques; frontotemporal dementia (FTD) is characterised by the aggregation of tau proteins or a build-up of protein TDP-43; and Lewy body dementias (including dementia with Lewy Bodies [DLB] and Parkinson's disease dementia [PDD]) are characterised by an accumulation of α-synuclein aggregates (Allegri, 2020).

Epidemiologically, proteinopathic-related dementias (PRDs) account for most cases of the neurodegenerative disorders (Rahimi & Kovacs, 2014). AD by itself accounts for more than 60% of dementia cases globally (Alzheimer's Association, 2022). Although limited data exists regarding the prevalence of both AD and other subtypes of PRDs in LMICs, the increasing number of older adults in those countries likely means there is an increased demand for clinical services to alleviate the burden of those dementias (Whittington et al., 2019). However, because healthcare systems in LMICs have limited resources, patients do not undergo the routine neuroimaging or biomarker examinations recommended for the differentiation of PRDs from dementias with other aetiologies (e.g., vascular dementia [VaD]). Instead, clinicians tend to rely on time-intensive neuropsychological testing to identify patterns of cognitive impairment that might support fine-grained differential diagnoses without first determining whether the patient is a candidate for the broader category of PRD to begin with (Akinyemi et al., 2022).

Although some studies have identified neuropsychological characteristics that distinguish different subtypes of PRDs, the cognitive impairment observed in these patients

overlaps in many ways (see, e.g., Burrell & Piguet, 2015; Foguem & Manckoundia, 2018). This overlap, in combination with the fact that PRDs are neuropathologically distinguishable from other types of dementia, provides reason to suggest that PRDs may share a common differential neuropsychological profile. However, no research has explored whether there is a common neuropsychological profile that can differentiate patients with dementia due to abnormal protein accumulation from those without such neuropathology. The identification of such a profile might ensure that patients receive the correct prognosis and efficient, appropriate management plans (Jolley et al., 2006; Ramirez-Gomez et al., 2017).

In addition to identifying a common neuropsychological profile, a pivotal step in alleviating the burden of dementia in LMICs would be to optimise neuropsychological test batteries so as to reduce their length while still ensuring diagnostic accuracy for PRDs. The time-intensive nature of neuropsychological assessments, as well as the lack of specialist services dedicated to assessing dementia in LMICs, means that such optimization is indeed crucial in ensuring better patient care in those countries (Gauthier et al., 2021; Seeher et al., 2022).

Of relevance here, then, is machine learning (ML), a branch of artificial intelligence that is able to pick out information from various sources and produce an integrated system that can aid decision-making in various contexts (Sidey-Gibbons & Sidey-Gibbons, 2019; Tariq et al., 2020). In the healthcare context, this advanced computational technique uses medical records from previously solved cases as the training set to learn the relationship between input variables (e.g., hypertension, diabetes, high cholesterol) and response variables (e.g., the presence or absence of cerebrovascular disease). Once relationships have been learned, an algorithm is produced that predicts a way to classify individuals based on the input variables. This classification prediction is then applied to an independent set of participants, known as the test set, to assess and determine the reliability and validity of the learned model (Weakley et al., 2015). Numerous studies indicate that ML techniques improve the accuracy of medical diagnostic decisions while reducing error and excess costs (for review, see Bhavsar et al., 2021).

Several previously published studies indicate that ML techniques can successfully optimise neuropsychological test batteries to detect dementia (see, e.g., Battista et al., 2017; Datta et al., 1996; Er et al., 2017; Hogervorst et al., 2003; Joshi et al., 2009; Williams et al., 2013). However, these studies have focused almost exclusively on creating algorithms that accurately classify the *presence and severity* of dementia, and not on classifying *type* of dementia. For instance, using a cohort of 272 participants and various ML techniques (e.g.,

decision tree, naïve Bayes, and logistic regression models), Weakley et al. (2015) evaluated the contribution of 27 neuropsychological tests in classifying older adults as having either no cognitive impairment, mild cognitive impairment (MCI), or dementia (as measured by scores on the Clinical Dementia Rating [CDR]; Morris, 1997). Their findings showed that only 6 of the 27 tests were needed to classify dementia-related cognitive impairment with an accuracy rate above 80%. Similarly, Shankle et al. (1998) used decision-tree algorithms to successfully reduce the amount of information required to estimate CDR severity score with only a slight loss of accuracy. Further, Bhagyashree et al. (2018) showed that ML may be helpful when identifying Indian older adults with a 10/66 criterion diagnosis of dementia (Prince et al., 2008).

Although the body of research reviewed above focuses on the utility of ML in reducing the amount of information required for classifying the presence and severity of dementia, one might assume that the patterns of data will generalise to the classification of categories of dementia. Hence, given that PRDs have several overlapping cognitive features, it is reasonable to suggest that ML techniques can be used to (1) identify a common neuropsychological profile for PRDs, (2) reduce the number of neuropsychological tests and other clinical outcomes required to classify PRDs while still retaining high rates of accuracy, and (3) automate aspects of neuropsychology-based differential diagnosis of PRDs.

However, no published study has explored the use of ML to optimise neuropsychological test batteries for diagnosing PRDs. In light of this gap in the literature, and of the potential benefits (particularly for LMIC clinicians) of such exploration, we aimed to use ML techniques to (1) identify the minimum number of neuropsychological tests and other relevant clinical variables (e.g., vascular risk factors, functional abilities) required to diagnose PRDs in an older adult sample from a LMIC population, and (2) derive a decision tree algorithm that diagnoses these types of dementias accurately.

Materials and Methods

Participants

We used a database containing records of patients assessed at the University of Cape Town / Groote Schuur Hospital Memory Clinic (hereafter, simply Memory Clinic) between January 2014 and January 2020. The assessments were conducted by a multidisciplinary team of neuropsychologists, psychiatrists, and geriatricians. Diagnostic decisions were informed by standard clinical criteria using information obtained from a clinical interview, neuropsychological test battery, physical and neurological examinations, and a case

conference (American Psychiatric Association, 1994; McKhann et al., 1984; Román et al., 1993).

The Memory Clinic database during the period under consideration contained 370 patient records. Of those, 117 were excluded from study consideration because the patient either (1) did not receive a definitive diagnosis, (2) did not complete ≥ 20% of the Memory Clinic neuropsychological battery, or (3) scored ≤ 10 on the Mini-Mental State Examination (MMSE; Folstein et al., 1975). The MMSE eligibility criterion was set to ensure that participants were not at late stages of dementia; at these stages, cognitive impairment is so global and generalised it is difficult to make differential diagnoses (Perneczky et al., 2006; Pimentel, 2009). Hence, the final sample of patient records used for analysis consisted of 253 cases containing medical, neuropsychological, and diagnostic information (participant age range = 34–90 years; M = 66.04, SD = 10.29).

We divided the sample into two classification groups. The first consisted of patients diagnosed with a PRD (n = 130). The second, a comparison group (COMP), consisted of those without such a diagnosis (n = 123). Table 1 presents a breakdown of diagnoses within each of the classification groups.

Ethical approval for the study was granted by the relevant review board at our institution.

Table 1

Breakdown of Diagnoses within the Two Study Groups (N = 253)

Group / Diagnosis	*n* (%)
PRD (*n* = 130)	
Alzheimer's disease	77 (59.23)
Mixed dementia [a]	42 (32.31)
Frontotemporal dementia	6 (4.62)
Dementia with Lewy bodies	3 (2.31)
Parkinson's disease with dementia	2 (1.54)
COMP (*n* = 123)	
No dementia [b]	78 (63.41)
Vascular dementia	41 (33.33)
Ethanol use	3 (2.44)
HIV	1 (0.81)

Note. PRD = diagnosed with proteinopathic-related dementia; COMP = comparison group; not diagnosed with proteinopathic-related dementia; HIV = human immunodeficiency virus.

[a] Diagnosed with Alzheimer's disease and either vascular dementia, Parkinson's disease with dementia, or dementia with Lewy bodies.

[b] Diagnosed with either no cognitive impairment, mild cognitive impairment (MCI), cognitive impairment secondary to traumatic brain injury (TBI), psychiatric illness, encephalitis, or Cognitive Disorder Not Otherwise Specified.

Measures

The measures described below are all part of the neuropsychological test battery used at the Memory Clinic in the period under consideration. These standardised tests are used regularly in South African clinical practice and research (James et al., 2020; Ramlall et al., 2014). The battery assesses cognitive performance across multiple cognitive domains, including processing speed, attention, working memory, visuospatial and visuoconstructional abilities, language, memory, and executive function.

Scores on the Trail Making Test Part A (Trails A; Reitan, 1955) and on the Digit Span tests allowed estimation of performance in the domains of processing speed, attention, and working memory. Scores on the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph et al., 1998) Figure Copy subtest and the CLOX 2 test (Royall et al., 1998) allowed estimation of performance in the domains of visuospatial and visuoconstructional abilities. Scores on the Boston Naming Test – South African Short Form (BNT-SASF; Thomas et al., 2019) allowed estimation of performance in the language domain. Scores on the RBANS List Learning, Story Learning, List Recall, Story Recall, and List Recognition subtests allowed estimation of performance in the verbal memory domain. Scores on the RBANS Figure Recall subtest allowed estimation of performance in the visual memory domain. Scores on the verbal fluency tasks (semantic fluency – animals; phonemic fluency – letter 'F' or 'S'), MoCA Trails test (Trails MoCA; Nasreddine et al., 2005), Luria Hand Sequence and Recursive Figure tasks (Luria, 2012), and the CLOX1 test (Royall et al., 1998), as well the difference between scores on the CLOX2 and CLOX1 tasks (ΔCLOX2-1), and the difference between scores on semantic and phonemic verbal fluency tasks (VFΔS-P), allowed estimation of performance in the executive function domain.

Information regarding functional abilities was collected using the Bristol Activities of Daily Living Scale – Modified (BADLS-M; Bucks et al., 1996). Clinical information on the presence of vascular risk factors (including diabetes, heart disease, hypertension, claudication, hypercholesterolemia, atrial fibrillation, current smoking, and previous history of smoking) was collected from the patient's hospital folder. Using that information, we created a vascular risk factor scale (VRFS) ranging from 0 to 8.

Data Analysis

All statistical analyses were conducted using R version 4.0.3 (R Core Team, 2020). The threshold for statistical significance was set at $\alpha = .05$.

Variables. The input variables (referred to as *features*) for the statistical analysis consisted of the 22 measures mentioned above. The output variable was the classification group (valued at either PRD or COMP).

Data Cleaning. Before conducting the decision tree analysis, we (1) cleaned the data to ensure accurate coding of variables and removal of input variables that contained ≥ 20% of missing values, and (2) examined between-group differences using paired Wilcoxon Signed-Rank Tests for continuous variables and Fisher's Exact Test for categorical variables.

During the data cleaning process, we identified two input variables that had more than 20% of missing values (Trails MoCA and BADLS-M). These variables were removed from further analyses to avoid misclassification bias. The resulting dataset contained 21 variables (20 continuous input variables and 1 categorical response variable), with values missing at a frequency of 4% in the full dataset. Missing values were not imputed.

Decision Tree Algorithm. The predictive model was built using the C5.0 decision tree algorithm from the *C50* package (Kuhn & Quinlan, 2020). This algorithm works by generating logical decision rules that split any given sample into smaller sub-samples based on the feature values that provide the greatest information gain. The newly defined sub-sample is then split again using the same technique. This process continues until the sub-samples cannot be split any further (Toussi et al., 2009).

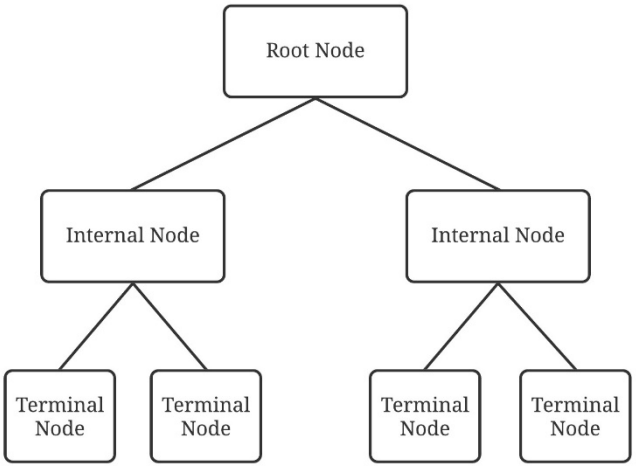
The resulting decision tree is presented in a hierarchical structure that contains (1) a *root node* situated at the top of the tree, thus representing the feature that has the greatest potential to split the sample into the classification outcomes; (2) *internal nodes* representing the other features relevant for classification; (3) *branches* representing decision rules; and (4) *terminal nodes* representing the classification outcome (see Figure 1 for an example of this tree-like hierarchy).

We chose the C5.0 decision tree algorithm as the classification method because it produces a model that is simple and easy to understand, making it convenient for use in clinical settings (Ramezankhani et al., 2014; Richard's & Solanas, 2008). Additionally, it is robust to missing data while still maintaining high accuracy rates. Furthermore, C5.0 provides a mechanism, known as winnowing, that pre-selects the features that are most useful to the classifier before constructing the decision tree (Kharat & Turukmane, 2014).

