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Contemporary Classifications of Alzheimer's Disease: A Critical Review of Clinical, Biological, Neuropathological, Functional, Phenotypic and Neuroinformational Frameworks

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Abstract. Alzheimer's disease is classified using multiple frameworks that do not always refer to the same construct. These include clinical severity, biological status, neuropathological burden, functional impairment, phenotypic presentation, genetic risk, neuropsychological profile and sensory impairment. This comprehensive critical review examines contemporary frameworks for classifying Alzheimer's disease and analyses their conceptual scope, methodological utility and principal limitations. The evidence base comprises studies, consensus documents, diagnostic criteria and neuropathological guidelines. The classification systems were organised into seven main categories: clinical and cognitive staging; biomarker-based frameworks; neuropathological classifications; functional scales; phenotypic variants; classifications by age at onset, genetics and risk; and sensory-neuroinformational approaches. The findings indicate that existing frameworks provide complementary yet fragmented perspectives. Clinical systems describe symptoms and severity, biomarker models define the biological status of the disease, neuropathological classifications assess post-mortem lesion burden, functional scales estimate dependency, and phenotypic classifications capture typical and atypical presentations. However, substantial ambiguity remains because these systems often overlap despite not being conceptually equivalent. This review sets out a multidimensional taxonomy intended to clarify what each classification framework measures and how it may be applied in research and clinical interpretation. As an original contribution, sensory neuroinformation is proposed as an emerging classificatory dimension based on latency, fidelity and integration. It may offer a complementary framework for understanding Alzheimer's disease as a progressive deterioration in sensory-cognitive information processing.

Keywords: *Alzheimer's disease; classification; staging; biomarkers; neuropathology; sensory processing; neuroinformation; scoping review.*

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1. Introduction

Alzheimer's disease (AD) is increasingly understood not simply as a single type of dementia, but as a multidimensional construct that may be classified along several axes: clinical, biological, functional, neuropathological, genetic and cognitive phenotype. This diversity has contributed to parallel classification systems that may not fully coincide, thereby creating potential diagnostic, methodological and conceptual ambiguity.

Historical reviews have suggested that the definition of 'what Alzheimer's is' has varied across clinicopathological, purely biological and clinical-biological approaches, without a consistently stable consensus (Rathore et al., 2017). The coexistence of different systems, including clinical, biological and neuropathological frameworks, may lead to:

- Diagnostic ambiguity: an individual may be classified as 'AD', 'at risk of AD' or 'not AD' depending on the framework used (Dubois et al., 2021; Hampel et al., 2021; Therriault et al., 2024; Trejo-Lopez et al., 2022; Rathore et al., 2017).
- Methodological ambiguity: longitudinal cohorts use different criteria for the same early stages, which may complicate comparisons and meta-analyses (Kobayashi et al., 2026; Trejo-Lopez et al., 2021; Kergoat et al., 2025).
- Conceptual ambiguity: there is debate as to whether early-stage cancer should be defined solely by lesions/biomarkers or as a clinical-biological entity requiring both symptoms and markers (Villalpando et al., 2026; Hampel et al., 2021; Therriault et al., 2024; Rathore et al., 2017).

Alzheimer's disease may be classified across clinical, biological, functional, neuropathological, genetic, phenotypic, neuropsychological, and sensory domains. This plurality reflects the complexity of the disease, which may present not only as a cognitive syndrome but also as a progressive neurobiological, functional, and behavioural process. However, because each framework organises the disease according to different criteria, their coexistence may create diagnostic, methodological, and conceptual ambiguity. Some classifications focus on clinical symptoms and cognitive impairment. Others prioritise biomarkers, neuropathological lesions, functional dependence, phenotypic variants, genetic risk, or specific patterns of brain damage.

The central challenge lies in the fragmentation of the systems used to describe, diagnose, and study Alzheimer's disease. The available classifications do not necessarily measure the same construct or serve the same purpose. They may address different levels of the disease, ranging from clinical presentation and biological pathology to functional severity and neuropsychological profile. Other frameworks focus on clinical phenotype, neuropathological burden, genetic risk, or possible sensory impairments. This lack of standardisation may complicate comparisons between studies, the interpretation of clinical findings, and the integration of evidence across disciplines. Consequently, a comprehensive framework may help to organise the principal classification dimensions of Alzheimer's disease and identify their overlaps and tensions. Such a framework would link biomarkers, clinical manifestations, functional impairment, phenotypes, genetics, sensory perception, and neural information.

Rather than merely cataloguing existing classifications of Alzheimer's disease, this review examines the object classified by each framework, the observational modality used to assess it, and its clinical or research purpose. On this basis, we distinguish classifications of disease biology, clinical syndrome, functional impairment, neuropathological burden, phenotypic presentation, susceptibility and risk, and sensory–neural information processing.

Building on this distinction, we propose a metataxonomy of Alzheimer's disease classification frameworks. Here, a metataxonomy is defined as a higher-order system that organises existing classifications across three analytically distinct layers. These comprise: (i) the object being classified; (ii) the modality through which that object is observed or measured; and (iii) the intended use of the resulting classification. This distinction may help to clarify why diagnostic criteria, staging systems, severity scales, biomarkers, phenotypic categories, and risk stratifications are not interchangeable descriptions of the same construct.

The review had five specific objectives: (1) to map contemporary clinical, biological, neuropathological, functional, phenotypic, genetic, sensory, and data-driven frameworks; (2) to identify the object classified by each framework; (3) to distinguish classification systems from measurement instruments; (4) to assess the conceptual and translational maturity of each framework; and (5) to propose an operational and testable neuroinformational extension based on latency, fidelity, and integration.

To our knowledge, previous reviews do not appear to have explicitly organised Alzheimer's disease classification frameworks across the three analytically distinct layers proposed here: the object being classified, the observational modality through which it is assessed, and the intended use of the resulting classification. Although multidimensional, biomarker-based, phenotypic, and computational approaches have previously been described, comparisons commonly place them at the same analytical level, even though they refer to different constructs. The principal conceptual contribution of this review therefore lies not in introducing an additional diagnostic category, but in developing a metataxonomic architecture that clarifies the

relationships and non-equivalence among existing frameworks. A second, hypothesis-generating contribution is the formulation of neuroinformational integrity as a multidimensional profile of latency, fidelity, and integration. Each component has precedents in psychophysics, neurophysiology, and network neuroscience; however, their combined use as an explicit classificatory framework for Alzheimer's disease remains to be empirically validated.

2. Methods

2.1 Review design

The methodological procedures used to identify, select, organise, and synthesise the literature on contemporary Alzheimer's disease classification frameworks are set out in this section. These procedures encompass the review design, research questions, information sources, search strategy, eligibility criteria, data-extraction process, conceptual synthesis, and assessment of framework maturity. The methodological approach was structured to distinguish the systematic mapping of evidence from the critical conceptual analysis through which the proposed metataxonomy and neuroinformational extension were developed.

We conducted a scoping review of contemporary frameworks used to classify, diagnose, stage, or characterise Alzheimer's disease. The review was designed in accordance with the methodological guidance of the Joanna Briggs Institute for scoping reviews and reported in accordance with the PRISMA (fig. 1) Extension for Scoping Reviews. A scoping design was selected because the relevant literature encompasses heterogeneous constructs. These include diagnostic criteria, clinical staging systems, functional scales, biomarker frameworks, neuropathological schemes, phenotypic categories, genetic risk classifications, sensory markers, and emerging computational models. The review combined systematic evidence mapping with critical conceptual synthesis. The systematic component identified and organised the available classification frameworks, while the conceptual component considered whether they addressed the same object or analytically distinct objects.

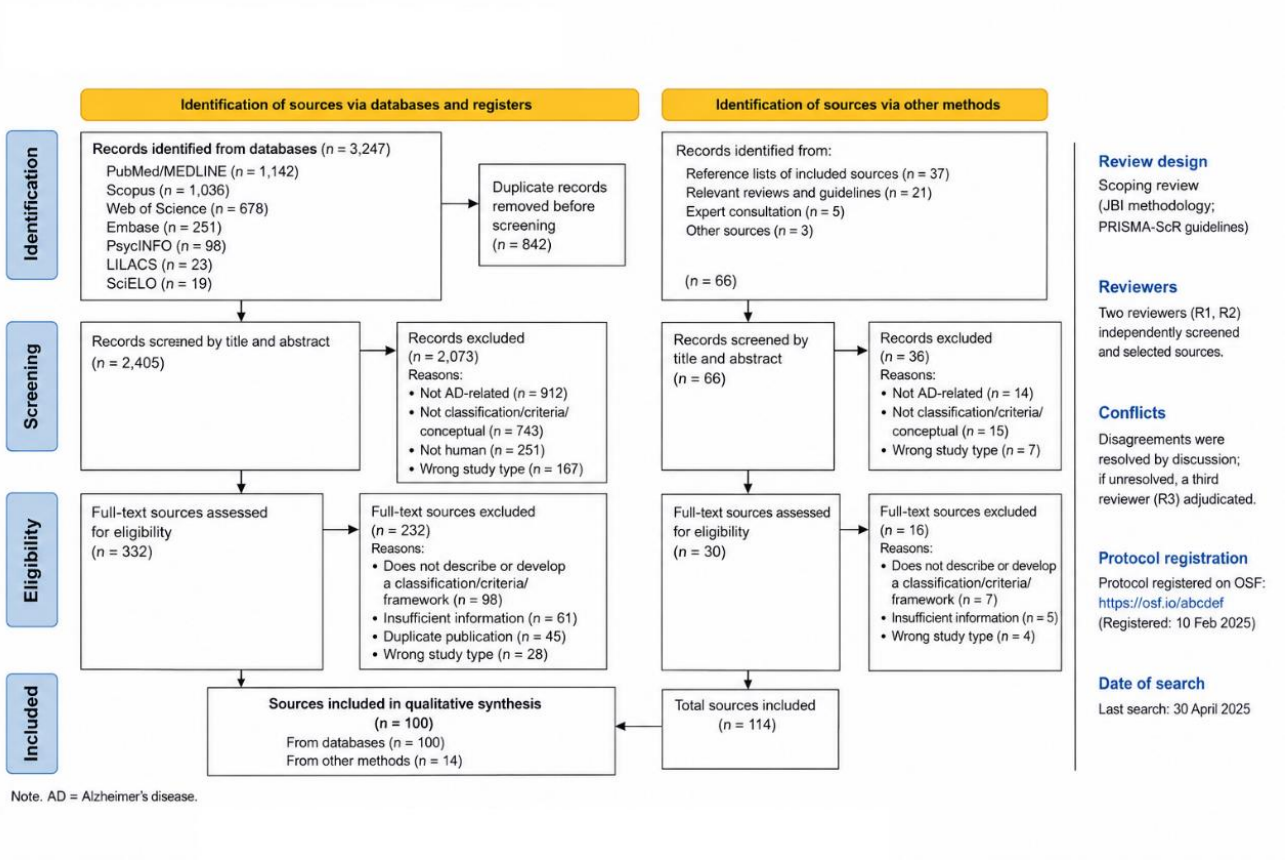

Fig. 1. *PRISMA-ScR study selection diagram.*

2.2 Research questions

The review addressed the following questions:

RQ1. What contemporary frameworks are used to classify, diagnose, stage, or characterise Alzheimer's disease?

RQ2. What object does each framework classify: biological pathology, clinical syndrome, functional impairment, neuropathological burden, phenotype, susceptibility, risk, or neural information processing?

RQ3. Through which observational modality is each classification derived?

RQ4. For what purpose is each framework used, including screening, diagnosis, staging, prognosis, monitoring, cohort stratification, or treatment selection?

RQ5. What is the conceptual, empirical, and translational maturity of each framework?

RQ6. To what extent can latency, fidelity, and integration be operationalised as a testable neuroinformational classification of Alzheimer's disease?

2.3 Information sources

The following databases were searched from inception to July 2026: MEDLINE/PubMed, Embase, Scopus, Web of Science Core Collection, PsycINFO, and the Cochrane Library. Additional searches were conducted in SciELO and LILACS to identify relevant Ibero-American literature. The reference lists of eligible consensus documents and reviews were manually screened. Google Scholar was used only as a complementary source for citation tracking and identifying grey literature.

2.4 Search strategy

The search strategy combined terms related to Alzheimer's disease with terms concerning classification, diagnosis, staging, taxonomy, biomarkers, neuropathology, phenotype, function, genetics, sensory processing, and neural information processing. The core search structure was as follows:

("Alzheimer disease" OR "Alzheimer's disease" OR "Alzheimer dementia") AND (classification OR staging OR taxonomy OR framework OR criteria OR subtype) AND (clinical OR functional OR cognitive OR biomarker OR neuropathological OR phenotypic OR genetic OR sensory OR neurophysiological OR neuroinformational).

2.5 Eligibility criteria

Eligible sources included peer-reviewed original studies, consensus documents, diagnostic criteria, clinical guidelines, systematic or scoping reviews, neuropathological guidelines, and methodological papers. To be included, a source had to propose, define, validate, compare, or apply a classification framework relevant to Alzheimer's disease.

Studies were eligible if they addressed at least one of the following domains: clinical diagnosis or staging; cognitive or functional severity; biomarker-based classification; neuropathological staging; phenotypic variation; genetic or age-of-onset classification; sensory or neurophysiological impairment; or data-driven disease subtyping.

Studies concerned exclusively with therapeutic efficacy were excluded unless they included an explicit classification or stratification component. Studies of non-Alzheimer dementias were excluded unless they contributed directly to differential classification, the interpretation of mixed pathology, or Alzheimer-related phenotypic interpretation. Sources that lacked sufficient methodological or conceptual detail to identify the classification system used were also excluded.

2.6 Data extraction

Data were extracted using a standardised form developed for this review. For each source, we recorded the publication characteristics, the name of the classification framework, the primary object classified, the observational modality, the categories or stages generated, and the intended use. We also recorded the target population, validation evidence, reproducibility, clinical utility, research utility, accessibility, major limitations, and maturity level.

The extraction form distinguished explicitly between classification systems and the instruments used to generate evidence for classification. For example, biomarker frameworks and diagnostic criteria were coded as classification systems, whereas cognitive tests were coded as measurement instruments unless they directly defined categorical stages.

2.7 Conceptual synthesis

Frameworks were synthesised using a three-layer analytical model:

- Layer 1: the object classified;
- Layer 2: the observational modality;
- Layer 3: the intended use.

This approach allowed us to distinguish between frameworks that use similar measurements to classify different constructs and those that classify similar constructs using different measurements.

2.8 Assessment of framework maturity

Each classification framework was assigned a maturity level according to six criteria: conceptual clarity, empirical validation, reproducibility, external replication, clinical or research implementation, and incorporation into guidelines or consensus recommendations. The assessment focused on the specific framework rather than on the broader classificatory domain to which it belonged.

Maturity (Table 1) was not considered equivalent to scientific validity or importance. An established framework may remain conceptually limited, whereas an emerging or hypothesis-generating framework may be scientifically innovative but not yet sufficiently validated to inform clinical decision-making.

Table 1. Maturity levels for classification frameworks.

Level	Category	Operational definition
M5	Established	Incorporated into major guidelines, consensus criteria, or standard practice; supported by extensive validation, external replication, and broad implementation
M4	Clinically validated	Supported by multiple validation studies, acceptable reproducibility, and demonstrated clinical utility
M3	Research framework	Conceptually defined and used in research, with partial empirical validation but limited implementation in routine clinical practice
M2	Emerging	Supported by preliminary or heterogeneous evidence; procedures, categories, or thresholds remain under development
M1	Hypothesis-generating	Primarily theoretical or exploratory; lacks prospective validation, external replication, and established decision thresholds

The maturity levels indicate developmental and translational status rather than scientific value.

