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EARLY DIAGNOSIS OF COGNITIVE IMPAIRMENT IN ALZHEIMER'S DISEASE

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Abstract. Alzheimer's disease (AD) is the most common cause of dementia and is characterized by progressive cognitive decline. Early identification of AD is essential to stage the disease, assess risk, and prepare an advance care plan for the patient and family. This review discusses clinical and biological notions of "early" AD, and summarizes a stepwise diagnostic pathway: clinical evaluation, brief cognitive screening, functional assessment, exclusion of reversible causes, structural neuroimaging, and targeted use of biomarkers (CSF, PET, and blood-based markers). The recent expansion of blood-based biomarkers can make early diagnosis more accessible, but these tests must not be used as stand-alone screening or diagnostic tools; results require interpretation within the clinical context.

Keywords: Alzheimer's disease; mild cognitive impairment (MCI); early diagnosis; cognitive screening; functional assessment; biomarkers; AT(N); MRI/CT; PET; blood-based biomarkers.

INTRODUCTION

Early diagnosis of cognitive impairment serves two main purposes in clinical practice: first, early intervention in reversible or modifiable causes (vitamin B12 deficiency, thyroid dysfunction, depression, adverse drug effects, sleep disorders, vascular factors); and second, in progressive neurodegenerative processes such as Alzheimer's disease, staging the disease, assessing risk, and building an advance care plan for the patient and family. The term "early" here has two layers: an early clinical stage (subjective complaints, mild cognitive impairment—MCI) and an early biological stage (biomarker-positive with minimal or no symptoms).

In the traditional approach, AD diagnosis relied mainly on the clinical syndrome: decline in episodic memory, disorientation in time and place, changes in language and executive functions, and impact on daily activities (ADL/IADL). However, the development of biomarkers has made it possible to define the disease through "pathophysiological processes." The NIA-AA Research Framework proposes the AT(N) classification, which aims to construct a biological profile using biomarkers from the amyloid (A), pathological tau (T), and neurodegeneration/neuronal injury (N) groups. [6] The revised criteria published in 2024 further strengthen the biological definition principle and emphasize that biomarker positivity may indicate the disease process regardless of whether clinical signs are present.The urgency of early diagnosis is not limited to "making a diagnosis." First, delayed diagnosis complicates safety planning for the patient and family (medication adherence, traffic safety, nutrition, falls at home), social support, rehabilitation, and allocation of caregiving resources. Second, etiological precision is increasingly important for selecting targeted therapies such as anti-amyloid treatments; when available, these therapies typically require biomarker-confirmed amyloid pathology. Thus, biomarkers are moving from being "additional evidence" to a "strategic

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criterion" in clinical decision-making. At the same time, the key practical question is: in which patient, when, and in what sequence should investigations be performed? Biomarker tests are not always available, may be expensive, and some are invasive (CSF) or involve radiation exposure (PET). The expansion of blood biomarkers can simplify selection, but carries a risk of being misinterpreted as "mass screening." Both the FDA authorization and the Alzheimer's Association guidance stress that blood tests are not a stand-alone diagnosis and that results must be interpreted together with the clinical context.

This article proposes a step-by-step algorithm for early diagnosis: (1) define the complaint and risk profile, (2) brief cognitive screening, (3) functional assessment, (4) exclude reversible causes with laboratory tests, (5) structural assessment with MRI/CT, (6) targeted use of biomarker testing, and (7) integrated diagnosis and staging.

METHODOLOGY:The article was prepared as a narrative synthesis (evidence-informed review). The evidence base included: (a) the updated 2024 diagnostic and staging criteria and their emphasis on biological definition [1,2]; (b) the NIA-AA Research Framework that systematizes the AT(N) biomarker concept [6]; (c) the FDA press release and 510(k) documents describing the intended use, limitations, and clinical performance of the Lumipulse G pTau217/β-Amyloid 1-42 Plasma Ratio test [3,7]; (d) the Alzheimer's Association clinical practice guideline on blood-based biomarkers and its implementation principles [4]; and (e) major cohorts and clinical studies on the diagnostic accuracy of p-tau217 and other blood biomarkers [5]. The unit of analysis was the "diagnostic pathway" (care pathway): primary-care screening → specialist assessment → etiological clarification via biomarkers → staging and care plan. For each stage, the paper outlines: (1) the minimum recommended examinations, (2) precautions for interpretation (education, language, comorbidities, depression, polypharmacy), and (3) criteria for referral to the next stage. This article does not replace a clinical protocol; it is written as a scientific–practical review.

RESULTS:Based on the synthesized evidence, a practical model of early diagnosis in AD was summarized into the following outcome blocks.

