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Master Thesis

Role of Biomarkers for Differential Diagnosis of Dementias

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Table of contents

Abstract

Dementia is a complex neurodegenerative disorder which presents with many subtypes. Patients often have overlapping symptoms, and diagnosis is often missed initially. Making an early diagnosis and accurately differentiating between AD, VaD, DLB, FTD, and RPD remains a critical challenge in practice. This thesis explores the role of biomarkers in the diagnosis as well as differential diagnosis between the various dementia subtypes, emphasizing the current and prospective roles that CSF markers, blood-based biomarkers, neuroimaging techniques, and genetic and novel biomarkers play. While CSF analysis and neuroimaging are widely used currently, their cost and invasiveness highlight the need for accessible fluid-based alternatives. Modalities such as mass spectrometry, ELISA, SIMOA, and proteomics play an important role in biomarker research and validating fluid-based biomarkers for use in clinical practice. AI and machine learning will also play a key role in biomarker research and the diagnosis of dementia. Despite significant progress, standardization, and clinical validation of these biomarkers remain key challenges. This thesis highlights the transformative potential of biomarker research in revolutionizing dementia diagnosis.

Abbreviations

- (PiB): [11C]Pittsburgh Compound B
- 14-3-3: 14-3-3 Protein
- ACh: Acetylcholine
- AD: Alzheimer's Disease
- ADRD: Alzheimer's Disease and Related Dementias
- AHA: American Heart Association
- API: Atrophy Pattern Index
- APOE ε4: Apolipoprotein E epsilon 4 allele
- ASA: American Stroke Association
- ASI: Atrophy Subtype Index
- ASL: Arterial spin-labelling
- AUC: Area under the curve
- Aβ: Amyloid-beta

- Aβ42/Aβ40: Amyloid-beta 42 to 40 ratio
- BBB: Blood-Brain Barrier
- BBM: Blood-Based Biomarker
- BD-tau: Brain-derived tau
- bvFTD: behavioral variant Frontotemporal Dementia
- C9orf72: Chromosome 9 Open Reading Frame 72
- CAA: Cerebral Amyloid Angiopathy
- CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
- CDT: Clock Drawing Test
- CJD: Creutzfeldt–Jakob disease
- CRP: C-reactive Protein
- CSF: Cerebrospinal Fluid
- CTE: Chronic Traumatic Encephalopathy
- CU: Cognitively unimpaired
- CVD: Cardiovascular Disease
- DAT: Dopamine transport
- DLB: Dementia with Lewy Bodies
- DM: Diabetes Mellitus
- DPRs: Dipeptide Repeat Proteins
- EEG: Electroencephalography
- FDA: Food and Drug Administration
- FDG-PET: Fluorodeo)glucose PET
- FTD: Frontotemporal Dementia
- GFAP: Glial Fibrillary Acidic Protein
- HC: Healthy Controls
- H-FABP: Heart-Type Fatty Acid Binding Protein
- IHD: Ischemic heart disease
- IL-6: Interleukin 6
- IP-MS: Immunoprecipitation-Mass Spectrometry
- MCI: Mild Cognitive Impairment
- miRNA: MicroRNA
- MMSE: Mini-Mental State Examination
- MoCA: Montreal Cognitive Assessment
- MRI: Magnetic Resonance Imaging
- MS: Multiple sclerosis
- NFL: Neurofilament Light Chain
- NFT: Neurofibrillary Tangle

- nfvPPA: non-fluent variants of primary progressive aphasia
- NIA-AA: National Institute on Aging–Alzheimer's Association
- OND: other neurological disorders
- P-SYN: phosphorylated alpha-synuclein
- p-tau: Phosphorylated Tau
- PDD: Parkinson's Disease Dementia
- PET: Positron Emission Tomography
- PrP: Prion Protein
- PRS: Polygenic risk score
- PSD: Post Stroke Dementia
- PSEN1: Presenilin 1
- pSer129-α-syn:α-syn phosphorylated at serine 129
- PWD: Persons with Dementia
- RBD: REM sleep behavior disorder
- RNFL: Retinal nerve fiber layer
- RNS: Reactive Nitrogen Species
- ROS: Reactive O)gen Species
- RPD: Rapidly Progressive Dementias
- RT-QuIC: Real-Time Quaking-Induced Conversion
- rtvFTD: right lobe variant Frontotemporal Dementia
- Simoa: Single Molecule Array
- SNAP-25: Synaptosomal-associated protein 25
- SVCI: Subcortical vascular cognitive impairment
- SVD: Small Vessel Disease
- svPPA: semantic variants of primary progressive aphasia
- SWI: susceptibility-weighted imaging
- t-tau: Total Tau
- TDP-43: TAR DNA-binding Protein 43
- TLP: Temporal Lobe Pattern
- TMT: Trail Making Test
- TNF-α: Tumor Necrosis Factor-alpha
- TSPO: Translocator Protein
- TSPO-PET: Translocator Protein PET
- VaD: Vascular Dementia
- VCID: Vascular cognitive impairment and dementia
- VRS: Virchow–Robin spaces
- WHO: World Health Organization
- WMC: White matter changes

- WMH: White matter hyperintensity
- α-Syn: Alpha-synuclein

Keywords: Alzheimer’s disease, Vascular dementia, Lewy Body dementia, Frontotemporal dementia, rapidly progressive dementia, biomarkers, neuroimaging, CSF, blood-based biomarkers

1. Introduction

Dementia is a complex neurodegenerative disorder, encompassing many different diseases. In this thesis, we will primarily focus on AD, VaD, DLB, FTD, and RPD. Patients with dementia present with highly variable symptoms, many of them overlapping. Individuals living with dementia encounter the condition in unique ways influenced by their specific disease risk, personal and social circumstances, environmental factors, preferences, and the resources or support available to them (1).

This thesis is a literature review that will explore the current literature on established core biomarkers associated with these dementias. In the first part, dementia will be introduced. In the second part, each subtype of dementia will be reviewed in greater detail to better understand the role of biomarkers in this disease. In the third section, the actual literature review of the current biomarkers will be discussed. Finally, in part four, new prospective and emerging biomarkers will be presented, as well as the use of AI and machine learning, and the latest research advancements in dementia research. By addressing these aspects, this work aims to highlight the transformative impact of dementia biomarker research in bridging the gap between scientific understanding and practical clinical applications.

Dementia imposes significant burdens on patients, caregivers, and healthcare infrastructure, resulting in steep societal costs and growing challenges for governments to tackle. Research has shown that between 1990 and 2016, the global population affected by dementia was estimated to have grown by 117%, primarily due to an aging population (2). Demographic trends show that the driver forces are declining fertility rates and increasing life expectancy, resulting in significant shifts in population age structure, with more individuals reaching advanced ages than in the past (2). These changes, coupled with relatively stable age-specific prevalence rates and overall population growth, have contributed to a substantial rise in dementia cases. As these trends are projected to continue, the number of individuals living with dementia is expected to increase (2). It is anticipated that throughout this time, the number of cases in Europe alone will rise by almost 80%, from 14.1 million to 25 million by 2050 (3). Globally, the cost of dementia is forecast to exceed $2 trillion by 2030, up from $818 billion in 2015 (4). Research shows that

the diagnosis of dementia causes an average increase of $15,700 in Medicare expenses over five years, with 50% of these expenses incurred during the first year (5). The higher costs related to dementia diagnoses highlight the need for biomarkers to screen and diagnose the disease in a timely manner.

Socioeconomic barriers also influence preventable risk factors for dementia. Sedentary lifestyles, the perception that physical activities are too costly, smoking, alcohol consumption, and poor diets all contribute to cognitive impairment, increasing the risk of inflammation and CVD and AD burden, which subsequently increases the risk of dementia (6). Meanwhile, regardless of subgroup, women are more impacted by ADRD than men are (1). Postmenopausal women account for more than 60% of individuals affected by AD and carry the greatest burden of the syndrome (7). Prediabetes has been shown to be linked to earlier onset of dementia in women, but not in men (8). Research using mouse models and high-fat diets has shown that female mice with mixed dementia exhibited increased cognitive impairment, more proteinopathies compared to male mice, and that prediabetes was correlated with increased hippocampal microgliosis (8). Genetics in women also play a role in the risk of progressing to AD. For example, females with only a single copy of the ApoE4 allele have a similar risk profile to develop the disease as males who have both copies of the gene(7).

Dementia arises from the interaction between specific molecular pathways. This affects cellular functions, leading to loss of synaptic connections, cell death, gliosis, inflammation, and disruption of functional networks underlying cognition, personality, behavior, and sensorimotor functions, eventually leading to loss of autonomy in patients (10). The definition of dementia has changed over time to reflect that dementia isn't simply memory loss but a change in many cognitive domains and behaviors that lead to a decline in patients from their normal functioning (10). In 2011, the new definition postulated that a diagnosis of dementia requires the patient to show impairments in at least two neuropsychiatric or cognitive domains that cannot be better explained by nondegenerative or primary psychiatric disorders, or systemic conditions such as delirium (10).

Dementia can present itself clinically as mixed pathology, for example, such as AD with VaD or AD with TDP and AD with Lewy bodies (11). Neurodegenerative proteinopathies classify most non-vascular dementias into six major types: amyloid-β (Aβ), microtubule-associated protein tau, TAR DNA-binding protein 43 (TDP-43), fused in sarcoma (FUS), α-synuclein, and prion protein (10). As for RPD, it's fast-progressing dementia that includes prion disease, infectious encephalitis, immune-mediated encephalitis, rapidly progressing AD, and vascular causes, which accelerate the cognitive decline in patients (12).

In the following chapter, a comprehensive overview of the different types of dementia subtypes will be presented to set the foundation for understanding how biomarkers play a key role in the differential diagnosis of dementia. A specific focus will be placed on patient symptoms, the diagnostic criteria, the pathophysiological underlying mechanism of each dementia subtype, and other relevant information.

2. Dementia Overview

2.1 Alzheimer's Disease

In this section AD will be introduced. Then the focus will be shifted to the disease spectrum and subtypes as well as AD epidemiology and risk factors. Additionally, this section will detail about how it's diagnosed and discuss AD classifications, such as the ATN framework. Lastly, the pathophysiology of AD will be reviewed by focusing on the amyloid hypothesis, Aβ deposition, NFTs, and finally cholinergic deficits in this disease.

AD is the primary form of dementia, defined as a progressive neurodegenerative disorder marked by distinctive pathological characteristics, including Aβ plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein (13). These changes affect the medial temporal lobe and neocortex, leading to cognitive decline, behavioral changes, and functional impairments in affected patients (13). Clinically, AD manifests along a continuum starting with the preclinical phase, where patients don't complain of any symptoms, later to MCI and, finally full-blown dementia (13). Within AD, several subtypes exist, including the genetically determined forms,

the language-dominant types, typically presenting before age 70, and most commonly the amnestic variant, which is seen in older adults (14).

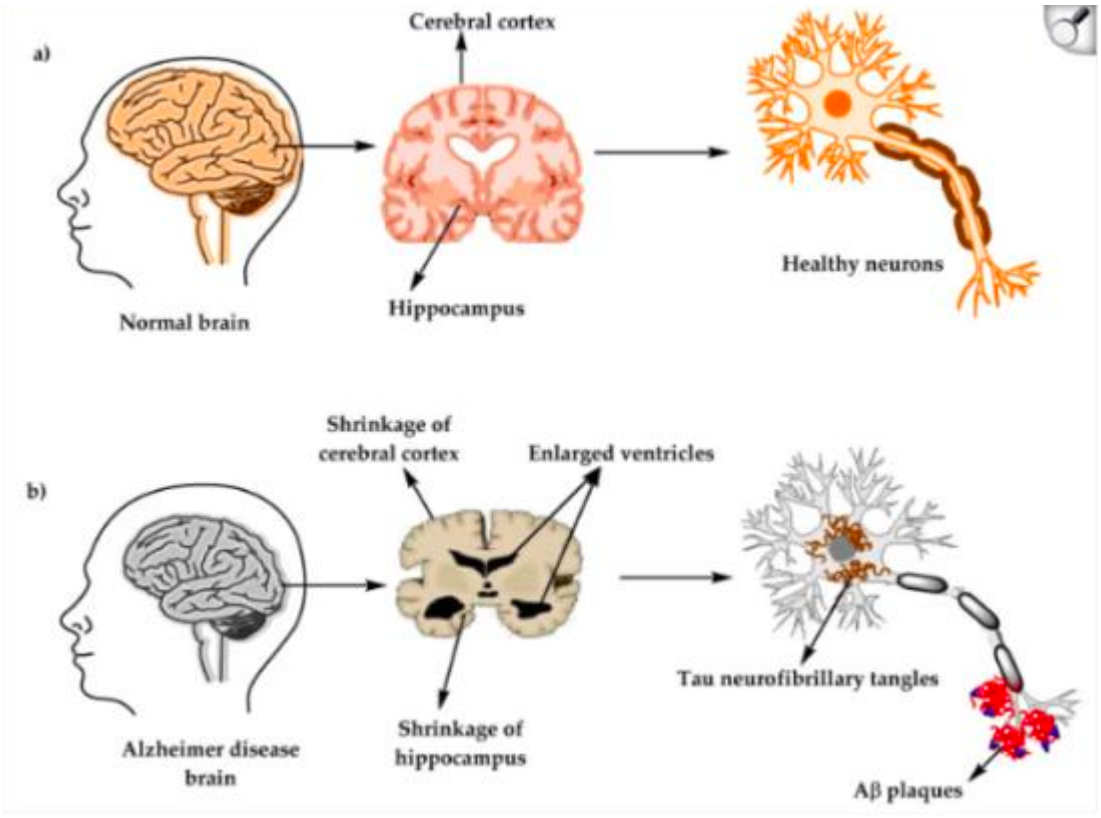

Image: A shows a healthy brain; B shows the result of AD on the cerebral cortex and neurons (13)

The global burden of AD is immense, with over 50 million people affected worldwide—a figure projected to rise to 152 million by 2050 (13). In developed countries, about one in ten elderly people that are 65 and over are affected by AD in its earliest stages, while more than one third of people 85 and over may already be at the advanced stages presenting with prominent symptoms (15). In Europe, the median survival time is 6 years after AD is diagnosed (14). A multicenter study in individuals aged 70 estimated that the duration of the preclinical stage is 10 years, the prodromal stage of MCI is 4 years, and finally the dementia stage of AD is 6 years (14).

The 2 biggest risk factors for Alzheimer's disease are being older than 65 years and carrying at least one APOE ε4 allele (14). Researchers studying twins concluded that the risk of AD is 60–80% dependent on heritable factors and that on average, mutations of the ε4 allele occurred in

about one-fifth of patients with AD, affecting nearly 65% of all patients (14). In ε4 allele mutation carriers, the risk of developing AD increases threefold (15). In EOAD, it's associated with mutations in APP, PSEN1, and PSEN2, which increase Aβ production in patients (13).

The classification and diagnostic criteria for AD have evolved significantly over time. First, in 1984, the National Institute of Neurological and Communicative Disorders and Stroke, in cooperation with the Alzheimer's Disease and Related Disorders Association, implemented a clinical criterion for AD diagnosis (13). It was divided into three categories:

1. Probable AD: Defined by progressive dementia captured by neuropsychological testing, with patients showing evidence of memory loss, aphasia, apraxia, and agnosia. Patients were required to display these symptoms between the ages of 40 and 90, in the absence of any other disease (13).
2. Possible AD: Applied when other conditions, such as systemic diseases or psychiatric disorders, can contribute to dementia but are not the primary cause of AD (13)
3. Definite AD: Required histopathological confirmation of the disease by performing an autopsy or brain biopsy, revealing AB plaques and NFT's (13)

The National Institute on Aging—Alzheimer's Association revised the diagnostic criteria of AD in 2011 to incorporate recent advances in biomarker research and improve diagnostic accuracy (13). Key updates included:

- Recognizing AD in its initial stages, where biomarkers could help identify the pathology before symptoms even first appear in patients (13).
- Introducing biomarkers into clinical diagnosis and AD research, divided into two categories:
    1. Amyloid biomarkers, including PET and CSF Aβ42 (13).
    2. Neuronal injury markers like CSF tau, FDG-PET for metabolic brain activity, and MRI to scan for brain atrophy (13).

The development of biomarkers has greatly advanced diagnostic approaches for AD. Jack and colleagues introduced the ATN framework, which places biomarkers into three groups: A (amyloid β), T (phosphorylated tau), and N (neurodegeneration) (14). This framework allows

AD to be diagnosed reliably solely on biomarker evidence, emphasizing the presence of amyloid β and phosphorylated tau as defining pathological features of the disease (14). Even without clinical symptoms, the presence of amyloid β is classified as an AD pathological change (14).

