A large green rectangular area with several white five-pointed stars scattered across it, serving as a background for the title text.

# Discussion paper on ethical issues linked to the changing definitions/use of terms related to Alzheimer's disease





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## Foreword



It is a great pleasure for me to present this discussion paper on the ethical issues linked to the changing definitions of Alzheimer's disease (AD). The definitions and the changing use of existing terms, which are the focus of this paper, have developed over

several years as a result of biomedical research carried out by renowned researchers and clinicians in the field of AD. Such research is ongoing and it is likely that there will be further developments and adaptations to the terms which have been introduced in recent years. I am hopeful that the knowledge gained will lead to advancements in the treatment, care and support of people with AD, and even, eventually, to delaying or preventing the onset of AD dementia.

As Chair of Alzheimer Europe and as a geriatrician and researcher, I think it is important that we already start to reflect on the possible ethical implications of the changing definitions of AD. Everyone risks developing AD at some point in their life and as a caring, responsible society, it is important that we are all aware of the possible ethical implications of the changing definitions at the level of the individual, communities and wider society. In this

way, we can try to ensure that people affected by AD can continue to enjoy the same rights and opportunities as everyone else and play an equal role in society, that they are equally valued and that they are not subjected to any form of discrimination.

I congratulate the Alzheimer Europe Ethics Working Group on having rendered the new definitions of AD and the accompanying AD model more accessible to people who are not necessarily biomedical researchers or clinicians. This is important if people from all walks of life and from different groups (e.g. policy makers, health and social care professionals, the media and the general public), including people who have or may develop AD, are to be able to reflect together on the possible ethical implications of the new definitions. To conclude, I would like to express my sincere gratitude to the members of Alzheimer Europe's Ethics Working Group, chaired by Dianne Gove (namely, Hilary Doxford, Karine Fauria, Jean Georges, Julian Hughes, Tina Leonard, Anneli Sarvimäki, Mark Schweda, Sarah Smith, Hinesh Topiwala and Guy Widdershoven), for contributing their expertise and for their extensive work, which made this discussion paper possible.

Iva Holmerová  
Chair of Alzheimer Europe

“ Everyone risks developing AD at some point in their life and as a caring, responsible society, it is important that we are all aware of the possible ethical implications of the changing definitions at the level of the individual, communities and wider society. ”

## Preface

This discussion paper has been prepared by a multi-disciplinary group of experts in the field of ethics, the experience of dementia, ageing, psychiatry, psychology, dementia research and policy. This group was set up by Alzheimer Europe to respond to growing concerns about the ethical implications linked to the changing definitions/use of terms related to Alzheimer's disease with regard to individuals, families, informal carers, health/social care professionals, researchers, the media and policy makers. We would like to express our utmost gratitude to the following members of this group for having generously shared their expertise and invested their time and energy during 2016 to make this publication possible (further details about the experts can be found in Appendix 1):

- **Ms Hilary Doxford**, Vice Chair of the European Working Group of People with Dementia, United Kingdom
- **Dr Karine Fauria**, Barcelonaβeta Brain Research Center, Spain
- **Mr Jean Georges**, Alzheimer Europe, Luxembourg
- **Dr Dianne Gove**, Alzheimer Europe, Luxembourg
- **Prof. Julian Hughes**, University of Bristol, United Kingdom
- **Ms Tina Leonard**, Alzheimer's Society of Ireland
- **Dr Anneli Sarvimäki**, The Age Institute, Finland
- **Dr Mark Schweda**, University Medical Center Göttingen, Germany
- **Dr Sarah Smith**, School of Dementia Studies, Bradford University, United Kingdom
- **Dr Hinesh Topiwala**, Centre for Dementia Prevention, University of Edinburgh, United Kingdom
- **Prof. Guy Widdershoven**, VU University Medical Center, Amsterdam, the Netherlands

# 1. Introduction

Ethics aims to reflect and deliberate on the basic conditions of leading a good life and on responsibilities towards other people: How can we achieve individual and collective wellbeing and flourishing, also under conditions of impairment, disease and disability? How can we ensure that others, especially vulnerable people, are treated well and are respected and supported in living a meaningful life? This is especially relevant in healthcare, as people in need of care are particularly vulnerable. That is why they have rights and are protected by the law. However, laws alone do not guarantee that people in the area of healthcare are adequately supported and treated fairly. Ethical reflection is needed to gain insight into the consequences of (changing) definitions of disease on being diagnosed and offered treatment or care. If a person is diagnosed with a disease, this may enable him/her to receive proper attention by professional caregivers and other people, which may support him/her in living life in a meaningful way. Being diagnosed with Alzheimer's disease (AD) may make one's forgetfulness and other possible symptoms understandable and provide a basis for adapting to the situation. However, a diagnosis may also lead to a person being perceived as different from others (as of course can also happen with diagnoses of other medical conditions) and hinder his/her participation in normal life (e.g. perhaps resulting in driving restrictions, which may or may not be justifiable in individual cases, or discrimination in the workplace or with regard to various insurances). Such possible consequences call for ethical reflection and deliberation.

This paper starts with a brief explanation of the recent changes in terminology surrounding Alzheimer's disease (AD) and AD dementia. This is followed by an exploration of the concepts of health and disease and a call for a critical reflection about terms related to AD in view of their ethical implications and consequences. We then reflect on the possible ethical implications of these changing definitions on the individual and on his/her life and relationships with others. This leads on to a discussion about the potential impact of the changing definitions on diagnosis, treatment and health/social care in terms of needs and provision, followed by a discussion about the ethical implications of the new definitions in the context of research. Finally, we focus on broader societal issues such as citizenship and equal value/opportunities in society and possible implications for politics and policies, as well as for the media and public awareness.

Some degree of detail is necessary to enable readers to understand the concepts we are discussing, the context in which they were developed and the ethical issues we would like to raise. Nevertheless, we have tried to limit the use of scientific jargon to help ensure the accessibility of the document to a broad audience. We have also included a glossary (see section 8) containing straightforward explanations of some of the scientific terms (those highlighted in bold), which may be unfamiliar to some readers.

“ Laws alone do not guarantee that people in the area of healthcare are adequately supported and treated fairly. Ethical reflection is needed to gain insight into the consequences of (changing) definitions of disease. ”

## 2. The new AD definitions and the ethical implications of the way we represent health and disease

### The new and changing definition of Alzheimer's disease

In 1906, Dr Alois Alzheimer first described the symptoms and the **amyloid plaques** and **neurofibrillary tangles** in the brain, which have come to be considered as the hallmarks of Alzheimer's disease (AD). Now, more than a hundred years later, the exact causes of AD are still unknown and a cure is not available.

However, significant progress has been made in understanding AD and especially in biomarker research. A biomarker is a biological substance (e.g. a protein that may or may not be detected in a body fluid) or a structure (such as some changes in size in specific parts of the brain) that is considered as a "mark" indicative of a disease. Biomarkers can change, appear or disappear during the development of a particular **pathology**. They can be detected through tests and technologies such as neuroimaging (brain scans) and through the analysis of cerebrospinal fluid (**CSF** – a body fluid found around the brain and spine) and blood.

Signs of abnormal changes in the brain associated with AD can now be detected long before the occurrence of any symptoms of AD dementia. These recent advances are also leading to a radical change in the way that AD is conceptualised (i.e. as a manifestation of the disease which can be observed before the occurrence of any symptoms of dementia). In this first section of the discussion paper, we provide a brief overview of the developments which led to this new way of understanding AD. A more detailed explanation can be found in Appendix 2.

In 1984, the "NINCDS-ADRDA" criteria for AD were proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (McKhann 1984). These criteria permit a probable **clinical diagnosis** of AD that can be confirmed as definite only after the person's death if an autopsy is performed and the plaques and tangles mentioned earlier are observed. These criteria therefore result in a long period of uncertainty because the definite

diagnosis of AD can only be made after a **post mortem** analysis of the person's brain. Furthermore, researchers have shown that these criteria have low accuracy (Hyman & Trojanowski 1997; Beach et al. 2012) and that only 70% of diagnoses were correct, the others being **false positive or false negative cases**.

The last decade of research has been a testimony to changes in the conceptual approach to AD. Two main research groups comprised of world-renowned scientists and clinicians specialised in AD have been developing criteria aiming at improving AD diagnosis and related research. The first is the International Working Group (IWG and IWG2) led by Dubois et al. (2007, 2014 & 2016) and the second is the National Institute on Aging and the Alzheimer's Association (NIA-AA) (see Jack et al., McKhann et al., Albert et al. and Sperling et al., all in 2011). Despite a few differences, both research groups agree that AD should be considered as a continuum. Both groups also agree on the importance of biomarkers in the procedure leading to a potential diagnosis of AD dementia. In order to reach a consensus on the diagnostic criteria and harmonisation of standards for research, IWG and IWG2 developed and recently revised a new consensus lexicon to unify all definitions, stages and processes (Dubois et al. 2010 & 2016). According to this new lexicon, the definition of AD has been extended to encompass the full spectrum of the disease, including both pre-dementia (preclinical and prodromal AD or MCI due to AD) and dementia phases and its diagnosis can be established *in vivo* (in a living person).

The term "AD pathology" is used to refer to the changes in the brain underlying AD, irrespective of the stage or phase (i.e. with or without **dementia**). The following table summarises the different stages/syndromes along the AD continuum (adapted from the lexicon by Dubois et al. 2010 & 2016). The preclinical terminology is currently only proposed for use in the context of research. The other terms are used in the context of diagnosis and research.



**Preclinical state:**

The long asymptomatic stage between the earliest changes underlying AD pathology and the first cognitive symptoms. This has two sub-groups:

- i. The asymptomatic at risk group which includes people with pathological/abnormal changes in their brains, specific to AD but without clinical symptoms of AD
- ii. The pre-symptomatic group which includes people who carry a dominant genetic variant of AD but do not yet have clinical symptoms of AD. This genetic variant is rare and does eventually lead to AD dementia, but accounts for less than 1.5% of AD dementia cases

**Prodromal AD (IWG) or Mild Cognitive Impairment (MCI) due to AD (NIA-AA):**

The early symptomatic, pre-dementia phase of AD. During this phase, clinical symptoms are present but not severe enough to affect activities of daily life and are associated with specific biomarker changes.

**AD dementia:**

The stage of the disease in which cognitive symptoms are severe enough to affect not only memory but also daily life activities.

To facilitate discussion, in this paper, we will refer to the IWG and NIA-AA collectively as “the new AD model” and specify “IWG” or “NIA-AA”, if necessary, to distinguish between the two approaches. AD dementia is the most advanced of three phases described in the new AD continuum model. We will therefore use the term “AD dementia” whenever referring to dementia due to AD. Most of the ethical issues addressed in this report are related to the conceptualisation of AD as a continuum and to the subsequent extension of the term AD to include a preclinical

phase and a pre-dementia phase. The use of the term “AD dementia” in relation to different diagnostic approaches and definitions should therefore not be problematic. We would like to emphasise that our use of the newly developed terms related to AD in this discussion paper is for the purpose of reflecting on potential ethical issues they raise. Our use of the new terms in this document should therefore not be interpreted as an unquestioning acceptance of them or of the AD models on which they are based.

## Representations of health and disease

At first glance, questions regarding concepts of health and disease seem to refer to purely scientific facts. Whether a specific condition is a disease or a particular person is affected by it seems to be just a matter of objective natural, biological or medical states that leave little room for interpretation or even controversy. However, it is important to acknowledge that conceptual representations of disease also have evaluative and normative implications as well as individual and social consequences: they are based on certain value judgments and decisions and affect the ways we perceive and treat ourselves and others (Fulford 1989). Therefore changes in their definition and/or use deserve ethical attention and reflection.