This ability to winnow irrelevant features before generating the decision tree prevents overfitting and often leads to simpler classifiers with higher predictive accuracy (Galathiya et al., 2012). We ran the C5.0 algorithm with and without winnowing enabled to examine whether this was the case in our decision tree.

Figure 1

Decision Tree Example



Procedure for Building the Decision Tree. The analysis followed a two-step modelling procedure. First, we assessed whether winnowing should be enabled when building the C5.0 decision tree. To do this we used 10-fold cross validation to estimate the classification accuracy, sensitivity, specificity, and Cohen's κ of the C5.0 decision trees both with and without winnowing. The C5.0 decision tree method with the greatest cross-validated model performance estimates was chosen for further analyses (Mokeddem, 2018). After establishing whether winnowing should or should not be enabled in the C5.0 algorithm, we continued to the second step, which was training and testing the C5.0 decision tree.

To train and test the decision tree, we divided the full dataset into two randomly assigned subsets: (1) the *training set*, which contained 75% (n = 191) of the full dataset, and (2) the *test set*, which contained the remaining 25% (n = 62). We used stratified random sampling so that the proportion of participants in each classification group was the same as observed in the full dataset. By doing this, we ensured that both subsets were balanced and representative of the sample as a whole.

Twenty features were used as input variables when training the C5.0 decision tree. The validity of the resulting tree was examined by evaluating the performance of the predictive model when applied to the testing set. We examined the following classification performance indices: classification accuracy, sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), positive predictive value (PPV), and negative predictive value (NPV; for summary, see, Fletcher & Fletcher, 2005).

Results

Descriptive Statistics

The total dataset comprised 253 participants, of whom 51.38% (n = 130) were diagnosed with a PRD. Table 2 summarises the sociodemographic characteristics and MMSE scores of the participants, as well as their scores on scales measuring vascular risk factors and functional abilities. As the table shows, on average participants in the PRD group were significantly older, had lower MMSE scores, and had significantly fewer vascular risk factors than those in the COMP group.

Table 2

Sociodemographic Characteristics, MMSE Scores, VRFS scores, and BADLS-M Scores: Descriptive Statistics and Between-Group Comparisons (N = 253)

		Group			
Variable	Entire Sample (N = 253)	PRD (n = 130)	COMP (n = 123)	p	ESE
Age (years) [a]				< .001***	0.54
M (*SD*)	66.04 (10.30)	71.50 (7.22)	60.49 (10.00)		
Range	34–90	53–90	34–88		
Missing	15	10	5		
Sex [b]				0.051	0.13
Female	147	82 (66.1%)	65 (53.3%)		
Male	99	42 (33.9%)	57 (46.7%)		
Missing	7	6	1		
HLOE [b]				0.256	0.14
None	2	0 (0.0%)	2 (1.8%)		
Primary	44	26 (25.0%)	18 (16.4%)		
Secondary	129	60 (57.7%)	69 (62.7%)		
Tertiary	39	18 (17.3%)	21 (19.1%)		
Missing	39	26	13		
MMSE [a]				< .001***	0.39
M (*SD*)	23.40 (4.65)	21.66 (4.70)	25.24 (3.83)		
Range	11–30	11–29	13–30		
Missing	0	0	0		

VRFS [a]				0.024*	0.16
M (*SD*)	2.14 (1.45)	1.90 (1.35)	2.39 (1.52)		
Range	0–6	0–6	0–6		
Missing	41	21	20		
BADLS-M [a]				0.102	0.14
M (*SD*)	6.60 (5.97)	7.27 (6.14)	5.66 (5.63)		
Range	0–27	0–27	0–22		
Missing	112	47	65		

Note. Data are raw scores unless otherwise noted. MMSE = Mini-Mental State Examination; VRFS = vascular risk factor scale; BADLS-M = Bristol Activities of Daily Living Scale – Modified; PRD = diagnosed with proteinopathic-related dementia; COMP = comparison group, not diagnosed with proteinopathic-related dementia; ESE = effect size estimate; HLOE = highest level of education.

[a] Significance test = Wilcoxon Signed-Rank Test; effect size = Pearson *r* correlation.

[b] Significance test = Fisher's Exact Test; effect size = Cramer's *V*.

*$p < .05$. **$p < .01$. ***$p < .001$.

Table 3 summarises the neuropsychological test data. As expected, the average performance of participants with PRD was significantly worse than those without. The largest between-group differences were observed on memory tests (specifically, those assessing delayed recall of verbal and visual material): RBANS List Recall, effect size $r = .42$; RBANS Story Recall, $r = .43$; RBANS List Recognition, $r = .48$; and RBANS Figure Recall, $r = .45$.

Table 3

Cognitive Test Performance: Descriptive Statistics and Between-Group Comparisons (N = 253)

Domain / Subtest	Entire Sample (*N* = 253)	Group PRD (*n* = 130)	Group COMP (*n* = 123)	*p*	ESE
Processing Speed					
Trails A				.018*	.15
M (*SD*)	92.16 (62.68)	103.53 (71.30)	80.19 (49.65)		
Range	11–375	11–375	13–307		
Missing	19	10	9		
Attention and Working Memory					
Digit Span (Forward)				.978	.002
M (*SD*)	3.52 (1.11)	3.52 (1.06)	3.51 (1.17)		
Range	1–5	1–5	1–5		
Missing	1	0	1		
Digit Span (Backward)				.911	.007
M (*SD*)	1.66 (1.04)	1.66 (1.06)	1.65 (1.02)		
Range	0–5	0–5	0–5		
Missing	5	3	2		
Visuospatial/Visuoconstructional					
RBANS Figure Copy				.035*	.14
M (*SD*)	14.37 (4.29)	13.73 (4.56)	15.00 (3.92)		
Range	0–20	0–20	0–20		
Missing	10	10	0		

Domain / Subtest	Entire Sample (N = 253)	Group: PRD (n = 130)	Group: COMP (n = 123)	p	ESE
CLOX2				< .001***	.25
M (*SD*)	12.64 (2.42)	12.06 (2.82)	13.26 (1.71)		
Range	0–15	0–15	4–15		
Missing	6	3	3		
Language					
BNT-SASF				.007**	.17
M (*SD*)	11.85 (2.50)	11.45 (2.59)	12.29 (2.33)		
Range	3–16	3–16	5–16		
Missing	6	2	4		
Verbal Memory					
RBANS List Learning				< .001***	.30
M (*SD*)	16.91 (6.08)	15.14 (5.58)	18.74 (6.05)		
Range	0–32	0–32	4–32		
Missing	5	4	1		
RBANS Story Learning				< .001***	.27
M (*SD*)	9.96 (5.33)	8.64 (5.28)	11.27 (5.07)		
Range	0–24	0–24	0–22		
Missing	10	9	1		
RBANS List Recall				< .001***	.42
M (*SD*)	1.64 (2.09)	0.84 (1.57)	2.46 (2.23)		
Range	0–8	0–7	0–8		
Missing	9	6	3		
RBANS Story Recall				< .001***	.43
M (*SD*)	3.22 (3.28)	1.90 (2.84)	4.50 (3.18)		

Domain / Subtest	Entire Sample (N = 253)	Group: PRD (n = 130)	Group: COMP (n = 123)	p	ESE
Range	0–12	0–10	0–12		
Missing	14	12	2		
RBANS List Recognition				< .001***	.48
M (*SD*)	15.21 (3.70)	13.54 (3.68)	16.95 (2.83)		
Range	0–20	0–20	8–20		
Missing	4	3	1		
Visual Memory					
RBANS Figure Recall				< .001***	.45
M (*SD*)	4.95 (4.71)	2.91 (3.89)	6.89 (4.60)		
Range	0–20	0–6	0–20		
Missing	15	14	1		
Executive Functioning					
Verbal Fluency: Semantic				< .001***	.25
M (*SD*)	11.15 (4.65)	9.98 (4.07)	12.37 (4.91)		
Range	2–15	2–21	2–25		
Missing	1	1	0		
Verbal Fluency: Phonemic				.016*	.15
M (*SD*)	7.10 (3.79)	6.46 (3.22)	7.78 (4.23)		
Range	0–17	0–16	0–17		
Missing	7	3	4		
MoCA Trails				.439	.06
M (*SD*)	86.60 (68.10)	91.88 (74.61)	80.93 (60.22)		
Range	6–330	6–330	13–240		
Missing	69	35	34		
Luria Hand Sequences				.009**	.17
M (*SD*)	5.63 (2.15)	5.26 (2.24)	6.01 (1.98)		
Range	0–8	0–8	0–8		
Missing	12	7	5		

Domain / Subtest	Entire Sample (N = 253)	Group PRD (n = 130)	Group COMP (n = 123)	p	ESE
Luria Recursive Figures				.001***	0.25
M (*SD*)	2.95 (1.37)	2.65 (1.42)	3.25 (1.25)		
Range	0–4	0–4	0–4		
Missing	15	10	5		
CLOX1				.019*	.15
M (*SD*)	10.29 (2.98)	9.83 (3.17)	10.79 (2.70)		
Range	0–15	0–15	1–15		
Missing	3	1	2		
ΔCLOX2-1				.718	.02
M (*SD*)	2.30 (2.57)	2.20 (2.87)	2.41 (2.22)		
Range	-13–12	-13–10	-3–12		
Missing	8	4	4		
VFΔS-P				.060	.12
M (*SD*)	4.01 (4.08)	3.57 (4.09)	4.48 (4.03)		
Range	-7–27	-7–20	-6–16		
Missing	7	3	4		

Note. Data are raw scores unless otherwise noted. In each case, the significance test was the Wilcoxon Signed-Rank Test, and the effect size was Pearson's *r* coefficient. PRD = diagnosed with proteinopathic-related dementia; COMP = comparison group, not diagnosed with proteinopathic-related dementia; ESE = effect size estimate; BNT-SASF = Boston Naming Test - South African Short Form; ΔCLOX2-1= difference between CLOX2 and CLOX1 scores; VFΔS-P = difference between semantic fluency and phonemic fluency scores.

*p < .05. **p < .01. ***p < .001.

Decision Tree Algorithm

Winnowing. Table 4 presents the classification performance estimates for the 10-fold cross-validation analysis of C5.0 decision tree algorithms, both with and without winnowing. The analyses suggest that, although sensitivity estimates were similar in magnitude, the decision tree with winnowing outperforms that without winnowing with regard to values for classification accuracy, specificity, and Cohen's Kappa. Hence, we decided to enable winnowing when building the final C5.0 decision tree model.

When building the model, 10 of the 20 features used as inputs were winnowed using the C5.0 algorithm. The remaining 10 features were estimated as important for differentiating patients with PRD from those without. These were: RBANS Figure Recall, VRFS, Phonemic Verbal Fluency, RBANS List Recall, RBANS List Recognition, RBANS Figure Copy, Digit Span Backward, CLOX1, CLOX2, and ΔCLOX2-1.

Table 4

C5.0 Decision Tree: 10-Fold Cross-Validated Classification Performance Indices, With and Without Winnowing (N = 253)

