What is Alheimer disease and what is its diagnosis ?

GRAL-BARROW Conference - January 2025

Bruno Dubois
Salpêtrière Hospital - Sorbonne University
Past-President of the French Society of Neurology (SFN)
Académie Nationale de Médecine

Groupe Hospitalier Pitié - Salpêtrière

institut de la mémoire et de la maladie d'Alzheimer

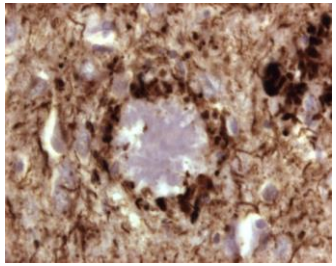
SORBONNE UNIVERSITÉ

Inserm
Institut national de la santé et de la recherche médicale

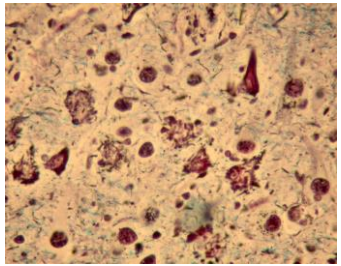
Historical definition

I- A clinical-pathological entity

- Memory disorders
- Orientation deficits
- Impaired comprehension
- Aphasia, agraphia
- Behavioral changes
- Agitation/agressivity
- Paranoïa
- Hallucinations



Amyloid plaques



NFT (Taupathology)

Nov 4, 1906 Tübingen

NINCDS-ADRDA criteria for Probable AD

II- A clinical entity

- **Dementia**
- Deficits in at least two areas of cognition (memory essential)
- **Impact on ADL**
- **Absence of other systemic or brain disease** that could account for the condition

McKhann G, et al. 1984

Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria

Bruno Dubois*, Howard H Feldman*, Claudia Jacova, Steven T DeKosky, Pascale Barberger-Gateau, Jeffrey Cummings, André Delacourte, Douglas Galasko, Serge Gauthier, Gregory Jicha, Kenichi Meguro, John O'Brien, Florence Pasquier, Philippe Robert, Martin Rossor, Steven Salloway, Yaakov Stern, Pieter J Visser, Philip Scheltens

III- A clinical-biological entity (IWG-2)

Clinical phenotype	+	Biomarker positivity
Typical AD amnestic S hippocampal type **Atypical AD** Posterior cortical Logopenic variant Frontal variant		**CSF** Abeta + and T/P tau + **PET** Amyloid +

Dubois et al, The Lancet Neur 2007, 2014

IV - Toward a purely biological definition of the disease

1) Jack C et al, 2018

	Cognitively unimpaired	MCI	dementia
$A^-T^-N^-$	normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
$A^+T^-N^-$	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
$A^+T^-N^+$	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with dementia
$A^+T^+N^-$ $A^+T^+N^+$	Preclinical Alzheimer's disease	Alzheimer's disease with MCI (Prodromal AD)	Alzheimer's disease with dementia

The presence of A + and T + markers is sufficient to define Alzheimer's disease

2) July 2023

DRAFT as of JULY 15, 2023 For Public Comment @ AAIC23

NIA-AA Revised Clinical Criteria for Alzheimer's Disease

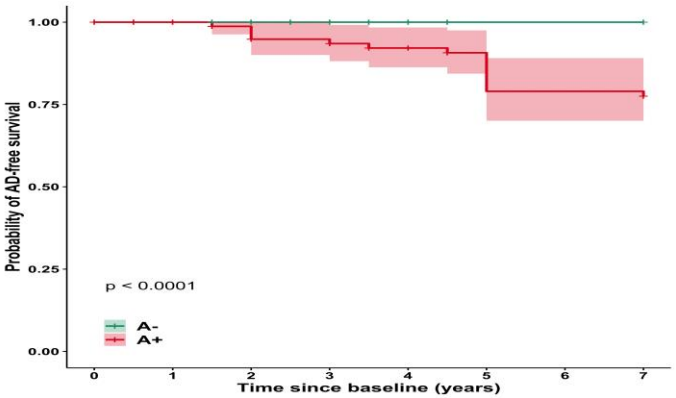
since then several have. In response, the present document has progressed from a framework for research, to criteria for diagnosis and staging that are intended for clinical use as well as research. Second, validated biomarkers in 2018 were based on either CSF assays or imaging. Since then, plasma-based biomarkers with excellent diagnostic performance have been developed and clinically validated. The present document has correspondingly incorporated