In general, concepts of health and disease are based on theoretical assumptions and definitional decisions that require justification (e.g. the decision to set the cut-off value defining hypertension at around 140/90 rather than 135/90 or

145/95 mmHg). They rely on certain common standards of normality, functioning, wellbeing or human flourishing. Some philosophical theories suggest that these standards of health and disease are ultimately individual or social values and norms. From this perspective, being healthy means having the ability to pursue certain acknowledged vital goals and having a disease accordingly translates into being in an individually undesirable or socially deviant state that calls for corrective measures (Nordenfelt 1995).

Furthermore, assigning the label “disease” also has many far-reaching and morally ambivalent practical consequences. We have specific expectations towards people who are ill and often treat them differently. Having a disease or being ill confers certain moral and legal rights and responsibilities, for example regarding personal behaviour (e.g. we are usually more indulgent and considerate vis-à-vis people with health conditions), working life (e.g. sick

leave, sickness benefits etc.), coverage of healthcare costs (health insurance) or legal liabilities (Parsons 1951). Sometimes, disease labels can also be used to stigmatise people or discriminate against them as in the case of HIV/AIDS or certain psychiatric disorders (Goffman 1963).

The history of Alzheimer's disease (AD) provides an example of changing views with social and moral consequences. When Alois Alzheimer first described the "peculiar disease of the cerebral cortex" that was later named after him, the case he had in mind was an instance of what we now call early onset AD dementia. Consequently, for a long time, AD dementia was by definition a rather rare disease affecting people between 45 and 65. Since the 1970s, however, scientists, politicians and activists have made efforts to eliminate the age criterion. In 1980, AD dementia was included in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III) as a diagnostic category without any age restriction (Ballenger 2006a, 101–112).

When the age criterion for AD dementia was dropped, older people who had previously been vaguely described as "senile" increasingly found themselves confronted with a specific medical diagnosis. This conceptual shift had many consequences. On one hand, it facilitated a general re-evaluation of ageing. Mental deterioration or diminished control were no longer considered signs of an age-associated weakness of character or moral degeneration, or as part of normal ageing. Instead, they were increasingly recognised as symptoms of a distinct medical condition. This was one reason why the elimination of the age criterion was actively supported and applauded by prominent senior advocates. However, replacing senile dementia with AD dementia did not eradicate stigma and age discrimination. "Alzheimer's" became a concept associated with derogative labels like "living death" or "empty shells" (Ballenger 2006b). Moreover, the "medicalisation" of senility (i.e. linking what was previously described as senility to a medical diagnosis of AD dementia) may have increased the tendency to pathologise old age, to neglect the role of psychological and social factors and to prioritise medical research and treatment over care or social support (Bond 1992).

Since conceptual questions regarding health and disease do not just refer to objective scientific facts, but also to certain interpretative and evaluative matters, the current changes in the definition of AD need critical reflection in view of their ethical implications and consequences. This reflection becomes particularly relevant insofar as the newly introduced early stages are not only employed as methodologically useful conceptual constructs in neuroscientific research, but increasingly find their way into clinical practice and diagnostic procedures (Schickel et al. 2014). The fact that there are different evolving terminologies in the United States and in Europe underlines the need for clarification and

standardisation. After all, these terminologies can have different practical and ethical implications, some of them rather far reaching. Thus, taking the NIA-AA terminology literally, a person without any clinical symptoms but an increased risk of developing MCI due to AD or AD dementia (based on having a positive biomarker specifically for AD) actually already counts as having (a "preclinical" stage of) the disease (Sperling et al. 2011, 282).

In general, the definition of earlier stages of AD without any clinical symptoms amounts to a considerable expansion of the concept. It becomes possible to be classified as having AD without showing any symptoms of dementia such as memory loss. This could have serious consequences for the people concerned (e.g. stress, insecurity, worries about insurance, self-stigmatisation and depression). It could also spread stigma to larger groups of the population who now count as diseased, turning them into patients and their whole demeanour into potential psychological and behavioural symptoms. At the same time, however, learning that larger segments of the general population could be affected might also promote a normalisation and thus a de-stigmatisation of AD.

Furthermore, the definition of stages of AD prior to AD dementia seems to be part of a general trend: Health and disease are no longer simply two discrete, mutually exclusive states; they become a matter of graduation, of probabilities, of risk factors that need to be identified, calculated and controlled (Karlawish 2011). This might help reduce the tendency to oversimplify notions of health and disease and thus also alleviate stigma (since there is no clear distinction but rather a continuum between people with and without dementia). However, it could also promote a view in which developing the disease becomes a sign of personal failure (e.g. of a reckless lifestyle or failure to take preventive measures) and people are eventually blamed for having AD, which may in turn increase the likelihood of stigmatisation (Weiner, Perry & Magnusson 1988). In any case, the knowledge that many people might have "silent" AD might lead to increased stigma, with any instance of forgetfulness being perceived as a sign of dementia and suggesting the need for treatment.

Finally, the concept of AD is no longer limited to expert biomedical discourses, but is increasingly being adopted and integrated into public imagination and popular culture, gaining multiple new interpretations, evaluations and functions in a variety of cultural domains (e.g. literature, visual arts, film and the media). Therefore, changing biomedical conceptions of AD are not just a question affecting scientific research or healthcare. They may have great influence on public representations of the condition as well (Swinen & Schweda 2015), hence the importance of involving the public in debates surrounding the changing definitions of AD.

## 3. Personal identity and personhood

In this section of the discussion paper, we will explore the ethical implications of the changing definitions and conceptualisation of AD for personal identity and personhood. We will start at the level of the individual, and then look at relationships with others, which includes a closer look at stigma.

### The individual

Receiving a diagnosis of Alzheimer's disease (AD) is often associated with shock and despair (e.g. Johannessen & Möller 2011) and many older people are afraid of such a diagnosis (Corner & Bond 2004; Kekki & Mankkinen 2016). Why is that? Why doesn't being diagnosed with diabetes or a cardiovascular disease, for example, evoke the same reactions? Perhaps AD is experienced as a threat to personhood and personal identity in a way that diabetes and cardiovascular diseases are not. Diseases involving mental impairment also tend to be more stigmatising than physical illnesses (Kendell 2001, McManus, Stubbings & Martin 2006). As the definitions and use of terms related to AD change, the questions that arise are: What do these changes mean to the person living with AD and to his/her personal identity, and what are the ethical implications of these changes?

AD dementia may be perceived as a threat to personhood, if personhood is conceived in terms of mental capacities such as autonomy and rationality. From a contextual and relational perspective, on the other hand, being a person means having the status of an "embodied agent", an acting person living in a body within a historical and cultural context (Kitwood 1997; Hughes 2001). From this perspective, AD dementia need not be a threat to personhood, even though it typically involves changes related to psychological capacities and identity. On the other hand, this threat to personhood is also a threat to someone's human rights being ignored or abused, through not being empowered to participate, through discrimination, by legal rights not being observed and through a lack of accountability by society and its organisations.

From a psychological perspective, a person's identity is his or her sense of self, of being who he or she is. This sense of being who one is, of "I", stands for continuity in life. Through passing years and changing life situations, I am still "I", the person who hopes, dreams, remembers and acts. Identity is shaped throughout life, mainly though during childhood and youth (Erikson 1997). It is influenced

by genetic dispositions, social relationships and significant life-events. Life experiences and memories of the past are important parts of a person's identity. AD does not necessarily touch upon these aspects of personal identity, as memories of important life-events and relationships in the distant past tend to remain vivid for quite some time. However, the ability to integrate these memories into a whole coherent life story usually decreases. In addition, the loss of the ability to recognise loved ones may also be associated with loss of identity. So-called self-referential thoughts and emotions (i.e. a person's self-concept and feelings about her/himself) are important as well (Zinck 2008). People can be proud or ashamed of themselves, feel guilty or be content with what they have achieved. AD dementia may seriously influence such thoughts and emotions, since not being able to remember things or to retrieve memories may be at odds with a person's self-concept and social role.

Against this backdrop, news about the presence of markers of AD, albeit in the absence of symptoms, may also cause some anxiety, perhaps making the perspective of the future seem gloomy and frightening. What psychological and emotional effect might such news therefore have on me? Well I might withdraw from society, or try to make the most of the healthy life I can still enjoy or perhaps be more practical and make plans for the future. Some people may start thinking of themselves as "sick" and take on the role of a patient even before the disease influences daily life. Others may start to feel that they are no longer capable of taking care of themselves or making decisions about everyday life. One extreme effect is that I might decide that life is not worth living and even consider suicide or euthanasia, where this is legalised (Draper et al. 2010). Opportunities for dialogue with experienced and knowledgeable professionals, combined with ethical procedures for the disclosure of information linked to risk, are needed to help ensure that people do not contemplate such radical measures on the basis of a poor understanding of the information provided, particularly concerning probability, risk and AD dementia.

People often use a range of self-protecting strategies and coping mechanisms to integrate various impairments into their new life situation and deal with challenges linked to those impairments (Steeman et al. 2006; de Boer et al.

2007). How people deal with those challenges, and perhaps also information about risk, depends to a large extent on their social relationships, attitudes within their social environment and society's capacity to deal with diversity.

## Relationships with others and the issue of stigma

The knowledge that a person has AD may trigger a variety of reactions amongst relatives, friends and acquaintances. Those who have known the person with AD for many years are particularly important. They know who s/he is; they share memories and life experiences. Their support is thus crucial to the maintenance of the identity and personhood of the person with AD dementia. However, family and friends often start to distance themselves following the diagnosis of a person with MCI or AD dementia (Werner 2005; Corner and Bond 2006). They may feel uncomfortable in his/her company and not know what to say or how to react, perhaps resulting in them visiting less often or not inviting the person to social events as often as they did in the past. This may undermine personhood.

Misunderstandings about legal capacity, combined sometimes with paternalistic attitudes and behaviour towards people with AD dementia, may also occur (Beard and Fox 2008). If other people no longer consider someone a person with capabilities and resources, then that person may start to think so too. The negative conception communicated by other people, which in many cases is linked to a devaluation of the person concerned, easily becomes internalised into a negative self-concept. Demeaning comments and acts may threaten the person's self-esteem, making life seem like a continuous struggle to defend a sense of value (Steeman et al. 2007).

What happens at the interpersonal level (i.e. between individuals) may also occur at the societal level. In their own eyes, many people with AD dementia may still feel that they are the same person, even though their personality may be impacted by the disease and their self-esteem may fluctuate. Society, however, including the health and social system, may label them differently. This raises the question of who has the right and the power to define a person both from the viewpoint of personhood ("Am I still a person with dignity and rights in a socio-cultural context?") and personal identity ("Who am I?"). In this respect, the concept of stigma is particularly relevant.

Goffman described stigma as something that reduces someone in other people's minds from a "whole and usual person to a tainted, discounted one" (Goffman 1963, 12). It is a complex social phenomenon impacting individuals, relationships and society. It typically involves labelling and attaching negative stereotypes to people who have

a particular attribute, considering them as different and of less value and discriminating against them (Link and Phelan 2001 & 2006).

"One particularly troubling factor about the negative views about dementia that are still widely held is the way such views can lead to people living with dementia (both individuals with dementia and carers) feeling deeply stigmatised: as if the disorder were in some way a disgrace or discredit to them."

*Nuffield Council on Bioethics 2009, 60, §4.7*

"The phrase "coming out" is an accurate and resonant term ... with all its associations with the gay rights movement. It feels like that for me. Some close friends expressed their concern that it was professional suicide to do it, and cautioned me to hesitate. In fact, I believe the degree to which they were correct to fear this for me is the degree to which the stigma does indeed exist."

*Ronan Smith, Vice Chair of the Irish Dementia Working Group 2015*

Stigma extends to family carers too in that they may feel stigmatised through their association to the person with AD dementia (MacRae 1999; Werner, Goldstein & Buchbinder 2010). Stigma can also be structural. This means that the negative stereotyping, devaluation and discrimination are inherent in the system. This is often unintentional but can nevertheless be harmful. Nearly one in four people with dementia hides or conceals their diagnosis, citing stigma as the main reason (ADI 2012). Moreover, people with dementia and carers often feel marginalised by society and sometimes by their own friends and relatives, with 40% reporting they are not included in everyday life (ADI 2012). In some cultures, the stigma of dementia is such that it can influence the marriage prospects of younger family members (ADI 2012).

