

REVIEW ARTICLE

Fourier-transform infrared spectroscopy as a potential screening and diagnostic tool for Alzheimer's disease: A comparative review

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Abstract

Background: Alzheimer's disease (AD) is a debilitating neurodegenerative disease and the main cause of age-related dementia. The incidence and financial burden of this brain disorder are expected to increase significantly in the coming decades. Establishing a definitive diagnosis of AD is a long and costly process involving multiple clinical assessments and a range of imaging and laboratory tests. **Aim:** This review investigates the potential application of Fourier-transform infrared (FTIR) spectroscopy in the diagnosis and screening of AD in the elderly, highlighting the advantages and limitations of this optical diagnostic method compared with those currently used in clinical practice. Additionally, this review examines the utility of FTIR spectroscopy in the differential diagnosis between AD and closely related neurodegenerative diseases. **Conclusion:** FTIR spectroscopy-based analysis of blood plasma possesses attractive properties to qualify as a promising screening and diagnostic test for AD. It can also be a potential tool for differentiating between AD and dementia with Lewy bodies with relatively high accuracy. This vibrational spectroscopic technique overcomes many, if not most, of the limitations associated with the laboratory and imaging methods used for AD diagnosis. **Relevance for patients:** Early detection of AD can be of immense benefit to patients, their caregivers, and society as a whole. It enables patients to plan their lives while retaining full decision-making capacity. It also allows patients to start appropriate treatment early in the disease course, which can delay their need for healthcare services.

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1. Introduction

Dementia is a neurocognitive syndrome affecting 55 million individuals globally.¹ It is associated with cognitive and behavioral impairments that severely impact the patient's quality of life.² Therefore, it is considered a major cause of disability worldwide.² The number of people living with dementia is projected to increase to 78 million by 2030 and to 139 million by 2050.¹ The healthcare cost for people suffering from this neurological disorder reached USD 1.3 trillion in 2019.² This financial burden is expected to double by 2030.¹

Dementia is an age-related condition caused by brain pathologies that occur in later life.³ Common underlying causes of dementia include Alzheimer's disease (AD),

vascular diseases, Lewy body disease, and Parkinson's disease.^{3,4} AD is a common neurodegenerative disease of the central nervous system⁵ and the main cause of age-related dementia.^{4,6} It accounts for approximately 70% of all dementia cases.^{4,7} Meanwhile, vascular dementia represents 20% of the total cases, followed by dementia with Lewy bodies (DLB) and Parkinson's disease dementia.⁴

Clinical diagnosis of dementia is relatively simple. However, accurate differential diagnosis between the various types of dementia is much more challenging,⁸ particularly when discriminating between AD dementia and DLB.⁸ The overlapping clinical symptoms of these two types of dementia, especially during the early stages, can often be misleading to clinicians. At the same time, this task is of paramount clinical importance because it allows the healthcare provider to forecast the clinical course of the disease and predict the pharmacotherapy side effects.⁸ The absence of a low-cost and non-invasive differential diagnostic test further complicates this task.⁸ Therefore, the development of a suitable approach to overcome this obstacle would represent a breakthrough in the diagnosis and management of dementia.

It is estimated that 315 million individuals worldwide are in the preclinical stage of AD. In addition, the prevalence rates of this neurodegenerative disorder are projected to escalate in the coming years due to increasing life expectancy and the growth of the aging population, especially in industrialized countries.⁹ Therefore, there is an urgent need for cost-effective screening and diagnostic approaches to detect the disease during the preclinical stage or early in the disease course. Early detection of AD will allow the patient to access appropriate medical treatment. In addition, it will enable the healthcare provider to implement effective measures to delay the onset of the disease and, consequently, postpone the subsequent dementia. This will have a positive impact on patients' cognition and quality of life, as well as on their family, caregivers, and society as a whole.¹⁰

The biochemical changes associated with human diseases can be traced in body fluids using various analytical methods. For example, the increased levels of blood hemoglobin A1c associated with type 2 diabetes can be detected by high-performance liquid chromatography and enzymatic immunoassay.¹¹ Optical sensing of human diseases is an emerging concept that has attracted the attention of scientists and clinicians worldwide.¹²⁻¹⁷ It is based on the combined use of vibrational spectroscopies and chemometrics to detect disease-specific biochemical changes in body fluids.^{12,13,15,16} Vibrational spectroscopies, including Raman and infrared (IR) spectroscopies, are universal optical sensing techniques that analyze the

interaction between a light beam and the sample being tested to produce a spectrum. Raman spectroscopy relies on the use of a laser beam as incident light and analyzes the light inelastically scattered (Raman scattering) by the tested sample. Meanwhile, IR spectroscopy uses mid-IR radiation as incident light and detects the frequencies absorbed by the tested sample.^{12,13,18-20}

In both cases, the obtained spectrum is generally determined by the chemical composition of the tested sample and the molecular vibrations of its functional groups. Therefore, a spectrum generated by a given body fluid represents a unique fingerprint that can be used to deduce important information regarding the biochemical composition of the fluid being tested.^{12,13,18,19} This principle has been exploited to identify the biochemical changes associated with many diseases and, hence, to establish a clinical diagnosis of the disease in question.^{12,13}

In the past decade, intensive research has been carried out to explore the potential applications of vibrational spectroscopies in the diagnosis of multiple cancers²¹⁻²³ and of various metabolic,^{24,25} autoimmune,^{12,26} and infectious diseases.^{13,16} The outstanding performance of these optical sensing techniques in diagnosing a wide variety of human diseases has resulted in many patents. For example, the use of Raman spectroscopy to evaluate the cancer state in biological tissues was patented in 2015 by the Institution for the Advancement of Learning (Polyvalor LP) and École Polytechnique de Montréal (Royal) (patent international publication number: US20170020460A1; <https://patents.google.com/patent/US20170020460A1/en>). Further in this context, the use of FTIR spectroscopy in the diagnosis of inflammatory bowel disease was patented in 2016 by Georgia State University Research Foundation (patent international publication number: WO2016201408A1; <https://patents.google.com/patent/WO2016201408A1/en>). Therefore, vibrational spectroscopies might soon find their place in clinical laboratories for routine analyses and diagnostic purposes.

The potential application of IR spectroscopy in the diagnosis of neurodegenerative diseases of the central nervous system has been investigated in many studies.²⁷⁻³⁵ For instance, it has been recently demonstrated that Fourier-transform infrared (FTIR) spectroscopy-based analysis of serum can detect multiple sclerosis with a high level of accuracy (96%). In addition, it can be used to differentiate between multiple sclerosis and a closely related neurological disease known as neuromyelitis optica.²⁸

Therefore, this review aims to explore the potential application of FTIR spectroscopy in screening and diagnosing AD in the elderly population. It also aims to discuss the advantages and limitations of this optical

diagnostic method compared with the traditional and gold-standard methods used for this purpose. In addition, this review aims to explore the potential use of this analytical technique in the differential diagnosis between AD and closely related neurological diseases.

The majority of research works addressing the previous points are discussed in this review. However, the most recently published studies and those involving the highest number of patients are given particular attention and are discussed in greater depth. All the searches performed during the preparation of this review were carried out using Google, Google Scholar, and PubMed as search engines. The keywords “Fourier-transform infrared spectroscopy” and “Alzheimer’s disease” were used to conduct the searches.

The searches were limited to studies published between January 1, 2000, and January 1, 2025. Based on the search parameters described above, a total of 353 papers were obtained in a preliminary search using the biomedical search engine PubMed. The identified papers were examined individually to select those related to the potential application of FTIR spectroscopy in the diagnosis of AD. As a result, 18 studies were selected for inclusion in this review.

The selected works were further classified into three groups based on the type of test sample used in the investigations. The first group included 12 papers that used blood-derived test samples to carry out the analysis. Meanwhile, the second group involved four papers that used tissue biopsies as test samples. Lastly, the third group contained two papers that used cerebrospinal fluid (CSF) as analytical sample. For a better understanding of this review, a brief background related to dementia and AD has been included. In addition, a short but comprehensive explanation of the fundamental principles of IR spectroscopy is also provided in this review.