3. Taxonomy of classifications of Alzheimer's disease

The principal contemporary frameworks used to classify Alzheimer's disease are mapped in this section, with particular attention to the construct addressed by each. The analysis begins with the proposed three-layer metataxonomy before considering clinical, functional, cognitive, age-related, genetic, biological, neuropathological, phenotypic, sensory, and neurophysiological approaches. Rather than merely enumerating the available systems, the analysis examines what each framework classifies, how the relevant information is obtained, and which clinical or research decisions the resulting classification is intended to support.

3.1. Proposed three-layer metataxonomy

A metataxonomy is defined here as a higher-order structure that organises classification systems according to the object classified, the observational modality and the intended use. Unlike a conventional taxonomy, it classifies frameworks rather than individual patients.

The proposed metataxonomy (Table 2) distinguishes the ontological object of classification from both the modality through which it is observed and the purpose for which the classification is applied. This separation may help to prevent technologies such as neuroimaging, artificial intelligence, or cognitive testing from being treated automatically as independent dimensions of disease. Instead, these technologies constitute observational or analytical modalities that may contribute to the classification of different underlying objects.

Table 2. Three-layer metataxonomy of Alzheimer's disease classification

Layer	Categories included	Function
Object classified	Biological pathology; clinical syndrome; functional impairment; neuropathological burden; phenotype; susceptibility and aetiology; neuroinformational function	Specifies what aspect of the disease or its expression is being classified
Observational modality	Clinical examination; psychometric assessment; fluid biomarkers; neuroimaging; histopathology; neurophysiology; sensory testing; computational analysis	Specifies how the classificatory object is measured or inferred
Intended use	Screening; diagnosis; staging; prognosis; monitoring; research stratification; treatment selection	Specifies the decision or research purpose supported by the classification

Under this model, a single patient may receive multiple simultaneous classifications without contradiction. For example, the same individual may be classified biologically as A+T+, clinically as stage 3, functionally as largely independent, phenotypically as amnestic, and neuropsychologically as showing predominant episodic-memory impairment. These labels are not redundant because each refers to a distinct object of classification.

Table 3 compares representative Alzheimer's disease classification frameworks and supporting assessment instruments according to the objects they classify or measure, their observational modalities, types of output, intended uses, inferential limitations, and maturity levels.

Table 3. Comparative matrix of Alzheimer's disease classification frameworks and supporting instruments

Framework or instrument	Primary object classified	Observational modality	Type of output	Intended use	What it does not establish	Maturity
Alzheimer's Association 2024 criteria	Biological Alzheimer pathology	Plasma, CSF, or PET biomarkers	Biological diagnosis and stage	Diagnosis, staging, and treatment eligibility	Clinical impairment or functional dependency	M3 — Consensus framework
International Working Group (IWG) criteria	Clinical–biological Alzheimer's disease	Clinical phenotype plus biomarkers	Clinical–biological diagnosis	Symptomatic diagnosis and differential diagnosis	Purely asymptomatic disease classification	M3 — Consensus framework

Framework or instrument	Primary object classified	Observational modality	Type of output	Intended use	What it does not establish	Maturity
Braak staging	Distribution of neurofibrillary pathology	Histopathology	Ordered neuropathological stage	Post-mortem characterisation	Clinical severity in an individual patient	M5 — Established
Thal phases	Distribution of amyloid deposition	Histopathology	Amyloid phase	Neuropathological assessment	Cognitive or functional state	M5 — Established
CDR	Global clinical and functional severity	Patient and informant interviews	Ordinal severity stage	Staging and longitudinal monitoring	Alzheimer's disease-specific aetiology	M4 — Clinically validated instrument
MoCA	Global cognitive performance	Psychometric testing	Continuous score or screening threshold	Screening and cognitive characterisation	Biological diagnosis of Alzheimer's disease	M4 — Clinically validated instrument
Posterior cortical atrophy classification	Phenotypic presentation	Clinical and neuropsychological assessment	Phenotypic category	Differential diagnosis and subtype characterisation	Specific underlying pathology in the absence of biomarkers	M3 — Research/consensus framework
Neuroinformational model	Efficiency of neural information processing	Psychophysics and neurophysiology	Multidimensional profile	Early detection, stratification, and mechanistic research	Alzheimer's disease-specific diagnosis pending validation	M1 — Hypothesis-generating

Abbreviations: CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; IWG, International Working Group; MoCA, Montreal Cognitive Assessment; NIA–AA, National Institute on Aging–Alzheimer's Association; PET, positron emission tomography.

The table includes both classification frameworks and supporting instruments because clinical and research practice often combines them. However, they should not be regarded as conceptually equivalent. The NIA-AA and IWG frameworks define disease-related categories, Braak and Thal classifications describe neuropathological distribution, the CDR stages clinical and functional severity, and the MoCA measures cognitive performance.

3.2 Clinical and functional classifications

Alzheimer's disease has historically been classified on the basis of clinical criteria relating to symptoms. However, the current approach, led by the National Institute on Aging and the Alzheimer's Association (NIA–AA), has increasingly shifted towards defining AD according to its underlying biology using biomarkers, irrespective of symptoms. The most recent criteria were published in June 2024 by the Alzheimer's Association Workgroup (Jack et al., 2024). These revised criteria build on the 2018 NIA–AA Research Framework and represent a further development of the diagnostic approach first established in McKhann's 1984 publication.

3.2.1 Clinical diagnostic and biological frameworks

The conceptual basis of Alzheimer's disease diagnosis has evolved from clinicopathological criteria towards biological and clinical–biological definitions. The National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria classified cases as possible, probable, or definite

Alzheimer's disease. Probable disease was defined primarily by a progressive dementia syndrome without a more plausible cause, whereas a definite diagnosis required neuropathological confirmation.

The NIA–AA recommendations published in 2011 expanded this approach by distinguishing preclinical Alzheimer's disease, mild cognitive impairment (MCI) due to Alzheimer's disease, and dementia due to Alzheimer's disease. Biomarkers were incorporated as supportive evidence, reflecting the recognition that Alzheimer-related pathological changes may precede overt cognitive and functional impairment.

The 2018 NIA–AA Research Framework represented a substantial conceptual transition by defining the Alzheimer continuum according to the AT(N) biomarker scheme: amyloid pathology (A), pathological tau (T), and neurodegeneration or neuronal injury (N). This framework separated biological disease status from clinical expression and was conceived primarily for research use.

The 2024 Alzheimer's Association criteria further developed the biological approach by incorporating contemporary fluid and imaging biomarkers and distinguishing among biomarkers contributing to biological diagnosis, staging, prognosis, and the identification of concomitant pathology. Biological status and clinical severity are thus treated as related but analytically distinct dimensions.

The 2024 criteria broaden the biological definition of Alzheimer's disease by adopting a multimodal profile that distinguishes among diagnostic, staging, and copathology-related biomarkers (Jack et al., 2024; Kobayashi et al., 2026).

By contrast, the International Working Group (IWG) defines Alzheimer's disease as a clinical–biological construct. Under the IWG approach, diagnosis requires a compatible clinical phenotype together with Alzheimer-specific biomarker evidence. Cognitively unimpaired individuals with positive biomarkers are considered to be at increased risk rather than diagnosed with symptomatic Alzheimer's disease. The principal difference between the Alzheimer's Association and IWG frameworks therefore lies in whether biological positivity alone is considered sufficient to define Alzheimer's disease (Table 4).

Table 4. Evolution of major Alzheimer's disease diagnostic frameworks

Framework	Primary basis	Main output	Principal limitation
NINCDS–ADRDA 1984	Clinical syndrome; neuropathology for definite diagnosis	Possible, probable or definite AD	Limited capacity to identify preclinical disease
NIA–AA 2011	Clinical stage supported by biomarkers	Preclinical AD, MCI due to AD and dementia due to AD	Variable implementation of biomarkers
NIA–AA Research Framework 2018	AT(N) biomarker profile	Biological Alzheimer continuum	Developed principally as a research framework
Alzheimer's Association criteria 2024	Core fluid and imaging biomarkers, with separate clinical staging	Biological diagnosis and disease stage	Biomarker positivity does not independently establish functional impairment
IWG 2021/2024	Compatible clinical phenotype plus Alzheimer-specific biomarkers	Clinical–biological diagnosis	Does not diagnose cognitively unimpaired biomarker-positive individuals as symptomatic AD

Abbreviations: AD, Alzheimer's disease; IWG, International Working Group; MCI, mild cognitive impairment; NIA–AA, National Institute on Aging–Alzheimer's Association; NINCDS–ADRDA, National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association.

3.2.2 Functional and global severity staging

Functional and global staging instruments describe the severity and consequences of impairment rather than its underlying aetiology. The Global Deterioration Scale (GDS) organises cognitive and functional decline into seven broad stages, ranging from no impairment to very severe dementia. The Functional Assessment Staging Test (FAST) offers a more detailed account of the sequential loss of activities of daily living, particularly in advanced disease.

The Clinical Dementia Rating (CDR) assesses memory, orientation, judgement and problem-solving, community affairs, home and hobbies, and personal care through structured interviews with the patient and an informant. It generates either a global ordinal stage or a Clinical Dementia Rating–Sum of Boxes (CDR-SB) score suitable for longitudinal monitoring and clinical trials.

GDS, FAST, and CDR are useful for severity staging, prognosis, care planning, and outcome assessment. However, none of these instruments independently establishes Alzheimer's disease pathology as the cause of the observed impairment.

Table 5. Functional and global staging instruments

Instrument	Primary construct	Output	Main use	What it cannot establish independently
GDS	Global cognitive and functional deterioration	Seven ordinal stages	Broad clinical staging and communication	Alzheimer-specific aetiology
FAST	Sequential loss of functional abilities	Stages and substages of functional dependency	Functional staging and advanced-care planning	Underlying biological pathology
CDR/CDR-SB	Global clinical and functional severity	Global stage or sum-of-boxes score	Staging, monitoring and clinical-trial outcomes	Alzheimer-specific diagnosis

Abbreviations: CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating–Sum of Boxes; FAST, Functional Assessment Staging Test; GDS, Global Deterioration Scale.

3.2.3 Cognitive assessment instruments supporting classification

The Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) are not, in a strict sense, classifications of Alzheimer's disease. They are cognitive assessment instruments that generate scores used for screening, characterisation, eligibility decisions, or longitudinal monitoring. Although score thresholds may be used to describe normal cognition or varying degrees of impairment, these categories do not independently establish an Alzheimer-specific aetiology.

The MMSE provides a brief measure of global cognition but has limited sensitivity to subtle impairment and is influenced by education, language, and cultural background. The MoCA gives greater weight to executive, visuospatial, and attentional functions and is commonly used to screen for possible mild cognitive impairment. ADAS-Cog assesses cognitive severity and longitudinal change and is used predominantly as an outcome measure in clinical trials.

Accordingly, these instruments are included as observational tools that support classification and staging rather than as disease taxonomies in their own right. Their interpretation requires population-appropriate normative data and should not be based on universal cut-off values.

Table 6. Cognitive instruments supporting Alzheimer's disease classification and monitoring

Instrument	Primary construct	Appropriate role	Output	What it cannot establish independently
MMSE	Global cognitive performance	General screening and longitudinal assessment	Continuous score, usually 0–30	Alzheimer-specific pathology or aetiology
MoCA	Global cognition with sensitivity to mild impairment	Screening and cognitive characterisation	Continuous score, usually 0–30	Cause of cognitive impairment
ADAS-Cog	Cognitive severity and longitudinal change	Clinical trials and treatment-outcome monitoring	Continuous impairment score	Biological Alzheimer status

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive Subscale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment.

Additional instruments may complement the characterisation of Alzheimer's disease without constituting classification systems in their own right. Functional measures, such as the Functional Activities Questionnaire, the National Alzheimer's Coordinating Center (NACC) Functional Assessment Scale, scales of basic and instrumental activities of daily living, and the Everyday Cognition questionnaire, describe the effects of impairment on everyday functioning. Domain-specific neuropsychological tests, including measures of verbal learning and episodic memory, provide more detailed cognitive profiles, whereas instruments such as the Neuropsychiatric Inventory and the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) quantify behavioural and neuropsychiatric symptoms. These tools may support staging, longitudinal monitoring, and differential characterisation, but they do not independently establish an Alzheimer-specific aetiology.

Composite outcomes that combine cognitive and functional information, such as the integrated Alzheimer's Disease Rating Scale, may be more sensitive to longitudinal change than isolated measures in some clinical trial contexts. Nevertheless, their role is outcome measurement rather than disease classification.

3.2.4 Age-of-onset and genetic classifications

Age at onset and genetic architecture provide complementary classificatory dimensions of Alzheimer's disease. Age-based classifications commonly distinguish early-onset from late-onset Alzheimer's disease. This distinction is clinically useful because early-onset cases are relatively more frequently associated with atypical phenotypes and highly penetrant genetic variants, whereas late-onset disease is more commonly associated with complex, polygenic susceptibility. Nevertheless, age at onset does not identify a single biological mechanism, and the boundary between early- and late-onset forms should not be interpreted as an absolute etiological division.

Autosomal-dominant Alzheimer's disease is most strongly associated with pathogenic variants in APP, PSEN1, and PSEN2. In appropriately selected families, these variants may support an etiologically specific classification. However, early-onset disease is not synonymous with autosomal-dominant disease, as many early-onset cases lack an identifiable highly penetrant mutation or exhibit more complex familial patterns.

Late-onset Alzheimer's disease generally reflects a multifactorial architecture involving age, environmental exposures, vascular and metabolic factors, and multiple genetic variants. APOE ε4 is the most prominent common genetic risk factor, but it is neither necessary nor sufficient to establish a diagnosis. Polygenic risk scores may estimate aggregate susceptibility,

although their predictive performance and transferability vary across populations. Moreover, they do not independently establish whether an individual has Alzheimer's disease.

Accordingly, genetic classifications should distinguish among causal variants, susceptibility variants, and aggregate polygenic risk. These categories differ in penetrance, predictive value, and clinical interpretation and should not be treated as equivalent diagnostic labels.

Table 7. Age-of-onset and genetic classifications of Alzheimer's disease

Classification	Primary basis	Main interpretive value	Principal limitation
Early-onset Alzheimer's disease	Relatively early clinical onset	Clinical and epidemiological stratification; recognition of atypical presentations and possible inherited disease	Does not imply a specific mutation or inheritance pattern
Late-onset Alzheimer's disease	Relatively late clinical onset	Epidemiological and risk stratification	Represents a heterogeneous and predominantly multifactorial category
Autosomal-dominant Alzheimer's disease	Pathogenic variants, principally in APP, PSEN1 or PSEN2	Aetiologically specific classification, family studies and genetically targeted research	Accounts for only a minority of Alzheimer's disease cases
Familial non-Mendelian Alzheimer's disease	Familial aggregation without a confirmed dominant causal variant	Identification of increased familial susceptibility	Familial aggregation may reflect multiple genes and shared environment
Sporadic Alzheimer's disease	Absence of a recognised Mendelian inheritance pattern	Broad clinical and epidemiological classification	"Sporadic" does not imply absence of genetic susceptibility
APOE-associated susceptibility	APOE genotype	Risk estimation and research stratification	Neither necessary nor sufficient for diagnosis
Polygenic risk classification	Combined effects of multiple susceptibility variants	Aggregate risk estimation and cohort stratification	Population dependence, incomplete predictive accuracy and limited individual determinism

3.3 Biological and biomarker-based classifications

Biomarker-based frameworks classify Alzheimer's disease according to measurable pathological processes rather than exclusively on the basis of clinical symptoms. They therefore distinguish biological disease status from clinical expression, enabling individuals to be positioned along the Alzheimer continuum before cognitive or functional impairment becomes apparent. A biological classification, however, does not independently establish clinical severity, functional dependency, or individual prognosis.