AD pathophysiology is primarily thought to be caused by Aβ deposition, tau protein accumulation, neuroinflammation, and deficits of neurotransmitters (15). The amyloid hypothesis states that the accumulation of Aβ drives AD development (13). It's supported by genetic evidence: mutations in APP, PSEN1, and PSEN2 which are linked to familial AD and lead to increased Aβ production (13). In healthy individuals, β-amyloid is a small, water-soluble peptide produced from the cleavage of APP, a glycoprotein located in the cell membranes of neurons (15). This process involves α-secretase, β-secretase, and γ-secretase (15). Disruption of APP cleavage forms toxic oligopeptides 39-43 amino acids long (15). These fragments can aggregate into deposits that can be identified with microscopy (15). The Aβ-42 isoform is neurotoxic and generates ROS which damage the neuronal cells (15). These plaques affect how neurons communicate, trigger neuroinflammation , and cause neurotoxicity (13) In healthy patients, Aβ is efficiently cleared, but in AD, an overproduction of Aβ42 leads to the formation of insoluble extracellular plaques (13).

Tau protein promotes the assembly of tubulin, which further polymerizes to form microtubules (15). In AD, hyperphosphorylation of tau leads to the formation and deposition of NFT's (15). Tau neurotoxicity is caused by the loss of its normal function, which destabilizes microtubules, and the gain of a toxic function, which stimulates apoptosis of neurons (15). Additionally, research shows a strong correlation between β-amyloid accumulation and tau aggregation, as both play complementary roles in AD pathology (15).

As Aβ deposition in the brain occurs, microglia are activated (15). Chronic activation leads to the release of pro-inflammatory cytokines such as IL-1β and TNF-α as well as ROS, further exacerbating damage to the neuronal cells (15). The gene TREM2 influences how the immune system reacts by impairing microglial function (14). Continuous neuroinflammation is a hallmark of AD and plays a major role in its progression (14).

Researchers in the 1970s identified neocortical and presynaptic cholinergic deficits linked to acetyltransferase, which plays a major role in the synthesis of ACh (13). ACh is a key

neurotransmitter that plays a critical role in cognition, such as memory and attention, and this discovery led to scientists developing the cholinergic hypothesis (13). Additionally, β-amyloid is thought to interfere with cholinergic neurotransmission, reducing both choline uptake and the release of ACh (13). Finally, the cholinergic hypothesis suggests that cognitive decline in AD is partly due to the degeneration of acetylcholine-producing neurons in the nucleus basalis of Meynert and that over the course of the disease more than 90% of cholinergic neurons in this part of the brain were damaged (15).

The brain, an organ highly metabolically active and sensitive to hypoxia, consumes approximately 20% more o)gen than other organs, making it particularly vulnerable to reactive ROS and RNS (15). These molecules are highly unstable due to the presence of an unpaired electron. In individuals with AD, oxidative damage to neuronal tissue is frequently observed (15). ROS and RNS interact with neurons, which are rich in polyunsaturated fatty acids, leading to lipid oxidation, disruptions in the redox potential of β-amyloid metal ions, and mitochondrial dysfunction, and it contributes to neuronal apoptosis (15). Oxidative stress-induced lipid oxidation and DNA damage also accelerate neuronal aging and degeneration (15). In AD, mitochondrial dysfunction is closely linked to the failure of protective mechanisms that defend against ROS (15).

2.2 Vascular Dementia

In this section, the concept of VCI and VaD will be introduced. Then important risk factors for the development of this disease will be highlighted before the different classification systems for VCI and VaD are presented. Finally, pathophysiology of this disease and the role a patient workup plays in VaD diagnosis will also be reviewed.

It is estimated that one in three people over the age of 65 will suffer from a stroke, dementia, or both in their lifetimes (16). A Framingham Heart study found that the lifetime risk for developing hypertension was more than 90% (16). It is also estimated that diseases such as hypertension, hypercholesterolemia, diabetes mellitus, and habits such as smoking at midlife are associated with a 20-40% increased lifetime risk of developing VaD (16). Based on growing evidence, it is now theorized that cerebrovascular pathology is the most critical contributor to

dementia and that there are synergistic interactions with other neurodegenerative pathologies such as AD (16).

A study conducted by the Religious Orders Study and Memory and Aging Project identified autopsy samples and found that, while only 9 percent of dementia patients had isolated AD, 40 percent had AD plus some sort of prominent vascular pathology, such as atherosclerosis, or CAA (16). It is hypothesized that cerebrovascular diseases cause VCI, which then leads to vascular brain injury, causing a disruption of the cognitive networks (17).

VCI and VaD cause 20-40% of all dementias (16). The concept of VCI was first introduced in 2006 by the National Institute of Neurological Disorders and Stroke in collaboration with the Canadian Stroke Network (16). Then in 2011, AHA and ASA released a scientific statement expanding the understanding of VCI (16). This statement addressed the full spectrum of VCI, covering all forms of vascular brain injury, whether caused by atherosclerosis, ischemia, haemorrhage, cardioembolism, or genetics (16). It proposed using VCI as a comprehensive term for all cognitive disorders linked to cerebrovascular disease (16). VCI includes a wide range of cognitive impairments, from mild deficits to multifocal impairments and severe vascular dementia that impacts quality of life (16).

The 2011 AHA/ASA statement defined VCI as "a syndrome with evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain." (16). Unlike in AD, memory impairment is not required for a VCI diagnosis, as memory-related structures such as the hippocampus and thalamus can remain unaffected in VCI (16). Recently, the international Vascular Impairment of Cognition Classification Consensus Study (VICCCS-1 and 2) developed a clear framework and standardized diagnostic criteria for VCI and VaD, dividing them into mild and major categories (16). In VICCCS-1, the major VCI category includes four subtypes: PSD, subcortical ischemic vascular dementia, multi-infarct (cortical) dementia, and mixed dementia (16). VICCCS-2 emphasized the importance of neuroimaging markers for VCI, highlighting MRI as the primary diagnostic tool (16).

Timing plays an important role in diagnosing cognitive impairment. After a stroke, cognitive test scores in patients often show big declines, but retesting the patient a few weeks later can reveal improvements (18). As a result, a definitive diagnosis of PSD should be postponed until at least six months after the stroke (18). According to the VICCCS criteria, these cognitive deficits must be present either immediately after or within 6 months of the patient suffering a stroke (16). The two most common causes of VCI are subclinical cerebral white matter lesions and microinfarcts of brain vessels (16).

Contributing modifiable and non-modifiable risk factors such as age, genetics, environment, and lifestyle choices lead to the development of vascular risk factors as well as subclinical arterial and cerebral diseases, resulting in cerebral blood flow and networking dysfunction (16). Other factors such as brain hypoxia and BBB permeability are also thought to affect pathology leading to VCI (16). The regulation of cerebral blood flow is a complex process working to get the brain enough o)gen and nutrients while also quickly adjusting to changes in blood flow dynamics (16). Although the brain makes up only about 2% of the body's weight, it uses roughly 20% of the o)gen and 25% of the glucose, making it highly energy-demanding compared to other organs (16). However, the brain has very limited energy reserves, making it dependent on a constant supply of blood to meet its metabolic needs (16). Cerebral blood flow regulation is vital to maintaining a steady supply of energy, keeping blood flow and intracranial pressure stable, and protecting the brain's delicate microvascular system from damage caused by high-pressure blood flow from larger vessels (16). Studies in animals have shown that a long-term decrease in blood brain flow can lead to brain atrophy, damage to white matter, small lacunar strokes, bleeding, memory problems, and even contribute to the development of AD (16).

When assessing VCI and dementia, a detailed physical exam can help identify important signs of cardiovascular risk (17). An eye exam may show signs of hypertensive retinopathy; examination of the legs might reveal skin changes from peripheral vascular disease or swelling caused by heart failure (17). Additionally, auscultation of the heart and lung exams can detect irregular heart rhythms like atrial fibrillation, a whooshing sound in the neck termed carotid bruit from plaque buildup in large arteries, or lung crackles caused by fluid buildup from heart failure (17). Lastly, tests can reveal neurologic focal signs as well as gait disturbances (17). Vascular brain

injury shows a wide variety of effects, but certain patterns can be identified (17). For instance, fluent and nonfluent aphasia are linked to strokes in the area supplied by the left middle cerebral artery (17). Problems with executive function are often connected to small, deep brain lacunar infarcts and widespread damage to the white matter (17). VCI can present in more stepwise degradation, such as in PSD and multi-infarct stroke, or patients can present with a slower progressive decline with intact memory, which is usually caused by subcortical ischemic vascular disease (17).

2.3 Lewy Body Diseases

In this chapter, LBD and its subtypes, DLB and PDD, will be introduced and explained. This subsection will contrast important definitions, symptoms and core features that patients exhibit with these diseases. Finally, the pathophysiology of LBD subtypes will be touched upon as well.

Lewy body diseases are a form of synucleinopathies, which include neurodegenerative diseases such as LBD and PD (19). LBD is a broad term for both DLB and PDD (20). Synucleinopathies can be defined as pathological aggregates of neural and glial α-synuclein in the form of Lewy bodies, Lewy neurites, and cytoplasmic inclusions in both neurons and glial cells (19). Lewy body dementias are the second most common type of neurodegenerative dementia in patients over the age of 65 (21). On autopsy, 10-15 percent of dementia subjects exhibit Lewy body pathology, while in PD, up to 80% of patients will eventually develop dementia (22).

The timing of the onset of dementia is the main differentiating point between the DLB and PDD. In DLB, although not all patients will have parkinsonism, dementia occurs either before or concurrently with Parkinson's-like symptoms or within a one-year time frame after the onset of motor deficits (21). For PDD, the onset of dementia is more than one year after the diagnosis of PD was established (21). DLB is frequently preceded by MCI-Lewy Body and a prodromal period in which autonomic symptoms and sleep disorders may appear (20).

In all types of synucleinopathies, the buildup of α-synuclein in Lewy bodies and the associated loss of dopamine-producing neurons in the substantia nigra pars compacta contribute to both motor and non-motor symptoms (19). The cardinal motor symptoms of patients with PD include

bradykinesia, tremors, muscle stiffness, as well as postural instability and balance problems (19). The tremor is usually seen unilaterally at rest in the leg, chin, or lips (19). The patients struggle with their posture and struggle with going from a static state such as standing or sitting to moving (19). Patients with Lewy body dementias also tend to show profound cholinergic deficits, which are even more apparent than those observed in AD (22).

The central features of DLB include progressive dementia, which severely interferes with daily activities, and patients showing clear deficits in tests for attention, executive functioning, and visuospatial ability, the latter being prominent (21). Core features for DLB include fluctuation in cognition, recurrent visual hallucinations, and spontaneous parkinsonism (21). Some more suggestive features of DLB include rapid eye movement sleep behavior disorders, patient hypersensitivity to antipsychotics, and showing low dopamine transporter uptake in the basal ganglia on neuroimaging (21). For PDD, the diagnosis of PD should be made according to the Queen Square Brain Bank Criteria (21).

While many of the core and suggestive features between DLB and PDD overlap, patients with PDD should show cognitive impairment in at least two domains: attention, executive function, visuospatial function, or free recall (21). There are clear challenges to the diagnosis of DLB. DLB is routinely misdiagnosed as AD, and one in three cases are missed (20). Clinicians should focus on obtaining a comprehensive history in order not to miss DLB (20). For example, asking the patient about problems sleeping could lead to finding out the patient suffers from REM sleep disorders, or if there is uncertainty, polysomnography can confirm such disorders, which would strengthen DLB diagnosis (20). Additionally, a physical examination, neuropsychological testing, and imaging are required to make the diagnosis of DLB (20).

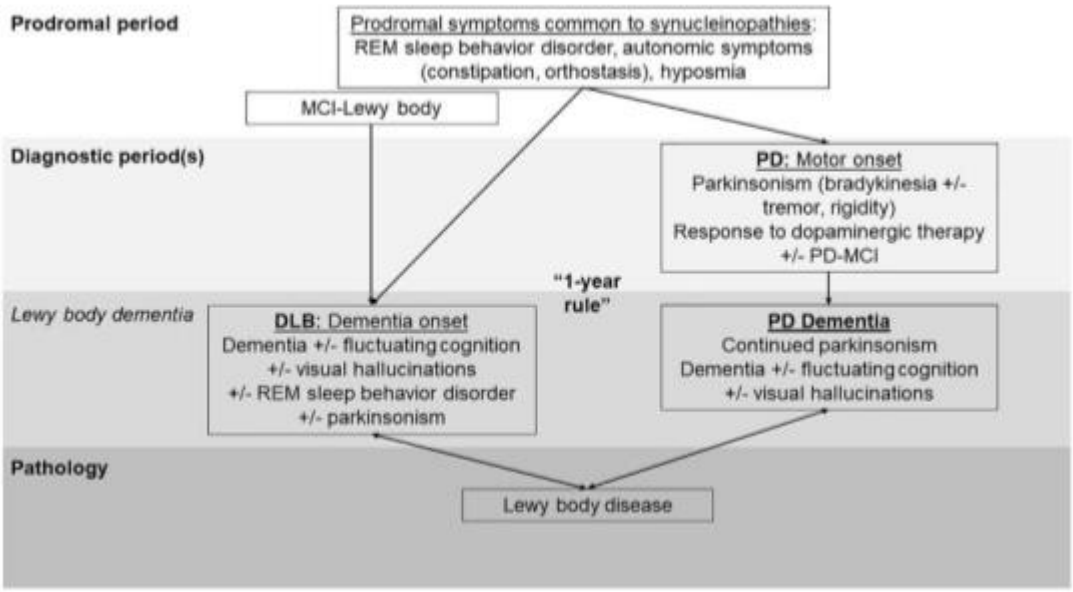

Diagram: A look at how LBD subtypes progress from the prodromal period to highlighting patients' symptoms (20)

2.4 Frontotemporal Dementia

This section will begin by introducing FTD and going over its subtypes. Then the epidemiology of this disease, its genetics and prognosis will be reviewed. Lastly, in great detail the core features and symptoms of each subtype of FTD will be explained.

In 1892, Czech neurologist Arnold Pick provided the earliest documented description of a patient exhibiting symptoms consistent with FTD (23). He described a case of progressive language deterioration linked to left temporal lobe atrophy, a condition that today would be classified as svPPA (23). Frontotemporal lobar degeneration refers to a group of pathological changes occurring in the brain's frontal and temporal lobe regions (24). One of the most prominent disorders within this group is FTD, a progressive neurodegenerative disease primarily characterized by changes in behavior, language, and executive functions (24). FTD encompasses various clinical subtypes, including bvFTD, svPPA, nfvPP, and rtvFTD (24). Among purely neurodegenerative forms, FTD is the most common cause of cognitive decline in individuals under the age of 65, with the typical age of onset for FTD beginning around the fifth decade of life (24). Research shows that 10% of FTD cases occur in patients younger than 45 years, and

roughly 30% occur in patients older than 65 (25). The most common subtype is bvFTD, accounting for almost 70% of all FTD cases (25).

FTD tends to progress more rapidly than AD, leading patients dying at younger ages (24) The survival period varies significantly depending on the subtype, ranging from around 3 years for patients with FTD-MND to over 12 years for those with svPPA (24). Genetics are involved in about 30–50% of FTD cases, with autosomal dominant inheritance being the most common inheritance pattern (23). Several gene mutations have been identified as contributors to FTD, including C9orf72, which is often linked to psychosis and is primarily associated with bvFTD and FTD-MND (24). Other key genetic factors include mutations in the MAPT, GRN, and VCP1 genes (24). MAPT mutations are linked to familial parkinsonism with FTD, while GRN mutations are closely associated with bvFTD and nfvPPA (24).

BvFTD typically presents with a gradual onset and progressive changes in behavior, often beginning around the late 40s (24). In younger individuals, FTD is often initially misdiagnosed as a psychiatric disorder, such as schizophrenia, bipolar disorder, or major depression, due to overlapping early symptoms (24). Diagnosis generally requires the presence of at least three out of six key symptoms: disinhibition, apathy, loss of empathy, altered eating habits, stereotyped behaviors, and impaired executive functioning (24). Patients who present with symptoms consistent with bvFTD but with normal brain imaging are classified as having possible bvFTD (25). Patients who meet at least 3 out of 6 required symptoms associated with showing focal atrophy, hypometabolism, or hypoperfusion in the frontal or temporal lobes on brain scans are classified as having probable bvFTD (25).

The hallmark behavioral symptoms of bvFTD are closely linked to dysfunction in key paralimbic brain regions, such as the medial and orbital frontal lobes, anterior cingulate cortex, and frontoinsular cortex (23). Right hemisphere atrophy, in particular, has been strongly associated with significant behavioral changes, including impulsivity and poor decision-making (23). Disinhibition is characterized by inappropriate actions, such as using offensive language, impulsive behavior, or violating social norms (23). Affected individuals may display behaviors such as oversharing personal information, acting childishly, using sexually inappropriate terms, or showing aggression (24). They may also engage in behaviors like gambling, theft, or reckless

decisions without concern for consequences (24). Studies indicate that 37% to 54% of bvFTD patients exhibit new criminal behaviors as part of their symptom profile (23). This loss of behavioral control is attributed to degeneration of the right orbital frontal cortex, which is specifically tied to disinhibition (23). Apathy, another key feature of bvFTD, has been linked to atrophy in the medial prefrontal lobes and anterior cingulate cortex (23). This condition can be misinterpreted as depression but is distinguished by its sudden onset and absence of mood-related symptoms and is typically not associated with suicidal ideation (24). Affected individuals may display a lack of motivation, reduced social engagement, and diminished interest in previously meaningful activities.