2. Fundamental principles of infrared spectroscopy

2.1. Molecular vibrations and absorption of electromagnetic radiation

Molecular vibrations, or the normal modes of vibration, refer to the continuous periodic motions of atoms within the molecule of a given chemical compound.^{12,18,36} They are generally classified by physicists into two categories including stretching and bending. Stretching refers to periodic changes in the length of a chemical bond between two atoms within the compound, whereas bending refers to periodic changes in the angle between two chemical bonds within the compound, while the lengths of these

bonds remain constant.^{12,18,36,37}

At a defined energy level, each normal mode of vibration occurs at a frequency determined by the molecular masses of the atoms involved in the vibration, the type of chemical bond between the vibrating atoms, and the vibration mode itself. However, the frequencies of most molecular vibrations fall within the range of 10^{13} – 10^{14} Hz.^{12,18,38} All vibrational modes interact with electromagnetic radiation, and the outcome of this interaction is determined by the frequencies of the incident radiation. Maximum interactions occur when the frequencies of the incident radiation are close or identical to those of the vibration modes; that is, when the frequencies of the incident radiation fall within the range of 10^{13} – 10^{14} Hz. In these conditions, the outcome of the interaction is the absorption of the incident radiation, resulting in excitation to a higher vibrational energy state. Electromagnetic radiation corresponding to the frequency range of 10^{13} – 10^{14} Hz falls within the mid-IR region.^{12,13,18,38} In summary, molecular vibrations can be excited by the absorption of mid-IR radiation.

2.2. Principles of Fourier-transform infrared spectroscopy

Infrared spectroscopy analyzes the interaction between mid-IR radiation and the test sample to produce an IR absorption spectrum. The absorption peaks within the spectrum indicate the frequencies absorbed by the analyte and the extent of absorption. They are defined by the functional groups of the analyte and their normal modes of vibration. Therefore, the IR absorption spectrum is a highly specific spectral signature that can be used for the fingerprint identification of the analyte.^{12,18,37} From an optical standpoint, FTIR spectroscopy comprises three main components, namely an IR radiation source, an interferometer, and a detector.^{36,39,40} The interferometer is a device composed of a beam splitter, a stationary mirror, and a moving mirror (Figure 1A). The function of this device is to convert the IR radiation originating from the source into an IR beam with continuously changing frequencies in the range of 400 cm^{-1} to $4,000\text{ cm}^{-1}$.^{12,39,40} The beam splitter divides the IR radiation originating from the source into two identical beams. The first beam is directed to the stationary mirror; meanwhile, the second beam is directed to the moving mirror. The beams reflected by the mirrors recombine to form a new beam with continuously changing frequencies. The continuous change in the frequencies of the new beam is due to the continuous movement of the moving mirror (Figure 1A).^{12,39,40}

Various modalities of FTIR spectroscopy are currently

in use, including attenuated total reflection (ATR) FTIR spectroscopy, transmission FTIR spectroscopy, and diffuse reflectance FTIR spectroscopy.⁴¹ ATR-FTIR spectroscopy is the standard and most popular modality. Despite its lower sensitivity compared with transmission FTIR spectroscopy, it has a noise-canceling effect that considerably improves the quality of the spectral signal. In addition, it is compatible with various types of samples and requires minimal pretesting preparation.^{36,39-41} ATR-FTIR spectroscopy relies on the use of an ATR crystal with a low critical angle as a sample support (Figure 1B). ATR crystals are generally made of an IR-transparent material such as diamond or germanium. Inside the crystal, an IR beam with an incidence angle higher than the critical angle of the crystal undergoes a series of total internal reflections on the crystal's inner surfaces. During its journey through the crystal, the IR beam comes into contact with the test sample multiple times. As a result, specific frequencies of the IR beam are absorbed by the sample at each contact (Figure 1B). After multiple steps of absorption and internal reflection, the remainder of the IR beam leaves the ATR crystal to reach the detector.^{36,39-41}

3. Alzheimer's disease

Alzheimer's disease is a progressive neurodegenerative disorder that develops over years and affects the brain, causing cognitive impairment and other psychological and behavioral symptoms.^{9,42} The cognitive impairment manifests in loss of short-term memory and a decline in the patient's communication abilities. Additionally, impulsivity, depression, and social isolation are among the most commonly reported psychological signs of AD. Moreover, motor symptoms such as gait abnormalities, frequent falls (due to visuospatial deficits), and tremors are also observed in patients with this brain illness.^{42,43}

The development of AD is mediated by three pathophysiological mechanisms impacting the patient's brain.⁴⁴⁻⁴⁶ The first mechanism is related to the accumulation of β -amyloid ($A\beta$) in the brain extracellular matrix. $A\beta$ is a product of the proteolytic cleavage of a transmembrane protein involved in various biological functions.⁴⁷ Misfolding of accumulated $A\beta$ leads to the formation of amyloid plaques, also known as senile plaques.⁴⁸ Aggregation of amyloid plaques is considered the main

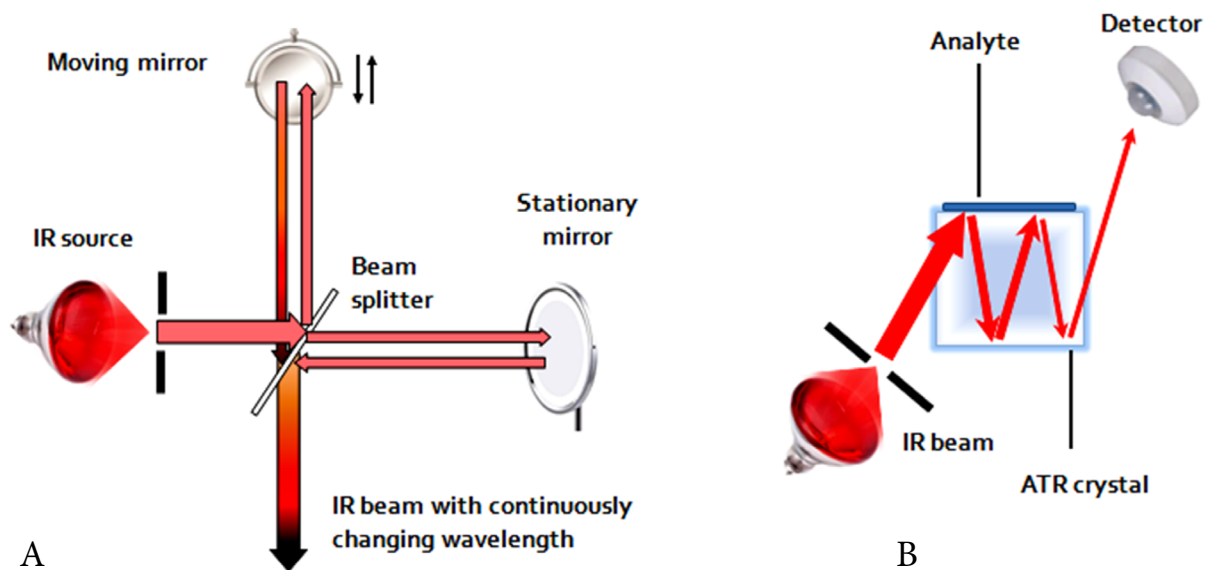


Figure 1. Principles of ATR-FTIR spectroscopy. (A) Interferometer principle: The IR radiation produced by the source is divided by the beam splitter into two beams; the first one is directed toward the moving mirror, while the other is directed toward the stationary mirror. The beams reflected from the mirrors recombine to produce a new beam with continuously changing frequencies. (B) ATR principle: The incident IR beam penetrates the vertical side of the ATR crystal to reach its internal surface. At this point, the beam interacts with the test sample loaded on the upper surface of the crystal. As a result, the sample absorbs specific IR frequencies, and the remainder of the IR beam is totally internally reflected to the opposite surface. The absorption and internal reflection events are repeated multiple times until the IR beam leaves the ATR crystal from the opposite vertical side to reach the detector.

