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REVIEW ARTICLE

Evaluating Diagnostic Tools for Frontotemporal Dementia: Current Limitations and Emerging Advances

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ABSTRACT: Frontotemporal dementia (FTD) is associated with one of the highest patient burden rates among all dementia types, typically affecting individuals between the ages of 40 and 65. Diagnosing FTD is challenging due to its symptomatic overlap with other neurodegenerative disorders, such as Alzheimer's Disease (AD). Clinical data show that only one-third of suspected FTD cases are ultimately confirmed, while almost half of misdiagnoses stem from misinterpreted neuroimaging. Current diagnostic methods lack FTD-specific biomarkers, instead relying on indicators shared with AD, compromising accuracy. This review synthesizes current limitations in primary diagnostic approaches for FTD, highlighting how integrative methods in neuroimaging and cerebrospinal fluid biomarkers, alongside advancements in genetic screening, may substantially improve diagnostic precision. Genetic testing effectively identifies pathogenic variants, which can be enhanced by incorporating modifier genes that influence disease onset and progression. Neuroimaging tools like MRI and FDG-PET provide structural and metabolic information about the brain, and their limitations can be alleviated through artificial intelligence and multimodal integration. Cerebrospinal fluid biomarkers—including neurofilament light chain, t-tau, and inflammation-related markers—support differential diagnosis. Multi-protein panels demonstrate high specificity with an AUC ranging from 0.91 to 0.96 in distinguishing FTD. Together, these findings support early detection and address a critical diagnostic gap.

KEYWORDS: Behavioral and Social Sciences, Neuroscience, Frontotemporal Dementia (FTD), Biomarkers, Diagnostic Tools.

Introduction

Frontotemporal dementia (FTD) remains one of the most frequently misdiagnosed neurodegenerative disorders. This is largely due to overlapping behavioral symptoms and a limited number of reliable biomarkers. This diagnostic limitation contributes not only to delayed treatment but also to prolonged psychological and emotional burden for patients and their families. The difficulty in distinguishing the primary causes of FTD through current biomarkers represents a critical area of research focused on improving biomarker accuracy. FTD refers to a group of neurodegenerative disorders that primarily cause damage to the neurons in the frontal and temporal lobes. This degeneration ultimately leads to the atrophy of nerve cells.[1] This targeted damage results in two major variants: behavioral variant FTD (bvFTD) and primary progressive aphasia (PPA), as illustrated in Figure 1.

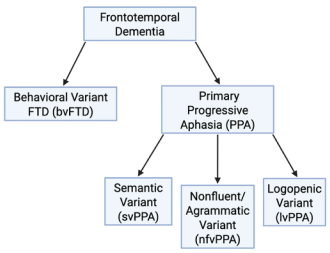

Figure 1: Major Variants that Make Up FTD. This diagram presents the major clinical subtypes of FTD, organized into behavioral and language-based categories. Each subtype is associated with distinct patterns of neurodegeneration and symptoms. Information gathered from the National Institute on Aging and created using Biorender.

Generally, symptoms of FTD can be associated with the region of the brain that has experienced atrophy. Although that is the primary cause of FTD symptoms, the neurodegeneration itself is driven by underlying causes such as protein accumulation and genetic mutations. Determining reliable biomarkers that can pinpoint the primary underlying causes of FTD remains a complex and ongoing area of research. This requires relying on diagnosis based on personal history and behavioral symptoms, which can result in symptoms being overlooked or misdiagnosed. For instance, behavioral variant FTD—the most common variant of FTD, is frequently misdiagnosed for psychiatric and other neurological disorders due to its symptoms overlapping. This pattern persists across other subtypes of FTD, where there is a lack of identified biomarkers that can provide a near-definite diagnosis and prevent misinterpretation of FTD.

A 2025 study by the University of Queensland found that of the 100 patients used in their study, only 34 of them were found to be true-positive cases of FTD.[2] It was later concluded that misinterpretation of nuclear imaging was the cause of about 50% of all falsely diagnosed cases. FTD is one of the most common types of young-onset dementia, typically affecting individuals between the ages of 40 and 65. It accounts for about 5-15% of all dementia cases.[3] FTD's nature to affect a younger population compared to other dementias often contributes to the high rates of misdiagnosis since it falls out of the age range that dementia is usually associated with.

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Another study conducted in Brazil, by two researchers, examined the diagnostic outcomes across 30 patients, which included 10 with FTD, 10 with Alzheimer's disease, and 10 with no neurodegenerative disorders. During the span of 12 months, it was found that FTD patients exhibited the highest misdiagnosis rate, often diagnosed with psychiatric disorders such as depression, bipolar disorder, schizophrenia, and obsessive-compulsive disorder, especially common for the behavioral variant.[4] These data can be linked to FTD cases being more likely to be misdiagnosed as a psychiatric disorder if the patient has a personal history of psychiatric disorders.