The 2018 NIA–AA Research Framework organised biomarkers into three groups: amyloid-β pathology (A), pathological tau (T), and neurodegeneration or neuronal injury (N). Amyloid status may be assessed using amyloid positron emission tomography (PET) or cerebrospinal fluid (CSF) Aβ42/40; tau status using phosphorylated-tau biomarkers or tau PET; and neurodegeneration using structural magnetic resonance imaging (MRI), fluorodeoxyglucose positron emission tomography (FDG-PET), total tau, or neurofilament light chain (NfL). Each category may be coded as positive or negative, producing biological profiles such as A−T−N−, A+T−N−, and A+T+N± (Jack et al., 2018).

Within this framework, amyloid positivity positions an individual within the Alzheimer pathological continuum, whereas tau positivity may provide stronger evidence of Alzheimer's disease pathology. Neurodegeneration is clinically and prognostically relevant but is not specific to Alzheimer's disease. Consequently, profiles such as A−T+N+ may reflect non-Alzheimer or mixed pathological processes rather than typical Alzheimer biology.

The AT(N) framework has been used primarily for biological characterisation, cohort stratification, clinical trial enrichment, and standardised biomarker reporting. Its translation into routine clinical practice remains limited by differences among analytical platforms, biomarker thresholds, population characteristics, and the imperfect equivalence of plasma, CSF, and imaging measures. Biomarker status must therefore be interpreted alongside clinical phenotype, functional status, and relevant comorbidities.

The 2024 Alzheimer's Association criteria expanded the earlier AT(N) structure by distinguishing biomarkers involved in biological diagnosis from those contributing principally to staging, prognosis, and the detection of concomitant pathology. Core 1 biomarkers include amyloid and early phosphorylated-tau measures, whereas Core 2 biomarkers reflect aggregated tau pathology and contribute more directly to biological staging. Additional categories describe neurodegeneration, inflammation, and common copathologies.

Biomarkers now serve multiple contexts of use in Alzheimer's disease trials, including participant eligibility, target engagement, and outcome assessment (Osse et al., 2026).

Table 8. Biomarker groups in the 2024 Alzheimer's Association criteria

Biomarker group	Representative markers	Principal interpretation
Core 1: A and T1	Amyloid PET, CSF Aβ42/40, plasma or CSF phosphorylated-tau biomarkers	Biological diagnosis of Alzheimer pathology
Core 2: T2	Tau PET and microtubule-binding region tau (MTBR-tau) biomarkers	Biological staging and prognosis
N	Structural MRI, FDG-PET and NfL	Neurodegeneration or neuronal injury
I	Glial fibrillary acidic protein (GFAP) and related inflammatory markers	Astroglial or inflammatory response
V	Infarcts and white-matter hyperintensities on MRI	Vascular pathology
S	α-Synuclein seed-amplification assays	Concomitant synucleinopathy

Abbreviations: CSF, cerebrospinal fluid; FDG-PET, fluorodeoxyglucose positron emission tomography; GFAP, glial fibrillary acidic protein; MRI, magnetic resonance imaging; MTBR-tau, microtubule-binding region tau; NfL, neurofilament light chain; PET, positron emission tomography.

Core 1 biomarker abnormalities may support a biological diagnosis of Alzheimer's disease, whereas Core 2 biomarkers contribute primarily to disease staging and prognosis. The N, I, V, and S categories provide information about neuronal injury and concomitant pathological processes, although they are not independently specific to Alzheimer's disease.

Proposed extensions, such as ATX(N), ATI(N), and multidimensional molecular taxonomies, incorporate inflammation, synaptic dysfunction, vascular injury, blood–brain barrier alterations, and omics-derived information. These approaches may enhance biological stratification, but most remain research-oriented and require harmonised thresholds, external replication, and evidence of clinical utility before they can be applied to routine individual-level classification.

3.4 Neuropathological classifications

Neuropathological classifications assess the type, anatomical distribution, and burden of lesions associated with Alzheimer's disease. Unlike clinical or biomarker-based frameworks, these systems rely primarily on direct histopathological examination and therefore retain high pathological validity but have limited applicability to ante-mortem screening. Neuropathological stage should not be interpreted as directly equivalent to clinical severity because substantial lesion burdens may occur in cognitively unimpaired individuals and because clinical expression is influenced by cognitive reserve, comorbidities, and concomitant pathologies.

The principal Alzheimer-related neuropathological systems are Braak staging, Thal amyloid phases, the CERAD neuritic-plaque score and the integrated ABC assessment (Braak & Braak, 1991; Thal et al., 2002; Mirra et al., 1991; Hyman et al., 2012). Concomitant pathologies, including LATE-related TDP-43 pathology, Lewy body disease and cerebrovascular lesions, may substantially modify the clinical expression of Alzheimer-related neuropathological change (Nelson et al., 2019; McAleese et al., 2021; Mehta & Schneider, 2021). Accordingly, neuropathological interpretation of dementia requires Alzheimer-related lesions to be assessed alongside other age-related neurodegenerative and vascular pathologies (Schneider, 2022).

The ABC framework integrates Thal phase (A), Braak stage (B), and CERAD score (C) to classify Alzheimer's disease neuropathological change as not, low, intermediate, or high.

These systems provide complementary forms of information rather than interchangeable classifications. Braak characterises tau distribution, Thal characterises amyloid distribution, CERAD estimates neuritic plaque burden, and ABC combines the three dimensions into an overall neuropathological category. Nevertheless, none independently accounts for the complete clinical phenotype. Concomitant pathologies—including Lewy body disease, LATE-related TDP-43 pathology, and cerebrovascular lesions—are common in older individuals and may modify cognitive decline and the threshold at which dementia becomes clinically apparent. Neuropathological reports should therefore describe both Alzheimer-related changes and relevant copathologies.

Table 9. Principal neuropathological classifications associated with Alzheimer's disease

System	Principal lesion or construct	Categories	Main use	Principal limitation
Braak staging	Anatomical distribution of neurofibrillary tau pathology	Stages I–VI: transentorhinal, limbic and isocortical progression	Characterisation of the topographical progression of tau pathology	Neuropathological stage does not correspond automatically to clinical severity
Thal phases	Anatomical distribution of amyloid-β deposition	Phases 0–5	Characterisation of the anatomical spread of amyloid pathology	Describes distribution more directly than lesion density or cognitive status
CERAD score	Density of neocortical neuritic plaques	None, sparse, moderate or frequent	Semiquantitative assessment of neuritic-plaque burden	Plaques may occur in cognitively unimpaired individuals
ABC assessment	Integrated amyloid, tau and neuritic-plaque burden	Not, low, intermediate or high AD neuropathological change	Standardised overall assessment of Alzheimer-related neuropathological change	Primarily post-mortem and does not capture all clinically relevant copathologies

The metataxonomic distinction is particularly important in this domain. Neuropathological classifications establish lesion type and burden but do not independently classify current cognitive performance, functional dependency, or symptomatic phenotype. Their principal roles are pathological confirmation, clinicopathological correlation, and the validation of in vivo biomarkers.

3.5 Phenotypic classifications

Phenotypic classifications describe the predominant clinical expression of Alzheimer's disease rather than its underlying pathology or severity. Although the typical presentation is characterised by early and progressive episodic-memory impairment, Alzheimer's disease pathology may also produce predominantly visual, language, executive, or behavioural syndromes. These atypical presentations may reflect the selective vulnerability of different large-scale cortical networks and appear to occur more frequently in younger-onset disease (Graff-Radford et al., 2021).

Phenotype and aetiology must nevertheless be distinguished. Posterior cortical atrophy (PCA) and the logopenic variant of primary progressive aphasia (PPA) are clinical syndromes that may be associated with Alzheimer's disease pathology but may also arise from other neurodegenerative processes. Consequently, labels such as 'PCA due to Alzheimer's disease' or 'logopenic aphasia due to Alzheimer's disease' require biomarker or neuropathological evidence supporting the underlying aetiology (Crutch et al., 2017; Dubois et al., 2024; Gorno-Tempini et al., 2011).

The present metataxonomy retains four principal phenotypic presentations: typical amnestic, posterior cortical, logopenic, and behavioural/dysexecutive. These categories are not necessarily mutually exclusive, particularly as the disease progresses and impairment extends across multiple cognitive domains (Graff-Radford et al., 2021).

Table 10. Principal phenotypic presentations associated with Alzheimer's disease

Phenotype	Predominant domain	Core clinical presentation	Useful assessment modalities	Principal differential diagnoses	Key sources
Typical amnestic presentation	Episodic memory	Progressive impairment in learning and retaining new information, frequently followed by multidomain cognitive decline	Episodic-memory assessment, structural MRI and Alzheimer-specific biomarkers	Depression, LATE, vascular cognitive impairment, dementia with Lewy bodies and normal ageing	Graff-Radford et al. (2021); Dubois et al. (2024)
Posterior cortical atrophy	Visuospatial and visuoperceptual processing	Progressive impairment of higher-order visual processing, spatial orientation, reading, calculation or praxis, with relative early sparing of memory and behaviour	Visuoperceptual assessment, MRI or FDG-PET, and biomarkers to establish the underlying pathology	Dementia with Lewy bodies, corticobasal degeneration, prion disease and disorders of the visual pathways	Crutch et al. (2017)

Phenotype	Predominant domain	Core clinical presentation	Useful assessment modalities	Principal differential diagnoses	Key sources
Logopenic variant primary progressive aphasia	Language and phonological working memory	Word-finding pauses, impaired repetition of sentences and phrases, and phonological errors, with relative early preservation of grammar and semantic knowledge	Detailed language assessment, left temporoparietal neuroimaging and Alzheimer-specific biomarkers	Nonfluent/agrammatic PPA, semantic PPA and other frontotemporal lobar degeneration syndromes	Gorno-Tempini et al. (2011)
Behavioural/dysexecutive presentation	Executive function and behaviour	Progressive impairment in planning, organisation, cognitive flexibility or judgement, with or without early apathy, disinhibition or personality change	Executive and behavioural assessment, structural or functional imaging and Alzheimer-specific biomarkers	Behavioural-variant frontotemporal dementia, vascular cognitive impairment and primary psychiatric disorders	Ossenkoppele et al. (2015); Townley et al. (2020)

Abbreviations: FDG-PET, fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; PPA, primary progressive aphasia.

The distinction between syndrome and aetiology is particularly important for atypical phenotypes. Posterior cortical atrophy, logopenic aphasia, and behavioural or dysexecutive syndromes describe the clinical expression of disease; they do not independently identify Alzheimer's disease pathology. Biomarkers therefore operate at the aetiological layer, whereas clinical and neuropsychological findings operate at the phenotypic layer.

Corticobasal and rapidly progressive presentations may occur in association with Alzheimer's disease pathology, but they are not retained here as primary phenotypic classes. Corticobasal syndrome has limited pathological specificity, while rapidly progressive Alzheimer's disease is more appropriately regarded as a descriptor of disease tempo rather than a distinct cognitive phenotype.

3.6 classified according to the age

Cases may be classified according to the age at which symptoms first emerge. Early-onset disease refers to clinical presentation before the age threshold defined by the individual study or diagnostic framework. This category is particularly relevant when considering a possible genetic contribution or an atypical phenotype; however, early onset should not automatically be interpreted as evidence of familial inheritance. By contrast, late-onset disease develops at an older age and accounts for the majority of sporadic cases. This classification is especially useful in epidemiological research and prevention studies, although interpretation may be complicated by the high prevalence of comorbid conditions in older populations.

From a genetic perspective, autosomal dominant disease is associated with a pathogenic familial mutation, most commonly involving genes such as APP, PSEN1, or PSEN2. Although these variants are rare at the population level, their identification has important implications for genetic counselling, family assessment, and research. Sporadic disease, in contrast, lacks a clear Mendelian inheritance pattern and is generally understood to arise from a complex interaction of genetic, environmental, and lifestyle factors. Genetic susceptibility may also be assessed through risk alleles or polygenic risk scores, including APOE status; nevertheless, these indicators are intended for risk stratification and should not be considered diagnostic in isolation.

3.7 Sensory and neurophysiological approaches

Sensory alterations have increasingly been investigated as potential markers, risk modifiers, and clinical correlates of Alzheimer's disease. The evidence is strongest for olfaction, hearing, and vision, whereas taste, somatosensation, proprioception, vestibular function, and interoception remain substantially less studied. Sensory impairment should not, however, be interpreted automatically as evidence of Alzheimer's disease pathology because it may result from normal ageing, peripheral sensory disease, vascular or metabolic comorbidity, medication effects, or other neurodegenerative disorders (Albers et al., 2015; Lad et al., 2024; Murphy, 2019).

Olfactory dysfunction is among the most consistently reported sensory abnormalities in mild cognitive impairment and Alzheimer's disease. Deficits may involve odour identification, discrimination, detection thresholds, and olfactory memory. Its potential relevance may be related to the early involvement of olfactory and medial temporal structures in neurodegenerative processes. Nevertheless, olfactory impairment is not specific to Alzheimer's disease and may also occur in Parkinson's disease, Lewy body disorders, sinonasal disease, smoking, and normal ageing. Olfactory testing should therefore be considered a complementary marker rather than an independent diagnostic classification (Jung et al., 2019; Murphy, 2019).

Age-related hearing loss has been associated with cognitive decline and dementia through several non-exclusive mechanisms, including increased cognitive load, reduced sensory stimulation, social isolation, and shared vascular or neurodegenerative processes. Visual impairment may similarly reduce environmental and cognitive stimulation or reflect retinal and central visual-system alterations. The coexistence of hearing and visual impairment has been associated with a higher risk of dementia than impairment in either modality alone, which may support the use of multimodal sensory assessment in risk stratification. These associations do not, however, establish that sensory loss causes Alzheimer's disease or that sensory rehabilitation prevents its development (Hwang et al., 2020; Lad et al., 2024; Tarawneh et al., 2022).

Evidence concerning tactile discrimination, proprioception, vestibular processing, taste, and interoception remains preliminary and heterogeneous. Alterations in these domains may influence balance, gait, nutrition, spatial orientation, and bodily awareness, but Alzheimer-specific thresholds and longitudinal trajectories have not been validated. These modalities should therefore be treated as candidate research dimensions rather than recognised diagnostic markers.

From the perspective of the present metataxonomy, sensory tests constitute observational modalities that measure peripheral or central sensory function. They do not independently classify Alzheimer's disease pathology. Interpretation must distinguish peripheral receptor or nerve impairment from deficits in cortical processing, attentional demands, and multisensory integration. Accordingly, sensory approaches are classified here as M2—emerging: they have a plausible empirical basis but lack standardised protocols, Alzheimer-specific thresholds, and sufficient external validation for routine disease classification.