Cognitive deficits in bvFTD include problems with attention, planning, flexibility, problem-solving, and verbal fluency (24). Individuals with C9orf72-related mutations often experience early psychotic symptoms, such as hallucinations, bizarre delusions, and occasionally Diogenes syndrome, which involves neglect of personal hygiene and self-care (24). Patients also often struggle with recognizing emotions and empathizing with others, interpreting social cues, and making moral or social judgments (24). They may have difficulty understanding sarcasm or grasping the potential consequences of their actions, leading to socially inappropriate behavior mentioned previously (24). Clinical evaluations often reveal impulsive or apathetic behaviors, poor personal hygiene, lack of self-awareness, and environmental dependency, where patients frequently manipulate nearby objects (24). These findings contribute to the overall diagnosis and help distinguish bvFTD from other neurodegenerative conditions.

In svPPA, atrophy of the brain cortex typically begins asymmetrically, affecting either the left or right anterior temporal lobe (24). Approximately 70% of the left anterior temporal lobe is affected during the early stages of the disease (24). SvPPA is the least likely out of all FTD subtypes to exhibit a familial or genetic cause (23). When the left anterior temporal lobe is primarily affected, patients experience significant language impairments (24). Although their speech remains fluent, it often lacks meaningful content and is filled with semantic paraphasia; patients use more words than needed to get their point across, termed circumlocutions, and they exhibit difficulty recalling phrases, a condition known as anomie (24). As the condition progresses, patients lose the ability to understand word meanings, initially struggling with less commonly used words before eventually encountering difficulties with more familiar terms (24).

Despite these semantic deficits, their verbal fluency, grammar, and syntax generally remain intact (24). In cases where the right anterior temporal lobe is affected, patients tend to exhibit behavioral symptoms like those seen in bvFTD (24). Additionally, right-lobe dysfunction often leads to an impaired ability to interpret and respond to others' emotions, largely due to the right amygdala, a brain region critical for emotional processing, being affected (24).

Nearly 25% of FTD patients have the nfvPPA clinical subtype (24). The primary feature of nfvPPA is progressively impaired speech, characterized by nonfluency, labored speech, and frequent hesitations (24). Patients also show reduced speech output, shorter sentence lengths, and frequent phonemic errors (24). Grammatical errors are also common in spontaneous speech, such as making mistakes in verb tense selection and omitting prepositions when talking (24). The neuroanatomical regions that correlate with the symptoms of nfvPPA are Broca's area, which matches Brodmann's areas 44 and 45, located in the left inferior frontal gyrus and the anterior insula (23). Two key symptoms distinguish this condition: agrammatism, which is difficulty forming grammatically correct sentences, and apraxia of speech, which is difficulty planning and coordinating the motor movements necessary for speech (24).

2.5 RPD's

In this chapter, the definition of RPD will be introduced and some of its most common causes will be explained. Then primary and secondary RPD will be discussed. Finally, patient's symptoms and work up of RPD will be highlighted as well.

RPD progresses over one to two years, occasionally more rapidly, as observed in metabolic encephalopathies or encephalitis, which may induce cognitive impairment within weeks (12). Historically, RPD has been closely linked to CJD (12). Certain causes of RPD are possibly reversible, rendering precise and prompt diagnosis imperative (12).

The progression of RPD can generally be categorized as either primary or secondary (12). Primary RPD results from diseases that directly affect neurons (12). In secondary RPD, a pre-existing, gradually advancing CNS disorder is exacerbated by additional variables including seizures, cerebrovascular disease, or the coexistence of numerous overlapping neurological conditions (12).

Patients with sCJD deteriorate quickly and present with neurological findings like ataxia, myoclonus, and vision deficits (12). Pathologically, sCJD is marked by abnormal prion protein aggregates, spongiform brain changes, neuronal damage, and gliosis (12). Distinct subtypes of sCJD have been linked to variations in prion protein structure (12). The predominant subtype of CJD, MM1/MV1, accounts for approximately 65% of cases (12). This subtype is lethal, advancing rapidly and resulting in mortality within four to five months (12). The VV2 subtype constitutes perhaps 15–20% of cases (12). The MV2 variant, comprising roughly 10% of patients, is marked by a prolonged disease duration and presents a range of symptoms, at times resembling other neurodegenerative conditions such as α-synucleinopathies (12).

In immune-mediated encephalitis, antibodies can target neuronal proteins, ion channels, or receptors, with certain cases linked to underlying malignancies (12). Metabolic and toxic encephalopathies are supplementary factors in RPD, representing 6–16% of patients (12). Alcohol-related dementia accounts for up to 10% of early-onset dementia cases (12).

In clinical settings, it's essential to differentiate RPD from delirium during the initial patient assessment (12). Acute cognitive deterioration occurring within minutes to hours suggests acute conditions such as stroke or seizures, while certain inflammatory CNS disorders and metabolic encephalopathies usually develop over days (12). Prion diseases usually present with progressive dementia weeks to months after the first symptoms appear, and other RPDs may emerge over a longer period (12). The patient's age at symptom onset is an important factor, as prion diseases typically occur between ages 60 and 69 (12). Lastly, certain clinical signs may provide diagnostic clues for clinicians, such as stimulus-sensitive myoclonus in CJD (12).

3. Literature Review of Biomarkers

The primary sources for this literature review section were accessed on PubMed, covering the period range from 2013 to 2025. This chapter will start by providing an overview of biomarkers. Next, some common tests that clinicians can do with patients, like the MMSE and MoCA will be reviewed. Then, the use of neuroimaging markers, such as MRI and radionucleotide imaging, will be explored in the context of the diagnosis and differentiation of dementia subtypes. Lastly, the general biomarkers of dementia such as GFAP and NFL that can be used to screen patients for dementia, will be highlighted.

Biomarkers are measurable biological indicators that provide critical insights into the underlying mechanisms of diseases, enabling earlier and more accurate diagnoses, monitoring of disease progression, and evaluation of treatment responses. In the context of dementia, biomarkers play a vital role in differentiating between the various subtypes, such as AD, VaD, FTD, PDD, DLB, and RPD, which often present with overlapping clinical symptoms. In the following section, general biomarkers and neurophysiological tests will be discussed for dementia.

The establishment of a cognitive impairment and dementia diagnosis starts with the first patient-clinician interaction. A clinician can assess for signs of cognitive decline by observing the patient, asking relatives questions, and conducting an array of neurophysiological tests. The MMSE, MoCA, Mini-Cog, CDT, and the AD8 dementia screening interview are commonly used in primary care settings to assess cognitive decline in patients (26). Many consensus groups have advocated for routine screening of at-risk populations such as people older than 65 (26). These advocates argue that dementia fulfills the WHO disease screening criteria (26). They point to the fact that the negative outcomes, such as missed or delayed diagnoses, can lead to a loss of treatment opportunities and can increase the disease burden on patients and their caretakers (26).

The MMSE is an easy-to-administer, quick screening tool that allows clinicians to test various cognitive domains such as orientation, recall, attention, arithmetic, language, and constructional praxis (27). Unfortunately, the test is not very sensitive for dementia diagnosis, as scores may be influenced by different factors, including age, education, language barriers, and any motor and visual deficits (27). The MMSE also possesses a limited ability to assess progressive cognitive decline patients over time (27). The MoCA has become the most popular test to screen for cognitive impairment and dementia in older patients(27). When compared to the MMSE, it's more sensitive for detection of MCI and tests for a wider range of cognitive domains such as memory, language, attention, visuospatial, and executive functions (27). Studies have also shown that MoCA has a stronger diagnostic reliability for MCI, as its AUC was 0.846 while that of the MMSE was 0.736 (28). To facilitate screening in busy clinical settings, a few abbreviated versions of the MoCA have been validated, including the MoCA 5-min protocol, which is feasible for telephone administration (27).

The Mini-Cog is an easy to administer quick test that is highly sensitive test for predicting dementia status, and its benefits are that results are not influenced by the patient's educational status or language comprehension (27). The test consists of two parts, the first is a three-item recall test for memory, and the second is a clock drawing test (27). The results of the clock drawing test are considered normal if all numbers are drawn in the correct order and the hands display the correct time in a readable way (27).

Like the Mini-Cog, the CDT requires the patient to draw a clock from memory with the hands indicating a specific time (26). Although simple to administer, this test requires the patient to possess a strong base of knowledge of all cognitive functions involved in the execution of the test, such as semantic memory processing, on top of evaluating constructional and visuo-spatial skills (26).

Lastly, the AD8 Dementia Screening Interview is a useful screening tool that can be administered by a nurse and consists of an eight-item questionnaire addressed to the patient's loved one or caretaker to detect dementia and cognitive impairment (27). The questionnaire asks the patient's loved one or caretaker if they have noticed any increase or worsening in eight domains or behaviors (27). A positive response to two or more questions has shown a sensitivity of 93% and a specificity of 46% (27).

Neuroimaging techniques play an invaluable role in diagnosing dementia and are now included in updated diagnostic criteria for the various dementia subtypes (29). For example, brain MRI scans are the primary neuroimaging method recommended by the imaging guidelines for dementia, as outlined by the American Academy of Neurology, the National Institute on Aging, and the American College of Radiology (30).

The two primary neuroimaging techniques most utilized as biomarkers for neurodegeneration and dementia are MRI and radionucleotide imaging, which includes SPECT and PET (31). Among these, structural MRI is the most frequently used method for studying anatomical changes and neurodegeneration in living patients (31). It enables the assessment of both

widespread and localized brain atrophy (31). Software tools can also assess structural changes by examining the volumetric changes in the brain seen on MRI (30). Additionally, more advanced MRI techniques, such as DWI, diffusion DTI, MRS, and perfusion imaging, are often employed in dementia research settings (31). Cerebral perfusion, a crucial factor in neurodegeneration and dementia research, can be measured using MRI-based methods such as dynamic susceptibility contrast-enhanced MRI or ASL),as well as with SPECT or PET imaging (31). MRI is also employed to evaluate brain function (31). Functional MRI assesses brain activity during cognitive, sensory, or motor tasks and at rest by analyzing blood flow and o)gen levels in the blood (31).

SPECT and PET imaging employ radiolabeled tracers to examine cerebral perfusion, metabolism, and chemical processes in living subjects (31). SPECT is primarily used to assess blood flow in the brain (31). PET, on the other hand, utilizes a range of tracers for various purposes, including (1) FDG to measure glucose metabolism in the brain; (2) tracers for detecting protein deposits, particularly amyloid accumulation, such as PiB and [18F]florbetapir; (3) tracers that target neurotransmitters such as dopamine, serotonin, and ACh; and (4) tracers that assess microglial activation, such as [11C]PK11195, for example (31).

While in subsequent sections, specific biomarkers crucial for the differential diagnosis of different subtypes of dementia will be covered, there are certain fluid-based biomarkers that may help clinicians in screening for and diagnosing MCI. Testing positive for such biomarkers could then warrant closer patient monitoring and additional testing with other more specific biomarkers. For example, GFAP and NFL are biomarkers that are sensitive for neuroinflammation and neuronal damage, pathophysiological mechanisms that play a critical role in cognitive decline (32). A major study consisting of almost 50,000 participants in the UK revealed that peripheral GFAP and NFL levels increased up to 15 years in patients before the diagnosis of dementia was established (32). Additionally, worsened numeric memory and prolonged reaction time were found to correlate with the incremental increases of NFL levels (32). Furthermore, a greater annual rate of change in peripheral GFAP level was strongly correlated with a rapid global cognitive decline in patients (32). Researchers also found that increase of GFAP with a hazard ratio ranging from 2.25 to 3.15 and that of NFL ranging from

1.98 to 4.23, increased the risk for all subtypes of dementia (32). Lastly, it was concluded that GFAP and NFL significantly improved the predictive values for dementia, showing that the AUC ranged from 0.80 to 0.89, making both biomarkers strong contenders as potential tests for dementia (32).

3.1 Biomarkers for AD

This chapter on AD biomarkers will start by introducing CSF biomarkers like β42, Aβ40, and the Aβ42/Aβ40 ratio, t-tau, and phosphorylated tau. Next, biomarkers like NFL, GFAP, SNAP-25, CSF YKL-40, FABP3 and their measurement in CSF will also be discussed. Then, it will shift to focus to neuroimaging and reviewing MR techniques such as serial MRI and DTI among other and how they can help diagnose and differentiate typical and atypical AD from each other and other dementias. Additionally, Aβ and FDG PET and what findings we might see in AD patients will be highlighted. Lastly BBMs and challenges that arise with blood biomarkers in AD will be discussed as well as their potential and clinical uses.

CSF and neuroimaging currently play a critical role in diagnosing AD. Recently, researchers have been searching for plasma and fluid as well as other non-invasive, cheaper biomarkers that could help screen, diagnose, track, and monitor disease progression and which could help with developing and validating anti-AD therapies. Historically, CSF biomarkers have been more effective than blood or plasma biomarkers for AD diagnosis because of the brain's interstitial fluid and its direct access to CSF as well as the fact that the blood-CSF barrier limits the transport of proteins into the peripheral fluids (33). As a result, this makes CSF analysis a valuable tool for detecting neurodegenerative disease markers in living patients (33).

3.1.1 AD CSF biomarkers

The CSF biomarkers currently measured clinically are Aβ42, Aβ40, and the Aβ42/Aβ40 ratio, t-tau, and phosphorylated tau isoforms (34). In AD, both tau and p-tau are released into the extracellular space, resulting in elevated CSF tau levels (33). Aβ plaques start to form often a decade before the onset of symptoms, making CSF Aβ-42 an important early diagnostic marker (33). In contrast, CSF tau biomarkers appear later in the disease process and correlate strongly with cognitive decline (33). Additionally, CSF t-tau and p-tau are strongly associated with a

rapid clinical disease deterioration (35). Patients with higher levels possess an increased risk of hospitalization and death (36). Lastly, increased tau protein levels in patients with AD correlate with significant brain atrophy, particularly in the hippocampus (36).

The core CSF biomarkers of Aβ42, t-tau and P-tau181 have been validated in the revised AD diagnostic criteria (33) (37). Identifying abnormalities in these biomarker levels can help detect AD before patients display cognitive impairment (33). Normal levels of all three biomarkers effectively rule out AD, while intermediate levels require further monitoring (33). As the disease progresses, Aβ42 concentrations decrease in AD patients, whereas P-tau181 and T-tau levels rise compared to HC's (33). The combined measurement of Aβ1-42, T-tau, and P-tau181 provides the most reliable means of distinguishing AD from cognitively healthy individuals (33).

Decreased levels of CSF Aβ42 have been validated in a meta-analysis as a reliable biomarker for AD diagnosis (35). Aside from Aβ42, Aβ40 is the most abundant Aβ marker in CSF found at concentrations approximately ten times higher than Aβ42 (35). In 1998, an initial study demonstrated that combining Aβ42 and Aβ40 analysis enhanced the diagnostic accuracy of AD (35). Additional research found that while CSF Aβ40 shows no significant rates of change in AD, the CSF Aβ42/Aβ40 ratio outperforms Aβ42 alone in identifying AD (35). Recent findings also suggest that the Aβ42/Aβ40 ratio aligns more closely with amyloid PET positivity and holds significant diagnostic value in clinical practice (35). Aβ42/40 also reliably distinguishes AD from PDD and DLB compared to stand-alone testing of CSF Aβ42 and Aβ40 (38).

Complementary biomarkers such as NFL, GFAP, and SNAP-25 can also be measured in CSF (34). The combination of CSF p-tau 181, NFL, and GFAP strongly correlates with disease progression and worsening in AD patients (34). SNAP-25 is a biomarker of synaptic transmission and neurotransmitter release and is highly specific for AD in the early stages of the disease (34). Meanwhile, when Ng, a biomarker measuring synaptic dysfunction in the brain, is combined with CSF biomarkers Aβ42/40, pTau181, t-Tau, and SNAP-25, it could help differentiate EOAD from HCs and other early onset dementias (39).

An increase in p-tau is very specific to the typical and atypical variants of AD (40). In patients with an atypical presentation of the disease, a decreased CSF Aβ42/40 ratio is indicative of atypical AD, even when other test results are deemed inconclusive (40). Lastly, CSF levels of Ng, SNAP-25 and synaptotagmin-1, as well as NFL increase in atypical forms of AD (41).