Several biomarkers used in diagnosis are not exclusive to FTD but are shared across multiple diseases. This can impede an accurate diagnosis by making the misinterpretation of biomarkers harder to avoid. Research conducted by the University of Washington in 2025 analyzed over 10,000 samples and found that 996 proteins are shared across Alzheimer's, Parkinson's, and FTD.[5] Protein accumulation, along with genetic mutations in FTD, is challenging to identify, and various studies urge researchers to focus on distinguishing biomarkers specifically for FTD.

Frontotemporal dementia, like most neurodegenerative diseases, lacks a definitive cure, with current therapies focused primarily on symptom management. The delay in diagnosis prevents individuals with FTD from accessing appropriate treatment for several years. Without an accurate diagnosis, patients may receive ineffective treatment while the disease continues to progress. This outcome is preventable—however, doing so requires a deeper understanding of FTD and its diagnostic indicators. This study addresses this need by evaluating current diagnostic tools and proposing strategies to overcome their limitations, with the goal of identifying reliable FTD-specific biomarkers.

Methodology

This study is a literature review focused on the most prevalent diagnostic tests used in FTD diagnosis to identify strengths and limitations based on various research articles. After identifying a gray area in diagnosis, this research analyzed emerging evidence on potential biomarkers that display the potential to enhance diagnostic accuracy. To conduct this research, this paper solely used online and published sources from scientific databases such as the National Library of Medicine and the National Institute of Health. The selection criteria required that all sources be peer-reviewed when applicable and published within approximately the last ten years, generally between 2015 and 2025. In addition to peer-reviewed studies, reputable scientific and medical websites such as the Wisconsin Alzheimer's Institute were included when they provided foundational or contextual information necessary to understand diagnostic procedures or biomarker mechanisms. Using these criteria, a total of 55 sources were reviewed. Searches were conducted using terms such as "FTD emerging biomarkers 2020-2025," "FTD brain scans compared to AD," "emerging advances in FTD diagnosis," and similar variations to capture both established and developing diagnostic approaches. First, research papers containing current diagnostic methods for FTD were gathered to understand the procedure for the diagnostic test and to then recognize the limitations of what each test could detect. Afterwards, papers that focused on investigating biomarkers that may eliminate the limitation identified through experiments and trials were analyzed to see if the results supported the use of the biomarker for the diagnosis of frontotemporal dementia. The primary goal of this paper is to highlight biomarkers and diagnostic tests that provide a high diagnostic accuracy for FTD. After an in-depth analysis of current diagnosis methods, this review was able to find promising biomarkers that require further research to be able to implement them in current diagnosis. As this study relied solely on literature-based sources and did not involve any physical tools, materials, or human participants, no ethical considerations were required.

Discussion

Frontotemporal Dementia:

Frontotemporal Dementia (FTD) is a term used to describe a group of neurodegenerative disorders that belong to a broader category of frontotemporal lobar degeneration (FTLD). Within FTD, different variants arise, which can be characterized by symptoms including difficulty in emotional and behavioral control. In addition to psychological abnormalities, FTD may result in executive dysfunction. This includes difficulty in movement or walking and trouble verbally communicating. These various symptoms are the result of damaged neurons in the brain, which gradually lead to shrinkage in the area in which the damage occurred.[6]

Degeneration caused by FTD primarily takes place in the frontal and temporal lobes of the brain. The lobe of the brain that is affected first or most is dependent on which symptoms appear first. If a common pattern of difficulty in decision making or using appropriate behavior in a specific setting is found, then it can be correlated to degeneration in the frontal lobe. The same can be observed with degeneration in the temporal lobe, which is associated with symptoms like language comprehension and processing auditory information.[1]

The cause of FTD is not yet identified, but there is evidence of underlying causes that can trigger progressive degeneration of neurons. One of the major contributors to atrophy is protein aggregation—a common characteristic in neurodegenerative diseases.[7] An error in protein misfolding is a common occurrence within cells, and it is often managed through cellular mechanisms that have evolved to ensure proper folding. These cellular mechanisms include a variety of molecular chaperones that facilitate either refolding misfolded proteins or redirecting proteins that cannot be refolded to ubiquitin and autophagy, which are cellular mechanisms that are able to degrade the misfolded protein.[8] If these mechanisms fail to eliminate the misfolded proteins, over time, the proteins will abnormally cluster and accumulate in the frontal and temporal lobes of the brain, which will lead to neurotoxicity and neurodegeneration.[9] The specific proteins that are associated with the development of FTD through protein aggregation are tau pathology and TDP-43 proteinopathies. The mislocalization

and buildup of these proteins have been linked to neuronal atrophy.[10, 11]

