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ETHICAL CHALLENGES IN THE DISCLOSURE OF BIOMARKER-BASED INFORMATION IN THE EARLY STAGE OF ALZHEIMER'S DISEASE

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General introduction

Background

Setting the scene: the difference between Alzheimer's Disease and dementia

Alzheimer's Disease (AD) is a severe neurodegenerative disorder of the brain that is characterized by memory loss and cognitive decline [1]. AD should not be confused with dementia, as many people mistakenly believe the terms to be equivalent. The National Institute on Aging describes dementia as an umbrella term used to describe a set of symptoms such as impaired thinking and memory decline. AD may be the most common cause of dementia, with estimated numbers between 50 to 70 percent of all dementia cases and with the majority of AD cases being sporadic and less than 2.5% of AD cases having a genetic deposition [1]. Other diseases may cause dementia, such as vascular dementia, frontotemporal lobe dementia, Lewy Body, Parkinson's and Creutzfeldt-Jakob [1]. In sum, there are two important differences between AD and dementia:

First, AD is an irreversible disease, which is also incurable at this time. Clinicians can prescribe one of the following five approved medications: four cholinesterase inhibitors (tacrine, donepezil, rivastigmine, galantamine) and an N-methyl-D-aspartate (NMDA) receptor AD antagonist (memantine) [2][3][4]. These medications may provide symptomatic relief and may delay further cognitive decline, yet without guaranteed success for all patients. However, it is possible that some forms of dementia, such as, a vitamin deficiency may be temporary and reversible with the administering of certain medications.

Second, when a patient is diagnosed with dementia, then the cause of the symptoms is not or not yet known. This is in contrast with an AD diagnosis, which implies that the symptoms of impaired thought are attributed to AD.

Third, in contrast with AD in the prodromal phase, dementia requires a significant impact on the instrumental daily activities (IADL) such as shopping for groceries, handling finances and taking care of medication [5].

From a post-mortem diagnosis toward an early diagnosis of AD: historical evolution and the impact of biomarkers on the AD continuum

AD can be traced back to the first case (cf. known as the 'Auguste D case') described by dr. Aloysius (Alois) Alzheimer in 1906. The German psychiatrist and neuropathologist was the first person to link symptoms of memory loss and psychological changes to brain changes [6][7]. In the autopsy

of the patient's brain, he detected severe shrinkage and abnormal deposits in and around nerve cells [7][8]. Four years later, in 1910, it was one of his colleagues, Emil Kraepelin, who named the disease after dr. Alois Alzheimer. Despite the efforts of many researchers and clinicians worldwide to understand the disease, we had to wait until 1984 for the discovery of amyloid beta (Aβ) and the discovery of tau protein in 1986 as another pathophysiological marker for AD [9].

From 1984 onward, several criteria were published to define AD, such as in the fourth edition of the Diagnostic and the Statistical Manual of Mental Disorders (DSM-IV) and the 10th revision of the International Classification of Diseases (ICD-10) [9][10]. The National Institute of Neurological and communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) also published a set of criteria to define AD. The NINCDS-ADRDA criteria were the ones most commonly used in AD research (see Table 1 for a brief overview of the most important aspects of these criteria) [11].

1. The NINCDS-ADRDA criteria (1984):
• Patients need to have a cognitive deficit and a functional compromise severe enough to meet criteria for dementia. • A confirmed diagnosis depends on postmortem examination. • The most accurate diagnosis that the clinician can make for the living patient was a 'probable' diagnosis of AD. • Other possible causes of cognitive impairment have to be excluded by the clinician. • The cognitive deficits are not operationalized for characteristics of disease severity.

Table 1: Summary of the NINCDS-ADRDA criteria. Table adapted from [9] and [12].

The NINCDS-ADRDA criteria highlighted that a diagnosis of AD could only be considered as a 'probable' diagnosis [13]. At that time, AD could only be confirmed postmortem, via autopsy examination. The criteria also imply that a 'probable' diagnosis of AD could only be made when the severity threshold for dementia was reached and when other potential etiologies of dementia were excluded. In other words, clinicians could, at that moment in time, not establish an AD diagnosis based on positive evidence for AD [8][14].

In the past three decades since the publication of the NINCDS-ADRDA criteria and the development of in vivo biomarkers of amyloid and tau pathology, it has become possible to identify in-vivo evidence of the specific neuropathology of AD by using validated and disease-specific biological markers or biomarkers for AD [1][13]. In this way, the discovery and evolution of AD biomarkers has marked a shift from a 'probable' or a post-mortem diagnosis toward an early diagnosis of AD [13].

In 2005, Dubois and colleagues referred to the scientific growth of knowledge based on these biomarker findings, such as the improved recognition of non-AD dementia, frontotemporal lobar degenerations, dementia with Lewy-Bodies, and the improved identification of AD phenotype [15].

Hence, in 2007 the NINCDS-ADRDA and the DSM-IV-TR criteria were revised and included with this biomarker information [15]. This consequently resulted in new criteria, known as the International Working Group criteria (IWG criteria from 2007 and IWG-2 update from 2010). For a brief overview of the most important aspects of these criteria, see Table 2.

2. IWG criteria (2007):
• The diagnosis of AD can be made in the living individual and is no longer dependent on autopsy confirmation. • The diagnosis of AD can be made with greater certainty and does not use the terminology of 'probable AD'. • Other diseases can be excluded with biomarkers. • The diagnosis of AD can be made prior to the onset of dementia. • And so on.

Table 2: Summary of the IWG-criteria. Adapted from [15] and [12].

The IWG-criteria made it clear, based on biomarker knowledge, that although no symptoms of AD are present within the individual, the presence of a positive biomarker does represent a risk factor for future disease progression [12][15].

In 2011, three working groups from the National Institute on Aging-Alzheimer's Associations (NIA-AA) developed new criteria [11]. In sum, the NIA-AA criteria have many similarities with the IWG-criteria. However, they are also different from the IWG criteria as visualized in figure 1. These differences are mostly related to the cognitive criteria (e.g. non-memory impairments), the use of combined biomarkers for AD diagnosis, the difference in terminology (e.g. MCI due to AD versus prodromal AD, preclinical AD versus asymptomatic at-risk for AD) and disease staging [16][17]. Here, it is not the right place, nor the aim of our study, to discuss in depth all differences between IWG- and NIA-AA criteria. However, both set of criteria are of great importance in the field of AD, as they both implemented a new framework that represents the clinical stages of AD by including biomarker information (see Figure 1).

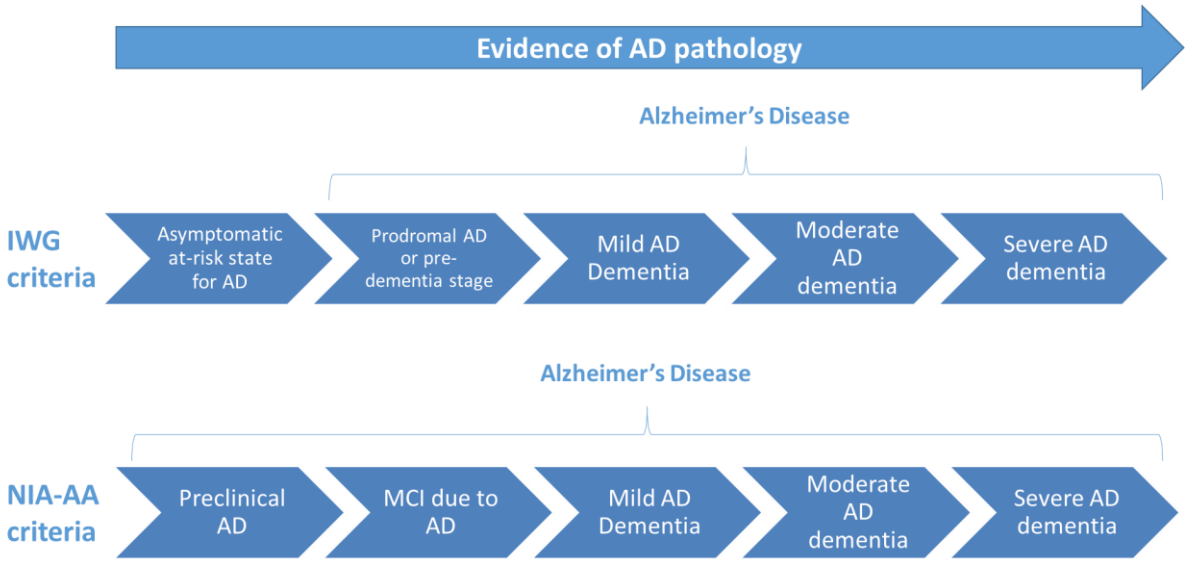

Figure 1: Alzheimer's Disease continuum based on the IWG-criteria and NIA-AA-criteria (Figure adapted from Downing et al. [17].

In the previous paragraphs, we have briefly sketched the most important historical findings and major scientific contributions within AD research. Within that overview, the discovery of biological markers for AD were mentioned. Now it is time to provide more insight in the meaning of biomarkers for AD.

First, we ought to distinguish diagnostic and progression markers. A diagnostic marker is disease specific, but often shows less the clinical severity of the disease. A progression marker shows less disease specificity, but indicates the clinical severity. Several criteria have been put forward in order to be a useful diagnostic marker. These criteria are, for example, the need for a high sensitivity and high specificity of the marker, the reproducibility in other laboratory, the non-invasiveness of the marker, good cut-off values to distinguish diseases, cost-effectiveness, and so on [1].

Secondly, we need to distinguish between genetic, biochemical and neuroimaging markers for AD:

(1) *Genetic biomarkers.* Genetic tests for AD are available for individuals who have family members with early-onset familial AD. These tests examine Apolopoprotein (APOE), presenelin 1 (PSEN 1), presenelin 2 (PSEN 2) and amyloid precurson protein (APP) [2][3]. APP and PSEN mutations are rare (estimated 2 - 5% of all familial cases), which implies that currently screening for these mutations has to be organised on an ad hoc basis [2]. When an assessed individual is carrier of the APOE allele e4 this will increase the likelihood of developing AD, yet it does not provide a guarantee that AD will occur later on. This is why

APOE e4 is classified as a risk gene for AD [2]. The other three genes (APP, PSEN 1 and PSEN 2) are deterministic genes, which implies that these genes will cause AD [3].

(2) *Biochemical biomarkers.* Here changes are being sought in cerebrospinal fluid (CSF) [4]. Via the procedure of a lumbar puncture (LP), whereby a spinal needle is inserted between the third and fourth lumbar vertebrae, CSF can be obtained. There are four established CSF biomarkers: Aβ40, Aβ42, total tau and phosphorylated tau. Aβ40, Aβ42 and phosphorylated tau provide information about the disease process in AD, and more specifically on the levels of brain amyloid and cortical neurofibrillary pathology [2]. Total tau is considered to be a nonspecific marker for neuronal loss as part of the neurodegenerative process [2]. Currently under further evaluation are other CSF candidates, such as Aβ oligomers, β-site amyloid precursor protein-cleaving enzyme 1 (BACE1) activity and concentration, secreted isoforms of APP and Aβ degradation [2]. Due to the invasiveness of LP and the possible side-effects (e.g. headache, nausea, dizziness and vomiting) for the assessed individual, researchers are continuing to search for non-invasive markers in other fluids, such as blood, saliva and urine [1][4]. However, many researchers believe that biochemical changes are more likely to appear in CSF since CSF is in direct contact with the brain [5].

(3) *Neuroimaging biomarkers*, which provide information on the structure, the metabolism and the function of specific brain regions [2]. Neuroimaging is further divided into three types of imaging: First, structural imaging provides information about the shape, the position or the volume of brain tissue. Structural techniques include magnetic resonance imaging (MRI) and computed tomography (CT). Second, functional imaging reveals how well cells in various brain regions are working by showing how actively the cells use sugar or oxygen. Functional techniques include positron emission tomography (PET) and functional MRI (fMRI). Third, molecular imaging uses highly targeted radiotracers to detect cellular or chemical changes linked to specific diseases. Molecular imaging technologies include PET, fMRI and single photon emission computed tomography (SPECT) [2].

To conclude this section: the ongoing search for novel biomarkers and the evaluation of current biomarkers will allow researchers and clinicians to continue refining the AD disease continuum.