The introduction of prodromal AD, MCI due to AD and pre-clinical classifications, that may also carry with them a stigma, has the potential to exacerbate these problems. Even though they do not have AD dementia, the label of

AD may affect their autonomy and decision making, largely through paternalistic attitudes (reflected, for example, in concerns about them going out alone, driving and making decisions). However, attributes (such as AD) are not inherently stigmatising (Jones et al. 1984). Rather, it is the meanings that people attach to them which make them **socially salient** and result in them becoming a stigma.

Certain factors, such as fear or perceived threat, have been found to increase the likelihood of a particular attribute being considered a stigma (Jones et al. 1984; Stangor and Crandall 2003). Discrimination, as well as the fear of being discriminated against, plays an important role in stigma (Quinn, Williams & Weisz 2015). Discrimination can affect a person's opportunities regarding life insurance, mortgages, other insurance premiums. With the new definitions of AD, this might, if appropriate measures are not taken, do so at an earlier stage than would have been the case previously. As Werner and colleagues state, "structural discrimination must end if all citizens are to receive truly fair and equitable health care services and benefits" (Werner, Goldstein & Buchbinder 2010).

With the new definitions and growing knowledge about AD, the meanings that are constructed around it become more varied and nuanced, and an even larger group of people may feel that their identity and personhood are threatened. Link and Phelan (2006) emphasise that stigma always involves the exercise of power. With reference to the question raised earlier as to who has the right and power to define others, it is important that the new definitions of AD are widely discussed in the broader social context, that the voices of people at all stages along the AD continuum are heard and that specific issues are challenged if necessary. We can use our increasing knowledge about AD to provide people with different degrees of cognitive impairment with appropriate information, treatment and support, which reinforces their sense of identity and promotes respect for their dignity and personhood. The new definitions of AD and the new model of AD will hopefully lead to timely and accurate diagnosis which is an important step in providing appropriate treatment and support. The next section explores the ethical issues in these two areas and in relation to research.

## 4. Ethical issues linked to diagnosis, healthcare and research

In the next part of this discussion paper, we will reflect on the ethical implications of the changing definitions of AD for matters related to people's health, care and wellbeing, in the context of:

- Diagnosis
- Treatment and health/social care
- Research

### Diagnosis

In this sub-section on diagnosis, we focus on prodromal AD (IWG) and MCI due to AD (NIA-AA), as pre-clinical AD is currently a research classification and not a clinical diagnosis. We briefly refer to preclinical AD at the end of the sub-section in relation to issues surrounding information about risk status.

#### Introduction of the new terminology and definitions of AD in the context of diagnosis

The new AD terminology is gradually being adopted in the clinical setting. However, Morris et al. (2011) describe a 17-year gap for research evidence to reach clinical practice. Moreover, the preclinical research terminologies are still in need of validation for clinical use. It may therefore be some time before diagnoses of prodromal AD (IWG) or MCI due to AD (NIA-AA) become common in clinical settings across Europe. Meanwhile, old diagnostic criteria specifically for AD, such as the NINCDS-ADRDA (McKhann et al. 1984) described earlier or more global classification tools such as the **ICD-10** or ones which are specific to mental disorders and diseases such as the Diagnostic and Statistical Manual (DSM) for Mental Disorders, are most commonly used. Prior to a diagnosis of AD dementia, people with cognitive impairment and little functional impact associated with this are typically diagnosed with Mild Cognitive Impairment (MCI) (Petersen 2004). However, the connection between research and healthcare should not be underestimated. Many centres for the diagnosis of AD, such as memory clinics, take part in research. Thus, the time-lag

between research and clinical practice may sometimes be less than in other areas of healthcare.

Until recently, MCI has been considered as a condition which does not necessarily lead to dementia, with many people reverting back to normal cognitive functioning or remaining stable over time (Petersen et al. 2014). In the new AD model, however, the sub-category known as MCI due to AD (NIA-AA), which is more specific than MCI in general, is considered as a stage of AD. According to Dubois et al.:

"The proposed conceptual shift is to consider a patient previously diagnosed as having MCI (ie, with an amnesic syndrome of the hippocampal type and with biomarker evidence positive for brain amyloidosis) to be no longer at risk for developing AD dementia, but to recognise that they already have AD at a prodromal stage with an inevitable progression to AD dementia over time."

*Dubois et al. 2010, 1123*

The inevitable progression to AD dementia mentioned above is an important piece of information, but at present conjecture, as research in this area is not yet conclusive. The classifications are relatively new and the inevitable progression over time therefore remains to be proven. Studies are needed which span lengthy periods of time during which people are likely to progress along the AD continuum, thus making it possible to determine whether progression to AD dementia is inevitable.

<sup>1</sup> This is a sub-category of MCI

## The timeliness of diagnosis

In recent years, the importance of the timeliness of diagnosis has been emphasised (e.g. see Scottish Government, 2013). Whilst the terms “timely” and “early” diagnosis are often used interchangeably, “timely” refers to a diagnosis which is made at the right time for a particular person, whereas “early” focuses on a diagnosis which is made as early as possible (i.e. in the chronological sense) (Dhedi et al. 2014). According to Woods et al. (2003, p.321) timely diagnoses “prevent crises, facilitate adjustment and provide access to treatments and support”. In keeping with a person-centred approach, timely diagnosis is not linked to a particular disease stage but to benefit to the individual patient (Brayne, 2012 in Dhedi et al. 2014). Although, there is, as yet, no treatment or post-diagnostic support for people with prodromal AD (IWG) or MCI due to AD (NIA-AA), some people may find it beneficial to know their AD status so as to plan for the future. On the other hand, this may in some cases involve planning for a future which does not happen and result in unnecessary distress and lifestyle changes. A potential and significant benefit at the level of society, however, is that through the identification of these subgroups, it may eventually be possible to achieve targeted therapy. This involves identifying the “at risk” person and tailoring treatment to reduce modifiable risks, enhance resilience and potentially modify the course of the disease through specific drug interventions.

Potential harm must also be considered (e.g. stigma, the consequences of incorrect diagnosis and various emotional and psychological reactions). There is as yet insufficient evidence about harm linked to a diagnosis of prodromal AD (Dubois et al. 2016). However, it must be considered whether certain diagnostic procedures such as lumbar punctures, which are potentially burdensome and involve some degree of risk, are justifiable in the absence of curative treatment. In keeping with the principle of respect for autonomy, people should be given the opportunity to decide whether or not they would like to be informed of their diagnosis (Molinuevo and Rami 2013). The right not to know is equally important (Marzanski 2000) and for this to be a genuine choice, people need to understand fully what such a diagnosis means. Potential confusion and conflicting messages surrounding AD-related terms (see next sub-section) may lead to uncertainty about what a person would or would not want to know.

Timely diagnosis and subsequent treatment should be based on sufficient scientific evidence and ethical reflection. However, “therapeutic nihilism” often interferes with timely diagnosis of AD. This involves the belief held by some healthcare professionals that it is pointless to diagnose AD (i.e. AD dementia) as there is no treatment, a risk of stigma and as they feel they have nothing to offer (van

Hout et al. 2000; Vernooij-Dassen, Moniz-Cook et al. 2005). The likelihood of a yet earlier diagnosis being perceived by professionals as beneficial is likely to be even lower. Another key barrier is confidence in the diagnosis and in the ability to diagnose (Koch and Iliffe 2010). The new definitions could help clarify whether a person has AD dementia or another dementia-related condition. Ongoing education of healthcare professionals is therefore vitally important to ensure that the new diagnostic criteria and AD model do not increase uncertainty about the value of diagnosis but rather empower healthcare professionals by contributing towards greater diagnostic precision and eventually to the possibility to offer more targeted treatment and care.

## Communication of the new definitions of AD in the context of diagnosis

Respect for autonomy involves giving people the opportunity to make voluntary decisions (e.g. about whether they want to be informed of a diagnosis and/or about their lives following diagnosis) based on a full understanding of the facts. Doctors often use euphemisms or non-medical terms to help patients understand diagnoses of dementia (Cody et al. 2002; Downs et al. 2002). However, the use of a mixture of terms related to AD (e.g. reflecting AD as a form of dementia or as a continuum covering both pre- and post-dementia stages) may sometimes contribute towards misunderstandings. In addition, lay people may find some of the new terms confusing. “MCI due to AD”, for example, could be interpreted as referring to a form of MCI which is due to AD or as implying that MCI (i.e. in general) is due to AD. Similarly, prodromal is not an everyday term and most people will not know what it means. Sometimes, the term “MCI/prodromal AD” is used and it is not clear whether the “AD” is linked solely to prodromal or also to MCI (Jessen et al. 2014) and AD continues to be described in numerous publications as a form of dementia.

There is also a risk of some healthcare professionals interpreting or framing a diagnosis of prodromal AD (IWG) or MCI due to AD (NIA-AA) as a very mild form of AD dementia (e.g. in an attempt to make the diagnosis meaningful to their patients). In this way, people may be exposed to potentially conflicting messages from different reliable sources. This may cause distress and undermine trust in healthcare professionals. Doctors may need more time than is typically available, as well as the appropriate skills and training, first to grasp and secondly to make the new definitions of AD understandable to their patients. This discussion paper will hopefully serve as a starting point for clarification and for dialogue with different target groups but it is essential to understand how people from different groups in society make sense of the information they receive (please see section on Media/Public Awareness).

## Social justice

In keeping with the principle of social justice, which involves the fair distribution of resources, opportunities and potential burden and benefits within society, if there are benefits to be had from being diagnosed with AD, then everyone should have the opportunity to receive such a diagnosis. Benefits for people diagnosed with prodromal AD or MCI due to AD (where this is already occurring), in terms of care, currently seem fairly limited and the burden of the tests (e.g. worry, discomfort or some degree of pain, perceived risk of complications) might for some individuals insufficiently outweigh any perceived benefits. This and the cost or lack of access to lumbar punctures and PET scans may lead to inequity in access to diagnosis.

Research is currently being carried out to develop a “low cost” battery of measures (e.g. simple tests and games) which would enable a cost-efficient, more holistic and non-invasive early detection of people at risk of developing dementia (PredictND 2016). Ideally, such methods might eventually contribute towards diagnosis in cases where access to the necessary diagnostic tools is unfortunately lacking or where people do not wish to undergo the tests proposed. Nevertheless, the tests currently being developed are aimed at earlier detection of cognitive decline rather than actual diagnosis and such approaches to diagnosis might be considered second best if other methods are not available.

## Preclinical AD and diagnosis

So far, we have focused on diagnosis in relation to prodromal AD (IWG) and MCI due to AD (NIA-AA), as pre-clinical AD is currently a research classification and not a clinical

diagnosis. However, the term “diagnosis” is sometimes used in connection with preclinical AD, perhaps because of the blurred boundaries between research and clinical practice mentioned earlier. The value of labelling asymptomatic-at-risk people as having a disease, when many of them may never develop any symptoms, has nevertheless been questioned (Giaccone et al. 2011; Covinsky 2011).

“A person who has pathological changes that are unlikely to cause symptoms is better classified as normal than as having preclinical disease. Diagnosing preclinical Alzheimer’s disease in someone destined to never have cognitive problems should be viewed as a misdiagnosis.”

*Covinsky 2011*

On the other hand, if a risk has been detected, people should have the opportunity to be informed of it in keeping with the principle of respect for autonomy. Such information would enable them to decide whether or not to take advantage of any preventive treatment that might eventually become available and/or to participate in preventive clinical research, also deciding what risks, if any, they might be willing to take in connection with these two possibilities. Nevertheless, more research is needed into the psychological, emotional and social impact of receiving information about AD at all stages along the continuum (linked to diagnosis for prodromal AD or MCI due to AD and for AD dementia, and about risk status in relation to preclinical AD). Adequate pre-diagnostic counselling and post-diagnostic support should be provided to help maintain the equal standing of individuals within the civil, social and political community.