Many FTD patients share clinical symptoms that AD patients may also present with, making biomarkers critical to differentiate between the two diseases (42). An analysis of CSF biomarkers for differential diagnosis of FTD and AD found that the p-tau/Aß42 ratio reached acceptable levels of sensitivity and specificity to differentiate AD from PPA (42). Other CSF biomarkers couldn't differentiate AD from the bvFTD (42). In the FTD-phenotype of AD, the p-tau181/Aβ42 ratio is useful for differentiating AD from FTD (41). For the distinction of AD from DLB, studies show that P-tau181 and P-tau 231 concentrations are significantly higher in the CSF of AD patients compared to DLB patients (43).

A Lithuanian study from 2021, investigated CSF YKL-40, a lectin which is expressed in neuroinflammatory conditions and is involved in ECM remodelling, as potential biomarker for MCI and AD (44). The researchers found that increased YKL-40 levels in the CSF of AD patients correlated strongly with neuroinflammation and microglia in the pathophysiology of AD (44). The study concluded that YKL-40 levels can be used together with other biomarkers for the prognosis of MCI and its likelihood of progressing to AD (44).

Inclusion bodies composed of α-syn are key pathological markers in PD and DLB that can also be found in specific areas like the amygdala in AD patients (45). FABP3, a small cytosolic protein playing a role in regulating membrane lipid composition in the brain, has been shown to influence the formation of synapses and the function of cholinergic and glutamatergic neurons (45). A study of 200 patients in Europe found that FABP3 levels were significantly increased in AD and DLB patients compared to those with PD and other neurodegenerative conditions (45). Additionally, the study reported that CSF t-tau, p-tau, and α-syn levels were notably higher in AD patients than in those with PDD, DLB, PD, and OND (45). Lastly, researchers concluded that a combination of FABP3 and p-tau demonstrated higher sensitivity in differentiating AD

from DLB with an AUC 0.92, while a combination of p-tau, FABP3, and α-syn strongly differentiated AD from PDD with an AUC of 0.96 (45).

3.1.2 Neuroimaging in AD

Neuroimaging biomarkers used for AD diagnosis are MR, amyloid PET, and FDG-PET. Structural MRI in AD shows atrophy of the grey matter as well as volume loss indicative of neurodegeneration (40). Structural MR imaging plays a major role in differentiating between AD and non-AD dementias while estimating preclinical or prognostic tissue damage in vulnerable regions of the brain, such as the hippocampus and entorhinal cortex (46). Structural MR imaging also helps exclude non-AD causes such meningioma, glioma, subdural hematoma, vascular malformation, and normal pressure hydrocephalus (46). Distinct patterns of cortical atrophy and vascular pathology on MRI can distinguish AD from other neurodegenerative dementias, including FTD, CBD, PSP, and vascular dementia (46).

Serial structural MRI imaging is used to track AD disease progression (40). Other techniques, like DTI, can assess white matter damage in the brain, while resting- state functional MRI can assess changes in functional brain connectivity (40). T2-weighted or susceptibility-weighted MRI is used to assess vascular activity and identify CAA in patients (40). On structural MRI, atrophy in AD begins in the medial temporal lobe and then further progresses to the lateral-temporal and parietal cortices (40).

Motor-sensory cortices are relatively spared from AD (31). MCI patients display intermediate atrophy between that of AD patients and HC, further supporting MCI as an intermediate clinical stage between healthy aging and AD (31). In predicting MCI to AD progression, MRI measures of volume, morphometry, and rates of brain atrophy alongside with significantly reduced hippocampal and entorhinal cortex volumes and reduced cortical thickness in the medial and lateral temporal cortex, parietal lobes, and frontal lobes are critical for detecting AD (49). Changes in these indices appear in probable AD (MCI-converters), up to 2 years prior to clinical conversion to AD (31). Patients with AD lose about 4.5 % of their hippocampal volume

annually; MCI patients have an annual rate of hippocampal loss of 3%, while HCs only show 1% loss per year (31). Another recognized feature of AD is also the atrophy of the amygdala (47).

In atypical forms of AD, atrophy is usually most prominent in regions corresponding to the clinical phenotype and often spares the hippocampus early in the disease process (40). Neuroimaging studies in familial AD patients, such as those with APP, PS1, or PS2 mutations, show greater brain atrophy, faster longitudinal atrophy rates, and white matter abnormalities when measured using DTI (31). Neuroimaging in PCA patients demonstrates significant atrophy in posterior brain regions, such as the posterior temporal, parietal, and occipital lobes (49).

Changes on MRI imaging correlate to those in FDG-PET, but usually appear later in the disease process (40). Using 7T MRI scanners, with "T" referring to the strength of the magnetic field, offers a possible alternate approach to discovering more sensitive imaging biomarkers (48). This increased imaging power offered by 7 T MRI scanners allows for better resolution of small structures in the brain, including subfields of the hippocampus (48). Analysis of the hippocampus suggests that the pre-subiculum is the earliest subfield to be involved in AD, with it experiencing the greatest atrophy (48).

Aβ and tau PET imaging can serve as an important tool in clinical trials due to its ability to detect regional changes in vivo preceding significant atrophy in different regions of the brain (49). A study looking at the amyloid PET on the management of patients with dementia or MCI of uncertain cause, called Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) found that physicians change medical prescriptions or treatment recommendations for 67.8% of MCI patients and 65.9% of people with dementia in response to PET data (50). A study of 60 participants from Argentina found that 83% of those with AD type were amyloid positive using (11-C-PIB) compared to only 14% of controls, whilst a similar report from Brazil found that 74% of AD patients had positive PIB–PET scans compared to 21% of controls (51).

In autopsy-proven AD pathology, PET correctly identifies the presence or absence of AD in 88% of cases, displaying a sensitivity of 94% and a specificity of 73% (52) Amyloid PET is the most extensively validated biomarker for the identification of amyloid plaques in the brain,

demonstrating 92% and 100% sensitivity and specificity, respectively (40). Tau PET, which identifies neurofibrillary tangles, is predominantly used in research (40). Compared to amyloid PET, tau PET can predict cognitive decline in HCs with no visible cognitive deficits and is instrumental in predicting cognitive decline in a 3-to-5-year span in such patients (40).
In contrast to amyloid PET, tau PET is also a topographic technique and displays deposition patterns that are more reflective of the clinical phenotype of patients (40). Tau PET ligand binding in AD is greater in occipital regions in PCA, left frontal regions in logopenic aphasia, and medial temporal regions in patients with typical AD (40). Tau PET patterns differ between typical and atypical AD (40). Other types of PET biomarkers currently under investigation for AD include synaptic vesicle glycoprotein 2A PET, which measures synaptic density, and translocator protein PET for neuroinflammation (40).

[11C] PiB studies show that 96% of AD patients displayed significant amyloid accumulation in the brain compared to two-thirds of patients with MCI, who showed significant amyloid accumulation (31). In addition, MCI patients with large amyloid accumulation are significantly more likely to convert to AD (31). Thus, so far researchers believe that amyloid deposition in the brain occurs early in the disease process, and by the time patients display sufficient cognitive decline to establish a diagnosis of AD, brain amyloid burden stabilizes, and there is minimal increase in deposition thereafter (31).

Using PET techniques with tracers specific for acetylcholinesterase to measure ACh synaptic density shows substantial reductions in binding in the temporal lobe in AD and MCI patients (31). In AD patients, 11C -PIB shows increased cortical uptake with the highest retention being seen in the frontal, cingulated, precuneus, striatum, parietal and lateral temporal cortex (47). Although amyloid PET is useful at detecting MCI, abnormal tracer uptake is found in up to 30 % of cognitively normal elderly subjects (47). Amyloid PET is therefore highly sensitive for AD diagnosis but not very specific (47).

In FDG-PET, patterns of regional hypometabolism reflect cognitive deficits in various AD subtypes (40). AD patients usually have bilateral hypometabolism in regions of the brain, such as the parietal and medial temporal regions and the precuneus (40). Numerous studies over many

years have all found a constant reduction in brain glucose metabolism in the precuneus, posterior cingulate, parietal, and temporal cortex in clinically affected patients (53). Similarly, glucose hypometabolism extends to the frontal cortex and the entire brain as the disease worsens in patients (53). Glucose metabolism is usually unaffected in the primary motor sensory cortices, primary visual cortices, striatum, thalamus, and cerebellar hemispheres (53). FDG-PET also detects patterns of hypometabolism specific to non-AD dementias, helping in the differential diagnosis with DLB and FTD (40). Although FDG-PET provides greater diagnostic information than MRI, it is not as widely used in clinical settings yet (40).

A comprehensive meta-analysis found that amyloid PET plays an important diagnostic role in relatively young, demented patients since amyloid positivity dramatically increases with age, such as in healthy patients over the age of 70 and in non-AD dementia (54). In logopenic aphasia, SPECT and FDG PET studies showed reduced perfusion and brain metabolism in the left temporoparietal lobe in these patients (31) Using [18F]florbetapir, patients with AD showed increased amyloid retention in the frontal, temporal, occipital, parietal, cingulate, and precuneus cortical areas compared to HC's (47). If clinicians suspect AD but atrophy on imaging isn't found, it has been suggested that FDG-PET plays an important role in the diagnosis of AD (29).

In vivo imaging of dementia-related pathology using PET radioligands offers several advantages (55). First, a preclinical detection of the disease can be observed by examining early molecular changes (55). In addition, succeeding in differentiating between AD and other neurodegenerative disorders can be achieved by refining the focus on characteristic neuropathological mechanisms (55).

3.1.3 Blood based biomarkers for AD

BBMs have a major potential to revolutionize dementia diagnosis and improve the design of clinical trials (51) . The major challenge in implementing BBM's in AD diagnosis is that brain Aβ and tau exist in very low concentrations in the blood due to dilution and degradation (50).) In contrast to well-established CSF and PET biomarkers, BBMs offer a less invasive, more accessible, and cost-effective option in clinical settings. P-tau, Aβ 42/Aβ40, NFL, and GFAP

have been identified as the most promising BBMs (51). The shift from CSF to plasma will greatly enhance AD diagnostics in disease monitoring and response to treatment.

Using the Spearman correlation analysis to test whether levels of proteins increase or decrease consistently from the early stages of AD, researchers found that four proteins—NFL, p-tau181, GFAP, and p-tau231—showed a strong link with disease progression (34). These changes were seen in both CSF and blood plasma (34). Among them, NFL had the strongest correlation, meaning it was the most closely linked to disease worsening (34). Researchers also found that GFAP, NFL, and p-tau181 were the top three biomarkers for tracking disease progression in AD (34). In plasma, it was observed that the best biomarkers for early AD detection were Aβ42/40, p-tau231, and GFAP (34). According to an ROC analysis, GFAP performance was better in plasma than in CSF (34). Plasma GFAP enabled the distinction between HCs and each of the AD groups (34). Serum GFAP is also associated with the rate of cognitive decline in the domains of memory, attention, and executive functioning (56). These results highlight that CSF assays to plasma don't translate equally, since some of the measured biomarkers had a lower AD specificity in plasma, such as total tau and NFL (34).

In CSF, Aβ42/40, p-tau181, p-tau231, and GFAP are AD-specific biomarkers, while in plasma, they're less specific for AD and overlap with FTD (34). Aβ42/Aβ40, GFAP, and p-tau231 in plasma showed the biggest rate of change at the transition point for each of the three A/T/N categories (34). The two plasma biomarkers that detect the earliest Aβ changes are the Aβ42/Aβ40 ratio (57) and p-tau231 (58).

Using the SIMOA technique, four studies have confirmed that plasma p-tau231 can accurately identify AD patients and distinguish them from older adults without amyloid-β, achieving high accuracy with an AUC between 0.92–0.94 (59). SIMOA also successfully differentiated AD patients from those with non-AD neurodegenerative disorders (AUC = 0.93) (59). Additionally, plasma p-tau231 successfully distinguished individuals across all Braak stages of AD, including early stages (Braak 0 to Braak I–II), a distinction that plasma p-tau181 did not demonstrate (59).

In familial AD, plasma p-tau levels start increasing in individuals long before they show symptoms, sometimes over a decade before cognitive decline begins (60). In patients with APP and PSEN1 mutations, plasma p-tau181 and p-tau217 were elevated in both those who already had symptoms and those who were still symptom-free, compared to individuals without these mutations (60). Notably, plasma p-tau217 levels began increasing nearly 20 years before the expected onset of MCI, while p-tau181 levels increased about 16 years before cognitive symptoms appeared (60). Differentiating AD from DLB can be challenging because up to 50% of DLB patients also have AD-related changes in their brains. However, plasma p-tau181 successfully distinguished AD from DLB in autopsy-confirmed cases, and it was also found that DLB patients with co-existing AD pathology had higher p-tau levels than those without it (60). When it comes to diagnosing AD, plasma p-tau181, p-tau217, and p-tau231 each outperformed traditional markers like APOE ε4 status, plasma NFL, t-tau, and plasma Aβ42/Aβ40 measured by SIMOA (60). Additionally, p-tau217 is a more accurate and reliable biomarker than p-tau181 for detecting AD and predicting disease progression (61).

The faster turnover of Aβ42 relative to Aβ40 in plasma is similar to changes in CSF kinetics, but of smaller magnitude (62). Aβ42/40 also reached an 81% positive predictive value of high cortical Aβ burden, more than double what would be expected to find in the general population (63).

A composite biomarker including the plasma APP669–711/Aβ42 ratio and Aβ40/42 ratio can accurately diagnose AD (50). This composite biomarker achieved approximately 90% accuracy in two separate studies when compared to Pittsburgh compound B (PIB)-PET scans, which serve as the gold standard for detecting amyloid plaques (50) .

The accuracy of plasma Aβ42/Aβ40 tests varies significantly depending on the assay, with mass spectrometry-based tests performing much better with an AUC 0.84–0.87 than commonly used immunoassays, achieving an AUC 0.64–0.69, for detecting amyloid pathology (64).

A large-scale study of plasma NFL levels in AD dementia found that plasma NFL levels closely correlated with CSF 66). Researchers found its level was elevated in both AD dementia patients

and amyloid-positive individuals with MCI and had a diagnostic accuracy comparable to established CSF biomarkers (65). Additionally, higher plasma NFL levels were associated with cognitive decline and characteristic neuroimaging changes, both at baseline and during follow-up (65). In terms of brain imaging, plasma NFL was associated with enlarged lateral ventricles, reduced hippocampal volume, and thinner AD-related cortical regions, both at baseline and throughout disease progression, as well as with increasing brain hypometabolism over time (65). However, as a standalone biomarker, it lacks specificity for AD and cannot be used to distinguish AD from other conditions (65). Instead, as previously mentioned, NFL may serve as a general biomarker for neurodegeneration rather than an AD-specific diagnostic tool (65).

3.2 VaD Neuroimaging biomarkers

This section will primarily focus on the various neuroimaging biomarkers to diagnose VaD. As of date, no single biochemical marker exists to diagnose VaD and its subtypes (66) (67). Also Binswanger's disease and CADASIL will be briefly discussed.

Patients with significant cognitive impairment and worsening in ADLs can be diagnosed with VaD (31) and neuroimaging biomarkers help detect patterns that strengthen the diagnosis. A major challenge in identifying VCI is its frequent overlap with other diseases like AD (29). Only 2-24% of patients have pure VaD while 4% to 22% have mixed AD/VaD (29).

On imaging, VaD presents with extensive confluent white matter lesions, multiple lacunes or bilateral small thalamic infarcts (47). SVD being the most common cause of VaD, may additionally present with small infarcts in the deep perforating vessels region (47). White matter lesions, mostly caused by chronic hypertension, can be best visualized with FLAIR (30). The white matter lesions and changes are commonly seen in the periventricular and subcortical regions or deep within the white matter itself (30). White matter lesions in SVD appear hyperintense on FLAIR and on T2 MRI imaging (47).

Researchers have developed several rating scales to describe white matter changes in SVD (47). The Fazekas scale is the simplest and most standardized scale and it uses four steps (47). A score

of zero corresponds to no observed WMC; one point indicates only punctate small WMC; a score of two signifies early confluent WMC; and lastly, patients scoring three points show confluent WMC (47). A score of one can be considered normal in subjects over the age of 65; a score of two is deemed abnormal in patients younger than 70; and a score of three is always considered abnormal (47).

DTI imaging studies of white matter integrity correlate with the severity of dementia, decreased cognition, motor function, and increased cerebral atrophy (31). Lacunar infarcts are characterized by lacunes and are typically confined to the white matter and subcortical grey matter in the brain (29). Novel quantitative biomarkers of SVD include enlarged VRS observed on T2 sequences, which are associated with an increased risk of dementia in healthy elderly patients (29). These enlarged fluid-filled spaces, which line the brain vessels, are correlated with WMHs, lacunar strokes, and MCI-AD (29). Cortical microinfarcts have emerged as a potential biomarker for SVD, and they can be best visualized using 7T MRI but also on high-quality 3T machines (29).

MR perfusion imaging can locate restrictions of cerebral blood flow in small or large vessel disease(47). A study where researchers used the ASL technique, found that patients with diffuse confluent WMH have approximately 20% less blood flow in the cerebrum than patients with punctiform or early confluent WMH (47). On structural MRI, patients in the early stages of VaD, show changes such as cortical thinning that can be seen in frontal, temporal, and occipital regions of the brain (31). With volumetric MRI, VaD can be accurately identified with 96% sensitivity (68).