Abbreviations: ATR: Attenuated total reflection; FTIR: Fourier-transform infrared; IR: Infrared.

cause of axonal damage and synaptic loss observed in AD patients.⁴⁵

The second mechanism is ascribed to the accumulation of neurofibrillary tangles (NFTs) inside neuronal cells. NFTs are formed from a misfolded, hyperphosphorylated, and oxidized protein called tau.⁴⁸ Under physiological conditions, tau binds to microtubules, playing a key role in the assembly and stabilization of these cytoskeletal proteins.⁴⁹ However, in AD patients, the aforementioned chemical changes cause the dissociation of tau protein from microtubules, resulting in their disassembly. Thus, chemically modified tau molecules aggregate with each other, forming threads and, subsequently, tangles inside neurons. The accumulated NFTs impair intracellular neuronal transport, causing synaptic dysfunction.^{50,51} Hyperphosphorylation of tau protein is partly mediated by A β aggregation.⁴⁸ The buildup of senile plaques and NFTs are considered the main hallmarks observed in the brains of AD patients.^{44,45,48}

The third pathophysiological mechanism is related to brain neurotransmission. A deficit in neurotransmission and a decline in the production of some neurotransmitters, such as acetylcholine, have been observed in the brains of AD patients.⁴⁴

The clinical course of AD is divided into different stages based on the occurrence of histopathological markers and the presence of cognitive and functional impairments.⁴² The International Working Group and the National Institute on Aging–Alzheimer's Association have proposed five clinical stages for this neurodegenerative disease.^{42,52,53} The first stage is an asymptomatic preclinical stage associated with the accumulation of senile plaques and NFTs in the patient's brain. The second stage is a prodromal stage during which mild cognitive decline can be observed along with the previous histopathological changes. The last three stages are called AD with dementia. They are described as mild, moderate, and severe. In these stages, the aforementioned histopathological markers can be detected along with the cognitive and functional impairments.^{42,52,54}

Notably, several risk factors have been linked to AD, including advanced age, genetic predisposition, being female, and head injuries. In addition, unhealthy lifestyle habits, such as lack of exercise, smoking, and alcohol consumption, are also considered contributing factors. Moreover, environmental factors, such as poor diet and air pollution, are also implicated in the development of AD.^{45,55} Recent global estimates indicate that 315 million individuals around the world are in the preclinical stage of AD. Meanwhile, the total number of patients in the prodromal stage and in the AD with dementia stages is

estimated to be 69 million and 32 million individuals, respectively.⁵⁶ These numbers represent 22% of the global population aged over 50 years.⁵⁶ The disease affects men with a prevalence rate of 3.31%. Meanwhile, the prevalence rate of AD in women is significantly higher, reaching up to 7.13%.^{9,57}

4. Diagnosis of Alzheimer's disease

Diagnosis of AD is a long process that relies on multiple clinical assessments and various laboratory and imaging tests.^{42,58–61} In clinical practice, once the signs of cognitive impairment have been identified, a standard multistep protocol must be followed to establish a definitive diagnosis of AD or to rule it out. [Table 1](#) lists the recommended imaging and laboratory tests for each step and the corresponding sensitivity and specificity for AD.

4.1. Preliminary assessment

The diagnostic protocol for AD starts in primary care with a preliminary assessment aiming to identify any predisposing factors, such as a family history of AD or the presence of cardiovascular disease. The assessment also aims to identify any other elements that might cause cognitive impairment, such as depression, medication, narcotics, epilepsy, or other reversible causes.⁴² A quick cognitive assessment (<10 min) can also be performed at this stage by the primary care clinician to confirm the presence of cognitive impairment.⁴² Rapid cognitive tests, such as the Mini-Mental State Examination, can be used for this purpose.⁴²

Based on the outcome of the initial assessment, patients who need to be further investigated for AD are referred to a specialist neurologist, who can initiate the next phase of the diagnostic protocol. It is important to mention that plasma levels of phosphorylated isoforms of tau protein, including p-tau181 and p-tau217, have shown great potential in predicting AD in patients manifesting signs of cognitive impairment.^{62,63} Therefore, these two biomarkers have been proposed as screening biomarkers for AD.^{63,64} Considering the ease of blood sampling, these potential blood biomarkers could be used during the preliminary assessment stage to identify patients who need to be referred to a specialist neurologist.^{63,64} However, these biomarkers are still under clinical evaluation to validate these findings and to optimize the measurement methods.^{65,66}

4.2. Specialist assessment

The purpose of this stage is to evaluate the symptoms related to AD and rule out any other underlying causes.⁶⁰ Therefore, during this phase, the patient undergoes multiple assessments and physical examinations to detect

any cognitive, functional, or behavioral impairments. In this connection, a set of internationally recognized tests can be used to identify these impairments and assess their severity.^{42,60} For example, cognitive decline can be evaluated using the Montreal Cognitive Assessment or the Mini-Mental Assessment Instrument. Meanwhile,

the Instrumental Activities of Daily Living scale or the Functional Activities Questionnaire is recommended for assessing functional impairment. The patient's behavior can be examined using the Neuropsychiatric Inventory Questionnaire.^{42,60}

It is important to note that the aforementioned

Table 1. Recommended imaging and laboratory diagnostic tests for each stage of the Alzheimer's disease diagnostic protocol

Test	Sensitivity for AD	Specificity for AD	Reference
Stage 1: Blood biomarkers ^a			
p-tau217	95%	95%	63
p-tau181	93%	93%	63
Total plasma A β 42/40 ratio	81% accuracy	-	67,68
Stage 2: Clinical diagnosis	93%	55%	69
Stage 2: <i>APOE</i> genotyping			
One ApoE- ϵ 4 allele	65%	86%	69
ApoE- ϵ 4/ApoE- ϵ 4 genotype	93%	39%	69
FDG-PET scan	91%	86%	70
Stage 3: Amyloid PET scan			
Visual reading	84.6%	38.1%	71
Quantitative assessment	92.3%	90.5%	71
Stage 3: CSF biomarkers			
A β 42 ^b	85%	89%	72
A β 40	50%	64%	72
Ratio A β 42/A β 40	95%	95%	72
t-tau	>81%	57%	73
p-tau	>90%	Higher than t-tau	74
p-tau181	97%	71%	75
p-tau217	93%	88%	75

Notes: ^aBlood biomarkers and their use in primary assessment and definitive diagnosis remain under clinical investigation. A low total plasma A β 42/40 ratio has an 81% positive predictive value of high cortical A β burden. ^bThe sensitivity and specificity of A β isoforms biomarkers depend on the analytical method used. The data reported in the table were obtained using the Meso Scale Discovery immunoassays.

Abbreviations: A β : β -amyloid; AD: Alzheimer's disease; ApoE: Apolipoprotein E; CSF: Cerebrospinal fluid; FDG: Fluorodeoxyglucose; PET: Positron emission tomography.

assessments have high levels of sensitivity for AD. However, their specificities remain mediocre (Table 1).⁶⁹ Therefore, they must be accompanied by thorough laboratory investigations to exclude any disease that might underlie the cognitive decline, including those related to the functions of the thyroid, liver, and kidney. Vitamin deficiencies, particularly vitamin B12 and folate, may also be implicated in the cognitive decline and, therefore, should be investigated by checking the serum levels of these two vitamins.^{42,59} Moreover, at this stage, a genetic analysis should be performed to identify the alleles of the *APOE* gene present in the patient's genome.⁴² The *APOE* gene codes for a lipid carrier—apolipoprotein E (ApoE)—that plays a key role in transporting lipids to brain cells.⁷⁶ It has been shown that homozygous individuals who carry two copies of the ApoE- ϵ 4 allele have an increased risk of developing AD.⁷⁷ Hence, combining the results of *APOE* genetic analysis with those of the clinical examination might improve diagnostic accuracy.⁷⁸ The sensitivity and specificity of this genetic marker (Table 1) vary significantly between studies, depending on the number of enrolled patients.^{69,78} *APOE* genotyping can be performed using polymerase chain reaction or polymerase chain reaction combined with restriction-fragment–isotyping.⁶⁹

Moreover, brain imaging using fluorodeoxyglucose–positron emission tomography (FDG-PET) and magnetic resonance imaging (MRI) is also recommended at this stage. An FDG-PET scan allows the identification of brain areas with decreased glucose metabolism, which might indicate AD.⁷⁹ This diagnostic scan has a relatively high level of sensitivity and an acceptable level of specificity for AD (Table 1).⁷⁰ However, the high cost of this test may limit its use.⁴² Further in this regard, MRI is useful in the differential diagnosis between AD and other types of neuropathology due to neoplasm, microbleeding, or surgical intervention. It can detect medial temporal lobe atrophy, which is considered a good indicator of AD.^{60,80} Although brain computed tomography (CT) can be used for this purpose, MRI has higher sensitivity than CT in detecting the early stages of medial temporal lobe atrophy in AD patients. Therefore, the use of MRI in the diagnosis of AD is preferred.⁸¹

4.3. Definitive diagnosis

The third phase in the diagnostic protocol aims to establish a definitive diagnosis before initiating a suitable medical treatment. This purpose can be achieved by confirming the presence of A β in the patient's brain and/or by detecting AD-specific biomarkers in the patient's biofluids.⁴² Detection of A β in the patient's brain relies on a scanning test called amyloid PET.^{79,82–84} The test allows visualization of A β in the patient's brain using a specific

tracer. The sensitivity and specificity of this diagnostic scan vary depending on the reading method. A quantitative assessment of the global cortex, although time-consuming, can substantially improve the sensitivity and specificity of this test (Table 1).⁷¹ It should be noted that the high cost of this diagnostic scan may limit its use in the general population.⁷⁹