The presence of A + marker is sufficient to define Alzheimer's disease

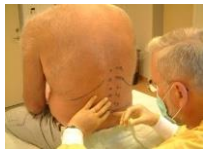
INSIGHT-Study: a 7 year follow-up of aged amyloid (+) cognitively normal subjects

- 320 cognitively Nl subjects
- 76y old
- **88/320: Amyloid PET (+)**

Lancet Neurol 2018; 17: 335–46



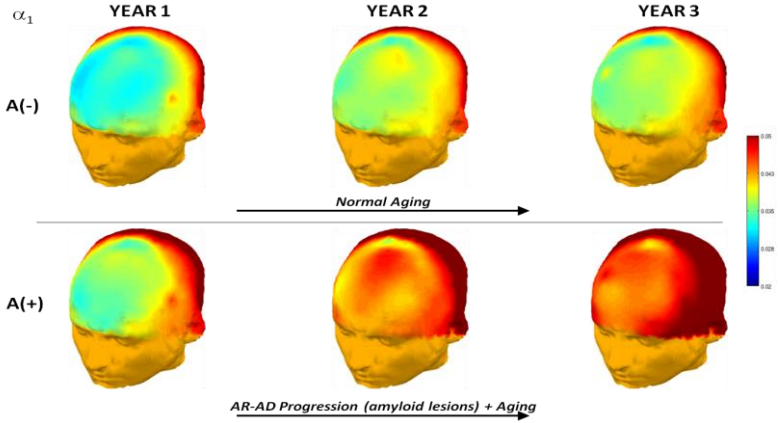
ONLY 16 SUBJECTS PROGRESSED TO PRODROMAL AD



55 CSF
10 A+T+

7 y

2 prodromal AD



LONGITUDINAL α/θ POWER RATIO CHANGES (rEEG)

At M0, M12 and M24 in the (A-) and (A+) groups

Concept of brain resilience

In cognitively normal subjects:

In longitudinal studies, Amyloid + cannot predict a further occurrence of symptoms:

- A majority of isolated (A+) subjects remain CN over time even **after several years** (*Dubois B et al, TLN, 2021; Burnham SC et al, TLN 2016)* or **in their lifetime** *(Brookmeyer & Abdalla, AlzDem, 2018)*
- Only 35% (6/17) of CN progressed to AD after 7 years of follow-up of a longitudinal **amyloid and tau PET** study *(Hanseeuw BJ et al. JAMA Neurol, 2019)*

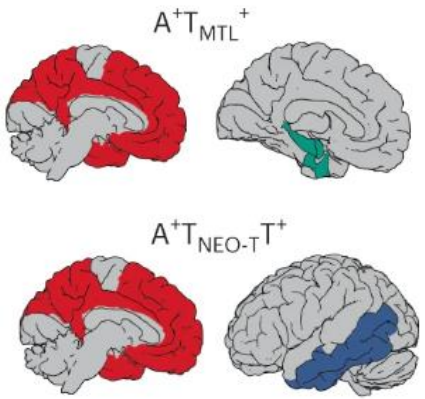
Lifetime risks (%) of AD dementia for females based on screening for amyloidosis (A), neurodegeneration (N), and mild cognitive impairment (MCI) by age

Age	Normal state 1	A state 2	N state 3	A & N state 4	MCI & A & N state 5	MCI & N state 6
60	20.1 (10.6–34.0)	31.0 (20.7–42.4)	30.3 (15.9–53.2)	41.9 (31.2–52.7)	95.6 (94.8–96.3)	78.1 (70.9–84.9)
65	18.7 (9.7–32.0)	29.3 (19.4–40.5)	27.6 (14.5–48.0)	40.8 (30.3–51.4)	93.6 (92.3–94.5)	71.4 (63.7–79.2)
70	16.6 (8.4–29.0)	26.9 (17.6–37.6)	24.5 (12.9–42.3)	38.9 (28.7–49.3)	90.1 (88.2–91.4)	63.0 (55.1–71.6)
75	13.8 (6.8–24.9)	23.5 (15.1–33.4)	20.8 (10.8–36.0)	35.9 (26.2–45.8)	84.7 (82.1–86.7)	53.2 (45.5–62.1)
80	10.4 (4.9–19.5)	19.1 (12.0–27.8)	16.5 (8.5–29.0)	31.2 (22.4–40.3)	76.2 (72.8–78.9)	42.0 (35.1–50.5)
85	7.1 (3.2–13.7)	13.8 (8.4–20.6)	11.9 (6.0–21.2)	24.7 (17.4–32.5)	63.8 (59.7–67.2)	30.3 (24.8–37.5)
90	4.1 (1.8–8.4)	8.4 (4.9–13.0)	7.3 (3.6–13.4)	16.9 (11.6–22.6)	46.7 (42.7–50.2)	19.1 (15.4–24.3)