Table 11. Sensory and neurophysiological dimensions relevant to Alzheimer's disease

Modality	Candidate measurements	Potential relevance	Principal confounders
Vision	Visual acuity, contrast sensitivity, motion perception, visuospatial tasks, visual evoked potentials and retinal imaging	Visual-processing impairment, posterior cortical phenotypes and possible risk stratification	Cataract, glaucoma, macular disease, refractive error and lighting conditions
Hearing	Pure-tone audiometry, speech-in-noise testing, auditory brainstem responses, mismatch negativity and P300	Peripheral and central auditory dysfunction, cognitive load and dementia-risk assessment	Presbycusis, noise exposure, hearing-aid use and middle-ear disease
Olfaction	Odour identification, discrimination, detection threshold and olfactory memory	Candidate early or prodromal marker and association with medial temporal dysfunction	Age, smoking, rhinitis, respiratory infection, Parkinson's disease and Lewy body pathology
Somatosensation and proprioception	Tactile discrimination, vibration threshold, position sense and sensory-evoked responses	Exploratory assessment of sensorimotor processing, gait and functional vulnerability	Peripheral neuropathy, diabetes, musculoskeletal disease and motor impairment
Vestibular function	Vestibulo-ocular reflex, posturography, balance and spatial-orientation tasks	Exploratory relationship with navigation, balance and falls	Peripheral vestibular disease, medication, visual impairment and mobility limitations
Taste and interoception	Taste detection and identification, electrogustometry, autonomic responses and internal-state discrimination	Exploratory relationship with nutrition, eating behaviour and bodily-state processing	Olfactory dysfunction, medication, oral disease, nutrition and metabolic disorders

The available evidence therefore supports sensory assessment as a complementary dimension of Alzheimer's disease research, not as a stand-alone diagnostic taxonomy. Its principal future value may lie in multimodal profiles that combine sensory performance with cognitive assessment, neurophysiology and established biological biomarkers.

3.8 Proposed neuroinformational framework

The hypothesis-generating neuroinformational extension of the proposed metataxonomy is introduced in this section. The framework considers whether the efficiency of sensory–cognitive information processing can be characterised through three complementary dimensions: latency, fidelity, and integration. The subsections that follow clarify the model's conceptual status, specify candidate operational measures, formulate testable hypotheses, and set out the conditions under which the framework would be weakened or falsified. It is presented as an experimental research architecture rather than as a validated diagnostic or staging system.

3.8.1 Conceptual definition and status

We define neuroinformational integrity as the capacity of the nervous system to encode, transmit, discriminate, and integrate the information required for adaptive perception and cognition. The proposed framework does not equate sensory impairment with Alzheimer's disease. Instead, it examines whether alterations in information-processing efficiency may provide a complementary dimension for characterising the disease.

The framework represents neuroinformational integrity as a multidimensional profile:

$N = (L, F, I)$

where (L) denotes processing latency, (F) denotes representational fidelity, and (I) denotes within-modal or cross-modal integration. The model is not intended to replace clinical, biological, functional, or neuropathological frameworks, but rather to provide an additional layer through which sensory–cognitive information processing can be investigated.

Under the maturity scale adopted in this review, the latency–fidelity–integration model is classified as M1—hypothesis-generating. It currently lacks prospective validation, external replication, and established clinical decision thresholds.

3.8.2 Operational dimensions

Latency

Latency refers to the time elapsed between stimulus presentation and a predefined neural, perceptual, or behavioural response. For sensory modality (m), latency may be expressed as:

$$L_m = t_{\text{response},m} - t_{\text{stimulus},m}$$

Candidate measures include reaction time, event-related potential (ERP) latency, sensory-evoked response latency, and temporal discrimination thresholds. Studies of event-related potentials have reported altered response speed and changes in the latencies of P300 and related components in mild cognitive impairment and Alzheimer's disease. These findings indicate that this dimension can be measured, without establishing its specificity to Alzheimer's disease (Papaliagkas et al., 2008; van Deursen et al., 2009).

Fidelity

Fidelity refers to the degree to which a neural or behavioural response preserves discriminable information about the stimulus that elicited it. Depending on the experimental design, it may be operationalised using perceptual accuracy, error rate, signal-to-noise ratio, trial-to-trial reliability, representational similarity, or mutual information. One possible normalised formulation is:

$$F_m = \frac{I(S_m; R_m)}{H(S_m)}$$

where (Sm) represents the stimulus, (Rm) represents the measured neural or behavioural response, (I(Sm;Rm)) denotes their mutual information, and (H(Sm)) denotes the entropy of the stimulus set. This equation is an illustrative operationalisation rather than a universal metric. Information-theoretic measures, including transfer entropy, have already been applied experimentally to electroencephalography (EEG) signals to differentiate among control, mild cognitive impairment, and Alzheimer's disease groups. However, these applications do not validate the present framework as a diagnostic system (McBride et al., 2015; Shannon, 1948).

Integration

Integration refers to the capacity to combine information across sensory modalities, neural features, processing stages, or large-scale brain systems. It may be assessed using multisensory gain, temporal-binding measures, cross-modal synchronisation, effective connectivity, network participation coefficients, or global integration–segregation indices. No single equation should be imposed across all these measurement levels. EEG network studies have reported reduced global integration and increased segregation in Alzheimer's disease. These findings provide empirical grounds for examining this dimension without establishing an Alzheimer-specific classification threshold (Kabbara et al., 2018).

3.8.3 Operational summary

To facilitate the empirical application of the proposed neuroinformational framework, its core dimensions should be translated into measurable constructs. Table 12 operationalises the three principal dimensions—latency, fidelity, and integration—by defining each construct, identifying candidate measurements, outlining the expected direction of alteration, and highlighting the principal potential confounders.

This structure is intended to inform the design and interpretation of future experimental and clinical studies. The dimensions are considered jointly rather than as isolated markers, allowing researchers to examine whether neurocognitive dysfunction is characterised primarily by slowed processing, degraded information representation, impaired cross-system integration, or a combination of these alterations. Consideration of the principal confounders is particularly important because observed differences may reflect age-related, sensory, pharmacological, attentional, or comorbid influences rather than the neuroinformational mechanism under investigation.

Table 12. Operational components of the proposed neuroinformational framework

Dimension	Operational definition	Candidate measurements	Expected alteration	Principal confounders
Latency	Time required to generate a neural, perceptual or behavioural response	Reaction time, ERP latency, sensory-evoked responses, temporal discrimination	Increased latency	Age, motor slowing, attention, medication and peripheral sensory loss
Fidelity	Degree to which the response preserves information about the stimulus	Accuracy, error rate, signal-to-noise ratio, mutual information and response reliability	Reduced fidelity	Task difficulty, fatigue, education, sensory acuity and measurement noise
Integration	Capacity to combine information across modalities, features or neural systems	Multisensory gain, temporal binding, synchronisation, connectivity and network integration	Reduced or inefficient integration	Vascular burden, arousal, medication, sensory asymmetry and comorbid neurological disease

Abbreviation: ERP, event-related potential.

3.8.4 Testable hypotheses

The proposed framework generates four principal hypotheses:

H1. Greater clinical or biological disease burden will be associated with longer processing latency after adjustment for age, education, motor speed and peripheral sensory function.

H2. Greater disease burden will be associated with reduced stimulus–response fidelity, expressed through lower discrimination accuracy, reduced response reliability, lower signal-to-noise ratio or reduced mutual information.

H3. Individuals across the Alzheimer continuum will show reduced or less efficient sensory and network-level integration relative to appropriately matched controls.

H4. A multidimensional latency–fidelity–integration profile will provide incremental explanatory or predictive value beyond demographic variables and conventional cognitive measures.

3.8.5 Falsification criteria

The framework would not be supported if latency, fidelity and integration showed no reproducible association with clinical, cognitive or biological disease burden; if the associations disappeared after adjustment for age, sensory acuity, motor speed, education, vascular burden and relevant comorbidities; if the measurements lacked acceptable test–retest or cross-centre reproducibility; or if the multidimensional profile provided no incremental value beyond established cognitive and biomarker measures.

The latency–fidelity–integration model should therefore be interpreted as a testable research framework rather than as a validated classification or staging system. Its progression from M1 to an emerging or research-level framework would require standardised tasks, prespecified metrics, prospective cohorts, external replication and demonstration of longitudinal or clinically meaningful associations.

4. Comparative synthesis of classification frameworks

The comparative analysis suggests that contemporary Alzheimer's disease classification frameworks are complementary but not interchangeable. Apparent disagreements among them often arise because they classify different objects, rely on different observational modalities, and inform different clinical or research decisions. Biological frameworks identify pathological processes; clinical frameworks describe symptomatic expression; functional instruments quantify dependency; neuropathological systems assess lesion type and burden; phenotypic classifications describe patterns of presentation; and genetic frameworks characterise aetiology or susceptibility.

4.1 Non-equivalence, discordance and overlap

A biomarker-positive individual may be biologically classified within the Alzheimer continuum while remaining cognitively unimpaired and functionally independent. Conversely, an individual may present with a dementia syndrome clinically compatible with Alzheimer's disease but have inconclusive, negative, or mixed biomarker findings. These situations do not necessarily represent classification errors. Rather, they may reflect the analytical distinction between biological status, clinical expression, and functional severity (Jack et al., 2018, 2024; Dubois et al., 2021, 2024).

A similar lack of equivalence applies to neuropathological and phenotypic classifications. Braak, Thal, CERAD, and ABC describe lesion distribution or burden but do not determine the precise clinical phenotype or degree of dependency in an individual patient. Likewise, posterior cortical atrophy, logopenic aphasia, and behavioural or dysexecutive presentations describe patterns of clinical expression but do not independently establish Alzheimer-specific pathology (Hyman et al., 2012; Crutch et al., 2017; Gorno-Tempini et al., 2011; Graff-Radford et al., 2021).

Global cognitive and functional instruments may also underrepresent atypical disease trajectories. A patient with posterior cortical or language-predominant impairment may experience substantial domain-specific disability despite obtaining scores that do not align neatly with conventional amnestic staging models. Cognitive tests and functional scales should therefore be interpreted as measurement instruments that support classification rather than as complete representations of disease biology or phenotype.

The metataxonomic framework accommodates these distinctions by permitting multiple simultaneous classifications. For example, the same individual may be classified biologically as A+T+, clinically as mildly impaired, functionally as largely independent, and phenotypically as logopenic. These labels are not contradictory because each refers to a different object of classification.

Biological positivity should not be taken to imply a deterministic prognosis for an individual, nor should it be regarded, in isolation, as sufficient to establish the same treatment pathway for all biomarker-positive individuals (Rossini & Pappalettera, 2026).

4.2 Scenario-specific applicability

Table 13 summarises the most appropriate Alzheimer's disease classification frameworks for different clinical, research, and neuropathological scenarios. It highlights the principal purpose, complementary approaches, and key interpretative limitations associated with each framework.

Table 13. Scenario-specific applicability of Alzheimer's disease classification frameworks

Scenario	Primary framework or instrument	Principal purpose	Complementary approaches	Principal caution
General clinical consultation	Clinical assessment and functional staging	Identify symptomatic impairment, severity and care needs	Cognitive testing and biomarkers when clinically indicated	Clinical severity does not establish Alzheimer-specific aetiology
Specialist memory clinic	Clinical–biological criteria and phenotypic assessment	Aetiological diagnosis and differential characterisation	Neuropsychology, MRI, fluid biomarkers and molecular imaging	Biomarkers must be interpreted in relation to phenotype and comorbidities
Clinical trial recruitment	Biological profile plus clinical stage	Participant selection, cohort enrichment and reduction of biological heterogeneity	Cognitive, functional, genetic and phenotypic stratification	Biomarker eligibility does not guarantee homogeneous progression or treatment response
Longitudinal monitoring	CDR/CDR-SB, cognitive measures and functional instruments	Quantify clinical and functional change over time	Biomarkers and digital measures	Outcome measures are not disease taxonomies
Neuropathological assessment	Braak, Thal, CERAD and ABC	Characterise lesion distribution, burden and Alzheimer neuropathological change	Clinical history and systematic assessment of copathologies	Post-mortem lesion burden does not map directly onto ante-mortem severity
Genetic counselling and familial disease	Causal-variant and familial classifications	Identify autosomal-dominant disease and interpret inherited susceptibility	Clinical phenotype, biomarkers and family history	APOE and polygenic risk are not diagnostic
Risk and prevention research	Biomarkers, genetics and longitudinal cognitive assessment	Identify populations with increased probability of future decline	Vascular, lifestyle, sensory and digital measures	Risk classification must not be presented as certain individual prognosis
Mechanistic and exploratory research	Sensory, neurophysiological and neuroinformational frameworks	Investigate latency, fidelity, integration and early information-processing alterations	Established biomarkers, neuroimaging and cognitive assessment	Neuroinformational profiles remain hypothesis-generating and cannot support clinical diagnosis

No single classification framework is optimal for every scenario. The appropriate system depends on the decision being made and the object to be classified. Clinical care prioritises symptoms, functional status, and differential diagnosis; clinical trials require biological and clinical stratification; neuropathological assessment focuses on lesion burden and copathologies; and exploratory research may incorporate sensory and neuroinformational measures. Multidimensional integration should therefore retain the distinctions among frameworks rather than collapse them into a single universal score.

5. Gaps, challenges and future directions

The principal gaps in contemporary Alzheimer's disease classification may be organised as a sequence linking current conceptual and methodological limitations to the scientific challenges required to address them and, in turn, to the resulting opportunities for research and clinical translation (Figure 2).