## Treatment and health/social care

The changing definitions of Alzheimer’s disease (AD), if adopted clinically, will have an inevitable impact on the nature and extent of health and social care services provided for people with AD pathology. Although the purpose of changing definitions has been driven by the field of research, it is acknowledged that a related purpose of the lexicon is to impact on clinical communities (Dubois et al. 2010). Their adoption will depend on the perceived utility of the definitions from the perspective of practitioners, as well as from the perspective of people who receive health and social care. There are implications linked to the impact that changing terminologies will have on consumer relationships with healthcare services, related to both pharmaceutical and psychosocial treatment options. In addition, the adoption of the prodromal AD (IWG) or MCI due to AD (NIA-AA) classification by clinicians will open

a discussion regarding the eligibility for treatment and access to health and social care services for people with this category of diagnosis.

## Health and social care interventions

The prodromal AD (IWG) and MCI due to AD (NIA-AA) classifications, evidence of pathology and early clinical symptoms, loosely align to the current use of terminology such as MCI in practice (albeit to a sub-category of MCI). Current treatment options for MCI are typically limited to monitoring the progression of symptoms to detect clinically significant decline (e.g. UK-based NICE 2006 guidance). However, there is evidence that individuals with MCI could benefit from receiving targeted interventions. For example, there is evidence that cognitive training can reduce memory



impairment in MCI (Moro et al. 2012). Furthermore, there is evidence that potential significant benefit for this group can be achieved by lifestyle changes (Palmer et al. 2010). Active informational interventions promoting the benefits of exercise and a healthy diet could be worthwhile for this group. Still, it should be considered that, even though cognitive training and lifestyle changes have shown a benefit to targeted groups in the population with specific characteristics, they may not be effective for each individual.

If AD is accepted as a continuum, and prodromal AD (IWG) or MCI due to AD (NIA-AA) as a precursor to AD dementia, the question arises whether existing interventions recommended for people with AD dementia should be extended to this group. There is increasing evidence for the efficacy of cognitive-based interventions for people with dementia. A systematic review of 15 **randomised controlled trials (RCTs)** of cognitive stimulation therapy, and **meta-analysis** of results for 718 participants confirm the benefits of this approach for cognition and quality of life in people living with dementia (Woods et al. 2012). Policy initiatives in the UK, for example, recommend that all people with mild/moderate dementia of all types be given the opportunity to participate in cognitively stimulating activities. Indeed “early” adoption of these activities has been linked to improved outcomes. On this basis, it could be argued that these types of interventions should be extended to people with prodromal AD (IWG) or MCI due to AD (NIA-AA). Research should therefore be carried out to check the benefit of existing interventions in this population and to guide the development of specific interventions for this group.

On the other hand, there may be existing therapeutic interventions or treatment options available through health and social care services for people living with AD dementia that are simply not suitable for people with a clinical classification of prodromal AD (IWG) or MCI due to AD (NIA-AA). The characteristics of people in this classification group is likely to be different from those of people currently receiving a diagnosis of AD dementia, particularly in relation to age and functional ability to engage with different interventions or activities. We can learn lessons from examining the experience of people with early onset dementia and the suitability of some of the health and social care services to which they have been referred. Typically, services for people with dementia are integrated into older people’s services (Haase, 2005; Alzheimer’s Society 2006, 2007). Referral to such services that do not meet the needs of younger people can have a negative impact on a person’s sense of self and identity (Harris & Keady 2009). This suggests that services should be developed for people in the newly classified groups, which are based on a careful analysis of their needs. Existing services which were designed for people with other

conditions should not be offered unless they also correspond to those identified needs.

## Existing and future possible drug treatments

Introducing a clinical classification of prodromal AD (IWG) or MCI due to AD (NIA-AA) in practice raises issues regarding the suitability, availability and efficacy of pharmaceutical treatments for this group. A survey of over 4,000 respondents, 2,889 with experience of at least one medication used for the treatment of dementia, indicated that three quarters of respondents, including people with dementia, carers and professionals, were largely positive and felt that dementia medication was to some degree beneficial (Alzheimer’s Society 2004). This shows an expectation that pharmaceutical treatment options are part of the care pathway. However, at present, most anti-dementia drugs are not licensed for people without a diagnosis of AD dementia<sup>2</sup>. From a research perspective, prodromal AD (IWG) and MCI due to AD (NIA-AA) are good targets for testing new pharmaceutical interventions, so in the future treatment options may also be developed which are suitable for earlier phases of AD.

Increasing interest in developing drugs for at-risk groups may eventually lead to new drug interventions which are successful for these groups. However, given the potential side effects of the medication, the risks of treatment will need to be carefully balanced against the potential benefits (Molinuevo et al. 2016). This benefit/risk assessment needs to be done differently for people with prodromal AD (IWG) or MCI due to AD (NIA-AA), who already have some symptoms than for people who are asymptomatic but at risk of AD. Moreover, given that the latter exhibit no clinical symptoms of disease, it would have to be ascertained whether treatment should be afforded within the field of health and social care, or if this type of intervention falls in the domain of public health.

## Coping with diagnosis and the need for post-diagnostic support

Existing research indicates that readiness and preparedness to deal with a diagnosis impacts on patient outcomes. Preparing people to adjust to a diagnosis and supporting them through this transition is one of the goals of health and social care services. Negotiating this transition relies on the quality of the treatment provided, as well as on factors related to the individual. In response to a diagnosis of dementia, people tend to fall on a continuum between taking

<sup>2</sup> There are a few exceptions e.g. Rivastigmine is licensed for mild to moderate dementia associated with Parkinson’s disease (<https://www.evidence.nhs.uk>)

a self-maintaining stance – whereby they try to normalise and minimise their difficulties, or a self adjusting stance in which new information about their cognitive status and difficulties that may lie ahead are integrated into their new sense of self (Clare 2003). These stances are related to different coping styles; self-maintaining to avoidant coping, and adjusting to problem-focused coping. A prodromal AD (IWG) or MCI due to AD (NIA-AA) diagnosis would provide practitioners with opportunities to prepare people better for the transitions associated with the progression along the AD continuum. If good quality informational services are provided at the earliest possible stage, this may facilitate the adoption of a self-adjusting stance with potentially better patient outcomes. Conversely, a prodromal AD (IWG) or MCI due to AD (NIA-AA) diagnosis could potentially encourage individuals to be hyperaware, seek to identify problems that do not exist, and increase anxiety and psychological distress; potentially leading to overuse and unnecessary use of health and social care services.

### Socio-economic and cultural issues

There is a pervading question concerning resource use and financial burden that arises from introducing new diagnostic classifications. It would be reasonable to assume that introducing categories that identify AD pathology at earlier stages will increase the number of people with a diagnosis or who are deemed at-risk, and thus the cost to services. The World Alzheimer Report (ADI 2010) indicates

that the average annual societal costs are USD32,865 per person with dementia. However, the report suggests that early diagnosis of dementia costs USD5,000 per person and that early diagnosis costs are offset by projected future savings from delayed institutionalisation, with savings of USD10,000 per person across the disease course. Introducing the preclinical categories may eventually help us to identify people who are likely to progress to AD dementia at an earlier point, and potentially result in savings to treatment costs. However, more research would be required to investigate the cost/saving benefit of the classifications.

A further consideration regarding the impact of the new classifications relates to cultural variations in the use of health and social care services. Owing to cultural variations in the perceptions of dementia, socioeconomic issues and social conventions, there already exist variations in the extent to which people from Black, Asian and Minority Ethnic (BAME) communities access health and social care services. In addition, we need to ensure that services themselves are culturally appropriate for people from different cultural backgrounds. For example, in the UK it is acknowledged that treatment and support services for people from BAME groups are inappropriate and lacking (APPG Dementia 2013). The provision of appropriate and high quality treatment and services for all cultural groups related to existing classifications of AD needs to be addressed, and a sensitive understanding of the implications for introducing new diagnostic classifications is needed.

## Research

Even if today, in 2016, we still do not know the precise causes of AD and how to treat it, recent research has resulted in in-depth knowledge about the underlying changes which occur in the brain many years before the onset of AD dementia. The common lexicon proposed by Dubois et al. in 2010 represents an important step towards helping ensure that researchers literally speak the same language and permitting the production of a body of comparable research findings. Although the lexicon has been helpful in providing clarity, the new model and related AD-terms continue to evolve, with new scientific publications linked to the new AD model in the pipeline, in parallel with the increase in knowledge and discoveries related to AD pathology. Confusion and uncertainty may therefore persist for some time as researchers strive to grasp and consistently apply the new definitions, and lay people, health and social care professionals, the media and policy makers attempt to interpret their personal and societal significance and implications.

### Promoting understanding and respecting autonomy

Although the preclinical AD classification is not a clinical diagnosis and is currently limited to the research domain, the disclosure of risk status may nevertheless have an impact on people's lives. The difference between a research classification and a clinical diagnosis may be unclear to some participants, especially if such information is provided by a person whom they perceive as a medical doctor. As many biomedical researchers are also healthcare professionals, the boundaries between research and clinical practice may at times be somewhat blurred. Despite strict adherence to relevant guidelines for good clinical and ethical practice in human research, some research participants still confuse medical care with research (e.g. assuming that the aim of a study is to improve their own health rather than to produce generalisable knowledge). The term “therapeutic misconception” was coined by Appelbaum and colleagues in 1982 to describe the failure to appreciate the

difference between research and treatment. It remains a challenge for researchers to ensure that participants fully understand the information they provide.

As mentioned earlier in relation to diagnosis, people may interpret information about the new definitions of AD within the framework of their current knowledge about AD and dementia. Consequently, there is also a risk, in the context of research, that they might interpret categories such as preclinical AD, prodromal AD (IWG) or MCI due to AD (NIA-AA) as forms of dementia. This may have ethical implications linked to informed consent (i.e. it could not be considered as informed if based on a misunderstanding). As not all participants taking part in preclinical studies will develop AD dementia, Molinuevo et al. (2016) suggest using the term “asymptomatic at risk for cognitive impairment” when communicating with research participants. Whilst not an everyday term that people are familiar with, it emphasises an at risk status of a condition that people are perhaps less likely to associate with AD dementia. The impact of providing information about a risk of AD dementia is currently being explored by the European Prevention of Alzheimer’s Dementia (EPAD) study, which amongst other things is also exploring whether reactions to the disclosure of risk status differ depending on the nature of the risk (e.g. linked to genetics, lifestyle factors or biomarkers).

The right not to know must be equally respected. It would be unethical to thrust information about AD status on people, on the pretext that they must be informed, especially in the absence of support and treatment. Consequently, a disclosure process similar to genetic counselling is often used by researchers whereby the possible significance of information they might receive (e.g. about being in a pre-dementia stage of AD) is explained to participants before they are asked whether or not they would like to receive such information.

### Possible impact of communication of risk status

For some research participants, the disclosure of risk, and frequent reminders about that risk throughout the duration of the study, may plunge them into a period of uncertainty (Molinuevo et al. 2016). Awareness of risk status may even affect the performance of some research participants on certain tasks through stereotype threat (Molinuevo et al. 2016). Stereotype threat means that a person who has been labelled as having a particular attribute, for which there is a negative stereotype, may feel apprehension about confirming that stereotype when performing a task (Steele 1997). Molinuevo et al. (2016)

describe a study in which people who were informed that they had a risk of developing AD dementia had a poorer score on cognitive tests compared to others with the same risk who had not been informed about their risk status. The issue of stereotype threat may also be relevant in everyday life (e.g. in relation to managing personal finances and administrative matters). However, there are individual and environmental factors which affect whether and if so how people are likely to be affected by stereotype threat, and it is important to explore methods to mitigate this effect (Singletary et al. 2009).

