

# Towards a future where Alzheimer's disease pathology is stopped before the onset of dementia

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# Towards a future where Alzheimer's disease pathology is stopped before the onset of dementia

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Alzheimer's disease (AD) is a major healthcare challenge with no curative treatment at present. To address this challenge, we need a paradigm shift, where we focus on pre-dementia stages of AD. In this Perspective, we outline a strategy to move towards a future with personalized medicine for AD by preparing for and investing in effective and patient-orchestrated diagnosis, prediction and prevention of the dementia stage. While focusing on AD, this Perspective also discusses studies that do not specify the cause of dementia. Future personalized prevention strategies encompass multiple components, including tailored combinations of disease-modifying interventions and lifestyle. By empowering the public and patients to be more actively engaged in the management of their health and disease and by developing improved strategies for diagnosis, prediction and prevention, we can pave the way for a future with personalized medicine, in which AD pathology is stopped to prevent or delay the onset of dementia.

Alzheimer's disease (AD) is among this century's major healthcare challenges. It is characterized by progressive decline in the individual's cognitive abilities. Worldwide, 55 million patients suffer from dementia<sup>1</sup>. AD is the most common cause of dementia. Therefore we focus on AD, but we also discuss studies that do not specify the cause of dementia and acknowledge that much of the reasoning holds for other pathologies causing dementia as well. While most prevalence studies do not specify dementia subtype, advances of biomarkers for AD pathology enable more precise estimates of dementia due to AD at 32 million worldwide<sup>2</sup>. In fact, dementia is only the late stage of a disease that takes years to develop in the brain. Biomarkers allow us to estimate the size of populations in pre-dementia stages of AD; first estimates indicate 69 million individuals with mild cognitive impairment (MCI) due to AD and >300 million individuals having preclinical AD<sup>2,3</sup>. MCI refers to the prodromal

stage of AD in which there is some cognitive impairment that does not suffice for a diagnosis of dementia. Preclinical AD refers to the presence of AD pathology in individuals without any signs or symptoms. It is not yet clear, however, whether all individuals with preclinical AD progress to symptomatic AD and dementia. Nonetheless, the biomarker-based prevalence estimates of the AD continuum illustrate that we need to disentangle the concepts of AD from dementia<sup>4-6</sup>. While AD refers to the disease or pathological process that takes years to develop, dementia refers to a late-stage, detrimental outcome of this disease. There is no cure for AD yet, nor for other dementia-causing diseases. In a large proportion of patients with AD, a diagnosis is only made at a late disease stage. The same holds for other dementia-causing diseases. As a result, care is too often untimely and insufficiently adjusted to patients' needs, resulting in frustrations in patients as well as health

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professionals, high costs and a compromised quality of life<sup>7</sup>. Treatment strategies for AD that lead to even small delays in onset of dementia and progression of the disease or enable self-management of patients would not only considerably reduce the prevalence of dementia but also the individual and socioeconomic burden<sup>8,9</sup>. It is therefore critical to bring therapy and support to individuals in as timely and adequately a manner as possible.

AD pathology should be targeted before the onset of dementia. Research has shown that AD develops in the course of 20–30 years<sup>10,11</sup>. By the time AD manifests as dementia, the brain can no longer be rescued. This provides a huge window of opportunity for preventive action. To optimally employ these possibilities, we need a paradigm shift with a focus on (1) individual characteristics and preferences and (2) the stages before dementia to ultimately (3) prevent progression to dementia. Effective deployment of preventive strategies requires timely identification of individuals who would benefit the most. Further development of diagnostic tests to detect early AD pathophysiological changes, also capturing differences in pathological pathways between patients, is therefore warranted. Individual preferences and patient-reported outcomes should be the starting point for high-quality individualized care<sup>12,13</sup>.

Based on observations in the consultation room—where the information need of patients boils down to three questions: ‘Doctor, what diagnosis do I have?’, ‘What can I expect?’ and ‘What can I do?’—in this Perspective, we outline the preparatory steps to ready society for a future with personalized medicine for AD. We discuss the need for preventive strategies, outlining the importance of both disease-modifying drugs and lifestyle interventions. We also reflect on the importance of timely and molecular diagnosis of AD, where blood-based biomarkers, genetic information and digital tools can be incorporated into the AD diagnosis framework. Moving toward earlier stages of the disease, personal risk profiles should provide prognostic information on outcomes that matter to patients. Finally, we recommend promoting patient-orchestrated care by engaging older adults (at risk of) AD throughout their health and disease management, with a keen eye for an inclusionary approach to keep healthcare affordable and accessible. As such, we describe a direction for the future in which patient-orchestrated AD healthcare entails accurate and timely diagnosis with prediction of meaningful outcomes to ultimately achieve prevention of dementia.

## Prevention

Dementia risk reduction is one of the strategic action areas of the World Health Organization’s global action plan on dementia, outlining steps to be taken on a global, national and regional level<sup>14</sup>. To ultimately reduce the global burden of AD and other causes of dementia, we should move the needle forward to pre-dementia stages of disease. The report identified a wide gap between the need for prevention and treatment and the actual provision of services. It stresses the need for a collective effort to understand how we can prevent or at least delay onset of the disease. Prevention encompasses both pharmacological and non-pharmacological strategies. These are not mutually exclusive but rather complementary strategies. For complex diseases such as AD, we need to employ every possible strategy that may help to reduce the disease burden, that is, focus on risk reduction, while also developing disease-modifying treatment, with the ultimate question of what works for whom.

## Pharmacological interventions

In the dementia stage, it is too late to rescue the brain, and most pharmacological treatment is therefore aimed at slowing the progression of symptoms, in fact, tertiary prevention. For future pharmaceutical strategies to be most effective, however, they probably should be provided in the pre-dementia stages. After aducanumab in 2021, the approval of lecanemab by the Food and Drug Administration at the beginning of 2023 heralds the second drug with disease-modifying properties<sup>15,16</sup>.