FDG-PET studies in VaD patients detect hypometabolism in a scattered pattern in cortical and subcortical regions as well as deep grey matter and the cerebellum, helping distinguish it from AD (31). Furthermore, amyloid PET can help rule out VaD as tracers show minimal binding in the majority of patients with VaD in the absence of CAA (31).

Binswanger’s disease is a prototypical clinical manifestation of VCI (29). Neuroimaging of patients with disease shows progressive confluent subcortical and periventricular white matter degeneration (29). CADASIL is the most common genetic cerebrovascular disease caused by a

mutation of the notch-3 gene (47). In these patients, they tend to get strokes in the 4th or 5th decade of life, which later then progress to subcortical dementia (47). The neuroimaging patterns of CADASIL show significant white matter lesions that affect the temporal lobes and external capsules, and these patients all exhibit infratentorial and basal ganglia microbleeds (47).

3.3 DLB biomarkers

In this section, the current guidelines for DLB dementia diagnosis, which include indicative biomarkers and supporting biomarkers, will be reviewed and detailed. Next, modalities like DAT imaging, MIBG cardiac scintigraphy, polysomnography, and EEGs will be discussed. Then, the focus will be shifted to the role neuroimaging plays in DLB diagnosis, highlighting occipital hypometabolism found on FDG-PET as well as the "swallow tail sign" on MRI.

To date, there are no established and applicable CSF, blood, or other peripheral biomarkers for DLB (69). Although genetics do play a role in the pathogenesis of the disease, genetic testing is also not recommended in clinical settings or for dementia screening (69).

Essential criterion: Dementia, typically with noticeable and early significant deficits in attention, executive function, and visuoperceptual abilities (memory involvement more severe as it progresses)
Core clinical features: Fluctuating cognition, spontaneous parkinsonism (the presence of one or more of cardinal features - bradykinesia, resting tremor, rigidity), visual hallucinations, and RBD.
Supportive clinical features: Frequent falls, syncope, autonomic dysfunction, hypersomnia, increased severe antipsychotic sensitivity
Indicative biomarkers: Decrease in basal ganglia dopamine transporter uptake (SPECT/PET), reduced uptake on MIBG myocardial scintigraphy and PSG confirmation of REM sleep without atonia
Supportive biomarkers: Relative preservation of medial temporal lobe structures on CT/MRI scan, generalized low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± the cingulate island sign on FDG-PET imaging, and prominent posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/ theta range.

Table: Diagnostic Criteria for DLB, including indicative and supporting biomarkers (70)

FP-CIT SPECT demonstrates normal dopamine tracer uptake in the caudate and putamen in AD patients and HCs (47). Meanwhile, in DLB patients, dopamine uptake is severely reduced in the putamen in the basal ganglia, and this technique is 80–90% accurate in detecting DLB or PDD

(47). DAT imaging also plays a crucial role in differentiating DLB from other non-parkinsonian neurodegenerative disorders, such as AD (29). The diagnostic accuracy of DAT scans is even higher when applied in autopsy-proven cases of DLB, as one study found that SPECT imaging had a sensitivity of 100% and a specificity of 92% for diagnosing DLB at autopsy (71).

MIBG cardiac scintigraphy is used to test postganglionic sympathetic degeneration in the heart, which is a major finding in DLB (72). Studies have generally excluded patients with comorbidities or on medications since they can produce abnormal MIBG images (69). Clinicians should carefully interpret MIBG results in patients who suffer from IHD, DM, heart failure, peripheral neuropathies, or patients that take any medications that can cause reduced uptake, like labetalol (69).

According to the fourth consensus statement of the DLB consortium, polysomnography recordings that investigate REM sleep without atonia are indicative biomarkers for DLB diagnosis (73). If the recording shows REM sleep without atonia in a patient with a history of RBD but no confirmed dementia, there is more than a 90% chance that the patient has a synucleinopathy, and in these cases, it's sufficient to justify a probable DLB diagnosis even in the absence of any other core features or biomarkers (69). RBD is strongly linked to DLB, with up to 76% of DLB patients experiencing RBD. RBD can appear years before patients exhibit signs of cognitive decline, making it a useful screening tool for DLB and PD (74).

EEGs are another important biomarker that are highly specific for DLB diagnosis (75). In DLB, abnormalities on EEG are found in posterior regions , and these patients show increased posterior slow-wave activity, which is specific for DLB, while patients with AD, the regions affected on EEGs are the temporal lobes (75). The advantages of performing EEGs are that they are non-invasive, low-cost, accessible, and easy to use compared to PET, SPECT, or MRI (76). They are also reliable, presenting with similar sensitivities to SPECT, and they're repeatable, making it suitable for regular monitoring of dementia patients (76).

MRIs are not very specific neuroimaging biomarkers for DLB but still can play a complementary role in the diagnosis (77). In the early stages of the disease, voxel-based morphometry can detect atrophy specifically in the anterior cingulate cortex, which is crucial for attention and decision-making, and the insular cortex, which is linked to emotions and awareness (77). As DLB

progresses to the established stage, the temporal lobe loses volume, but in a pattern different from AD (77). Unlike AD, DLB does not significantly affect the Ammon's horn or subiculum, which are parts of the hippocampus crucial for memory (77). Instead, DLB affects other areas such as the parahippocampal gyrus, which is involved in visual processing, and the striatum, which is associated with movement and cognition (77).

The "swallow tail sign," a feature seen on MRI scans and considered specific for PD, has a moderate ability to correctly detect the DLB in studies, displaying a 93% sensitivity and 87% specificity (78). The best results were obtained using 7T machines, and it was found that using thinner imaging slices can improve accuracy (78). Additionally, MRI can show focal cortical thinning in patients with DLB, affecting posterior structures like the inferior parietal, posterior cingulate, and fusiform gyrus (79).

Other imaging modalities like DTI have shown to be a promising tool to help differentiate DLB from AD (29). Researchers found that DLB patients have reduced white matter tract integrity primarily in the posterior parietal and occipital regions, which presents a distinct pattern from that observed in AD (80). Another PET-based measure, the cingulate island sign ratio, which has been suggested as a supportive biomarker for DLB, showed moderate accuracy ranging from 79% to 92% in different studies (74). In a different study, it was reported that the cingulate island sign is linked with medial temporal lobe atrophy and with cognitive impairment and visual hallucinations in DLB patients (81). FDG-PET imaging can differentiate DLB from AD by looking at occipital hypometabolism, a common DLB feature (74). FDG-PET can be very accurate, with specificities as high as 92% in detecting DLB (74).

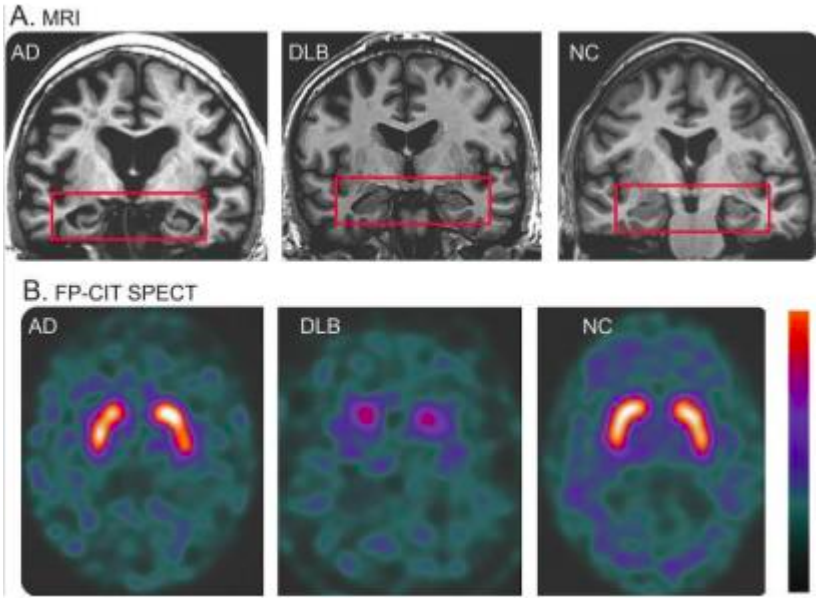

Image: MR and SPECT imaging distinguishing DLB from AD and normal controls (69)

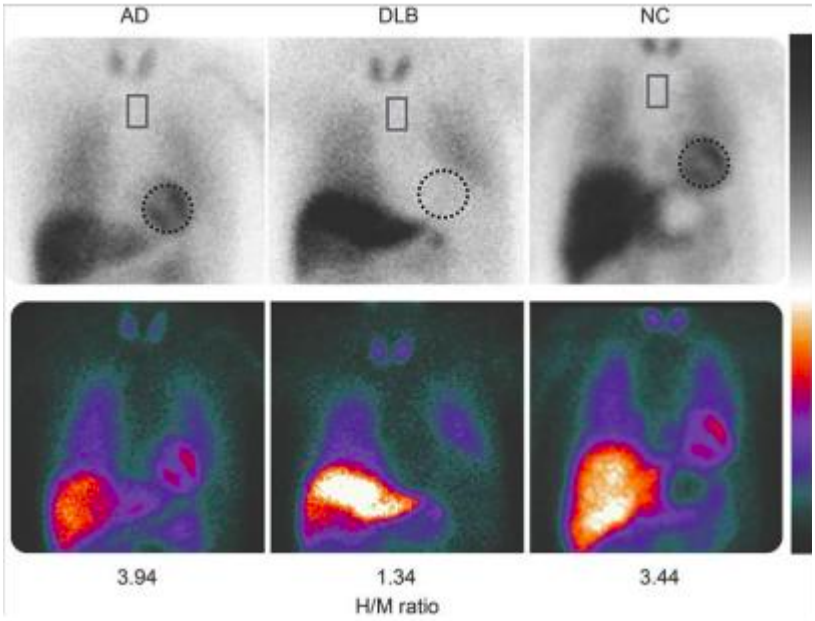

Image: Pictures of MIBG taken 3 hours after injection are shown in 2 color scales: heart (dotted circle) and upper mediastinum (rectangle); heart -to-mediastinum (H/M) ratios. Reduced uptake in DLB is seen (69)

3.4 FTD biomarkers

The key focus in this section will be on genetic testing, which plays a more prominent role in diagnosing FTD, neuroimaging techniques, and other biofluid markers, which can help differentiate various FTD subtypes from one another and from other diseases. Testing C9orf72 and GRN mutations will be discussed and the role of progranulin and NFL in FTD will be mentioned as well. For neuroimaging, each subtype of FTD will be reviewed, with a focus on modalities like MRI, DTI highlighting white matter damage as well as ASL and FDG-PET.

A C9orf72 mutation is usually tested for through repeat-primed PCR and confirmed with Southern blotting, while GRN can be identified by targeted next-generation sequencing panels or increasingly commonly through exome or genome sequencing (82). There are currently no specific biomarkers that can identify MAPT mutations in either biofluids or any of the rarer genetic causes (82). In FTD, progranulin levels are lower in the CSF of patients with bvFTD and svPPA, which are mainly linked to TDP-43 protein buildup in the brain (24). In contrast, nfvPPA, which is more associated with tau protein, does not show the same reduction in progranulin levels (24). Those patients with GRN gene mutations have low progranulin levels in both blood and CSF, making it an effective biomarker in diagnosing familial FTD cases.

In prodromal stages of FTD, higher NFL levels can indicate that a patient possesses a genetic mutation such as GRN, MAPT, or C9orf72 and is likely to convert to full-blown dementia (83). Additionally, higher baseline NFL levels are linked to faster cognitive decline, worsening behavior and functioning, and more rapid brain changes, making NFL useful for tracking disease progression in FTD (83) . A study found that CSF NFL levels were more than three times higher in FTD patients compared to HCs (84). The increase in NFL was observed to be even greater in FTD than in AD, likely because FTD more severely affects the frontal and temporal lobes leading to increased degeneration and involves the subcortical brain regions (84) Serum NFL levels were significantly higher in FTD patients than in those with psychiatric disorders, which allows clinicians to reduce misdiagnosis and diagnostic delays in patients (85). Additionally, a study investigating CSF biomarkers to differentiate between MCI-AD and FTD confirmed that NFL levels were significantly higher in FTD compared to MCI-AD and found that NFL was associated with markers of tau pathology but not with amyloid pathology, such as the Aβ42/40 ratio (86). Lastly, an important feature of the NFL biomarker is that NFL levels in blood closely

mirror those in CSF, making blood tests a less invasive but still reliable option for assessing neurodegeneration (87).

BvFTD is characterized by asymmetrical frontal and temporal atrophy, with the orbitofrontal sulci widening early in the disease process (88). Over time, atrophy extends to the insula, anterior cingulate, amygdala, thalamus, and striatum, causing behavioral and personality changes in patients (88). However, the specific pattern of brain atrophy varies depending on the underlying disease pathology (31). In FTD caused by Pick's disease, atrophy is predominantly observed in the prefrontal cortex, temporal lobes, anterior cingulate, and insula, typically occurring on both sides but with slightly greater atrophy affecting the left side (31). The frontal atrophy in Pick's-related FTD is often more severe than in other forms of FTD, such CBD, bvFTD due to MAPT mutations, or FTD with TDP-43 pathology (31).

Patients with MAPT mutations exhibit a diverse range of atrophy patterns in the frontal and temporal lobes, insula, anterior cingulate, parietal lobe, basal ganglia, and brainstem, with more pronounced temporal lobe shrinkage (31). Those with FTD linked to TDP-43 pathology display widespread atrophy in the frontal, temporal, and parietal lobes, which is often asymmetric, with the parietal lobes being more severely affected (31). Mutations in the GRN result in a similar pattern of frontal, temporal, and parietal atrophy but tend to cause greater asymmetry than TDP-43 FTD without GRN mutations (31). Patients with FTD caused by FUS pathology, which is rare and typically sporadic, show a distinct pattern of severe caudate atrophy as well as frontal lobe atrophy (31).

Some challenges that exist in neuroimaging biomarkers in FTD are that studies show only 10% of MRI reports correctly diagnosed bvFTD (29). Advanced imaging techniques can help (29). DTI shows white matter damage, especially in the frontal lobes, while ASL perfusion imaging differentiates bvFTD from AD (29). In comparison to AD, bvFTD patients exhibit greater white matter damage in the frontal lobes, including the anterior cingulum, anterior corpus callosum, and uncinate fasciculus (31).

Research data suggests that ASL has sensitivity and specificity like FDG-PET, with ASL achieving 83% sensitivity and 93% specificity in distinguishing bvFTD from AD, compared to 89% and 78%, respectively, for FDG-PET (31).

In svPPA, which is usually linked to TDP-43 pathology, the most noticeable shrinkage happens on the left side of the brain, especially in the front and lower parts of the temporal lobes, impacting areas like the temporal pole, perirhinal cortex, fusiform gyrus, hippocampus, and amygdala (31). As the disease progresses, atrophy spreads to other parts of the left temporal lobe, frontal lobe, insula, and anterior cingulate and can also spread and affect the right temporal lobe (31). DTI testing shows that patients with svPPA are damaging the white matter in both temporal lobes, particularly on the left side, impacting pathways like the inferior longitudinal fasciculus and uncinate fasciculus (31). On PET and SPECT, reduced perfusion and metabolism mainly in the left anterior temporal lobe are observed (31).

In nfvPPA, atrophy is usually first detected in the left inferior frontal lobe, insula, and premotor cortex, with further progression involving the frontal, temporal, and parietal lobes, as well as deeper structures like the caudate and thalamus (31). Additionally, DTI studies show damage to white matter pathways involved in speech and motor function, particularly in the left arcuate fasciculus, superior motor pathway, and perisylvian regions (31). Lastly, FDG-PET imaging detects low metabolism in important speech-related areas such as the left inferior frontal gyrus, frontal operculum, insula, and supplementary motor areas (31).

Imaging patterns can distinguish different subtypes of FTD with motor symptoms (31). Patients with PSP-bvFTD have atrophy in the posterior cerebellum, some atrophy in the frontal lobe, but their temporal lobes stay normal, while those with CBD-bvFTD typically show even shrinkage in the front part of the brain, around the Rolandic area, and in the striatum (89) Atrophy in CBD is usually asymmetric, whereas PSP is more symmetrical (31). DTI studies in CBD patients have demonstrated loss of white matter integrity in the motor thalamus, precentral gyri, and postcentral gyri, while in contrast, PSP patients show damage in the anterior thalamus, cingulum, and fronto-orbital white matter (31). ASL imaging in CBD shows reduced blood flow in the right hemisphere, while SPECT studies have detected reduced neurotransmitter function, including dopaminergic and cholinergic deficits in the striatum, anterior cingulate, and thalamus (31).

FDG-PET studies in CBD and PSP show that patients exhibit hypometabolism in motor-related brain regions, with CBD patients showing metabolic reductions on the side opposite the affected

body part, while PSP displays widespread hypometabolism in the prefrontal cortex, caudate, thalamus, and midbrain (31).