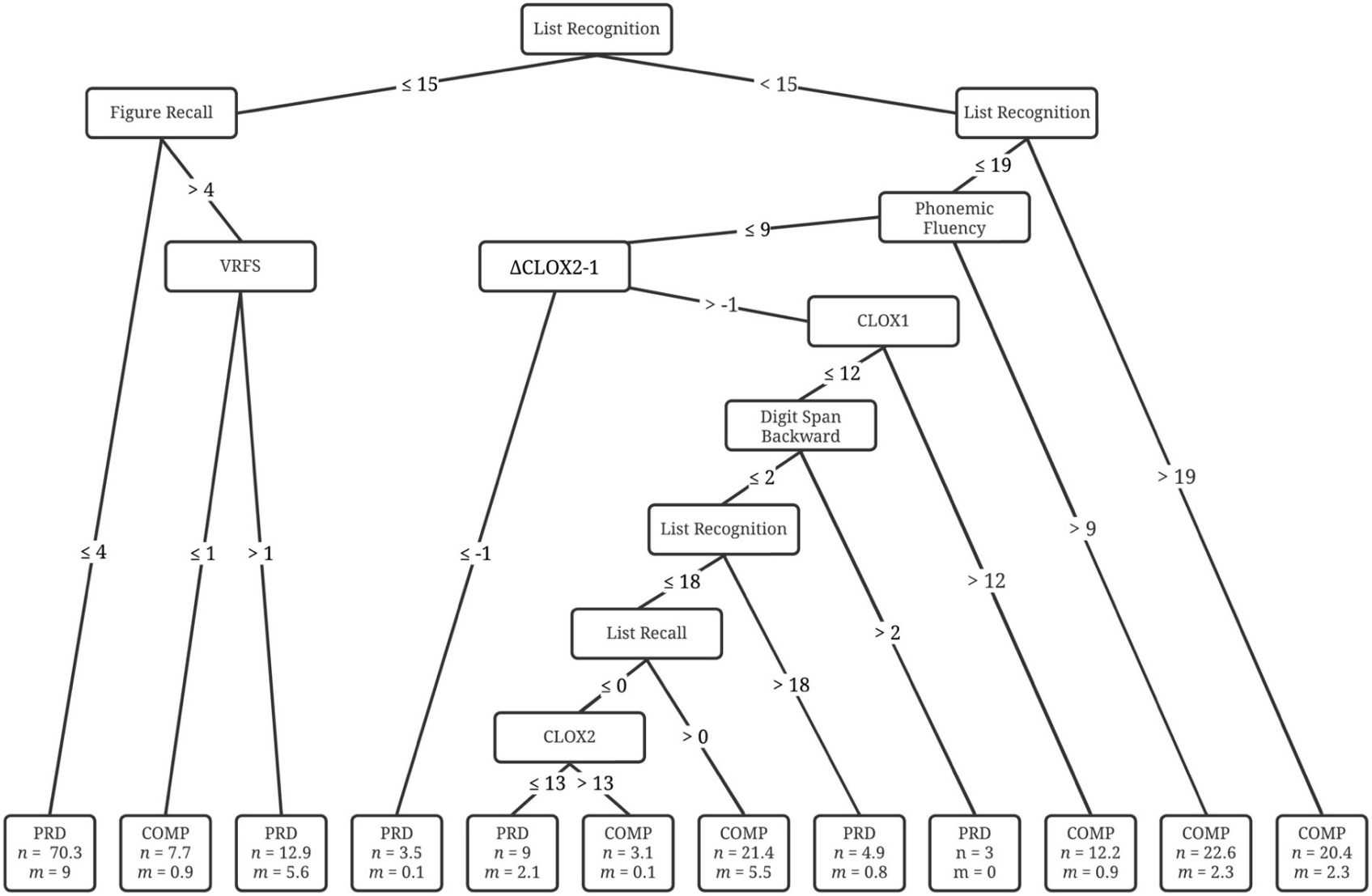
	With Winnowing			Without Winnowing		
		95% CI			95% CI	
	Value	LL	UL	Value	LL	UL
Accuracy	70.25%	49.42	86.06	68.74%	47.62	85.25
Sensitivity	70.74%	40.86	90.83	70.76%	41.59	90.03
Specificity	69.60%	39.12	90.41	66.52%	35.94	88.97
Cohen's Kappa	.40			.37		

Note. 95% CI = 95% confidence interval for the value; LL = lower limit; UL = upper limit.

Model. The resulting C5.0 decision tree was built using those 10 features. The training dataset contained 11 internal nodes and 12 terminal nodes (see Figure 2). That is, based on the branches of the C5.0 decision tree, 11 possible classification rules were extracted, each relating to one of 12 different terminal nodes.

Figure 2

Decision Tree for the Classification of PRD (N =253)



Note. n = number of participants mapped to the terminal node. m = number of participants misclassified at each terminal node. Non-integral numbers of participants are mapped to terminal nodes because some participants in the training set had missing feature values, causing the C5.0 algorithm to split the cases and send a fraction down each branch. PRD = diagnosed with proteinopathic-related dementia; COMP = comparison group; not diagnosed with proteinopathic-related dementias; VRFS = vascular risk factor scale.

As Figure 2 shows, RBANS List Recognition appears as the root node. This indicates that scores on that task were the most important predictor in the model, with the greatest potential to differentiate patients with PRD from those without. The next most important predictor of PRD patient status was score on the RBANS Figure Recall task. Figure 2 also shows that although RBANS Figure Copy was initially estimated as one of the 10 important features, it was not included in the derived decision tree. Table 5 presents the complete list of the remaining 9 selected features and their relative degree of prediction importance.

Table 5

Proposed C5.0 Decision Tree Model: Feature Importance

Feature	Overall Importance (%)
Selected	
RBANS List Recognition	97.91
RBANS Figure Recall	43.46
Verbal Fluency: Phonemic	41.88
ΔCLOX2-1	30.37
CLOX1	28.80
Digit Span Backward	23.04
RBANS List Recall	17.28
VRFS	12.57
CLOX2	7.85

Note. Feature importance is measured in terms of the extent to which features are used by the training set during the classification process. For example, the full training set makes use of the feature at the root node. Hence, that feature has an importance measurement of 100% (provided there are no missing values) while features farther down the tree are used less frequently and therefore have a lower importance measurement. RBANS = Repeatable Battery for the Assessment of Neuropsychological Status; ΔCLOX2-1 = difference between CLOX2 and CLOX1 scores; VRFS = vascular risk factor scale.

The decision tree model also provides insight into higher-order interactions between the features. For instance, scores on the RBANS List Recognition task had a relationship with those on RBANS Figure Recall task in that patients who scored ≤ 15 on the former task *and* who scored ≤ 4 on the latter task were mapped to a terminal node that classified them as having PRD (see Figure 2).

After creating the C5.0 decision tree classification model, we applied it to the testing set to examine the validity of the trained tree. Table 6 presents the classification performance indices and their associated 95% confidence intervals for the derived C5.0 decision tree when

applied to the test set. Accuracy, sensitivity, and specificity values were all greater than 70%, indicating that the model has relatively good predictive abilities. The PPV and NPV statistics indicate that, after factoring in prevalence rates of PRD in the test set, 73.53% of the sample who were classified as having PRD truly belong to that group while 75% of those predicted to not have PRD truly did not have PRD. The fact that PPV and NPV were similar in magnitude suggest that the information provided by the resulting C5.0 decision tree is almost equally reliable for individuals with and without PRD.

Further confirmation that the resulting C5.0 decision tree has clinical importance is shown by the PLR being 2.60 (well above the acceptable value of 1) and the NLR being 0.31 (close to the acceptable value of 0; McGee, 2002).

Table 6

C5.0 Decision Tree: Classification Performance Indices When Applied to the Test Set

		95% CI	
Classification Index	Value	LL	UL
Accuracy	74.20%	61.50	84.47
Sensitivity	78.13%	60.03	90.72
Specificity	70.00%	50.60	85.27
Positive Predictive Value	73.53%	55.63	87.12
Negative Predictive Value	75.00%	55.13	89.31
Positive Likelihood Ratio	2.60	1.46	4.64
Negative Likelihood Ratio	0.31	0.16	0.63

Note. 95% CI = 95% confidence interval for the value; LL = lower limit; UL = upper limit.

Discussion

The prevalence of Alzheimer's disease (AD) and other subtypes of proteinopathic-related dementias (PRDs) are increasing at a rapid rate in low- or middle-income countries (LMICs). The wide-ranging social and economic consequences of PRDs means there is an urgent need for clinical services dedicated to their early and accurate detection. Because LMIC clinics typically do not have access to routine neuroimaging and biomarker screening, clinicians in those settings tend to rely on time-intensive neuropsychological test batteries for screening and detecting PRDs. Under optimal conditions (e.g., using psychometrically acceptable instruments, administering the test in the patient's home language, and ensuring a distraction-free environment), these test batteries provide valid and reliable data supporting the process of differential diagnosis (Begali, 2020). However, the test batteries are, broadly speaking, designed to distinguish between different subtypes of PRDs, and so the assessment misses a

pivotal first step: the determination of whether the patient is a candidate for PRD to begin with. Therefore, reducing the number of tests used to identify PRDs is a crucial step in enhancing time- and cost-efficiency at LMIC memory clinics.

Recently, machine learning (ML) techniques have been used to optimise neuropsychological test batteries for the purpose of classifying the presence and severity of dementia (see, e.g., Bougea et al., 2022; Yim et al., 2020; Zhu et al., 2020). However, the utility of existing models is limited in that they (1) do not classify PRDs specifically (instead, they focus on broadly-defined dementia and/or on subtypes of dementia), and (2) generate algorithms that are not easily interpretable in clinical settings.

To address those knowledge gaps, the present study used data from a memory clinic sample of South African older adults ($N = 253$) to derive a C5.0 decision-tree model that could identify people with ($n = 130$) or without ($n = 123$) PRDs using the minimum number of neuropsychological tests required. To our knowledge, this is the first study to explore the use of classification trees in identifying the presence of PRDs in an LMIC sample using only clinical variables (neuropsychological test data and vascular risk factor information).

Our results showed that the C5.0 algorithm reduced the number of clinical variables for screening PRDs from 20 (the number of tests used from the Memory Clinic's complete neuropsychological battery plus the vascular risk factor variable) to 9 (RBANS Figure Recall, VRFS, phonemic verbal fluency, RBANS List Recall, RBANS List Recognition, Digit Span Backward, CLOX1, CLOX2, and ΔCLOX2-1), and that it classified the validation sample with an accuracy exceeding chance performance.

Consistent with existing neuropsychological literature, the features selected in the current model (i.e., tests assessing memory and executive function) reflect those on which patients with PRDs performed similarly, while those excluded (i.e., tests assessing language, semantic verbal fluency, visuospatial/visuoconstructional abilities) reflect those that differentiate subtypes of PRDs (Ala et al., 2001; Cahn-Weiner et al., 2003; Schmidtke & Hüll, 2002). For example, previously published studies suggest that patients with AD and mixed dementia perform similarly (i.e., both groups perform more poorly than matched controls or normative standards) on tests of delayed verbal and visual memory, list recognition, and phonemic verbal fluency, thus supporting the selection of these variables in the current decision tree model. In contrast, patients with AD tend to perform significantly more poorly than those with mixed dementia on tests of semantic verbal fluency (Dong et al., 2013; Kang et al., 2016), thus supporting the removal of this test from the current model. The removal of tests assessing confrontation naming and semantic verbal fluency as features for

our model is supported by Diehl et al. (2005): Analysis of data from a comprehensive neuropsychological test battery indicated that performance on an animal fluency task together with that on the Boston Naming Test correctly classified 90.5% of the patients in their sample with either FTD or AD.

As noted above, our model indicated that performance on tests assessing memory and executive functioning were the features that predominantly distinguished the PRD and comparison groups from one another. This finding is consistent with literature suggesting that performance within those two cognitive domains is important when differentiating people with PRDs from those without (Dong et al., 2013; Feng et al., 2021; Tierney et al., 2001). For instance, using a decision tree algorithm and a sample of 329 Spanish older adults, Garcia-Gutierrez et al. (2021) found that memory (as measured by the Free and Cued Selective Reminding Test; Grober et al., 1987) and verbal fluency (as measured by Addenbrooke's Cognitive Examination III; Hsieh et al., 2013) played a central role in differentiating people with either AD (n = 170) or behavioural variant FTD (n = 72) from healthy controls (n = 87), with an accuracy of 0.84 (± 0.04). Similarly, Tierney et al. (2001) reported that, of the 10 neuropsychological tests under their consideration, performance on the recognition memory trial of the Rey Auditory Verbal Learning Test (Schmidt, 1996) and on a phonemic verbal fluency test (as measured by the Controlled Oral Word Association Test; Benton et al., 1994) accurately differentiated patients with AD (n = 31) from those with vascular dementia (n = 31).

Additional evidence that the algorithm achieved what would be expected based on the literature is provided by the model-generated order of importance of the variables required for classifying PRDs. The model identified RBANS List Recognition as the biggest distinguishing factor between PRD and the comparison group; impairment on tests of list recognition has consistently been identified as important when differentiating dementia patients from non-demented elderly people (Gupta & Kahali, 2020; Schmidtke & Hüll, 2002). For instance, Er et al. (2017) used various ML techniques to establish that list recognition (as measured by Ö-VMPT; Oktem, 1992) was the most important of 23 input variables for distinguishing older adults with normal age-related cognitive decline (n = 30) from those with probable AD (n = 20).

The creation of an easily interpretable algorithm makes the current decision tree model valuable in clinical settings. Our results suggest that achieving a perfect score (20/20) on the RBANS List Recognition task predicts that the patient does not have a PRD and thereby excludes them from further assessment, thus saving time and resources. Additionally,

when scores on RBANS List Recognition are ≤ 15 and those on RBANS Figure Recall are ≤ 4, the model suggests that the probability of having a PRD is 88.67%. In contrast, when scores on RBANS List Recognition are between 15 and 19 and those on phonemic verbal fluency are > 9, the probability of having a PRD is 0.09%. The precision of the model for persons with PRDs is 73.53% (as indicated by the positive predictive value [PPV]), suggesting that these rules can identify people with PRDs with reasonably good confidence.

We note that discussing the potential application of the model (as we do above) is not an endorsement of complete reliance on it as a diagnostic tool for PRDs. Convention in the literature suggests that useful diagnostic tests have a combined specificity and sensitivity value of at least 1.50 (Power et al., 2013). The combined value for our model was 1.48, and therefore we suggest it would be better suited as a screening, rather than as a diagnostic, tool.