People who believe they are at increased risk of AD dementia may be particularly interested in participating in studies into the prevention of AD dementia. When designing measures to protect research participants who are at risk of AD dementia from harm, it is important that researchers consider the possible impact of knowledge about risk status and the timing of disclosure of that risk on the decision whether to participate or remain in a study. Providing information which may cause concerns about health (i.e. disclosure of risk status) whilst offering a possibility to do something which might be perceived as reducing the likelihood of it occurring (e.g. based on the therapeutic misconception mentioned earlier) could be experienced as a subtle form of persuasion/pressure.

### Privacy and confidentiality issues

The acquisition of information about the risk of developing AD dementia also raises ethical issues linked to privacy and confidentiality. Schicktanz et al. (2014) emphasise the need to pay attention to questions of disclosing, storing and passing on such information. They suggest that measures need to be taken not only in relation to potential psychological distress but also to familial issues and possible social discrimination. According to Molinuevo et al. (2016), legal safeguards to protect biomarker data provided by research participants are currently inadequate. They suggest that participants should not hesitate to ask researchers what measures are being taken to protect their data.

### Sharing potential risks and benefits

In keeping with the principles of equity, solidarity and autonomy all members of society should, in the context of research, be protected from harm but also have an equal opportunity to participate and potentially benefit from a particular study (either personally or through the satisfaction of being able to do something for the good of future patients and society). However, by extending the definition of AD to incorporate an at-risk stage and a pre-dementia stage such as prodromal AD (IWG) or MCI due to AD (NIA-AA), in addition to the

dementia phase, participants may eventually be involved in AD research for longer periods of time than in the past (Molinuevo et al. 2016), either by participating in several consecutive studies or by being involved in longitudinal studies (studies which involve participation over a fairly lengthy period of time). If the same people are constantly solicited (as they have been identified and it is often difficult to recruit a sufficient number of participants), they may be disproportionately exposed to research, sometimes with risk. Those who have specific biological characteristics of particular interest to researchers (e.g. a certain gene known as ApoE4) may be particularly sought after for further studies.

This issue is not limited to biomedical research or clinical trials. Researchers conducting other types of research are also increasingly interested in involving participants with a greater likelihood of developing AD dementia in the course of their study in order to provide evidence for or against their research questions or **hypotheses**. In providing a possibility to identify groups of people with very specific biological and clinical criteria, which are more likely to shed light on their hypotheses, the new AD criteria may contribute towards minimising the unnecessary involvement of some participants (Molinuevo et al. 2016).

The new AD model represents an important step towards developing measures which might eventually reduce dementia by delaying or preventing its onset and hence improving the quality of life of many people. According to Leibing (2015), this reflects a more general trend towards healthy and active ageing, incorporating the identification of at-risk groups and a focus on prevention for a range of medical conditions. However, this model and the AD-related terms also have implications for equity in research on quality healthcare. They may lead to a disproportionate focus on preventing or delaying the onset of AD dementia and less interest in and hence reduced funding for research aimed at finding more effective therapies (or better care) for people who already have AD dementia. This would mean paying less attention to improving the treatment of one group of people and more attention to improving the treatment of another group of people, based on a new model and hypotheses which have yet to be confirmed. On the other hand, it is important to understand that the new emphasis on the earlier stages in the disease process is partly in response to disappointing results in the development of new drugs for AD dementia. Many researchers now believe that it may be necessary to start therapies much earlier in the disease process, before the onset of dementia (Winblad et al. 2016).

## 5. Broader ethical issues at the level of society

Having discussed the possible ethical implications of the changing definitions of AD for personal identity and personhood, and for issues related to health and care, we will now turn to broader socio-political issues. The remainder of the discussion paper explores ethical issues linked to:

- Citizenship and equal value/opportunities in society.
- Politics and policy
- Media and public awareness

### Citizenship and equal value/opportunities in society

#### Citizenship, disability and dementia

Citizenship refers to membership status in a political community. It implies both rights and obligations. Being a citizen suggests that the person will have liberty to pursue certain goals and to be free from some forms of pressure to conform. Such rights are codified, for example, in the European Convention on Human Rights (Council of Europe 1953). They apply to all citizens with a degree of agency within a particular (political) community. For instance, citizenship typically implies the right to vote, which can itself be compromised in dementia (Redley, Hughes & Holland 2010), but also duties or obligations: voting itself might be regarded as a responsibility of citizenship. In some countries, voting is obligatory although certain members of society may be “excused” from this obligation.

Dementia can be regarded as a disability, at least in terms of some internationally accepted definitions, such as the definition contained in the United Nations document, the Convention on the Rights of Persons with Disabilities (CRPD). This states in Article 1 that,

“Persons with disabilities include those who have long-term physical, mental, intellectual or sensory impairments which in interaction with various barriers may hinder their full and effective participation in society on an equal basis with others.”

<http://www.un.org/disabilities/convention/conventionfull.shtml>

The rights set out in the CRPD are in large measure intended to support the person’s standing as a citizen despite any

disabilities he or she might have and even though some people with dementia may (as they should be at liberty to do) resist the label of disability. The so-called disability rights movement pursues political activism to secure opportunities and equal rights for people with disabilities, including people with dementia. There has been a move away from a medical model of disability, with a focus on the symptoms and difficulties residing in the individual, towards recognition of the way that society contributes towards disability. To a significant extent, there has also been a movement away from a more biomedical model of disease and towards a more overtly psychosocial understanding of dementia. The work of Tom Kitwood (1997), Steve Sabat (2001) and many others has led to the development of a new culture of dementia care, where the possibility of living well with dementia is emphasised. This approach has tended to stress the importance of the psychosocial environment in determining the wellbeing of people with dementia. Implicit in this work has been the thought that people with dementia can still participate in and contribute to society and, by implication, to the political community as citizens.

#### Citizenship of people with AD: responsibilities and obligations of individuals and society

What, then, are the implications of the emergence of biomarkers and the possibility of earlier diagnosis of AD (i.e. prior to dementia) for the standing of people with AD as citizens? Citizenship might be affected in a variety of ways, because people might, depending on how they are affected by such information (see earlier section on Personal Identity and Personhood), be more or less likely to engage in

activities. They might see themselves as diminished in some way, as less able to participate, or they might, on the contrary, see their lives as being at a point where they need to take a more active stand in the political community, to enable the voices of those under threat of these conditions to be heard more widely. So being diagnosed with earlier forms of AD or being informed about being at risk of developing AD dementia has the potential to affect a person's standing in the political community and their opportunities in society despite an absence of symptoms of dementia that might actually hinder their participation.

Society has a responsibility towards people with dementia, and we could argue also towards people identified and labelled as being at some point along the AD continuum. Citizenship is not only about exercising agency (i.e. fulfilling one's role as a member of society with the ability to participate in economic, social and political actions). It is also about people gaining access to what they are entitled to, based on the fact that they are equal citizens. Bartlett and O'Connor propose a useful definition of what they call "social citizenship", specifically in relation to dementia.

"Social citizenship can be defined as a relationship, practice or status, in which a person with dementia is entitled to experience freedom from discrimination, and to have opportunities to grow and participate in life to the fullest extent possible. It involves justice, recognition of social positions and the upholding of personhood,

rights and a fluid degree of responsibility for shaping events at a personal and societal level."

*Bartlett and O'Connor 2010, 37*

This ties in with the concept of "capabilities" which can be understood as people's opportunities as well as their abilities to achieve outcomes that they have reason to value. Nussbaum (2011) has identified ten basic capabilities which governments should strive to ensure and which focus on human dignity. One of these ("control over one's environment"), covers being able to participate effectively in political choices and being able to hold property, seek employment on an equal basis with others and enter into meaningful relationships of mutual recognition with other workers. This might include the ability to remain an active member of society, to live within a community or to have a say in the way society is run (if these are things a person values). It is also about not being deprived of such capabilities by society (e.g. by ignorance, the way AD is perceived and portrayed, lack of resources and structural discrimination).

The changing definitions of AD call for reflection on responsibilities and obligations of individuals and societies to ensure that people with AD (with and now, also, without dementia) are empowered as citizens, equally valued, and have the same opportunities as other members of society.

## Politics and policies

The new model of AD creates responsibilities for policy makers in relation to employment, equal access to goods and services and the provision of appropriate healthcare and support. To develop relevant policies in these areas, policy makers need facts and figures. However, they, like other lay people, may be unfamiliar with the new AD model and this may affect their interpretation of available information and the identification of priorities.

### The need for clarity regarding the number of people affected

Misunderstandings about the number of people with AD may occur. Reliable statistics on the **incidence** of preclinical and prodromal AD (IWG) or MCI due to AD (NIA-AA) are not yet available as there are no prevalence studies. The **prevalence** of AD dementia is not usually calculated directly but rather on the basis of population statistics and prevalence rates for dementia, with a further estimation then being

made of the number of AD cases. Policy makers risk drawing false conclusions about the number of people with AD dementia based on the co-existence of different definitions of AD. They may, for example, wrongly assume that prevalence figures for AD include people with preclinical AD and prodromal AD (IWG) or MCI due to AD (NIA-AA). Such false estimations of the actual number of people with AD dementia may result in false estimations of the need for more support and care for this group.

The widening of the span of AD, to include people who are also at risk of AD dementia, could have a range of implications for policy makers. It could lead to a perceived increase in the number of people with AD and to a sense of greater urgency to take action, based on the observation that more people are affected by AD than in the past and from an earlier age. It could also lead to the normalisation of AD based on the realisation that people can have prodromal AD (IWG) or MCI due to AD (NIA-AA) for many years without it having a significant negative impact on their lives,

perhaps suggesting less urgency to take action. The consequences for the wellbeing and quality of life of people with AD are considerable.

### Agreeing on public health priorities

The focus of research based on the new AD model has been predominantly on biomarkers and the development of drugs for the secondary prevention of AD dementia. There is a danger of these research goals overshadowing other important areas of research such as non-pharmacological and social science research, treatment for advanced AD dementia or for other causes of dementia and the development of appropriate care and support, all of which may be at least equally important to people with and at risk of dementia. This reflects debates in the 1980s and 1990s in America about the need to prioritise biomedical research and prevention over care, whereby prevention was considered by some as ultimately reducing the number of people requiring care. Ballenger (2006) described this as “medical triumphalism” and the “marginalization of care” and questioned whether there actually needed to be a trade-off between funding for research and funding for caregiving or not. More recently, it has been suggested that research focusing on the prevention of AD dementia nevertheless raises awareness of the need for appropriate support and care for people who already have AD dementia (Molinuevo et al. 2016).

Recognition of preclinical and prodromal stages of AD (or of MCI due to AD) calls for a response from policy makers to address a range of issues which are not identical to those currently experienced by people within the more general/global classification of MCI or who already have AD dementia. Policy makers need to consider at what point support should be provided, and the kind of support needed and desired at stages of AD which do not involve dementia.

The new category of prodromal AD (IWG) or MCI due to AD (NIA-AA) also raises the issue of equity as policy makers are faced with decisions about the fair distribution of healthcare resources. Respect for the principle of equity requires measures to ensure that people have equal access to diagnosis and subsequent care or treatment. This applies within countries, but also between countries. The research developments discussed here are developments in the higher income countries of the world. The middle and lower income countries are unlikely to see benefits from the research for some time. Indeed, a question can be raised as to whether it is equitable for high income countries to be targeting research funding on people who are essentially well when there are so many people living in poverty and requiring basic care (WHO 2015). The obvious justification would be if the benefits

of the new research were likely to reach poorer people too, either directly or indirectly.