Around 30% of all FTD cases have a strong family history. This heritability is attributed to the genetic mutations that are passed down in an autosomal dominant pattern. The mutated genes that have been identified to cause FTD are *MAPT*, *GRN*, and *C9orf72*. These genes encode for cellular functions in the nervous system and contain the instructions for coding specific proteins. These proteins include tau and TDP-43: a mutation in these genes often results in improper protein formation, hence becoming an underlying cause for FTD. Tau pathology is the result of a mutation in the *MAPT* gene, while TDP-43 proteinopathies are the result of mutations in the *GRN* and *C9orf72* genes. Besides disrupting protein synthesis, these three genes can also interfere with cellular mechanisms that monitor protein folding and eliminate any improperly folded proteins.[12]

Prevalence & Demographics:

Over 10,000 papers dedicated to FTD research have been published between 2000 and 2022. These papers have been published in over 900 academic journals from over 80 countries/regions.[13] These articles touched upon various topics with a trend of research in the pathological mechanisms of FTD. Even though FTD is classified as a rare disease with a global prevalence rate of 15-22 per 100,000 among individuals aged 45 to 64, FTD remains a disease worth researching.[14] Studying FTD unlocks a broader path of understanding mechanisms like protein aggregation, tauopathy, and TDP-43 pathology. Additionally, FTD has a strong link with mutations in the *MAPT*, *GRN*, and *C9orf72* genes, which are prevalent in other neurodegenerative diseases—for example, Progressive Supranuclear Palsy (PSP), Corticobasal Degeneration (CBD), Parkinson's Disease (PD), and Amyotrophic Lateral Sclerosis (ALS).[15] Apart from how many people this neurodegenerative disease affects, it is important to understand how this disease affects the quality of life for someone who struggles with FTD.

While prevalence remains low, the age distribution is notable as approximately 60% of all FTD cases occur between the ages of 45 and 60. This dementia tends to occur at a younger age compared to most dementias and is also known as a young-onset dementia.[6] Due to this disease affecting the individuals earlier than most neurodegenerative diseases, it contributes to a wide range of challenges across physical, financial, emotional, and psychological domains. These challenges can be experienced both by the individual with FTD, who often experiences behavioral and psychological symptoms, and by caregivers who manage the resulting demands of care. To quantify these domains, clinical assessments such as the Neuropsychiatric Inventory (NPI), which measure patient neuropsychiatric symptoms severity, and the Zarit Burden Interview (ZBI), which measures caregiver burden, are commonly used.

Scales for Patient Symptom Severity & Caregiver Burden	Description	Scoring Index	FTD	AD
Neuropsychiatric Inventory	Measures the presence, frequence, and severity of behavioral and psychological symptoms in dementia patients	Total score range: 0 to 144 Higher scores indicate higher symptom severity	58.0 ± 19.3	3.6 ± 4.7
Zarit Burden Inventory	Assessing caregivers' emotional, physical, and social burden	Total score range: 0 to 48 0-10: no to mild burden, 10-20: mild to moderate burden, > 20: high burden	23.62 ± 15.9	12.26 ± 9.74

	FTD	AD
Financial Patient Burden (annual direct cost in USD)	$47,916	$28,078

Aside from direct cost, there are indirect costs such as loss of productivity and income for the patient and caregiver. This may significantly add to the annual cost in addition to the direct cost.

Figure 2: Comparison of Patient Symptom Severity and Caregiver Burden Between FTD and AD. When these three aspects of burden were compared—patient symptom severity (NPI), caregiver burden (ZBI), and financial burden—were compared between FTD and AD, individuals with FTD and their caregivers experienced significantly greater overall burden. Information gathered from Cummings, Bahia & Viana, Wisconsin Alzheimer's Institute, Liu *et al.*, Galvin *et al.*, and Nandi *et al.* Created using Biorender.

Cummings provides a comprehensive overview and description of the NPI, an assessment developed to assess behavioral and psychological symptoms of dementia. The NPI includes multiple variations, such as the original full version, which consists of all twelve domains, and the questionnaire version, a shortened, self-administered version.[16] Bahia & Viana conducted research that suggests that the original version of the NPI was used for both FTD and AD patients due to the number of domains evaluated; the comparative results are displayed in Figure 2.[17] In addition to the NPI, caregiver burden was assessed using the ZBI, which also includes different variations of the assessment.[18] When evaluating the caregiver burden for FTD and AD, Liu *et al.* likely used the short 12-item ZBI version, as indicated by the scoring range.[19] The last aspect used to compare patient burden between FTD and AD in Figure 2 is the financial burden in USD. The annual direct costs in USD for FTD and AD were sourced from Galvin *et al.* and Nandi *et al.*, respectively.[20, 21] Collectively, these three aspects demonstrate the challenges associated with a young-onset neurodegenerative disease.