There are no universal standards for what might be minimum acceptable specificity and sensitivity values for cognitive screening tools. Rather, decisions regarding the usefulness of a cognitive screening tool involve weighing the consequences of misclassifying healthy individuals as having the disease (false positives) against leaving cases undetected (false negatives; Herman et al., 2002). The current model is more sensitive than it is specific, meaning that it is likely to identify more false positives than false negatives. In the context of diagnosing PRDs, this trade-off between sensitivity and specificity is ideal because, although receiving a false positive diagnosis of a PRD may initially be distressing for the patient, that negative effect may dissipate after administration of further diagnostic testing (Trevethan, 2017). Selection of a useful screening tool also relies on considerations of practicality, such as accessibility and demands on the healthcare system (Mahé & Gaffikin, 2005). The low cost and simplicity of the decision tree, in combination with the relatively low impact of receiving a false positive, makes the current model particularly useful as a broad screening tool (Leeflang et al., 2008).

Limitations

We emphasise that the model created and described here is not ready for use in clinical settings; rather, it demonstrates the potential utility of machine learning methods in diagnosis of dementia, and specifically in diagnosing PRDs. Further, we recognise that there is a potential issue regarding non-independence of input and response variables in our model: the dementia diagnoses used for classification in the model (i.e., the gold standard against which we compared the ML model's predictions) were based partially on the patient's neuropsychological test results. We note, however, that the diagnoses recorded in the Memory Clinic folders were made by a multidisciplinary team (psychiatrists, geriatricians, as

well as neuropsychologists) that interpreted the results of neuropsychological tests within the broader context of the patient's personal, medical, psychiatric, and neurological history (acquired from the referral letter, medical records, from interviews with the patient and an attending family member or friend, and, in some cases, neuroimaging). Hence, although there is not complete independence of input and response variables, the diagnostic decision making is not completely circular. Moreover, the sensitivity and specificity of clinically-based dementia diagnoses vary significantly for different types of dementia when diagnosed during life rather than post-mortem (Hogervorst et al., 2003). Therefore, for more accurate results future studies should consider using biomarker tests and/or autopsy-verified diagnoses.

The classification performance indices (both sensitivity and specificity) were, as noted above, less than ideal. Compromised specificity may have resulted from the relatively high prevalence of AD and mixed dementia in the PRD group. However, the class imbalance in our sample mimics real life because AD and mixed dementia are among the most prevalent PRDs in LMICs (Piovezan et al., 2020). Additionally, including VaD in the comparison group may have further compromised the specificity of the model because, although by definition it is not considered a PRD, it does involve an accumulation of proteins as it progresses (Lewis et al., 2006). Future studies should consider including a third classification group (i.e., one including only VaDs) to improve performance indices.

Summary and conclusion

This study's results demonstrate the promising nature of decision tree methods in PRD screening and the potential utility of such methods to optimise neuropsychological tests for the purposes of differential diagnosis. In LMICs, where time-intensive neuropsychological test batteries are often the only available tool for differential diagnosis of PRDs, using this decision tree model as a screening tool has the potential to free up strained resources and to allow clinical expertise to be employed more selectively. Rather than providing all patients presenting with PRD-related complaints with brain scans, clinical interviews, and medical examinations that are costly and that may result in delayed decision making, with further reliability testing the derived model in this study could easily be administered as part of standard clinical practice to identify patients who would benefit most from these confirmatory diagnostic procedures. This in turn may lead to patients receiving diagnoses earlier so that appropriate management plans can be implemented more efficiently, thereby alleviating at least some of the burden of PRDs in these countries.

Chapter 4:
Extended Method Section

The research article included in this thesis (Chapter 3, pages 23-46) provides a clear but abbreviated (due to word-limit constraints imposed by the journal to which the manuscript was submitted) description of the study's methods, materials, procedures, and analyses. This chapter is included in the Master's thesis as an accompanying piece, elaborating on the study's design and setting, participants, materials, data management and statistical analyses, and ethical considerations.

Design and Setting

The study used archival data obtained from the University of Cape Town (UCT) / Groote Schuur Hospital (GSH) Memory Clinic (hereafter, simply Memory Clinic) database. The Memory Clinic was established in 1999 and is a weekly half-day outpatient clinic that serves the wider population of Cape Town (Kalula et al., 2010). At the Memory Clinic, a multidisciplinary team of neuropsychologists, psychiatrists, and geriatricians assess, diagnose, and make treatment recommendations for older adults referred with possible dementia-related cognitive decline. The team's diagnostic decisions are informed by standard clinical criteria using information obtained from a clinical interview, neuropsychological test battery, physical and neurological examinations, and a case conference (American Psychiatric Association, 1994; McKhann et al., 1984; Román et al., 1993).

At the Memory Clinic, the neuropsychology team administers an hour-long standardized test battery that assesses performance across multiple cognitive domains, including processing speed, attention, visuospatial and visuoconstructional abilities, language, memory, and executive function. To reach a differential diagnosis, test performance is interpreted within the broader context of the patient's personal, medical, and psychiatric history (acquired from medical records, as well as from interviews with the patient and an attending family member or friend).

All of the collected data from each patient is stored in a secure purpose-designed database.

Participants

As described in Chapter 3 (pages 27–28), patient records used in the present study were from assessments conducted at the Memory Clinic between January 2015 and January 2020. The sample was limited to this time period because the Memory Clinic test battery underwent a major revision in December 2014, with several new tests being added while

several others were dropped; only minor cosmetic revisions have been implemented since then. The Memory Clinic database during the period under consideration contained 370 patient records.

Eligibility Criteria.

All included case records were from Memory Clinic patients who had (a) received a diagnosis from the Memory Clinic team, based on their assessments and case conference discussion, (b) completed the full Memory Clinic neuropsychological test battery, and (c) scored >10 on the Mini-Mental State Examination (MMSE; Folstein et al., 1975). The MMSE eligibility criterion was set to ensure that participants were not at the late stages of dementia; at these stages, cognitive impairment is so global and generalized it is difficult to make differential diagnoses (Chua et al., 2019; Perneczky et al., 2006). The final sample of patient records used for analysis consisted of 253 cases containing medical, neuropsychological, and diagnostic information (participant age range = 34–90 years; M = 66.04, SD = 10.29).

Materials

It is important to emphasise that the measures described below were not explicitly selected for this study and that the study's aims were constrained by the available data.

All measures used in this study are part of the neuropsychological test battery used at the Memory Clinic during the period under consideration. These measures were, by and large, developed and normed in high-income countries of the global north (i.e., the United States and the United Kingdom), and hence are most appropriately used to assess Westernised, English-speaking populations (Howieson, 2019; Kisser et al., 2012; Tan et al., 2021). Nonetheless, these tests were chosen by a team of experts from UCT, GSH, and the Albert and Walter Sisulu Institute of Ageing in Africa (IAA) due to their regular use in both research and clinical practice in South Africa (James et al., 2020; Ramlall et al., 2014; Thomas et al., 2019).

Hence, an important note here is that although the patients seen at the Memory Clinic are almost all able to at least converse in English, they are linguistically and culturally diverse with many speaking Afrikaans, and a few speaking Xhosa, as their first language.

Mini-Mental State Examination (MMSE)

This widely used instrument (Folstein et al., 1975; see Appendix A) is the most well-known dementia screening tool. It assesses orientation in space and time as well as basic

memory, language, calculation, attention, and constructional abilities. The possible range of scores is 0–30, with lower scores indicating more cognitive impairment.

A large body of literature indicates that the MMSE is a reliable and valid measure in detecting cognitive impairment in elderly populations (for a review, see Gallegos et al., 2022). The MMSE has acceptable psychometric properties, with moderate internal consistency ($\alpha = .69$), and high test-retest reliability ($r > 0.85$; Mitchell, 2017). In memory clinic and hospital settings, it has been found to have a sensitivity of 81.3% and a specificity of 89.1% in classifying individuals with dementia (Mitchell, 2017). Although the MMSE has not been formally validated in South African contexts, several studies conducted in multi-cultural LMIC settings have indicated that the MMSE is a valid instrument when used to detect dementia (see, e.g., Fountoulakis et al., 2000; Kalpani et al., 2020; Mitrushina et al., 2005; Rowland et al., 2006).

Repeatable Battery for the Assessment of Neuropsychological Status – Immediate Memory Index (RBANS-IMI)

This index of the RBANS (Randolph et al., 1998; see Appendix B) is comprised of two subtests used to measure immediate verbal memory. The *List Learning* subtest involves the test administrator reading a 10-item list of semantically unrelated words and subsequently asking the test-taker to recall as many of them as possible. This process is repeated four times. An overall List Learning score is calculated by summing the number of correctly recalled words across the four trials. Hence, the overall List Learning score ranges from 0–40, with higher scores indicating greater immediate memory capacity. The *Story Learning* subtest involves the test administrator reading a short story and subsequently asking the test-taker to recall as many details of the as story possible (there are 12 discrete details, but the test-taker is not alerted to that fact). This process is repeated twice. An overall Story Learning score is calculated by summing the number of correctly recalled details across the two trials. Hence, the overall Story Learning score ranges from 0–24, with higher scores indicating greater immediate memory capacity.

The RBANS-IMI is reported to have acceptable psychometric properties among older community-dwelling adults, with moderate internal reliability ($\alpha = .57$; Cheng et al., 2011) and good test-retest reliability ($r = .70$; Duff et al., 2005).

Repeatable Battery for the Assessment of Neuropsychological Status – Figure Copy (RBANS-FC)

This RBANS subtest (see Appendix C) measures visuospatial ability. It requires the test-taker to copy a geometric figure comprised of 10 distinct parts (again, the test-taker is not alerted to that fact). Scoring is based on the test administrator's judgement of how accurately the test-taker has drawn and placed each of the 10 parts. A score of 0 is assigned if the part is drawn inaccurately and placed poorly; a score of 1 is assigned if the part is drawn inaccurately or placed poorly; and a score of 2 is assigned if the part is drawn accurately and placed correctly. Hence, the overall Figure Copy score ranges from 0–20, with higher scores indicating greater visuospatial ability.

Among older community-dwelling adults, the RBANS-FC is reported to have an internal reliability of $\alpha = .42$ (Cheng et al., 2011) and a test-retest reliability of $r = .51$ (Duff et al., 2005).

Repeatable Battery for the Assessment of Neuropsychological Status – Delayed Memory Index (RBANS-DMI)

This index of the RBANS (see Appendix D) is comprised of four subtests used to assess delayed verbal and visual memory. They are administered about 25–30 minutes after the conclusion of the RBANS-IMI subtests. The *List Recall* subtest requires test-takers to recall, without receiving any cues, the words presented during the List Learning subtest. An overall score is calculated by summing the number of correctly recalled words. Hence, List Recall scores can range from 0–10, with higher scores indicating greater delayed verbal memory capacity. The *List Recognition* subtest assesses recognition memory for the words presented during the List Learning subtest. The test-taker is presented with 20 words (10 targets and 10 foils), one at a time, and is asked to respond either yes (i.e., the word was part of the earlier list) or no (i.e., the word was not part of that list). An overall score is calculated by summing the number of words correctly identified as being on the list or not on the list. Hence, List Recognition scores can range from 0–20, with higher scores indicating greater delayed verbal recognition memory capacity. The *Story Recall* subtest requires test-takers to recall, without receiving any cues, the details of the story presented during the Story Learning subtest. Hence, scores can range from 0–12, with higher scores indicating greater delayed verbal memory capacity. The *Figure Recall* subtest requires test-takers to recall, without receiving any cues, the figure presented during the Figure Copy subtest. The scoring is

identical to that of the Figure Copy subtest. Hence, scores can range from 0–20, with higher scores indicating greater delayed visual memory capacity.

The RBANS-DMI is reported to have reasonably good psychometric properties among older community-dwelling adults, with good internal reliability ($\alpha = .73$; Cheng et al., 2011) and acceptable test-retest reliability ($r = .72$; Duff et al., 2005).

Boston Naming Test – South African Short Form (BNT-SASF)

This instrument is a locally modified and culturally appropriate version of one of the classic confrontation naming measures (Thomas et al., 2019; see Appendix E). Test-takers are asked to spontaneously name 15 black and white line drawings of objects presented serially in graded order of difficulty. If the item is not named correctly within 20 seconds, a semantic cue is given. If the item is still not named correctly, a phonemic cue is given. The overall test score is calculated by summing the number of correct responses made either spontaneously or following a semantic cue. Hence, scores can range from 0–15, with higher scores indicating greater confrontation naming ability.

The BNT-SASF was developed by a team of South African clinicians and researchers who evaluated each of the original instrument's 60 items, grouped into 15 pools of 4, for cultural appropriateness. Ultimately, they came to a consensus on the most culturally appropriate item in each pool, thus arriving at a 15-item short form.

The BNT-SASF has basic psychometric properties that are equivalent to short forms of the BNT developed elsewhere in the world (e.g., $\alpha = .35$).

Verbal Fluency

Two tests in the Memory Clinic battery assess verbal generativity (Strauss et al., 2006). The *semantic fluency* test requires test-takers to name as many different animals as they can within 1 minute. The phonemic fluency test requires test-takers to name as many words as they can that begin with the letter 'F' within 1 minute, without producing any proper nouns or numbers and without repeating words emerging from the same root. Both tests generate continuous scores, with higher scores indicating greater semantic / phonemic fluency capacity. I generated a *VerbalS-P* score by subtracting the *z*-score of the phonemic fluency test from that of the semantic fluency test, with higher scores thereby indicating greater executive function ability.