1) Early clinical signs and "red flags." In early AD, episodic memory impairment (remembering recent events) is often the leading feature, but it is not limited to memory alone: planning and executive function, word-finding (anomia), navigation, social decision-making, and gradual changes in personality traits are also important. "Red flags" include: rapid progression (within months), focal neurological signs, delirium, new-onset seizures, signs of brain tumor/hydrocephalus, onset at ≤55 years, and a strong family history. In such cases, differential diagnosis and imaging are prioritized; biomarker testing is considered later, once clinical justification is established.

2) Brief cognitive screening and functional assessment. In primary care, 5–15-minute screening tests (Mini-Cog, MoCA, MMSE) answer the question of "who needs deeper evaluation." The most important rule is to interpret results together with education level, language, hearing/vision, depression, and fatigue. These tests do not "make the diagnosis"; they stratify risk. Functional assessment (FAQ, ADL/IADL, CDR) shows the impact of symptoms on daily life and is key for distinguishing MCI from dementia. In MCI, independence is usually preserved, but noticeable—yet not fully disabling—difficulties may appear in complex instrumental activities (financial calculations, medication schedules, transport).

3) Excluding reversible causes. Within early diagnosis, a minimal laboratory panel includes: vitamin B12, folate, TSH, glucose/HbA1c, electrolytes, liver/kidney indicators, complete blood

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count, and, when needed, infection screening. Medication review is also necessary: anticholinergics, sedatives, some hypnotics, and polypharmacy can reduce cognitive function. Depression and anxiety (e.g., PHQ-9) can amplify cognitive complaints; differentiating depression-related "pseudodementia" from AD is clinically important.

4) The role of structural neuroimaging. MRI (preferred) or CT is used to evaluate stroke, tumor, subdural hematoma, normal pressure hydrocephalus, vascular lesions, and the distribution of atrophy. MRI may show medial temporal atrophy characteristic of AD, but this alone is not sufficient for etiological confirmation; it gains value when interpreted within the clinical–biomarker context. If vascular changes (leukoaraiosis, lacunar infarcts) are present, vascular dementia or mixed dementia should be considered, and aggressive control of risk factors becomes part of the care plan.5) Biomarkers as the "key" to etiological clarity. The AT(N) approach considers biomarkers in three groups: amyloid (A), tau (T), and neurodegeneration (N). [6] Amyloid PET or CSF Aβ42/40 indicates amyloid pathology; CSF p-tau or tau PET reflects tau processes; and the N group includes indicators such as MRI atrophy, FDG-PET hypometabolism, or CSF total tau. The 2024 criteria are noted to strengthen the concept of biologically defining AD based on "core" biomarkers. [1,2] Practically, this means that even when clinical symptoms are minimal, an A+ (and especially A+T+) profile suggests AD pathophysiology; however, clinical assessment remains central for prognosis, phenotype, and care planning.6) Practical role of blood biomarkers. Blood tests are developing rapidly as a non-invasive, scalable option. Plasma p-tau217 immunoassays have been reported to show accuracy close to CSF biomarkers in detecting amyloid and tau pathology. On May 16, 2025, the FDA authorized the Lumipulse G pTau217/β-Amyloid 1-42 Plasma Ratio test for marketing; it is intended to aid in diagnosing amyloid pathology in symptomatic patients aged 55 years and older. [3] The FDA emphasizes high concordance with PET or CSF results, but also notes that the test is not for screening or stand-alone diagnosis and must be interpreted together with other clinical information. [3] The Alzheimer's Association guidance discusses adding BBM tests to diagnostic workups within specialty care, using paradigms such as an "indeterminate zone" and a two-cutoff approach, and optimizing the need for confirmatory tests based on results. [4,5]

7) Applied algorithm (integration) and staging. As a result of evidence synthesis, an algorithm for early diagnosis is proposed (Figure 2): screening → reversible causes → MRI/CT → biomarker pathway → integrated conclusion. The final conclusion highlights three aspects: (a) syndrome level (subjective complaint, MCI, dementia), (b) probable etiology (high/low probability of AD, mixed, other), and (c) staging and care plan (safety, rehabilitation, follow-up interval, family support). This approach can be adapted to resource-limited settings by separating "minimal" and "extended" stages.

The figures and tables below visualize the resulting model: Figure 1 shows the clinical–biological spectrum, Figure 2 shows the diagnostic flow, and Figure 3 shows interpretation based on the AT(N) profile.

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Figure 1. Clinical–biological spectrum in AD: from the preclinical stage to dementia.