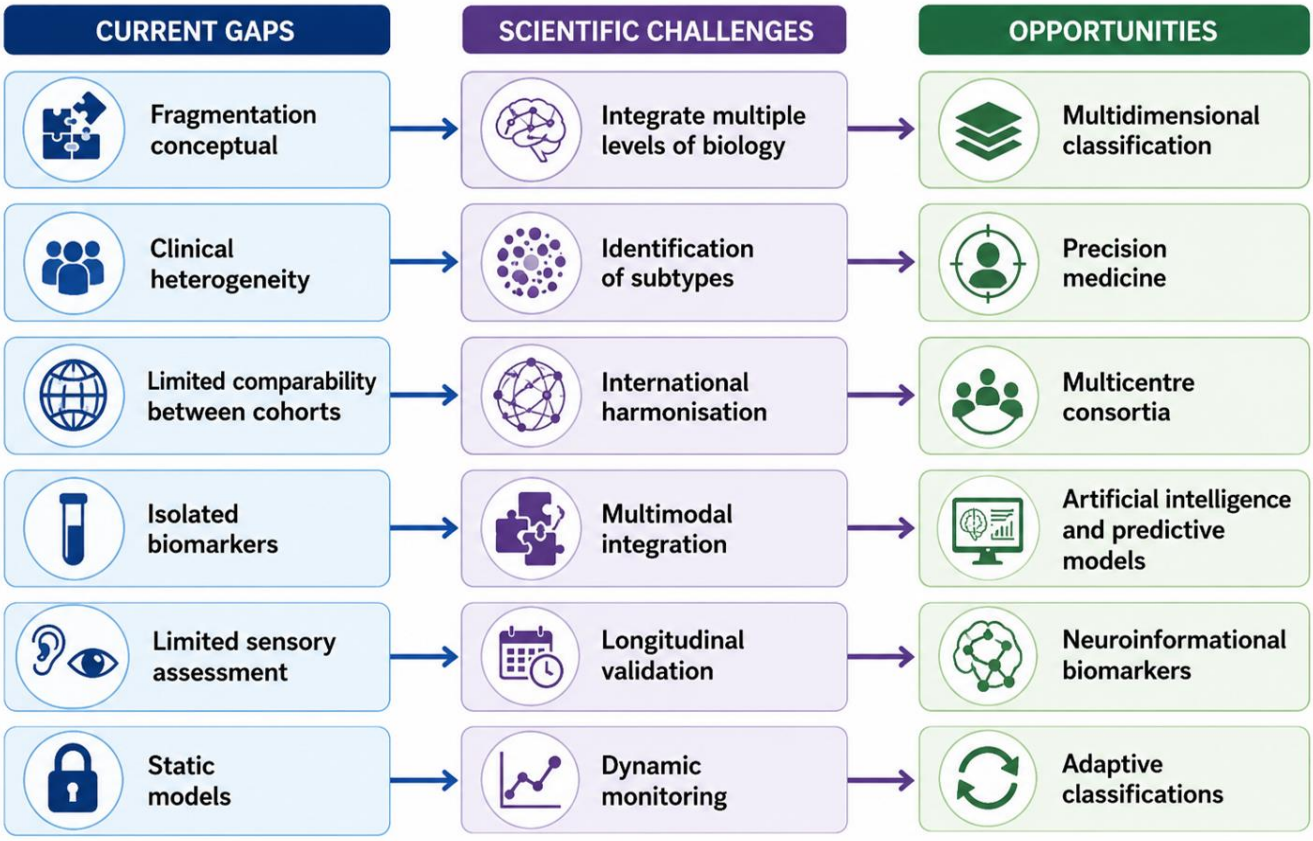

Figure 2. *Current gaps, scientific challenges and research opportunities in contemporary Alzheimer's disease classification. The figure links unresolved conceptual and methodological limitations with priority scientific challenges and potential translational opportunities. The proposed neuroinformational measures remain hypothesis-generating and require standardised protocols, longitudinal assessment and external multicentre validation.*

These relationships should not be interpreted as deterministic one-to-one pathways. Each opportunity depends on progress across several challenges simultaneously. For example, precision stratification requires not only the identification of reproducible subtypes but also harmonised measurements, longitudinal validation and integration across biological, clinical and functional levels.

5.1 Conceptual non-equivalence and biological heterogeneity

One of the principal challenges in contemporary Alzheimer's disease classification is that frameworks addressing different objects often coexist but are interpreted as though they were interchangeable. Biological criteria identify Alzheimer-related pathological processes, whereas clinical criteria describe symptomatic expression. Functional instruments quantify dependency, neuropathological systems assess lesion distribution and burden, and phenotypic classifications describe patterns of presentation. Consequently, the same individual may receive different yet simultaneously valid labels, depending on the dimension examined. The distinction between purely biological and clinical–biological definitions remains particularly important for cognitively unimpaired individuals with positive biomarkers (Dubois et al., 2021, 2024; Jack et al., 2018, 2024).

A second challenge is the biological heterogeneity obscured by apparently similar diagnostic categories. Individuals with comparable clinical syndromes may differ in amyloid and tau burden, neurodegeneration, vascular injury, inflammation,

resilience, and concomitant pathologies. Conversely, individuals with similar biomarker profiles may follow different clinical trajectories. This heterogeneity limits deterministic interpretations of individual biomarkers and supports the use of classifications that document both Alzheimer-related processes and relevant copathologies (Mehta & Schneider, 2021; Scheltens et al., 2021).

5.2 Standardisation and translational challenges

International comparison remains limited by differences in cohort definitions, biomarker platforms, positivity thresholds, neuropsychological instruments and procedures for assigning clinical stages. Future frameworks should therefore specify the object classified, the measurement modality, the analytical platform, the decision threshold and the intended use. Harmonisation should not require a single immutable classification; rather, it should permit different frameworks to coexist while ensuring that their outputs and inferential limits are reported transparently.

Digital biomarkers and machine-learning methods may enrich classification through longitudinal measures of speech, movement, navigation, sleep, device interaction and everyday functioning. However, these technologies should be treated as observational and analytical modalities rather than independent disease classifications. Their clinical translation remains constrained by small or selected samples, inconsistent protocols, data leakage, limited external validation and reduced generalisability across demographic and clinical populations (de la Fuente Garcia et al., 2020; Kourtis et al., 2019; Wen et al., 2020).

5.3 Research priorities

Three priorities emerge from this review. First, future studies should preserve the distinctions among biological status, clinical expression, functional severity, phenotype, and risk rather than collapsing them into a single universal category. Second, multimodal models should undergo longitudinal evaluation and external validation to determine whether they improve diagnosis, prognosis, or treatment selection beyond established clinical and biomarker frameworks. Third, emerging sensory and neuroinformational measures require standardised tasks, reproducible metrics, and explicit assessment of incremental validity.

The latency–fidelity–integration model proposed in this review is intended to address the third priority by representing neural information processing as a multidimensional profile rather than as an ordinal disease stage. Existing evidence suggests that sensory and network-level alterations can be measured in Alzheimer's disease, but it does not yet establish Alzheimer-specific thresholds or a validated neuroinformational classification. The model should therefore remain designated M1—hypothesis-generating until prospective multicentre studies provide evidence of reliability, longitudinal sensitivity, specificity, and added value beyond conventional cognitive and biological measures (Albers et al., 2015; Kabbara et al., 2018).

Table 14. Principal gaps and research priorities in Alzheimer's disease classification

Gap	Consequence	Priority action
Conceptual non-equivalence	Apparently contradictory diagnoses or stages	Report separately the object classified, modality and intended use
Biological heterogeneity	Variable clinical trajectories within similar biomarker profiles	Incorporate copathologies, resilience and longitudinal multimodal information
Platform and threshold heterogeneity	Limited comparability across cohorts and centres	Harmonise acquisition, analytical procedures and reporting standards
Limited generalisability of digital and AI models	Inflated performance and uncertain clinical utility	Require external validation, transparency and demographically diverse cohorts
Lack of validated neuroinformational measures	Inability to use latency, fidelity or integration clinically	Develop standardised tasks, normative data and prospective validation

The central opportunity is therefore not to replace existing classifications with a single comprehensive score, but to construct an interoperable architecture in which different frameworks retain their conceptual identity while contributing complementary information to diagnosis, staging, prognosis and research stratification.

6. Conclusions and Directions for Future Work

Future research should focus less on developing additional isolated classification systems and more on evaluating interoperable architectures that integrate biological status, clinical expression, functional severity, phenotype, and longitudinal change. Rather than reducing heterogeneous information to a single universal score, such architectures should preserve its multidimensional structure. Their value will depend on evidence that integration improves diagnosis, prognosis, treatment selection, or research stratification beyond the contribution of each framework considered separately (Jack et al., 2024).

6.1 Multimodal and blood-based biomarkers

A central priority is the prospective validation of multimodal biomarker profiles. Plasma phosphorylated tau, amyloid-related measures, neurofilament light, and glial fibrillary acidic protein may improve access to biological assessment. However, their interpretation depends on assay characteristics, prespecified thresholds, clinical context, and the reference standard used. Their principal future value may lie in staged diagnostic pathways that combine accessible blood tests with clinical evaluation and, where necessary, confirmation through cerebrospinal fluid analysis or molecular imaging (Palmqvist et al., 2024; Teunissen et al., 2022).

Future studies should therefore prioritise cross-platform calibration, prespecified cut-offs, population diversity, longitudinal change, and incremental value beyond established clinical and cognitive assessments. Multimodal integration should examine the relationships among biomarkers rather than merely increasing the number of variables incorporated into predictive models.

6.2 Trustworthy artificial intelligence and digital monitoring

Artificial-intelligence methods may support the integration of neuroimaging, molecular, clinical, speech, and behavioural data. Their translation into clinical classification, however, requires safeguards against data leakage, overfitting, dataset shift, and limited external generalisability. Models should be evaluated in independent cohorts, with transparent reporting of participant selection, preprocessing, missing-data handling, and model calibration (de la Fuente Garcia et al., 2020; Wen et al., 2020).

Explainable artificial intelligence may improve the interpretability of algorithmic predictions, but explanation methods should not be assumed to guarantee clinical validity or trustworthiness. Future studies should assess whether explanations are stable, clinically meaningful, and useful to their intended stakeholders, rather than merely producing visually plausible feature rankings (Shankar et al., 2025).

Digital biomarkers derived from speech, gait, navigation, sleep, device interaction, and everyday activities may permit more frequent and ecologically relevant monitoring than periodic clinic-based assessments. Their incorporation into classification frameworks will depend on standardised metrics, longitudinal reliability, evidence of clinical relevance, appropriate data governance, and the protection of privacy and autonomy (Piau et al., 2019).

Although multimodal artificial-intelligence models frequently outperform unimodal approaches, their apparent performance remains strongly influenced by dataset composition, validation design, and the availability of external multicentre evaluation (Yu et al., 2026).

6.3 Validation of the neuroinformational framework

The latency–fidelity–integration model proposed in this review should remain classified as M1—hypothesis-generating until it has undergone prospective validation and external replication. Initial studies should establish standardised tasks, modality-specific measurements, normative distributions, test–retest reliability, and sensitivity to peripheral sensory impairment, attention, motor slowing, and relevant comorbidities.

Subsequent studies should determine whether neuroinformational profiles are associated with recognised clinical or biological stages, whether they change longitudinally, and whether they provide incremental value beyond conventional cognitive assessments and established biomarkers. Existing evidence suggests that sensory dysfunction and altered network integration can be measured in Alzheimer's disease, but does not establish Alzheimer-specific neuroinformational thresholds or a validated staging system (Albers et al., 2015; Kabbara et al., 2018).

6.4 Harmonisation and dynamic classification

Validation of multidimensional classifications is likely to require multicentre collaboration, harmonised acquisition and reporting protocols, demographically diverse cohorts, and shared longitudinal datasets. Harmonisation should not impose a single classification across all contexts. Instead, it should ensure that each framework explicitly reports the object classified, observational modality, decision threshold, intended use, and inferential limitations.

Future classifications may therefore become more dynamic, with biological, clinical, and functional profiles updated as new observations become available. Such models should preserve the distinctions among disease status, current symptoms, dependency, phenotype, and future risk. The objective is not to replace established classifications but to make them interoperable within a longitudinal architecture suitable for clinical care, clinical trials, and mechanistic research Future classifications may therefore become more dynamic, with biological, clinical, and functional profiles updated as new observations become available. Such models should preserve the distinctions among disease status, current symptoms, dependency, phenotype, and future risk. The objective is not to replace established classifications, but to enable their interoperability within a longitudinal architecture suited to clinical care, clinical trials, and mechanistic research.

Future Alzheimer's disease classifications should therefore be evaluated not by the volume of information they combine, but by whether such integration is reproducible, interpretable, and clinically or scientifically useful.

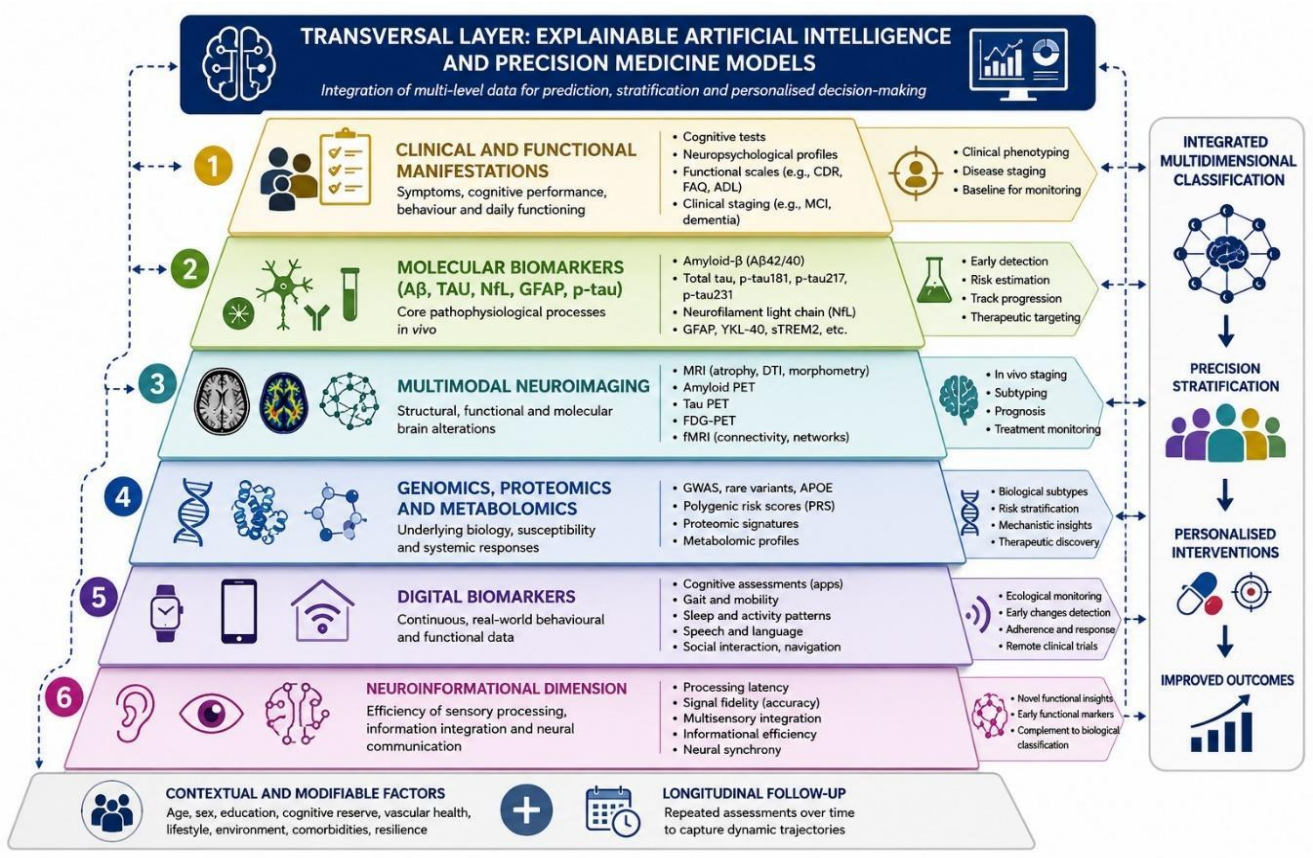

Figure 3. *Roadmap towards an interoperable and longitudinal architecture for Alzheimer's disease classification. Clinical, biological, neuropathological, genetic, phenotypic, digital and neuroinformational information is integrated through transparent analytical methods while retaining the conceptual identity of each classificatory domain.*

Contemporary classifications of Alzheimer's disease describe distinct but complementary aspects of the disorder. They should not be interpreted as interchangeable representations of a single construct. Biological frameworks identify Alzheimer-related pathological processes, whereas clinical systems describe symptomatic expression and functional instruments quantify the consequences of impairment. Neuropathological classifications characterise lesion distribution and burden, while phenotypic frameworks distinguish patterns of presentation. Genetic approaches, in turn, classify aetiology or susceptibility. Apparent disagreement among these systems often arises because they classify different objects, rely on different observational modalities, and serve different clinical or research purposes.