Detection of AD-specific biomarkers in the patient's biofluids can be used as an alternative or confirmatory test for amyloid PET scans. It relies on inspecting the presence of these biomarkers in the patient's CSF and potentially blood.^{62,85,86} The isoforms A β 40 and A β 42, which represent the major constituents of senile plaques, are the most relevant biomarkers that can be detected in the CSF of AD patients. Clinicians recommend the use of the ratio A β 42/A β 40 as a more accurate index for AD than the level of A β 42 alone.^{87,88} Although the sensitivity and specificity of this index vary slightly between studies,^{89,90} a recently published study demonstrated satisfactory results (Table 1).⁸⁹ The remaining CSF biomarkers include the total amount of tau protein (t-tau) and its phosphorylated form (p-tau). An increase in the CSF levels of p-tau is a strong indication of the occurrence of NFTs in the patient's brain. Meanwhile, the level of t-tau reflects the degree of neurodegeneration.^{74,91} It should be noted that p-tau has a higher level of specificity for this brain disease than t-tau. Therefore, it is used to differentiate between AD and other neurodegenerative diseases.⁷⁴ Furthermore, the phosphorylated isoforms of tau protein, including p-tau217 and p-tau181, have recently attracted the attention of neurologists as potential biomarkers for AD. The sensitivity and specificity of these two isoforms are significantly higher than those of t-tau and p-tau (Table 1).^{75,92} A Quanterix[®] immunoassay for CSF p-tau181 is authorized for use in clinical practice both in the United States and the European Union.⁹³ The CSF levels of these biomarkers are usually determined using immunoassays such as enzyme-linked immunosorbent assay and electrochemiluminescence (Meso Scale Discovery).⁹¹

Regarding blood biomarkers for AD, they are currently limited to a few electrochemiluminescence immunoassays that measure p-tau isoforms⁶³ uniquely due to the low levels of A β and p-tau isoforms in the blood of AD patients compared to CSF.^{42,64} Added to that, the inconsistency associated with A β assays which was attributed to the masking of A β epitopes by plasma proteins.⁶⁴ Increased plasma levels of p-tau181 and p-tau217 have been reported in AD patients.⁶³ In addition, the plasma levels of these two isoforms have shown great potential in the differential diagnosis between AD and other neurodegenerative disorders.^{63,64} Therefore, blood levels of these two proteins

can be used by specialist neurologists for both definitive and differential diagnosis.⁹⁴ Nevertheless, the implementation of these blood tests in clinical practice is still under clinical investigation.^{63,95,96}

5. Limitations associated with Alzheimer's disease diagnosis methods

5.1. Clinical examination

Identifying the early signs of AD during the disease course is essential for initiating further investigations to establish a definitive diagnosis. Once confirmed, an appropriate medical treatment can be initiated, which positively impacts the patient's quality of life.⁹⁷ Specifically, it can prolong the patient's autonomy and delay their dependency on others, thereby reducing healthcare costs.⁹⁸ This is particularly important in countries with high incidences of AD or where incidence rates are projected to increase. However, detecting early signs of AD in clinical practice is challenging due to their insidious nature. These signs are often misinterpreted by healthcare professionals as normal symptoms of aging, and clinicians may not identify them during time-limited patient interviews.⁴² It should be added that establishing an accurate clinical diagnosis is further complicated by the limited sensitivity of standard cognitive tests, which may fail to detect mild cognitive decline in the early stages of AD. In addition, the day-to-day variability in patients' responses may further reduce tests reliability.⁹⁹ Moreover, cognitive and behavioral symptoms can overlap with those of other conditions, such as depression,¹⁰⁰ apathy,¹⁰¹ or loss of meaningful purpose in life. The time-dependent variability in mood and cognition can help distinguish depression.¹⁰² Finally, functional tests alone may not suffice to evaluate functional impairment; clinicians often need to gather information from the patient's caregivers to accurately assess daily life activities.¹⁰³

5.2. Cerebrospinal fluid biomarkers

Despite the high sensitivity of CSF biomarkers for AD, their specificity remains unsatisfactory (Table 1).^{73,74,89} For example, t-tau is a marker of neuronal death and has low specificity for AD;^{73,104,105} elevated levels of t-tau are observed in cases of stroke and brain injuries.^{104,105} However, the diagnostic accuracy of A β 42/A β 40, t-tau, and p-tau is relatively high, especially when used in combination. Moreover, these markers have higher sensitivity than PET imaging in detecting early neurological changes specific to AD.¹⁰⁶

Considering the high cost of PET imaging, CSF biomarkers can provide a reliable alternative. However, some patients are reluctant to undergo CSF assessment.¹⁰⁷ Quantitative analysis requires sampling of the patient's

CSF via lumbar puncture,¹⁰⁸ which must be performed by a trained clinician, preferably in a hospital setting.¹⁰⁹

A day before the procedure, patients must be informed about the process and potential complications, and questioned about medications that might affect blood clotting. A blood coagulation test should be performed to assess clotting ability and reduce the risk of bleeding that could damage nerves near the puncture site.^{109,110} Moreover, the patient's intracranial pressure should be assessed to avoid herniation in cases of elevated pressure. Funduscopic examination is the most popular test used for this purpose. The test detects swelling in the optic disc; which is considered a reliable indicator of high intracranial pressure. Brain X-rays and computed cranial tomography are used occasionally.^{109,111-113} It should be noted that lumbar puncture is contraindicated in certain clinical situations, including infection at the puncture site and spinal cord abnormalities.¹⁰⁹

Cerebrospinal fluid sampling by lumbar puncture involves inserting a spinal needle into the subarachnoid space between vertebrae L3–L4 or L4–L5 to collect 8–15 mL of CSF.¹¹⁰ Despite the invasive nature of this procedure, it is considered relatively safe. However, multiple reports describe associated complications.^{110,114-118} Headache is the most common complication, occurring in approximately 40% of patients and lasting up to one week;^{114,119} in some cases, it can persist for up to a year.¹¹⁴ Other complications, such as hemorrhage,¹¹⁸ cerebral herniation,¹¹⁷ back pain, injury of the nerve root, and meningitis, are infrequently reported (0.3–0.5% of cases).^{114,117} Furthermore, lumbar puncture can negatively affect a patient's psychological well-being, with many reporting fear and anxiety prior to the procedure.¹¹⁴

5.3. Imaging methods

5.3.1. Magnetic resonance imaging

Magnetic resonance imaging is a moderately expensive diagnostic method, and excessive use can impose a significant financial burden on healthcare systems, particularly in developing countries.¹²⁰ Access may also be limited for patients in underserved or rural areas. MRI is relatively time-consuming, lasting 1.5–2 h, during which patients must remain immobile to produce high-quality images. This can be challenging for infants or claustrophobic patients. In such cases sedation or anesthesia may be required, necessitating the involvement of an anesthetist alongside radiology staff.¹²¹

Magnetic resonance imaging is contraindicated in patients with ferromagnetic implants, such as cardiac pacemakers, which may malfunction or be altered by the MRI's magnetic field. Additionally, all ferromagnetic

objects, including surgical instruments, vials, and metallic pens, can be propelled by the magnetic field, posing a risk of injury. Strict precautions are required to prevent such incidents.¹²²

5.3.2. Positron emission tomography

Amyloid PET is a molecular imaging method increasingly used in the diagnosis and therapeutic management of AD.¹²³⁻¹²⁵ The procedure involves intravenous administration of an amyloid-specific radiotracer, followed by scanning of the patient's brain to detect the tracer accumulation.¹²⁶ Due to the complexity and high cost of this diagnostic technique, expert guidelines have been established to ensure cost-effective use while maintaining optimal care for AD patients.¹²⁶⁻¹²⁸

The most recent guideline recommends the test for specific patient groups: those with a probable AD diagnosis based on clinical examination, patients with early-onset gradual cognitive decline, and patients with dementia suspected to have multiple causes.¹²⁶ The guideline also specifies several contraindications. Notably, the test is not recommended for patients without a confirmed clinical diagnosis of AD, for screening in the preclinical stage or asymptomatic individuals, or for those with a family history of AD or the ApoE-ε4 genotype. Additionally, the test cannot be used to assess the severity of dementia.^{126,127} Nonmedical use, such as in legal investigations, life and health insurance, or pre-employment checks, is also disapproved.¹²⁶

The duration of the test ranges from 0.5 to 2 hours, depending on the radiotracer used, with scanning itself lasting 10–30 minutes.¹²⁶ All procedures must be performed and interpreted by qualified and trained clinicians and technicians.¹²⁸

Similar to amyloid PET, experts have proposed guidelines for the effective use of FDG-PET.^{129,130} The test is strongly indicated for early diagnosis of AD in patients with mild cognitive decline.¹²⁹ It is also recommended for early diagnosis of dementia and for differentiating between its various subtypes.¹²⁹ Considering the relatively low specificity of FDG-PET for AD (Table 1), its results should be combined with those of amyloid PET to significantly improve diagnostic accuracy.¹³¹