This marks a milestone heralding the dawn of a new era, in which drugs that alter the biological disease pathways in AD are a realistic opportunity. Market access of these drugs will impact the patient journey, not only in terms of treatment, but also in terms of diagnosis, monitoring and prognosis. In particular, this illustrates the necessity to focus on underlying pathology, rather than syndrome outcome. There are a number of challenges to address related to integrating this new class of drugs in clinical care. We need to obtain better understanding of their clinical impact as well as the putative side effects. Risk–benefit assessment for use of the drugs, that is, who will benefit most while taking into account who is at most risk of side effects, needs to take place on an individual basis. One might argue that, initially, treatment should only take place in certified centers with sufficient expertise. At the same time, we need to make sure that healthcare remains accessible and sustainable. Clear stop criteria, that is, stopping when all amyloid has been removed or when the drug is not successful in doing so, will be indispensable to keep costs at bay.

Despite the positive news on anti-amyloid treatment, we know that AD is far too complex a disease to be stopped by targeting amyloid only. The drug pipeline is much wider, however, as there are currently 143 drugs being studied in clinical trials, the large majority of which are disease-modifying therapies<sup>17</sup>. Non-amyloid targeting targets include tau, inflammation, synaptic plasticity and many others. Compared to clinical stage interventions, the portfolio of targets for treatment in preclinical studies is even broader, with an increasing focus on targets associated with AD risk genes, including apolipoprotein E (ApoE) and lipids, lysosomal–endosomal targets and proteostasis<sup>18</sup>. This further illustrates how developments in treatment strategies also impact the needs in diagnosis, for example, that genetic workup will have a role in future diagnosis, as a starting point to identify suitable treatment strategies.

## Lifestyle interventions

It is estimated that up to 40% of dementia risk is attributable to 12 modifiable risk factors<sup>19</sup>. Risk factors vary across the lifespan, for example, from less education in early life, hypertension and obesity in midlife and social isolation, depression and physical inactivity in later life. It is not clear whether they relate to AD pathology specifically or rather to all-cause dementia. Neither is it entirely clear whether all 12 factors indeed constitute risk factors or whether some of them (for example, depression and social isolation) are in fact early features of disease. Nonetheless, these modifiable factors offer attractive targets for intervention.

Several large population-based cohort studies indicate that prevalence of all-cause dementia is increasing less than expected, and age-specific incidence is even declining in the Western world<sup>20,21</sup>. A recent post-mortem study showed a decline in vascular pathology but not in pathological AD diagnosis over a period of 25 years<sup>22</sup>. This suggests that, even in those with AD pathology, lifestyle-targeting interventions may help to prevent clinical manifestation of disease. The increasing number of studies examining modifiable risk factors has created momentum for developing intervention strategies to maintain cognitive health and ultimately prevent dementia. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study took as a starting point not one single modifiable risk factor but rather a multi-domain approach and showed somewhat improved cognitive functioning<sup>23</sup>. These findings are now being replicated through multiple studies testing similar intervention strategies in diverse populations and settings. This collaborative action of the World-Wide FINGERS Network is an example of how international and national collaboration drives strengthening evidence and moving the field forward<sup>24</sup>.

It is yet unknown whether lifestyle interventions still delay cognitive decline when AD pathology has started to accumulate, although there is some evidence suggesting that this may be the case<sup>25,26</sup>.

Therefore, there is a need to better understand the value of lifestyle improvements in people that worry about their memory or have MCI. The beneficial effect of lifestyle interventions may be attributable to improving resilience against pathological processes<sup>27</sup>. Resilience encompasses cognitive reserve, or adaptability of cognitive processes to pathology, brain maintenance, referring to reduced accrual of pathology over time, and brain reserve, directly related to the individual's structural characteristics of the brain. To what extent these concepts are specific to AD pathology or rather generic to any type of brain pathology remains to be discovered.

There are several challenges in the translation of multicomponent lifestyle interventions into practice. We need to improve the evidence base on potential modifiable risk factors in the clinical context to set realistic expectations. In addition, one of the major challenges is to reach under-represented groups that have, for example, an ethnic or cultural minority status, low socioeconomic status or low levels of education<sup>28</sup>. Tailoring lifestyle interventions in practice to the knowledge, needs and preferences of these under-represented high-risk groups is essential. Secondly, communicating about dementia prevention comes with important ethical challenges, for example, to avoid 'blaming the victim'. Strategies based on fear and stigma, such as those used in anti-smoking campaigns, should be avoided to not increase the stigma that dementia already has for people currently living with dementia<sup>28</sup>. In addition, implementing multicomponent lifestyle interventions in practice is complex and requires collaborative capacity to take collective action on a societal level. Preventive action for a disease that mostly occurs in late life should already start in midlife. Collaborating with established prevention programs in the public health domain and primary care setting, for example, by teaming up with cardiovascular disease prevention, could facilitate this.

### Public participant involvement and recruitment

The dawn of the first effective strategies underlines and increases the need for clinical research in both patients and at-risk groups. Finding enough participants is an important bottleneck to finding effective intervention strategies<sup>29</sup>. Moreover, the lack of diversity in populations participating in clinical trials may be an important explanation of the limited breakthroughs in intervention strategies that are translated into clinical practice, given the disparities in disease risk and burden in some communities. Therefore, it is essential that clinical trials enroll diverse populations<sup>30</sup>. Remote strategies may facilitate the recruitment of diverse populations<sup>31</sup>.

Online platforms such as Brain Health Registry, Join Dementia Research or <https://Hersenonderzoek.nl> can help to involve citizens and patients to accelerate research<sup>32–34</sup>. In addition to providing more effective recruitment and making it easier to reach diverse populations, these platforms actively engage individuals with research, which ultimately leads to better treatment and care. Taking public and patient views into account from the start of the project will also lead to better translation of findings to clinical practice. The online platform to support communication in diagnosis (<https://www.adappt.health>) is an example, in which we combined rigorous statistical modeling based on biomarkers with a process of co-creation to determine how these models should be translated into clinical practice<sup>35</sup>. More recently, the response to coronavirus disease 2019 (COVID-19) has shown that research can be a major part of management for a large number of patients and leads to constant updating of best practices.