The principal contribution of this review is the proposed three-layer metataxonomy. It organises Alzheimer's disease classification frameworks according to: (i) the object being classified; (ii) the modality through which that object is observed or measured; and (iii) the intended use of the classification. This distinction may provide a conceptual basis for integrating multiple classifications without collapsing biological status, clinical syndrome, functional dependency, phenotype, neuropathological burden, and future risk into a single undifferentiated category. The framework may therefore improve the interpretation of apparently discordant classifications and support more transparent reporting in clinical practice, cohort design, and translational research.

A further proposal concerns neuroinformational integrity, defined through latency, fidelity, and integration, as a hypothesis-generating dimension for investigating alterations in sensory–cognitive information processing. This model should not currently be regarded as a diagnostic or staging system. Its principal value may lie in generating testable hypotheses about whether slowed processing, degraded stimulus representation, or impaired within-modal and cross-modal integration provide information beyond established cognitive, functional, and biological measures.

Several limitations should be acknowledged. The reviewed frameworks differ substantially in their conceptual foundations, evidential maturity, target populations, measurement platforms, and intended applications. These differences constrain direct comparison across frameworks. Emerging sensory, digital, computational, and neuroinformational approaches remain affected by methodological heterogeneity, limited external replication, and the absence of standardised decision thresholds. In addition, the proposed metataxonomy and neuroinformational framework require prospective evaluation and should not be interpreted as clinically validated models. Future studies should assess their reproducibility, longitudinal sensitivity, cross-population generalisability, and incremental value beyond established biomarkers and cognitive assessments. Progress towards a multidimensional architecture for Alzheimer's disease classification will therefore require harmonised protocols, diverse multicentre cohorts, and explicit reporting of inferential limitations. It will also require preservation of the conceptual distinctions among disease biology, clinical expression, functional impact, phenotype, and risk.

References

Albers, M. W., Gilmore, G. C., Kaye, J., Murphy, C., Wingfield, A., Bennett, D. A., Boxer, A. L., Buchman, A. S., Cruickshanks, K. J., Devanand, D. P., Duffy, C. J., Gall, C. M., Gates, G. A., Granholm, A.-C., Hensch, T., Holtzer, R., Hyman, B. T., Lin, F. R., McKee, A. C., ... Zhang, L. I. (2015). At the interface of sensory and motor dysfunctions and Alzheimer's disease. *Alzheimer's & Dementia, 11*(1), 70–98. https://doi.org/10.1016/j.jalz.2014.04.514

Alzheimer's Association. (2024). 2024 Alzheimer's disease facts and figures. *Alzheimer's & Dementia, 20*(5), 3708–3821. https://doi.org/10.1002/alz.13809

Bateman, R. J., Aisen, P. S., De Strooper, B., Fox, N. C., Lemere, C. A., Ringman, J. M., Salloway, S., Sperling, R. A., Windisch, M., & Xiong, C. (2011). Autosomal-dominant Alzheimer's disease: A review and proposal for the prevention of Alzheimer's disease. *Alzheimer's Research & Therapy, 3*, Article 1. https://doi.org/10.1186/alzrt59

Bernhardt, A. M., Tiedt, S., Teupser, D., Dichgans, M., Meyer, B., Gempt, J., Kuhn, P.-H., Simons, M., Palleis, C., Weidinger, E., Nübling, G., Holdt, L. M., Hönikl, L., Gasperi, C., Giesbertz, P., Müller, S. A., Breimann, S., Lichtenthaler, S. F., Küster, B., ... Levin, J. (2023). A unified classification approach rating clinical utility of protein biomarkers across neurologic diseases. *EBioMedicine, 89*, Article 104456. https://doi.org/10.1016/j.ebiom.2023.104456

Bisogno, A., Scarpa, A., Di Girolamo, S., De Luca, P., Cassandro, C., Viola, P., Ricciardiello, F., Greco, A., De Vincentiis, M., Ralli, M., & Di Stadio, A. (2021). Hearing loss and cognitive impairment: Epidemiology, common pathophysiological findings, and treatment considerations. *Life, 11*(10), Article 1102. https://doi.org/10.3390/life11101102

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica, 82*(4), 239–259. https://doi.org/10.1007/BF00308809

Braak, H., Alafuzoff, I., Arzberger, T., Kretzschmar, H., & Del Tredici, K. (2006). Staging of Alzheimer disease-associated neurofibrillary pathology using paraffin sections and immunocytochemistry. *Acta Neuropathologica, 112*(4), 389–404. https://doi.org/10.1007/s00401-006-0127-z

Breier, J. I., & Fletcher, J. M. (2002). Diseases of the nervous system and sense organs. In S. B. Johnson, N. W. Perry Jr., & R. H. Rozensky (Eds.), *Handbook of clinical health psychology: Vol. 1. Medical disorders and behavioral applications* (pp. 173–201). American Psychological Association. https://doi.org/10.1037/10469-006

Cheng, Y., Chen, S.-F., Zhang, Y.-R., Guo, Y., Wu, K.-M., Huang, Y., Aerqin, Q., Kuo, K., Li, H.-Q., Chen, S., Liu, W., Dong, Q., & Yu, J.-T. (2024). Novel diagnostic and prognostic approach for rapidly progressive dementias: Indicators based on amyloid/tau/neurodegeneration (ATN) framework. *CNS Neuroscience & Therapeutics, 30*(7), Article e14857. https://doi.org/10.1111/cns.14857

Cruchaga, C., Del-Aguila, J. L., Saef, B., Black, K., Fernandez, M. V., Budde, J., Ibanez, L., Deming, Y., Kapoor, M., Tosto, G., Mayeux, R. P., Holtzman, D. M., Fagan, A. M., Morris, J. C., Bateman, R. J., Goate, A. M., Harari, O., the Dominantly Inherited Alzheimer Network, the Alzheimer's Disease Neuroimaging Initiative, & the NIA-LOAD Family Study. (2018). Polygenic risk score of sporadic late-onset Alzheimer's disease reveals a shared architecture with the familial and early-onset forms. *Alzheimer's & Dementia, 14*(2), 205–214. https://doi.org/10.1016/j.jalz.2017.08.013

Crutch, S. J., Schott, J. M., Rabinovici, G. D., Murray, M., Snowden, J. S., van der Flier, W. M., Dickerson, B. C., Vandenberghe, R., Ahmed, S., Bak, T. H., Boeve, B. F., Butler, C., Cappa, S. F., Ceccaldi, M., de Souza, L. C., Dubois, B., Felician, O., Galasko, D., Graff-Radford, J., ... Fox, N. C. (2017). Consensus classification of posterior cortical atrophy. *Alzheimer's & Dementia, 13*(8), 870–884. https://doi.org/10.1016/j.jalz.2017.01.014

Cummings, J. L. (2019). The National Institute on Aging—Alzheimer's Association Framework on Alzheimer's disease: Application to clinical trials. *Alzheimer's & Dementia, 15*(1), 172–178. https://doi.org/10.1016/j.jalz.2018.05.006

de la Fuente Garcia, S., Ritchie, C. W., & Luz, S. (2020). Artificial intelligence, speech, and language processing approaches to monitoring Alzheimer's disease: A systematic review. *Journal of Alzheimer's Disease, 78*(4), 1547–1574. https://doi.org/10.3233/JAD-200888

Delmotte, K., Schaeverbeke, J., Poesen, K., & Vandenberghe, R. (2021). Prognostic value of amyloid/tau/neurodegeneration (ATN) classification based on diagnostic cerebrospinal fluid samples for Alzheimer's disease. *Alzheimer's Research & Therapy, 13*, Article 84. https://doi.org/10.1186/s13195-021-00817-4

Deng, J., & Gao, X. (2024). Analysis of genetic mechanisms, clinical characteristics and pathological changes in familial Alzheimer's disease and sporadic Alzheimer's disease. *BIO Web of Conferences, 111*, Article 03001. https://doi.org/10.1051/bioconf/202411103001

Dubois, B., Villain, N., Frisoni, G. B., Rabinovici, G. D., Sabbagh, M., Cappa, S., Bejanin, A., Bombois, S., Epelbaum, S., Teichmann, M., Habert, M.-O., Nordberg, A., Blennow, K., Galasko, D., Stern, Y., Rowe, C. C., Salloway, S., Schneider, L. S., Cummings, J. L., & Feldman, H. H. (2021). Clinical diagnosis of Alzheimer's disease: Recommendations of the International Working Group. *The Lancet Neurology, 20*(6), 484–496. https://doi.org/10.1016/S1474-4422(21)00066-1

Dubois, B., Villain, N., Schneider, L. S., Fox, N. C., Campbell, N., Galasko, D., Kivipelto, M., Jessen, F., Hanseeuw, B., Boada, M., Barkhof, F., Nordberg, A., Froelich, L., Waldemar, G., Frederiksen, K. S., Padovani, A., Planche, V., Rowe, C. C., Bejanin, A., ... Frisoni, G. B. (2024). Alzheimer disease as a clinical-biological construct—An International Working Group recommendation. *JAMA Neurology, 81*(12), 1304–1311. https://doi.org/10.1001/jamaneurol.2024.3770

Elahi, F. M., & Miller, B. L. (2017). A clinicopathological approach to the diagnosis of dementia. *Nature Reviews Neurology, 13*(8), 457–476. https://doi.org/10.1038/nrneurol.2017.96

Giangrande, C., Delatour, V., Andreasson, U., Blennow, K., Gobom, J., & Zetterberg, H. (2023). Harmonization and standardization of biofluid-based biomarker measurements for AT(N) classification in Alzheimer's disease. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 15*(3), Article e12465. https://doi.org/10.1002/dad2.12465

Goldman, J. S. (2012). New approaches to genetic counseling and testing for Alzheimer's disease and frontotemporal degeneration. *Current Neurology and Neuroscience Reports, 12*(5), 502–510. https://doi.org/10.1007/s11910-012-0296-1

González-Ortiz, F., Turton, M., Kac, P. R., Smirnov, D. S., Premi, E., Ghidoni, R., Benussi, L., Cantoni, V., Saraceno, C., Rivolta, J., Ashton, N. J., Borroni, B., Galasko, D., Harrison, P. J., Zetterberg, H., Blennow, K., & Karikari, T. K. (2023). Brain-derived tau: A novel blood-based biomarker for Alzheimer's disease-type neurodegeneration. *Brain, 146*(3), 1152–1165. https://doi.org/10.1093/brain/awac407

Gorno-Tempini, M. L., Hillis, A. E., Weintraub, S., Kertesz, A., Mendez, M., Cappa, S. F., Ogar, J. M., Rohrer, J. D., Black, S., Boeve, B. F., Manes, F., Dronkers, N. F., Vandenberghe, R., Rascovsky, K., Patterson, K., Miller, B. L., Knopman, D. S., Hodges, J. R., Mesulam, M. M., & Grossman, M. (2011). Classification of primary progressive aphasia and its variants. *Neurology, 76*(11), 1006–1014. https://doi.org/10.1212/WNL.0b013e31821103e6

Graff-Radford, J., Yong, K. X. X., Apostolova, L. G., Bouwman, F. H., Carrillo, M., Dickerson, B. C., Rabinovici, G. D., Schott, J. M., Jones, D. T., & Murray, M. E. (2021). New insights into atypical Alzheimer's disease in the era of biomarkers. *The Lancet Neurology, 20*(3), 222–234. https://doi.org/10.1016/S1474-4422(20)30440-3

Grøntvedt, G. R., Lauridsen, C., Berge, G., White, L. R., Salvesen, Ø., Bråthen, G., & Sando, S. B. (2020). The amyloid, tau, and neurodegeneration (A/T/N) classification applied to a clinical research cohort with long-term follow-up. *Journal of Alzheimer's Disease, 74*(3), 829–837. https://doi.org/10.3233/JAD-191227

Günaydın, T., & Varlı, S. (2025). Computer-aided decision support systems of Alzheimer's disease diagnosis—A systematic review. *Current Medical Imaging, 21*, Article e15734056359358. https://doi.org/10.2174/0115734056359358250516101749

Gutierrez-Tordera, L., Papandreou, C., Novau-Ferré, N., García-González, P., Rojas, M., Marquié, M., Chapado, L. A., Papagiannopoulos, C., Fernàndez-Castillo, N., Valero, S., Folch, J., Ettcheto, M., Camins, A., Boada, M., Ruiz, A., & Bulló, M. (2024). Exploring small non-coding RNAs as blood-based biomarkers to predict Alzheimer's disease. *Cell & Bioscience, 14*, Article 8. https://doi.org/10.1186/s13578-023-01190-5

Hampel, H., Cummings, J., Blennow, K., Gao, P., Jack, C. R., Jr., & Vergallo, A. (2021). Developing the ATX(N) classification for use across the Alzheimer disease continuum. *Nature Reviews Neurology, 17*(9), 580–589. https://doi.org/10.1038/s41582-021-00520-w

Hashemifar, S., Iriondo, C., Casey, E., Hejrati, M., & Alzheimer's Disease Neuroimaging Initiative. (2022). *DeepAD: A robust deep learning model of Alzheimer's disease progression for real-world clinical applications* [Preprint]. arXiv. https://doi.org/10.48550/arXiv.2203.09096

Hestad, K., Ellertsen, B., & Kløve, H. (1998). Neuropsychological assessment in old age. In I. H. Nordhus, G. R. VandenBos, S. Berg, & P. Fromholt (Eds.), *Clinical geropsychology* (pp. 259–288). American Psychological Association. https://doi.org/10.1037/10295-022

Hofmann-Apitius, M., Ball, G., Gebel, S., Bagewadi, S., De Bono, B., Schneider, R., Page, M., Kodamullil, A. T., Younesi, E., Ebeling, C., Tegnér, J., & Canard, L. (2015). Bioinformatics mining and modeling methods for the identification of disease mechanisms in neurodegenerative disorders. *International Journal of Molecular Sciences, 16*(12), 29179–29206. https://doi.org/10.3390/ijms161226148

Huang, Y., Guan, X., Lu, X., Liang, X., Miao, X., Xie, J., Liu, W., Ma, L., Tang, S., Zhang, Z., & Zhan, J. (2023). *OpenAPMax: Abnormal patterns-based model for real-world Alzheimer's disease diagnosis* [Preprint]. arXiv. https://doi.org/10.48550/arXiv.2307.00936

Huang, Y., Liang, X., Lu, X., Miao, X., Xie, J., Liu, W., Zhang, F., Kang, G., Ma, L., Tang, S., Zhang, Z., & Zhan, J. (2023). *OpenClinicalAI: An open and dynamic model for Alzheimer's disease diagnosis* [Preprint]. arXiv. https://doi.org/10.48550/arXiv.2307.00965

Huang, Y., Xu, J., Zhou, Y., Tong, T., Zhuang, X., & Alzheimer's Disease Neuroimaging Initiative. (2019). Diagnosis of Alzheimer's disease via multi-modality 3D convolutional neural network. *Frontiers in Neuroscience, 13*, Article 509. https://doi.org/10.3389/fnins.2019.00509

Hwang, P. H., Longstreth, W. T., Jr., Brenowitz, W. D., Thielke, S. M., López, O. L., Francis, C. E., DeKosky, S. T., & Fitzpatrick, A. L. (2020). Dual sensory impairment in older adults and risk of dementia from the GEM Study. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 12*(1), Article e12054. https://doi.org/10.1002/dad2.12054

Hyman, B. T., Phelps, C. H., Beach, T. G., Bigio, E. H., Cairns, N. J., Carrillo, M. C., Dickson, D. W., Duyckaerts, C., Frosch, M. P., Masliah, E., Mirra, S. S., Nelson, P. T., Schneider, J. A., Thal, D. R., Thies, B., Trojanowski, J. Q., Vinters, H. V., & Montine, T. J. (2012). National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimer's & Dementia, 8*(1), 1–13. https://doi.org/10.1016/j.jalz.2011.10.007

