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

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1 **Alzheimer disease is a clinical-biological construct: An IWG recommendation**

2

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11



1 **Abstract (347 words)**

2 **Importance:** Since 2018, a movement has emerged to define Alzheimer disease (AD) as a  
3 purely biological entity based on biomarker findings. The recent revision of the Alzheimer  
4 Association (AA) criteria for AD furthers this direction. However, concerns about a purely  
5 biological definition of AD being applied clinically, the understanding of AD by society at  
6 large, and the translation of blood-based biomarkers into clinical practice prompt this  
7 International Working Group (IWG) updated recommendations.

8 **Objective:** To consider the revised AA criteria and to offer an alternative definitional view of  
9 AD as a clinical-biological construct for clinical use. We update recommendations of the  
10 2021 IWG diagnostic criteria for further elaborating at risk and presymptomatic states.

11 **Evidence Review:** We searched PubMed for articles published between Jul 1, 2020, and  
12 March 1, 2024, using the terms “biomarker” OR “amyloid” OR “tau” OR  
13 “neurodegeneration” OR “preclinical” OR “CSF” OR “PET” OR “plasma” AND  
14 “Alzheimer’s disease”. We also searched the references of relevant articles.

15 **Findings:** In the new AA diagnostic criteria, AD can be defined clinically as encompassing  
16 cognitively normal people having a core 1 AD biomarker. However, recent literature shows  
17 that the majority of biomarker positive cognitively normal individuals will not become  
18 symptomatic along a proximate timeline. In the clinical setting, disclosing a diagnosis of AD  
19 to cognitively normal people with only Core 1 AD biomarkers, represents the most  
20 problematic implication of a purely biological definition of the disease.

21 **Conclusions and Relevance:** the ultimate aim is to foster effective AD treatments, including  
22 preventing symptoms and dementia. We consider that the approach of diagnosing AD without  
23 a clinical and biological construct as being unwarranted and potentially concerning without a

1 clear knowledge of when or whether symptoms will ever develop. We recommend that  
2 amyloid-positive only and more generally most of biomarker positive cognitively normal  
3 individuals should not be labeled as having AD. Rather they should be considered as being  
4 atrisk. We see the expansion of presymptomatic AD as being a better diagnostic construct for  
5 those with a specific pattern of biomarkers, indicating that they are proximate to the  
6 expression of symptoms in the near future.

7

1 The recently revised AA criteria for Alzheimer disease (AD)<sup>1</sup> propose to define AD on  
2 biological evidence only. The diagnosis of AD can be provided to cognitively normal people  
3 with evidence of “core 1 AD biomarkers” encompassing CSF ABeta and Tau ratios and  
4 plasma phosphoTau217 validated against amyloid PET, even though these new criteria do not  
5 recommend testing for these biomarkers in cognitively normal individuals. This raises the  
6 question of the role and influence of biomarkers in the diagnostic workup.

7

### 8 **The value of biomarkers**

9 In 2007, the International Working Group (IWG) revised the 1984 diagnostic criteria for AD  
10 and were the first to propose that the diagnosis of AD in patients with cognitive deficits could  
11 be anchored around the presence of biomarkers to support more accurate and earlier disease  
12 diagnosis<sup>2</sup>. Since then, brain amyloid PET has been shown to correlate with the presence and  
13 density of beta-amyloid plaques in autopsy-derived brain tissue samples. CSF and plasma  
14 amyloid and phospho-tau biomarkers have been validated against amyloid PET. These  
15 validations justify the inclusion and reimbursement of biomarkers in diagnostic work-ups in  
16 different countries. However, the clinical value and utility of these biomarkers or tests differ  
17 depending on the context, e.g., research or clinical settings, in which they are used<sup>3,4</sup>.