Verbal fluency tests such as these have acceptable psychometric properties in LMIC countries, with good internal reliability (Cronbach's α above .80 for both phonemic and

semantic verbal fluency; Tombaugh et al., 1999; Zegarra-Valdivia et al., 2022) (and acceptable test-retest reliability (Strauss et al., 2006; Zegarra-Valdivia et al., 2022).

Digit Span Test.

This measure is comprised of two subtests (see Appendix F), *forward digit span* and *backward digit span*. These subtests assess auditory attention span and working memory, respectively (Lezak et al., 2012). In the forward digit span test, the test administrator reads a string of numbers and then asks the test-taker to repeat the sequence. If the repetition is accurate, the test administrator reads the next string, which is one digit longer. If the repetition fails, the test administrator reads a string of equivalent length. If the repetition fails twice at the same length, the test is discontinued. In the Memory Clinic battery's version of Digit Span, the forward digit span test begins at a string of 3 numbers and ends either with discontinuation or successful repetition of a 7-digit string. The backward digit span test is identical, except that the test-taker is asked to repeat the presented sequence in reverse order. The total score on both tests corresponds to the number of digits in the longest sequence attained. Hence, scores can range from 3–7, with higher scores indicating greater auditory attention or working memory capacity.

Broadly speaking, digit span subscale scores are known to have high internal consistency and test-retest reliability, with Cronbach's α and test-retest stability coefficients reportedly above .80 for both forward and backward subtests (Gignac et al., 2019; Groth-Marnat & Baker, 2003).

CLOX Task

This two-part test is designed to help distinguish patterns of dementing processes by discriminating between constructional impairment of a visuospatial nature and those of an executive nature (Royall et al., 1998; see Appendix G). The first part, *CLOX1*, assesses constructional difficulties of an executive nature by asking test-takers to draw a clock spontaneously but following certain given rules (e.g., hands must be set to a particular time). The second part of the test, *CLOX2*, assesses constructional difficulties of a visuospatial nature by asking individuals to copy a clock drawn by the test administrator. Both parts are scored out of 15, with individual points awarded for meeting certain criteria (e.g., the drawing must contain only two hands, and all hands must be presented as arrows). Higher scores indicate greater constructional abilities of an executive nature (CLOX1) and of a visuospatial nature (CLOX2). *A CLOX Δ2-1* score is yielded by subtracting the score from CLOX1 from the score on CLOX2, with higher difference scores indicating greater executive dysfunction.

CLOX has good psychometric properties, with good internal consistency (α = .82), and a high degree of interrater reliability (CLOX1: r = .94; CLOX2: r =.93; Royall et al., 1998). Additionally, it has been validated in several LMICs, including China, Brazil, and Greece (Bozikas et al., 2008; Fuzikawa et al., 2003; Yap et al., 2007).

Trail Making Test

This instrument is comprised of two subtests (Nasreddine et al., 2005; Reitan, 1955; see Appendix H). *Trails A* is designed to assess processing speed, visual attention, and sequencing abilities (Lezak et al., 2012). Test takers are presented with a page containing an array of numbers ranging from 1 to 25, and are asked to draw an unbroken line connecting the numbers in sequential order. The second subtest, which is the formal equivalent of *MoCA Trail*, is designed to assess everything that Trials A assesses as well as mental flexibility and response inhibition (Julayanont et al., 2013). Test takers are presented with a page containing an array of both numbers and letters, and are asked to draw an unbroken line connecting the letters and numbers in alternating sequence (1 – A – 2 – B, and so on). If an error in sequencing is made, the examiner corrects it before allowing the test taker to continue, For both Trails A and the MoCA Trail, the outcome variable is a continuous score corresponding to the time taken (in seconds) to complete the task, with higher scores indicating deficits in processing speed, attention, sequencing, mental flexibility, and/or response inhibition.

The original version of the Trail Making Test (Reitan, 1955), which features a longer form of the MoCA Trail, has adequate psychometric properties, with a test-retest coefficient of .75 for Trails A, and .85 for Trails B (Giovagnoli et al., 1996). Numerous studies have reported culture-specific sets of normative data for this measure (for a review, see Mitrushina et al., 2005).

Luria Hand Sequence Task

This measure is designed to assess the ability to complete complex motor sequences (Luria, 2012; see Appendix I). During this task, test takers are asked to perform a two- and a three-step series of hand movements as quickly as possible. In the Memory Clinic battery, the scoring for each series of hand movements ranges from 0 (*unsuccessful despite prompting/modelling*) to 2 (*three consecutive series by themselves*). An overall test score is calculated by summing the scores on both hand movement series. Hence, scores range from 0–4, with higher scores indicating greater motor programming function.

The Luria hand sequence task is widely used in clinical neuropsychological practice (Mitsuhashi et al., 2018; Varkovetski et al., 2020).

Luria Recursive Figures

This task is designed to identify frontal dysfunction including perseveration, omission, and commission tendencies (Luria, 2012; see Appendix J). Test takers are asked to continue two sequences that are drawn at the top of an otherwise blank page. The first sequence is a series of alternating squares and triangles, and the second is a series of loops. In the Memory Clinic battery, the scoring for each sequence ranges from 0 (a sequence with two or more errors) to 2 (a sequence with no errors). The overall test score is calculated by summing the scores on both sequences. Hence, scores range from 0–4, with higher scores indicating less perseveration, omission, and commission tendencies.

The Luria recursive figure task is widely used in clinical neuropsychological practice (Nõmm et al., 2016; Zarembo et al., 2021).

Bristol Activities of Daily Living Scale – Modified (BADLS-M)

This carer-rated scale measures basic and instrumental activities of daily living (ADL) functioning in patients with dementia (Bucks et al., 1996; see Appendix K). The measure has been modified for use at the Memory Clinic, including 17 of the original 20 items. Hence, scores on this measure range from 0–51 (i.e., a minimum of 0 and a maximum of 3 per item), with higher scores indicating lower levels of functioning and greater dependence on caregivers for assistance in completing ADLs.

The BADLS is a valid and reliable measure, with excellent test-retest reliability (r =.95), and good convergent validity (r =.65; Bucks & Haworth, 2002). Although there are few studies validating the use of BADLS in LMICs, it is sensitive to a wide range of ADL performance in people with varying levels of functioning and its overall score correlates well with the overall MMSE score (Bucks et al., 1996; Sikkes et al., 2009; Umayal et al., 2010).

Vascular Risk Factor Scale (VRFS). This 8-item purpose-designed scale was used to measure the presence of vascular risk factors in patients (see Appendix L). The selection of vascular risk factors used in this scale (diabetes, heart disease, hypertension, claudication, hypercholesterolemia, arterial fibrillation, current smoking, and previous history of smoking) was determined by questions asked routinely during the Memory Clinic clinical interview. Each item is scored as 1 for the presence of a risk factor and 0 for its absence. An overall score is calculated by summing the score on each item. Hence, scores can range from 0–8, with higher scores indicating a greater risk for cerebrovascular disease.

Procedure

All case records that met the eligibility criteria for the study were extracted from the Memory Clinic archive, which is held in the IAA offices in GSH. Where necessary (e.g., in cases where the archival record was missing key pieces of information), I requested hard copies of the original medical records from the GSH Records Office. Once all records were compiled, they were grouped into two categories: patients with PRDs and a comparison group of patients without PRDs (COMP; see Chapter 3, pages 28-29 for group allocation criteria). Neuropsychological data for the resulting sample were then extracted from the Memory Clinic database, which is also held in the IAA offices.

Data Management and Statistical Analyses

The statistical analyses used in the present study are described clearly in Chapter 3 (pages 30-32). Rather than repeating what is said there, I will use this section to define the machine learning (ML) terminology used in this thesis.

When building an ML model, it is common practice to divide the full dataset into two randomly assigned subsets: (a) the *training set*, which typically contains around 75% of the full dataset and which is used to build the predictive model, and (b) the *test set*, which typically contains the remaining 25% and which is used examine the validity of the resulting model when applied to a new sample.

When assessing the validity of a model, several classification performance indices are reported. The indices used in the present study reflect those commonly used in the literature. In the context of the model derived in this study, (a) *classification accuracy* describes the percentage of individuals in the test set accurately classified to the PRD or COMP group, (b) *sensitivity* describes the percentage of individuals in the PRD group who were correctly classified as having the disease, (c) *specificity* describes the percentage of individuals in the COMP group who were correctly classified as not having the disease, (d) *positive predictive value* (*PPV*) describes the probability that individuals in the test set are correctly identified as having PRDs, (e) *negative predictive value* (*NPV*) describes the probability that individuals in the test set are correctly identified as not having PRDs, (f) *positive and negative likelihood ratio* describe the discriminating ability of the test, such that models with a positive likelihood ratio (PLR) value ≥1, and a negative likelihood ratio (NLR) approaching zero, have greater ability to discriminate between individuals with PRDs and those without (Appels & Scherder, 2010; McGee, 2002).

Ethical Considerations

As noted above, the measures used in this study are part of a neuropsychological / clinical test battery that is administered routinely to all patients referred to the Memory Clinic. As part of their consent to receive clinical services at the Memory Clinic, patients agree to allow Memory Clinic-affiliated researchers to use the information obtained from their assessment. They are informed that (a) their data will be kept confidential, (b) there are no risks or benefits associated with providing consent, and (c) they may request, without penalty and without having their treatment affected in any way, that their data not be used. The study procedures received ethical approval from the Research Ethics Committee of the UCT Faculty of Humanities (PSY2020-040).

Chapter 5:
General Discussion

The research described in this thesis aimed to contribute to the body of literature exploring the utility of machine learning (ML) techniques to assist and enhance the process of dementia diagnosis in low- and middle-income countries (LMICs). More specifically, the study presented here aimed to derive an efficient and accurate model that can aid the diagnosis of proteinopathic-related dementias. To accomplish these aims, I used data from a memory clinic sample of 253 South African older adults (130 with PRDs, 123 without) and applied C5.0 algorithms to (a) identify the most important clinical features for PRD diagnosis, and (b) derive a decision tree algorithm that could accurately diagnose these types of dementia.

This chapter reviews and discusses the research set out in this thesis. It outlines the rationale and overall aims of the study, summarises the findings, elaborates on the unique contribution that these findings make to scientific knowledge and clinical practice, and discusses the study's overall limitations. References are made to previous chapters, including the relevant page numbers.

Rationale and Overall Aims

The prevalence of dementia is increasing at an unprecedently fast rate in LMICs. Given the wide-ranging consequences of the disease, coupled with the fact that limited resources are dedicated to its early and accurate detection in those countries, the relevance and importance of optimising diagnostic pathways for dementia in LMICs are clear.

Most dementias are considered to be proteinopathies; that is to say, the clinical deficits that characterise them are associated with the accumulation of abnormal protein aggregates in the brain. As highlighted in Chapter 2 (pages 12-22), one way to optimise diagnostic pathways for dementia in LMICs is to differentiate, early in the diagnostic process, patients with proteinopathic-related dementias (PRDs) from those without. A major benefit of such early differentiation is that patients can be referred to appropriate specialists and will need fewer resource-heavy clinical services that are required to ensure an accurate and timely diagnosis.

Machine learning (ML) techniques have been used widely to optimise neuropsychological test batteries to detect dementia. However, a review of the literature in Chapter 2 (pages 12-22) identified a lack of research into the use of ML techniques to

optimise neuropsychological test batteries for the specific diagnosis of PRDs. In light of this gap in the literature, and the potential benefits (particularly for LMIC clinicians) of such exploration, the research presented in this thesis aimed to use ML techniques to:

a) identify the minimum number of neuropsychological tests and other relevant clinical variables (e.g., vascular risk factors, functional abilities) required to diagnose PRDs in an older adult sample from a LMIC population, and
b) derive an easily interpretable decision tree algorithm that diagnoses these types of dementias accurately and efficiently.

Summary of Findings

The study presented in this thesis demonstrated that C5.0 algorithms with the wrapper method successfully reduced the number of clinical variables for screening PRDs from 20 (the number of tests used from the memory clinic's complete neuropsychological battery plus the vascular risk factor variable) to 9 (Repeatable Battery for the Assessment of Neuropsychological Status [RBANS] Figure Recall, vascular risk factor, Phonemic Verbal Fluency, RBANS List Recall, RBANS List Recognition, Digit Span Backward, CLOX1, CLOX2, and ΔCLOX2-1). The features identified reflect clinical variables that are most important for differentiating between people with PRDs compared to those without.

Further, the C5.0 algorithm was able to derive an easily interpretable decision tree that classifies individuals with PRDs based on their performance on a subset of selected variables. The resulting decision tree identified 11 possible classification rules, each relating to 12 different terminal nodes. When validating the decision tree model, classification performance indices suggest that the model can identify people with PRDs with reasonably good confidence.