Prior to FDG-PET, the patient must abstain from food and drink for 4–6 hours to ensure optimal tracer uptake by the brain.¹²⁹ Image quality can be affected by blood glucose concentration; therefore, plasma glucose levels must be assessed before tracer injection, particularly in diabetic patients.¹³²⁻¹³⁴ In addition, sedation and continuous monitoring may be necessary, especially for epileptic patients or those with cognitive decline.¹²⁹ Other factors,

including corticosteroid treatment, alcohol consumption, and cessation of drug abuse, can also interfere with the test due to their potential effects on brain metabolic activity.¹³⁵⁻¹³⁷ Whenever possible, brain scanning before tracer administration is recommended to minimize such interference.¹²⁹

It is important to note that no defined threshold clearly differentiates normal from pathological PET images. Consequently, visual interpretation may vary depending on the radiologist's experience.¹³⁸ To optimize interpretation, acquisition of a control scan immediately before radiotracer administration is highly recommended.¹³⁸

Finally, PET is contraindicated in patients with ferromagnetic implants such as cardiac pacemakers, neurostimulators, or other metallic devices. In pregnant women, the benefit of the test must be carefully considered against potential fetal risk, and breastfeeding should be suspended 24 hours after tracer injection.¹²⁹

6. Fourier-transform infrared spectroscopy-based diagnosis of Alzheimer's disease

Fourier-transform infrared spectroscopy has shown promising applications in the diagnosis of malignancies^{15,22,23} and a wide range of metabolic,^{24,139} autoimmune,^{12,27} and infectious^{14,140,141} diseases. Intensive efforts have been undertaken to explore the utility of this optical sensing technique in the diagnosis of neurological diseases, including multiple sclerosis,^{12,27,28,30} Parkinson's disease,^{31,142} and AD.^{32-34,143-148} Studies related to AD have been conducted using various test samples, including tissue biopsies^{149,150}, oral buccal cells,¹⁵¹ and body fluids (e.g., blood plasma^{32,33,146} and CSF^{144,152}). Although most of these studies were conducted on small cohorts of human participants, their results are still promising.

The potential application of FTIR spectroscopy in the diagnosis of AD was first proposed in 1993—a Canadian research team demonstrated that IR spectra of autopsied brains from AD patients share common features with spectra generated by aggregates of synthetic analogues of Aβ42.¹⁵⁰ Two years later, the same team performed chemometric analysis on IR spectra of brain autopsies from AD patients and control subjects. They demonstrated that IR spectroscopy can differentiate between these autopsies with a success rate of 100%. In addition, using histopathological examination as a reference, this spectroscopic technique achieved a 90% success rate in classifying autopsies of AD patients as slightly, intermediately, or severely affected.¹⁴⁹

In addition, FTIR spectroscopy-based imaging was used to monitor the hippocampal content of unsaturated lipids in a mouse model of AD. Interestingly, the findings

indicate that the development of AD in mice was associated with a progressive decline in the level of unsaturated lipids in hippocampal white matter.¹⁵³ After adipose tissues, the brain is the richest organ in lipids in the human body. Lipids represent 50% of the dry weight of the human brain and play key biological roles in this vital organ. Most importantly, they are essential for neurogenesis, synaptic transmission, signal transduction, and cognitive function.¹⁵⁴ Therefore, developing a non-invasive FTIR spectroscopy-based imaging method to monitor the brain content of unsaturated lipids may provide a reliable tool for monitoring the development of AD in individuals at high risk. It may also be useful in tracking disease progression in clinically diagnosed patients.

Additionally, a pioneering study recently demonstrated that FTIR spectroscopy-based analysis of oral buccal cells can be used for early diagnosis of AD.¹⁵¹ In the study, chemometric analysis was performed on spectral data of oral buccal cells collected from 17 patients with AD and 12 age-matched control individuals. The findings indicate that this analytical approach can discriminate between AD patients and control individuals with 88% accuracy (76% sensitivity and 100% specificity).¹⁵¹ The presence of AD biomarkers in oral buccal cells has been attributed to their secretion by cranial nerves into the salivary glands¹⁵⁵ or diffusion from blood to saliva.^{156,157}

Further studies have investigated the potential application of FTIR in the diagnosis of AD using other types of test samples, including body fluids such as CSF¹⁵² and blood plasma,^{32,145-147,158,159} in addition to white blood cells (WBCs).^{145,147}

6.1. Cerebrospinal fluid

In 2007, Griebel *et al.*¹⁵² used FTIR spectroscopy to examine CSF samples collected from 71 patients with AD and 66 control subjects. Chemometric analysis of the produced spectral data allowed differentiation between both types of samples with a sensitivity and specificity of 88.5% and 80%, respectively. The diagnostic precision of this method is comparable to, if not better than, that of established CSF biomarkers, including tau, A β 40, and A β 42.^{87,88} These findings were further confirmed in a later study performed on CSF samples collected from patients at different stages of AD and age-matched control individuals. The study highlighted that spectral regions corresponding to lipids and proteins could differentiate between AD patients and control individuals.¹⁴⁴

6.2. Blood components

Multiple studies have investigated the potential application of FTIR spectroscopy in diagnosing AD using plasma

and WBCs as test samples.^{32-34,145-148,158,159} Some of these studies explored the utility of this optical sensing method in the differential diagnosis between AD and other neurodegenerative diseases, such as DLB.^{147,158} In addition, FTIR spectroscopy-based analysis of serum-derived exosomes has been proposed as a potential diagnostic method for AD.¹⁶⁰ Exosomes are a subtype of extracellular vesicles secreted by nearly all cell types in the human body. Through their cell-derived cargo of proteins, lipids, microRNAs, and other bioactive molecules, they play an important role in cellular communication and in regulating many cellular functions.^{161,162} In the brain, exosomes are released by all cell types and play a crucial role in the pathological process of AD.¹⁶³ By carrying AD-specific biomarkers in their vesicles, they contribute to disease propagation.^{164,165} At the same time, they represent a potential diagnostic resource for AD.¹⁶⁵

Table 2 summarizes all studies based on plasma and WBCs as test samples.^{32-34,145-148,158} It is important to outline that the number of recruited AD patients and age-matched healthy controls varied significantly between studies. In addition, the detection sensitivity for AD ranged between 70%¹⁵⁸ and 89%,³² while the detection specificity ranged between 70%¹⁵⁸ and 92%.³² Three studies reported increased sensitivity (up to 100%) of FTIR spectroscopy-based analyses in mild or early-stage cases of AD,^{32,34,158} whereas a slight decrease was observed in only two studies.^{145,159} These findings indicate that FTIR spectroscopy may be suitable for screening and early diagnosis of AD.

Regarding the differential diagnosis between AD and DLB, two studies highlighted the potential of this optical sensing method in discriminating between both diseases with an accuracy rate ranging between 90 and 93%.^{147,158} These findings represent a breakthrough in the differential diagnosis between the two diseases and indicate that FTIR spectroscopy may be an ideal diagnostic test for clinical implementation.

It should be emphasized that the most recent and large-scale study was conducted by a Chinese research team in 2023. Li *et al.*¹⁵⁹ used machine learning technology along with chemometrics to analyze the spectral data of plasma samples collected from 323 AD patients at different stages and 348 age-matched healthy controls. They proposed a hierarchical discrimination model to differentiate between both groups with sensitivity $\geq 89.3\%$ and specificity $\geq 85.7\%$ (Table 2). The findings indicate that FTIR spectroscopy-based analysis of plasma could be a reliable diagnostic test for AD. The sensitivity and specificity levels of this diagnostic method are comparable to those obtained using traditional diagnostic methods, including CSF biomarkers and brain imaging techniques (Table 1). However, FTIR

spectroscopy-based plasma analysis is complication-free, patient-friendly, and more cost-effective than these conventional approaches. Finally, it is worthwhile outlining that the combined use of Raman and FTIR spectroscopies in plasma analysis can produce a significant increase in diagnostic accuracy for AD, reaching up to 94%.^{32,33}

7. Spectral signatures of Alzheimer's disease and associated biochemical changes

The biochemical changes associated with AD have been closely investigated in patients' plasma using FTIR

Table 2. Summary of blood-based studies investigating Fourier-transform infrared spectroscopy for Alzheimer's disease diagnosis and differential diagnosis from related neurodegenerative disorders