In the Netherlands, we recently initiated the ABOARD (short for 'a personalized medicine approach for AD') cohort, a societal initiative aiming for large-scale engagement of citizens and patients with research (Box 1). The ABOARD cohort takes a direct-to-participant recruitment strategy, putting research participants themselves in an active position. This is further reinforced by the installment of a participant panel that ensures active involvement of the end users. Recruitment is supported by a Facebook campaign from Alzheimer

## BOX 1

### Dutch ABOARD project

ABOARD is a nationwide, public–private project that aims to prepare for a future in which Alzheimer's disease (AD) is stopped before the onset of dementia. This is realized by improving timely and accurate diagnosis, developing individualized risk profiles and initiating nationwide data collection with a focus on patient-reported outcomes and a focus on prevention strategies by creating awareness around dementia and brain health. In addition, readiness of the Dutch healthcare system for disease-modifying treatment is evaluated.

ABOARD takes as a starting point the fact that AD develops over a period of over 20 years. ABOARD therefore focuses on the stages before onset of dementia, working toward prevention. In addition, AD is highly heterogeneous, both in underlying biology and specific pathways involved and in needs and preferences of patients and their care partners. The wishes and needs of patients should be the starting point of care, and ABOARD develops tool and etools to support patient-orchestrated care. Realizing that one size does not fit all, ABOARD envisions a future with individualized prevention encompassing tailored combinations of lifestyle and disease-modifying interventions.

The ABOARD project includes the recently initiated ABOARD cohort, a nationwide initiative to involve in research a large number of Dutch citizens with or at risk of AD. Based on the collection of patient-reported outcomes and consent to link to existing data, we create an infrastructure to study the entire AD disease trajectory, allowing extrapolation of prediction models beyond the initial research population and fostering collaboration between research projects. An active participant panel guarantees that participants are actively involved in choices regarding setup and execution of the project.

In the ABOARD project, over 30 partners representing the entire translational value chain work together. Partners include the five Dutch Alzheimer centers, Alzheimer Nederland and partners from academic and applied research, healthcare, private, semi-private and public organizations, all dedicated to achieving personalized medicine for AD. More information on this 5-year project (2021–2026), including an overview of partners, can be found on the website at <https://www.aboard-project.nl>.

Nederland (the Dutch Alzheimer society). In this way, the ABOARD cohort achieves large-scale engagement of citizens; it provides data to study trajectories of disease in a real-life, national sample. And finally, it lays the foundation for national rollout of future studies.

### Translation to clinical practice

There are a number of prerequisites for translation of effective preventive strategies, whether lifestyle or pharmacological interventions, into clinical practice. First, an accurate, etiological diagnosis is essential to start treatment. Second, when diagnoses need to be made before the stage of dementia to allow preventive action, adequate information on prediction and prognosis becomes highly relevant. A citizen wants to know what to expect, to prepare for what is ahead and to make balanced decisions with regard to potential risks and benefits of proposed preventive strategies. Finally, this illustrates that we need to empower the public and patients to be more actively engaged in the management of their own health and disease. When we think of a future with a broader array of potential preventive strategies, the associated risks

and benefits of which may differ depending on individuals' characteristics, also taking into account their preferences and needs, it becomes clear that shared decision making should become more common practice in the diagnosis and management of AD.

### Diagnosis

The diagnosis of AD dementia is based on clinical criteria. Patients with cognitive complaints or changes in behavior present to the primary care physician, who performs cognitive tests and initial examinations and can decide to refer the patient to a memory clinic for further diagnostic investigation<sup>20</sup>. Clinical diagnosis relies on careful history taking from the patient and family by a skilled clinician. A cognitive screening test, such as Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA), is useful to obtain a crude indication of cognitive functioning. Patients can be referred to a memory clinic for a more thorough investigation. Standard diagnostic workup includes neuropsychological investigation and inventory of activities of daily living<sup>20</sup>. There is a need for an inclusive approach, ensuring that tests and questionnaires have validity across language and cultural barriers<sup>36</sup>. Imaging and routine laboratory tests serve to rule out other causes of cognitive decline. Diagnosis and management plans are decided by consensus in a multidisciplinary meeting.

In addition to this routine diagnostic practice, there have been tremendous advances in both imaging and fluid-based diagnostic tests providing evidence for underlying AD pathophysiology. This has culminated in the launch of the National Institute on Aging and Alzheimer's Association (NIA-AA) research framework, which provides a biological definition of AD<sup>5</sup> (Box 2). This framework provides syndrome staging of cognitive impairment (subjective cognitive decline, MCI and dementia). It also categorizes AD biomarkers based on the ATN classification (as summarized in Table 1 and Box 2), where A refers to amyloid pathology (cerebrospinal fluid (CSF) amyloid- $\beta$  or amyloid positron emission tomography (PET)), T refers to tau pathology (CSF phosphorylated tau (p-tau)/total tau or tau PET) and N refers to neurodegeneration (CSF neurofilament light chain protein (NfL) or [<sup>18</sup>F] Fluorodeoxyglucose PET (FDG-PET) or magnetic resonance imaging (MRI)). There is ongoing debate about the ATN framework, which is currently being revised, as it does not capture the full complexity of AD-related pathophysiology. For example, synaptic loss and inflammation, also part of AD pathophysiology, are not accounted for. Moreover, the clinical syndrome in most patients results from mixed pathologies, for example, with co-occurring cerebrovascular disease,  $\alpha$ -synucleinopathy or TAR DNA-binding protein 43 (TDP-43). The NIA-AA research framework does not account for mixed pathology. Nor do any other sets of diagnostic criteria, for that matter. There is an urgent need for criteria and guidelines for diagnosing mixed types of pathologies, particularly when we are moving toward a future with disease-modifying treatment.

Currently, a diagnosis is the starting point for initiating appropriate care and symptomatic treatment. In a future with personalized medicine, the choice of disease-modifying strategy is directly related to the presence of a specific type of pathology. This highlights a need for molecular diagnosis.

### Molecular biomarkers

A key to delaying the onset of dementia is an early and timely detection of AD-associated pathophysiological processes. The different AD-associated pathophysiological processes, namely, amyloid and tau pathology as well as neurodegeneration, can be identified using different biomarker modalities (as summarized in Table 1). Each modality of testing presents with advantages as well as limitations in capturing the spatiotemporal progression of AD pathology with a degree of affordability, accessibility and scalability<sup>37</sup>. For example, while structural MRI provides high spatial resolution and simultaneous presentation of information on multiple pathologies (for example, cerebrovascular pathology), it is not specific for the AD pathophysiological processes.