Jack, C. R., Jr., Andrews, J. S., Beach, T. G., Buracchio, T., Dunn, B., Graf, A., Hansson, O., Ho, C., Jagust, W., McDade, E., Molinuevo, J. L., Okonkwo, O. C., Pani, L., Rafii, M. S., Scheltens, P., Siemers, E. R., Snyder, H. M., Sperling, R., Teunissen, C. E., & Carrillo, M. C. (2024). Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimer's & Dementia, 20*(8), 5143–5169. https://doi.org/10.1002/alz.13859

Jack, C. R., Jr., Bennett, D. A., Blennow, K., Carrillo, M. C., Dunn, B., Haeberlein, S. B., Holtzman, D. M., Jagust, W., Jessen, F., Karlawish, J., Liu, E., Molinuevo, J. L., Montine, T., Phelps, C., Rankin, K. P., Rowe, C. C., Scheltens, P., Siemers, E. R., Snyder, H. M., & Sperling, R. (2018). NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia, 14*(4), 535–562. https://doi.org/10.1016/j.jalz.2018.02.018

Jack, C. R., Jr., Bennett, D. A., Blennow, K., Carrillo, M. C., Feldman, H. H., Frisoni, G. B., Hampel, H., Jagust, W. J., Johnson, K. A., Knopman, D. S., Petersen, R. C., Scheltens, P., Sperling, R. A., & Dubois, B. (2016). A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers. *Neurology, 87*(5), 539–547. https://doi.org/10.1212/WNL.0000000000002923

Jack, C. R., Jr., Wiste, H. J., Therneau, T. M., Weigand, S. D., Knopman, D. S., Mielke, M. M., Lowe, V. J., Vemuri, P., Machulda, M. M., Schwarz, C. G., Gunter, J. L., Senjem, M. L., Graff-Radford, J., Jones, D. T., Roberts, R. O., Rocca, W. A., & Petersen, R. C. (2019). Associations of amyloid, tau, and neurodegeneration biomarker profiles with rates of memory decline among individuals without dementia. *JAMA, 321*(23), 2316–2325. https://doi.org/10.1001/jama.2019.7437

Jarmolowicz, A. I., Chen, H.-Y., & Panegyres, P. K. (2015). The patterns of inheritance in early-onset dementia: Alzheimer's disease and frontotemporal dementia. *American Journal of Alzheimer's Disease & Other Dementias, 30*(3), 299–306. https://doi.org/10.1177/1533317514545825

Jayadev, S. (2022). Genetics of Alzheimer disease. *Continuum, 28*(3), 852–871. https://doi.org/10.1212/CON.0000000000001125

Jo, T., Lee, E. H., & Alzheimer's Disease Sequencing Project. (2025). *Uncertainty-aware genomic classification of Alzheimer's disease: A transformer-based ensemble approach with Monte Carlo dropout* [Preprint]. arXiv. https://doi.org/10.48550/arXiv.2506.00662

Jung, H. J., Shin, I. S., & Lee, J. E. (2019). Olfactory function in mild cognitive impairment and Alzheimer's disease: A meta-analysis. *The Laryngoscope, 129*(2), 362–369. https://doi.org/10.1002/lary.27399

Kabbara, A., Eid, H., El Falou, W., Khalil, M., Wendling, F., & Hassan, M. (2018). Reduced integration and improved segregation of functional brain networks in Alzheimer's disease. *Journal of Neural Engineering, 15*(2), Article 026023. https://doi.org/10.1088/1741-2552/aaaa76

Kalia, L. V., Berg, D., Kordower, J. H., Shannon, K. M., Taylor, J. P., Cardoso, F., Goldman, J. G., Jeon, B., Meissner, W. G., Tijssen, M. A. J., Burn, D. J., & Fung, V. S. C. (2024). International Parkinson and Movement Disorder Society viewpoint on biological frameworks of Parkinson's disease: Current status and future directions. *Movement Disorders, 39*(10), 1710–1715. https://doi.org/10.1002/mds.30007

Kang, J. H., Korecka, M., Lee, E. B., Cousins, K. A. Q., Tropea, T. F., Chen-Plotkin, A. A., Irwin, D. J., Wolk, D. A., Brylska, M., Wan, Y., & Shaw, L. M. (2023). Alzheimer disease biomarkers: Moving from CSF to plasma for reliable detection of amyloid and tau pathology. *Clinical Chemistry, 69*(11), 1247–1259. https://doi.org/10.1093/clinchem/hvad139

Knopman, D. S., Amieva, H., Petersen, R. C., Chételat, G., Holtzman, D. M., Hyman, B. T., Nixon, R. A., & Jones, D. T. (2021). Alzheimer disease. *Nature Reviews Disease Primers, 7*(1), Article 33. https://doi.org/10.1038/s41572-021-00269-y

Kobayashi, G., Hirata, K., Ono, M., Kasuga, K., & Takado, Y. (2026). The 2024 NIA-AA biological definition of Alzheimer's disease: Linking biomarkers to clinical practice. *Frontiers in Dementia, 5*, Article 1736297. https://doi.org/10.3389/frdem.2026.1736297

Kourtis, L. C., Regele, O. B., Wright, J. M., & Jones, G. B. (2019). Digital biomarkers for Alzheimer's disease: The mobile/wearable devices opportunity. *npj Digital Medicine, 2*, Article 9. https://doi.org/10.1038/s41746-019-0084-2

Kumar, S., Earnest, T., Yang, B., Kothapalli, D., Aschenbrenner, A. J., Hassenstab, J., Xiong, C., Ances, B., Morris, J., Benzinger, T. L. S., Gordon, B. A., Payne, P., & Sotiras, A. (2025). Analyzing heterogeneity in Alzheimer disease using multimodal normative modeling on imaging-based ATN biomarkers. *Alzheimer's & Dementia, 21*(4), Article e70143. https://doi.org/10.1002/alz.70143

Lad, M., Sedley, W., & Griffiths, T. D. (2024). Sensory loss and risk of dementia. *The Neuroscientist, 30*(2), 247–259. https://doi.org/10.1177/10738584221126090

Lad, M., Sedley, W., & Griffiths, T. D. (2024). Sensory loss and risk of dementia. *The Neuroscientist, 30*(2), 247–259. https://doi.org/10.1177/10738584221126090

Lista, S., Imbimbo, B. P., Grasso, M., Fidilio, A., Emanuele, E., Minoretti, P., López-Ortiz, S., Martín-Hernández, J., Gabelle, A., Caruso, G., Malaguti, M., Melchiorri, D., Santos-Lozano, A., Imbimbo, C., Heneka, M. T., & Caraci, F. (2024). Tracking neuroinflammatory biomarkers in Alzheimer's disease: A strategy for individualized therapeutic approaches? *Journal of Neuroinflammation, 21*, Article 187. https://doi.org/10.1186/s12974-024-03163-y

Livingston, G., Huntley, J., Liu, K. Y., Costafreda, S. G., Selbæk, G., Alladi, S., Ames, D., Banerjee, S., Burns, A., Brayne, C., Fox, N. C., Ferri, C. P., Gitlin, L. N., Howard, R., Kales, H. C., Kivimäki, M., Larson, E. B., Nakasujja, N., Rockwood, K., ... Mukadam, N. (2024). Dementia prevention, intervention, and care: 2024 report of the Lancet Standing Commission. *The Lancet, 404*(10452), 572–628. https://doi.org/10.1016/S0140-6736(24)01296-0

Marcolini, S., Mondragón, J. D., Dominguez-Vega, Z. T., De Deyn, P. P., Maurits, N. M., & Alzheimer's Disease Neuroimaging Initiative. (2024). Clinical variables contributing to the identification of biologically defined subgroups within cognitively unimpaired and mild cognitive impairment individuals. *European Journal of Neurology, 31*(5), Article e16235. https://doi.org/10.1111/ene.16235

Masellis, M., Sherborn, K., Rosa-Neto, P., Sadovnick, A. D., Hsiung, G.-Y. R., Black, S. E., Prasad, S., Williams, M., & Gauthier, S. (2013). Early-onset dementias: Diagnostic and etiological considerations. *Alzheimer's Research & Therapy, 5*(Suppl. 1), Article S7. https://doi.org/10.1186/alzrt197

Matsubara-Tsutsui, M., Yasuda, M., Yamagata, H., Nomura, T., Taguchi, K., Kohara, K., Miyoshi, K., & Miki, T. (2002). Molecular evidence of presenilin 1 mutation in familial early onset dementia. *American Journal of Medical Genetics, 114*(3), 292–298. https://doi.org/10.1002/ajmg.10250

Mazer, N. A., Hofmann, C., Lott, D., Gieschke, R., Klein, G., Boess, F., Grimm, H. P., Kerchner, G. A., Baudler-Klein, M., Smith, J., & Doody, R. S. (2023). Development of a quantitative semi-mechanistic model of Alzheimer's disease based on the amyloid/tau/neurodegeneration framework (the Q-ATN model). *Alzheimer's & Dementia, 19*(6), 2287–2297. https://doi.org/10.1002/alz.12877

McAleese, K. E., Colloby, S. J., Thomas, A. J., Al-Sarraj, S., Ansorge, O., Neal, J., Roncaroli, F., Love, S., Francis, P. T., & Attems, J. (2021). Concomitant neurodegenerative pathologies contribute to the transition from mild cognitive impairment to dementia. *Alzheimer's & Dementia, 17*(7), 1121–1133. https://doi.org/10.1002/alz.12291

McBride, J., Zhao, X., Munro, N., Jicha, G., Smith, C., & Jiang, Y. (2015). Discrimination of mild cognitive impairment and Alzheimer's disease using transfer entropy measures of scalp EEG. *Journal of Healthcare Engineering, 6*(1), 55–70. https://doi.org/10.1260/2040-2295.6.1.55

Mehndiratta, M. M., Singla, M., & Dixit, A. (2025). Unlocking the future of Alzheimer's disease: Innovations in diagnosis and therapy. *Journal of the Association of Physicians of India, 73*(8), 92–97. https://doi.org/10.59556/japi.73.1075

Mehta, R. I., & Schneider, J. A. (2021). What is Alzheimer's disease? The neuropathological heterogeneity of clinically defined Alzheimer's dementia. *Current Opinion in Neurology, 34*(2), 237–245. https://doi.org/10.1097/WCO.0000000000000912

Mirabnahrazam, G., Ma, D., Beaulac, C., Lee, S., Popuri, K., Lee, H., Cao, J., Galvin, J. E., Wang, L., Beg, M. F., & Alzheimer's Disease Neuroimaging Initiative. (2023). Predicting time-to-conversion for dementia of Alzheimer's type using multi-modal deep survival analysis. *Neurobiology of Aging, 121*, 139–156. https://doi.org/10.1016/j.neurobiolaging.2022.10.005

Mirabnahrazam, G., Ma, D., Lee, S., Popuri, K., Lee, H., Cao, J., Wang, L., Galvin, J. E., Beg, M. F., & Alzheimer's Disease Neuroimaging Initiative. (2022). Machine learning–based multimodal neuroimaging genomics dementia score for predicting future conversion to Alzheimer's disease. *Journal of Alzheimer's Disease, 87*(3), 1345–1365. https://doi.org/10.3233/JAD-220021

Mirra, S. S., Heyman, A., McKeel, D., Sumi, S. M., Crain, B. J., Brownlee, L. M., Vogel, F. S., Hughes, J. P., van Belle, G., & Berg, L. (1991). The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. *Neurology, 41*(4), 479–486. https://doi.org/10.1212/WNL.41.4.479

Modat, M., Cash, D. M., Dos Santos Canas, L., Bocchetta, M., & Ourselin, S. (2023). Machine learning for Alzheimer's disease and related dementias. In O. Colliot (Ed.), *Machine learning for brain disorders* (Neuromethods, Vol. 197, pp. 807–846). Humana. https://doi.org/10.1007/978-1-0716-3195-9_25

Mohi ud din dar, G., Bhagat, A., Ansarullah, S. I., Othman, M. T. B., Hamid, Y., Alkahtani, H. K., Ullah, I., & Hamam, H. (2023). A novel framework for classification of different Alzheimer's disease stages using CNN model. *Electronics, 12*(2), Article 469. https://doi.org/10.3390/electronics12020469

Morris, G. P., Clark, I. A., & Vissel, B. (2018). Questions concerning the role of amyloid-β in the definition, aetiology and diagnosis of Alzheimer's disease. *Acta Neuropathologica, 136*(5), 663–689. https://doi.org/10.1007/s00401-018-1918-8

Murphy, C. (2019). Olfactory and other sensory impairments in Alzheimer disease. *Nature Reviews Neurology, 15*(1), 11–24. https://doi.org/10.1038/s41582-018-0097-5

Nelson, P. T., Dickson, D. W., Trojanowski, J. Q., Jack, C. R., Boyle, P. A., Arfanakis, K., Rademakers, R., Alafuzoff, I., Attems, J., Brayne, C., Coyle-Gilchrist, I. T. S., Chui, H. C., Fardo, D. W., Flanagan, M. E., Halliday, G., Hokkanen, S. R. K., Hunter, S., Jicha, G. A., Katsumata, Y., ... Schneider, J. A. (2019). Limbic-predominant age-related TDP-43 encephalopathy (LATE): Consensus working group report. *Brain, 142*(6), 1503–1527. https://doi.org/10.1093/brain/awz099

Nicolas, G. (2024). Recent advances in Alzheimer disease genetics. *Current Opinion in Neurology, 37*(2), 154–165. https://doi.org/10.1097/WCO.0000000000001242

Nogueira, G. N., de Oliveira, N. B., Dal Boni, A. M., Santos, A. L. S., & Barbosa, A. R. (2024). Relation between hypoacusis and Alzheimer's development later in life: A narrative review. *Revista CPAQV—Centro de Pesquisas Avançadas em Qualidade de Vida, 16*(1), 1–18. https://doi.org/10.36692/v16n1-10r

Ortíz, G. G., Pacheco-Moisés, F. P., González-Renovato, E. D., Figuera, L. E., Macías-Islas, M. Á., Mireles-Ramírez, M., Flores-Alvarado, L. J., Sánchez-López, A. L., Nuño-Penilla, D. G., Velázquez-Brizuela, I. E., Sánchez-Luna, J. P., & de la Rosa, A. C. (2015). Genetic, biochemical and histopathological aspects of familiar Alzheimer's disease. In I. Zerr (Ed.), *Alzheimer's disease—Challenges for the future*. InTech. https://doi.org/10.5772/59809

Osse, A. M. L., Zhou, Y., Kinney, J. W., et al. (2026). Biomarkers in Alzheimer's disease clinical trials: 2025. Alzheimer's & Dementia: Translational Research & Clinical Interventions, 12(1), Article e70217. https://doi.org/10.1002/trc2.70217

Ossenkoppele, R., Pijnenburg, Y. A. L., Perry, D. C., Cohn-Sheehy, B. I., Scheltens, N. M. E., Vogel, J. W., Kramer, J. H., van der Vlies, A. E., La Joie, R., Rosen, H. J., van der Flier, W. M., Grinberg, L. T., Rozemuller, A. J. M., Huang, E. J., van Berckel, B. N. M., Miller, B. L., Barkhof, F., Jagust, W. J., Scheltens, P., … Rabinovici, G. D. (2015). The behavioural/dysexecutive variant of Alzheimer's disease: Clinical, neuroimaging and pathological features. *Brain, 138*(9), 2732–2749. https://doi.org/10.1093/brain/awv191