How Findings Add to the Literature

The study presented in this thesis demonstrates the utility of ML techniques in clinical settings. More specifically, the research findings make at least three specific contributions to the literature on ML in dementia diagnosis.

Firstly, this study validated the utility of ML techniques for identifying clinically relevant predictor variables for the classification of PRDs. Overall, use of the 9 selected features mentioned above improved classification accuracy compared to models that classified PRDs using the full set of 20 features. This result provides insight into which neuropsychological tests should be prioritised in clinical settings (particularly low-resource settings where speed and efficiency of diagnosis are essential) when screening for PRDs.

According to the derived model, clinicians should prioritise tests assessing memory and executive functions, rather than tests assessing language and visuospatial/visuoconstructional functions, when diagnosing PRDs. Additionally, clinicians should pay careful attention to the presence of vascular risk factors when diagnosing PRDs. Applying this knowledge in clinical practice has the potential to reduce assessment time while maintaining accuracy rates.

Secondly, the present research demonstrates the ability of ML techniques to produce an easily interpretable decision tree algorithm that can be used to classify individuals with PRDs with reasonably good accuracy rates, based on their performance on a subset of selected variables. Given the low cost and simplicity of the derived decision tree, in combination with the relatively low impact of receiving a false positive diagnosis, the current decision tree model may be particularly useful as a broad screening tool for PRDs (Leeflang et al., 2008).

This data-driven approach is particularly valuable considering that the algorithm applied in the current study was able to successfully detect PRDs without any supportive information that is typically available to clinicians (e.g., age, sex, education, laboratory results, neuroimaging data, psychiatric history, and family history). Further, the neuropsychological tests selected for classification are standardised tests and require minimal clinical expertise to administer. Moreover, the derived decision tree is simple and easy to follow in order to reach a diagnostic decision. Taken together, this means that the derived screening model in this study can be administered and interpreted by primary healthcare practitioners with limited dementia-specific clinical expertise. This is particularly valuable in LMICs, where relatively few health professionals have dementia expertise (see Chapter 2, pages 12-22).

Thirdly, the success of the ML techniques in identifying complex interactions and data patterns and in mapping neuropsychological test performance onto PRDs, suggests a common neuropsychological profile may exist for PRDs. To our knowledge, no research has attempted to identify whether these types of dementia fit together neuropsychologically. This is certainly a fruitful avenue for future research exploration.

Limitations

The research article included in this thesis (Chapter 3, pages 45-46) concluded with a brief examination of the study's methodological and other limitations. While acknowledging the existence of these limitations, this section focuses on broader constraints that affected the research project as a whole. These more general limitations should be kept in mind when

assessing the overall relevance of the thesis findings in LMIC clinical settings and when preparing future research based on, and attempting to extend, the current results.

A primary limitation concerns the generalisability of our findings. The data used in this study were collected from a single LMIC region (Cape Town, South Africa). Although Cape Town is comprised of a culturally diverse population with varied languages and sociocultural and experiential backgrounds, limited sample diversity may restrict the generalisability of the results and raises concerns regarding variability that exists between LMICs. However, we note that, despite the cultural diversity within the dataset used, the derived decision tree was able to classify individuals with relatively good classification indices. This provides reason to assume that the successful application of ML techniques in this context may hold in other LMICs.

An additional limitation is that, although the neuropsychological tests used as input variables in the study are used regularly in South African clinical practice and research, they may not be appropriate in other LMICs, and hence there might be limited utility of the derived decision tree in other LMICs. However, the finding that tests assessing memory and executive function are important for classifying PRDs likely holds across LMICs and therefore standardized tests assessing these cognitive domains should be prioritised when classifying PRDs, regardless of the setting. It would be interesting for future studies to conduct similar studies using a multicentric sample from LMICs to see whether a similar common neuropsychological profile for PRDs is identified.

Overall Summary and Conclusions

Overall, the results from the research presented here demonstrate that PRDs may share aspects of a common neuropsychological profile and can be classified, with a relatively high degree of accuracy, using 9 clinical variables (standardised neuropsychological test and vascular risk factor information) and following an easily interpretable decision tree.

Perhaps the major implication of this study's results is that they demonstrate the promising nature of decision tree methods in PRD screening and the potential utility of such methods to optimise neuropsychological tests for the purposes of differential diagnosis. In LMICs, where time-intensive neuropsychological test batteries are often the only available tool for differential diagnosis of PRDs, using this decision tree model as a screening tool has the potential to free up strained resources and to allow clinical expertise to be employed more selectively. Rather than providing all patients presenting with PRD-related complaints with brain scans, clinical interviews, and medical examinations that are costly and that may result

in delayed decision-making, the derived model in this study could easily be administered as part of standard clinical practice to identify patients who would benefit most from these confirmatory diagnostic procedures. This in turn may lead to patients receiving diagnoses earlier so that appropriate management plans can be implemented more efficiently, thereby alleviating at least some of the burden of PRDs in these countries.

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Appendix A

Mini-Mental State Examination (MMSE)

Preamble and instructions for administering the MMSE

I am now going to ask you some questions and I'd like you to do your best to answer them. Some of them you might find fairly easy and others you might find quite difficult. You shouldn't worry about this as the questions are designed to test a broad range of things to give us an idea of how your thinking is working.

Note that this test should only be administered to patients who are alert. For questions 6, 7, 8, 9, 10 and 11 patients with significantly impaired eyesight or deafness should be scored 'E' or 'D'.

	Possible Points	Score
1. a. What year is this? b. What season are we in? c. What month are we in? d. What is the date? e. What day of the week is it?	1 1 1 1 1	... ...
2. a. What country are we in? b. Which province are we in? c. In which town or city are we? d. In which hospital are we? e. On which floor/clinic/ ward are we?	1 1 1 1 1	... ...
3. Tell the patient: *"I am going to say three words that I want you to remember."* Then say (only once, taking 1 second for each): *"apple, pen, table."* Then ask the patient to repeat all three. Score 1 point for each correct answer. Then say: *"I want you to remember those words because I am going to ask you to repeat them later."*	3	

	Possible Points	Score
7. Tell the patient: *"I am going to say something once and then I want you to repeat it."* Then say (taking care to pronounce the final s's clearly): *"No ifs, ands or buts."* Penalise the patient if he/she omits the final s's.	1	
8. Ask the patient to follow this 3-stage command: *"Take this paper in your right hand, fold the paper in half, and put it on the floor."* Then hand the patient the paper. Penalise if the patient folds the paper more than once.	3	
9. Ask the patient to read and obey the printed instruction to "close your eyes" (see separate sheet).	1	
10. Ask the patient to: *"Write a sentence of your choice."* The sentence should contain a subject and a verb. Ignore spelling errors when scoring.		

4. a. Say: *"If you had 100 cents and you spent 7 cents, how much would you have left?"*
Then say: *"Now take away another 7 cents."*
Stop after 5 answers (do not correct wrong answers).
Score 1 point for each correct answer (e.g., 93, 88, 81, 64, 59 scores 2).

5	

4. b. Ask the patient to: *"Spell the word WORLD for me."*
Correct any errors, and rehearse until the patient spells it correctly.
Then ask the patient *"Now spell WORLD backwards."*
Score 1 point for each correctly placed letter (e.g., DLORW = 3; DWR = 2).

5	

Best of 4a or 4b

5	

5. Ask the patient to *"Please repeat the three words that I asked you to remember"* (as in item 3).
Score 1 point for each correct answer.

3	

6. Point to a pen and a watch.
Ask the patient to name them as you point.

2	

1	

11. Ask the patient to copy the pentagram design (see separate sheet).
Score 1 point if all sides and angles are preserved AND if the intersecting sides form a diamond shape.

1	

I 1Total Score (maximum 30): _____

Date: _____ Age: _____

Years of schooling: _____
Able to read: Yes / No
Able to hear: Yes / No

Scoring:
For a person with 7 years of schooling, good eyesight and hearing, a score of less than 24/30 is highly suggestive of dementia or delirium.
Where illiteracy or poor eyesight is relevant, the score is expressed as x/(30-y), where y is the number of disqualified questions and x is the number of correct answers.

Appendix B

Repeatable Battery for the Assessment of Neuropsychological Status – Immediate Memory Index

RBANS List Learning

Instruction:

Trial 1: Say to the patient: *I am going to read you a list of words. I want you to listen carefully and, when I finish, repeat back as many words as you can. You don't have to say them in the same order that I do – just repeat back as many words as you can remember, in any order. Okay?*

Trials 2-4: Say to the patient: *I am going to read the list again. When I finish, repeat back as many words as you can, even if you have already said them before. Okay?*

(Record responses in order, including any errors/repetitions)

List	Trial 1	Trial 2	Trial 3	Trial 4
Market				
Package				
Elbow				
Apple				
Story				
Carpet				
Bubble				
Highway				
Saddle				
Powder				

Number Correct				

Score: Each correctly recalled word = 1 point (per trial)

Maximum points: 40 ☐

RBANS Story Learning

Instruction:

Trial 1: Say to the patient: *I am going to read you a short story. I would like you to listen carefully and, when I finish, repeat back as much of the story as you can remember. Try and use the same wording if you can. Okay?*

Once you have read the story, say: *Now repeat back as much of that story as you can.*

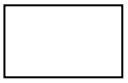
Trial 2: Say to the patient: *I am going to read you the same story again. When I finish, I want you to again repeat back as much of the story as you can remember. Try to repeat it as exactly as you can.*

Once you have read the story, say: *Now repeat back as much of that story as you can.*

(Record responses in order, including any errors/repetitions)

Story	Responses	Trial 1 Score (0 or 1)	Trial 2 Score (0 or 1)	Total Score (0 - 2)
On **Tuesday,**				
Fourth				
of **May,**				
in **Bothasig,** Free state				
a **serious**				
fire broke out.				
Two				
hotels				
and a **restaurant**				
were **destroyed**				
before the **firemen** *(firefighters)*				
were able to **put it out** *(extinguish it)*.				
	Total			

Score: Each VERBATIM recall of **bold** words or alternatives, shown in *italics* within parentheses = 1 point (per trial)

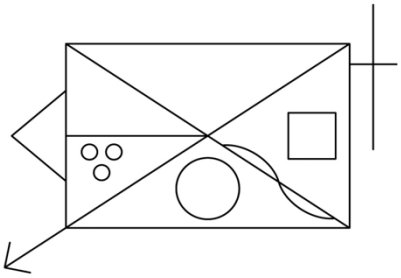
Maximum points: 24 

Appendix C

Repeatable Battery for the Assessment of Neuropsychological Status – Figure Copy

Instruction: Present the patient with the Figure Copy Drawing Page and the stimulus sheet. Say to the patient: *In front of you is a figure. I want you to make an exact copy, but, before you begin, I need to tell you I will be timing you. It is important that you make an exact copy of the figure. To let me know you understand can you tell me what I have asked?*

Correct as necessary and reinforce exactness of copy.



Score: Drawing (correct/complete) of item = 1point (per item)
Proper placement of item = 1point (per item)

Item	Drawing (0 or 1)	Placement (0 or 1)	Score (0 - 2)	Scoring Criteria
Rectangle				**Drawing:** lines unbroken & relatively straight; it appears a rectangle. **Placement:** not rotated more than 15 degrees
Diagonal Cross				**Drawing:** lines are unbroken, relatively straight & approx bisect each other. **Placement:** ends of lines should meet corners without significant overlap or significant distance from the corners.
Horizontal Line				**Drawing:** line is unbroken & relatively straight; should not exceed approx ½ of the width. **Placement:** from approximately the centre of the left side & intersect at approximately the diagonal cross.

Circle				**Drawing:** relatively round, unbroken, & relatively closed; diameter should be approx ¼ - ⅓ height of triangle. **Placement:** placed in appropriate segment; not touching any other figure.
3 Small Circles				**Drawing:** relatively round, unbroken & relatively closed; approx equal in size; approx triangular arrangement; not touching each other. **Placement:** in appropriate segment; not touching figure; triangle formed not rotated more than approx 15 degrees.
Square				**Drawing:** relatively closed; appears to be a square; lines relatively straight & unbroken; height is approx ¼ - ⅓ of triangle. **Placement:** in appropriate segment; not touching any other part of figure; not rotated more than approx 15 degrees.
Curving Line				**Drawing:** 2 curved segments; approximately equal in appearance; correct direction of curves. **Placement:** ends of lines approx touch diagonal; do not touch very corner of rectangle or diagonal intersection.
Outside Cross				**Drawing:** vertical line is relatively parallel to side of rectangle; horizontal line crosses the vertical at approx 900 degrees & is between 20-50% of length of vertical line. **Placement:** horizontal line touches rectangle higher than ⅔ height of rectangle, but below top; it approx touches the rectangle; vertical line stretches above the height of the rectangle & down to approx the mid-point of the rectangle.
Triangle				**Drawing:** angle formed by 2 sides is between approx 60-100 degrees; sides are relatively

				straight, unbroken & meet in a point; distance on vertical side of triangle subsumed is approximately 50% of the height of vertical side. **Placement:** approx at top of rectangle.
Arrow				**Drawing:** relatively straight & unbroken; lines forming arrow are approx equal in length. **Placement:** protrudes from appropriate corner of rectangle; it appears an approx continuation of diagonal staff.