18 The availability of these biomarkers has radically changed both observational and clinical trial  
19 research<sup>5</sup>. They are regularly used to identify and confirm the presence of AD pathology with  
20 a strong emphasis on amyloid, to study the natural history of disease biology, to evaluate  
21 pharmacodynamic effects of treatment candidates, and as surrogate clinical outcomes in  
22 clinical trials. At variance with post-mortem investigation, which provides the final definitive  
23 but static information about lesions in the brain, these biomarkers allow dynamic in-vivo  
24 monitoring of pathological changes and inform about their relationships to the onset and  
25 progression of symptoms<sup>6</sup>. Each biomarker provides information about a type of pathological

1 lesion or a process that has its own weight and contribution to the natural history of the  
2 disease. However, the so-called “AD core 1 biomarkers” are individually insufficient to  
3 account for the many mechanisms and interactions underlying the disease process. In turn,  
4 selected tau and amyloid biomarkers should be conceptualized as AD risk factors with  
5 different/specific weights and synergies across the disease continuum. The potential of many  
6 other biological markers is currently being actively investigated including markers of glial  
7 activation and neuroinflammation, such as GFAP and YKL-40; neurodegeneration, such as  
8 neurofilament light chain (NfL); as well as synaptic dysfunction and degeneration, such as  
9 neurogranin and SNAP-25<sup>7</sup>.

10 In the clinical setting, amyloid and tau biomarkers are used to support or refute a clinically  
11 suspected diagnosis. As acknowledged by neuropathologists in a National Institute of Aging  
12 conference consensus in 2012<sup>8</sup>, Alzheimer neuropathologic changes are necessary but not  
13 sufficient for establishing the diagnosis of AD. They concluded, aligned with its historical  
14 definition, that ‘Alzheimer disease’ is a clinico-pathological entity that should be disentangled  
15 from Alzheimer pathological changes, which are frequently observed in post-mortem brains  
16 of aged individuals who died without any cognitive or functional decline<sup>9</sup>. Additionally,  
17 lesions of different pathological nature are frequently observed post-mortem due to the high  
18 prevalence of comorbidities and to the synergy between pathologies<sup>10</sup>: combinations of alpha-  
19 synuclein aggregates (Lewy bodies), insoluble aggregates of TAR DNA-binding protein 43  
20 (TDP-43), non-AD tauopathies, and vascular pathologies commonly exist alongside with  
21 amyloidopathy and AD tauopathy. These are more the norm than the exception in  
22 pathological studies<sup>11</sup> on sporadic cases.

23

24 The inherent logic of the new AA criteria leads to the conclusion that the development of  
25 emerging biomarkers of co-pathologies, e.g., alpha-synuclein, TDP-43, and others in the

1 future, could result in the diagnosis of two, three, or more different neurodegenerative  
2 diseases in a cognitively normal person, as a norm.<sup>11</sup> While multiple diagnoses are common in  
3 elderly patients, it took decades of studies to demonstrate the superiority of the comorbidity-  
4 based versus the additive single-disease approach, now accepted as a valid clinical  
5 construct<sup>12</sup>. Therefore, we argue that biomarkers alone should remain markers of pathological  
6 processes and not markers of a specific disease<sup>8</sup>. Furthermore, the contribution of biomarkers  
7 in the clinical setting depends on the context of use<sup>3</sup> and, importantly, should differ between  
8 the assessment of cognitively impaired and unimpaired individuals<sup>4</sup>.

9

#### 10 **Contribution of biomarkers in cognitively impaired patients**

11 The combination of common (amnesic syndrome of the hippocampal type, logopenic  
12 aphasia, posterior cortical atrophy) or uncommon (cortico-basal syndrome, behavioral and  
13 dysexecutive variants) clinical phenotypes and the positivity of pathophysiological amyloid  
14 and tau biomarkers establishes the diagnosis of AD<sup>4</sup>. This association defines the clinical-  
15 biological entity of the disease, proposed by the IWG<sup>4</sup>, in line with the clinical-pathological  
16 description by Alois Alzheimer<sup>13,14</sup> and the neuropathological consensus<sup>8</sup>. This scenario also  
17 enables a clinical-biological diagnosis at an early prodromal stage, i.e., once mild but definite  
18 symptoms are in place. The concept of AD as a clinical-biological entity has played a vital  
19 role in the FDA's approval of anti-amyloid monoclonal in prodromal AD<sup>15-17</sup>. The clinical  
20 implications and associated diagnostic narrative of the IWG and AA criteria are similar in the  
21 case of such cognitively impaired biomarker-positive patients, but very different in  
22 cognitively normal individuals<sup>18</sup>.