Moving toward an earlier detection and diagnosis of AD

In the previous section, we have discussed what biomarkers for AD are and how their discovery and evolution has made it possible to detect the disease in an earlier stage. In this section, we will explore the rationale behind the movement toward earlier detection and diagnosis of AD, which is supported by many clinicians, researchers, pharmaceutical companies, patient advocacy groups, dementia organisations, and by politics. Earlier detection has gained considerable momentum due to several reasons:

(1) A first reason is the continued growth of the elderly population, whereby a new term has been introduced to describe the population changes: 'the oldest-old' [18]. For example, Christensen *et al.* have stated that "More than half of children born today are expected to celebrate their 100th birthday [19]." This is also linked with the increase of people living with AD and the fact that AD doubles in frequency every five years after the age of sixty-five [20]. Consequently, the published results from the 2016 annual report by the Alzheimer's Association were no surprise [18]. In their annual report, the Alzheimer's Association stated how there is an estimated increase from 5.3 to nearly 15 million people living with AD by 2025 in the United States of America alone [18]. On a global level, it is estimated that by 2050 there will be 100 million of people affected by the disease [2][18][21]. This is also a reason why the G8 and, for example, former US president Barack Obama made a presidential proclamation in October 2015 [8][22][23][24]. In that statement, he announced that by 2025 a treatment should be available to prevent, slow down, or cure AD in order to reduce the patients and their families affected by the disease [22].

(2) A second reason is that in many cases AD does not only financially burden the patient and his family, but also impacts society's health care costs [21]. For example, the 'World Alzheimer Report' in 2015 stated that the total estimated worldwide costs of dementia are 604 billion US dollar in 2010 [25]. In the 2016 report by the Alzheimer's Association, a survey showed that carers spent an average of 5155 US dollars (range between $<$ 1000 and $>$ 100000 US dollar) out of their own pocket each year to take care of a relative or friend with AD or other dementias [18].

(3) A third reason is the development and evolution of AD biomarkers. As previously mentioned in the introduction, biomarkers have allowed researchers and clinicians to detect disease abnormalities earlier and to establish a diagnosis with more diagnostic certainty compared to a probable diagnoses based on clinical criteria only [8].

(4) A fourth reason is the approval by regulatory authorities such as the Food and Drug Administration (FDA) and the European Medicine Agency (EMA) of the three amyloid tracers

(flutemetamol, florbetapir, and florbetaben labelled with $^{(18)}$F for PET imaging of beta-amyloid plaques in the brain) for diagnostic purposes in cognitively impaired patients who are being evaluated for AD [26][27][28]. In the research setting, the previous mentioned FDA and EMA approval was also used as a reason to start disclosing individual research results, such as amyloid PET scans, to the research participant [29]. This is one of the main topics investigated in this thesis.

(5) A fifth, and perhaps the most compelling reason, is that treatment might have a better outcome when initiated in an early stage before irreversible brain damage has occurred [30][31][32]. For example, Aisen and colleagues suggested that using anti-amyloid agents may be optimized by intervening before non-amyloid processes prevail and neurodegeneration begins [33][34]. Also, earlier recognition and thus intervention that could delay the clinical onset of dementia by one year, could result into an estimated reduced number of 9 million cases by 2050 [30][35]. This reasoning is also due to the current failure of drug trials. A recent publication has shown a 99.6 % failure drug rate for AD between 2002 and 2012 [20]. According to Cummings and colleagues, the rates continue at the same level [2][20]. So not just drug treatment, but also other forms of early intervention, such as cognitive rehabilitation, might lead to a better outcome for the patient when initiated in an earlier stage.

The previous mentioned reasons have been used to support and favour an earlier recognition and disclosure of AD. However, it is time to look at all possible ethical arguments and challenges that will provide us with a broader view on this particular topic. Hence, several ethical questions emerge. What are the ethical benefits and risks of an early disclosure? Is an early disclosure desirable and beneficial for the patient when treatment options are limited? Is it ethically justifiable to disclose biomarker-based results that have a limited predictive value and that lack individual timelines for future disease progression? How and under which conditions should the researcher disclose these results, such as amyloid PET, to the tested individual? Are patients and their relatives ready to live longer with the diagnosis of the disease due to an early disclosure of this information?

Differentiating between clinical setting, research setting and screening for Alzheimer's Disease

Before going in depth into the concrete details of this doctoral dissertation, we need to clarify the differences between the clinical, the research and the screening setting. Here, we shall briefly focus on the aims and purposes of each setting:

First, the clinical setting is perhaps the most well-known, as most individuals have consulted the clinical setting at least once during their lifetime with the aim of receiving medical advice and

help. Receiving medical advice is based on the initiative of the patient (and often due to the initiative or the presence of a relative in case of minors, patients with a cognitive impairment, and so on). Here the goal of the clinical setting is to focus on the health of these patients and to provide the necessary care.

Second, there is the research setting. Here, investigations are done based on the initiative of the researcher and the research team, whereby the main goal of research is to establish (new) medical knowledge, to validate new tools and to test (new) medical treatments. It is possible that research may benefit patients (e.g. therapeutic trials where patients may have access to otherwise unavailable treatment options), yet this is not the primary focus of this setting.

Last, there is the screening setting. Here screening is not done based on the initiative of the patient, nor of the researcher, but mostly by invitation of the government. This has to do with the primary goal of screening, which is focused on health profit and reducing societal burden [36]. For example, many countries are screening for colorectal cancer as this is ranked in Europa as the second most common cancer after lung cancer [37]. With this fact in mind, the Flemish Government (Belgium) started to screen for colorectal cancer in 2013 as this type of cancer significantly impacts the health care system. It must be nuanced that screening may benefit individuals to seek diagnostic consult after being screened for a certain disease, leading to health care interventions, lifestyle changes and so on. However, recent reports have also shown that not all screened individuals continue diagnostic consult. Due to this finding, the purpose of screening is often questioned; yet, the main goals of screening are to reduce societal impact in the long term.

In the field of AD, the rapidly growing elderly population, the increase of people at-risk of developing AD, the improved health care system for people with AD and their relatives, and so on, have been put forwards as arguments in favour of screening for AD [38]. However, screening for AD, or identifying people with a cognitive impairment that might be due to AD, is currently not recommended by, for example, the US Preventative Service Task Force and The UK National Screening Committee, since the criteria of the World Health Organisation (WHO) from 2008 cannot be fulfilled [36][38][39]. The WHO criteria (Table 3) were based on an earlier report developed by Wilson and Jungner in 1968 [40][41].

WHO-criteria (2008):
• The disease you want to screen for must be an important health problem. • There must be an acceptable and available treatment for the disease. • There must be a reliable method to detect and diagnose the disease. • The costs of screening should be acceptable compared to the cost on the health care system. • The advantages of screening have to outweigh possible disadvantages. • And so on.

Table 3: WHO-criteria. Adapted from [40] and [41].

When we apply the WHO-criteria to the field of AD, then we can conclude that the first criterion is applicable as AD poses a major health problem. However, there are no reliable predictors who in the population will convert to AD, there is no available treatment and it is unknown whether the costs of certain biomarker tests outweigh the cost on the health care system [42][43][38]. It is currently being reviewed whether advantages (e.g. to make lifestyle changes, to plan for the future,…) would outweigh possible risks and harms (e.g. emotional harm, expensive costs of screening, side-effects of treatment,…) of screening for AD [36][38][42].

In reality, there is no sharp distinction between the three settings. A few examples may clarify this. A first example is that referral to clinical trials often results from a visit from the patient to their clinician [44]. A second example is that screening in a certain population is often combined with additional research with the aim of further validating particular screening tools. Another example is amyloid imaging, which is mostly used in the research setting as one of the tests to include participants into trials. Since 2013, three tracers (florbetaben (Neuraceq, Piramal Imaging Limited); flutemetamol (GE Healthcare); florbetapir (Amyvid, Eli Lilly)) that bind to amyloid-beta have been approved for clinical use in patients with a cognitive deficit [26][27][45]. Consequently, appropriate use criteria have been formulated to facilitate amyloid imaging in the clinical setting [46][47]. However, amyloid imaging is currently less used within the clinical setting due to limited predictive value and the high expenses of the test, which are mostly not reimbursed by insurers [43]. The expenses from these tests are due to the limited availability of centres capable of performing a reliable analysis, and due to limitations in access to the radiotracers. For example, ^{11}C-labelled PiB has a half-life of 20 minutes, and ^{18}F-labelled tracers have a half-life of 90 minutes [45]. Despite the mentioned disadvantages and the less frequent use of amyloid imaging in the clinical setting, the approval of the three tracers may nevertheless blur the line between the research and the clinical setting.

Doctoral project

Scope of this doctoral project

Multiple domains, such as neuroscience, neuropathology, neuropsychology, and so on, are currently putting a large amount of work and effort in investigating all possible aspects of AD. However, in this doctoral dissertation we will limit the scope and focus on the following three aspects:

(1) First, the *early stage of AD*, which we have defined in our doctoral dissertation as *Mild Cognitive Impairment* (MCI).

(2) Second, we will limit our scope to *biomarkers* and in particular, we will focus on the use of amyloid PET imaging. We have decided to focus on amyloid PET imaging for the following three reasons: (a) amyloid PET is used within both the research setting and the clinical setting, (b) the approval and the appropriate use criteria of the amyloid tracers by health authorities allows its use within the clinical setting for patients with a cognitive deficit, which matches our targeted population of MCI patients [26][27], and (c) only first initiatives and reports on how to disclose amyloid PET scan results to the tested individual are available [48][49][50].

(3) Lastly, we want to focus on the *ethical issues* involved in an early biomarker-based result in both the clinical and the research setting as less research attention has been paid to this specific topic.

We acknowledge that this focus also implies a limitation on this doctoral dissertation. However, we do believe that our findings may provide valuable information and insight that may be elaborated on by further research.

Central research questions, general methodology and objectives

Central research question and methodology

The *central research question* of this doctoral dissertation focuses on mapping, analysing and providing an ethical reflection on the ethical issues regarding: (a) a clinical biomarker-based diagnosis in the early stage of Alzheimer's Disease, and (b) the return of individual research results, and in particular amyloid PET scan results in the research setting.

To answer the previous mentioned research questions, the Centre for Biomedical Ethics and Law upholds a empirically-informed *method of ethical reflection,* which was developed in 2005 by Borry and colleagues [51]. This method was further developed and implemented throughout many doctoral

dissertations in multiple domains (genetics, nursing ethics, research integrity, and so on) within the field of biomedical ethics [52][53][54][55][56]. Hence, the method of ethical reflection has proven to be a solid, well-developed and well-implemented method to conduct scientific research [51]. According to this process, the first step is to represent the state-of-the-art on the current available literature of the given topic. In a second step, empirical research provides a practical insight into the theoretical literature, as the opinions and views of lay people and professionals are explored. Based on the findings from the previous two steps, general principles and particular judgements are thereby brought into conversation with each other, with the aim of progressing in ethical reflection or resulting in concrete ethical recommendations [51].

Based on the general methodology of ethical reasoning, this consequently results in the following *three objectives* as part of this doctoral dissertation:

(1) To gain insight on the existing scientific literature on the ethical aspects of a biomarker-based results in the early stage of AD.

(2) To analyse and compare the current ethos and moral attitudes of the patients and other stakeholders (healthy adults, family members, caregivers, clinicians/researchers) about early AD disclosure with the existing ethical literature.

(3) To generate new ethical insights and reflection resulting in concrete recommendations to improve and facilitate disclosure of biomarker-based results.

Study population

To avoid confusion, it is important to define the study population that will be used for the qualitative empirical study as part of this doctoral dissertation. MCI is not the same as preclinical AD (before the appearance of symptoms) nor as early-onset (before the age of 65) AD. MCI is a concept that was introduced by Flicker *et al.* and by the Mayo Clinic Group to fill the gap between cognitive changes associated with normal aging and those associated with dementia [57]. MCI typically characterises the presence of an acquired objective cognitive deficit over the age of 50 which cannot be accounted for by other causes such as depression, medication or obstructive sleep apnea syndrome [8]. MCI is further divided according to the cognitive domain that is mainly affected, most frequently episodic memory and executive function [8]. MCI patients constitute a significant portion of patients consulting a memory clinic and may identify those ware are at risk of developing dementia in the future [57]. Current estimates suggest that up to 50% of MCI patients have underlying AD [9]. If the underlying pathology of MCI is AD, MCI due to AD or prodromal AD is used.

Figure 2 shows on the AD continuum how cognitive functions deteriorate compared to normal aging.