A dementia is classified as a young-onset dementia if the onset of symptoms occurs before the age of 65. The symptoms of young-onset dementia can vary from those seen initially in older adults. These symptoms include behavior, language, personality change, and executive dysfunction. These symptoms can be commonly found in FTD variants such as bvFTD. The early development of dementia is linked to the heritability of dementia. This is demonstrated in FTD as it is more likely to be inherited than other dementia types, highlighting how genetic mutations have a strong influence on its development. Genetic mutations can trigger disease-causing processes like protein aggregation to occur at a younger age. Although FTD development happens before most dementias, it does not necessarily make it easier to detect. In fact, there remain various hurdles in concluding an accurate diagnosis.[22] These difficulties are derived from FTD's overlapping symptoms with psychiatric disorders or AD. Since several of the initial symptoms are

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behaviorally related changes, it can be easily misinterpreted. Moreover, there is no definitive test for FTD, and it takes various diagnostic tests to come to a diagnosis. Interpreting the results of multiple diagnostic tests can be challenging, often making it difficult to arrive at an accurate diagnosis. However, the available diagnostic tests can detect biomarkers indicative of FTD, aiding in the identification of its primary causes.[23]

Current Limitations and Emerging Advances in Diagnostic Tools:

Genetic Testing:

Genetic testing is a well-established and highly accurate diagnostic test, especially for neurodegenerative disorders, with underlying causes that include genetic factors like FTD. As medicine advanced, the complexity of genetic testing grew as its scope for identifying genetic mutations spread from single gene analysis to examining the entire genome.[24] Genetic testing's ability to detect pathogenic variants plays a critical role in accurate diagnosis. Genetic mutations are a prominent factor, occurring in nearly 40% of all identified cases of FTD, and have the potential to provide an accurate diagnosis.[25]

Typically, genetic testing is recommended when a family history of a specific disease is found in the patient's records. A strong family history of a disease can indicate that a genetic cause is triggering the development of the disease. Genetic testing may also be recommended if a clinician identifies a trend in the patient's symptoms or from previous diagnostic test results. Aside from clinician recommendations, it can additionally be used as predictive testing. If the patient is aware of a family history of FTD or related disorders like ALS, it may become a way of testing and diagnosing a patient before the symptoms develop. An early diagnosis of neurodegenerative disorders is the most desirable outcome, as symptoms can be immediately treated.

Genetic tests analyze deoxyribonucleic acid (DNA), which is acquired from samples of blood, hair, skin, amniotic fluid, or other tissues. The DNA is further examined in a laboratory where it is inspected for changes in chromosomes, DNA, and protein.[26] In the case of FTD, the most common mutations found from genetic tests occur in the *MAPT*, *GRN*, and *C9orf72* genes. More rare genetic mutations include *TARDBP*, *VCP*, *FUS*, *CHMP2B*, *SQSTM1*, *UBQLN1*, or *TBK1* genes.[25]

	Protein & Function	Prevalence in FTD	Penetrance	Disease Duration
C9orf72	**C9orf72** Lysosomal homeostasis	20-25% of familial FTD & 6-8% of sporadic FTD	~0% at age 35 years, 50% at age 58 years, & near 100% at age 80 years	6.4 years on average
GRN	**Progranulin** Lysosomal homeostasis; inflammation	5-25%of familial FTD & 5% of sporadic FTD	Over 60% affected by age 60, rising to 90% by 75 and over 95% by 70	3-12 years
MAPT	**Microtubule-associated protein tau** Microtubule stabilization and assembly	5-20% of familial FTD & 2% of sporadic FTD	Typically a fully penetrant disorder, with rare cases of reduced penetrance in some families with specific *MAPT* variants	9.3 years on average

Figure 3: Summary of Mutated Genes Directly Linked to FTD. The table depicts each gene and the protein associated with the gene, its prevalence in FTD, the proportion of individuals with FTD who will show the associated signs and symptoms, and the duration of the FTD for an individual with that mutated gene. Information gathered from Sirkis *et al.*, Zampatti *et al.*, Gossye *et al.*, Hsiung *et al.*, Rohrer *et al.* Created using Biorender.