23

#### 24 **Contribution of biomarkers in asymptomatic at-risk and presymptomatic AD**

1 Many cognitively normal people, with or without cognitive complaints, seek expert advice for  
2 their memory concerns, subjective perception of cognitive decline, positive family history of  
3 AD, or simply the wish to know their risk of AD. These persons can present with normal  
4 objective memory and cognitive performance and ask for evidence-based and clinically  
5 meaningful answers. Here, it is again necessary to distinguish between research and clinical  
6 settings.

7

8 In the research setting, there is major interest in developing effective drugs or other  
9 interventions at the earliest point in time possible in persons with an increased risk of  
10 progression to AD dementia. Functional recovery as a treatment outcome is highly unlikely  
11 once the degeneration in neural networks has reached a threshold of severity. We are in  
12 support of all research efforts in the field to move towards the goal of decreasing the  
13 incidence of cognitive impairment in cognitively normal persons at risk. As brain  $\beta$ -  
14 amyloidosis is an acknowledged risk factor for the onset of clinical symptoms, we endorse the  
15 view that clearing amyloid burden may possibly reduce the risk of future cognitive  
16 impairment –under certain conditions– analogous to treating vascular risk factors to prevent  
17 myocardial infarction or stroke. The vascular analogy has been endorsed by the international  
18 Dominantly Inherited Alzheimer Network, which has used the hypercholesterolemia/heart  
19 disease analogy to interpret their results on biomarker changes in autosomal dominant AD<sup>19</sup>.

20

21 In the clinical setting, extending the diagnosis of AD to cognitively normal people with only  
22 core 1 AD biomarkers, represents the most problematic implication of diagnostic criteria that  
23 have a purely biological definition of the disease. The argument invoked by the AA  
24 workgroup is the analogy with cancer, where less severe stages, such as in situ gastric or  
25 breast cancer, allow the earliest possible diagnosis and the most favorable outcomes<sup>1,20</sup> In

1 these cancer scenarios, an asymptomatic incubation period is followed by gradual and steady  
2 growth resulting in the occurrence of the clinical symptoms over a fairly predictable time  
3 course. This scenario is fitting for the autosomal dominant form of AD, where fully penetrant  
4 monogenic mutations in the *APP*, *PSEN-1*, and *PSEN-2* genes identify persons who will  
5 almost invariably develop symptoms during their normal lifespan and to Down syndrome  
6 where the abnormal production of  $\beta$ -amyloid is responsible for the almost universal  
7 development of AD dementia<sup>21</sup>.

8 The model cannot be transferred to cognitively normal individuals with sporadic Alzheimer  
9 pathologic changes, as their lifetime risk of becoming symptomatic is much lower. Indeed, the  
10 lifetime risk of AD dementia in a 65-year-old man who is amyloid-biomarker positive has  
11 been estimated at 21.9%, a mere 1.7 times higher than the risk of amyloid negative of similar  
12 age<sup>22</sup>. Other reports have confirmed these estimates, with a lack of significant clinical  
13 progression in the ADNI cohort in cognitively normal individuals with isolated abnormal  
14 amyloid biomarker after an 8-year follow-up<sup>23</sup>, while in research cohorts, only 17% of these  
15 individuals of cognitively normal individuals with isolated abnormal amyloid biomarker  
16 progressed to mild cognitive impairment over six years<sup>24</sup>. Therefore, the revised AA criteria,  
17 proposing that a diagnosis of AD can be reduced to the sole presence of one AD core 1  
18 biomarkers, may introduce major uncertainty and variability in the clinical prognosis of  
19 patients diagnosed with AD<sup>1</sup>. The risk of progression of those who have abnormal amyloid  
20 biomarker is marginally increased, including in those with combined abnormal amyloid and  
21 tau biomarkers (i.e., soluble AD Tau biomarkers [“T1” biomarkers according to the AA  
22 framework: HR = 1.08-1.31]<sup>25</sup>, and unstratified Tau PET positivity [35% of progression after  
23 7 years of follow-up])<sup>25, 26</sup>. However, the risk of progression to AD dementia significantly  
24 increases when the aggregated forms of tau spread out in neocortical areas<sup>24</sup>. This biomarker  
25 profile, together with other specific conditions (Panel 1), suggests that the underpinning