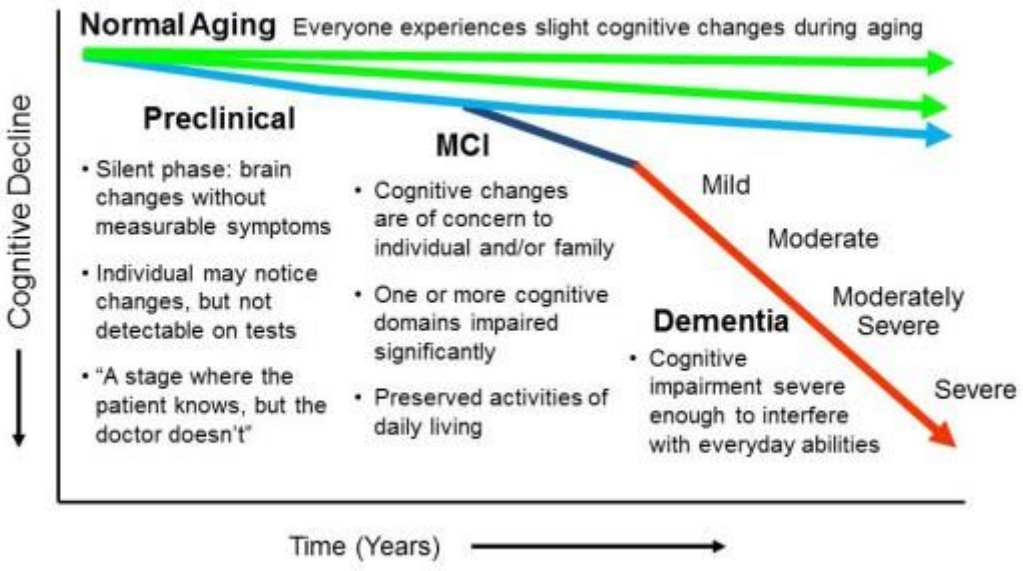

Figure 2: Normal aging versus progression to AD or other dementia's. Figure adapted from [58].

In 2010, three important clinical criteria for MCI have been put forward in order to support a diagnosis of MCI [59]. These criteria are:

(a) A concern regarding a chance in cognition in comparison to the person's prior level. This concern may be obtained from the patient, from an informant who knows the patient well or from a skilled clinician observing the patient [59].

(b) An impairment in one or more cognitive domains that is greater than would be expected for the patient's age and educational background [59].

(c) Preservation of independence in functional abilities. In other words, MCI patients mostly maintain their independence in their daily activities, although performing and executing these daily activities may take more time, and may be less efficient [59].

Overview of the doctoral dissertation

We would like to note that we have followed regulations from our *Doctoral School of Biomedical Sciences* (Patient-Related and Public Health, KU Leuven), which implies that our doctoral dissertation consists of publications, submitted to peer-reviewed journals, and presented here as chapters. There is a conceptual line throughout this dissertation, which allows us to present the published papers in a coherent manner. To avoid multiple overlaps with the chapters, this general introduction only briefly refers to the background and the used methodology. Before going in-depth into each chapter, we would like to address the main overview of the doctoral dissertation according to its objectives and consequent chapter publications (Table 4).

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Table 4: Overview of the doctoral dissertation.

Part 1 - Literature study

The purpose of conducting a literature study is to gain a clear understanding of the ethical challenges that have been reported in the available literature. Additionally, it is an exploratory step which is essential in developing and defining pitfalls, which are in need of further empircal investigation. In this doctoral dissertation, the literature study will be conducted in two steps:

First, we will conduct a review *on the ethical issues of an early biomarker-based diagnosis of Alzheimer's Disease in the clinical setting.* This review will explore the theoretical bioethics literature by creating a search algorithm in several databases, such as Pubmed, Web of Science and Embase [60][61]. Additional articles may be retrieved by using the `snowballing method', i.e., where the reference lists of selected articles will be consulted.

Second, we will explore the literature regarding *the early disclosure of individual research results and focus on biomarker-based results in the field of AD, with a specific attention to amyloid PET scan results.* We will cluster and discuss the ethical issues by using the model of '*Principlism'* (autonomy, beneficence, non-maleficence and justice) as described by Beauchamp & Childress [62]. This model is a framework commonly used within biomedical ethics, with the aim of clustering a wide range of moral arguments.

Part 2 - Qualitative Empirical Study

In this doctoral dissertation, the empirical study consists of both interviews with patients and focus group interviews with stakeholders.

Semi-structured interviews with amnestic Mild Cognitive Impairment patients (aMCI)

In order to obtain a better understanding of study participants' decisions to enroll in a research study and their reasons for opting in for the disclosure of their amyloid PET scan result, there is an increased need for qualitative research. Hence, we will conduct an interview study, with the aim of providing in-depth and in-detail insights into the motivations, opinions and experiences toward clinical trial participation and the disclosure of amyloid PET. To our knowledge, this is one of the first qualitative studies with amnestic MCI patients as a part of a clinical trial where participants could opt in for the disclosure of their result (option to receive their brain amyloid PET scan binary visual read result).

We will conduct three semi-structured interviews at different time interval with each study participants who agrees to take part in the substudy of the BioAdaptAD study:

(1) A pre-interview before the disclosure of the result.

(2) A first post-interview two weeks after the disclosure of their amyloid PET scan result.

(3) A second post-interview six months after the disclosure of their amyloid PET scan result.

The study protocol and interview guide will be developed based on the first phase (literature study) of this doctoral dissertation. The interviews will be analysed using the NVIVO 11 software and until data saturation is reached, which is a commonly used method of analysing qualitative data [63][64][65].

Focus group interviews with stakeholders

In order to obtain a better understanding of stakeholders about an early AD disclosure and about whether or not to volunteer in a clinical trial on AD, a qualitative study is necessary. A focus group interview will provide an in-depth discussion about the above mentioned topics, with the aim of capturing the opinions and experiences of several participants in one group [66][67][68]. We aim to conduct focus groups that consist of five to ten participants with the following stakeholders: (a) healthy elderly (60+), (b) family members/caregivers, (c) nursing staff of an elderly care home and (d) clinicians/researchers with expertise in AD/dementia. Recruitment will be done through a contact person who matches the specific criteria of the focus group: for example, a clinician who contacts other clinicians [63]. Recruitment will only take place after approval of the '*Social and Societal Ethics Committee'* (SMEC). We shall use a relatively structured format for the discussions, by using three cases and a starting or opening question. These cases will be developed based on the ethical issues that have emerged in our literature study. The focus group interviews will be audiotaped, and analysed via the NVIVO 11 software via the methodology of content analysis [63][64].

Part 3 - Ethical recommendations and concluding remarks

In the final stage of the doctoral project, we will integrate the findings from our empirical studies with the results from our review investigation, resulting in ethical recommendations to facilitate and to improve the disclosure of biomarker-based diagnosis in the early stage of AD and the return of amyloid PET scan results in the research setting. This will represent the final chapter and concluding remarks of the doctoral dissertation.

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Chapter 1 Review of the ethical issues of a biomarker-based diagnoses in the early stage of Alzheimer's Disease

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Abstract

Background: Today, many healthcare or dementia organizations, clinicians, and companies emphasize the importance of detection of Alzheimer's disease in an early phase. This idea has gained considerable momentum due to the development of biomarkers, the recent FDA and EMA approval of three amyloid tracers, and the failure of a number of recent therapeutic trials conducted in the early dementia phase. On the one hand, an early aetiological diagnosis can lead to early and more efficacious intervention. On the other hand, it is questioned how early an etiological diagnosis is beneficial to the patient. Here we consider ethical issues related to the process of biomarker testing and the impact on the diagnostic disclosure to patients with mild cognitive impairment due to prodromal Alzheimer's disease.

Methods: A systematic review of the theoretical bioethics literature was performed by using electronic databases. The review was limited to articles published in English between 2003 and 2016.

Results: A total of twenty articles were included in our effort to make an analysis of the ethical challenges. One of the biggest challenges was the uncertainty and the predictive value of the biomarker-based diagnosis where patients can be amyloid positive without full certainty whether or when they will develop symptomatic decline due to Alzheimer's disease. Another challenge was the tension between the right to know versus the wish not to know, the limited efficacy of currently available treatment options, and the opportunities and consequences after receiving such an early diagnosis.

Conclusion: Based on the results and the additional comments in the discussion, several unanswered questions emerged. Therefore, careful consideration of all these ethical issues is required before the disclosure of a biomarker-based diagnosis to the patient with mild cognitive impairment due to Alzheimer's disease.

Background

The development of biological markers or biomarkers, such as cerebrospinal fluid (CSF) and amyloid positron emission topography (PET), and the recent Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval of three amyloid tracers makes it possible to diagnose Alzheimer's disease(AD) at an earlier, pre-dementia or even at a preclinical stage. Biomarkers may be of potential clinical utility to detect abnormalities either before the appearance of symptoms or when the first subtle symptoms appear. The use of biomarkers approved for clinical use can allow the clinician to make an earlier diagnosis and to monitor these patients better [1][2].The current review solely focuses on the ethical issues that may arise for the patient, caregivers and the physician.

It has become clear that intensive research has been carried out and is still ongoing to define the accuracy and clinical utility of AD biomarkers [3]. Here, some of the ethical questions raised by the availability of AD biomarkers in the predementia phase and their impact on the disclosure debate, will be discussed. Awareness of these ethical challenges and the medical-ethical principles that are at stake is important to avoid any form of harm due to the diagnostic disclosure to the patients and their family.

Even though considerable research has been devoted to ethics in dementia or Alzheimer's disease [4][5][6][7][8][9][10][11][12], rather less attention has been paid to the ethical aspects in mild cognitive impairment (MCI) and MCI due to AD. MCI refers to the presence of an acquired objective cognitive deficit above the age of 50 with limited impact on the activities of daily living and which cannot be accounted for by other causes such as depression, medication or obstructive sleep apnea syndrome [13]. MCI is further divided according to the cognitive domain that is mainly affected, most frequently episodic memory and executive function [13]. MCI patients constitute a significant portion of patients consulting a memory clinic [14]. Current estimates suggest that up to 50 per cent of MCI patients have underlying AD [15].

Therefore, a systematic review was performed that focuses on the ethical issues in a biomarker-based diagnosis in the early stage of AD. Since approval of Amyloid tracers by the regulatory authorities is limited to patients who are evaluated for cognitive decline, this review will be restricted to the impact of a biomarker-based diagnosis in MCI due to AD, or prodromal Alzheimer's disease. For this review, their application in persons who do not have cognitive symptoms or signs (referred to as preclinical AD) will not be considered.

Methods

Aim

In this article, our aim was to investigate the theoretical literature that addresses ethical issues related to an early biomarker-based diagnosis of AD. Here, an early diagnosis of AD refers to the MCI due to AD or prodromal AD. This aim can be achieved by using the tool of a systematic review that has been described by, for example, McDougall [16]. According to McDougall, there has been interest in applying the techniques of systematic review to the bioethics literature [16]. Systematic reviews are a standard technique in medical fields, used to assemble the existing evidence about a particular medical intervention or about a medical topic; they follow a formal method, aiming for a comprehensive review of the literature with minimal bias [16].

Literature search

An initial search using 'prodromal Alzheimer's disease' only yielded a limited result. Searching for MCI due to AD gives us a vast number of articles but in combination with the search for ethical issues that are applicable for early diagnosis, the results are again very limited. Based on these first manual explorations of the literature, we opted for the general terminology of Alzheimer or dementia in our search algorithm instead of explicitly focussing on MCI due to AD and pAD. Using the broad term of AD in our search string was done for two reasons: (a) Articles about the early stages of AD often use general key words, such as Alzheimer's disease and dementia to increase potential readers. This way, specific articles on MCI due to AD will still emerge in our search algorithm. (b) Searching in the general AD literature on this topic makes it possible to see which ethical issues are addressed in general AD literature and which are applicable to MCI due to AD. This way, we can see possible differences between regular AD and an early diagnosis of MCI due to AD.

This resulted in the following search algorithm: ((Alzheimer* OR dementia) AND (ethic* OR ethical) AND (biomarker* OR test*) AND (diagnos* OR disclosure)). Four databases were used: Pubmed, Hubmed, Web of Science and Embase.

The search was conducted in January 2016 and the results from Pubmed, Web of Science and Embase were saved so that electronic updates (until April 2016) could provide a weekly update if new articles were published.

We limited our search algorithm to articles published between January 2003 and January 2016. We chose a timeframe of thirteen years, to exclude the reviews published in the nineties and in the beginning of the new millennium, that focused on the ethical issues related to AD and to continue the exploration of more recent published articles [9][10][11][12][17]. There was a systematic review published in 2013 by Strech *et al* which summed up all the ethical issues related to dementia care in general [18]. However, this list contained no further elaboration on the ethical issues and did not refer to MCI due to AD. This clarifies why our search algorithm started in 2003 and not in 2013 based on the review of Strech and colleagues [18].

Electronic database searches

The search yielded a total of 516 articles (Figure 1). These articles were screened in the following order:

(1) In the first phase, the articles were screened based on the title and abstract. In this phase, 228 duplicate articles were excluded. A further 237 articles were excluded based on one (or both) of the following two criteria: (a) articles that were guidelines or empirical studies, (b) articles that emerged with the same or similar key words that matched our search string but did not have relevance to the research question. This is not uncommon in systematic reviews [16].

(2) The second phase of screening looked at the full text. Out of the fifty-one remaining articles, we excluded thirty-three articles because they did not discuss ethical issues. One more article was excluded as there was no full text available.