Sirkis *et al.* emphasizes FTD's heritability and provides a summary of the major mutated genes in FTD including each gene's associated protein and function, as well as the prevalence rates that were used in Figure 3.[27] Information on penetration and disease duration for *C9orf72* was gathered from Zampatti *et al.* and Gossye *et al.* respectively; both articles investigated the genetic complexity of FTD, particularly in relation to *C9orf72*.[28, 29] Similarly, the penetration and disease duration estimated for *GRN* were derived from Hsiung *et al.*, and for *MAPT* from Rohrer *et al.*[30, 31]

For over a decade, mutations in genes such as *C9orf72*, *GRN*, and *MAPT* have served as key diagnostic markers for FTD and have been identified through genetic testing. However, this diagnostic test does not complete the full picture of a patient's genetic risk. A positive genetic test result indicates that the individual carries the genetic mutation in their DNA. It is important to note that a positive test result may indicate the risk of developing the disease, but it is still possible that the individual may never actually develop the disease. If the individual has already developed FTD and the diagnostic test is being used as a means of diagnosis, it would be able to confirm that the individual has FTD, but it would provide limited information on how the disease would affect the individual.[32]

In order to enhance diagnosis results, it is important to take a step further than identifying the genetic mutation. There have been several cases where the genetic mutation in a gene has been established, but the age of onset and symptoms can vary. This becomes a more prevalent problem when several diseases share the same genetic mutations. Although genetic testing is an accurate diagnostic test, it is crucial to integrate other biomarkers and tests when intending to diagnose a patient and ensure the individual gets access to proper treatment.

Modifier Genes:

Modifier genes are defined as genetic loci that influence the expression of a primary disease-causing mutation, affecting parameters of a disease such as age at onset, severity of disease, and the duration of a disease.[33] This biomarker holds significant relevance for neurodegenerative diseases, as its integration into existing genetic testing could potentially enhance the ability to predict an individual's disease progression. Modifier genes have been identified in FTD, causing mutated genes which include *C9orf72*, *GRN*, and *MAPT*.

These common FTD-linked mutated genes demonstrate notable variability when it comes to expression in the individual. This variability can be attributed to genetic modifiers. For example, this can be observed in the *GRN* gene, which produces proteins called progranulin—a critical protein for the survival of nerve cells in the brain.[34] The FTD-causing gene mutation that occurs in this gene is known as a haploinsufficiency mutation, which suggests that an insufficiency of progranulin protein leads to neurodegeneration. Although the haploinsufficiency mutation itself drives degeneration in the brain, gene modifiers such as *SORT1* significantly impact the onset and severity of FTD, as variation near *SORT1* affects the production of progranulin. Modifier genes have also been identified for *C9orf72*, which has been mechanically linked

to *TMEM106B*—another modifier linked to progranulin, which influences lysosomal size and number. A specific variant of *TMEM106B—rs1990622 G* allele has been found to accelerate FTD's onset in *C9orf72* carriers. In contrast, the same gene modifier has also been found to affect *GRN*, but instead of accelerating the disease onset, the *rs1990622 G* allele is able to delay the disease.[35] There is not yet an identified gene modifier for the *MAPT* gene, like there is for *GRN* or *C9orf72* genes. Although there has been research done that found *TMEM106B* may have a link with tauopathies, which may suggest that *TMEM106B* could potentially be linked to *MAPT* as a modifier gene.[36]

Modifier genes clearly influence how FTD develops, which reinforces why it is essential to consider integrating the detection of modifier genes into genetic screening. Currently, there are established tests able to examine vast amounts of genomic data, including whole genome sequencing (WGS) and genome-wide association studies (GWAS). While researchers have been able to confirm that these tests can be utilized to detect modifier genes, they are typically used in research settings rather than as a diagnostic test.[37] Although modifier genes are more difficult to identify—since they do not directly cause the disease—it is still a promising emerging diagnostic test with potential to enhance diagnostic results as the field continues to evolve.

Neuroimaging:

Accurate diagnosis of FTD heavily relies on neuroimaging techniques that are able to identify patterns in neurodegeneration. Several neuroimaging techniques are utilized in diagnosis, one of the most widely used being magnetic resonance imaging (MRI). MRI scans—specifically structural MRIs—are commonly used due to their ability to analyze and present brain atrophy, which can potentially be used to recognize atrophy patterns and link those patterns to a disease.[38] For example, bvFTD typically exhibits atrophy on the frontotemporal lobes, with the right hemisphere often displaying more extensive atrophy than the left side.[39] For more specific results, clinicians often rely on volumetric MRIs—a type of structural MRI—which provide an analysis of the volume of a particular brain region. To analyze the volumes, the scans taken are compared to a database of healthy brains of individuals with similar age and sex to pinpoint changes in volume. This is an effective tool for monitoring neurodegenerative diseases and potentially detecting minor changes in brain volume that could otherwise be missed.[40]

Additionally, fluorodeoxyglucose positron emission tomography (FDG-PET) serves as a neuroimaging technique used in FTD diagnosis, by characterizing patterns of neurodegenerative and hypometabolism.[41] It is generally used when an MRI scan is inconclusive to make a clearer distinction by increasing sensitivity/specificity or providing more information on whether the disease is or is not present in an individual. In the early stages of dementia, FDG-PET outperforms MRIs in sensitivity, while MRIs outperform FDG-PET in specificity.