1 pathological processes are active and that the development of clinical symptoms in the near  
2 future may be virtually inevitable. We do foresee the evolution of the diagnostic construct we  
3 have introduced previously of presymptomatic AD as applying well within the diagnostic  
4 lexicon. In its initial iteration, it was introduced within the IWG framework for monogenic  
5 fully penetrant AD mutations. We foresee being able to add new biomarker profiles within  
6 this presymptomatic grouping. Currently, long-term evidence for clinical progression remains  
7 limited and estimates are based on non-representative convenience cohorts of relatively small  
8 group size.

9  
10 To summarize, the IWG approach allows the identification of two different categories of  
11 cognitively normal biomarker-positive subjects with different specific management strategies  
12 (Panel 1). First, individuals who are (A+) and (A+ and T1+) have an increased but far from a  
13 convincing benchmark of certainty of developing clinical AD within their expected lifetimes.  
14 These subjects should be labeled “at-risk,” and their follow-up in longitudinal cohorts will  
15 identify the modulating factors increasing/decreasing the risk of dementia and the likely  
16 emergence of symptoms. Second, individuals who are cognitively normal but are already on  
17 the path to clinical disease. We anticipate a realistic future where more and more of these  
18 individuals could be considered presymptomatic AD on the basis of models that incorporate a  
19 multiplicity of predictive biomarkers. (Panel 1)

20

### 21 **The pathophysiological framework**

22 The above classification derives from a theoretical pathophysiological framework recently  
23 developed as a revision of the traditional amyloid cascade, the probabilistic amyloid cascade  
24 model<sup>27</sup>. This model postulates decreasing penetrance of the phenotype from autosomal  
25 dominant mutations (almost complete penetrance) to *APOEε4* carrier status (intermediate



1 penetrance) and *APOE*ε4 non-carrier status (lowest penetrance) due to the increasing effect of  
2 stochastic factors (non-*APOE* genes, environmental exposures, co-pathology). It further  
3 implies that brain amyloidosis in cognitively normal persons is a risk factor for cognitive  
4 impairment and dementia, and that the risk is higher in *APOE*ε4 carriers.

5

6 The model further implies that the risk of progression to cognitive impairment in the  
7 asymptomatic at-risk can be estimated by considering both markers of Alzheimer pathology  
8 (amyloid and tau), other pathologies including TDP 43, vascular and Lewy body, resilience,  
9 lifetime and environmental factors, genetics, and other biomarker risk factors<sup>10,28</sup>. The model  
10 is consistent with the view that amyloid and tau biomarkers can be used in combination to  
11 diagnose AD in cognitively impaired patients.<sup>29</sup>

12

### 13 **The societal impact**

14 the consideration of whether cognitively normal persons with positive biomarkers for  
15 Alzheimer pathology should be labeled as asymptomatic atrisk or already affected by AD, is  
16 not “just semantics”, because behind the different concepts and semantic differences lie  
17 different strategies of management of these persons (Table 1). There is a need to acquire  
18 detailed personalized risk knowledge and to be able to communicate this effectively in clinical  
19 practice.