(3) Finally, three more articles were added based on the reference list of the included articles. One of the included articles based on this snowballing method was a systematic review on empirical studies that was added due to the importance and ethical reflections throughout the article.

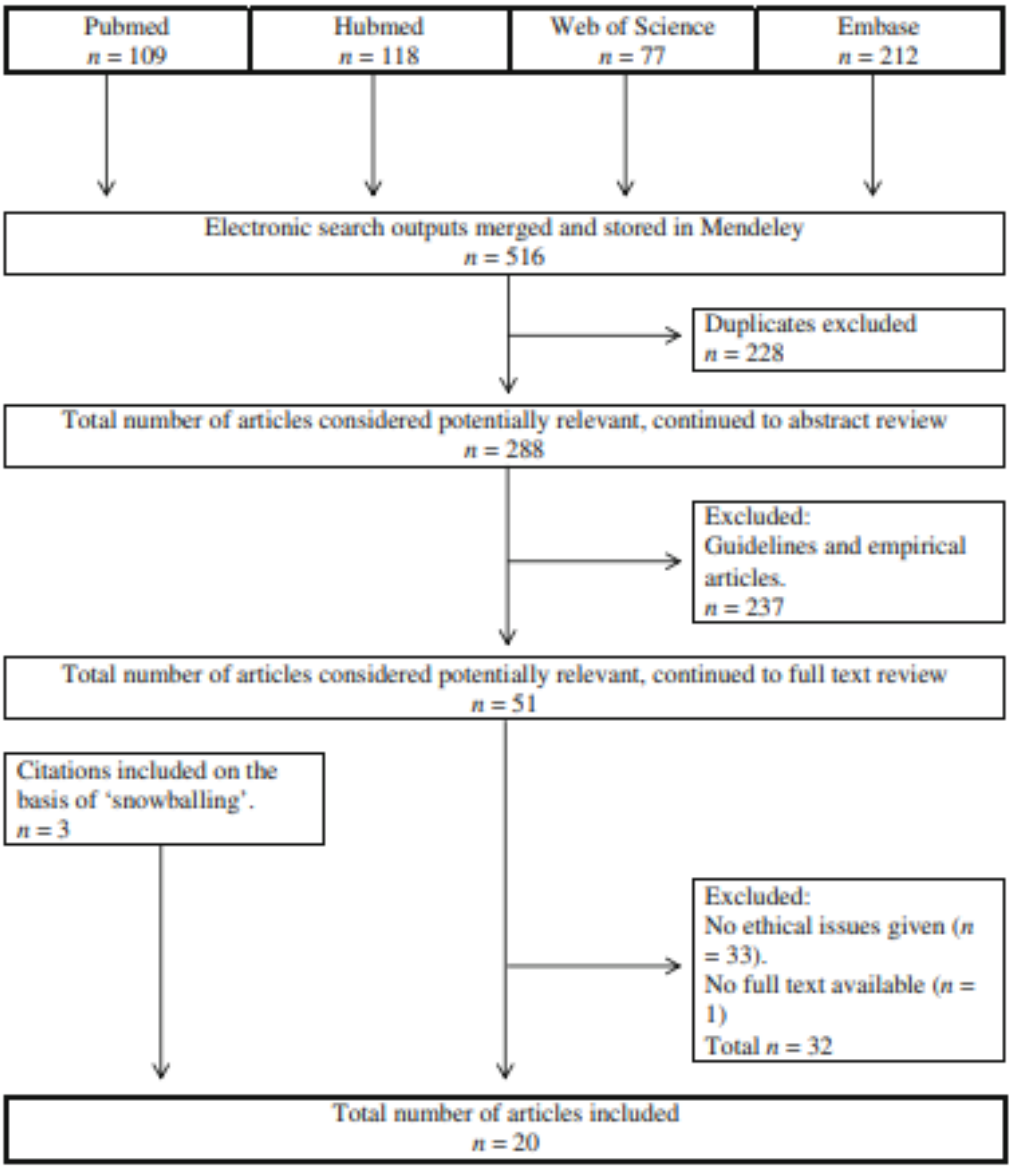

Figure 1: Results of the search algorithm in the electronic database.

Results

A total of twenty articles were included for this systematic review: seventeen articles from the electronic databases and three articles based on the 'snowballing method'. Appendix 1 indicates which articles and type of articles were included, where they were published and if the articles contain general AD literature or provides specific issues on MCI (due to AD) or pAD. The results were structured into ethical issues that occur during the process of diagnosing and those that occur after the disclosure of the diagnosis.

Ethical issues before and during the process of diagnosing

Right to know and the wish not to know

Patients have the right to decide for themselves whether they want to undergo specific clinical tests and whether they want to know the diagnosis based on the outcome of these tests [1][18].When patients decide to undergo clinical testing and when they express the wish to know, clinicians should inform them about their clinical test results and diagnosis. After testing, some clinicians use the ethical principle of non-maleficence to restrict or 'to soften the blow' of the information that is provided to the patient [18]. This principle requires that the clinician does everything to prevent and avoid possible physical, emotional or psychological damage to the patient [1], using, for example, an adapted, less harsh, diagnosis, such as: "you have troubles remembering" [18]. Antoine and Pasquier also indicate that due to the risk of making an erroneous diagnosis (for example, Mattsson *et al* indicate that even a test with diagnostic accuracy of > 90 per cent still results in a number of people being misdiagnosed [19]) and in combination with the fact that patients have a subtle cognitive deficit, it may be difficult for the clinicians to communicate this uncertainty as it can cause distress to the patient [20]. Howe describes it as a reluctance to diagnose the patient with AD or MCI due to the fear that this uncertain information (a patient with MCI due to AD does not always progresses towards dementia) may have the effect of placing 'a dark cloud' over the remainder of the patient's life [21]. However, Antoine and Pasquier indicate that clinicians should not deprive the patients of their right to be informed. Even if the news is about a possible future diagnosis or if there is uncertainty involved with the diagnosis, patients mostly want to be told their diagnosis instead of being kept ignorant [17].

The right to know is not only questioned based on the ethical principle of non-maleficence but also due to the cognitive impairment of patients diagnosed with Alzheimer's disease [20]. Once patients have evolved into a more severe dementia stage, patients with AD may lack capacity and

may be considered incapable of making informed decisions and under such conditions others, most often family members, must make decisions on their behalf [21]. Here, advance directives (e.g. about future care and treatment) are important so that the patient can reflect on these topics in advance and can make certain decisions before the patient is deprived of their decision-making capabilities when the cognitive deficit becomes too severe [1][21].

In the case of an early diagnosis the awareness and the capabilities to understand the diagnosis is mostly preserved [20]. This means that the patient is still capable and well aware, but that the decision-making capacity may be slightly impaired when the patient with MCI is experiencing subtle memory complaints [22]. Based upon this right to know, some patients could feel dissatisfied or upset if they found out that the clinician adapted this information [20]. Returning to the ethical principle of non-maleficence, this would imply that not supplying this information early in the AD stage may go against the patient's best interests [22]. Additionally, these patients could also feel harmed because they did not receive all the proper information concerning their own health.

The practice of healthcare professionals not being truthful with the patient or withholding the diagnostic information can result in a loss of trust and can impact the physician-patient relationship but also the patient-family relationship [21]. According to Cornett and Hall, it is important to take the patient's individual capacity, level of awareness and wishes into consideration before deciding to directly disclose the diagnosis or "to soften the blow of the diagnosis" [21]. For the clinician, this is a complex situation as it is difficult and time consuming to get concrete knowledge about the awareness and capabilities of the patient and to estimate how the patient might emotionally respond to this information [20].

While most patients would want to know their diagnosis as early as possible, it is possible that some patients express the wish not to continue further clinical investigation and not to be informed about a certain or any test result [3][17][22]. This right not to know makes the challenge more complex since clinicians can never generalize that every patient wants to know a test result or a diagnosis [3][20][22]. For example, these patients may believe that they would lead a better life not knowing whether they have or will develop AD [22]. According to Howe, if a clinician wishes to support patients who do not want to know they have or will develop AD, the clinician must respect the patients' wish [22].

The uncertainty and the limited predictive value of the diagnosis

Biomarker tests currently do not allow the clinician to express a definitive diagnosis due to the predictive nature of biomarker tests and the uncertainty of biomarker results that pose a critical concern [2][20][23]. These tests may give "guidance" as described by Werner and Korczyn as to

who may progress more rapidly. As of yet, there are no clear timelines or good indicators to show when the patient with MCI will convert towards dementia due to AD [24][25]. This means that a positive amyloid result does not establish a definitive diagnosis of AD and does not automatically imply that the patient with MCI will develop dementia due to AD in the foreseeable future [24][26]. However, a negative amyloid result greatly reduces the likelihood that the patient with MCI has an underlying AD pathology causing MCI. Awareness about using accurate terms is needed. For example, Werner and Korczyn state that it would be erroneous to view MCI automatically as "very mild AD" [25]. This may only be the case once it is known that the underlying pathology in MCI is AD [25].

It is important to explain the uncertainty and the predictive nature of the biomarker-based diagnosis to the patient and relatives prior to testing. According to Antoine *et al* this is a rather "delicate exercise" as such time-consuming but necessary communication requires knowledge of the patient' wishes, preferences and capabilities to comprehend medical information [20]. Awareness on how clinicians feel when communicating this uncertain diagnostic information was also mentioned in the literature [20]. In many cases, the clinician is perceived by the patient as an expert and holder of truth. With this in mind, receiving an uncertain diagnosis may dissatisfy certain patients and lead to a situation where patients seek a second medical opinion elsewhere as they prefer receiving a straightforward "yes" or "no" diagnosis to the question whether or not they have or will have AD in the future [20].

Even though the use of AD biomarkers has the positive advantage of informing patients and their family, there are also serious disadvantages with the use of these biomarkers [27]. As was mentioned above, MCI patients with abnormal AD biomarkers have an uncertain outcome, in particular regarding the timeline of future cognitive decline at the individual level [25], and information on the presence of biomarkers may, according to Visser *et al,* cause stress to patients and their family [27].

To keep the rate of a false-positive biomarker diagnoses at a minimum, it is necessary to avoid potential negative emotional reactions, such as fear and feeling worried, in subjects that are not affected by a neurodegenerative disease [1][2]. Since a false-positive diagnosis will most likely result in a treatment, any harmful side effect, is according to Mattson *et al* "*a serious infringe"* on the basic ethical principle of non-maleficence [19]. The risk of serious adverse effects from treatments under development should not be underestimated. In addition, starting a treatment, without proven benefit as was mentioned above, could also be expensive for patients and society, especially when it's in a false-positive case [19].

On the flip side, false negative biomarker-based diagnosis should also be avoided. This way, the patient does not feel falsely reassured and deprived of several opportunities such as arranging future care and starting interventions that can provide symptomatic relief and delay progression [1].

Treatment

There is currently no treatment available to prevent or cure Alzheimer's disease [2][21][22]. There is the possibility to use drugs, such as acetylcholinesterase inhibitors (AChE-1) and memantine [2]. These drugs can provide symptomatic relief, delay progression and sometimes improve the quality of life of the patient. These medications modestly improve cognitive, functional and behavioural symptoms across the AD dementia spectrum [2]. Unfortunately, this will only be of help for some patients and does not imply guaranteed success for every patient [1][23].

Despite the limited efficacy of drug treatment, patients can adjust their lifestyle through physical, mental and social activities [22][24], even though there is no consensus regarding the impact of these dietary and lifestyle factors. This physically active lifestyle is known to be beneficial for general health and may also possibly delay further cognitive decline [24].

In the literature, the question is raised whether or not it is meaningful to provide an early diagnosis to the patient in the asymptomatic or the very early symptomatic stages of the disease [2]. Disclosing the diagnosis without the possibility of providing an effective treatment endangers the ethical principle of non-maleficence since the early diagnosis can potentially cause (emotional) harm to the patient [1]. For example, patients can feel shocked or astonished when finding out that there is no treatment that can help them in the near future. Other patients may even rebel against news of a diagnosis that is not accompanied by the possibility of changing the outcome of the disease. And yet, not disclosing the diagnosis would also harm the patient's right to be informed. Moreover, the absence of an early disclosure renders it impossible for patients and their family to make appropriate arrangements for the future when cognitive and functional levels still allow patients to accomplish this in a self-determined way [2]. Although drug treatment has limited efficacy, not disclosing the diagnosis and not starting therapy in an early stage, takes away the opportunity to provide symptomatic relief and to possibly delay further cognitive deterioration in MCI due to AD and AD [1][20].