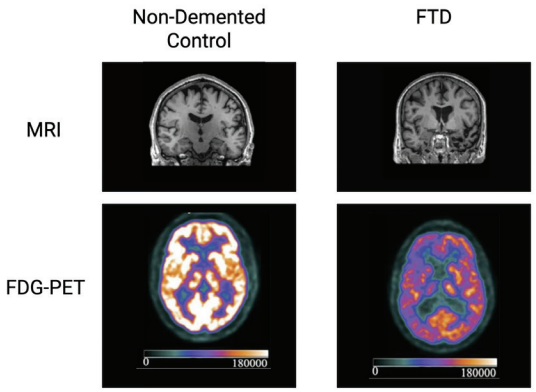

Figure 4: Comparison of MRI and FDG-PET Scans for Non-Demented Control and FTD Brain. The images captured using an MRI scan demonstrate how a brain looks after it has experienced atrophy due to FTD, while the images captured using an FDG-PET scan show the metabolic levels between the non-demented control and the individual with FTD. The color scale located at the bottom of the FDG-PET images indicates that the colors closer to 180000 convey a higher metabolic activity, whereas the colors closer to 0 imply a lower metabolic activity. Adapted from Chouliaras and O'Brien, and Ward *et al.* Created using Biorender.

Figure 4 compares the MRI scans from a FTD patient and a non-demented control, adapted from Figure 1 in Chouliaras and O'Brien's study, which explores how advanced brain imaging methods, such as MRI, can improve early detection and classification of dementia types.[42] These images highlight atrophy patterns that may aid in identifying or diagnosing FTD. Additionally, Figure 4 includes FDG-PET scans of a FTD patient and a control, adapted from Figure 3 in Ward *et al.*, providing a side-by-side comparison of two neuroimaging techniques.[39] This comparison demonstrates how combining biomarkers such as brain atrophy and metabolic changes may contribute to higher diagnostic accuracy.

However, it is important to note the risk modifiers that may alter findings of FDG-PET scans, such as traumatic brain injuries, diabetes mellitus, autoimmune disorders, and a family history of FTD. Studies have found that these diseases and illnesses may cause asymmetrical hypometabolism patterns. Therefore, it is crucial to take into account the individual's history of risk modifiers or other prior diseases or illnesses.[39]

Multimodal Imaging:

Structural MRIs along with FDG-PET scans are widely used and an established diagnostic tool for neurodegenerative diseases, including FTD. Combining the abilities of both neuroimaging techniques has shown significant improvements in diagnosis, as it provides a greater scale of biomarkers to examine when determining what neurodegenerative disease is being represented.[43] It is given that every scan provides a limited view of the brain: multimodal imaging is a technique that is able to overcome this gap by merging the strengths of multiple scans into one. This approach was demonstrated in a recent study using integrated PET/MR imaging to assess patients with FTD. Structural MRI was used to measure gray matter volume (GMV), while FDG-PET provided data on glucose metabolism, which was expressed as standardized uptake value ratios (SUVR). By acquiring both scans simultaneously, re-

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searchers were able to ensure precise spatial alignment, allowing for direct comparison across identical brain regions. Quantitative metrics, which refer to the measurable data extracted from each type of brain scan, were analyzed using voxel-wise analysis and region-of-interest (ROI) methods. These analysis tools essentially allowed the researchers to examine the brain in small 3D units called voxels, compare each voxel across subjects in order to detect subtle differences, and then zoom out to focus on larger name-based areas of the brain, such as the frontal lobe. Lastly, to verify anatomical consistency across scans and subjects, the study used the Automated Anatomical Labeling (AAL) atlas. This functioned as a detailed map of the brain, which divided the brain into named regions, each with clear boundaries. Multimodaling allows for a detailed analysis of the combination of data acquired from both scans.[44] This method is not flawless, but there are promising emerging fields that investigate how to further close the gaps of diagnosis, such as the use of artificial intelligence to enhance the accuracy of multimodal.