### Protecting the rights of people with AD

As more and more people are diagnosed at this earlier stage and for many at a younger age, the need to develop measures to protect the rights of people with AD who are still in paid employment or with family responsibilities will become increasingly urgent. Potential risks for the wider population of people with AD (with and without dementia) in certain professional posts (e.g. in connection with transport, health and safety, fund management or responsibility for vulnerable groups) will also need to be considered. Appropriate policies and measures are needed to avoid unfair discrimination, including structural discrimination, whilst protecting people’s rights and wellbeing, especially as some people with preclinical and prodromal AD (IWG) or MCI due to AD (NIA-AA) will never develop AD dementia. At the same time, greater clarity may be needed about personal responsibility and state protection. Three key questions could be asked:

1. What kind of legal protection is needed for information (including biomarker data) provided by research participants and how can such legal protection be enforced (also when shared between different countries)?<sup>3</sup>
2. At what point, in what circumstances (if at all) and to whom should a person who has been informed that s/he is at risk for AD or who has been diagnosed with prodromal AD (IWG) or MCI due to AD (NIA-AA) be obliged to disclose such information?
3. What kind of protection should be provided should such disclosure become obligatory at some point?

The cost of these earlier AD classifications and diagnoses (prior to dementia), which involve amyloid imaging and lumbar punctures, is higher than that of a general MCI diagnosis. Policy makers need to be able to justify the costs associated with diagnosis in the absence of treatment to delay or prevent the onset of AD dementia and of measures leading to better patient management and health outcomes. Measures are needed to ensure that the right “not to know” about a diagnosis or risk status is respected. Although a register may be beneficial in terms of monitoring public health, the issue of potential unfair discrimination, which might occur as a result of reporting diagnostic status, needs to be addressed. Even though the pre-clinical classification is currently only used in the research domain and should therefore not appear in health records, measures are needed to ensure that disclosure of that at-risk status does not ultimately lead to discrimination in the fields of employment and insurance.

<sup>3</sup> For more information on this topic, please see Nuffield Council on Bioethics report (2015).

## Media/public awareness

### The media lexicon and its potential impact on the general public

The words and images we use can strongly influence how others treat or view people with Alzheimer's disease (AD). Language is a powerful tool. Words and images frame **public discourse** and this means we have a responsibility when we use language, both verbal and visual. It has been recognised that AD dementia has a social, physical and psychological impact on people and that dementia is also a form of disability (Kitwood 1990 & 1997; Alzheimer Europe 2013). However, the changing definitions of AD has resulted in a growing need to communicate, in addition, new scientific representations of AD to various audiences including, amongst others, lay people and policy makers.

"The media, in its numerous forms, are probably the strongest vehicle for transmitting and popularizing these representational forms, which people then incorporate into their own lives. Furthermore, information presented through newspapers, the internet, and television frequently results in the over simplification of scientific ideas while simultaneously revealing core values of a given society."

*Leibing 2015, 282*

Given the widely acknowledged stigmatisation of AD dementia, if we seek a public discourse that is empowering and inclusive of the diverse experiences of people with AD, then we must choose language that supports that goal. Popular media use a lexicon that is reflective of the wider society it inhabits and portrays the commonly held beliefs and perspectives that it either supports or opposes. However, popular media not only reflects society's values but also helps promote and re-inforce beliefs, stigma and prejudice.

A study of dementia in the media by the University of Worcester (Peel 2014) found that "a panic-blame framework was evident in much of the print media coverage." The report showed that "dementia was represented in catastrophic terms, such as a "tsunami" and "worse than death", juxtaposed with coverage of individualistic behavioural change and lifestyle recommendations to "stave off" the condition." We are all familiar with the stigmatising language and visuals used to highlight dementia in the media. Worldwide representative examples include "Robin Williams driven to suicide by Lewy body dementia" from The Washington Post, "Dementia epidemic looms with 135 million sufferers seen by 2050" from Reuters and "Experts warn of dementia "time bomb" in the next 25 years" from

The Irish Times. Pictures often used are of an older person's hands; divorced from the body, from identity and from self.

These types of headlines create fear and anxiety (Peel 2014) and the media lexicon in turn influences and impacts across all sectors. Yet we know that dementia is not necessarily a defining aspect of life and that life does not stop when dementia starts; this can be conveyed in the verbal and visual language we use. Likewise using negative or derogatory language to describe AD or a person with AD can contribute to and re-inforce stigma and discrimination. This becomes even more complex if a range of relatively complicated definitions are used in a clinical setting. For reports and general mainstream media, information needs to be clear, concise and unambiguous. The lexicon we use in framing public discourse impacts not only on private perceptions but also influences policy approaches. While instances of exemplary experiences with health and social care services and personnel have been noted (Trinity College Dublin 2006), the opposite has also been found in the form of structural stigma (mentioned earlier in the section on Personal Identity and Personhood). This may also speak to the value being placed on both the person with AD dementia and the carer borne out of understanding or lack thereof. This is informed by general public discourse and the popular lexicon used within it.

### Addressing the knowledge gap in relation to the new definitions of AD

With existing lack of knowledge and understanding on the part of the media, how can they sensitively convey various classifications, including those of AD prior to AD dementia? In practice, we are in fact only at the start of a process of media developing an understanding of AD as newly redefined and reconceptualised, with its nuances and ranges. It is also relatively recently that national working groups comprised of people with dementia, who speak up for themselves with the consequence of contributing to changing perceptions, have been formed and developed. There is a growing number within Europe plus a European Working Group of People with Dementia (Alzheimer Europe 2016). Such groups may eventually need to consider whether to extend membership to people who have the AD pathology but as yet no symptoms or just symptoms of mild cognitive impairment so that they too can have a voice and influence perceptions, policies and practices.

This knowledge gap presents opportunities. The dialogue in relation to the language and also the visual narrative used to describe AD can change and indeed is changing. Alongside the dramatic headlines, others are beginning to emerge. Two



recent examples from Irish national newspapers (The Irish Examiner and The Irish Times) read: “Living with Alzheimer’s” and “I’m still the same woman I was when I got diagnosed with Alzheimer’s”. This language counters stereotypical associations with the illness and also associations with the word disease itself. Using pictures of the real, ordinary person being described creates further impact. By adopting a more personal, caring and human rights approach in verbal and visual language, re-framing occurs through the use of “counter-frames”: from loss of identity to change and humanity; from an enemy and thief to a social norm; from carer burden to “each in turn” and from fear of death to seizing life (Van Gorp, 2012). In the same vein, ethicists have argued for the importance of “counter-stories”, focusing on relationships and care, which nuance the dominant stories in society which reproduce the standard view of independence and rationality (Lindeman Nelson 2001).

Van Gorp (2012) notes, however, that it can be more difficult to mainstream the counter-frames because it seems the media do not want to hear these positive stories. But, to the extent that the counter-frames are accepted, they may have positive results, including a positive impact on policy and services. Some guidance exists on how to portray people with dementia, either visually, in writing or through images. Examples include “Guidelines for reflection linked to the portrayal of dementia” (Alzheimer Europe 2013) and

“Dementia words matter: Guidelines on language about dementia (DEEP 2014). A guide for journalists has also been produced by “YoungDementia UK” (2016), which not only provides guidance on language to avoid or use, but also essential facts and figures to help ensure a balanced portrayal of dementia (early onset in this case).

### **Moving towards a lexicon of the new definitions of AD for the wider public**

We now need a lexicon for the wider public that encompasses the concept of AD as a continuum and as a condition (or underlying pathology), which incorporates stages prior to AD dementia. At the same time, work is still needed to change the public view, perception, dialogue and impact of AD dementia. A basic understanding of AD dementia must be in place before further definitions of AD are introduced. Yet, the new terms for AD have already been introduced, albeit it in the research setting and to some extent in clinical practice, and the changing definition of AD is an ongoing, dynamic process. In addition to the media sector, a language guide should also be utilised by the research and clinical sectors working in the field of AD for their communication with research participants, patients and the media. Guidance on the use of language should also be provided to politicians and policy makers.

## 6. Conclusions

The new definitions of AD imply a continuum, starting with a preclinical phase, in which biomarkers indicate the disease, passing through a second phase of prodromal AD (IWG) or MCI due to AD (NIA-AA) and leading to a third phase of AD dementia. These definitions have been developed in a research context with the aim of being used in research for preclinical AD and in clinical practice for MCI due to AD dementia, but they also have relevance for diagnosis, treatment and societal views of AD. In this paper, we focused on ethical aspects of the new definitions in all these domains. Three issues stand out.

First, the new definitions may give rise to new societal views on AD. As more and younger people will be diagnosed with (early stages of) AD, the current stigma related to dementia may gradually diminish. However, it is also possible that the stigma might remain and be extended to more people, influencing their self-esteem and possibilities for social participation. Such problematic aspects of the new definitions should be investigated and possible negative consequences should be addressed by actively promoting counter-frames and counter-stories. The changing definitions of AD call for reflection and action by individuals and societies (e.g. restrictive confidentiality regulations regarding disclosure of AD) to ensure that people with AD are empowered as citizens, equally valued and have the same opportunities as other members of society.

Second, the new definitions may lead to shifts in research and care. Policy makers have an important role to play in helping ensure that the focus on biomedical research into the early stages of AD does not jeopardise social science research aimed at improving the quality of life of people with AD dementia. The focus on people in an early stage of AD may also lead to less attention being paid to improving care for people in the dementia stage. This raises questions concerning the fair distribution of resources in health care

and social care. On the other hand, if AD dementia can eventually be prevented or its onset delayed, this would have an impact on the availability of funds for care as well as for prevention. Researchers are currently exploring the socio-economic implications of a possible preventive measure for AD dementia. Meanwhile, policies are needed to promote an equal distribution of research funding and care provision between various socio-economic groups, at national level and between countries worldwide. Research and care must meet the needs of all people with AD.

Finally, the previous definition of AD was linked to some degree of uncertainty, but the new definitions also give rise to possible uncertainties and misunderstandings. People who are asked to participate in research, because biomarkers show they have the first or second phase of AD, may not be able to completely grasp the situation. They may think they have dementia, or will certainly develop dementia, whereas they are in fact merely at risk. This may hamper informed consent, which is a prerequisite for ethical research. Similar misunderstandings may arise in the clinical setting, leading to less than fully informed decisions being made by patients which are not fully informed. In order to deal with these ethical challenges, the importance of pre-diagnostic counselling and post-diagnostic support must be recognised. In addition, every effort must be made to train researchers and healthcare professionals and explain the new definitions to other members of society.

In sum, the new definitions of AD are not ethically neutral. Although they promise research developments which will be positive for people with AD and hopefully lead to a reduction in the number of people with AD dementia, the possible negative aspects, such as misunderstanding, unfair distribution of resources, and stigmatisation, require full attention and action, in order to really improve the lives of people with AD.

## 7. Our position

Recent and ongoing developments in the field of science into the causes and development of Alzheimer's disease (AD) have led to new ways of understanding this condition. Over the last decade, researchers have been developing a new model of AD and gaining knowledge about the role of various biomarkers in the disease process. They now suggest that AD should be considered as a continuum, ranging from an at risk state through to a dementia state. We congratulate the researchers involved in these scientific developments, as well as the participants and the funders, who have made this research possible. In so doing, they have contributed towards greater precision and clarity in identifying people's possible relationship to AD, especially in terms of underlying pathological changes and the likelihood of developing AD dementia. We welcome continued work towards a better understanding of AD, resulting in the possibility of preventive measures, effective treatments and good quality care.

The aim of this discussion paper was to reflect on the ethical implications of the new AD model and the definitions associated with it to try to ensure that these definitions have a positive impact on people who already have or may later have AD, that their rights and wellbeing are promoted and that broader society ensures that they are adequately supported, fully respected and fairly treated. In the position below we have summarised some of the key issues which we feel are important and should be addressed.