Year	Sample	Number of AD patients and HC	Results	Reference
2008	Plasma	40 AD patients; 112 HCs	Analysis of the spectral region 1,480–910 cm ⁻¹ distinguishes AD patients from HCs with an accuracy of 98.4%	146
2012	Peripheral mononuclear leukocytes	50 AD patients; 20 HCs	(i) Mild, moderate, and severe AD cases are distinguished from HCs with 82.1% sensitivity and 90.5% specificity (ii) Sensitivity increases to 90% when only mild and moderate AD cases are included	34
2013	Plasma	35 cases of AD, including 8 mild cases; 12 HCs	(i) Combined Raman and FTIR spectroscopy analyses distinguishes AD patients from HCs with 89% sensitivity and 92% specificity (ii) This combination detects mild AD cases with 100% specificity	32
2015	Plasma	50 AD patients; 14 HCs	Combined Raman and FTIR spectroscopy analyses distinguishes AD patients from HCs with 94% accuracy	33
2016	Plasma and WBC	20 AD patients; 26 HCs	(i) Mild, moderate, and severe AD cases are distinguished from HCs with accuracies of 85% (WBC) and 77% (plasma) (ii) The accuracy levels change to 83% and 89%, respectively, when only moderate and severe cases of AD are included	145
2017	Plasma	164 AD patients; 34 DLB patients; 149 patients with other neurodegenerative diseases; 202 HCs	(i) Identification of AD patients with a sensitivity and specificity rate of 70% (ii) Early-stage AD cases ($n = 14$) are identified with 80% sensitivity and 74% specificity (iii) Differentiation between AD patients and DLB patients with sensitivity and specificity levels as high as 90% (iv) The combination of FTIR spectroscopy-based analysis and genetic analysis of ApoE-ε4 can produce a significant increase in the detection sensitivity and specificity for AD up to 86%	158
2020	Plasma and WBC	20 AD patients; 10 DLB patients; 26 HCs	(i) Differentiation between both groups of dementia patients (AD and DLB) and HCs, with a success rate of more than 86% (ii) AD patients can be discriminated from DLB patients with an accuracy rate $\geq 93\%$ (iii) The best results are obtained when using WBCs as a test sample	147
2023	Plasma	323 AD patients including 182 early-stage patients, 96 middle-stage patients, and 45 late-stage patients; 348 HCs	AD patients vs. HCs: (i) 89.3% sensitivity and 85.7% specificity for early-stage AD patients; (ii) 92.8% sensitivity and 87.5% specificity for middle-stage AD patients; (iii) 100% sensitivity and 100% specificity for late-stage AD patients	159

Abbreviations: AD: Alzheimer's disease; DLB: Dementia with Lewy bodies; FTIR: Fourier-transform infrared; HC: Healthy control; WBC: White blood cell.

spectroscopy.^{143,146,148} As a result, AD-specific spectral signatures have been identified and linked to specific biochemical changes in the metabolism of lipids, proteins, and nucleic acids.^{143,146,148} Similar changes have also been reported in blood-derived extracellular vesicles,¹⁶⁶ which play a key role in cellular communication between adjacent and remote cells.^{167,168}

The most relevant spectral signature was identified in the 1,480–1,428 cm^{-1} range.^{146,148} involving a decrease in the 1,455 cm^{-1} peak magnitude. This change reflects alterations in the stretching vibrations of CH_2 groups in fatty acids, which was attributed to lipid oxidation. The latter is mediated by the oxidative stress commonly reported in AD patients.¹⁴⁶ In 2013, Liao *et al.*¹⁶⁹ used synchrotron FTIR imaging to examine autopsies collected from AD patients, demonstrating an intriguing connection between amyloid plaques and lipids. Amyloid plaques appeared to be surrounded by, and even infiltrated with, lipids.¹⁶⁹ However, FTIR-based imaging of brain autopsies from a mouse model of AD revealed decreased levels of unsaturated lipids in the hippocampus of AD mice.¹⁷⁰ These findings provide strong indications of lipid alterations during the course of AD.

A more recent investigation demonstrated co-localization of amyloid plaques and lipid oxidation in the brains of AD patients.¹⁷¹ FTIR spectroscopy-based tissue analysis of brain autopsies collected from AD patients revealed the association between senile plaques and oxidized lipids.¹⁷¹ Unsaturated lipids are intrinsically more susceptible to oxidation than saturated lipids, and the reduced levels of unsaturated lipids observed in AD models may reflect ongoing lipid peroxidation. Additionally, plasma from AD patients shows elevated levels of molecules associated with oxidative stress,¹⁴³ including carboxylic acids, reactive carbonyls, reactive oxygen species, and reactive nitrogen species.¹⁴³ The brain, and more precisely the neuronal membrane, is rich in iron and peroxidation-prone unsaturated lipids. These two factors are the main contributors to the oxidative stress-related lipoperoxidation observed in the neuronal membrane of AD patients.¹⁷²

Further signatures have been identified in the plasma spectra of AD patients.^{143,146,148} These include shifts in the absorption peaks at 1,128 cm^{-1} , 1,119 cm^{-1} , and 1,105 cm^{-1} , which correspond to changes in the vibrational modes of phosphate functional groups of nucleic acids.¹⁴⁶ A decrease in the intensity of peaks at 1,053 cm^{-1} and 930 cm^{-1} was also observed, attributed to alterations in the stretching vibrations of C–C/C–O bonds of deoxyribose moieties within the DNA skeleton.¹⁴⁶ These changes were attributed to oxidative damage to DNA nucleosides, which

is associated with oxidative stress in AD patients.^{143,146}

Fourier-transform infrared spectroscopy-based analyses also revealed changes in the conformation of plasma proteins, indicating the presence of highly stable parallel β -sheet structures in the plasma of AD patients,^{33,143} consistent with the formation of A β plaques,^{33,143} possibly related to increased plasma globulin levels in AD patients.^{173–177} Globulins, which are the most abundant plasma proteins after albumin, are rich in β -sheet structures.³³ It should be emphasized that oxidative modifications of proteins, lipids, and nucleic acids in the plasma of AD patients have been reported in numerous studies.^{32,143,146,172,178}

Further investigations have been conducted on CSF samples of AD patients.¹⁴⁴ Similar to the spectral signatures observed in plasma, the CSF spectra of AD patients show shifts in peaks corresponding to phospholipids, DNA, and proteins.¹⁴⁴ In addition, a progressive imbalance in the lipid/protein ratio has been reported at different stages of the disease; specifically, a decrease in lipid content has been observed during disease progression.¹⁴⁴

8. Advantages of Fourier-transform infrared spectroscopy-based diagnosis

Fourier-transform infrared spectroscopy is a universal analytical technique that can be used in numerous types of industrial,^{179–181} environmental,^{182–184} pharmaceutical,^{185–187} forensic,¹⁸ and biomedical^{188–191} analyses. It has a remarkably wide range of applications in clinical laboratories.^{188–190} Many studies have outlined its utility in analyzing various types of tissue biopsies, including those collected from steatohepatic, cirrhotic, and cancerous liver tissues.^{192,193} It can also be useful in analyzing tissue biopsies of prostate cancer^{194,195} and colorectal cancer.¹⁹⁶

Additionally, FTIR spectroscopy can be used to determine the levels of several biochemical components in blood, including glucose, urea, cholesterol, triglycerides, albumin, and total protein.¹⁹⁷ However, the most promising application of this optical sensing method lies in the detection of disease biomarkers. FTIR spectroscopy can be used to detect the biochemical signatures of various diseases by tracing their spectral fingerprints in body fluids, including blood plasma,^{32,33,148,198} serum,^{14,31,199} CSF,^{30,144} sputum,²³ saliva,^{200,201} and urine.²⁰² The utility of this spectroscopic technique in diagnosing various diseases has been documented in numerous studies.^{12,14,22–24,140,195,200}

The cost of a diagnostic test is determined by multiple factors, which vary depending on the requirements of the testing procedure. First, several diagnostic tests require skilled medical staff to perform the test and interpret the

results. For example, a specialized radiologist is needed to supervise the MRI imaging procedure and prepare a report for the referring clinicians,²⁰³ significantly increasing the cost of MRI imaging. Second, the time necessary to complete a diagnostic test is also an important factor influencing its cost. In most instances, radiological imaging and histopathological analyses are time-consuming and, therefore, their cost is relatively high. Additionally, the cost depends on the quantity and number of reagents required and their prices. Moreover, the need for specialized high-technology equipment requiring regular inspection and maintenance is also a cost-contributing factor. Finally, hazardous waste generated during some diagnostic procedures must be removed by specialized companies, thereby contributing to the testing cost.