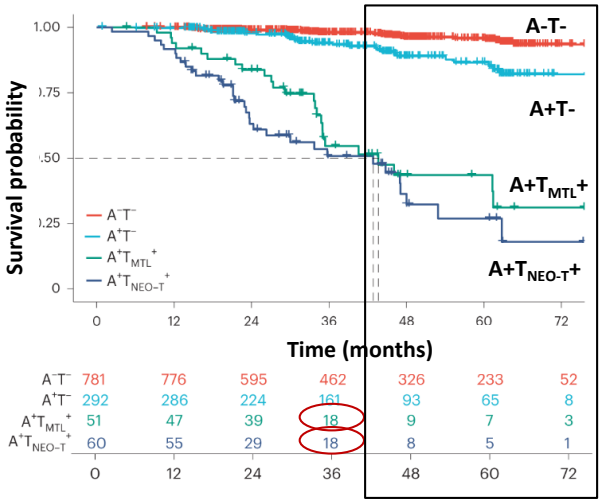
Brookmeyer & Abdalla, Alzheimers Dement, 2018

Data Informing IWG 2024 Recommendations
Outcomes in Cognitively Unimpaired (CU)

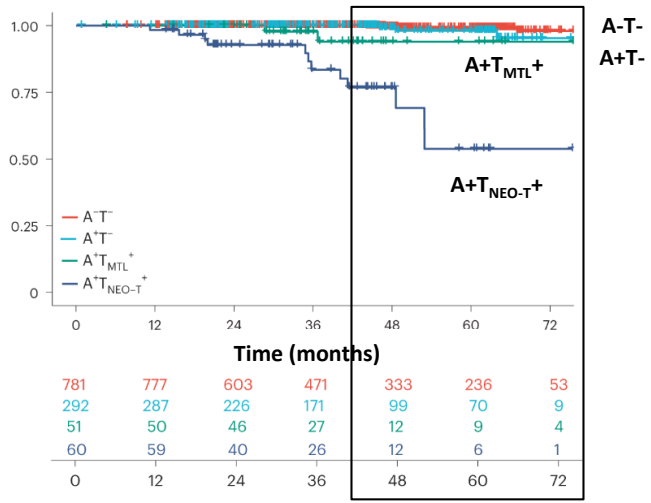
CUI – Multiple Cohorts – 4-6y follow-up



Progression to MCI



Progression to all-cause dementia



- A+ T-: Confirmed to be poor predictor of AD symptoms in CU (low risk)
- A+ T+: Risk stratification
  - Tau MTL and Tau Neo, incident MCI both significantly ↑ risk (high risk)
  - Tau MTL, incident dementia (some increased risk)
  - Tau Neo, incident dementia (very high risk)

Ossenkoppele, R., et al. Nat Med (2022)

What role for biomarkers?

- If a BM is a marker of disease, the development of new BM (α-synuclein, TDP 43...) will allow to diagnose 2, 3, 4 NDG diseases in CN subjects that they will probably never express.

- The neuropathologists identify lesions but not a disease: 'Alzheimer's disease is a clinical-pathological entity that should be disentangled from Alzheimer's pathology (NIA conference consensus, 2012).

- BM are markers of pathology, not markers of disease. They are risk factors of disease, with different level of risk

IWG: The new lexicon *(Dubois et al. Lancet Neurology, 2010)*

Preclinical states of AD (including both "asymptomatic at-risk state for AD" and "presymptomatic AD")

These terms refer to the long asymptomatic stage between the earliest pathogenic events/ brain lesions of AD and the first appearance of specific cognitive changes. Traditionally, a preclinical or asymptomatic phase was recognised post mortem by evidence of histological changes typical of Alzheimer's pathology in individuals considered as cognitively normal before death. Today, two preclinical states can be isolated in vivo:

- *Asymptomatic at-risk state for AD*—this state can be identified in vivo by evidence of amyloidosis in the brain (with retention of specific PET amyloid tracers) or in the CSF (with changes in amyloid β, tau, and phospho-tau concentrations). In the absence of knowledge about the value of these biological changes to predict the further development of the disease, the asymptomatic phase of AD should still be referred to as an "at-risk state for AD".
- *Presymptomatic AD*—this state applies to individuals who will develop AD. This can be ascertained only in families that are affected by rare autosomal dominant monogenic AD mutations (monogenic AD).