Ethical issues after receiving the diagnosis

Planning the future

After being informed about the diagnosis, there is the opportunity for patients and their family, to make certain decisions about the future [22][25]. Especially in the early disease stage, this is crucial as patients are still aware and capable of making autonomous decisions. As Viloria Jiménez *et al* write: "*Limiting patients from taking part in these clinical decisions reduces their autonomy and ignores the patient's will while they are still able to make such decisions"*[1]. These decisions can be, for example, about financial, legal matters and future care [2][20][27][28]. For example: "Can family members and relatives help out or will there be home support by professional caregivers?" "When the disease has become too severe and too burdensome for the family caregivers, can the patient go to a nursing home or is there any alternative available [20]?" For this purpose, it is important to anticipate daily aspects that in the near future will become difficult for the patient [20].

Advance directives are an appropriate way to determine the patient's wishes about test and treatment before the patient is incapable of expressing them at the severe stage of AD [1]. During the process of planning the future, the presence of relatives and caregivers is beneficial in order to know what their family member with MCI due to AD wants before the patient is no longer capable of expressing these wishes [1].

The review by Draper *et al* describes how there are patients who refuse to receive any type of treatment that can unnecessarily prolong their life with Alzheimer's disease [28]. There are also patients who express the wish to terminate their life, yet active life-ending interventions are only accepted in countries where euthanasia and physician assisted suicide under strict conditions are legal [28]. Currently it is unknown how many patients with mild cognitive impairment would consider euthanasia. Draper *et al.* and Davis [29] suggest that a patient might consider rational suicide based on financial reasons and to reduce family burden. Another reason suggested by these authors is to allow patients to end their lives in a manner that is consistent with the life they had before experiencing memory complaints [30].

Although an early diagnosis provides the patient and their family with an opportunity to make certain decisions, advance directives are often under debate because the patient's views on treatment, care, and end-of-life decisions can change as the illness progresses [30].

Possible consequences

The included articles mention how several consequences can occur after the disclosure of an early diagnosis. These implications are related to work, driver's licence, insurance, and stigmatization.

First diagnosis could impact on the patient's employment situation. This is can occur if a patient's medical records are not protected and an employer gains access to their personal information [20][27][31]. For patients who are still working, job loss may have a negative impact on self-confidence. For example, they may feel unappreciated or feel that they are no longer contributing to society. The financial impact of job loss may be higher if a patient is forced to resign or is fired before reaching the age of retirement. Alternatively, some patients may feel relief about quitting their job before cognitive deterioration worsens [3].

The literature also indicates that an AD or dementia diagnosis can place restrictions on the mobility of patients by precipitating the removal of their driver's licence [32][33][34][35]. On the one hand, this restriction is a measure to prevent car crashes and as a safety protection for the patient and society. On the other hand, patients may feel that this is a violation of their autonomy [32][34]. Although driving skills can worsen when a person is affected by cognitive decline, driving is not necessarily unsafe. Depending on the disease progression and the severity of Alzheimer's, problems can range from decreased comprehension of traffic signals to geographic disorientation. Carr and Ott indicate that "a diagnosis of dementia should not be the sole justification for the revocation of a driver's license"[35]. Especially in the earliest stages, such as MCI due to AD, it is recommended to monitor cognitive and functional skills before automatically restricting the patient's driver's license [34]. In case of doubt, an individual assessment of the patient's driving skills via an on-road driving test might be a valid predictor of crash risk and how the patient copes and responds to real-life traffic events [1][32][34]. An additional problem is that physicians often feel uncertain of their legal responsibility to report unsafe drivers to either the licencing authorities or the state. It is preferred that referral to the licence authority is done with the patient's knowledge. A consequence of reporting the patient to local licencing authorities is that this could affect the patient-physician relationship [36].

An additional consequence of the diagnosis is that it implies that this information becomes part of the medical record, and patients may fear that biomarker or genetic information may influence their insurance status. When there is no adequate protection of privacy and confidentiality, this can cause denial of coverage or excessively high premiums [2][32][27]. Even though insurers are not allowed to gain access to this medical information, this can be a problem

in countries where there is no specific regulation. To prevent pharmacy and medical records being disclosed to insurers, privacy and confidentiality laws are needed [31].

Scholars have also raised concerns about the possibility of stigmatization resulting from early diagnosis of AD. Stigmatization refers to society's negative perception whereby AD is often perceived as an awful disease that gradually leads to the loss of personality and capabilities [19][32]. Cornet and Hall refer to qualitative study on patient and family experiences from Smith and Beattie (2001) [37] and a questionnaire from Husband (2000) [38] to indicate that people with AD often feel that they are observed by others as being less capable compared to persons without AD [21]. To prevent a patient being confronted with stigmatization, clinicians often avoid full disclosure by using, for example, a less accurate word to describe the cognitive decline. Some clinicians consider this approach to be a 'preventive' measure [21]. However, not telling the truth or avoiding the label "Alzheimer's disease" could confuse the patient more and delay the process of facing the reality that they have a memory deficit which can deteriorate in the near future [20]. Due to this negative stigma, society is often more afraid of having AD than dying from a heart disease, diabetes or a stroke [20]. Commentators have suggested that laws should be changed and campaigns about what AD truly implies are needed in order to change this negative social perspective about AD [31][39]. An effort to decrease people's fears and to reduce the stigma of AD is needed. This can be done by expressing to the general public that AD does not necessarily entail disability [31][39].

Emotional responses

Patients emotionally respond and cope with news of a diagnosis in different way. On the one hand, patients can feel, for example, relief or a reduction in anxiety because they finally know what is wrong with them after a process of searching for the cause of their current memory complaints [1][25][27][28]. Howe describes how patients informed of their MCI diagnosis, sometimes feel better because they now understand why they are having these subtle memory problems [22]. On the other hand, patients can experience negative emotions after receiving the diagnosis. Especially in the three months after the disclosure, the patient might experience feelings, such as reduced hope and despair [25]. Serious fears include, becoming or already being a burden for their partner and relatives and losing their own autonomy and capabilities [20]. Receiving the diagnosis and often in combination with the negative perception of society about AD, the diagnosis can have a negative impact on the patient's self-confidence and self-appreciation [19][32]. The study by Cornet and Hall indicates that people with AD often feel ashamed compared to persons without AD [21].

After receiving the diagnosis, it is possible that patients would feel that they would have had a better life if they did not know their diagnosis [22].

The literature also explores the consequences of the diagnosis for relatives of a patient; partners and relatives not only have to cope with their own reaction but also with the reaction of the patient who received the diagnosis [20].

Another ethical issue described in the literature is the difficulty for the clinician to predict whether or not a patient is at risk of developing suicidal behaviour after receiving the diagnosis of AD [24][31][39]. Even though it is unclear if this is linked to the disclosure of the diagnosis or caused by the mood disorders secondary to the disease itself, awareness about the impact of a diagnosis remains important [19]. Patients with mild cognitive impairment in combination with high educational level and preserved insight are at risk for suicide. Even though this response is extremely rare, patients can be shocked by the news that they are at risk of developing AD dementia in the future [1][2].

Based on the fear of causing a negative emotional reaction, difficulties in coping with the diagnosis and the possibility of an increased suicidal risk, some family members request that the diagnosis should not be disclosed to their relative with AD [20][21]. Paradoxically, the family members or caregivers of patients do express the wish to be informed themselves of an AD diagnosis, even though they do not always wish the patient to be informed [20]. However, the option not to fully disclose the diagnosis without allowing the patient to express their own opinion and preferences, can consequently result in the feeling of being held in ignorance and in a loss of trust their relatives and in the clinician [20][21]. Although the diagnosis is often seen as potentially harmful knowledge, a "conspiracy of silence" as described by Viloria Jiménez *et al* put it, should also be avoided [1][19][31].

Discussion

The high percentage of reviewed articles published after 2010 indicates that academic interest in this issue has not declined during the past few years. There are fewer articles specifically on MCI due to AD compared to the general AD literature. However, many articles on AD address the ethical challenges and opportunities related to MCI due to AD, yet without explicitly stating that most of these challenges are applicable to this early stage. Although there are many similarities between a general AD diagnosis and a MCI due to AD diagnosis, such as the emotional responses and coping strategies of patients after receiving the diagnosis, there are important differences and ethical issues in need of more in-depth reflection.

The results indicate that patients have a right not to know their diagnosis. The right not to know is a relatively new concept in bioethics that has been brought to the attention by genetic testing for Huntington disease (HD) [40][41]. The right of the patient not to undergo testing and/or not to receive a test result is based on three moral grounds: (a) autonomy, (b) no-harm and (c) the right for protection of the personal atmosphere [42]. (a) Patients have the right to make an autonomous decision about their own health and whether or not they should undergo a genetic test and receive a test result. (b) No-harm refers to avoiding potential (physical) risks during testing and emotional or psychological difficulties after receiving the test result and the fear of being discriminated against based on a positive test result. (c) The right for protection of the personal sphere implies that the patient has a right to know certain medical information, but not a duty to receive all this information. In this case, receiving unwanted information can be seen as an invasion into the personal life of this person [42]. The right (not) to know in the context of MCI due to AD is based on the same three ethical principles as described above. However, a rationale for not undergoing testing and for not wanting to know the outcome of these specific tests, is that a positive result in HD is different from a positive result in MCI. For example, a positive genetic test result for HD implies that the person will develop HD in x-amount of time to come. A positive amyloid PET scan for MCI implies that the underlying pathology is due to AD, yet does not mean the patient will necessarily develop dementia due to AD in the future. In addition, in HD a positive test result also has implications toward heritability aspects for relatives, which is not the case for amyloid PET scans. This is often another reason why some individuals prefer to remain in ignorance for HD.

It might be difficult for family members, relatives and clinicians to understand why the patient does not want to know, yet as Vandenberghe *et al.* write: "*It is ethically important to avoid situations where the*

patient knows more than what he or she would consider desirable or beneficial" [15]. This statement is based on the concept of "power" which can be clarified in two ways. On the one hand, this quote refers to the power of choice, whereby the patient is empowered to make an autonomous decision about whether to undergo biomarker-based testing and to know the outcome of these tests. For example, up to 70 per cent of AD patients want to know what is wrong with them [50]. This is in contrast with the findings reported in empirical studies [49][52][53][54][55], whereby some GPs tend to avoid giving full disclosure to the patient based on the principle of non-maleficence (no-harm). More concretely by the fear of causing (emotional) harm to the patient. In our opinion, telling the full truth about the diagnosis, and in this way respecting the autonomous decision made by the patient, is important to maintain the level of trust between patient and family and patient and clinician. The entire truth about the diagnosis provides patients and their family with the opportunity and "power" to be prepared for possible cognitive deterioration in the near future. Patients with MCI are still aware and competent to make an autonomous decision and to plan ahead. This is a major difference with the severe stages of AD, where the autonomy and the decision-making capabilities can be affected. For example, when these decision-making capabilities are affected, the patient legally can no longer request euthanasia. Although planning the future and making certain arrangements are of importance in each stage of the disease, it is of most importance to arrange these matters when capabilities of the patient still allow him to do so. With this information in mind, it is important to discuss the benefits and risks with the patient and the degree of disclosure prior to the biomarker-based testing instead of using a paternalistic approach where the decision is made by the clinician and family members of the patient.

On the other hand, knowledge about an early MCI due to AD diagnosis does not always imply "power" since current drug treatment options do not cure and only have limited efficacy. Although treatment options are limited for both MCI and AD, the difference lies within the severity of the disease. Treatment options in the dementia stage of AD will focus more on symptomatic relief and arranging palliative care. Treatment in MCI due to AD may include the use of *cholinesterase inhibitors*. Yet current evidence about the efficacy of these drugs in the MCI stage of AD is lacking. Patients with mild cognitive decline can be eligible for participation in clinical trials where new diagnostic and treatment options are being tested and evaluated in MCI due to AD.

Multiple surveys have indicated the difficulties that general practitioners (GP) experience in diagnosing AD. A first difficulty is the pressure to give a diagnosis within a consultation time of approximately fifteen to twenty minutes. The lack of time to make a proper diagnosis by taking the patient's individual situation into account is problematic [43][44]. A second struggle refers to the difficulty in recognizing the symptoms of AD. One GP in the survey conducted by Van Hout *et al*

indicated how rarely he noticed what was really going on during the consultation time but only afterwards he realized something was wrong [43]. A third difficulty is the fact that GPs can find it difficult to take the initiative for cognitive testing and to disclose a diagnosis as it immediately puts a 'label' on the patient [43][45]. These difficulties were identified for a general AD diagnosis, yet are of pressing concern in MCI and pAD. GPs might overlook the first symptoms of MCI and misinterpret these symptoms as signs of a burn-out or stress [45]. Literature describes how it can take up to two years between the first consultation and the disclosure of the diagnosis [18][45]. This can be problematic as in many cases the GP is mostly the first clinician to be contacted by the patient or even the only clinician involved in making the diagnosis [43].