Compared with traditional diagnostic techniques used in clinical laboratories, FTIR spectroscopy-based analyses are simple and generally do not require highly specialized medical personnel. A few microliters of the test sample are deposited on the ATR crystal and allowed to dry out before acquiring the spectrum.^{33,143} In addition, the testing procedure is almost reagent-free and does not generate hazardous waste. Moreover, the time necessary to perform the test is relatively short (2 min),²⁰⁴ and the obtained spectrum is usually compared with a standard model to reach a decision within seconds. Therefore, there is no need for a specialist to interpret the results.

Finally, FTIR spectroscopy is a relatively compact and low-cost instrument. These characteristics make this optical technique suitable for large-scale screening purposes and accessible to many patients, especially those with low income or living in poor communities. In addition to being an environmentally friendly diagnostic tool, FTIR spectroscopy is also patient-friendly. It can be used for non-invasive disease diagnosis using sputum,²³ saliva,^{200,201} or urine²⁰² as test samples. Furthermore, FTIR spectroscopy-based analyses of plasma^{32,33,148,198} and serum^{14,31,199} are minimally invasive and can be used for diagnosing a variety of diseases.

9. Limitations of Fourier-transform infrared spectroscopy-based diagnosis

It is important to note that FTIR spectroscopy-based analyses are strongly influenced by the presence of water in the test samples. This phenomenon arises from the fact that water molecules strongly absorb mid-IR radiation. Consequently, their absorption signal can overlap with, and even overshadow, the spectral signature of clinically relevant biomarkers present in the analyzed sample.²⁰⁵ Therefore, water-related interference must be minimized. Scientists have proposed three strategies to minimize the

interaction of water molecules in FTIR spectroscopy-based analyses: (i) drying the test sample; (ii) subtracting the water signal from the obtained spectrum using arithmetic methods; and (iii) passing the incident IR beam through pure water.¹⁴³ It should be noted that drying the test sample, although time-consuming, is the most practical approach.¹⁴³

Patients' biofluids contain high concentrations of specific macromolecules and a wide range of minor constituents, including disease biomarkers. Therefore, the IR absorption spectrum of most biofluids is usually dominated by the signals of their abundant constituents, whereas signals arising from minor constituents are often masked or overshadowed. For example, the signal of albumin, the most abundant macromolecule in blood serum and plasma, may overshadow signals associated with disease biomarkers, which are clinically the most relevant. Consequently, eliminating abundant constituents from biological samples, or reducing their concentrations, may significantly improve the sensitivity of FTIR spectroscopy-based analyses. This hypothesis was confirmed by Bonnier *et al.*,²⁰⁶ who used FTIR spectroscopy to examine serum samples spiked with increasing concentrations of glycine.²⁰⁶ They employed size exclusion chromatography to deplete the most abundant high molecular weight proteins present in the serum. As a result, the pre-analytical use of size exclusion chromatography increased the detection sensitivity for the spiked glycine by 50-fold.²⁰⁶ Therefore, the sensitivity of FTIR spectroscopy-based analyses can be significantly improved by eliminating abundant, and often non-relevant, constituents.

The IR absorption spectrum of biological samples varies depending on multiple instrumental and sample-related factors.²⁰⁷ Differences in the pre-analytical preparation of test samples are considered a major source of variability. Moreover, light scattering and noise resulting from variations in electrical, mechanical, and environmental parameters are also major sources of inconsistency in the IR absorption spectra of biological samples.²⁰⁷ To minimize errors arising from these factors and improve spectral consistency, standard preprocessing protocols must be followed. In addition, the adoption of standardized technical protocols to reduce noise and light scattering should be considered.²⁰⁷ Standard guidelines have been proposed to optimize the use of FTIR spectroscopy in clinical practice.²⁰⁸ These guidelines may facilitate the effective translation of FTIR spectroscopy into clinical diagnostics.

Table 3 summarizes the advantages and limitations of FTIR spectroscopy compared with traditional and standard diagnostic methods for AD.

10. Discussion

Dementia is a major public health problem affecting approximately 55 million individuals worldwide.¹ Nearly

70% of dementia cases are attributed to neurodegeneration caused by AD.^{4,7} The number of individuals in the preclinical stage of AD is estimated at 315 million,⁵⁶ which is expected

Table 3. Advantages and limitations of Fourier-transform infrared spectroscopy-based diagnosis of Alzheimer's compared with traditional diagnostic methods

Test	Advantages	Limitations	Reference
Clinical examination	(i) High level of sensitivity for AD (ii) Detection of cognitive, functional, and behavioral impairments	(i) Low level of specificity for AD (ii) Time-consuming and requires the intervention of a specialist neurologist (iii) The early symptoms associated with AD can be insidious and can be easily misinterpreted by clinicians during the limited interview time with the patient (iv) The standard tests may not be sensitive enough to detect mild cognitive decline during the early stage of AD (v) The day-to-day variability in the patient's response may necessitate the interrogation of the patient's entourage	42,99-103
CSF biomarkers	(i) High level of sensitivity for AD, especially when it comes to detecting the early neurological changes (ii) Can be a reliable alternative for PET imaging methods	(i) Unsatisfactory specificity for AD (ii) Necessitate CSF sampling by lumbar puncture, a procedure that may be associated with serious complications and requires: • Prior preparation of the patient • The intervention of a trained clinician • Hospitalization (iii) Sophisticated and time-consuming	73,74,89,106-111
Radiological imaging (MRI, FDG-PET, and amyloid PET)	(i) MRI is useful in the differential diagnosis between AD and other types of neuropathologies, such as neoplasm and microbleeding (ii) The sensitivity and specificity levels of the amyloid PET test can be substantially improved by using a quantitative assessment of the global cortex (iii) FDG-PET has a relatively high level of sensitivity for AD	(i) The high cost of these tests might limit their use in underserved communities or for screening purposes in individuals with high risk for AD (ii) Considering the relatively low specificity of these tests for AD, the result of FDG-PET must be considered in combination with that of amyloid PET (iii) Require the intervention of trained medical staff to perform the test, interpret the image, and write a report for the referring clinician (iv) Require prior preparation of the patient (v) Contraindicated in patients implanted with ferromagnetic devices (vi) PET requires the administration of a radiotracer. Therefore, it might pose a risk for the fetus and the breastfeeding baby (vii) Cannot assess the severity of AD (viii) Complex and time-consuming	70,71,79,120,122,126-129,131,138,209

(cont'd...)

Table 3. (Continued)

Test	Advantages	Limitations	Reference
FTIR spectroscopy	<ul style="list-style-type: none"> (i) Plasma-based analysis has a high level of sensitivity ($\geq 89.3\%$) and an acceptable level of specificity ($\geq 85.7\%$) for AD (ii) Plasma-based analysis can detect mild and early-stage cases of AD with reasonably high levels of sensitivity and specificity (iii) Plasma- and WBC-based analyses can differentiate between AD patients and DLB patients with an accuracy level $\geq 90\%$ (iv) Plasma- and WBC-based analyses are minimally invasive (v) Plasma- and WBC-based analyses are patient-friendly, as they cause no complications and do not require prior patient preparation (vi) Universality: FTIR spectroscopy can be used for multiple diagnostic purposes (vii) Short testing time (2 minutes) (viii) Environmentally friendly (minimal amount of hazardous wastes). (ix) Requires a minimal amount of test sample (x) Minimum requirements for test reagents (xi) Simplicity: trained medical staff is not required to perform the test and interpret the results (xii) Low cost 	<ul style="list-style-type: none"> (i) Additional studies on large cohorts of previously undiagnosed elderly individuals are needed to compare the performance of this optical diagnostic method with other screening and diagnostic methods (ii) Further studies are needed to examine the performance of this optical sensing method in AD patients with underlying diseases (iii) Comparative studies are needed to evaluate the performance of this spectroscopic technique relative to standard AD diagnostic methods (iv) The IR absorption spectrum is highly influenced by water in the test samples. Therefore, it is important to remove water by drying, which may extend the testing time by a few minutes. (v) Signals from abundant constituents in biological samples may mask those of clinically relevant biomarkers. Molecular fractionation to remove or reduce these abundant constituents may significantly improve sensitivity, although this step may increase testing time and cost (vi) There is an urgent need for a scientific consensus on the adoption of standard chemometric models specific to AD (vii) Adoption of standard protocols for sample processing and calibration of environmental and instrumental parameters is essential to minimize inconsistencies in the absorption spectrum 	12,14,22-24, 32,33,34,140, 143,147,158,159, 195,200,204, 205,206,207

Abbreviations: AD: Alzheimer's disease; CSF: Cerebrospinal fluid; DLB: Dementia with Lewy bodies; FDG: Fluorodeoxyglucose; FTIR: Fourier-transform infrared; MRI: Magnetic resonance imaging; PET: Positron emission tomography; WBC: White blood cell.

to contribute to the projected increase in dementia cases in the coming decades.^{1,2} Consequently, the global financial burden of this brain syndrome is projected to reach USD 2.8 trillion by 2030.¹

Establishing a definitive diagnosis for AD in clinical practice is challenging and time-consuming, as patients must undergo multiple cognitive and functional assessments. In addition, clinicians rely on various laboratory and imaging tests.^{210,211} Consequently, the diagnostic process is often costly and may not be affordable for all patients presenting with cognitive impairment. Moreover, the invasive nature of some tests and the associated risk of complications and patient discomfort can further complicate the diagnostic process. Therefore, the development of a reliable and less complex diagnostic test capable of overcoming these limitations would represent a major advancement in the medical management of AD. These challenges also further complicate large-scale screening for AD in the elderly population.