## BOX 2

### Diagnostic framework based on NIA-AA

The diagnostic framework according to NIA-AA specifies both syndrome staging of cognitive impairment and biomarker categories to define AD<sup>5</sup>.

#### Syndrome staging of cognitive impairment

##### Dementia

- Substantial cognitive impairment affecting several cognitive and/or behavioral domains.
- Progressive in nature; becomes worse over time.
- Evident functional impact on daily life. No longer fully independent. May be further characterized as mild, moderate and severe.

##### Mild cognitive impairment

- Cognitive performance below expected range (can be primarily amnesic or non-amnesic).
- Decline in cognitive performance as compared to before.
- Performs daily life activities independently, although there may be mild functional impact.

##### Subjective cognitive decline<sup>86</sup>

- Worries about cognitive performance.
- Cognitive performance within the expected range.

Note that the NIA-AA framework proposes preclinical AD; from a clinical, diagnostic perspective, we mention here subjective cognitive decline because without complaints, there is no reason to seek help.

#### Assessment of Alzheimer's disease is based on biomarker evidence, based on A (amyloid), T (tau) and N (neurodegeneration)

ATN profile	Biomarker category	
A <sup>-</sup> T <sup>-</sup> N <sup>-</sup>	Normal Alzheimer's disease (AD) biomarkers	
A <sup>+</sup> T <sup>-</sup> N <sup>-</sup>	AD pathologic change	AD continuum
A <sup>+</sup> T <sup>+</sup> N <sup>-</sup>	AD and concomitant suspected non-AD pathologic change	
A <sup>+</sup> T <sup>-</sup> N <sup>+</sup>	AD	
A <sup>+</sup> T <sup>+</sup> N <sup>+</sup>	ADAD	
A <sup>-</sup> T <sup>-</sup> N <sup>+</sup>	Non-AD pathologic change	
A <sup>-</sup> T <sup>+</sup> N <sup>-</sup>	Non-AD pathologic change	
A <sup>-</sup> T <sup>-</sup> N <sup>+</sup>	Non-AD pathologic change	

PET tracers allow visualization and quantification of the spatial distribution of amyloid and tau pathology, but they provide information on a single type of pathology (for example, amyloid or tau). Moreover, the costs and infrastructural requirements are high, which limit their utility<sup>38</sup>. CSF-based biomarkers present the opportunity to evaluate multiple markers from one sample, which is scalable and a cost-effective option compared to neuroimaging; however, there is no localization of pathology and the invasive nature of the lumbar puncture is a limitation<sup>39</sup>. More recently, blood-based biomarkers have developed rapidly that provide an opportunity to detect multiple markers that are more affordable, accessible and scalable, compared to all other biomarker modalities, albeit unable to provide information on the localization of pathophysiological processes<sup>40</sup>. Hence, there is potential

**Table 1 | Overview of diagnostic tests that can be used to measure amyloid, tau and neurodegeneration**

	MRI	PET	CSF	Blood
Biomarker	N	A, T, N	A, T, N	A, T, N
Process	<ul style="list-style-type: none"> <li>Atrophy</li> <li>(Vascular pathology)</li> </ul>	<ul style="list-style-type: none"> <li>Amyloid</li> <li>Tau</li> <li>FDG</li> </ul>	<ul style="list-style-type: none"> <li>Amyloid 42</li> <li>Amyloid 42/40</li> <li>Total tau</li> <li>p-tau (for example, p-tau181 and p-tau217)</li> </ul>	<ul style="list-style-type: none"> <li>Amyloid 42/40</li> <li>p-tau (for example, p-tau181 and p-tau217)</li> <li>NfL, GFAP</li> </ul>
Pros	<ul style="list-style-type: none"> <li>High resolution</li> <li>Information on multiple pathologies</li> <li>Widely available</li> </ul>	<ul style="list-style-type: none"> <li>Localization</li> <li>Quantification</li> </ul>	<ul style="list-style-type: none"> <li>Affordable</li> <li>Accessible/ scalable &gt; PET</li> <li>Multiple markers from one draw</li> </ul>	<ul style="list-style-type: none"> <li>Affordable/ available/ scalable &gt; PET, CSF</li> <li>Multiple markers in one drop of blood</li> <li>Repeated measurement</li> </ul>
Cons	<ul style="list-style-type: none"> <li>Not specific for pathology</li> </ul>	<ul style="list-style-type: none"> <li>Expensive</li> <li>Scan for each biomarker</li> <li>Radiotracer</li> <li>Infrastructure requirements</li> </ul>	<ul style="list-style-type: none"> <li>No localization</li> <li>Invasive (lumbar puncture)</li> </ul>	<ul style="list-style-type: none"> <li>Further from brain</li> <li>Additional validation ongoing</li> <li>Not yet available for clinical use</li> </ul>

Overview of different modalities and tests that can be used to measure Alzheimer's pathophysiology. Each modality of testing has its own pros and cons. GFAP, glial fibrillary acidic protein.

for blood-based biomarkers in the future as a biomarker modality for screening and monitoring the disease and treatment response<sup>41</sup>. Despite being highly promising, blood-based biomarkers are not ready for use in a clinical setting. Challenges in translating blood-based biomarkers to clinical practice include identifying the most promising biomarkers (and combinations thereof) and effective measurement platforms, prospective validation in real-life populations, in vitro diagnostic assay development and activities to obtain regulatory approval and refunding<sup>40</sup>. While validation studies are still ongoing, a first step toward implementation is the recent definition of appropriate use recommendations<sup>42</sup>.

Future developments in molecular diagnosis also contribute to further refinement of the diagnosis. AD is a highly heterogeneous disease, with multiple pathological pathways involved. Refining diagnosis for patient stratification is a next step toward personalized medicine of AD. Patient stratification using CSF-proteomic-based strategies has resulted in subgroups of AD with (1) hyperplasticity, (2) innate immune activation and (3) blood-brain barrier dysfunction<sup>43</sup>. It is likely that, when pathways from initial brain changes to late-stage dementia vary between individuals, this variability affects treatment response and/or risk of side effects.