Biomarker	Method of analysis	Advantages	Limitations
Imaging biomarkers			
Gray matter atrophy	Volumetric T1-weighted MRI	• Noninvasive • Ability to apply various different processing techniques • Discrimination between FTD and AD, as well as between some FTD subtypes	• Less sensitive to detecting changes in subcortical structures • Inconsistent results and correlation with time course of disease • Difficult to stratify FTD spectrum with structural imaging alone
White matter integrity loss	DTI	• Noninvasive • Can easily reflect changes in microstructures • Can detect white matter changes that precede gray matter changes in FTD • Sensitive differentiation of FTD from other types of dementia and control subjects	• Varying distribution patterns and rates of neurodegeneration observed among different individuals
Brain metabolism	FDG-PET	• Early visualization of alterations in brain metabolism that may precede gray matter atrophy • May reveal abnormalities in presymptomatic stage of FTD	• Expensive, not covered by many insurers • Requires prolonged positioning that is increasingly difficult in patients with advanced dementia or concurrent motor dysfunction
Fluid biomarkers			
NfL	CSF	• Strong correlation with disease severity, progression, survival, and cerebral atrophy	• Increased in several other neurodegenerative diseases • Must be combined with other disease-specific biomarkers • Equally elevated in FTD subtypes
Progranulin	Blood sample	• Discriminates between *GRN* mutation carriers and noncarriers with high sensitivity remains constant over disease	• Should be combined with CSF sample due to varying regulation • Does not reflect extent of neurodegeneration
Genetic biomarkers			
C9orf72*, *MAPT*, and *GRN	Blood sample	• Direct correlation between clinical manifestations and molecular mechanisms of pathology • Can potentially identify presymptomatic/prodromal carriers • Provides a basis for targeted therapies (i.e., ASOs)	• Genetic testing is generally restricted to patients with suggestive family history • Pleiotropic effects and incomplete penetrance further complicate identification of at-risk individuals • Availability limited to specialized clinical/research settings

Table: Summary of FTD biomarkers (90)

3.5 RPD biomarkers

To correctly address the role of biomarkers in RPD diagnosis, this section will first focus on the diagnostic algorithm in this disease before talking about specific biomarkers for the various conditions that fall under the umbrella of RPD like. The primary focus will be CSF-based

markers such as RT-QuIC for prion diseases, the 14-3-3 protein test using Western blot and DWI and FLAIR in RPD diagnosis.

In the context of RPD, the first step by any clinician should be to take the patient's history, track their symptom progression, and perform a neurological examination to determine whether the condition is neurodegenerative in nature or whether the pathology stems from infections, metabolic disorders, or autoimmune causes (12). As mentioned earlier, specific neurological signs, such as stimulus-sensitive myoclonus in CJD or aphasia in herpes encephalitis, can provide clues but do not confirm any diagnosis (12). Blood-based biomarkers play a crucial role in diagnosing reversible conditions such as metabolic imbalances, infections, or autoimmune disorders (12). Tests for inflammatory markers, vitamin deficiencies, and genetic mutations are useful in cases with unclear causes (12). CSF-based markers such as RT-QuIC for prion diseases support a diagnosis (12). Imaging studies play a critical role in RPD diagnosis. CT scans can help rule out emergencies like stroke or hydrocephalus, while MRI scans provide more detailed insights into neurodegenerative patterns, vascular conditions, or inflammatory diseases (12). DWI MRI is key for early CJD diagnosis (12). MRI sequences such as FLAIR and DWI can detect signal hyperintensities very early in the disease course and are included in the criteria for prion disease diagnosis (12). CSF analysis helps detect infections, autoimmune diseases, and neurodegeneration, with elevated white blood cells indicating encephalitis and extremely high tau levels suggesting CJD (12).

Additional testing, such as performing an EEG, can help rule out seizures or non-convulsive epilepsies, which can mimic RPD (12). For prion disease, the EEG presents with the classic periodic sharp and slow wave complexes later in the disease course, making it useful for diagnosis (12). PET scans can detect glucose metabolism changes in neurodegenerative diseases, while CT scans of the chest and abdomen can look for underlying cancers linked to paraneoplastic syndromes (12). Differentiating RPD from delirium and identifying its rate of progression is critical (12). Acute cognitive decline over minutes to hours suggests stroke, seizures, or metabolic encephalopathy, whereas prion diseases typically progress over weeks to months (12). Age of onset of symptoms also provides vital diagnostic clues, as prion diseases are most common between ages 60-69, while autoimmune encephalitis and metabolic disorders are more frequent in younger individuals (12).

RT-QuIC assays are very specific for prion disease diagnosis (91). SCJD being the prototypical cause of RPDs, is called the “great mimicker” given its wide phenotypic heterogeneity (91). This makes biomarkers that much more critical to help diagnose this disease (91). Currently, MRIs and CSF surrogate markers such as proteins (t)-tau and 14-3-3, and EEG examinations support the clinical diagnosis of probable CJD (91).

The 14-3-3 protein test, which can be detected with Western blotting, is widely used as a diagnostic tool for sCJD (92). A 2012 meta-analysis found that it has a sensitivity of 92% and a specificity of 80% (92). However, the test is less accurate in the early stages of the disease and does not perform as well in certain molecular subtypes of sCJD—specifically MV2 and MM2, where sensitivity levels drop off to 60-70% (92). Additionally, the specificity of the test varies widely, from 40% to 92%, depending on the study and the control group used (92). MRI also plays a crucial role in diagnosing sCJD and helps differentiate it from conditions such as stroke, encephalitis, and tumor (92).

Specific MRI patterns seen in DWI and FLAIR scans are considered characteristic of CJD and were incorporated into the WHO diagnostic back in 2009 (92). The pathognomonic neuroimaging findings associated with sCJD are T2/FLAIR and DWI hyperintensities in the cortex known as cortical ribboning and deep grey matter nuclei, which can be symmetric or asymmetric (29). A widely used diagnostic approach includes using DWI in combination with apparent diffusion coeficient maps, which allow the detection of restricted diffusion, a key feature of CJD where fluid movement in certain brain regions is abnormally limited (92). In sCJD, MRI findings commonly include cortical ribboning, which refers to restricted diffusion in at least two cortical regions, and involvement of the caudate nucleus, putamen, and thalamus areas (92).

A particularly strong indicator of variant CJD is the "pulvinar sign," which appears as high signal intensity in the posterior thalamus that is brighter than the anterior putamen on FLAIR and DWI imaging sequences (92). MRIs may be more accurate in diagnosing sCJD than CSF 14-3-3 and T-tau (92). Studies have indicated that MRI has a sensitivity of 91–96% and specificity of 92–94%, making it the best diagnostic biomarker for differentiating CJD from other RPDs (29).

Studies also demonstrate that diagnosing prion diseases, particularly sCJD, can be done with nearly 100% accuracy by using RT-QuIC testing on both CSF and olfactory mucosa OM samples (93). While CSF is the preferred sample for testing, negative results do not completely rule out the disease (93). In such cases, testing OM in nasal tissue can provide confirmation of the disease (93). This highlights the value of OM sampling as a supplementary diagnostic tool, especially when CSF results are unclear or when a lumbar puncture cannot be performed in patients suspected of having sCJD (93).

4. Discussion about the future direction of biomarkers

As covered in the previous section, biomarkers play a critical role in the differential diagnosis of dementia subtypes and establishing a diagnosis. However, there are limitations, as some of these biomarkers are invasive, costly, not readily performed or available at all clinics and hospitals, and don't have clearly defined cut-off values for diagnosis. Additionally, with the lack of disease-modifying drugs for dementia, clinicians must weigh the value of additional testing and imaging on patients. The previous sections discussed biomarkers that are currently validated and used in clinical settings, while the next chapters will address the great research being done on finding new biomarkers to overcome the current challenges. Many modalities and biomarkers offer great hope and may soon be available in clinical practice. They will play a key role in clinical trials for anti-dementia drugs. The focus of the next subsection will be neuroimaging, AI, diagnostic techniques, and cheaper biofluid alternatives to CSF biomarkers, both in general and for each specific dementia subtype.

4.1 Neuroimaging, AI and diagnostic techniques

Neuroimaging and AI are playing a leading role in establishing new biomarkers for dementia. Neuroimaging is being integrated with open science, particularly by creating large publicly available datasets for studying neurodegenerative diseases. (48). A more advanced form of AI, called deep learning, has achieved 96% accuracy in diagnosing dementia from brain scans (48). Additionally, machine learning in dementia research can identify risk factors and early warning signs by analyzing the medical records, brain scans, genetic profiles, and lifestyle data of patients (94). It can also predict disease progression by analyzing long-term health trends and help personalize treatments by determining which interventions work best for different groups of patients (94).

There are different types of machine learning used in dementia research prevention. First, there's unsupervised learning, which helps find hidden patterns in data without predefined labels (94). For example, it can group people into subtypes based on their dementia risk (94) Second is supervised learning, which uses labeled data, like known dementia cases, to train models that can predict at-risk groups or diagnose dementia from brain scans (94). Lastly, there is semi-supervised learning, which uses a mix of labeled and unlabeled data, and this method is particularly useful when medical records lack details (94).

Currently on the market, there are AI systems that analyze facial photos to detect signs of dementia, as aging affects both appearance and brain function (95). A deep-learning model called Xception has successfully achieved 92.56% accuracy in differentiating AD patients from HCs based solely on facial features (95). AI-based MRI analysis can also classify white matter damage using tools like the Fazekas scale and detect cerebral microbleeds (95).

One issue with deep learning models is that they may struggle to interpret data, and it's unclear how they reach their conclusions (48) . In practice, such shortcomings may deter clinicians, as they will remain hesitant to rely on diagnostic tools whose underlying processes they don't fully understand, increasing the risk of misdiagnosis and eroding trust with patients (48). Another challenge is the lack of standardized data to train AI models (48). To overcome that, efforts are being undertaken like the UK Biobank and the Human Connectome Project to create such standardized methods (48). Standardized guidelines and reporting frameworks such as TRIPOD-AI and FAIR are also being developed to ensure reproducibility and transparency in AI-based biomarker research (96).

Next, MRI techniques such as quantitative susceptibility mapping and MR elastography are being used to help measure structural changes in the brain (96). Quantitative susceptibility mapping is a specialized MRI technique that detects iron, calcium, and other magnetic substances in the brain (49 Ritman?). The advantage of this modality is that it can detect iron accumulation in the brain, which is linked to cognitive decline in AD and PD (48). In AD, iron is present in the plaques and tangles that characterize the disease (48).

ELISA is usually considered a basic method that detects molecules using antibodies; however, some more advanced immunoassays like SIMOA, Meso Scale Discovery, and Luminex xMAP

are being used to research protein biomarkers because of their increased sensitivity to detect them (97). Additional modalities include SomaScan which uses DNA-based aptamers instead of antibodies and mass spectrometry (UPLC-MS/MS) to measure lipids and small molecules (97). These modalities have been used to study cytokines such as TNF-α, IL-10, and Eotaxin, which were found to be increased in AD patients with the APOE ε4 gene (97). They have also been used to study peptides such as leptin and the neuropeptide Y family and BNP (97). Lastly, proteins such as ICAM-1 and Tenascin C, which are found to be increased in AD, are also being investigated as potential biomarkers using these different immunoassay techniques (97).

Mass spectrometry is becoming the preferred method for measuring biomarker levels due to its superior precision and accuracy, reduced testing variability, and capacity to measure multiple biomarkers concurrently (98). It is now being used to analyze Aβ peptide, tau proteins, and p-tau as well as other CSF biomarkers such as α-synuclein, SNAP-25, neurogranin, TREM2 and many others (98). Recently there have also been advancements in standardization efforts for mass spectrometry (98). Certified reference materials have been developed to improve standardization and there are now three of them used for the detection of Aβ42 levels in CSF that are now available in Europe and the USA to harmonize testing across different labs (98). Lastly, mass spectrometry is being utilized to help improve detecting blood-based biomarkers for AD diagnosis (98). For example, mass spectrometry can now detect Aβ42/Aβ40 ratios in plasma with high accuracy, predicting brain amyloid plaques before symptoms appear (98).

Newer techniques like TMT and SILK will help researchers measure multiple proteins at once (98). A large-scale proteomics platform was used to examine the association of 4877 plasma proteins with 25-year dementia risk in nearly 11,000 people (99). Researchers found 32 dementia-associated plasma proteins that were involved in proteostasis, immunity, synaptic function, and extracellular matrix organization (99). 12 of those 32 the proteins related to dementia were found to be correlated with CSF biomarkers of AD, neurodegeneration, or neuroinflammation (99). GDF15, a highly expressed marker in aging cells in the body, which is linked to neuroinflammation and cognitive decline, demonstrated the strongest association with 25-year dementia risk in patients (99). The study also found that some proteins involved in protein quality control and stress response, such as HSPA1B, DNAJB9, and GABARAPL1, were elevated decades before dementia onset (99).

4.2 Future of AD biomarkers

Research on AD-specific biomarkers is growing, with many showing promise for use in clinical settings in the near future. Many modalities are being used to enhance detection of known proteins of interest. A major challenge in blood-based biomarkers in detecting AD is that their concentrations are lower in the blood than in CSF. Techniques are needed to better detect abnormal proteins in the blood. In this chapter, we will focus on techniques like SIMOA and IP-MS, metabolomics and proteomics before talking about potential biomarkers for AD. Some biomarkers which will be discussed include lipid peroxidation biomarkers, the dielectric constant and conductivity in plasma, retinal imaging as well as the use of saliva and urine to detect AD.

Aβ42 and Aβ40 levels in plasma are much lower than in CSF, making their detection more challenging (100). However, with advanced hypersensitive methods, such as SIMOA and IP-MS, low concentrations of biomarkers can be detected. SIMOA has been shown to quantify Aβ42 by detecting levels as low as 0.04 pg/ml in blood (100).

The SIMOA and Meso-Scale Discovery methods have been used to detect p-Tau181 and p-Tau217 in large patient cohorts, confirming their elevation in AD patients compared to HCs (100). Studies using data from ADNI and BioFinder cohorts demonstrated that plasma p-tau levels were significantly elevated in patients who later developed AD in life (100). For example, the PrecivityAD test can accurately detect Aβ levels and APOE genotype, helping predict amyloid plaque buildup in patients (101).

Metabolomics & proteomics, 2 blood analysis techniques, are promising methods for understanding how oxidative stress contributes to AD and help in developing new biomarkers and have the potential to be combined with other biomarkers such as CSF and PET imaging to help guide personalized treatment strategies for AD patients (102). A study analyzing over 2,000 brain samples and nearly 400 CSF samples using mass spectrometry-based proteomics was done in order to understand how protein changes occur during AD progression (103). It found that the M4 protein module, which is linked to astrocyte and microglial metabolism, is strongly associated with AD (103). M4 typically increases with age but rises even more in AD cases (103). M4 proteins increase both in early and late AD stages, making them potential biomarkers for diagnosing and monitoring patients with AD (103).

Lipid peroxidation markers in plasma show promising results in detecting AD (104). Some promising lipid peroxidation markers include 4-hydro)nonenal, lipophilic fluorescent products, and isoprostanes, and recent studies showed they had an AUC of 0.87 (104).

Studies are also exploring new ways to detect AD by measuring electrical properties of blood plasma, specifically the dielectric constant and conductivity (105). Researchers use microwave frequencies to measure these properties in blood plasma (105). Detecting biochemical alterations linked to AD may be aided by variations in electrical characteristics (105). For example, it was shown that in HIV/AIDS-infected blood, chemically altered Aβ42 samples, and infected mucus from H1N1 virus samples all exhibit unique electrical properties (105). It was also found that Aβ42-altered blood plasma had a significantly different dielectric constant and conductivity than normal blood, suggesting a link to memory and cognitive decline in AD (105).

Retinal imaging also offers great potential to serve as a cheaper, non-invasive biomarker to diagnose AD(106). Retinal changes, including the accumulation of Aβ and tau proteins, have been observed in individuals with AD (106). Patients with AD have thinner retinas and maculas, which can be detected using OCT (106). Changes in the retinal blood vessels, including reduced vascular density and abnormalities in microvascular networks, have also been associated with AD pathology (106). OCT and its advanced version, OCT-A, allow for non-invasive retinal scans that can detect structural thinning and blood vessel changes (106). Retinal-based diagnostic techniques make for more accessible early screening in AD patients (106). Retinal imaging has demonstrated the ability to detect subtle retinal changes before cognitive symptoms of AD first appear, offering the potential for early diagnosis and disease progression(106). Furthermore, integrating AI into these imaging modalities could improve diagnostic accuracy by detecting patterns and abnormalities more efficiently (106). In the future, the combination of retinal imaging with AI-driven analysis and traditional diagnostic methods, such as MRI and PET scans, may help improve the accuracy of AD diagnosis (106).