Prior to testing it is important to inform patients about the following aspects. Firstly, the patient needs to be aware of the high cost of this biomarker test and the current lack of reimbursement of the amyloid PET scan in most health care systems [46][47]. This point already raises several ethical concerns on its own. For example, due to the lack of reimbursement of amyloid PET the question about equal access raises. Secondly, depending on the type of biomarker used, it is important to inform patients about the risks and any invasive aspect of these tests. For example, if patients opt for an amyloid PET scan, they need to be aware of the radioactive tracer injected into their veins. Thirdly, patients need to have a correct understanding of what the result upholds. As explained in the results, a positive Amyloid PET scan in a patient with MCI has a predictive value for future cognitive decline and AD dementia with an estimated five-year conversion sensitivity of 85 to 93 per cent and a specificity between 81-100% [48]. However, the time course of decline is currently hard to predict at the individual level based on Amyloid biomarkers alone [48]. A negative Amyloid PET does not exclude progression to dementia due to a non-AD cause [15]. The current lack of good individual predictive models implies that the diagnosis of amyloid positivity in a patient with MCI will prolong the phase during which a subject has to live with a diagnosis of MCI due to AD. If the perfect individual predictive model existed, the question would remain: "Do we really want to know? Are we well aware of all the (dis)advantages after receiving this news?"

As already mentioned in the results section, patients often expect a straightforward diagnosis. For example: "Yes, you have Alzheimer's disease or you have the first symptoms of Alzheimer's Disease." The difference lies within the fact that an AD diagnosis is more well-known among society compared to a MCI diagnosis. It is not uncommon that patients find it more difficult to understand what an MCI diagnosis implies compared to an MCI due to AD or AD diagnosis. The

disclosure of a cognitive deficit or an MCI diagnosis to the patient may seem to be as a softer or a less accurate medical diagnosis to the patient, yet can be considered as good clinical practice by the clinician when it is at that time unknown what is causing the initial symptoms or what the aetiological diagnosis of subtype is. For example, the difference between MCI and MCI due to AD is that the aetiology (in this case the subtype is AD) is already known and that there is causality: confirming to the patient that this mild cognitive impairment is due to AD and that the patient most likely will convert to Alzheimer's disease in the near future. If clinicians monitor the patient with MCI by providing the necessary follow-ups, then MCI is not a less accurate medical diagnosis than an MCI due to AD diagnosis. As already indicated, it may be difficult for clinicians to get clear-cut insight on the subtype of diagnosis. In order to avoid harm to the patient by providing an uncertain diagnosis, it may be better to only confirm that there is a cognitive deficit which the clinician is sure of. It will be important how the clinician explains and gives meaning to the type of diagnosis given to the patient.

Lastly, there is no consensus regarding how frequently stigmatization happens to patients who received an early diagnosis. It is not unlikely that stigmatization occurs due to society's often negative AD perception. The study by Johnson *et al.* indicates that the disclosure of an MCI diagnosis, which is often seen as a transitional stage between normal aging and probable AD, can lead to higher levels of stigma due to the uncertainty over whether or not the patient with MCI will decline to AD [49]. More empirical research about the impact of stigmatization on the patient with an early AD diagnosis and his family is needed. We have to keep in mind that difficulties can occur while defining the meaning of stigma and how patients and their family members interpret stigma. The latter indicates that researchers also need to investigate how patients perceive different levels of stigmatization.

Appendix

Appendix 1: Information on the included articles

Year of publi-cation	Author(s)	Title	Journal	Type of the article as described in the original article	Contains the article general AD literature and/or referral to MCI/pAD/early diagnosis?	Added based on snow-balling method?
2005	Snyder	Dementia and Driving: Autonomy Versus Safety	Journal of the American Academy of Nurse Practitioners	Literature review	General AD literature but refers to MCI.	
2008	Cornett & Hall	Issues in Disclosing a Diagnosis of Dementia	Archives of clinical neuropsychology: the official journal of the National Academy of Neuropsychologists	Article	General AD literature.	
2008	Werner & Korczyn	Mild Cognitive Impairment: Conceptual, Assessment, Ethical and Social Issues	Clinical Interventions in Aging	Article	Focus on MCI	
2009	Wright, Hall, Matthews & Brayne	Biomarkers, Dementia and Public Health	Annals of the New York Academy of Sciences	Literature article	General AD literature but refers to MCI.	
2010	Carr	The Older Adult Driver with Cognitive Impairment: 'It's a Very Frustrating Life',	Jama	Review	General AD literature but refers to MCI and early diagnosis.	
2010	Draper, Peisah, Snowdon & Brodaty	Early Dementia Diagnosis and the Risk of Suicide and Euthanasia	Alzheimer's & dementia: the journal of the Alzheimer's Association	Literature review of empirical studies	General AD literature but with recommend-dations for presymptomatic AD and early diagnosis.	Yes.
2010	Mattson, Brax & Zetterberg	To Know or not to Know: Ethical Issues Related to Early Diagnosis of Alzheimer's disease.	International journal of Alzheimer's disease	Review	General AD literature but with a focus on early diagnosis and refers to MCI	
2010	Porteri, Galuzzi, Geroldi & Frisoni	Diagnosis Disclosure of Prodromal Alzheimer's Disease: Ethical Analysis of Two Cases	Le journal canadien des sciences neurologiques	Case analysis	Focus on pAD.	
2011	Karlawish	Addressing the Ethical, Policy and Social challenges of Preclinical Alzheimer's Disease	Neurology	Literature article	Focus on preclinical AD	
2011	Prvulovic & Hampel	Ethical considerations of Biomarker Use in Neurodegenerative Diseases: a Case Study of Alzheimer's Disease	Progress in neurobiology	Commentary article	General AD literature with a focus on asymptomatic AD.	
2012	Leuzy & Gauthier	Ethical Issues in Alzheimer's Disease: an Overview	Expert review of neuro-therapeutics	Literature article	General AD literature but refers to pAD and preclinical AD.	
2012	Visser, Wolf, Frisoni & Gertz	Disclosure of Alzheimer's Disease Biomarker Status in	Biomarkers in medicine	Editorial	Focus on MCI.	

		Subjects with Mild Cognitive Impairment				
2013	Antoine & Pasquier	Emotional and Psychological Implications of Early AD diagnosis	The Medical Clinics of North America	Literature article	General AD literature and focus on early diagnosis	Yes
2013	Chiu & Brodaty	Arguments Against the Biomarker-Driven Diagnosis of AD	International psycho-geriatrics	Literature article	General AD literature, but refers to MCI.	
2013	Gauthier, Leuzy, Racine & Rosa-Neto	Diagnosis and Management of Alzheimer's Disease: Past, Present and Future Ethical Issues	Progress in neurobiology	Literature article	General AD literature but refers to MCI and pAD.	
2013	Viloria Jiménez, Chung Jaén, Vigara Garcia & Barahona-Alvarez	Decision-Making in Older People with Dementia	Reviews in Clinical Gerontology	Literature article	General AD literature but refers to MCI and early diagnosis.	Yes
2014	Howe	Clinical Implications of the New Diagnostic Guidelines for Dementia	Innovations in Clinical Neuroscience	Literature article + review of criteria	Focus on MCI, pAD and predictive testing	
2014	Porteri & Frisoni	Biomarker-Based Diagnosis of Mild Cognitive Impairment due to Alzheimer's Disease: How and What to Tell. A Kickstart to an Ethical Discussion	Frontiers in Aging Neuroscience	Literature article	Focus on MCI and pAD	
2015	Carr & O'Neill	Mobility and Safety Issues in Drivers with Dementia	International Psycho-geriatrics	Review	General literature but refers to MCI.	
2015	Draper	Suicidal Behavior and Assisted Suicide in Dementia	International Psycho-geriatrics	Systematic literature review	General literature but refers to pre-symptomatic and early diagnosis.	

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Chapter 2 Ethical challenges on the disclosure of amyloid PET scan results to the research participant.

Abstract

Background: In the field of Alzheimer's Disease (AD) research, it is questioned whether individual research results, such as amyloid PET scans, should be disclosed to the research participant. Despite the potential value of knowing one's result, there are many unanswered questions regarding the ethical implications of disclosing amyloid PET scan results to the research participant with Mild Cognitive Impairment (MCI).

Results: We have clustered the ethical arguments on amyloid PET disclosure via the four ethical principles as described by Beauchamp & Childress. (a) The right to know and to make an autonomous decision about being informed of their result is a first mentioned argument. However, will the participant be able to understand and to interpret their result correctly? What is the 'value' of knowing the amyloid PET scan result when there is a limited predictive value and when there is currently no disease-modifying treatment available for AD? (b) The principle of non-maleficence (no harm) often outweighs (c) the principle of beneficence (doing well), as it is difficult to resolve any possible harm (e.g. emotional risk, stigmatization, insurance implications, etc.) after the IRR disclosure has occurred. (d) Lastly, the principle of justice requires fairness and equality, which implies that the researcher does not minimalize the participant into a mere study object. However, disclosing results is expensive in time and money and often burdens the researcher and the research infrastructure.

Discussion: Based on the arguments as clustered under the four-principle approach, we support a qualified disclose policy in the field of AD research when certain criteria have been met (validation of result, type of population, etc.). Amyloid PET scan results can provide meaningful insight into their health condition for the participant with MCI. Despite certain advantages related to knowing one's result (e.g. emotional risk, limited predictive value, etc.), and depending on the attributed value and personal views of the research participant, these disadvantages may outweigh possible advantages (e.g. receiving an early diagnosis, to make future arrangements and lifestyle changes, etc.).

Background

In the research setting, there is currently no obligation for the researcher to disclose individual research results (IRR) to the participant. In the field of genetics, the debate about whether to return IRRs has received considerable research attention [1][2][3][4][5]. Especially the work by Bredenoord *et al* has provided meaningful insight into this debate [6]. These authors stated that no one favours full or no disclosure. Hence, two intermediate positions colour the IRR debate. These two intermediate positions are: the restricted disclosure policy and the qualified disclosure policy [6].

The restricted disclosure policy argues that research results should not be returned with the exception of life-saving data [6]. Arguments mentioned to support this position are, for example, the notion of therapeutic misconception, the harmful consequences and the unfeasible aspect of disclosing IRR [6]. The qualified disclosure policy argues that research results should be returned when they meet particular conditions [6]. Some of the arguments to support this disclosure policy are respect for participant's autonomy and that IRR disclosure would improve the public understanding and willingness of participants to volunteer in research [6][7].

In the field of Alzheimer's Disease (AD) research, a similar debate surrounds the development of biological markers as these markers can indicate the presence of a disease and can be used to support a clinical diagnosis [8]. One of the biomarkers to support a diagnosis of AD, is the use of amyloid PET scans [9][10]. From 2013 on, the Health Authorities approved three amyloid PET tracers for clinical use in patients with a cognitive impairment who are being evaluated for AD [11][12][13]. The approval of the three amyloid PET tracers, in combination with the evolutions in biomarker research, raised the question whether the no-disclosure policy in clinical trials needs to be changed [8][14].

The purpose of this article is to present the ethical arguments on amyloid PET disclosure to the research participant with Mild Cognitive Impairment (MCI). These amyloid markers for MCI individuals received regulatory approval and are thus possible candidates for disclosure in future research studies. This article will use the argument-based methodology to explore all the ethical arguments as mentioned in the published literature on this topic [15]. The raised arguments will be clustered according to the four-principle approach (autonomy, beneficence, non-maleficence and justice) as described by Beauchamp & Childress [16].

Clustering the ethical arguments according to the four principles in biomedical ethics

The ethical debate about whether to return IRRs can be clustered into four principles (autonomy, beneficence, non-maleficence and justice) as described by Beauchamp and Childress [16]. Principlism is a commonly used framework in the field of biomedical ethics to cluster and to compare moral arguments with each other. The first principle of autonomy implies acknowledging the value and decision-making rights of persons and enabling them to act autonomously [16]. The principle of autonomy is often simultaneously mentioned together with a person's right to know or not to know their own medical information [19]. The principle of beneficence and non-maleficence are two sides of the same medal, as they resemble close to each other, yet place different accents. Concretely, the principle of beneficence (*doing good* principle) refers to the moral obligation of the researcher to act for the benefit of the research participant, while the principle of non-maleficence (*no harm* principle) indicates that the researcher has the moral obligation to avoid harm to the participant [16]. The last principle is justice, which refers to the fairness and equality among individuals, or in this case, research participants [16]. To create fairness and equality, a basic form of respect to the research participant needs to be taken into consideration, whereby the researcher does not reduce the participant into a mere study object [20][21][22][23]. To create equality/fairness and to respect the participant, the notion of reciprocity is often mentioned, which implies a counter action from the researcher to the research participant [16].

Autonomy and the right to know

The principle of autonomy is often used as a reason pro disclosure of results, as this would respect the decision-making of the participant and their right to or not to know their medical information. This argument is often enhanced by referring to available studies that have reported on the desire of participants to be informed about their result [17][18]. Other arguments that have been put forward in the context of knowing the amyloid PET result in AD research are:

Firstly, the amyloid markers are validated and approved for clinical use by the Health Authorities for patients with a cognitive deficit [11][12][13].