Palmqvist, S., Tideman, P., Mattsson-Carlgren, N., Schindler, S. E., Smith, R., Ossenkoppele, R., Calling, S., West, T., Monane, M., Verghese, P. B., Braunstein, J. B., Blennow, K., Janelidze, S., Stomrud, E., Salvadó, G., & Hansson, O. (2024). Blood biomarkers to detect Alzheimer disease in primary care and secondary care. *JAMA, 332*(15), 1245–1257. https://doi.org/10.1001/jama.2024.13855

Panza, F., Lozupone, M., Sardone, R., Battista, P., Piccininni, M., Dibello, V., Montagna, M. L., Stallone, R., Venezia, P., Liguori, A., Giannelli, G., Bellomo, A., Greco, A., Daniele, A., Seripa, D., Quaranta, N., & Logroscino, G. (2019). Sensorial frailty: Age-related hearing loss and the risk of cognitive impairment and dementia in later life. *Therapeutic Advances in Chronic Disease, 10*, Article 2040622318811000. https://doi.org/10.1177/2040622318811000

Papaliagkas, V., Kimiskidis, V., Tsolaki, M., & Anogianakis, G. (2008). Usefulness of event-related potentials in the assessment of mild cognitive impairment. *BMC Neuroscience, 9*, Article 107. https://doi.org/10.1186/1471-2202-9-107

Papassotiropoulos, A., Streffer, J. R., Hock, C., & Nitsch, R. M. (2001). Genetics of Alzheimer's disease. *Schweizer Archiv für Neurologie und Psychiatrie, 152*(6), 278–287. https://doi.org/10.4414/sanp.2001.01243

Piau, A., Wild, K., Mattek, N., & Kaye, J. (2019). Current state of digital biomarker technologies for real-life, home-based monitoring of cognitive function for mild cognitive impairment to mild Alzheimer disease and implications for clinical care: Systematic review. *Journal of Medical Internet Research, 21*(8), Article e12785. https://doi.org/10.2196/12785

Pinsky, L. E., Burke, W., & Bird, T. D. (2001). Why should primary care physicians know about the genetics of dementia? *Western Journal of Medicine, 175*(6), 412–416. https://doi.org/10.1136/ewjm.175.6.412

Punjabi, A., Martersteck, A., Wang, Y., Parrish, T. B., Katsaggelos, A. K., & Alzheimer's Disease Neuroimaging Initiative. (2019). Neuroimaging modality fusion in Alzheimer's classification using convolutional neural networks. *PLOS ONE, 14*(12), Article e0225759. https://doi.org/10.1371/journal.pone.0225759

Rafii, M. S., Ances, B. M., Schupf, N., Krinsky-McHale, S. J., Mapstone, M., Silverman, W., Lott, I., Klunk, W., Head, E., Christian, B., Lai, F., Rosas, H. D., Zaman, S., Petersen, M. E., Strydom, A., Fortea, J., Handen, B., & O'Bryant, S. (2020). The AT(N) framework for Alzheimer's disease in adults with Down syndrome. *Alzheimer's & Dementia: Diagnosis, Assessment & Disease Monitoring, 12*(1), Article e12062. https://doi.org/10.1002/dad2.12062

Rathore, S., Habes, M., Iftikhar, M. A., Shacklett, A., & Davatzikos, C. (2017). A review on neuroimaging-based classification studies and associated feature extraction methods for Alzheimer's disease and its prodromal stages. *NeuroImage, 155*, 530–548. https://doi.org/10.1016/j.neuroimage.2017.03.057

Recharla, M. (2025). The science of Alzheimer's disease: Current research, therapies, and hope for the future. In *Pioneering biomedical breakthroughs: Advanced multidisciplinary research in neurological disorders, renal diseases, and postpartum health through technology and innovation* (pp. 20–43). Deep Science Publishing. https://doi.org/10.70593/978-81-988918-4-6_2

Ren, F., Wei, J., Chen, Q., Hu, M., Yu, L., Mi, J., Zhou, X., Qin, D., Wu, J., & Wu, A. (2025). Artificial intelligence-driven multi-omics approaches in Alzheimer's disease: Progress, challenges, and future directions. *Acta Pharmaceutica Sinica B, 15*(9), 4327–4385. https://doi.org/10.1016/j.apsb.2025.07.030

Ross, J. L., Sabbaghi, A., Zhuang, R., Bertolini, D., Alzheimer's Disease Cooperative Study, Alzheimer's Disease Neuroimaging Initiative, Critical Path for Alzheimer's Disease Database, European Prevention of Alzheimer's Disease Consortium, & Pooled Resource Open-Access ALS Clinical Trials Consortium. (2024). *Enhancing longitudinal clinical trial efficiency with digital twins and prognostic covariate-adjusted mixed models for repeated measures (PROCOVA-MMRM)* [Preprint]. arXiv. https://doi.org/10.48550/arXiv.2404.17576

Rossini, P. M., & Pappalettera, C. (2026). Should all MCI with Alzheimer's biological diagnosis receive anti-amyloid therapy? *Cell Death & Disease, 17*, Article 212. https://doi.org/10.1038/s41419-026-08456-z

Sato, H., Suzuki, K., Hashizume, A., Hanazawa, R., Sasaki, M., Hirakawa, A., Japanese Alzheimer's Disease Neuroimaging Initiative, & Alzheimer's Disease Neuroimaging Initiative. (2024). *Self-organized clustering, prediction, and superposition of long-term cognitive decline from short-term individual cognitive test scores in Alzheimer's disease* [Preprint]. arXiv. https://doi.org/10.48550/arXiv.2402.12205

Scheltens, P., De Strooper, B., Kivipelto, M., Holstege, H., Chételat, G., Teunissen, C. E., Cummings, J., & van der Flier, W. M. (2021). Alzheimer's disease. *The Lancet, 397*(10284), 1577–1590. https://doi.org/10.1016/S0140-6736(20)32205-4

Schneider, J. A. (2022). Neuropathology of dementia disorders. *Continuum: Lifelong Learning in Neurology, 28*(3), 834–851. https://doi.org/10.1212/CON.0000000000001137

Shaikh, M. R., Jeyabose, A., & Arjunan, R. V. (2025). Deep learning for Alzheimer's disease: Advances in classification, segmentation, subtyping, and explainability. *BioMedical Engineering OnLine, 24*, Article 150. https://doi.org/10.1186/s12938-025-01482-6

Shankar, R., Goh, Z., Devi, F., & Xu, Q. (2025). A systematic review of explainable artificial intelligence methods for speech-based cognitive decline detection. *npj Digital Medicine, 8*, Article 724. https://doi.org/10.1038/s41746-025-02105-z

Shannon, C. E. (1948). A mathematical theory of communication. *Bell System Technical Journal, 27*(3), 379–423. https://doi.org/10.1002/j.1538-7305.1948.tb01338.x

Shin, H.-C., Ihsani, A., Xu, Z., Mandava, S., Turuvekere Sreenivas, S., Forster, C., Cha, J., & Alzheimer's Disease Neuroimaging Initiative. (2020). *GANDALF: Generative adversarial networks with discriminator-adaptive loss fine-tuning for Alzheimer's disease diagnosis from MRI* [Preprint]. arXiv. https://doi.org/10.48550/arXiv.2008.04396

Shojaie, M., Tabarestani, S., Cabrerizo, M., DeKosky, S. T., Vaillancourt, D. E., Loewenstein, D., Duara, R., & Adjouadi, M. (2021). PET imaging of tau pathology and amyloid-β, and MRI for Alzheimer's disease feature fusion and multimodal classification. *Journal of Alzheimer's Disease, 84*(4), 1497–1514. https://doi.org/10.3233/JAD-210064

Szymkowicz, S. M., Gerlach, A. R., Homiack, D., & Taylor, W. D. (2023). Biological factors influencing depression in later life: Role of aging processes and treatment implications. *Translational Psychiatry, 13*, Article 160. https://doi.org/10.1038/s41398-023-02464-9

Tarawneh, H. Y., Jayakody, D. M. P., Sohrabi, H. R., Martins, R. N., & Mulders, W. H. A. M. (2022). Understanding the relationship between age-related hearing loss and Alzheimer's disease: A narrative review. *Journal of Alzheimer's Disease Reports, 6*(1), 539–556. https://doi.org/10.3233/ADR-220035

Teunissen, C. E., Kolster, R., Triana-Baltzer, G., Janelidze, S., Zetterberg, H., & Kolb, H. C. (2025). Plasma p-tau immunoassays in clinical research for Alzheimer's disease. *Alzheimer's & Dementia, 21*(1), Article e14397. https://doi.org/10.1002/alz.14397

Teunissen, C. E., Verberk, I. M. W., Thijssen, E. H., Vermunt, L., Hansson, O., Zetterberg, H., van der Flier, W. M., Mielke, M. M., & del Campo, M. (2022). Blood-based biomarkers for Alzheimer's disease: Towards clinical implementation. *The Lancet Neurology, 21*(1), 66–77. https://doi.org/10.1016/S1474-4422(21)00361-6

Thal, D. R., Rüb, U., Orantes, M., & Braak, H. (2002). Phases of Aβ-deposition in the human brain and its relevance for the development of AD. *Neurology, 58*(12), 1791–1800. https://doi.org/10.1212/WNL.58.12.1791

Therriault, J., Schindler, S. E., Salvadó, G., Pascoal, T. A., Benedet, A. L., Ashton, N. J., Karikari, T. K., Apostolova, L., Murray, M. E., Verberk, I., Vogel, J. W., La Joie, R., Gauthier, S., Teunissen, C., Rabinovici, G. D., Zetterberg, H., Bateman, R. J., Scheltens, P., Blennow, K., ... Rosa-Neto, P. (2024). Biomarker-based staging of Alzheimer disease: Rationale and clinical applications. *Nature Reviews Neurology, 20*(4), 232–244. https://doi.org/10.1038/s41582-024-00942-2

Townley, R. A., Graff-Radford, J., Mantyh, W. G., Botha, H., Polsinelli, A. J., Przybelski, S. A., Machulda, M. M., Makhlouf, A. T., Senjem, M. L., Murray, M. E., Reichard, R. R., Savica, R., Boeve, B. F., Drubach, D. A., Josephs, K. A., Knopman, D. S., Lowe, V. J., Jack, C. R., Jr., Petersen, R. C., & Jones, D. T. (2020). Progressive dysexecutive syndrome due to Alzheimer's disease: A description of 55 cases and comparison to other phenotypes. *Brain Communications, 2*(1), Article fcaa068. https://doi.org/10.1093/braincomms/fcaa068

Trejo-Lopez, J. A., Yachnis, A. T., & Prokop, S. (2022). Neuropathology of Alzheimer's disease. *Neurotherapeutics, 19*(1), 173–185. https://doi.org/10.1007/s13311-021-01146-y

van Deursen, J. A., Vuurman, E. F. P. M., Smits, L. L., Verhey, F. R. J., & Riedel, W. J. (2009). Response speed, contingent negative variation and P300 in Alzheimer's disease and MCI. *Brain and Cognition, 69*(3), 592–599. https://doi.org/10.1016/j.bandc.2008.12.007

Vanderbeek, A. M., Vidovszky, A. A., Ross, J. L., Sabbaghi, A., Walsh, J. R., Fisher, C. K., Critical Path for Alzheimer's Disease, Alzheimer's Disease Neuroimaging Initiative, European Prevention of Alzheimer's Disease Consortium, & Alzheimer's Disease Cooperative Study. (2023). *A weighted prognostic covariate adjustment method for efficient and powerful treatment effect inferences in randomized controlled trials* [Preprint]. arXiv. https://doi.org/10.48550/arXiv.2309.14256

Villain, N., & Michalon, R. (2024). What is Alzheimer's disease? An analysis of nosological perspectives from the 20th and 21st centuries. *European Journal of Neurology, 31*, Article e16302. https://doi.org/10.1111/ene.16302

Villalpando, J. M., Leclerc, B.-S., Le, M. T., Hudon, C., Bolduc, A., Kergoat, M.-J., & Consortium for the Early Identification of Alzheimer's Disease-Quebec. (2026). A comparison of clinical diagnostic classification criteria used in longitudinal cohort studies of the Alzheimer's disease continuum: A systematic review. *Neuropsychology Review, 36*(1), 3–24. https://doi.org/10.1007/s11065-025-09663-9

Waghmare, K. B., Rokade, S. S., Vedpathak, S. D., Jodave, R. R., Sable, V., Manshetti, M. P., & Bamane, D. R. (2025). Alzheimer's disease in the 21st century: Challenges, innovations, and the road ahead. *EPRA International Journal of Research & Development, 10*(8). https://doi.org/10.36713/epra23863

Wen, J., Thibeau-Sutre, E., Diaz-Melo, M., Samper-González, J., Routier, A., Bottani, S., Dormont, D., Durrleman, S., Burgos, N., & Colliot, O. (2020). Convolutional neural networks for classification of Alzheimer's disease: Overview and reproducible evaluation. *Medical Image Analysis, 63*, Article 101694. https://doi.org/10.1016/j.media.2020.101694

World Health Organization. (2021). *Global status report on the public health response to dementia*. https://www.who.int/publications/i/item/9789240033245

Yoon, J. H., Lee, H., Kwon, D., Lee, D., Lee, S., Cho, E., Kim, J., & Kim, D. (2024). Integrative approach of omics and imaging data to discover new insights for understanding brain diseases. *Brain Communications, 6*(4), Article fcae265. https://doi.org/10.1093/braincomms/fcae265

Young, V. M., Gates, S., Garcia, L. Y., & Salardini, A. (2025). Data leakage in deep learning for Alzheimer's disease diagnosis: A scoping review of methodological rigor and performance inflation. *Diagnostics, 15*(18), Article 2348. https://doi.org/10.3390/diagnostics15182348

Young-Pearse, T. L., Lee, H., Hsieh, Y.-C., Chou, V., & Selkoe, D. J. (2023). Moving beyond amyloid and tau to capture the biological heterogeneity of Alzheimer's disease. *Trends in Neurosciences, 46*(6), 426–444. https://doi.org/10.1016/j.tins.2023.03.005

Yu, Z., Mulholland, A., Huang, T., & Liu, Q. (2026). Multimodal AI for Alzheimer disease diagnosis: Systematic review of datasets, models, and modalities. *Journal of Medical Internet Research*, 28, Article e85414. https://doi.org/10.2196/85414

Zampatti, S., Ragazzo, M., Peconi, C., Luciano, S., Gambardella, S., Caputo, V., Strafella, C., Cascella, R., Caltagirone, C., & Giardina, E. (2021). Genetic counselling improves the molecular characterisation of dementing disorders. *Journal of Personalized Medicine, 11*(6), Article 474. https://doi.org/10.3390/jpm11060474

Zhou, H., Zhou, R., Liu, Y., Zhao, K., Shen, L., Chen, B. Y., Zhang, Y., He, L., & Alzheimer's Disease Neuroimaging Initiative. (2025). *Uncovering Alzheimer's disease progression via SDE-based spatio-temporal graph deep learning on longitudinal brain networks* [Preprint]. arXiv. https://doi.org/10.48550/arXiv.2509.21735