Other potential fluids that show potential as biomarkers include saliva and urine. Researchers investigated hundreds of different metabolites in saliva to study which ones may predict AD status (107). Their analysis found that salivary metabolite markers could discriminate between AD, presymptomatic, and MCI patients (107). AD and presymptomatic patients were identified

by the metabolite markers glucosylgalactosyl, hydro)lysine—H2O, and glutamine -carnitine with an AUC of 1.00 (107). In another study, it was reported that salivary lactoferrin levels were significantly reduced in AD patients but not in patients with FTD, suggesting a specific Aβ-related link (107). Reduced lactoferrin levels were associated with positive amyloid PET results, which further implies a link between lactoferrin and AD (107). Lastly, studies measuring oxidized protein and DNA products in urine, found that levels of 8-OHdG and ratio 8-OHdG/2dG were higher among the MCI-AD patients compared to HCs and that the results were statistically significant, making urine analysis a potential candidate for non-invasive biomarker testing (108).

4.3 VaD biomarker prospects

VaD research has marked a few emerging biomarkers, which would need more validation and standardization before being applied in clinical practice. These biomarkers offer the potential to improve detection and diagnosis of VaD and monitor therapeutics. In this section, inflammatory markers with potential, immune markers and how retinal imaging can be used to help diagnose VaD will be discussed.

Researchers have found important groups of biomarkers, which include inflammation markers like IL-6, CRP, and MMPs; markers that show brain injury such as NFL, MBP, and S100B; and blood clotting-related markers like fibrinogen, Lp-PLA2, and circulating microRNAs. A study analyzing six different research papers that measured IL-6 levels in the blood of individuals with VaD compared to both AD patients and HCs found promising results (109). The study showed that IL-6 levels were significantly higher in VaD patients compared to HCs with a standardized mean difference of 0.75, indicating a moderate to large difference (109). When researchers compared VaD patients to AD patients, IL-6 levels were also significantly higher in VaD, with a standard mean difference of 0.40, suggesting a moderate difference while also showing the differences between IL-6 levels in AD patients and HCs were not significantly different (109).

In another study, researchers also identified HMOX1, EBI3, CYBB, and CCR5, four key immune-related genes that are mainly involved in inflammation, immune responses, and vascular disease processes (110). In studies of Binswanger’s disease, it was noted that increased albumin

ratio, reduced MMP-2, and elevated NFL in the absence of a characteristic AD CSF profile were the most significant among biomarkers for this disease (66).

OCTA can also help reveal small blood vessel changes in the retina, which are often present in VaD (111). Studies have shown that retinal blood flow density is lower in VaD patients and correlates with WMHs but not with AD-related proteins such as Aβ and tau in CSF (111). This evidence suggests that OCTA could help distinguish VaD from AD (111). While in patients with SVCI, a subtype of VaD, studies found reduced capillary density in specific retinal layers, which was not observed in AD patients (111). CADASIL has also been present with lower retinal vessel density and choroidal thinning (111).

Despite promising findings, no single biomarker is sufficient to diagnose VCID, as the disease is complex and progresses differently in individuals (67). Standardization of laboratory methods and larger collaborative studies are needed to develop a reliable biomarker panel with high accuracy for clinical use. Future research should focus on identifying the best combinations of biomarkers to diagnose VCID and VaD, validate them and establish appropriate protocols so they can be used in practice (67).

4.4 DLB biomarker future direction

As mentioned previously, fluid and genetic markers for DLB have not yet been developed, but studies indicate that many might play an important role in revolutionizing DLB diagnostics. This section will begin by discussing proteomics in the development of DLB biomarkers and identify some of them like parkin, E3 ubiquitin and H-FABP. Then some synaptic proteins that show considerable promise in detecting DLB will be highlighted. Additionally, other biomarkers discovered using protein analysis, RT-QuIC for CSF α-Syn, imaging techniques and genetic testing that can help with diagnosing DLB will be revied. Finally, the potential of skin biopsies will be mentioned as well.

Proteomics can play an integral role in helping develop biomarkers for DLB diagnosis by highlighting how specific protein composition is associated with the disease process (44.) A study focusing on E3 ubiquitin ligases found that a few of them are suitable candidates as biomarkers for DLB (43). Ligases like parkin, which are linked to Lewy body pathology, have been found in DLB and PD (43). Researchers examined brain tissue from different types of PD

and DLB cases and found that parkin was present in Lewy bodies within key brain regions, such as the substantia nigra (43). Another E3 ligase, TRIM9, which is specific to the brain, was found to be greatly reduced in the temporal cortex and hippocampus of DLB patients but not in AD or HCs (43). Using western blotting, TRIM9 levels were reduced by up to 70% in DLB cases compared to controls (43).

Additionally, H-FABP, first discovered in heart muscle cells and used as a marker for MIs, is now thought to play an important role in the CNS (67). H-FABP is being studied as a potential biomarker for DLB due to its consistent results across different studies (43). H-FABP levels were significantly higher in AD and DLB patients compared to those without dementia (45). Combining H-FABP and p-tau181 levels was found to be the most accurate way to differentiate AD from DLB, achieving a diagnostic accuracy of 92% (45).

Recent research found that DLB and AD patients had lower levels of synaptic proteins such as Rab3A, SNAP25, and Ng across multiple brain regions (43). In CSF, Aβ40 was found to be significantly decreased in DLB compared to AD, and an oxidized α-helical form of the Aβ peptide was identified to be significantly increased in patients with DLB in comparison to PDD, yielding a sensitivity of 81% and specificity of 71% (75).

Using RT-QuIC for CSF α-Syn in experiments yielded an overall specificity of 98.0% and a sensitivity of 95.2% for DLB, highlighting strong potential as a future biomarker (112). In peripheral tissues, RT-QuIC assays demonstrated a high sensitivity of 98% and specificity of 100% (113).

A study using advanced protein analysis identified six CSF biomarkers for DLB: VGF, SCG2, NPTX2, NPTXR, PDYN and PCSK1N (114). These biomarkers were found to be lower in DLB patients when compared to patients with AD, PD, and FTD (114). Additionally, using machine learning, researchers determined that the combination of VGF, SCG2, and PDYN together provided the best accuracy in distinguishing DLB from other neurodegenerative conditions (114).

Genetic studies investigating sTREM2 showed that its levels increased more in DLB than in AD and could be related to the alpha-synuclein pathology in DLB patients (115). As for

neuroimaging markers, SWI may be a potentially cheaper alternative when compared to DAT-SPECT and nigrosome-1 degeneration in DLB and not in AD, with 90% accuracy as compared with 88.3% DAT-SPECT (116).

Lastly skin biopsies can help diagnose synucleinopathies and can detect abnormal P-SYN in over 92% of patients with PD and DLB (117) The concentrations of P-SYN in the skin also correlate with disease severity in patients (117).

4.5 Challenges and potential biomarkers for FTD

The development of biomarkers for FTD diagnosis remains a major challenge. In this chapter, these challenges will be highlighted, and some neurophysiological tests that can help with the diagnosis FTD and the PRS method will be discussed. Also, the role of FTD-43 as a biomarker, miRNA markers and also how biomarkers can be combined will be reviewed. Finally, the role of genetics and neuroimaging in FTD will also be mentioned.

Obstacles exist in diagnosing bvFTD as it shares symptoms with primary psychiatric disorders like depression, bipolar disorder, schizophrenia, and OCD (118). Many bvFTD patients initially receive a misdiagnosis of a psychiatric disorder, delaying proper diagnosis by 5–6 years on average (118). Adding a social cognition test such as the Ekman 60 Faces Test, SEA, or Mini-SEA to routine neuropsychological evaluations for bvFTD in addition to using high-resolution 3D-T1 brain MRI can improve the detection and diagnosis of bvFTD (118).

Other possible solutions to improve FTD diagnosis include adding PRS, a new method being used in neurodegenerative diseases to estimate an individual's own genetic risk for developing a disease. (119) It works by analyzing large amounts of genetic data to predict how likely someone is to inherit a certain disease (119). PRS has been widely used in cancer and heart disease research initially and is now being explored in FTD, AD, and ALS research (119). Studies have shown that higher polygenic risk for FTD is linked to worse executive function (119).

New studies are also showing that TDP-43 is the most important biomarker for FTD, as it's found in about 50% of FTD and ALS cases (120). TDP-43 is involved in gene regulation and RNA transport, but in FTD and ALS, it becomes abnormal due to modifications like

hyperphosphorylation and ubiquitination, leading to protein buildup in the brain (120). Among FTD patients, those with C9orf72 or GRN mutations tend to have higher TDP-43 levels than those with MAPT mutations or non-genetic cases of FTD (83). FTD patients also have much higher levels of TDP-43 in their blood than those with AD and PD, making it a promising clinical tool for diagnosing FTD (120).

Current biomarker research also focuses on miRNAs, which regulate gene expression and show altered levels in FTD patients (121). Various studies have analyzed miRNA changes in blood plasma, serum, CSF, and brain tissue to distinguish FTD from AD, ALS, and HCs (121). Specific miRNA combinations or ratios have been identified as potential biomarkers for FTD (121). In particular, miR-223-3p, miR-15a-5p, and miR-22-3p in blood and miR-124 in CSF have shown promise in helping differentiate FTD subtypes and track disease progression in patients (121).

Establishing combinations of biomarkers has shown promise to differentiate FTD from other diseases and healthy controls. For example, a combination of MFG-E8, tTau, and Aβ42 has shown promise in differentiating FTD from HCs with 82% specificity (122). The trio of YKL-40, pTau, and p/tTau ratio has been successful in differentiating FTD from AD and DLB with a 91% sensitivity and 84% specificity (122).

A study mapping out the progression of familial FTD by analyzing various fluid biomarkers found that CSF NPTX2 was the earliest biomarker to show abnormalities in patients, followed by NFL in blood and CSF (123). A different study examining CSF biomarkers to differentiate between bvFTD, primary psychiatric disorders, AD, and HCs found that lower levels of NPTX2 were specific to bvFTD (124). Adding NPTX2 to the established biomarker NFL slightly improved the ability to distinguish bvFTD from psychiatric disorders (124). Additionally, researchers determined that NPTX2 plays a key role in maintaining synapses and that its levels were lower in both genetic and non-genetic forms of bvFTD, suggesting it could be a useful biomarker for tracking disease progression (124). Finally, there is mounting evidence suggesting that plasma levels of the protein sST2 can be used in the detection of neurodegenerative diseases, with its highest concentrations being seen in FTD and increased levels also being seen in AD and PD (125).

Researchers have also investigated truncated STMN2 RNA as a potential biomarker for TDP-43 pathology in FTD (126). They found that truncated STMN2 levels were elevated in FTD and ALS patients with TDP-43 pathology, but not in those with PSP, connecting it to TDP-43 dysfunction (126). Poly (GP) has also shown strong evidence that it can play a role in the early detection of genetic FTD, as it's found in both symptomatic and presymptomatic carriers of C9orf72 mutations, indicating that C9orf72-related abnormalities begin before symptoms appear (127). Other fluid biomarkers that have been investigated, such as pNfH, GFAP, C3b, and C1q, have shown to become abnormal later in the FTD disease process and show promise as biomarkers to track disease progression (123).

In terms of developing neuroimaging biomarkers, certain modalities show promise as well. A study looking at MRIs developed three MRI-based imaging biomarkers, namely API, ASI, and TPL, to help diagnose FTD and distinguish its subtypes from one another (128). API was useful in identifying FTD from non-FTD and AD patients, performing with an accuracy of about 82-83% (128). ASI was particularly helpful in identifying two primary progressive aphasia subtypes, while TLP was highly specific for detecting svPPA (128).

4.6 RPD and its biomarker future

In this chapter, RT-QuIC RT, NFL and ELISA testing for detecting newer 14-3-3γ isoforms will be reviewed. The p-Tau/t-Tau ratio, alpha-synuclein and novel biomarkers like BD-tau which can be detected in CSF and plasma will also be discussed. Lastly, the role skin biopsies can play in detecting RPD will be briefly mentioned.

RT-QuIC shows major potential in diagnosing prion diseases and plays a major role in drug screening, prion strain discrimination, and detection of other protein misfolding diseases (92). Several studies have found that NFL levels in CSF are significantly higher in prion diseases compared to patients with and without other degenerative diseases (91). This suggests that NFL could serve as an initial screening tool for RPDs to quickly check for ongoing neuronal damage before clinicians perform other more specific tests like RT-QuIC or MRI (91). Additionally, tracking NFL levels over time could help monitor disease progression in prion disease patients (91). Higher NFL levels in CSF or blood seem to be linked to faster disease progression, greater

functional impairment in patients, and shorter survival time, making it a valuable marker for patient management and clinical trial planning (91).

Newer 14-3-3γ isoform ELISA assays have shown better diagnostic performance than the standard Western blot test, meaning it may be a more reliable tool for detecting sCJD in future clinical applications (92). CSF t-Tau has been shown to be significantly elevated in sCJD and has been suggested as a diagnostic biomarker by researchers (92). Most studies report that t-Tau has a high sensitivity and specificity, around 90%, meaning it can accurately detect sCJD (92).

Other studies comparing traditional t-tau and 14-3-3 proteins showed that t-tau is superior in diagnosing sCJD, particularly for MV2K cases (129). T-tau was also more reliable than 14-3-3, especially in differentiating sCJD from inflammatory conditions and subacute dementias (129). However, t-tau was less effective at distinguishing sCJD from AD, whereas Aβ42 and p-tau levels provided additional value. (129)

The p-Tau/t-Tau ratio shows higher accuracy than t-Tau alone for distinguishing sCJD from other neurological diseases (92). Studies show that this ratio has an AUC of 0.98-0.99, indicating extremely high diagnostic accuracy for differentiating sCJD from AD and other rapidly progressive dementias (92). Large studies have further confirmed that the p-Tau/t-Tau ratio outperforms t-Tau alone as a biomarker, making it more specific for diagnosing sCJD (92).

Then, alpha-synuclein, was also found to be significantly elevated in sCJD, likely due to rapid neurodegeneration in patients (92). A large multi-center study demonstrated that alpha-synuclein has excellent diagnostic accuracy, with an AUC greater than 0.99, a sensitivity of 98%, and a specificity of 97% in distinguishing sCJD from other neurological disorders, including dementia syndromes, using ELISA (92).

Currently, blood-based biomarkers exist that match the specificity of CSF RT-QuIC for diagnosing sCJD (92). One promising biomarker candidate is plasma or serum t-Tau, which has been found to be elevated in sCJD compared to HCs and those with other neurodegenerative conditions (92). Its diagnostic accuracy varies, with an AUC of 0.94 when distinguishing sCJD from HCs but dropping to 0.72 when differentiating sCJD from other dementia syndromes (92). Lastly, one study found that plasma t-Tau levels were better at predicting survival time in sCJD

than CSF t-Tau levels or other fluid biomarkers, suggesting it can be used in disease prognosis (92).

Novel biomarkers have also been researched. Studies have shown that novel biomarkers such as BD-tau are significantly increased in both CSF and plasma of CJD patients, particularly in the most common subtypes MMV1, VV2, and genetic CJD M1 (130). In comparing different diagnostic scenarios, CSF BD-tau in combination with t-tau performed better than all other biomarkers (130). Plasma BD-tau combined with t-tau/p-tau217 ratios reached a comparable diagnostic accuracy to that of CSF 14-3-3, making it a promising non-invasive blood test for RPD diagnosis (130). Another study looking at plasma GFAP found that its levels were significantly higher in CJD patients compared to other RPDs and HCs (131). This suggests that astrocyte activation is a key feature of prion disease (131). When assessing diagnostic accuracy, plasma GFAP performed similarly to plasma tau and better than NFL (131).

There have also been studies examining how well skin punch biopsies can detect prions in CJD patients (132). Researchers found that the Bv23-230 method was better at detecting the most common CJD subtype (sCJDMM1) than the Ha23-231 method (132). The test worked especially well for sCJDVV2 and MV2K subtypes, suggesting that prion activity in the skin is higher in these cases. (132) Genetic CJD also showed strong results, like CSF tests in patients (132). Researchers found that the neck is a more reliable location for sampling than the thigh (132). This study also found that prion levels in the skin increase as the disease progresses (132). For instance, a patient who initially had a negative thigh sample later tested positive in both the thigh and neck as the disease advanced (132). This suggests that prions spread from the brain to the skin over time (132). Overall, the findings by researchers confirm that skin biopsies using RT-QuIC are a highly accurate way to diagnose prion disease (132). Researchers stipulate that skin biopsies could be used alongside or instead of CSF testing, especially when a spinal tap isn't possible (132).