20 A rich literature is available on the safety of disclosure of amyloid status to cognitively  
21 normal people<sup>30,31</sup>. The disclosure narrative and the way results are communicated have a  
22 significant impact on patient experience and involve clarifying that amyloid status does not  
23 equal AD<sup>32,33</sup>.

24

25 We cannot see any benefit in providing a diagnosis of AD to those who are cognitively  
26 normal with positive biomarker subjects with a high chance of never developing cognitive

1 impairment in their lifetime. The resulting psychological and societal consequences of being  
2 diagnosed with AD and never developing symptoms can be consequential<sup>34,35</sup>. In addition,  
3 recent findings show that high-dose gantenerumab achieved similar amyloid PET clearance as  
4 approved aducanumab despite its lack of clinical effectiveness.<sup>36,37</sup> This demonstrates the  
5 potential liability of the clinical and biological dissociation of AD definition regarding drug  
6 approval. This decision becomes particularly challenging when dealing with biomarker-  
7 positive cognitively normal individuals, as the clinical effects may be more delayed in this  
8 population. There is a greater inclination to depend on a surrogate biomarker to account for  
9 the delayed clinical effect when evaluating this group<sup>38</sup>, which adds to the uncertainty in  
10 determining treatment efficacy, especially if the biomarker is definitive, as proposed by the  
11 AA.

12 Last, the potential for diagnostic error should not be underestimated, considering realistic  
13 statistical parameters of the respective biomarkers in real-world clinical practice, e.g., PPV  
14 and NPV, that are, by definition, influenced by the disease prevalence in a given context of  
15 use<sup>3</sup>. In principle, a protein biomarker always delivers a probabilistic distinction of groups as  
16 opposed to genetic biomarkers, which may offer a deterministic separation of groups. As an  
17 example, cut-off points for AD biomarkers extrapolated from White North American and  
18 European population samples to more diverse populations have uncovered significant  
19 differences.<sup>39</sup> Hence, interpreting biomarkers in the clinical context is crucial, as also  
20 emphasized by the AA criteria. This underscores the inherent limitations of relying solely on a  
21 biological definition of AD in clinical practice.<sup>1</sup>

22

23 The potential consequences are easily understandable for patients consulting for a benign  
24 memory complaint due to attention disorders or age-related changes and the biomarker  
25 positivity representing a false positive diagnosis<sup>40</sup>. These risks will be amplified when testing

1 is done directly to the consumer as it is currently becoming available commercially and  
2 through online sources without physician or clinician involvement. Given the current  
3 availability of blood-based biomarkers for amyloid and tau, an explosion of cognitively  
4 normal persons who are labeled as having “Alzheimer disease” on a purely biological  
5 definition of the disease may be expected<sup>41</sup>. As a result, increasing societal pressure for anti-  
6 tau or anti-amyloid drugs to prevent cognitive decline is foreseeable, including treatment  
7 offlabel in persons who are cognitively normal.

8

9 The AA's criteria do not endorse having the use of biomarkers to identify AD in those who  
10 are cognitively normal. Unfortunately, there may be no realistic way to control access to these  
11 biomarkers or diagnosis or treatment when a biomarker only diagnosis is made according to  
12 these criteria. Considering the concerns raised above, we believe that it is necessary to  
13 provide a clearer message on this critical issue. We recommend that routine diagnostic testing  
14 should not be performed in cognitively normal individuals outside of research purposes at this  
15 time. In this population, biomarkers of amyloid pathology are not diagnostic markers but risk  
16 markers. Risk assessment differs from diagnostic assessment, which can be done in the  
17 context of non-diagnostic patient journeys<sup>4142</sup>.