Secondly, knowing the presence or absence of amyloid plaques in the brain, may provide valuable information to the participant and family [33].

Thirdly, despite the lack of a cure for AD, the result may still be actionable when the individual with MCI has an amyloid positive scan as this may lead to changes in lifestyle or drug treatment [19][20][21].

There are also arguments mentioned in the literature that question the right to know of the participant. These are:

Firstly, a person with MCI has a cognitive deficit, which may affect the degree to which the participant can make a determined and autonomous decision. However, Grill et al nuanced that the presence of cerebral amyloid affects neither the patient's individual judgement nor how the patient estimates the risks and benefits of knowing an IRR in this early stage [22].

Secondly, participants might have trouble understanding the result, and may misinterpret or overestimate the result [23][24]. Research generally yields a large amount of technical data, which may be complex and hence difficult for the participant to understand. For example, the use of amyloid PET and Apolipoprotein E genotype (APOE) testing requires clear information on what a positive and negative amyloid PET scans result upholds. Despite clear information, the researcher has no control on how research participants will understand and perceive their received IRR afterwards. The Risk Evaluation & Education for Alzheimer's Disease (REVEAL) study concluded that most participants knew whether or not their IRR indicated an elevated risk for developing AD and that these results were not definitive, yet that many could not accurately recall the specific details of their results and often did not take the risk estimates at face value [25]. An interview study with MCI patients reports that despite clear information in the information brochure and an oral face-to-face explanation of what to understand of a positive and negative amyloid PET scan result, some patients with MCI confused the terminology of a positive result as implying they have received good news and a negative result as receiving bad news [26]. The latter study also indicated that patients understand the core message of the result, yet researchers ought to be aware of the misuse of the scientific terminology by participants [26]. Furthermore, the argument of misinterpreting the result can also be applied to the position of the researcher. Returning amyloid PET scan results requires that the visual read of the amyloid PET scan should be done by several certified independent blinded readers, in order to avoid misinterpretation of the amyloid PET scan. Sometimes, researchers will use multiple biomarkers or use quantification of the amyloid PET scan, to increase the accuracy of the given result [11][23][27][28].

Thirdly, participants can mistakenly believe that they will be fully informed about all test results. In the clinical setting, clinicians have to inform patients about relevant results. This can enhance

participant's assumptions and expectations regarding the return of research results. However, in the current research setting researchers are not obliged to disclose biomarker results to research participants. Fourthly, the value of knowing the result is questioned in AD due to the lack of a disease modifying treatment, the limited predictive value of the biomarker-based test and the lack of individual timelines toward disease progression [10][29][21][19][30][20]. For example, the limited predictive value of amyloid markers in MCI implies that a negative amyloid scan greatly reduces the likelihood that the individual has underlying AD pathology causing MCI. A positive scan increases the likelihood that the tested individual has MCI due to AD. However, a positive amyloid scan does not establish a definitive diagnosis of AD or does not automatically imply that the person with MCI will decline to AD. A negative amyloid scan does not mean that (s)he does not have a neurodegenerative disease [1][4][38]. The value of knowing the result will depend on what the participant expects and on the type of result (individual or aggregate results, clinically actionable or non-actionable results, validated or invalidated results) disclosed to the participant [31]. In the field of AD, the lack of good predictive models about future disease progression may alter individuals' decision to opt for this result. Also the knowledge of brain amyloid increasing in the brain may frighten some individuals [25]. Depending on the attributed value of the result, participants might prefer not to know their own result. Although previously mentioned studies reported high numbers of participants opting in for their result, there are still individuals who decide differently. It would be of great interest to explore the views of these participants who prefer not to know and to investigate their rationale, as these subjects may not be represented in research studies to the same degree as subjects who want to know the result. Only little research in the field of AD has focussed on this topic. More research is also needed to explore how participants' view and value their individual result, such as amyloid PET scans.

Beneficence and non-maleficence

In the research setting, the principle of 'no harm' often outweighs the principle of 'doing good'. In the framework of the ICH GCP guidelines the submission of the study protocol focuses on the reduction and avoidance of harms and risks related to the trial in order to receive positive appraisal from the institutional revision boards and/or ethics commissions [32]. However, the disclosure of the amyloid PET scan result could be a way to 'do well' to the participant in the research setting. A few studies, some of them in the context of genetic risk disclosure, have reported on the possible advantages that are in line with the criteria of 'doing well'. For example, the REVEAL study was the first randomized controlled trial to evaluate the impact of risk assessment for AD using

Apolipoprotein E genotype disclosure for AD [33]. The REVEAL study has indicated the value of life planning to adjust to the disclosure of such information [33][34]. Other mentioned advantages were that the result can satisfy the curiosity of the participant and relieve their anxiety [35]. The findings from the REVEAL study indicate that most participants experience the same or lower levels of anxiety after being informed of their APOE status [33]. Other studies have reported on similar and new advantages for the participant, such as: to know what is going on with their health, to receive a diagnosis in the early stage, to get access to treatment, to increase physical exercise or change lifestyle habits, to enjoy life more, to inform others of their health problem [17][26].

The principle of non-maleficence implies avoiding any form of harm to the participant. In the available literature, many articles have referred to the most common forms of harm that may occur. These are:

Firstly, the psychological impact of knowing the result. Careful attention about the previously mentioned 'relief' as part of the REVEAL study remains important, as not all patients will feel relief. There is always the risk of causing emotional harm (anger, depression, and so on) or the risk that participants fear disease progression in case of a positive amyloid PET scan result [36][23][37][35][38][7][39]. Psychological support and necessary follow-up is, for this reason, important because it is difficult for the researcher to interpret how a participant is going to respond to his result. Also receiving the result can cause a different reaction compared to their initial expectations. It is impossible to reliably predict how participants will react to amyloid disclosure [8]. For example, the knowledge about one's amyloid load in the brain, might trigger different cognitive, emotional and behavioural reactions due to the image of amyloid growing in the brain compared to more abstract knowledge of one's genotype [25]. A few qualitative empirical studies have provided more insight into possible reactions toward amyloid disclosure [17][18][26]. For example, receiving a positive amyloid PET scan result is no pleasant news, yet remaining in ignorance may be difficult too [26]. Also, a positive PET scan result could endorse the concerns about the memory complaints the patient already experiences [17].

A second form of harm is related to the possibility of higher premiums or denied insurance coverage in case of a positive amyloid PET scan result [19][40][41][42]. Hence, privacy and confidentiality laws are of great importance to prevent that insurance companies have access to medical and pharmacological records that contain information on a person's amyloid status [8][43]. However, insurers on their part counter argue that if they do not have access to this information, people who received their research result and know that they tested positive could purchase higher insurance coverage at too low prices. This can consequently lead to economic losses if the prices

are not adjusted [42]. The study from Zick *et al* confirms that out of 148 cognitively normal people participating in a randomized controlled trial, those who tested positive on the Apolipoprotein E genotype were 5.76 times more likely to have changed their long-term care insurance compared to the participants who did not receive their genotype disclosure [42].

A third form of harm that may occur is stigmatisation. This is related to the perception of AD as an awful disease whereby a person gradually loses personality and capabilities, even though the loss of personality and full capabilities occurs mainly in later stages of the disease [8][41][44]. Due to society's negative perception, a lot of people are therefore more afraid of having AD than dying from a heart disease, diabetics or a stroke [30]. Grill *et al* indicate that as of yet, it remains unclear how the public perceives amyloid positivity [8]. Receiving an amyloid positive scan result or having a diagnosis of preclinical AD may carry the same public perception and negative consequences as an AD diagnosis [8]. Will the public be able to understand what a positive and negative amyloid PET scan implies? Due to changing regulations in many countries where people have to work longer before reaching the age of retirement, participants evaluated with preclinical AD and patients with MCI could be affected by these stigmata. The clinical trial study of Christensen *et al* on APOE genotyping for AD risk confirms participants' discrimination fears (employment, health insurance and stigmatization) as a possible disadvantage when being informed about their APOE status. After a 12 month follow-up there was a small increase of these discrimination fears [45].

To avoid any form of harm to the research participant, it is important to explain all the details, risks and benefits in an easy and comprehensible language as required by ICH GCP [22]. However, two problems arise. First, it is questioned whether the researcher is the correct person to disclose the IRR. According to the Amyloid Imaging Task Force (AITF), the disclosure of amyloid PET results should be done by a dementia specialist who devotes at least 25% of their patient contact time to the evaluation and care of adults with cognitive impairment or dementia [27][29]. Secondly, researchers do not always know how to communicate, nor have the time to disclose this information to the research participant [20].

Justice

Justice is often translated in the literature as creating fairness and equality to the individual, i.e. the research participant. On the one hand, several advantages were reported under the principle of justice in order to support a disclosure policy. These arguments are:

Firstly, the *notion of reciprocity* implies an action from the researcher toward the research participant as a sign of appreciation and respect to the participant who contributed to a research study [38]. In the literature, reciprocity is often mentioned together with the notion of 'ancillary care' [6][46][47]. In this view, research participants are mostly put forward in a giving role, entrusting their health and medical data (e.g. human tissue,…) in the hands of the responsible researcher [6]. Even if the main goal of research is to provide generalizable medical knowledge, ancillary care indicates that the researcher still has other responsibilities toward the participant [6][46][47]. Participants often do not volunteer on pure altruistic reasons, and participants may expect something in return for their contribution to research [6][48][49]. Disclosure can be a way to answer the expectations of some participants [6]. However, a small financial compensation, a summary of aggregate results, and so on, would also imply gratitude from the researcher's side but would perhaps not satisfy the expectations of some participants. However, depending on what the participants expect and want, it is uncertain whether disclosure will meet their initial expectations since many participants often expect therapy or treatment [50]. It can be commented that in a therapeutic trial, it is understandable that a participant is hoping to benefit from a new type of therapy. Also, because the therapeutic benefit of an intervention for AD is greatest when it is administered in the early stage of the disease [8]. Therefore, patients may volunteer for research out of a sense of personal urgency to gain access to otherwise unavailable interventions [8]. For example, in the case of patients who already received an MCI diagnosis, participating and hoping for an intervention, may especially be true as they already feel that their memory is slightly affected. In addition, reciprocity also implies that disclosure can result in an improvement of the researcher-participant relationship [20]. Yet, the possibility of improving the relation between participant and researcher will also depend on the level of interaction (is there personal contact between researcher and participant?) and the duration (1 short intervention or multiple interventions?) of the interaction [49].

A second argument to support disclosure of amyloid PET refers to the transparency of research. Some researchers mention how disclosure would make research more transparent for society. This would then result in an improvement of the public understanding and an increase of participants' willingness to contribute to future research studies [6][24][51][52].

On the other hand, several disadvantages under the principle of justice were reported. These are: first, the risk of a selection of bias amongst participants who, for example, have a feeling that something might be wrong with their cognitive abilities. Some researchers are concerned that the disclosure of amyloid imaging results, especially in cognitively normal participants, can affect the neuropsychometric or affective data. This was commented by respondents in the survey of Alzheimer's Disease Neuroimaging Initiative (ADNI) investigators [53]. However, Grill *et al* showed that the disclosure of amyloid status does not pose a barrier in the number and nature of recruited participants [22].

A second disadvantage is the blurring line between research and clinical care. This is due to three elements:

(a) The therapeutic misconception. Researchers have the responsibility to prevent harm to the participant, but they do not have the task to provide special health care to the research participant [51].

(b) The fact that many participants mistakenly believe that the researcher always has the obligation to return all results. However, the main goal of research is to provide general knowledge instead of providing and returning individual knowledge to the research participant [7][40][55]

(c) Burdening the researcher and the research infrastructure [7][54][55][24][35][37][39][56]. Returning individual results requires, for example, careful administration in order to re-contact the participants and counselling as it would be unethical to return a result without helping participants to understand what the result actually implies and without providing follow-up [7][23][35][37][39]. In some extreme cases, returning results can lead to the cancellation of the study as many clinical trials are under restricted time and budget [35]. For this reason, it is according to some opponents of disclosure inappropriate and unjust to use research resources for the return of individual results since this is not the main goal of research and because it denies the broader society potential benefits that can be made with the research budget that is intended to make scientific improvements [51]. The amyloid PET scan, whether used in research or in clinical settings, is an expensive tool with limited availability and furthermore requires trained amyloid PET scan readers [28][8][28].

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Discussion

The clustered ethical challenges under the four principles, presented a broad overview of arguments that play a role within the disclosure debate. However, other factors may also influence the decision-making process, such as, biomarker and technology advances, new medication or treatments and the starting viewpoint. The latter factor refers to the difference between the views of researchers and research participants. For example, participants may value the principle of autonomy more compared to the principle of justice, whilst clinicians and researchers tend to focus more on not-harming (non-maleficence) the participant throughout the research study. Another factor is that researchers and participants may attribute a different weight to an ethical argument.