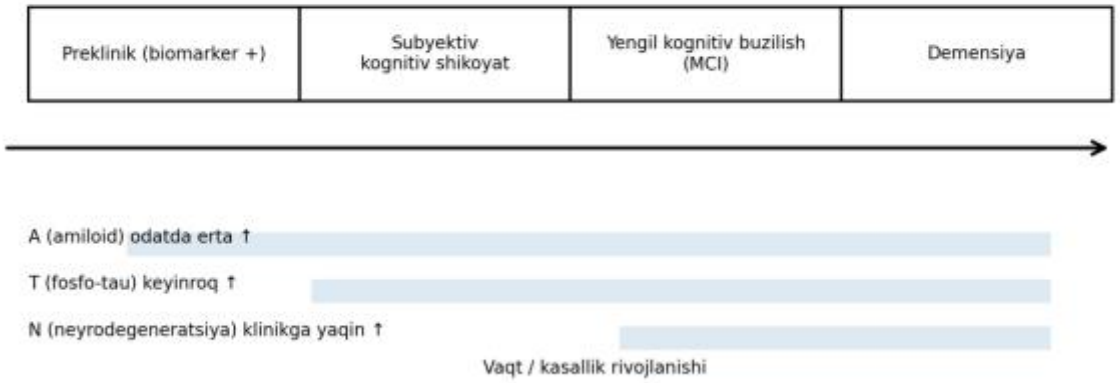

Figure 2. Step-by-step (staged) algorithm for early diagnosis (conceptual).

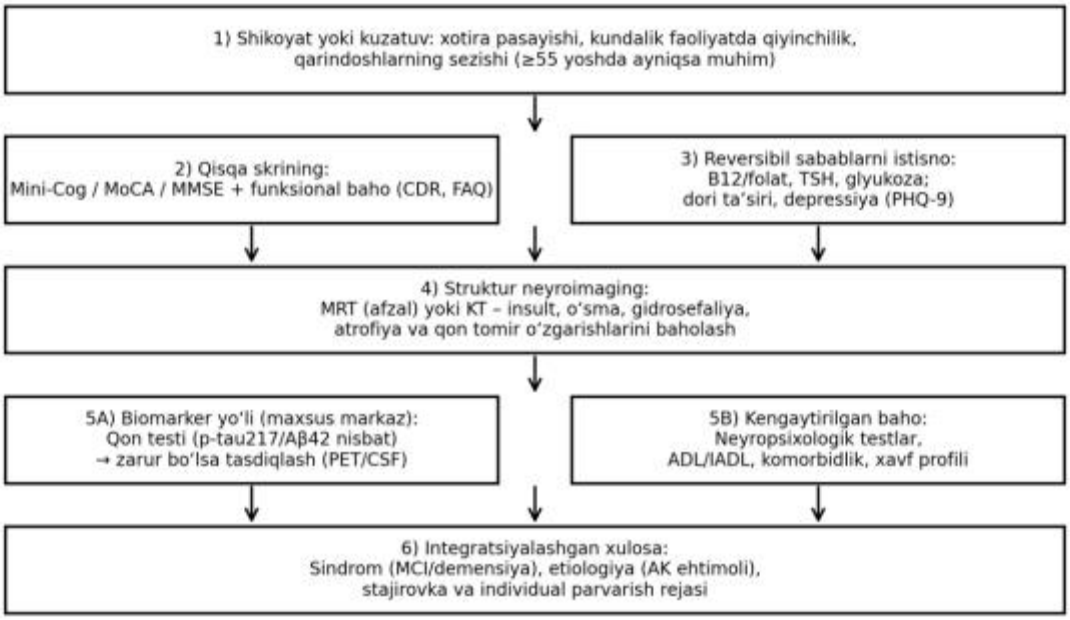

Figure 3. AT(N) biomarker profiles and brief interpretati

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Profil	Talqin (qisqa)	Klinik ahamiyat	Keyingi qadam
A+ T- N-	Amiloid erta bosqich	Klinik bo'lmasligi mumkin	Risk + kuzatuv, skrining
A+ T+ N±	AK biologiyasi ehtimoli yuqori	MCI/demensiyada etiologiya	Davolash/klinika + tasdiqlash
A- T+ N+	Boshqa tauopatiya/degeneratsiya	Differensial tashxis muhim	Mutaxassis + qo'shimcha test
A- T- N+	Noaniq (vaskulyar/metabolik)	Riskni nazorat qilish	MRT, laborator, kuzatuv

Table 1. Brief cognitive tests: use and practical characteristics.

Test	Time	Assesses	Strengths	Limitations
Mini-Cog	3–5 min	Memory + clock-drawing	Very quick; suitable for primary care	May vary by literacy and language
MoCA	10–15 min	Executive function, attention, memory, language	More sensitive for MCI/early AD	Requires training; influenced by education/language
MMSE	7–10 min	General cognition (orientation, attention, recall)	Widely used, easy to administer	Low sensitivity in early impairment; education effect
AD8 (informant)	3 daq	Yaqinlar kuzatuvi	Bemor inkorini chetlab o'tadi	Informant bo'lmasa qiyin

Table 2. Biomarkers: sample, what they provide, and clinical role.