Early diagnosis of AD provides significant benefits for patients, healthcare systems, and societies.¹⁰ Considering these factors, there is an urgent need for a simple, time-efficient, and cost-effective screening test for the early detection of AD. Such a test could facilitate the identification of individuals in the preclinical and prodromal stages, who are typically asymptomatic or present with mild cognitive impairment. In addition, the test should demonstrate high accuracy to provide a strong indication of AD, although it may not necessarily establish a definitive diagnosis.

Several screening tests have been proposed to identify patients with mild cognitive impairment who require further evaluation for AD.^{58,212,213} For example, olfactory tests,^{58,214,215} eye examinations,^{216,217} and blood proteomic analyses^{213,218,219} have been suggested as screening tools to identify patients who should be referred for more costly and invasive diagnostic procedures for AD. However, these tests are often time-consuming and may need to be used in combination in primary care settings.⁵⁸ In

addition, some of these tests, such as retinal imaging²¹⁷ and blood proteomics,²¹³ are technically complex and require specialist expertise. Moreover, most of these tests cannot reliably detect asymptomatic individuals in the preclinical stage of AD.

Recently, vibrational spectroscopy has been proposed as a potential approach for screening and diagnosing several human diseases, including chronic liver diseases¹³ and neurodegenerative disorders such as multiple sclerosis^{12,28} and Parkinson's disease.^{31,142} The majority of studies investigating the application of FTIR spectroscopy for AD diagnosis have reported promising performance of this analytical technique, regardless of the type of test sample used. Although blood plasma is commonly used as the sample of choice, the sensitivity reported in plasma-based studies ranges from 70%¹⁵⁸ to 89%.³² These variations may be attributed to several factors, including differences in the number of patients and healthy controls included, the chemometric methods used to analyze the experimental data, and the application of machine learning or artificial intelligence for spectral analysis. Additional factors may also contribute to discrepancies between studies. Variations in sample processing protocols and analytical procedures may significantly influence the stability of biochemical components in the sample and, consequently, their spectral fingerprints.^{207,208}

Regarding the sample preparation protocols, the methods vary widely across studies.^{32,145-147,158} For example, Peuchant *et al.*¹⁴⁶ diluted plasma samples with four different volumes of water prior to drying and subsequent measurement. Meanwhile, some studies diluted blood samples with one volume of Histopaque solution immediately after collection to facilitate isolation of WBCs.^{145,147} In contrast, Paraskevaidi *et al.*¹⁵⁸ analyzed undiluted plasma samples.

Regarding the test sample volume, considerable variation is also reported across studies. Some studies used 1 μ L of plasma,¹⁴⁵ whereas others used 35 μ L¹⁴⁶ or even 50 μ L.¹⁵⁸ Additionally, sample-drying conditions, including temperature and drying duration, differ between studies.^{32,145-147,158} Such methodological differences may partly explain the variability in the reported diagnostic accuracy.

Moreover, strict control of environmental conditions, particularly temperature and humidity during the sample-drying step, has been shown to improve the reproducibility of the spectral signatures of biofluids.²²⁰⁻²²² Fluctuations in temperature and humidity can influence the dynamics of droplet evaporation and, consequently, the density and crack formation within the dried sample spot.²²⁰⁻²²² Variations in environmental conditions during sample

processing are therefore considered major sources of inconsistency in the spectral signatures of biological samples.^{207,208}

For serum analysis, optimal results are achieved with a three-fold dilution of the serum sample.²²³ Moreover, for DNA analysis, a drying temperature of 30 °C yields the highest reproducibility of the spectral signature.²²⁴ In addition, the spectral signature of a biological sample may vary depending on instrumental factors, including fluctuations in electric current or differences in machine calibration. Thus, the adoption of standardized working protocols and defined instrumental and environmental parameters is essential to minimize errors and improve reproducibility.^{207,208}

It is important to note that the spectral signature of AD may be influenced by its stage, the presence of other underlying diseases, or pharmacotherapy administered to patients. Although several studies have considered patients at the early stage of AD independently,^{34,158,159} future studies should also evaluate patients with comorbidities or those receiving medications separately. The biochemical composition of blood plasma can be significantly affected by pharmacotherapy and inflammation resulting from infectious, metabolic, or autoimmune conditions, which may alter the spectral signature and consequently affect the diagnostic accuracy of FTIR spectroscopy-based analysis.

Reducing abundant constituents in biological samples can markedly enhance the sensitivity of FTIR spectroscopy-based analyses (Table 3).²⁰⁶ From this perspective, molecular fractionation to remove high-molecular-weight plasma proteins is recommended in future studies. Although time-consuming, this step may significantly increase the diagnostic accuracy. Finally, it is noteworthy that combining FTIR and Raman spectroscopy further improves the diagnostic accuracy for AD (Table 2),^{32,33} making this combination particularly useful for definitive diagnosis purposes.

11. Conclusion

This review evaluates the potential application of FTIR spectroscopy for screening AD in the elderly population and considers its possible use as a confirmatory test for establishing a definitive diagnosis of this neurodegenerative disease. Overall, FTIR spectroscopy shows promise as a screening tool for early detection of AD, with multiple studies highlighting its strong performance in identifying patients at an early stage during the disease course.^{32,34,158}

However, further large-scale screening studies are required to assess the efficacy of this analytical technique in detecting AD among previously undiagnosed elderly

individuals. Such studies will also clarify its ability to detect patients in the preclinical stage and evaluate its accuracy relative to traditional screening and diagnostic methods.

Blood plasma is the preferred sample in most studies investigating the use of FTIR spectroscopy for AD diagnosis.^{32,145-147,158,159} CSF is also suitable for this kind analyses.¹⁵² Compared with the highly invasive lumbar puncture required for CSF collection, blood sampling is minimally invasive and complication-free. A recent study suggested oral buccal cells as a potential non-invasive sample for FTIR-based AD diagnosis;¹⁵¹ however, further large-scale studies are needed to confirm the suitability of this sample type.

The accuracy of FTIR spectroscopy-based diagnosis of AD varies across studies (Table 2). Notably, the most recent study¹⁵⁹ reported sensitivity and specificity comparable to, or exceeding, those obtained using CSF biomarkers and imaging methods (Tables 1 and 2). At the same time, FTIR spectroscopy offers a more cost-effective diagnostic approach (Table 3). It is important to emphasize that FTIR spectroscopy-based analysis of plasma is a potentially promising test for diagnosing AD in clinical practice. Its simplicity, rapidity, low cost, and satisfactory accuracy—particularly in detecting mild and early-stage AD—support its potential as a screening test.

In addition, this analytical method may be employed by specialist neurologists as a confirmatory test for definitive diagnosis. Pioneering studies demonstrate promising performance of FTIR spectroscopy in differentiating AD from DLB,^{147,158} suggesting a practical solution for this challenging clinical task.⁸ Furthermore, FTIR spectroscopy shows considerable potential in differentiating AD from other closely related neurodegenerative disorders, such as Parkinson's disease.¹⁵⁸

The potential application of FTIR spectroscopy in the diagnosis of human diseases has been demonstrated in multiple studies.^{12,14,15,22-24,27,139-141} In addition, its use in diagnosing certain conditions, such as inflammatory bowel disease and lymphoma, has already been patented. Nevertheless, for AD, further cross-laboratory validation studies are required. These studies should involve the same cohorts of patients and healthy controls across multiple reference laboratories worldwide to verify the reproducibility and precision under varying working conditions. Such investigations will also facilitate international consensus on standard protocols, optimal instrumental parameters, and reference chemometric models for AD.

Furthermore, bridging trials across diverse global populations may be necessary to assess the reliability of

this technique in different ethnic groups and to confirm whether it achieves adequate sensitivity and specificity for AD diagnosis. Although most studies to date are single-center pilot investigations, their findings are encouraging, suggesting that FTIR spectroscopy has the potential to become a novel diagnostic method for AD with properties suitable for implementation in clinical practice.

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Conflict of interest

The author declares no conflict of interest.

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