Towards a personalised Alzheimer's disease risk profile in asymptomatic at-risk people

Factors that can increase the risk of progression to Alzheimer's disease

- Increased age
- Frailty
- Female sex
- Low education level
- Heterozygous *APOE* ε4 status
- Polygenic risk factors beyond *APOE*
- Family history of Alzheimer's disease
- Memory complaint or subjective cognitive decline
- Magnitude of brain lesions, inferred from pathophysiological biomarker results especially if searched with PET
- Presence of markers of neurodegeneration (ie, isolated hippocampal atrophy on MRI, ^{18}F-fluorodeoxyglucose-PET hypometabolism, or elevated CSF neurofilament light chain)
- Copathology

Factors that could decrease the risk of progression to Alzheimer's disease

- Protective genes, such as the presence of the *APOE* ε2 allele, the *APOE* ε3 Christchurch mutation, or the *A673T APP* Icelandic mutation
- Higher cognitive reserve

Factors that need further confirmation

- Pattern of neuroinflammation
- Functional brain marker of cognitive reserve (eg, connectivity on functional MRI)
- Lifestyle factors (eg, physical activity, sleep, social activity)
- Psychiatric diseases (eg, depression)

Dubois et al, Lancet Neurol, 2021

Proposed stratification of risk of asymptomatic subjects

People with absolute risk

Carriers of autosomal dominant mutations (*APP*, *PSEN1*, *PSEN2*, or trisomy 21)[106]

People with high risk

Cognitively unimpaired individuals with:

- CSF or PET that is amyloid-positive and tau positive[24–26]
- PET that is tau positive outside the limbic cortex (Braak stage 5 or higher)[107]
- *APOE* ε4 homozygosity[108]

People with undefined risk*

Cognitively unimpaired individuals with an incomplete biomarker pattern:

- Amyloid positive; tau negative or unknown[33]
- Amyloid negative; tau positive[51]

Defining different states in clinical practice

1- Alzheimer disease:

Encompasses 2 stages in the continuum:

- ***a dementia stage***
- ***a prodromal stage***

2- Subjects at-risk for AD:

Presymptomatic subjects:

= Subjects on the path of the clinical expression of the disease

because of a specific pattern of BM

because of an autosomal dominant mutation

Asymptomatic at-risk:

- In cognitively normal individuals with an undefined biomarker profile

Dubois, Villain, … Feldman, Frisoni. JAMA Neurol, 2024

Diagnosing AD

1) In cognitively impaired individuals

1) Amnestic Syndrome of hippocampal type

Memory measures	CSF (+) n=74	CSF (–) n=111	Effect size
FCSRT Total Recall	13.4	15.4	0.97
Logical Memory Delayed Recall	8.12	13.59	0.74
CERAD verbal Delayed Recall	4.22	5.63	0.71
CERAD verbal Delay Recognition	8.13	8.41	0.13

Total recall **with cueing** is the best predictor of AD pathology

Wagner M et al, Neurology 2012

5 Words Test

Normal Score = 10
Validation study on 86 AD/126 'functional'
Sensitivity: 91%; Specificity: 87%

+

CSF Abeta (+) and T-P tau (+)
OR
PET Amyloid (+)

2) Atypical AD

Posterior cortical
Logopenic variant
Frontal variant

Diagnosing AD

2) In cognitively unimpaired individuals

Research

- **They deserve all our attention**
- **CU subjects BM+ can be included in**
  - **Cohort studies (predictive algorithm, risk factors, preventive interventions…)**
  - **Clinical trials (secondary prevention protocols), specially for those who are presymptomatic, i. e. close to the onset of a clinical disease. Clearing amyloid burden can prevent the onset of cognitive impairment**

Clinic

- **The risk of cognitive impairment in CU individuals with isolated A(+) is only 17% over 6 years and not different from a group of A(-) individuals (Ossenkoppele, 2022)**
- **Ethical dilemma : to disclose a disease that may never develop**
- **Therefore, BM investigation should be performed in specialized centers which can manage counselling, multi-domain intervention and communication on risk**