18 Diagnostic criteria for AD can have far-reaching societal, political, organizational, and  
19 economic implications. We want to restrict the focus in this position paper to the scientific  
20 evidence and clinical impact on healthcare practice of these proposed revised criteria.  
21 Considering AD as a purely biological entity may be useful for research studies in cognitively  
22 normal individuals. However, the IWG's approach of considering biomarker positivity in the  
23 absence of cognitive impairment as a risk condition rather than a disease, in most cases,  
24 increases the motivation for secondary prevention treatments. It also enhances the societal  
25 relevance of AD, similar to the impact of risk factors for cardiovascular diseases<sup>4243</sup>. Instead,

1 it will help better assess the risk/benefit ratio of drugs according to each context of use.  
2 Moreover, communicating a risk condition may stimulate these individuals to control their  
3 risk factors and change their lifestyle, as well as prompting public health policymakers to  
4 foster initiatives and programs for reducing dementia risk at the population level.

5

#### 6 **The future: defining the risk in cognitively normal individuals.**

7 The conceptual approach proposed by the IWG is to maintain the essential clinical-  
8 pathological concept of AD<sup>14</sup>. We separate asymptomatic at-risk individuals from those who  
9 already have the disease. Persons who are asymptomatic at-risk deserve full research interest  
10 and engagement since current estimates of their cumulative risk of progression to cognitive  
11 impairment are undetermined and need to be defined according to their genetic and biomarker  
12 profile, factors of risk or prevention, lifestyle and potential mechanism of resilience.  
13 Individual cumulative risk profiling will drive strategies for risk reduction, including  
14 treatments with acceptable risk/benefit/cost ratio. The need is urgent to better estimate the risk  
15 of progression in the asymptomatic at-risk and the presymptomatic at large, from well-  
16 designed observational representative population-based studies with long follow-up and  
17 accurate measurements of baseline modifiable risk factors and biomarkers of Alzheimer  
18 pathology<sup>4344</sup>. The study of groups for whom this information is lacking (e.g., non-white and  
19 ethnic minorities and populations from low and middle-income countries) is of utmost  
20 importance, as their dementia risk factors may differ.

21

22 There are task forces actively engaged in devising practical solutions for the asymptomatic at-  
23 risk and the presymptomatic persons. In particular, Brain Health Services for the Prevention  
24 of Dementia (dBHS) will offer: i) evaluation of risk; ii) communication of risk; and iii) risk  
25 reduction interventions targeting modifiable risk factors and disease modifiers when these will

1 be shown effective<sup>42</sup>. Over time, the scenario might further evolve when well-tolerated drug  
2 treatments are developed. In such cases, a lower threshold of risk could be proposed for a  
3 preventive treatment in asymptomatic at-risk individuals.

4

5 To conclude, IWG continues to advocate for AD as is a clinical-biological entity.

6 In a clinical setting, a diagnosis of AD is made in the presence of established clinical  
7 phenotype with supportive pathophysiological biomarkers of AD pathology (CSF biomarkers,  
8 amyloid or Tau PET, or plasma biomarkers such as p-tau 217 pending their approval in  
9 clinical practice). The AD diagnosis encompasses the prodromal AD (predementia) and AD  
10 dementia stages, as these are just stages of the same disease.

11 The IWG discourages the use of biomarker investigation in cognitively normal individuals  
12 with or without complaints (e.g. in the so-called subjective cognitive decliners) to diagnose  
13 AD. Biomarker investigations in cognitively normal individuals can be done in the context of  
14 *ad hoc* non-diagnostic patient journeys aiming to evaluate the risk of future cognitive  
15 impairment, to communicate it, and to put in place risk reduction interventions. Pilot  
16 experiences of such patient journeys are currently in a research phase services, and might  
17 move into the clinic after due validation. Studies of cognitively normal subjects with positive  
18 AD biomarkers are important for defining predictive algorithms and risk estimates of  
19 progression to clinical symptoms. A very limited number of these subjects will be considered  
20 presymptomatic because of a genetic autosomal dominant mutation or because of a very high  
21 risk for imminent cognitive impairment due to a particular biomarker profile. All the other  
22 biomarker-positive individuals, much more numerous, should be considered as asymptomatic  
23 at-risk.