In addition, knowledge on the genetic determinants of AD is quickly increasing. To date, >80 risk and protective genes for AD have been identified, most with only very small effect sizes when evaluated on their own<sup>44</sup>. The *APOE* gene is the most important risk gene for AD. Other risk variants, for example, *TREM2* and *SORL1*, although far less common, also confer strongly increased risks. The effects of all risk genes can be combined in a polygenic risk score. To date, genetics are not part of the routine diagnostic workup and are only performed when the family history is highly suggestive of a mutation. It is conceivable that genomics will be incorporated in the diagnostic workup of the future, however<sup>44-46</sup>. Of note, genetic makeup not only predisposes for an increased risk but can also explain reduced risk or resilience<sup>47-49</sup>. In a

future with personalized medicine, certain genetic variants may predict treatment response for pharmaceutical strategies, both in terms of benefit and risk. As an example, homozygous *APOE* ε4 carriers have a strongly increased risk of severe side effects of anti-amyloid treatment, while the observed benefit may be less<sup>15</sup>. Finally, genetic variants that reveal specific pathways to be involved, such as *TREM2* or *SORL1*, may be the starting point of targeted therapeutic solutions<sup>50-52</sup>.

These developments show that we are making the transition to a biomarker-based diagnosis of AD. In the future, this may further develop to (1) a biomarker-based diagnostic fingerprint of different pathophysiological processes (mixed pathology) and (2) a more fine-grained diagnosis of AD, doing justice to the heterogeneity of the disease beyond the common ground of abnormal amyloid and tau. Detection of AD pathology across the spectrum (preclinical AD to dementia) provides a window of opportunity for therapeutic intervention to delay or even prevent the onset of AD dementia.

### Digital tools

In addition to the swift developments in molecular diagnosis, careful characterization of the patient in terms of their clinical, cognitive and behavioral functioning remains key. In this context, digital biomarkers are very promising<sup>53,54</sup>.

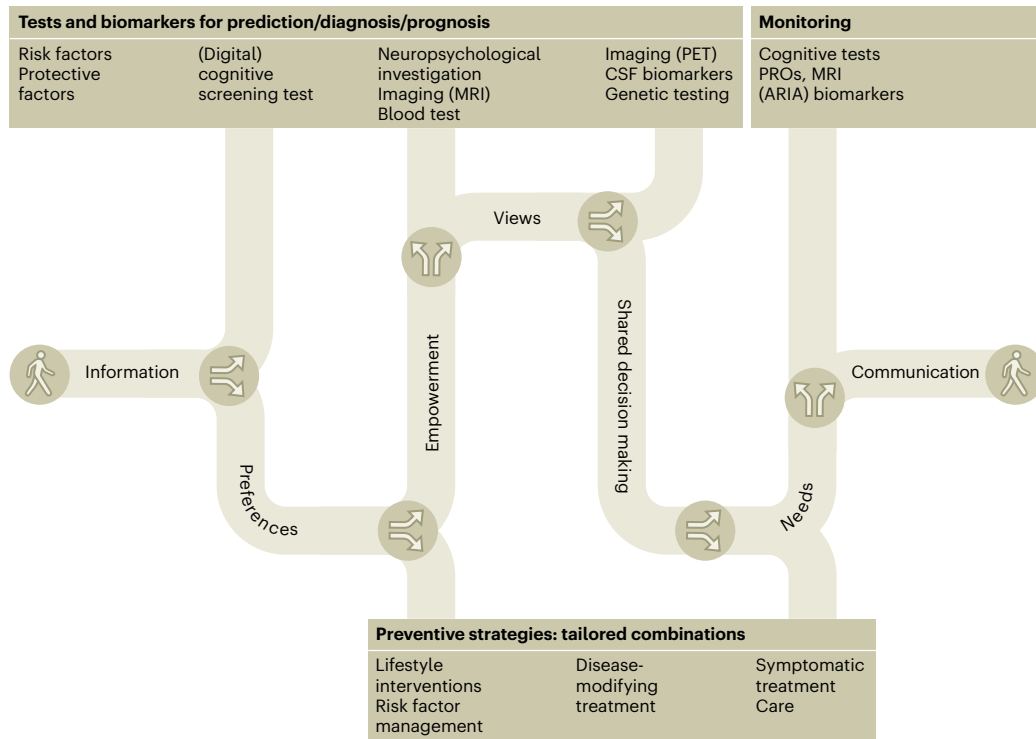
Digital tools include online cognitive tests and questionnaires that resemble their paper-and-pencil equivalents<sup>55,56</sup>. Digital tests and questionnaires have the advantage of increased reliability and potentially increased sensitivity, as they allow extraction of many more data points than paper-and-pencil administration of a similar test. They could be cost saving, as they require less-skilled staff to administer. Computer-adapted testing versions of these tests shorten the administration time. In this way, they help to make the patient journey more patient friendly. Online cognitive tests also provide the possibility for the same set of tests and questionnaires to be provided at home, at the primary care setting and at the more specialized setting. By harmonizing the patient journey in this way, monitoring the disease and tracking progression becomes easier.

In addition, increased digitalization of society and improved data-analysis methods (for example, with use of artificial intelligence) open up innovative opportunities for digital biomarkers that can be obtained from, for example, wearables or voice recording<sup>57-59</sup>. These tests could be performed remotely at home, and they have ecological validity, as they test actual behavior in the home situation. Digital biomarkers could serve as a self-test to funnel to additional medical care, to monitor disease progression remotely as part of the follow-up visits after diagnosis and to monitor treatment response, potentially even increasing adherence to the program.