Biomarker	Sample/Method	What it indicates	When useful	Limitation
Amiloid PET	Imaging	A (amiloid) +/−	Etiologik aniqlik, klinik noaniqlikda	Qimmat, radiatsiya, mavjudlik
CSF Aβ42	Cerebrospinal fluid (lumbar puncture)	Low Aβ42 suggests amyloid pathology	Early AD / preclinical stages	Invasive procedure

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CSF p-tau	Cerebrospinal fluid	Reflects tau pathology	Confirming AD pathophysiology	Invasive; assay variability
Tau PET	Imaging	T komponenti	Stajirovka va topografiya	Qimmat, cheklangan
CSF Aβ42	Cerebrospinal fluid (lumbar puncture)	Low Aβ42 suggests amyloid pathology	Early AD / preclinical stages	Invasive procedure

DISCUSSION

Discussion. The central idea of early diagnosis is that AD is not only a “clinical syndrome” but also a biological process that can begin long before clinical symptoms appear. [1,2,6] This approach affects practice in two ways. First, even in patients with minimal symptoms, biomarkers become important for etiological clarity. Second, biomarker positivity does not always mean “dementia”; it indicates a process and elevated risk, so staging and follow-up plans must be constructed cautiously. Especially at the stage of subjective cognitive complaints, there is a risk of overdiagnosis: if the diagnosis is detached from clinical reality, the patient may suffer psychological harm, stigma, and inappropriate treatment.The entry of blood biomarkers into clinical practice can make early diagnosis more convenient because they are less expensive and less invasive than PET or CSF. However, this opportunity also increases the risk of misuse. The FDA draws a clear boundary: the blood test is intended to help detect amyloid pathology in a symptomatic patient assessed in a specialty setting; it is not intended for screening, and results must be interpreted together with clinical information. [3] Therefore, a “test everyone who is older” approach in primary care is not scientifically or ethically justified; instead, screening and risk stratification (tests, labs, imaging) should identify a high-probability group, and only then should biomarkers be applied.The Alzheimer’s Association clinical practice guideline provides “performance-based” recommendations for BBM testing in specialty care: not the brand of the laboratory, but the clinical accuracy of the test (sensitivity, specificity), the proportion of indeterminate results, and the clinical consequences of false positives/false negatives are considered. [4,5] In practice, this approach facilitates two key decisions: (1) which patients require invasive or expensive confirmatory tests such as PET/CSF, and (2) in which patients etiological clarity is sufficient to initiate a care plan. At the same time, a BBM result does not mean “start treatment automatically”; comorbidities, clinical phenotype, and the risk–benefit ratio must be evaluated by a specialist.

In resource-limited areas (including many rural polyclinics), early diagnosis often depends on shortages of staff and time. Therefore, the “minimal package” concept is important as a practical solution: brief screening + functional assessment + basic laboratory tests + referral for CT/MRI. Even this stage detects many reversible conditions and improves patient safety. If etiological uncertainty remains, or if the patient is considered a candidate for targeted therapy, the biomarker stage is added. This approach supports rational allocation of healthcare resources.Limitations. This article is not an original clinical study but an evidence-informed review and conceptual integration. Availability of biomarker tests and imaging differs by region; therefore, when implementing the algorithm, infrastructure, laboratory quality control, and workforce training should be taken into account.

CONCLUSION

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Conclusion. Early diagnosis of cognitive impairment in Alzheimer's disease is a sequential process that starts with clinical screening and functional assessment, proceeds to exclusion of reversible causes, structural neuroimaging, and achieves etiological clarity through targeted biomarker testing. The 2024 criteria and the AT(N) concept strengthen the identification of AD as a biological disease and increase the importance of biomarkers that can indicate the process even before clinical symptoms appear. [1,2,6] The blood test based on the p-tau217/β-Amyloid 1-42 ratio authorized by the FDA in 2025 simplifies detection of amyloid pathology in symptomatic patients in specialty settings, but it is not a screening or stand-alone diagnostic tool and must be interpreted in conjunction with the clinical context.Practical recommendation: at the primary-care level, use standardized screening (MoCA/Mini-Cog), a minimal laboratory panel, and MRI/CT; at the specialty level, use biomarkers (blood, CSF, or PET) and an expanded neuropsychological assessment to stage the condition and develop an individualized care plan. This stepwise approach harmonizes early detection with clinical safety and resource efficiency.

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