5. Conclusion

This literature review went over a variety of validated biomarkers that can differentiate between types of dementia and other diseases that may be considered in the differential. Currently, neuroimaging and CSF biomarkers tend to be the most validated biomarkers to establish a diagnosis, but they are more costly and invasive. BBMs are beginning to play a more prominent role in the diagnosis of dementia, although they are found in smaller concentrations in diseases like AD. Genetics can also play an important role in the diagnosis of dementia, as seen in FTD. A lot of research is being conducted to find cheaper, less invasive, and more accessible biomarkers to screen for dementia and track its progression. It's imperative that CSF biomarkers be translated to other fluid-based biomarkers, and modalities such as proteomics, mass spectrometry, and SIMOA, among others, will play an important role in that development. AI and deep learning will also play a prominent role in the future of biomarkers of dementia, diagnosing dementia, and tracking disease progression in patients. Across-the-board standardization of biomarkers and diagnostic modalities is important. Future research should seek to validate non-invasive biomarkers. AI ethics and its role in biomarker research and application would be a good topic to study in the future. Lastly, another key aspect not addressed in this review and worth exploring is the link between biomarkers and disease-modifying treatment of dementia, as well as the role biomarkers can play in that regard.

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7. Annex #1

Biomarker/Test	Dementia Subtype or General	Key characteristics
MMSE	General	• Quick screening tool; tests cognitive domains such as orientation, recall, attention, arithmetic, language, and constructional praxis • Lacks sensitivity for dementia diagnosis
MoCA	General	• Screening tool • sensitive for detection of MCI and tests for a wider range of cognitive domains such as memory, language, attention, visuospatial, and executive functions than the MMSE • AUC of 0.846 for MCI detection
Mini-Cog	General	• Screening tool • results are not influenced by the patient's educational status or language comprehension • three-item recall test for memory + a clock drawing test
CDT	General	• Screening tool • the patient to draw a clock from memory with the hands indicating a specific time
AD8 Dementia Screening Interview	General	• screening tool • eight-item questionnaire addressed to the patient's loved one or caretaker to detect dementia and cognitive impairment • 93% sensitive but only 46% specific
GFAP	General	• Biomarker of neuroinflammation and neuronal damage

		• Levels are increased up to 15 years in patients before they're diagnosed with dementia • hazard ratio ranging from 2.25 to 3.15 • AUC between 0.8 and 0.89 • In plasma, it was observed that the best biomarkers for early AD detection; Plasma GFAP enabled the distinction between HCs and each of the AD groups
NFL		• Biomarker of neuroinflammation and neuronal damage • Levels are increased up to 15 years in patients before they're diagnosed with dementia • Hazard ratio from1.98 to 4.23 • Incremental increases correlate with worsened numeric memory and prolonged reaction time • AUC from 0.80 to 0.89 for dementia • Higher NFL levels can indicate that a patient that possesses a genetic mutation such as GRN, MAPT, or C9orf72 and is likely to convert to full-blown dementia • CSF NFL levels were more than three times higher in FTD patients compared to HCs • NFL levels were significantly higher in FTD compared to MCI-AD
CSF Aβ-42	AD	• Important early diagnostic marker • Normal levels in combination with t-tau and p-tau 181, rule out AD • The combined measurement of Aβ42, T-tau, and P-tau181 provides the most reliable means of distinguishing AD from cognitively healthy individuals • As the disease progresses, Aβ-42 levels decrease

		• combining Aβ42 and Aβ40 analysis enhanced the diagnostic accuracy of AD
CSF tau	AD	• Appear later in the disease process and correlate strongly with cognitive decline • CSF t-tau and p-tau are strongly associated with a rapid clinical disease deterioration • Increased levels correlate with significant brain atrophy, particularly in the hippocampus
CSF Aβ40	AD	• Most abundant Aβ marker in CSF found at concentrations approximately ten times higher than Aβ42 • Combining Aβ42 and Aβ40 analysis enhanced the diagnostic accuracy of AD
CSF Aβ42/Aβ40 ratio	AD	• Outperforms Aβ42 alone in identifying AD • Aligns more closely with amyloid PET positivity and holds significant diagnostic value in clinical practice • Reliably distinguishes AD from PDD and DLB compared to stand-alone testing of CSF Aβ42 and Aβ40 • In patients with an atypical presentation of the disease, a decreased CSF Aβ42/40 ratio is indicative of atypical AD
CSF p-tau 181	AD	• CSF p-tau 181, NFL, and GFAP strongly correlates with disease progression and worsening in AD patients • When combined with measurement of Aβ42, T-tau • Provides the most reliable means of distinguishing AD from cognitively healthy individuals • Concentrations are significantly higher in the CSF of AD patients compared to DLB patients
CSF SNAP-25	AD	• Biomarker of synaptic transmission and neurotransmitter release

		• Highly specific for AD in the early stages of the disease • Ng, SNAP-25 and synaptotagmin-1, as well as NFL increase in atypical forms of AD
CSF Ng	AD	• Biomarker of synaptic dysfunction in the brain • When combined with CSF biomarkers Aβ42/40, pTau181, t-Tau, and SNAP-25, it could help differentiate EOAD from HCs and other early onset dementias • Ng, SNAP-25 and synaptotagmin-1, as well as NFL increase in atypical forms of AD
CSF p-tau/Aß42 ratio	AD	• Reached acceptable levels of sensitivity and specificity to differentiate AD from PPA
p-tau181/Aβ42 ratio	AD	• Useful for differentiating AD from FTD
P-tau 231	AD	• Concentrations are significantly higher in the CSF of AD patients compared to DLB patients
CSF YKL-40	AD	• Increased levels in the CSF of AD patients correlated strongly with neuroinflammation and microglia in the pathophysiology of AD
CSF FABP3	AD and DLB	• Levels were significantly increased in AD and DLB patients compared to those with PD and other neurodegenerative conditions • FABP3 and p-tau demonstrated higher sensitivity in differentiating AD from DLB (AUC 0.92)
Plasma Aβ42/40	AD	• Was observed one of the best biomarkers for early AD detection • Reached an 81% positive predictive value of high cortical Aβ burden, more than double what would be expected to find in the general population
Plasma p-tau231	AD	• Was observed that the best biomarkers for early AD • Can accurately identify AD patients and distinguish them apart from older adults without

		amyloid-β, achieving with an AUC between 0.92–0.94 • Successfully distinguished individuals across all Braak stages • Outperformed traditional markers like APOE ε4 status, plasma NFL, t-tau, and plasma Aβ42/Aβ40 measured by SIMOA
Plasma p-tau 181	AD	• Levels increased about 16 years before cognitive symptoms appeared • Successfully distinguished AD from DLB in autopsy-confirmed cases • Outperformed traditional markers like APOE ε4 status, plasma NFL, t-tau, and plasma Aβ42/Aβ40 measured by SIMOA
Plasma p-tau 217	AD	• Levels began increasing nearly 20 years before the expected onset of MCI • Outperformed traditional markers like APOE ε4 status, plasma NFL, t-tau, and plasma Aβ42/Aβ40 measured by SIMOA • More accurate and reliable biomarker than p-tau181 for detecting AD and predicting disease progression
Plasma APP669–711/Aβ42 ratio	AD	• With Aβ40/42 ratio can accurately diagnose AD • This composite biomarker achieved approximately 90% accuracy in two separate studies when compared to Pittsburgh compound B (PIB)-PET scans, which serve as the gold standard for detecting amyloid plaques
MIBG cardiac scintigraphy	DLB	• Tests for postganglionic sympathetic degeneration in the heart • Exclude patients with comorbidities or on medications since they can produce abnormal MIBG images
Polysomnography	DLB	• If the recording shows REM sleep without atonia in a patient with a history of RBD but no

		confirmed dementia, there is more than a 90% chance that the patient has a synucleinopathy → sufficient to justify a probable DLB diagnosis
EEG	DLB and Prion disease	• Non-invasive, low-cost, accessible • Similar sensitivities to SPECT • Abnormalities on EEG are found in posterior regions • Increased posterior slow-wave activity, which is specific for DLB, while patients with AD, the regions affected on EEGs are the temporal lobes • For prion disease, the EEG presents with the classic periodic sharp and slow wave complexes later in the disease course, making it useful for diagnosis
C9orf72 mutation	FTD	• Tested for through repeat-primed PCR and confirmed with Southern blotting •
GRN	FTD	• Identified by targeted next-generation sequencing panels
Progranulin	FTD	• Levels are lower in the CSF of patients with bvFTD and svPPA
CSF RT-QuIC	RPD	• Support an RPD diagnosis • nearly 100% accuracy by using RT-QuIC testing on both CSF and olfactory mucosa OM samples
14-3-3 Protein	RPD	• Supports the clinical diagnosis of probable CJD • Which can be detected with Western blotting, is widely used as a diagnostic tool for sCJD • Sensitivity of 92% and a specificity of 80% (

Table 1: Summary of Neurophysiological, CSF, BBM and genetic biomarkers in dementia

Dementia subtype	Neuroimaging findings
AD	• Structural MRI: shows atrophy of the grey matter as well as volume loss indicative of neurodegeneration; atrophy in AD begins in the medial temporal lobe and then further progresses to the lateral-temporal and parietal cortices • MRI: Patients with AD lose about 4.5 % of their hippocampal volume annually • 7T MRI scanners: Analysis of the hippocampus suggests that the pre-subiculum is the earliest subfield to be involved in AD, with it experiencing the greatest atrophy • PET: correctly identifies the presence or absence of AD in 88% of cases, displaying a sensitivity of 94% and a specificity of 73%; Amyloid PET is the most extensively validated biomarker for the identification of amyloid plaques in the brain with a 92% sensitivity and 100% specificity • [11C] PiB : 96% of AD patients displayed significant amyloid accumulation in the brain compared to two-thirds of patients with MCI; increased cortical uptake with the highest retention being seen in the frontal, cingulated, precuneus, striatum, parietal and lateral temporal cortex • FDG-PET: bilateral hypometabolism in the parietal and medial temporal regions and the precuneus; glucose hypometabolism extends to the frontal

	cortex and the entire brain as the more severe the disease is • [18F]florbetapir: increased amyloid retention in the frontal, temporal, occipital, parietal, cingulate, and precuneus cortical areas compared to HC's
Atypical AD	• Structural MRI: prominent atrophy in most prominent in regions corresponding to the clinical phenotype; the hippocampus spared early on in the disease process • Tau PET ligand: binding is greater in medial temporal regions
VaD	• Extensive confluent white matter lesions, multiple lacunes or bilateral small thalamic infarcts • Structural MRI: patients in the early stages of VaD, show changes such as cortical thinning that can be seen in frontal, temporal, and occipital regions of the brain • volumetric MRI: VaD can be accurately identified with 96% sensitivity • SVD: small infarcts in the deep perforating vessels region; White matter lesions in SVD appear hyperintense • FLAIR: Can visualize white matter lesions that are caused by chronic hypertension; white matter lesions in SVD appear hyperintense

	• T2 MRI imaging: white matter lesions in SVD appear hyperintense; enlarged VRS observed in SVD • DTI imaging: imaging studies of white matter integrity correlate with the severity of dementia, decreased cognition, motor function, and increased cerebral atrophy • 7T MRI: Cortical microinfarcts in SVD • ASL: demonstrated that subjects with diffuse confluent WMH have approximately 20% lower cerebral blood flow measurements than subjects with punctiform or early confluent WMH • FDG-PET: in VaD patients detect hypometabolism in a scattered pattern in cortical and subcortical regions as well as deep grey matter and the cerebellum, helping distinguish it from AD • amyloid PET: can help rule out VaD as tracers show minimal binding in the majority of patients with VaD
DLB	• FP-CIT SPECT: dopamine uptake is severely reduced in the putamen in the basal ganglia, and this technique is 80–90% accurate in detecting DLB or PDD • DAT imaging plays a crucial role in differentiating DLB from other non-parkinsonian neurodegenerative disorders, such as AD • SPECT imaging: a sensitivity of 100% and a specificity of 92% for diagnosing DLB at autopsy

	• Voxel-based morphometry: detect atrophy specifically in the anterior cingulate cortex, which is crucial for attention and decision-making, and the insular cortex, which is linked to emotions and awareness • Swallow tail sign on MRI: 93% sensitivity and 87% specificity for DLB • Island sign ratio: PET based biomarker with 79% to 92% accuracy in detecting DLB
bvFTD	• Aymmetrical frontal and temporal atrophy, with the orbitofrontal sulci widening early in the disease process → over time, atrophy extends to the insula, anterior cingulate, amygdala, thalamus, and striatum, causing behavioral and personality changes in patients • Patients with MAPT mutations exhibit a diverse range of atrophy patterns in the frontal and temporal lobes, insula, anterior cingulate, parietal lobe, basal ganglia, and brainstem, with more pronounced temporal lobe shrinkage • Those with TDP-43 pathology display widespread atrophy in the frontal, temporal, and parietal lobes, which is often asymmetric, with the parietal lobes being more severely affected • GRN mutations: frontal, temporal, and parietal atrophy • DTI: white matter damage, especially in the frontal lobes • ASL: has sensitivity and specificity like FDG-PET, with ASL achieving

	83% sensitivity and 93% specificity in distinguishing bvFTD from AD • FDG-PET: sensitivity of 89% and specificity of 78% in distinguishing bvFTD from AD
svPPA	• The most noticeable shrinkage happens on the left side of the brain, especially in the front and lower parts of the temporal lobes, impacting areas like the temporal pole, perirhinal cortex, fusiform gyrus, hippocampus, and amygdala → As the disease progresses, atrophy spreads to other parts of the left temporal lobe, frontal lobe, insula, and anterior cingulate and can also spread and affect the right temporal lobe • DTI: damage to white matter in both temporal lobes, particularly on the left side, impacting pathways like the inferior longitudinal fasciculus and uncinate fasciculus • SPECT: reduced perfusion and metabolism mainly in the left anterior temporal lobe
nfvPPA	• Atrophy is usually first detected in the left inferior frontal lobe, insula, and premotor cortex, with further progression involving the frontal, temporal, and parietal lobes, as well as deeper structures like the caudate and thalamus • DTI: damage to white matter pathways involved in speech and motor function, particularly in the left arcuate fasciculus, superior motor pathway, and perisylvian regions • FDG-PET: low metabolism in important speech-related areas such as

	the left inferior frontal gyrus, frontal operculum, insula, and supplementary motor areas
PSP-bvFTD	• Display atrophy in the posterior cerebellum, some atrophy in the frontal lobe, but their temporal lobes stay normal • Symmetric atrophy • damage in the anterior thalamus, cingulum, and fronto-orbital white matter • FDG-PET: widespread hypometabolism in the prefrontal cortex, caudate, thalamus, and midbrain (
CBD-bvFTD	• Show even shrinkage in the front part of the brain, around the Rolandic area, and in the striatum • Asymmetric atrophy • loss of white matter integrity in the motor thalamus, precentral gyri, and postcentral gyri • ASL imaging: shows reduced blood flow in the right hemisphere • SPECT: reduced neurotransmitter function, including dopaminergic and cholinergic deficits in the striatum, anterior cingulate, and thalamus • FDG-PET: metabolic reductions on the side opposite the affected body part,
RPD	• CT: can help rule out emergencies like stroke or hydrocephalus • MRI: provide more detailed insights into neurodegenerative patterns,

	vascular conditions, or inflammatory diseases
CJD	• DWI MRI: key for early diagnosis; detect signal hyperintensities very early in the disease course and are included in the criteria for prion disease diagnosis; cortical ribboning and deep grey matter nuclei, which can be symmetric or asymmetric • FLAIR: detects signal hyperintensities very early in the disease course and are included in the criteria for prion disease diagnosis • MRI has a sensitivity of 91–96% and specificity of 92–94%, making it the best diagnostic biomarker for differentiating CJD from other RPDs

Table 2: Summary of Neuroimaging biomarkers for each dementia subtype

Annex #2

Annex 6. Pledge. To be completed by the student when uploading the thesis to the VUSIS; no separate submission of the pledge is required

Vilniaus universiteto studento, teikiančio baigiamąjį darbą, GARANTIJA	**PLEDGE of Vilnius University student submitting a thesis**
Vardas ir pavardė: Ron Heifets	Given name and surname: Ron Heifets
Padalinys: Faculty of Medicine	Faculty: Faculty of Medicine
Studijų programa: Medicine (English-full time studies)	Study programme: Medicine (English-full time studies)
Darbo pavadinimas: : Role of Biomarkers for Differential Diagnosis of Dementias	Thesis topic: Role of Biomarkers for Differential Diagnosis of Dementias
Darbo tipas: Literature Review	Thesis type: Literature Review
Garantuoju, kad mano baigiamasis darbas yra parengtas sąžiningai ir savarankiškai, kitų asmenų indėlio į parengtą darbą nėra. Jokio neteisėto atlygio už šį darbą niekam nesu mokėjęs. Šiame darbe tiesiogiai ar netiesiogiai panaudotos kitų šaltinių citatos pažymėtos literatūros nuorodose.	I pledge that my thesis has been prepared in good faith and independently and that there has been no contribution by other individuals to this thesis. I have not made any illegal payments related to this thesis. Quotes from other sources used in this thesis, directly or indirectly, are indicated in the list of references.
Aš, [Vardas Pavardė], patvirtinu (pažymėti) ☑	I, Ron Heifets *confirm (check)* ☑

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