JAMA Neurology | Special Communication

Alzheimer Disease as a Clinical-Biological Construct—An International Working Group Recommendation

Bruno Dubois, MD, MSc; Nicolas Villain, MD, PhD; Lon Schneider, MD, MSc; Nick Fox, MD, MA; Noll Campbell, PharmD, MSc; Douglas Galasko, MD, MSc; Miia Kivipelto, MD, PhD; Frank Jessen, MD; Bernard Hanseeuw, MD, PhD; Mercè Boada, MD, PhD; Frederik Barkhof, MD, PhD; Agneta Nordberg, MD, PhD; Lutz Frolich, MD, PhD; Gunhild Waldemar, MD, DMSc; Kristian Steen Frederiksen, MD, PhD; Alessandro Padovani, MD, PhD; Vincent Planche, MD, PhD; Christopher Rowe, MD; Alexandre Bejanin, PhD; Agustin Ibanez, PhD; Stefano Cappa, MD; Paulo Caramelli, MD, PhD; Ricardo Nitrini, MD, PhD; Ricardo Allegri, MD, PhD; Andrea Slachevsky, MD, PhD; Leonardo Cruz de Souza, MD, PhD; Andrea Bozoki, MD; Eric Widera, MD; Kaj Blennow, MD, PhD; Craig Ritchie, MD, PhD; Marc Agronin, MD; Francisco Lopera, MD; Lisa Delano-Wood, PhD; Stéphanie Bombois, MD, PhD; Richard Levy, MD, PhD; Madhav Thambisetty, MD, DPhil; Jean Georges, BA; David T. Jones, MD; Helen Lavretsky, MD, MSc; Jonathan Schott, MD, BSc; Jennifer Gatchel, MD, PhD; Sandra Swantek, MD; Paul Newhouse, MD; Howard H. Feldman, MD; Giovanni B. Frisoni, MD

JAMA Neurol. doi:10.1001/jamaneurol.2024.3770
Published online November 1, 2024.

Differentiating Diagnostic Approaches to AD

	AA 2024	IWG 2024
Definition of Alzheimer's disease	**Biological** ("AD should be defined biologically, not based on a clinical syndrome")	**Clinical-biological** ("AD is a clinical-biological construct")
Implications for the diagnosis in clinical setting	Presence of any abnormal Core 1 AD biomarker (i.e. fluid Aβ42/40 or pTau…) is sufficient. A biomarker positive cognitively normal person can be diagnosed with AD	Presence of objective cognitive deficits and AD biomarkers is needed. A cognitively normal person cannot be diagnosed with AD*
Implications in diagnostic disclosure of subject status	Cognitively normal persons with one positive core 1 AD biomarker can be told they have AD	Cognitively normal persons with positive AD biomarker can be told they are at risk for AD*
Implications for phase 3 preventive clinical trials	Biomarkers could be primary endpoints in clinical trials. Demonstration of efficacy on clinical parameters may not be necessary.	Biomarkers cannot be primary endpoints in clinical trials. Demonstration of efficacy on clinical parameters is necessary.

TAKE HOME MESSAGES (IWG)

We consider diagnosing AD without a clinical and biological construct as being unwarranted and potentially concerning without a clear knowledge of when or whether symptoms will ever develop.

Any benefit in providing a diagnosis of AD to those who are BM (+) cognitively normal with a high chance of never developing cognitive impairment in their lifetime. The resulting psychological and societal consequences of being diagnosed with AD and never developing symptoms can be consequential.

AD is a clinico-biological entity, in line with the historical definition

The clinician has to establish a diagnosis in **symptomatic patients**, not to make a pathological mapping in vivo in cognitively normal individuals

The potential for diagnostic error should not be underestimated in a purely biological diagnosis

TAKE HOME MESSAGES (IWG)

BM investigation should be restricted to specialists who can manage the problems related to the different conditions

- in asymptomatic at-risk:

modifiable lifestyle risk factor counselling and management,
communication of risk through ad hoc protocols,
implementation of multi-domain interventions,
and cognitive enhancement with physical and cognitive training…

- **In presymptomatic individuals**: in addition, these are good candidates for therapeutic protocols with disease-modifiers because of a previsible outcome and the absence no ethical limit. This is essential for testing the efficacy of DM drugs to delay the progression to AD.

If a BM investigation is done, BM+ CU Individuals should only be considered **at-risk for AD**.

This is not “just semantics”, because behind the different concepts lie different strategies of management of these persons