A European survey among professionals, patients and family members showed that a considerable majority had a positive attitude toward digital tools<sup>60</sup>. User friendliness and improved accuracy are main factors stimulating the adoption of a tool. Inadequate integration with electronic patient records and fear of losing important clinical information were most frequently indicated as barriers. Many patients and care partners showed interest in the possibility of using the tools themselves. Nonetheless, digital tools are still not used frequently in clinical practice. In addition to scaling practical hurdles and barriers, this also shows an urgent need for education of professionals and empowerment of patients and care partners. Use and development of digital tools has increased considerably during the COVID-19 pandemic, when testing remotely was a necessity when patients could not be seen in the clinic<sup>61</sup>. Finally, digital testing may contribute to making healthcare accessible also to low-literacy populations, particularly when cognitive testing is integrated in their daily lives, for example, by analyzing changes in use of their mobile devices or speech<sup>31</sup>.

### The future diagnostic workup

The future diagnostic workup has a stepped or funneled approach, needed to keep healthcare accessible to an increasing number of



**Fig. 1 | Patient journey of the future.** We are making the transition from a patient journey focused on diagnosis and post-dementia care to a patient journey in which diagnostic biomarkers increasingly serve the purpose of prediction and monitoring, and (preventive) treatment. Throughout the patient journey, information provision, when possible supported by e-tools, is key. This should entail information about what can be expected from the patient journey itself and information about the disease. In addition, there should be information about available options for diagnosis, prediction and prevention before embarking on testing or treatment, and information about what the results of specific tests mean for the individual lives of patients after testing and treatment. A prominent role for shared decision making promotes diagnosis and treatment to be more strongly aligned with the preferences, needs and wishes of patients and their families. The patient journey encompasses different settings (at home, primary care, secondary care and tertiary care) and may vary depending

on disease stage (cognitively normal, mild cognitive impairment, dementia). Memory clinics mainly have a role for symptomatic patients, while Brain Health Services are an emerging concept that may be closer to primary care and may cater to cognitively normal citizens<sup>84</sup>. In the future patient journey, the themes of prediction, identifying the optimal preventive strategy, monitoring disease progression (including side effects) and evaluating treatment response become increasingly relevant. Diagnosis has a more funneled approach. Individualized risk profiles can be based on different types of determinants, depending on an individual's disease characteristics and preferences. Treatment strategies have a stronger focus on prevention, encompassing both targeting of lifestyle (primary prevention), disease-modifying treatment (secondary prevention), symptomatic treatment (which could be referred to as tertiary prevention) and care. ARIA, amyloid-related imaging abnormalities; PRO, patient-reported outcome.

patients. The specific diagnostic strategy could vary, depending on patients' preferences and needs regarding diagnosis, prediction and prevention (Fig. 1). For example, one patient may want to know as much as possible about their genetic makeup and biomarker results to optimally prepare for the future, enroll in clinical trials or know their eligibility for disease-modifying treatment. For another patient, it may suffice to know that, at this time, cognitive impairment and daily functioning are still sufficiently intact and that they do not qualify for a syndrome diagnosis of dementia.

Initial testing should involve easily accessible and scalable tools that allow reliable ruling out of AD when negative, preventing the need for further expensive testing. Current testing in primary care mostly entails risk factor assessment, with medical history and a cognitive screening test. In the future, digital biomarkers in combination with blood tests could further improve this process. The initial tests can be used for more effective referral to specialist memory clinics for further, in depth diagnostic testing, for example, with more invasive or expensive tools such as MRI, CSF biomarkers or PET scans. In addition, memory clinics can provide further refinement of diagnosis, for example, based on proteomics or genomics. Finally, we foresee that computer-based tools, for example, making use of artificial intelligence solutions, will enable clinicians to extract maximum information from the available diagnostic test results. This will reduce practice variation

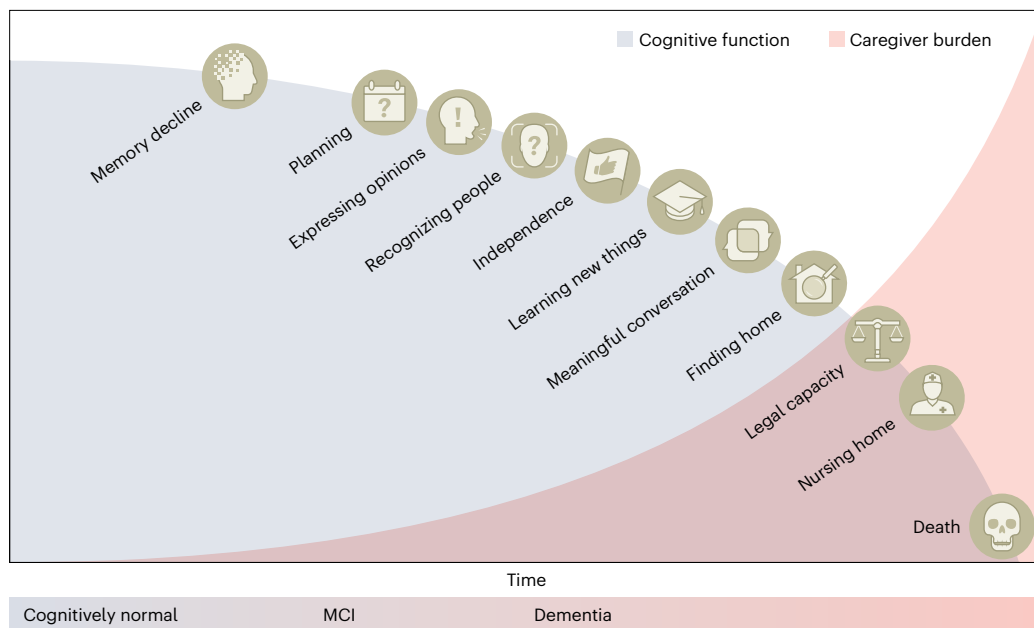
and improve accuracy but also deliver answers in an understandable way to both the professional and the patient. Timely and precise diagnosis will lead to a reduction in patient burden, costs and length of the diagnostic process and reduce the healthcare burden and costs in specialist settings (which are, by definition, more expensive).

### Prediction

A diagnosis is not the end point, but rather the beginning of the rest of the disease trajectory. Given that AD is a progressive disorder, patients want to know what they can expect<sup>62,63</sup>. Available prediction models are mostly based on community-based studies (cardiovascular risk factors and lifestyle) or selected research populations (biomarker based). The former have relevance for the general population or general practitioner setting and often refer to lifetime risk of dementia<sup>64–66</sup>, while the latter pertain to a tertiary memory clinic setting and short-term risk<sup>67,68</sup>. Prediction models should be clear about the time frame for which they make predictions.