Maximum points: 20 [ ]

Appendix D

Repeatable Battery for the Assessment of Neuropsychological Status – Delayed Memory Index

RBANS List Recall

Instruction: Say to the patient: *Do you remember the list of words that I read you a while ago? Tell me as many of those words as you can remember now.*

Do not read the list again.

(Record responses in order, including any errors/repetitions)

List	Response	Score (0 or 1)
Market		
Package		
Elbow		
Apple		
Story		
Carpet		
Bubble		
Highway		
Saddle		
Powder		

Number Correct		

Score: Each correctly recalled word = 1 point

Maximum points: 10 ☐

RBANS List Recognition

Instruction: Say to the patient: *I'm going to read you some words. Some of these words were on that list, and some of them weren't. I want you to tell me which words were on the list.*

Circle the letter corresponding to the patient's response (y = yes; n = no); bold letters indicate correct response.

List	Circle One	List	Circle One
Apple	**Y** N	**Bubble**	**Y** N
Honey	Y **N**	Desert	Y **N**
Market	**Y** N	**Highway**	**Y** N
Story	**Y** N	Oyster	Y **N**
Fabric	Y **N**	Student	Y **N**
Sailor	Y **N**	**Saddle**	**Y** N
Velvet	Y **N**	**Powder**	**Y** N
Carpet	**Y** N	Angel	Y **N**
Valley	Y **N**	**Package**	**Y** N
Elbow	**Y** N	Meadow	Y **N**

Score: Each correctly identified word = 1 point

Maximum points: 20 ☐

RBANS Story Recall

Instruction: Say to the patient: *Do you remember that story about a fire that I read to you earlier? Tell me as many details from the story as you can remember now.*
Do not read the story again.

(Record intrusions or variations in the Responses column)

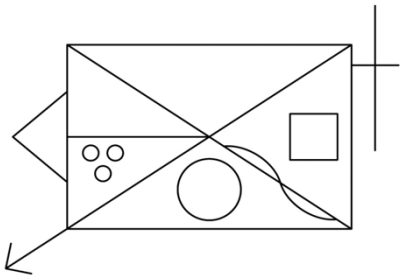
Story	Responses	Item Score (0 or 1)
On **Tuesday,**		
fourth		
of **May,**		
in **Bothasig,** Free state		
a **serious**		
fire broke out.		
Two		
hotels		
and a **restaurant**		
were **destroyed**		
before the **firemen** *(firefighters)*		
were able to **put it out** *(extinguish it).*		

Score: Each VERBATIM recall of **bold** words or alternatives, shown in *italics* within parentheses = 1 point

Maximum points: 12 ☐

RBANS Figure Recall

Instruction: Present the patient with the Figure Recall Drawing Page. Say to the patient: *Do you remember that figure that I asked you to copy? I want you to draw as much of it as you can remember now. If you remember a part, but you're not sure where it goes, put it anywhere. Try to draw as much of it as you can.*



Score: Drawing (correct/complete) of item = 1point (per item)
Proper placement of item = 1point (per item)

Item	Drawing (0 or 1)	Placement (0 or 1)	Score (0 - 2)	Scoring Criteria
Rectangle				**Drawing:** lines unbroken & relatively straight; it appears a rectangle. **Placement:** not rotated more than 15 degrees
Diagonal Cross				**Drawing:** lines are unbroken, relatively straight & approx bisect each other. **Placement:** ends of lines should meet corners without significant overlap or significant distance from the corners.
Horizontal Line				**Drawing:** line is unbroken & relatively straight; should not exceed approx ½ of the width. **Placement:** from approximately the centre of the left side & intersect at approximately the diagonal cross.
Circle				**Drawing:** relatively round, unbroken, & relatively closed; diameter should be approx ¼ - ⅓ height of triangle.

				Placement: placed in appropriate segment; not touching any other figure.
3 Small Circles				**Drawing:** relatively round, unbroken & relatively closed; approx equal in size; approx triangular arrangement; not touching each other. **Placement:** in appropriate segment; not touching figure; triangle formed not rotated more than approx 15 degrees.
Square				**Drawing:** relatively closed; appears to be a square; lines relatively straight & unbroken; height is approx ¼ - ⅓ of triangle. **Placement:** in appropriate segment; not touching any other part of figure; not rotated more than approx 15 degrees.
Curving Line				**Drawing:** 2 curved segments; approximately equal in appearance; correct direction of curves. **Placement:** ends of lines approx touch diagonal; do not touch very corner of rectangle or diagonal intersection.
Outside Cross				**Drawing:** vertical line is relatively parallel to side of rectangle; horizontal line crosses the vertical at approx 900 degrees & is between 20-50% of length of vertical line. **Placement:** horizontal line touches rectangle higher than ⅔ height of rectangle, but below top; it approx touches the rectangle; vertical line stretches above the height of the rectangle & down to approx the mid-point of the rectangle.
Triangle				**Drawing:** angle formed by 2 sides is between approx 60-100 degrees; sides are relatively straight, unbroken & meet in a point; distance on vertical side of triangle subsumed is approximately 50% of the height of vertical side.

				Placement: approx at top of rectangle.
Arrow				**Drawing:** relatively straight & unbroken; lines forming arrow are approx equal in length. **Placement:** protrudes from appropriate corner of rectangle; it appears an approx continuation of diagonal staff.

Maximum points: 20 

Appendix E

Boston Naming Test – South African Short Form

Instruction: Say to the patient: *I am going to show you some pictures. Please name the thing you see in each picture.* If the initial response is unknown or incorrect after 20 seconds, provide the stimulus cue. If the response remains unknown or incorrect 20 seconds after the stimulus cue is given, provide the phonemic cue. If the response remains incorrect or unknown 20 seconds after the phonemic cue is given, provide the four multiple choice items and ask the patient to select one.

Item	Uncued Response	Stimulus Cue	Phonemic Cue	Multiple Choice
1. **tr**ee (something that grows outdoors)				
2. **co**mb (used for fixing hair)				
3. **too**thbrush (used in the mouth)				
4. **han**ger (found in a cupboard)				
4b. **whee**lchair (found in a hospital)				
5. **be**nch (used for sitting)				
6. **sn**ail (an animal)				
7. **da**rt (you throw it)				
8. **rhi**noceros (an animal)				
9. **do**minoes (a game)				

10. **es**calator (you go up on it)				
11. **ste**thoscope (used by doctors & nurses)				
12. **fu**nnel (used for pouring)				
13. **co**mpass (for drawing)				
14. **sph**inx (it's found in Egypt)				
15. **pro**tractor (measures angles)				

Maximum points: 15 ☐

Appendix F
Digit Span Test

Forward Digit Span

Instruction: Say to the patient: *I am going to tell you a series of numbers. Please repeat them in the order that I give them to you.*

If the patient is able to repeat the first span of a sequence length correctly, offer the first span of the next length.

If the patient makes an error or is unable to repeat the first span of a sequence length at all, offer the second span of that length (in brackets). If the patient is able to repeat the second span of a sequence length correctly, continue as per instructions above.

If the patient is unable to the second span of a sequence length accurately, note the length of the last span the patient was able to repeat correctly and stop this part of the test.

	Sequence	**Response**	**Correct / Incorrect**	**Procedure**
3a	4-8-2			**Correct:** Skip to 4a **Incorrect:** Do 3b
3b	(5-3-8)			**Correct:** Do 4a **Incorrect:** End the test
4a	7-4-1-9			**Correct:** Skip to 5a **Incorrect:** Do 4b
4b	(3-6-2-8)			**Correct:** Do 5a **Incorrect:** End the test
5a	5-2-9-4-6			**Correct:** Skip to 6a **Incorrect:** Do 5b
5b	(2-8-5-3-9)			**Correct:** Do 6a **Incorrect:** End the test
6a	9-1-4-7-3-5			**Correct:** Skip to 7a **Incorrect:** Do 6b

6b	(3-8-2-6-1-7)			**Correct:** Do 7a **Incorrect:** End the test
7a	4-7-1-9-3-8-2			**Correct:** End the test **Incorrect:** Do 7b
7b	(5-8-2-1-4-9-3)			**Correct:** End the test **Incorrect:** End the test
K4.1	Length of the last forward digit span that was correct **(For scoring use)**		1 = 3 digits 2 = 4 digits 3 = 5 digits 4 = 6 digits 5 = 7 digits	

Backward Digit Span

Instruction: Say to the patient: *Now I am going to tell you a series of numbers as I just did, but this time I would like you to repeat the number is the reverse order. So for example, if I say 3 5, you would say 5, 3.*

Follow procedural instructions as for Forward Digit Span test.

	Sequence	**Response**	**Correct / Incorrect**	**Procedure**
3a	5-7-4			**Correct:** Skip to 4a **Incorrect:** Do 3b
3b	(2-5-9)			**Correct:** Do 4a **Incorrect:** End the test
4a	7-2-9-6			**Correct:** Skip to 5a **Incorrect:** Do 4b
4b	(8-4-1-3)			**Correct:** Do 5a **Incorrect:** End the test
5a	4-1-6-2-8			**Correct:** Skip to 6a **Incorrect:** Do 5b
5b	(9-7-5-2-6)			**Correct:** Do 6a

				Incorrect: End the test
6a	1-6-5-2-9-8			**Correct:** Skip to 7a **Incorrect:** Do 6b
6b	(3-6-7-1-4-9)			**Correct:** Do 7a **Incorrect:** End the test
7a	4-7-3-9-5-2-8			**Correct:** End the test **Incorrect:** Do 7b
7b	(3-1-7-9-5-4-2)			**Correct:** End the test **Incorrect:** End the test
K4.2	Length of the last forward digit span that was correct **(For scoring use)**		1 = 3 digits 2 = 4 digits 3 = 5 digits 4 = 6 digits 5 = 7 digits	

Appendix G
CLOX Task

Instruction:

CLOX 1: Turn over to the blank page. Say to the patient: *I want you to draw me a clock that says 1:45. Set the hands and numbers on the face so that a child could read them.* Repeat the instructions until they are clearly understood. Once the subject begins to draw no further assistance is allowed.

CLOX 2: Say to the patient: *Now I want you to watch me.* Let the patient observe you draw a clock in the circle below. Place 12, 6, 3, & 9 first. Fill in the rest of the numbers. Set the hands to 1:45. Make the hands into arrows. Make the hour hand shortest. Say to the patient: *I want you to copy my clock in the space next to it.*

Organizational Elements	**Point Value**	**CLOX 1**	**CLOX 2**
Does figure resemble a clock?	**1**		
Circular face present?	**1**		
Dimensions>1 inch?	**1**		
All numbers inside the perimeter?	**1**		
No sectoring or tic marks?	**1**		
12, 6, 3, & 9 placed first?	**1**		
Spacing Intact? (Symmetry on either side of 12 and 6 o' clock?)	**1**		
Only Arabic numerals?	**1**		
Only numbers 1 – 12 among the numerals present? (ignore notation)	**1**		
Sequence 1-12 intact? No omissions or intrusions.	**1**		
Only two hands present? (ignore sectoring/tic marks)	**1**		
All hands presented as arrows?	**1**		
Hour hand between 1 and 2 o' clock?	**1**		
Minute hand obviously longer than hour?	**1**		
None of the following: 1) hand pointing to 4 or 5 o' clock?	**1**		