24 Future research should study cognitively normal persons in two main directions: i)  
25 observational longitudinal studies with long follow-up where lifestyle risk factors and

1 biomarkers are simultaneously assessed to accurately estimate the independent weight of each  
2 on the incidence of cognitive impairment and dementia. ii) interventional clinical trials, to test  
3 the efficacy of drugs against Alzheimer pathology and other risk reduction strategies in  
4 reducing the incidence of cognitive impairment and assess the therapeutic risk/benefit  
5 profiles.  
6

1 **Panel 1- The 2024 IWG lexicon**

2 We encourage the use of the following terms “at-risk for Alzheimer disease”,  
3 “presymptomatic Alzheimer disease” and “Alzheimer disease” according to the following  
4 definitions.

5 **1) Asymptomatic at-risk for AD:**

6 -Refers to cognitively normal individuals at increased risk of developing cognitive  
7 impairment because of uncertain/undetermined risk associated with a given biomarker  
8 profile.

9 - With currently available data, the biomarker profile corresponds to brain amyloidosis  
10 either isolated or associated with tauopathy limited to the medial temporal regions or a  
11 positive phospho-tau fluid biomarker.

12 - The lifetime risk of progression to cognitive impairment is increased compared to  
13 biomarker-negative individuals but remains far from a deterministic rate for clinical  
14 progression.

15 - They should not be defined as having Alzheimer disease.

16 **2) Presymptomatic AD:**

17 - Refers to cognitively normal subjects with a specific pattern of biomarkers associated  
18 with an almost deterministic and very high lifetime risk of progression.

19 - Examples of biomarker profiles associated with presymptomatic conditions:

20 ○ Highly penetrant autosomal dominant genetic mutations associated with a  
21 close to 100% lifetime risk of clinical AD: APP, PSEN1, PSEN2

22 ○ Persons affected with Down syndrome

23 ○ Persons homozygous for the *APOE* e4 allele 4 with *SORL1* loss of function<sup>4,45</sup>.

24 (For these profiles, age and parental age is an additional factor to take into

1 account for the determination of the age at onset of the clinical expression of  
2 AD).

- 3 ○ Sporadic AD pathology biomarker changes (+/- genetic background)  
4 associated with a very high lifetime risk of clinical AD such as amyloid  
5 PET(+) with tau PET(+) in neocortical regions<sup>24</sup>.

6 Future studies from population-based cohort may identify distinct biomarker profiles  
7 including additional risk factors defining this subgroup.<sup>46</sup>

### 8 3) **Alzheimer disease:**

9 - Refers to cognitively impaired individuals with:

- 10 ○ Specific clinical phenotypes: common (amnestic syndrome of the  
11 hippocampal type, logopenic aphasia, posterior cortical atrophy) or  
12 uncommon (cortico-basal syndrome, behavioral and dysexecutive variants)
- 13 ○ And a positivity of CSF or PET pathophysiological AD biomarkers<sup>4</sup>.  
14 Plasma biomarkers such as p-tau 217 may soon enter the routine clinical  
15 workup.

16 - This includes the prodromal (mild cognitive impairment and no loss of function) and  
17 dementia (with loss of function) stages.

18

19



1 **Table 1: Differentiating Diagnostic Approaches to AD**

2

	<b>AA 2024</b>	<b>IWG 2024</b>
<b>Definition of Alzheimer disease</b>	<b>Biological</b> ("AD should be defined biologically, not based on a clinical syndrome")	<b>Clinical-biological</b> ("AD is a clinical-biological construct")
Implications for the diagnosis in clinical setting	Presence of any abnormal Core A AD biomarker (i.e., fluid A $\beta$ 42/40, pTau, etc) is sufficient.  A biomarker-positive cognitively normal person can be diagnosed with AD	Presence of objective cognitive deficits and AD biomarkers is needed.  A biomarker-positive 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.

3 AA= Alzheimer Association; IWG= International Working Group

4 BM= biomarker;

5 \*except in the rare cases fulfilling the requirements for presymptomatic AD (see text)

6

7

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