### Biomarker-based prognosis

With the use of biomarkers, prediction of dementia has become more accurate, particularly in the MCI stage, providing a view on a future with individualized risk predictions<sup>67,68</sup>. Prediction models in the stage of cognitively normal are less generalizable and, for that reason, more



**Fig. 2 | Disease trajectory with meaningful outcomes.** Alzheimer’s disease (AD) includes the clinical stages of preclinical AD (including subjective cognitive decline), MCI and mild, moderate and severe dementia. Most prediction studies take cognitively normal individuals or patients with MCI as the starting point and predict progression to dementia. Yet, onset of dementia is in fact rather an arbitrary moment in a disease trajectory that takes decades to unfold. In a former

study, we identified 13 outcomes that matter to patients and care partners, which may occur somewhere in the course of the disease<sup>71</sup>. Together, these meaningful outcome define the clinical trajectory of AD. To cater to the need of prognostic information for patients and their families, future studies should focus on prediction of these outcomes that matter.

difficult to translate to the individual level. Nonetheless, cognitively normal individuals who are positive for both amyloid and tau based on PET (hence, A<sup>+</sup>T<sup>+</sup>) have a 50% probability to progress to a symptomatic stage in the short term, while progression rates are very low when A and T are not both positive. These data emphasize that biomarkers hold important prognostic information<sup>69,70</sup>.

**Prediction of outcomes that matter**

When we diagnose AD before the stage of dementia, a diagnosis in fact becomes a prognosis, as patients and their families are worried about the detrimental clinical outcome, rather than the molecular nature of the disease. Most modeling efforts predict the outcome of dementia. In a disease trajectory that takes decades to unfold, onset dementia will not be the key reference to commencing treatment anymore, as the recently approved medications can be prescribed to patients with MCI and mild dementia. In addition, with respect to prognosis, other outcomes may have even more relevance from the perspective of patients and their families. In an effort to identify patient-relevant outcomes, we asked patients and caregivers which outcomes a hypothetical future medicine should prevent<sup>71</sup>. The core list of prognostic information relevant to both patients and care partners included items mostly related to cognitive decline, dependency and physical health (Fig. 2). This information should guide modeling efforts and trial design.

**Prediction in different settings**

Much work still needs to be accomplished: (1) risk models should be applicable in primary, secondary and tertiary care and be generalizable beyond research settings to the ‘typical patient’, (2) findings should be interpretable at the individual level, and (3) outcomes should reflect what really matters to patients. Development of generalizable, flexible and patient-relevant prediction models is essential to provide tailored prognostic information. Ultimately, individualized risk predictions will identify which individuals benefit most from which preventive strategies.

**Patient-orchestrated care**

With the number of options in diagnosis, prediction and prevention of AD rapidly increasing, it becomes ever more important to take the preferences, wishes and needs of patients and their families as a starting point for providing care. Patients and their families being actively involved in the management of their own health and disease can contribute to keeping healthcare affordable and sustainable.

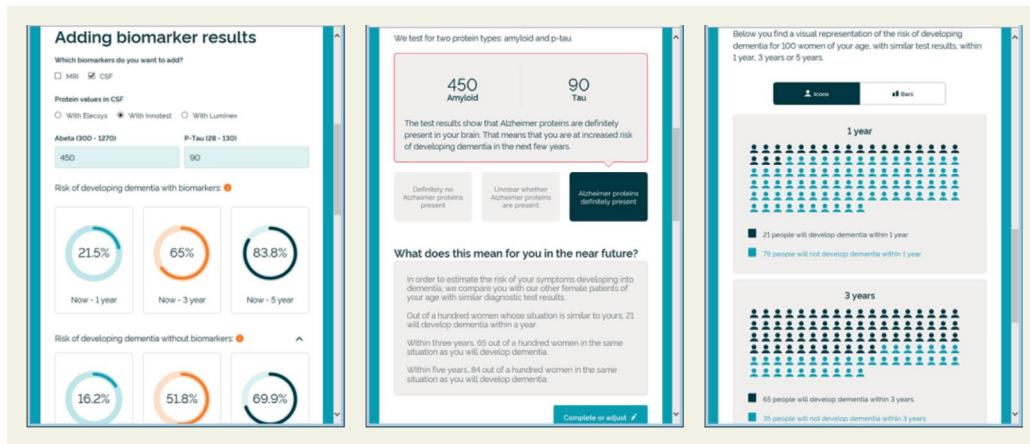
**Ethical aspects**

Now that it becomes possible to diagnose AD before onset of dementia, a next question is whether it is ethical to make such a diagnosis or inform individuals about their biomarker status or future risk of dementia<sup>72</sup>. Such knowledge may cause distress, as an exact prognosis cannot be provided and there is currently no curative treatment. Yet, is it ethical to withhold available information about AD risk when a person asks for it? The uncertainty of not knowing the cause of memory problems may be equally burdensome. Moreover, a diagnosis may provide an opportunity for preventive action to delay the start of dementia, help individuals and care partners to prepare for the future and allow participation in dementia-prevention trials. Of note, we only refer here to patients seeking help for their perceived problems at primary care or a memory clinic (that is, MCI or subjective cognitive decline). There is no reason to think that, at short notice, a widespread screening program in the general community would be useful. Nonetheless, individuals vary in their personal considerations regarding diagnosis, prediction and prevention of AD, and the question is how we can best accommodate these differences.