1. Careful consideration should be paid to the possible social, psychological and practical impact of the new definitions of AD on personal identity, relationships and citizenship (e.g. in relation to personhood, dignity, social exclusion, discrimination and/or stigma). Every effort should be made to prevent any negative impact by attention to the words used, the stance taken by researchers themselves and by encouraging positive social attitudes
2. Research should be carried out into the possible impact of the new definitions and to understand better how lay people and healthcare professionals understand the terminology surrounding the new model of AD
3. When assessing potential benefits of diagnosing what is currently defined as prodromal AD (IWG) or MCI due to AD (NIA-AA), there should be a focus on issues which are of relevance to patients
4. Politicians, the media and the general public should be provided with information about the new definitions and the new AD model to promote informed debate, avoid creating or perpetuating stigma and contribute towards more inclusive attitudes towards people with AD
5. Efforts should be continued to reduce negative stereotyping (i.e. which focuses on very advanced symptoms and on an absence of quality of life) of AD dementia
6. There should be an open and informed public debate about the prioritisation and public funding of research, treatment, care and support
7. People with AD (including those who do and do not have dementia) should be given a voice in the abovementioned debate. Alzheimer Europe, national Alzheimer associations and working groups of people with dementia need to consider how to ensure that this happens
8. The findings of research should be used to develop awareness-raising programmes targeted at the general public and appropriate educational and communication materials to be used by healthcare professionals and researchers when communicating with patients and research participants
9. Policies and legislation should be developed to ensure the protection of the rights of people with AD (e.g. in relation to confidentiality, decision making, access to services and support, and discrimination) to ensure that they can continue to play an active role in society and remain valued citizens and members of their communities
10. Careful attention should be paid by researchers to terminology surrounding what is currently defined as pre-clinical AD and to its possible impact on research participants and the general public. For example:
  - a. Researchers should use the term "disclosure of risk status" rather than "diagnosis", and "people" or "participants" rather than "patients" in all communication with research participants who are classified as asymptomatic, at risk for AD. This may change in the future if, with increasing knowledge, the at-risk state comes to be more clearly linked to the future disease state (as is the case with pre-symptomatic AD)
  - b. People classified as being in the asymptomatic, at-risk-for-AD group should be described as being at risk of AD rather than as having pre-clinical AD

## 8. Glossary of terms and abbreviations

<b>Amyloid plaques</b>	Abnormal clusters of "sticky" proteins called beta-amyloid that build up between nerve cells and interfere with signalling in the brain e.g. triggering inflammation and devouring disabled cells. One of the hallmarks of AD pathology.
<b>Asymptomatic at risk for AD</b>	In the context of the new AD definitions, a sub-group of preclinical AD consisting of pathological changes in people's brains which are specific to AD but with no clinical signs/symptoms of AD.
<b>Biomarker</b>	A biological marker/characteristic of a normal or abnormal process in the body that can be objectively measured and evaluated.
<b>CSF</b>	Cerebrospinal fluid (a body fluid found around the brain and the spine).
<b>Clinical-biological entity</b>	Something that has clinical and biological characteristics.
<b>Clinical diagnosis</b>	The act or process of discovering or identifying a disease or medical condition by means of a medical examination to detect signs and symptoms or laboratory tests etc., resulting in a decision or opinion being made based on such examination, and usually information being given to the patient, often along with a diagnostic label.
<b>Continuum</b>	A range or series of things that are slightly different from each other and that exist between two different possibilities/extremes (e.g. underweight/overweight, hypotension/hypertension).
<b>Dementia</b>	A set of symptoms that typically include loss of memory, mood changes and problems with thinking, orientation, comprehension, calculation, learning capacity, language and judgement. These symptoms are severe enough to interfere with daily functioning. Dementia isn't a specific disease. It is caused when the brain is damaged by diseases, such as Alzheimer's disease or a series of strokes.
<b>Dichotomous</b>	Divided into two distinct parts or states (e.g. heads or tails, rich or poor, healthy or sick).
<b>DSM-III</b>	The third edition of the Diagnostic and Statistical Manual of Mental Disorders which is the standard classification of mental disorders used mainly by mental health professionals in the United States of America (the latest version is DSM-V).
<b>et al.</b>	Stands for "and others" (e.g. the co-authors of a scientific article).
<b>False positives and false negatives</b>	A research or medical finding which suggests that a person has something that they don't have or doesn't have something which they do have.
<b>Hippocampal lesion</b>	Damage in the region of the brain known as the hippocampus, which is one of the first regions to suffer damage in the case of AD pathology and is known to be important for the person to recall new information.
<b>Hypothesis</b>	An assumption, usually expressed in the form of a statement, which is tested in the research project.

<b>ICD-10</b>	The tenth edition of the International Classification of Diseases developed by the World Health Organization.
<b>Incidence</b>	The number of new cases of people with a specified disease during a specified period in a specified population.
<b>IWG</b>	International Working Group (one of the main groups responsible for developing the new model and definitions of AD).
<b>MCI</b>	This stands for mild cognitive impairment.
<b>MCI due to AD</b>	In the context of the new AD definitions, this corresponds to the early symptomatic, pre-dementia phase of AD during which clinical symptoms are present but not severe enough to affect activities of daily life and are associated with specific biomarker changes. This term was coined by the NIA-AA.
<b>Meta-analysis</b>	The statistical analysis of the results of multiple scientific studies.
<b>NIA-AA</b>	National Institute on Aging and the Alzheimer's Association (one of the main groups responsible for developing the new model and definitions of AD).
<b>Neurodegenerative disease</b>	A disease which primarily affects neurons (it involves a degeneration of nerve cells).
<b>Neurobrillary tangles</b>	Twisted fibres of a protein called tau present inside the neurones. The twisted strands of tau interfere with the transportation of nutrients and other essential supplies in the brain and cause cells to die. One of the hallmarks of AD pathology.
<b>Neuroscientific</b>	Related to various scientific disciplines dealing with the structure, development, function, chemistry, pharmacology and pathology of the nervous system.
<b>Pathology</b>	Deviations from what is considered as normal in relation to diseases or biological processes.
<b>Pathophysiological</b>	The effects of disease on physiological processes (of the functioning of organisms).
<b>Physiopathology</b>	Relating to biological and physical manifestations of disease related to underlying abnormalities and physiological disturbances. About processes within the body that result in the signs and symptoms of a disease.
<b>Post mortem</b>	Latin for "after death".
<b>Preclinical</b>	In the context of the new definitions of AD, the long asymptomatic stage between the earliest changes underlying AD pathology and the first specific cognitive changes.
<b>Pre-dementia stage</b>	In the context of the new definitions of AD, the stage between "pre-clinical AD" (described above) and the "AD dementia". Pre-dementia therefore covers "prodromal AD" and "MCI due to AD".

<b>Presymptomatic AD</b>	In the context of the new definitions of AD, a sub-group of preclinical AD which includes people who carry of dominant genetic variant of AD which makes it almost certain that they will develop AD dementia.
<b>Prevalence</b>	The number of cases of a disease that are present in a particular population at a given time.
<b>Prodromal AD</b>	In the context of the new AD definitions, this corresponds to the early symptomatic, pre-dementia phase of AD during which clinical symptoms are present but not severe enough to affect activities of daily life and are associated with specific biomarker changes. This term was coined by the IWG.
<b>Public discourse</b>	Anything written, spoken, televised or heard via some media. A way to achieve mutual understanding through a rational exchange of arguments within the public sphere.
<b>Randomised controlled trial (RCT)</b>	A controlled experiment/study in which people are allocated (by chance alone) to receive one of several clinical interventions, one of which is the placebo (sometimes called the sugar pill), standard practice or simply no intervention. Differences between the results from the different groups are statistically analysed.
<b>Socially salient</b>	A particular attribute (e.g. having AD, having ginger hair or being blond, being unemployed etc.) that is considered by some people as being socially meaningful (i.e. it matters socially and may therefore have social implications).
<b>Syndrome</b>	A disease or disorder that involves a particular group of signs and symptoms OR a group of symptoms that together are characteristic of a specific disorder or disease.
<b>Stigmatisation</b>	When a person or group is devalued and discriminated against on the basis of a shared characteristic or attribute (e.g. having a tattoo, being divorced or having dementia) that is considered in some societies as socially significant. Negative stereotypes tend to be attached to the characteristic/attribute and there is a tendency to think of people with it as being in a group apart (i.e. "them" not "us").

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# 10. Appendices

## Appendix 1: Acknowledgements

Alzheimer Europe would like to express its sincere thanks to the members of the ethics working group who donated their time, energy and expertise to make it possible to produce this discussion paper. In the table below, you will find a bit of background information about the members of the group (in alphabetic order).

Hilary Doxford, at the age of 53, was diagnosed with early onset Alzheimer's disease. She was appointed to the World Dementia Council in 2015, is Vice-Chair of the European Working Group of People with Dementia and an ambassador for the Alzheimer's Society in England. Speaking nationally and internationally as a person living with dementia, she participates in research studies, champions "Join Dementia Research" and is contributing to the setting up of a working group of people with dementia in England and Wales.



Karine Fauria is the Scientific Manager of Barcelonaβeta Brain Research Center (BBRC), research institute of the Pasqual Maragall Foundation. The BBRC is devoted to research in Alzheimer's prevention. Karine started her scientific career in cognitive neuroscience and was awarded a PhD in visual orientation in 1998. She started to work at BBRC as part of the team which designed and managed the ALFA study, BBRC flagship project. ALFA study is a longitudinal cohort of sons and daughters of AD patients, developed to explore the preclinical stage of this condition with the aim of identifying novel risk factors and biomarkers.



Jean Georges has been the Executive Director of Alzheimer Europe since 1996. Prior to this, he worked as a journalist and as a parliamentary assistant to members of the Luxembourg and European Parliament. He was responsible for setting up the European Dementia Ethics Network in 2008 and has since contributed towards several ethics projects in that context.



Dianne Gove is Director for Projects at Alzheimer Europe. She is also Chair of Alzheimer Europe's Ethics Working Group. Her background is in psychology, education and psychotherapy (analytical Gestalt therapy). In 2013, she was awarded a PhD from the University of Bradford for her research into general practitioners' perceptions of dementia and how these relate to stigma. She has directed several projects focusing on issues such as legal rights, assistive technology, palliative care, advance directives, social support and continence care.



Julian C. Hughes is RICE Professor of Old Age Psychiatry in the University of Bristol. He is based at the Research Institute for the Care of Older People – the RICE Centre – in Bath and is an honorary consultant at the Royal United Hospital in Bath. Julian's areas of expertise are in the fields of Ethics and Philosophy in connection with dementia and ageing. He also has an interest in palliative care. Julian has served on a number of national and international committees. He is a Fellow of the Royal College of Psychiatrists and of the Royal College of Physicians of Edinburgh. He is currently a member and Deputy Chair of the Nuffield Council on Bioethics.



Tina Leonard is Head of Advocacy & Public Affairs at the Alzheimer Society of Ireland where she works on the development of communications, advocacy, public affairs, policy and research programmes. An experienced advocate, Tina has previously worked as a consumer journalist, author, media commentator and communications consultant and was previously Director of Ireland's European Consumer Centre.



Anneli Sarvimäki was Director of the Age Institute in Helsinki, Finland, for ten years and is now associated as expert with the institute. She has a doctoral degree in educational sciences and philosophy. She is also a registered nurse specialised in psychiatric nursing. Her main interests as a researcher and teacher are ethics in health care, experiential ageing, and ageing and the quality of life. Anneli Sarvimäki has directed several research projects and published articles and books on these topics.



Dr Sarah Smith is a Cognitive Psychologist and Senior Lecturer in the School of Dementia Studies at the University of Bradford. Her research interests concern how higher order cognitive processes, awareness of memory and subjective experiences associated with remembering, interact with memory function. She is particularly interested in understanding everyday memory deficits in people with less common forms of dementia. Her research has sought to understand how memory operates in the context of carrying out everyday tasks and remembering past personal events, establishing the significance for maintaining identity and engaging in cognitive rehabilitation.



Dr. Mark Schweda is research associate at the Department of Medical Ethics and History of Medicine (University Medical Center Göttingen) and junior research fellow for the ethics of living at the Lichtenberg-Kolleg Göttingen. His academic background is in philosophy and German literature. His research focuses on the philosophical, (bio-)ethical, and socio-cultural aspects of ageing and the human life course. Recent publications are concerned with representations of dementia in popular culture, as well as with the role of modern biomedicine for public perceptions of ageing and the life course.