Artificial Intelligence:

Recent research by Wahul *et al.* demonstrates that fusion of neuroimaging driven by artificial intelligence significantly improves early detection and subtype classification of neurodegenerative diseases such as AD and FTD.[45] The review highlights how multimodal outperforms unimodal, combined with the use of deep learning frameworks, achieving diagnostic accuracies exceeding 90%. For example, when an electroencephalogram (EEG) machine learning data model was used, it reported an 81.1% accuracy in differentiating FTD from AD. Another aspect to consider when implementing artificial intelligence is its subset, machine learning. A 2025 study investigated how AI-aided automated brain volume analysis could enhance clinical assessment of FTD, including the classification of specific subtypes within FTD. The researchers started by gathering 104 areas of patients' normalized regional brain volumes using VUNO-Med DeepBrain, an AI-based brain volumetrics software.[46] Afterwards, a comparative analysis was completed to explore the different distributions in regional volume to identify FTD subtypes based on atrophy patterns. The researchers then input the brain volume measurements for healthy controls and FTD into an algorithm called XGBoost. This algorithm was used to distinguish between the subtypes of FTD. This algorithm resulted in significant differences in atrophy patterns to be observed for subtypes such as the behavioral and semantic variants. The classification performance for XGBoost yielded an overall 95% confidence interval in accuracy, with the lowest percentage of accuracy for differentiating between subtypes and normal control at 79-81%.[47] Moreover, recent multimodal neuroimaging research demonstrates that AI-enhanced fusion of MRI, PET, and cognitive datasets yields substantially higher diagnostic precision for differentiating AD and FTD, with deep-learning-based cortical mapping outperforming traditional statistical pipelines across multiple cohorts.[48] Complementary evidence from a 2024 systematic review further confirms that machine learning architectures—particularly those integrating structural, functional, and clinical biomarkers—consistently elevate early-stage classification accuracy for neurodegenerative disorders, reinforcing the clinical utility of AI-driven diagnostic frameworks.[49] These results suggest that the usage of artificial intelligence could be beneficial in not just distinguishing subtypes but also between neurodegenerative diseases, including FTD and AD.

Fluid Biomarkers:

Cerebrospinal fluid (CSF) is a clear fluid that surrounds the brain and spinal cord, resulting in one of the most effective fluid biomarkers for detecting biochemical changes in brain tissue.[50] This fluid is collected through lumbar puncture, also referred to as a spinal tap. The procedure consists of a spinal needle injection between a patient's vertebrae, passing through the skin and tissue.[51] After collecting samples of a patient's CSF, it is sent to a lab to examine the proteins found in the fluid. These proteins are present in the CSF due to axonal damage or cell death, which causes the release of proteins from the neuron into the surrounding cerebrospinal fluid.[52] Depending on the neurodegenerative disorder, this protein and its concentration in the fluid may vary. In FTD cases, proteins such as amyloid-beta 42 (Aß42), t-tau, which serves as a general marker for neuronal damage, and p-tau, a more specific marker of tau pathology, have been widely studied. Researchers have used these proteins to differentiate FTD and AD, as CSF Aß42 levels were typically found to be lower, whereas t-tau/Aß42 and p-tau/Aß42 ratios were higher in patients with AD compared with those with FTD. However, while these markers provide valuable insight into neuronal damage, there are indicators that they are unreliable for FTD diagnosis.[53]

In addition to Aß42 proteins, neurofilament light chain (NfL) proteins have been proven to serve as a potential biomarker for FTD. When these proteins were researched in relation to each other and compared to determine the overall accuracy or AUC for differentiating FTD from AD, Nfl alone reported 0.67 AUC, t-tau at 0.89 AUC, and t-tau/NfL ratio with an AUC of 0.95. Despite the low AUC for Nfl alone, it was noted that the Nfl proteins were able to accurately identify neurodegenerative processes that were the underlying causes of cognitive symptoms. The results of these two studies indicate that Nfl, Aß42, and tau pathology are not reliable biomarkers when considered individually. When combined, however, they improve the accuracy of differentiating FTD from AD, primarily because they reflect the general neurodegenerative process. Since their utility lies in identifying neurodegeneration broadly rather than disease-specific mechanisms, they are better suited for differentiation than for positively diagnosing FTD, as demonstrated by Giuffrè *et al.*[54]

Hok-A-Hin *et al.* investigate this gap in diagnosis by analyzing the CSF proteome on a large scale to identify a biomarker that can be utilized specifically for FTD diagnosis. The study included CSF samples from patients with FTD, AD, and cognitively normal individuals.[55] A total of 665 CSF proteins were analyzed using proximity extension assays (PEA) and data from four cohort groups, which led to the development of custom multiplex panels with significant diagnostic capabilities. When a classification analysis followed by internal

cross-validation was performed to discriminate FTD from healthy controls, this resulted in the creation of two different types of panels: the first being a 14-protein panel that distinguishes FTD from healthy controls with a 0.96 AUC and a 13-protein panel that distinguishes FTD from AD with a 0.91 AUC, which was a subset of the 14-protein panel. These panels included proteins involved in inflammation, oxidative stress, and synaptic remodeling. Furthermore, the panels were able to outperform or match NfL, which was used as a benchmark biomarker, in identifying FTD itself, with the 14-protein panel having an AUC of 0.96 and the 13-protein panel with an AUC of 0.91. Although NfL was confirmed to be a stronger marker of general neurodegeneration, especially useful for distinguishing FTD from controls, there are still limitations, and the multi-protein panels offer a greater specificity.