**Shared decision making**

Empirical evidence on the implications of a pre-dementia diagnosis for the well-being of individuals is largely lacking, whereas such information can inform organization of the patient journey. Nevertheless, the weighing of the pros and cons of an early diagnosis and the decision of whether to initiate testing or not that follows from such deliberation





**Fig. 3 | Example of a patient communication sheet.** Screenshots of <https://ADappt.health>. Communication about risk and probability is challenging, because this information is hard to understand for patients and their families and difficult to explain for professionals. Yet, we can learn from other research fields such as oncology or cardiovascular disease, where there is substantial information about best-practice risk communication<sup>85</sup>. Here we provide an

example of the communication sheet at <https://ADappt.health>, which facilitates communication about the risk of dementia for patients with mild cognitive impairment, including use of natural numbers, graphical representation of risk, neutral framing and plain language<sup>35</sup>. It is recommended to provide patients with written information about their diagnosis and prognosis<sup>79</sup>. The communication sheet can therefore be printed for the patient to take home.

ultimately remains a highly individual process. Patients should be facilitated to articulate their voice in this decision as part of a shared decision-making process. Shared decision making refers to clinicians and patients (and/or their care partners) working together to decide which care plan best fits individual patients and their lives, given that there is more than one reasonable option<sup>73</sup>. To facilitate a process of shared decision making, we need to provide the public and patients with information to be able to make informed decisions. This information should include but not be limited to terminology (difference between AD and dementia), the advantages and disadvantages of existing diagnostic tests, possibility of misdiagnosis and mixed pathology, difficulty in personalized prognostication and risks and benefits associated with different treatment strategies.

### Tailoring information to promote an inclusive approach

Some individuals run the risk of being less informed and less involved in decision making than others as a result of diversity in cultural background, health and e-health literacy, and/or educational attainment. Special attention is warranted for the needs and preferences of these more vulnerable individuals to ensure that their perspective is also taken into account in the organization of care. Heterogeneity in needs and preferences regarding information and participation in decision making also result from individual differences in psychological characteristics such as coping style or tolerance for uncertainty as well as, for example, living situation<sup>62</sup>. All of this requires that care is tailored to individual patients' needs and preferences. Such tailoring is easier if patients (and their care partners) are in the lead. In former studies, we found that patients and their families hardly ask for additional information during diagnostic consultations, while afterward many still report a need for information<sup>74</sup>. To foster information provision, we developed a topic list and animation videos (<https://www.adappt.health>) that empower patients by informing them what to expect at the memory clinic and inviting them to think about the questions that they would like to ask<sup>63</sup>.

### Communication

Customization also necessitates optimal communication between care providers and patients. Given the current lack of curative treatment and uncertainty of outcomes of early diagnostic testing, clinicians are reluctant to provide risk information, arguing that this would burden patients<sup>75</sup>. By stark contrast, many patients and care partners explicitly

prefer to receive this probabilistic information, as it can help them prepare for the future<sup>63,76</sup>. To make well-informed choices, patients and care partners need to be able to understand and recall diagnostic and prognostic information in a way that allows them to make decisions and engage in preventive action that is in line with their needs and values. Hence best-practice recommendations are urgently needed to disclose results of new diagnostic tests, including the risk of dementia<sup>77-80</sup>. Such communication between healthcare professionals and patients can be supported by digital tools (see Fig. 3 for example). Online tools may help clinicians to provide information in an individualized and understandable way, thereby improving information retention and empowering patients<sup>35,81-83</sup>. Successful implementation of such tools in clinical practice calls for a co-creation process involving professionals as well as patients and care partners, considering diversity in needs, preferences and abilities.

### Concluding remarks

AD, being the major cause of dementia, is one of the largest healthcare challenges of our century. As such, AD is a major concern for us all, either as individuals living with or at risk of the disease, their family members and caregivers or professionals who encounter individuals with dementia in clinical practice and care. The sheer size of the population facing AD, the trend toward more active involvement of patients, families and citizens in the management of their own health and disease, in combination with the swift scientific progress in diagnosis, prediction and prevention, results in momentum for the field. We see the first AD disease-modifying treatments at the horizon, illustrating that we are swiftly moving toward a new era. Moreover, insight in the putative effect of lifestyle interventions is increasing, providing implications for actionability.

The next step is understanding how we can move toward a future of personalized medicine for AD, a future that will include not only technical and neuroscientific innovations but also has to find answers to ethical dilemmas, socioeconomic consequences and personal considerations, a dialog that we must embrace as a society. In this dialog, countries can learn from each other. Nonetheless, healthcare is largely organized by country; hence, it is essential to also conduct the dialog by country, involving all relevant stakeholders. In the Netherlands, we initiated the ABOARD project to provide a platform for this cross-sectoral dialog and to take the necessary preparatory steps for a future with personalized medicine (Box 1).

The imminent changes that convert AD into a treatable disease profoundly impact the entire patient journey. We need to address questions such as how to keep healthcare accessible and how to ensure scalability of new solutions for diagnosis, prediction and prevention. Figure 1 provides an outline of the patient journey of the future. Dementia risk assessment and easily accessible monitoring of cognitive function may already start at home, when citizens increasingly want to know what they can do themselves. When signs and symptoms warrant a physician visit, there will be a funneled approach toward accurate and molecular diagnosis, which is the starting point of tailored prevention strategies. This comes with additional challenges, such as how to monitor side effects, how to ensure equal access to care, how to evaluate treatment response and, particularly, how to identify those individuals who would benefit most from which intervention. Throughout the patient journey, adequate and easily digestible information is crucial. Educating professionals to optimally navigate their patients through this journey and to support a process of shared decision making is a necessary prerequisite. Finally, providing information to patients and their families about what to expect from the patient journey in terms of diagnostic tests, information about the disease and disease trajectory, and information about different types of prevention strategies is crucial to work toward patient-orchestrated care.

To see this future come to fruition, we need to invest in research in precise and molecular diagnosis and personalized risk profiles providing information on a person's likely trajectory of disease, which together form the basis for the selection of preventive strategies. To facilitate this, integrating shared decision making throughout the patient journey is crucial, and tools to support both patients and their families and professionals to effectively engage in such a process are clearly needed.

In conclusion, we provide an outlook on a future with personalized medicine for AD, in which patients and care partners are empowered and more actively engaged in the management of their health and disease and in which tailored combinations of lifestyle interventions and disease-modifying treatment are provided in a timely fashion to target AD pathology to prevent or delay the onset of dementia.

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## Author contributions

M.E.d.v. and M.B. drafted the section on prevention; C.E.T. drafted the section on diagnosis; E.M.A.S. drafted the section on patient-orchestrated care; W.M.v.d.F. drafted the remaining sections and critically revised the overall manuscript.

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