Hinesh Topiwala is a Clinical Research Fellow at the Centre for Dementia Prevention, University of Edinburgh. He works on the European Prevention of Alzheimer's Dementia (EPAD) Longitudinal Cohort Study. His main research interest is lifestyle and neurodegeneration in midlife. He completed Psychology (BSc) and Medicine (MBBS) degrees at University College London. He is member of the Royal College of Psychiatrists (MRCPsych) and sees patients in the NHS Young Onset Dementia Clinic, Fife, Scotland.



Guy A.M. Widdershoven is Professor of Philosophy and Ethics of Medicine, Head of the Department of Medical Humanities and senior researcher at the EMGO Institute for Health and Care Research of VU University Medical Center, Amsterdam. He has published on hermeneutic ethics and its application in empirical ethics, moral deliberation and ethics of chronic care. His research interests include autonomy in chronic care, coercion in psychiatry, evaluation of moral deliberation projects, end-of-life issues, genetics and public health genomics.



## Appendix 2: More information about the changing definition of AD

### Historical description

In 1906, Dr Alois Alzheimer first described the symptoms and the **amyloid plaques** and **neurofibrillary tangles** in the brain, which have come to be considered as the hallmarks of Alzheimer's disease (AD). More than a hundred years later, the causes of this **neurodegenerative disease** are still unknown and no cure is currently available, but it is important not to lose sight of how far we have come since then.

For a long time, dementia has been related to old age but the first patient described by Alois Alzheimer was actually quite young. For many years, AD dementia was also called "presenile dementia" and was used as a diagnosis for people aged between 45 and 65. It was only in the 1970s that a link was made between dementia in the young and old populations and the term AD dementia extended to old age.

In 1984, the NINCDS-ADRDA Alzheimer's criteria (McKhann 1984) were proposed by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (now known as the Alzheimer's Association). The NINCDS-ADRDA criteria were based on a "clinico-pathological dual diagnosis". This involves first determining clinically the presence of dementia and trying to rule out other possible diagnoses, which may account for the clinical presentation, and then, for a definite diagnosis, confirming AD brain pathology at **post mortem**. A direct consequence of such an approach is therefore the long period of uncertainty about the diagnosis. The clinical diagnosis can only be "probable" until the person dies and the plaques and tangles mentioned earlier can be detected in his/her brain. This "probable" diagnosis can only be made when the disease is sufficiently advanced to reach the threshold of dementia. Consequently, according to these criteria, a diagnosis of AD is synonymous with a diagnosis of AD dementia, even if the latter term is sometimes used.

Research has shown that these criteria have low accuracy as they do not take into account certain features of the disease such as **biomarkers** or **hippocampal lesions** (NIA and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease 1997; Beach et al. 2012) and as only 70% of diagnoses are accurate, the others being **false positive** or **false negative** cases.

The lack of precision in the diagnostic criteria and the discovery of AD pathology biomarkers made it necessary to reach a new consensus on diagnosis and evaluation. Since 2007, starting with the first International Working Group

proposal (Dubois et al. 2007, 2010) and followed by other groups' definitions such as the NIA-AA (McKhann et al. 2011) and IWG2 (Dubois et al. 2014), new conceptual approaches to the disease have been developed. All consider AD as a **clinical-biological entity** based on the presence of biomarkers. These new approaches could, if used in clinical practice, increase diagnostic accuracy and allow for an earlier diagnosis. In addition, when used in research settings, these new criteria could enable the development of standards that are critical for drug development (Cumming 2011).

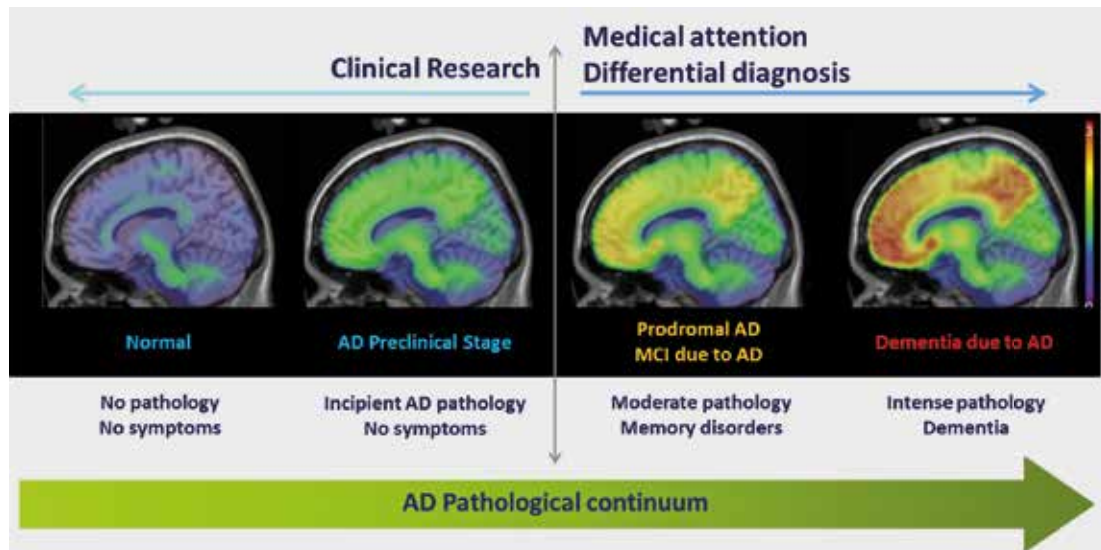
### The new approach: AD pathology as a continuum

The last decade of research has been a testimony to the change in the conceptual approach to AD. As described above, two main groups have developed criteria aimed at improving AD diagnosis and its related research. First, in 2007, an International Working Group (IWG) published its criteria (Dubois et al. 2007), followed by an update in 2014 (Dubois et al. 2014). In 2011 in the US, other criteria were published by three working groups in the National Institute on Aging and the Alzheimer's Association (NIA-AA) (Jack et al. 2011; McKhann et al. 2011; Albert et al. 2011; Sperling et al. 2011). Each set of criteria has a few differences, but all agree on the need to consider AD pathology as a **continuum** where biomarkers play an essential role. Both groups define AD as a **clinical-biological entity** that, through the identification of biomarkers, can be diagnosed during the lifetime of the patient. AD is also defined as a clinico-biological continuum, ranging from normal cognition to severe dementia, including three phases:

1. preclinical AD: asymptomatic at risk or presymptomatic AD (abnormal **pathophysiological** biomarkers and no cognitive impairment)
2. mild cognitive impairment due to AD (NIA-AA) or prodromal AD (IWG) (abnormal pathophysiological biomarkers and mild cognitive impairment)
3. AD dementia (abnormal pathophysiological biomarkers and dementia)

The image overleaf (from Molinuevo et al. 2013) shows the gradual changes in the brain along the AD pathological continuum.

The IWG (Dubois 2007) was the first to introduce the idea of a continuum. AD is defined as a clinico-biological entity based on a major clinical criterion, namely the deficit in episodic memory (i.e. long-term memory of specific events



and experience, technically known as “amnesic syndrome” of the “hippocampal type”), either on its own or associated with other cognitive or behavioural changes. The criteria also requires one or more AD pathology biomarkers. These include atrophy of the medial temporal lobe observed by MRI (shrinkage of a certain part of the brain as shown on a scan), changes in cerebrospinal fluid (CSF) biomarkers and alterations in PET scans. In 2007, all these biomarkers were treated equally. This was revised in 2014 by the IWG2. In this second diagnostic criteria consensus, the IWG considered weighting of clinical significance and specificities for biomarkers (i.e. certain characteristics, levels and combinations of biomarkers were given greater or lesser importance as diagnostic criteria).

The NIA-AA criteria focus on “syndromes” within the AD continuum. According to the NIA-AA, clinical diagnosis is based first on syndromic criteria (i.e. information about the syndromes), followed by the likelihood (high, intermediate or likely) of what is observed being due to AD, as assessed by use of biomarkers (if available). The continuum is divided into syndromes, which have been described in different papers: AD (Mac Khann et al. 2011), mild cognitive impairment (MCI) due to AD (Albert et al. 2011) and the pre-clinical phase (Sperling et al. 2011).

## A new lexicon

In order to reach a consensus on the diagnostic criteria and harmonisation of standards for research, a new consensus lexicon was needed to unify all definitions, stages and processes (Dubois et al. 2010). The lexicon developed by Dubois et al. (2010) was intended for researchers in the context of research protocols and clinical trials and to provide clinicians with a clear view of an evolving field. The new definitions are also described in the context of new diagnostic framework/criteria (Dubois et al. 2010 & 2016) which is still undergoing modifications. The definitions

below are presented as described in Dubois et al. (2010 and 2016). However, readers should bear in mind that there may be further changes in the upcoming years.

ALZHEIMER’S DISEASE is defined as a clinical entity that encompasses the full spectrum of the disease including both pre-dementia (prodromal) and dementia phases. Its diagnosis can be established *in vivo* based on a dual clinico-biological entity.

AD PATHOLOGY refers to the neurophysiopathological changes underlying AD. This terminology can be applied irrespective of the clinical manifestation.

PRECLINICAL STATE is the long asymptomatic stage between the earliest AD pathogenic and the first specific cognitive changes. It includes two different populations:

- i. ASYMPTOMATIC AT RISK: population that includes individuals experiencing pathological changes in their brain specific to AD but without clinical changes
- ii. PRESYMPTOMATIC: mutation carriers of the dominant genetic variants of AD

PRODROMAL AD (also called MCI due to AD by the NIA-AA) corresponds to the early symptomatic pre-dementia phase of AD. During this phase clinical symptoms are present but not severe enough to affect activities of daily life and are associated with specific biomarker changes.

MCI is applied when patients do not fulfil the criteria for the clinico-biological phenotype of prodromal AD (memory symptoms not characteristic of AD or biomarker negative).


AD DEMENTIA consists of the stage of the disease in which the cognitive symptoms are severe enough to affect not only memory but also daily life activities.

## A concept in constant evolution

There is currently agreement in the field of biomedical research on AD being a continuum, both from a biological and a clinical perspective, and current research criteria, whilst constantly in evolution, reflect this. Research and discussions are focusing on improving current research criteria through defining which biomarkers can, with sufficient accuracy, define the **physiopathology** of AD and its stages. Furthermore, even if today in 2016, we still do not know the causes of AD and how to treat it, research carried out worldwide has resulted in in-depth knowledge about the molecular and pathological changes occurring in the brain during the disease.

We are currently at the dawn of a new era of discoveries concerning the development of technologies for brain physiopathology research (neuroimaging, cerebrospinal fluid analysis and blood biomarkers identification and new biomarker research). This research will permit a better knowledge of the changes involved along the AD continuum. This valuable information is needed to better understand the different processes taking place during the course of the disease.

Nevertheless, it is essential to take into consideration that every day new results are obtained that provide new insights into the disease process and lead to more precise knowledge about AD. For this reason, we are facing a field in constant evolution where new criteria may emerge in the near future.

The background of the page is a solid green color with several large, white, five-pointed stars scattered across it, similar to the flag of the European Union.

In this discussion paper, Alzheimer Europe's Ethics Working Group reflects on a range of ethical issues linked to the recent changes in terminology surrounding Alzheimer's disease (AD) and AD dementia. The paper starts with an explanation of the context in which the definitions were developed and reflects on ethical issues linked to representations of health and disease. The paper then addresses issues of relevance to the individual, relationships and wider society (e.g. exploring the possible impact on personhood, citizenship, stigma, public awareness, policy making, diagnosis, healthcare and research). In addition to the main issues discussed, the paper contains an annex with further details about the development of the terms and a glossary aimed at making the paper accessible to a wide audience. At the end of the paper, readers will find the group's position on some of the key issues addressed.