Biomarker/Panel	Biomarker Type	Overall Accuracy (AUC) for Differentiating FTD from AD	Role in Differentiation
NfL	Single biomarker	0.67	Limited ability to distinguish FTD from AD
t-tau	Single biomarker	0.89	Reflects neuronal injury; provides strong differentiation between FTD and AD
t-tau/NfL	Combined ratio	0.95	Stronger differentiation when biomarkers are combined
13-protein panel	Multi-protein panel	0.91	High specificity for FTD vs AD
14-protein panel	Multi-protein panel	0.96	Strongest differentiation; separates FTD from controls

Figure 5: Overall Accuracy (AUC) of CSF Biomarkers and Multi-Protein Panels for Differentiating FTD and AD. This table presents the AUC values reported for individual CSF biomarkers, combined biomarkers, and multi-protein panels in distinguishing FTD from AD. It highlights the relative diagnostic performance of each biomarker, ranging from single-protein measures to multiplex panels with higher specificity. Information gathered from Giuffrè *et al.* and Hok-A-Hin *et al.* Created using Biorender.

While Aß42, t-tau, and p-tau are prominent biomarkers for AD, their inclusion in FTD diagnosis has been proven to provide valuable insight into differential diagnosis.[55] When examining NfL, there is strong evidence that it has the potential to serve as a sensitive marker of axonal damage and general neurodegeneration, as it results in elevated NfL levels. However, there are still noticeable limitations in each protein: this is where multi-protein panels could potentially be used in order to combine the benefits of multiple proteins. In order for the panel to be effective in both differentiating and diagnosing, it is crucial to include proteins that are specific to FTD pathology. Based on current research, the ideal multi-protein panel for FTD would include proteins involved in inflammation, oxidative stress, synaptic remodeling, neurotransmission, NfL, and t-tau. In current published research, panels that contain these proteins have achieved AUC values ranging from 0.91 to 0.96 in distinguishing FTD from AD and provide a wealth of information about how FTD affects a certain individual's brain biology, disease progression, and underlying pathology.[55] Incorporating such panels will not only improve the accuracy of FTD detection but also facilitate earlier diagnosis, potentially enabling individuals to access supportive care sooner and qualify for emerging clinical trials aiming to evaluate targeted therapies.

Conclusion

After analyzing the most effective diagnostic tools for FTD, it remains clear that FTD diagnosis is a complex challenge due to its heterogeneity and overlap with other neurodegenerative disorders. Current research and literature highlight the importance of implementing multiple diagnostic tools, such as genetic testing, neuroimaging, and body fluid biomarkers, to improve accuracy and potentially enable earlier detection. Genetic testing is highly reliable as it provides a specificity in identifying pathogenic variants, specifically in *C9orf72*, *GRN*, and *MAPT* genes, while modifier genes such as *TMEM106B* and *SORT1* offer greater insight into an individual's variability in disease onset and progression. Neuroimaging techniques, including structural and volumetric MRI, as well as FDG-PET scans, reveal brain atrophy and hypermetabolism patterns. These patterns can be more effectively interpreted through multimodal fusion frameworks enhanced by artificial intelligence, which allow for deeper interpretation of brain scans, improving diagnostic accuracy. Meanwhile, cerebrospinal fluid biomarkers such as NfL, t-tau, and proteins involved in inflammation, oxidative stress, synaptic remodeling, and neurotransmission contribute to differential diagnosis. Regarding the limitations of the proteins found in cerebrospinal fluid to function as a single marker for identifying FTD itself, it highlights how multi-protein panels may be the solution, as these panels provide a wide range of proteins that are able to measure a variety of FTD characteristics, exceeding a diagnostic accuracy of 90%. Together, these different diagnostic tools and approaches reveal a shift towards a more precise diagnosis of FTD, with the potential to lead to earlier disease intervention and possible personalized care.

Several emerging fields of diagnosis further expand on the diagnostic methods mentioned, but the application and implementation of these tools in diagnosis are crucial to improving FTD diagnosis. Adopting modifier genes into genetic screening, multimodal imaging into neuroimaging, and multi-protein panels into cerebrospinal fluid testing can all be beneficial in increasing diagnostic accuracy. Although these tools help cover gaps in diagnosis, they still have their limitations, which is why it is pivotal to continue identifying proteins or biomarkers that are FTD-specific. Further research into genes, brain atrophy and hypometabolism patterns, and proteins, which are the underlying causes of neurodegeneration, can substantially improve the identification and diagnosis of FTD.

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