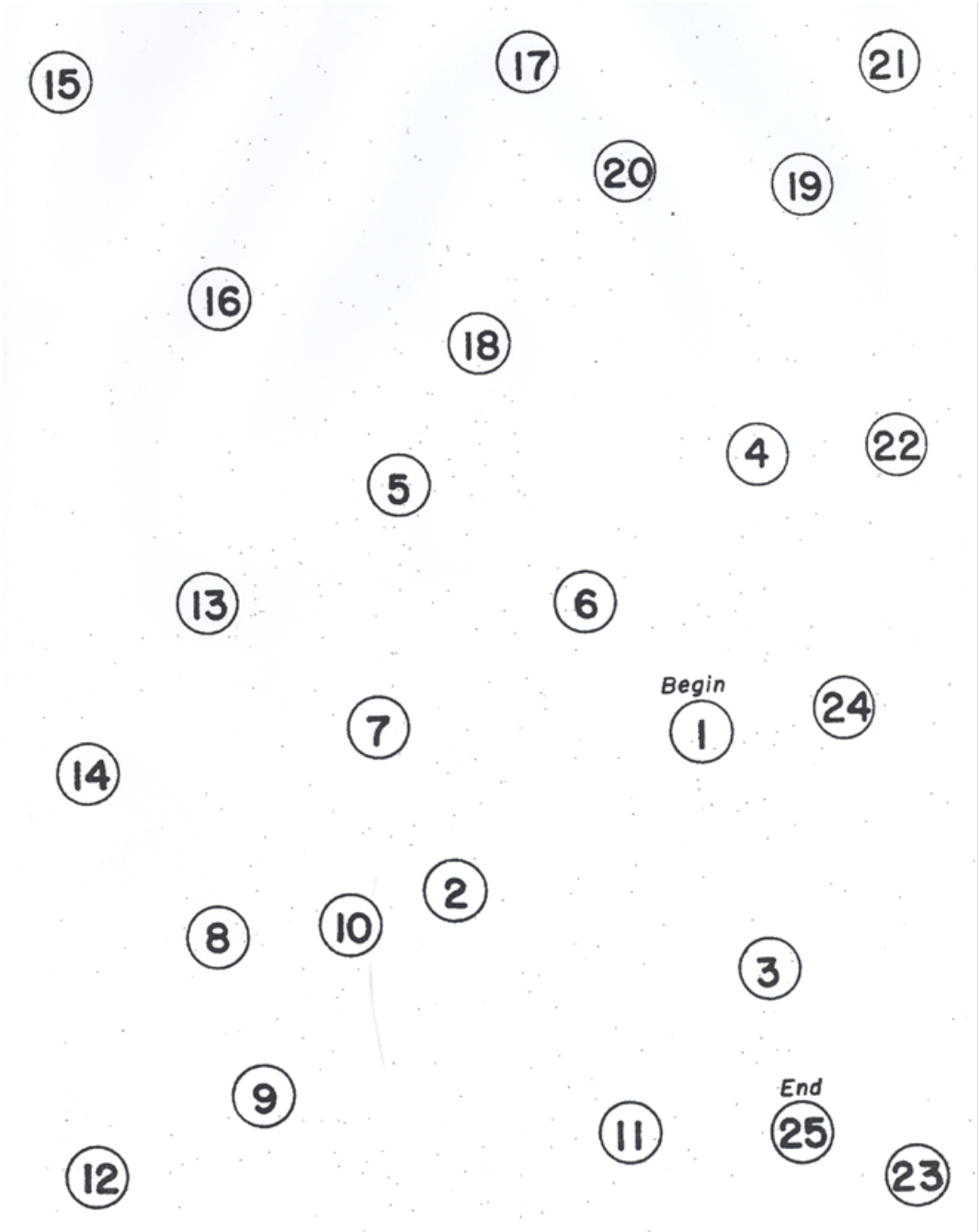
2) “1:45” present?			
3) Any other notation (e.g. “9:00”)?			
4) Any arrows point inward?			
5) Intrusions from “hand” or “face” present?			
6) Any letters, words or pictures?			
7) Any intrusion from circle below?			
	TOTAL		

Appendix H

Trail Making Test

Trails A

Instruction: Say to the patient: *I want you to connect these numbers in order, starting with number one and ending with number 25. Do it as quickly as you can without making any errors, and try not to lift your pen from the page.* Correct performance as necessary.

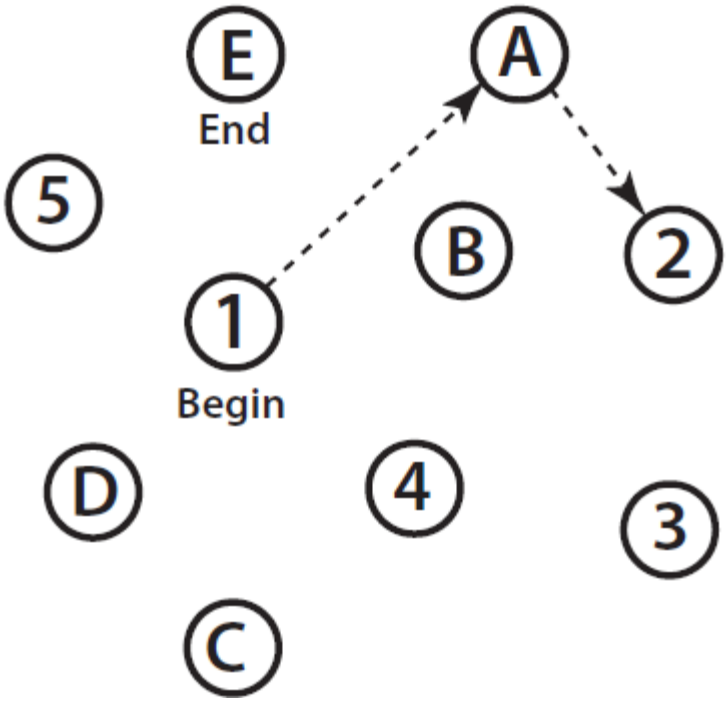


MoCA Trail

Instruction: Say to the patient: *Now I want you to connect these numbers and letters in order, starting with a number, and then a letter, and then a number and so on. So you would start with 1, then draw a line to A, and then draw a line to 2., alt the way to the letter E. Do it as quickly as you can without making any errors, and try not to lift your pen from the page.*

(Time for 4 minutes)

Test Item:

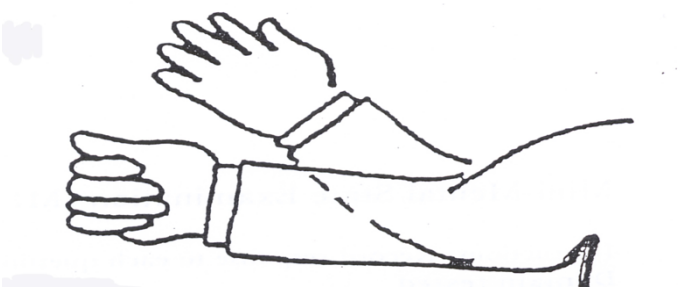


Appendix I

Luria Hand Sequences

Instruction: Say to the patient: *I want you to copy what I do...* (Using the patient's dominant hand). Alternate cut/fist action. Once the patient has started, say: *Now I'm going to stop and I want you to keep going.* Watch 3 cycles. Repeat exercise with patient's non dominant hand.

Sequence:



Score: 3 cycles without error after examiner stops = 2 points

3 cycles with additional verbal prompting or modelling = 1point

Unsuccessful despite prompting/modelling

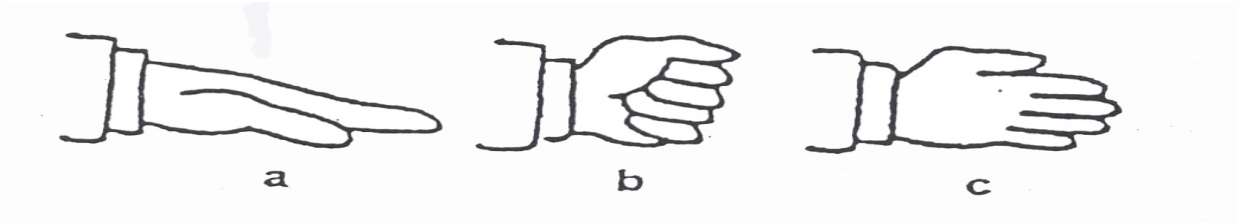
(watch for "midposition" stances) = 0 points

Dominant Hand ☐ Nondominant Hand ☐

Maximum Score: 2 ☐

Instruction: Ask the patient: *Can you do this?* (Using the patient's dominant hand). Model palm/fist/cut actions. Once the patient has started, say: *Now I'm going to stop and I want you to keep going.* Watch 3 cycles. Repeat exercise with patient's non dominant hand.

Sequence:



Score: 3 cycles without error after examiner stops = 2 points

3 cycles with additional verbal prompting or modelling = 1point

Unsuccessful despite prompting/modelling = 0 points

Dominant Hand ☐ Nondominant Hand ☐

Maximum Score: ☐

Appendix J

Luria Recursive Figures

Instruction: Say to the patient: *Please continue the pattern below until you reach the end of the page.*

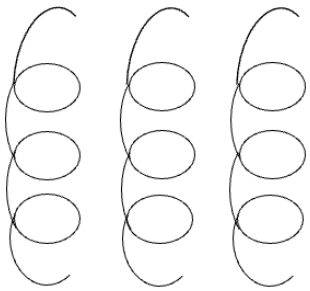
Pattern:

Score:		
	2 or more perseverative errors	= 0 points
	1 perseverative error	= 1 point
	Complete correct sequence	= 2 points

Maximum points: 2 ☐

Instruction: Say to the patient: *Please draw the same design until you reach the end of the page.*

Pattern:



Score:		
	2 or more errors of commission (i.e., 3 instead of 4 loops) and/or omission (i.e., 5 or more instead of 4 loops)	= 0 points
	1 error of omission or commission	= 1 point
	Complete correct sequence	= 2 points

Maximum points: 2 ☐

Appendix K

Bristol Activities of Daily Living Scale - Modified

Instruction: *C*ircle the response that best describes the patient's level of ability to perform that activity. Only one box should be marked for each activity. Where in doubt, choose the level of ability which represents the patient's average performance over the past two weeks.

1. **Food**		
a	Selects and prepares food	0
b	Able to prepare food only if ingredients are set out	1
c	Able to prepare food only if shown step by step	2
d	Unable to prepare food	3
e	Not applicable	0
2. **Eating**		
a	Eats as previously	0
b	Eats appropriately if food is made manageable and/or uses a spoon	1
c	Needs someone to help guide food to mouth	2
d	Needs to be fed	3
e	Not applicable	0
3. **Drink**		
a	Able to make tea/coffee as previously	0
b	Able to make tea/coffee only if ingredients are set out	1
c	Able to make tea/coffee only if shown step by step	2
d	Unable to make tea/coffee	3
e	Not applicable	0
4. **Dressing**		
a	Dresses as previously	0
b	Puts clothes on incorrectly or inappropriately	1
c	Unable to dress self but moves limbs to assist	2
d	Has to be dressed	3
e	Not applicable	0
5. **Hygiene**		
a	Washes self as previously	0
b	Able to wash self if given soap, towel and water	1

c	Able to wash self but needs help	2
d	Has to be washed	3
e	Not applicable	0

6. **Teeth**

a	Cleans teeth as previously	0
b	Cleans teeth only if given water and toothpaste or gargle	1
c	Able to clean teeth but needs help	2
d	Unable to clean teeth	3
e	Not applicable	0

7. **Toilet**

a	Uses toilet as previously	0
b	Able to use toilet (or bucket) if helped	1
c	Incontinent of urine	2
d	Incontinent of urine and faeces	3
e	Not applicable	0

8. **Transfers**

a	Able to get in/out of a chair as previously	0
b	Able to get in a chair but needs help to get out	1
c	Needs help getting in/out of a chair	2
d	Has to be lifted in/out a chair	3
e	Not applicable	0

9. **Mobility**

a	Walks independently	0
b	Walks with assistance, i.e. furniture, arm for support	1
c	Uses aid to walk, i.e. cane, frame	2
d	Unable to walk	3
e	Not applicable	0

10. **Orientation – Time**

a	Fully orientated to time/day/date, etc.	0
b	Unaware of time/day/date but seems unconcerned	1
c	Repeatedly asks the time/day/date	2
d	Mixes up night and day	3

e	Not applicable	0

11. **Orientation – Space**

a	Fully orientated to surroundings	0
b	Orientated to familiar surroundings only	1
c	Gets lost in home, needs reminding where toilet is	2
d	Does not recognise own home	3
e	Not applicable	0

12. **Communication**

a	Able to hold appropriate conversation	0
b	Understands others and tries to respond verbally with gestures	1
c	Can make self understood but has difficulty understanding others	2
d	Does not respond to or communicate with others	3
e	Not applicable	0

13. **Telephone**

a	Uses telephone appropriately	0
b	Uses telephone with help	1
c	Answers telephone but does not make calls	2
d	Unable/unwilling to use telephone	3
e	Not applicable	0

14. **Housework/gardening**

a	Able to do housework/gardening to previous standard	0
b	Able to do housework/gardening but not to previous standard	1
c	Limited participation in housework/gardening	2
d	Unwilling/unable to participate in previous housework/gardening activities	3
e	Not applicable	0

15. **Shopping**

a	Shops to previous standard	0
b	Only able to shop for 1 or 2 items without a list	1
c	Unable to shop alone, but participates when accompanied	2

d	Unable to participate in shopping even when accompanied	3
e	Not applicable	0

16. **Finances**

a	Manages own finances as previously	0
b	Recognises money values and can sign name	1
c	Does not recognise money values but can sign name	2
d	Unable to sign name or recognise money values	3
e	Not applicable	0

17. **Transport**

a	Able to drive, cycle or use public transport independently	0
b	Unable to drive but uses public transport, bike, etc.	1
c	Unable to use public transport alone	2
d	Unable or unwilling to use public transport even when accompanied	3
e	Not applicable	0

Score: Add encircled numbers for 17 activity domains

Maximum Score: 51 ☐

Total "not applicable" activities ☐

Appendix L

Vascular Risk Factor Scale

Indicate whether present (Y) or absent (N).

		Y	N
Vascular risk factors			
1	Diabetes	1	0
2	Heart disease	1	0
3	Hypertension	1	0
4	Claudication	1	0
5	Hypercholesterolemia	1	0
6	Atrial fibrillation	1	0
7	Current smoking	1	0
8	Previous history of smoking	1	0