Within AD research, it is still uncommon practice amongst researchers to actively disclose results to the research participant. Many researchers still feel reluctant to disclose results, such as amyloid PET scans, to the research participant, due to the fear that this may affect the research data and based on the limited predictive value and the fear of emotionally harming the participant. However, many challenges and opportunities for both the researcher and the participant may occur when deciding to disclose individual research results.

In the field of genetics, more research has focused on the disclosure debate, which is typically divided into four positions (two extreme positions: no disclosure of results or full disclosure of all results and two more intermediate positions: restricted disclosure or qualified disclosure) [6]. Based on the multiple ethical arguments as clustered under the four principles, we can conclude that it is time to move toward a qualified disclosure process in the field of AD research. A qualified disclosure process may not be confused with a full disclosure of all types of results, such as incidental findings, nor a full disclosure in all types of populations (e.g. discrepancy between disclosing information to healthy adults, patients in the prodromal stage of AD or patients in the severe stage of the disease course).

Arguments to support the qualified disclosure in AD research are: (a) amyloid PET scans are used in the clinical setting to support a diagnosis in patients with a cognitive deficit who are being evaluated for AD. (b) For participants who experience initial memory complaints, the return of their amyloid PET scan result can provide meaningful insight into their cognitive problems and may confirm their experienced memory complaints. (c) A qualified disclosure respects that the participant is not just a physical body used for experiments and tests. This type of disclosure respects a holistic view on humans, where also the autonomous decision-making and the desire of the participant to know is taken into consideration. (d) Despite the reported disadvantages, such as not knowing when and if the individual with a positive amyloid PET scan will decline toward

AD, there are also multiple advantages of knowing the result. These benefits can outweigh possible disadvantages depending on the personal views of both the participant and the researcher.

If researchers decide to change their no-disclosure policy in their research study, clear information prior to volunteering in the research study and prior to the biomarker-based testing is key. This is also a critical point for AD therapeutic trials where there is often an implicit disclosure (e.g. a positive amyloid PET scan as inclusion criteria of the trial). This is particularly relevant as clinical trials in AD move towards earlier disease stages, where the confidence about the etiology based on routine clinical work-up may be lower and the research amyloid PET would provide strong added diagnostic value. As part of an implicit disclosure, it should be clearly stated what it means if the participant is eligible for the study and how this may affect the participant. Hence, the information brochure presented to the volunteer participant should clearly and in an easy to understand language explain all possible benefits and risks, such as the limited predictive value and the lack of good individual timelines for disease progression. This can minimalize a wrong understanding or misinterpretation of what to expect from the result, yet never guarantees how the participant will perceive the result after it has been disclosed. In addition, researchers may request for additional funding in order to disclose these results. In this case, researchers who share their insights and experiences on amyloid PET disclosure would provide significant value for the design of future trials.

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Chapter 3 Amnestic MCI patients' perspectives on volunteer participation in a research context

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Abstract

Background: Inclusion of patients in research studies is immensely important when evaluating new biomarkers for Alzheimer disease (AD) and when the efficacy of possible treatment options is under trial investigation. If medical treatment is to advance in slowing the progression of AD, or even preventing it, voluntary participation of patients is not only important but also their reliable participation is key. To get closer in achieving this goal, researchers need to understand better what motivates research participants to enroll in a clinical trial and get insight into participants' expectations about their participation. Furthermore, what researchers perceive as benefits and risks of a study can differ from participants' view. This difference could lead to a situation in which researchers recruit fewer subjects than they expected or result in unreliable research subject participation.

Method: We conducted semi-structured in-depth interviews in 38 patients with amnestic mild cognitive impairment (aMCI) as part of a clinical trial on the predictive value of biomarkers for AD. Patients had the option of receiving their Individual Research Results (IRR; visual binary read amyloid PET results). In this study, the motivations and perceived advantages and disadvantages of trial participation were investigated from the patients' perspective.

Results: The two most frequently mentioned reasons for volunteering for the trial were to contribute to scientific progress and to receive their IRR. Participating to ameliorate scientific progress was not solely motivated by altruistic reasons; it was mostly mentioned along with the possibility of receiving a valuable result about their health condition, suggesting that self-interest also motivated patients to participate. The two most frequently mentioned disadvantages were the possible risks related to being subjected to invasive medical procedures and that volunteering was considered to be time consuming. Most patients felt that their partner and children supported their decision to enroll in the biomarker study.

Conclusion: aMCI patients have several reasons for wanting to volunteer in a clinical trial, with the option of IRR disclosure being the primary motivation for enrolling. Most of our patients felt that family members supported their decision to volunteer. However, researchers need to be cautious when recruiting subjects for clinical trials by ensuring that they truly desire to participate in the study and that family members are not coercing them into doing so.

Background

Reliable participation from volunteer subjects is of utter importance to draw firm conclusions from research data. This also applies to the study of Alzheimer's disease (AD), which often involves participation of healthy adults and patients with mild cognitive impairment (MCI). A common theme across AD studies relates to identifying biomarkers for accurate diagnosis and track disease progression. This is especially important because there is an urgent need to detect the disease at an earlier stage and to identify those subjects who are most likely to exhibit rapid disease progression in order to reduce healthcare burden and economic costs. Due to the difficulty in clearly recognizing the first symptoms of AD in a clinical setting, only an estimated one-half of all cases are diagnosed [1-2]. Therefore, diagnostic trials are important for developing and validating new biological markers for AD either as diagnostic or predictive tool. These markers could also be used in therapeutic clinical trials to evaluate new potential treatments. It has been a challenge to prevent and slow down disease progression in AD because of the limited efficacy of current treatment options. Researchers need to explore what motivates individuals to enroll in a clinical trial and what participants perceive as trial benefits and risks, and then leverage these vis-à-vis participation to stimulate and achieve reliable research subject participation [3].

The prevailing literature on motivations to participate in research studies concerns other research fields, such as genetics-related studies [3-4]. One focus group study by Lawrence et al. explored patient and carer views specifically on this topic [5]. However, their results were based on two different perspectives (patients and carer), which were conflated. Few studies have been done on participants' motivations in AD trials. There is therefore a need for more in-depth research on AD study subjects' motivations and perceptions of possible advantages and disadvantages of trial participation.

The current study is part of the BioAdaptAD study on the predictive value of biomarkers in a cohort of amnestic MCI (aMCI) patients who could choose to know their IRRs (visual binary read of amyloid PET scan). Findings from the participants' perspectives toward amyloid PET disclosure are reported previously in Vanderschaeghe *et al* [6]. In this study, we examined subjects' motivations and their perceived (dis)advantages of participating in a clinical trial by means of semi-structured interviews.

Methods

Recruitment

Recruitment of subjects took place between June 2015 and June 2016 after approval of the study by the Ethics Committee, University Hospitals Leuven. All participants provided written informed consent in accordance with the Declaration of Helsinki.

The study cohort consisted of a consecutive series of aMCI patients [7] recruited via the memory clinic of the University Hospitals Leuven. The interview was part of a substudy of the BioAdaptAD study, an investigator-driven longitudinal study of aMCI patients. The primary objective of the BioAdaptAD study (EUDRACT no. 2013-004671-12) is to evaluate the predictive value of baseline amyloid biomarker measurements for tracking longitudinal cognitive change over a two-year period.

According to Standard Operating Procedures, on occasion of a follow-up outpatient visit to the memory clinic, the patient was informed about the possibility to participate in a trial and the purpose and content of the trial was introduced to the patient by the physician and by the researcher (JS). The information brochure and the informed consent form was given to the patient so that the patient could discuss this further with anybody of their choice at home. One week later the patient was recontacted by phone to ask whether they had decided to volunteer in the clinical trial.

When candidate subjects met the inclusion criteria (see Appendix 1) of the BioAdaptAD study and decided to enroll in the trial, they were given an additional option to participate in a substudy investigating participant motivations for choosing to enroll in a clinical trial, their rationale for opting for their amyloid PET scan result and the ethical challenges associated with it. As mentioned in the introduction, the findings from the amyloid PET disclosure have been reported in another publication [6]. The same cohort population contributed to the current study. We conducted semi-structured interviews with participants who agreed to take part in the substudy in order to better understand their motivations, opinions, and experiences about their trial participation.

Before the start of the substudy, an informed consent brochure about the interviews was given to candidate subjects. The content of this brochure was based on the E6 Guideline of Good Clinical Practice (GCP) [8] and contained background information about the substudy, study objectives, the interview process, and research subjects' rights. Before the scheduled interview, the interviewer orally repeated the content of the informed consent brochure and asked the candidate

whether they had any further questions. If they hesitated or had doubts about participating, the interview was re-scheduled for a later time in order to give the candidate sufficient time to decide.

Data collection and analysis

The interview guide was developed by GV, KD, and RV, and its content was based on findings in the literature on the topic of IRR. The first two interviews constituted of a pilot study, which was used to evaluate the interview guide. The interview questions covered three content areas. The first part of the interview consisted of questions intended to better understand how patients describe and experience their current memory problems. The second part consisted of open-ended questions about why they chose to participate and expectations they had about being part of a clinical research trial. The third part consisted of hypothetical questions about how the participant thinks he would respond to a set of possible situations. Several interview techniques were used, such as rephrasing part of the participant's answer, asking yes or no questions, to briefly checking whether the interviewer understood the participant's answer correctly. Supplementary questions were also asked to get more in-depth information from the participant.

After a short introduction of the research set-up and what to expect in the interviews, patients were invited to sign the informed consent form. Patients also completed the sociodemographic information form. Completion of the latter form indicated that the patient understood that the study results and interview records would remain confidential, that participation in the interview was voluntary, and that it would have no impact on participation in the general study or on any other medical intervention the patient might undergo in a clinical context. Patients were informed that study results would be published in a scientific journal and that a lay description of results from the interviews would be provided to them after completion of the study.

The interviews were recorded on tape with the consent of the interviewee. A mixed-methods approach was used to analyze the interviews:

(1). Transcripts were analyzed using QSR International's Nvivo 11 software, and analysis was performed according to qualitative conventional content analysis methodology [9-10]. In the first phase, the interviewer (GV) coded the interviews at three separate time points, with an interval of a few weeks between each coding session. To protect against bias, in the second analysis phase, we had five interviews independently coded by a second researcher. In the final phase, we compared

the codes assigned by the interviewer and those done by the independent researcher (KD), working to reach a consensus on the final codes to be used.

(2). In addition, we used a quantitative approach to analyze the reasons, benefits, and disadvantages of receiving an IRR, as provided by the participants.

Interviews were conducted in Dutch, with the exception of one, which was conducted in English. For this interview, the patient preferred to speak in his native language, English. Quotations of patients presented here have been translated into English.

Results

Study population

Sixty-seven patients were invited to participate in the BioADadapt study; 26 of them decided not to volunteer, and three patients quitted the study after the first neuropsychological screening visit. Most of these individuals did not provide a reason or explanation for this decision, yet some referred to the burden of caring for a needy partner or to a lack of motivation. For the three patients who dropped out of the study, the following three reasons were mentioned; a lack of motivation, a refusing attitude from the patient his partner and an inability to schedule a new appointment that best suited the patient. This resulted in a study population that consisted of 38 aMCI patients who met the inclusion criteria of the study (Appendix 1). Table 1 summarizes the demographic information of participating aMCI patients and their scores on tests of the neuropsychological evaluation.

Characteristics	Number
Mean Age 71 ± 6.5 y (range: 55-83 y)	 -
Gender Male Female	 22 16
Highest educational level attained Primary school Secondary school Professional bachelor Academic master	 7 17 6 8
Marital status Married Widow/widower Divorced	 30 4 4
≥1 Children	36
Neuropsychological evaluation	**Mean score**
Global Clinical Dementia Rating scale	0.5
MMSE (/30)	27.8 (range: 25-30)
AVLT: Total Learning (/75)	36.2 ± 10.2
AVLT: long term % recall	61.7% ± 29.6%

Table 1. Demographic characteristics and neuropsychological evaluation scores of the study population of aMCI patients. Memory test results: MMSE = Mini mental state examination, AVLT = Rey Auditory Verbal Learning (AVLT) scores for Percentage Delayed Recall (%DR, score on 30 min delayed recall (/15) divided by the score on last trial (/15)) and Total learning (TL, /75).

Patients' motivation for enrolling in a clinical trial

We investigated what motivates participants to volunteer in a research study. In other words, what specific reasons do aMCI patients cite for enrolling in a clinical trial? From the interview transcripts, we identified seven main reasons for enrollment in this trial (Figure 1). Some participants mentioned two or three of these reasons.

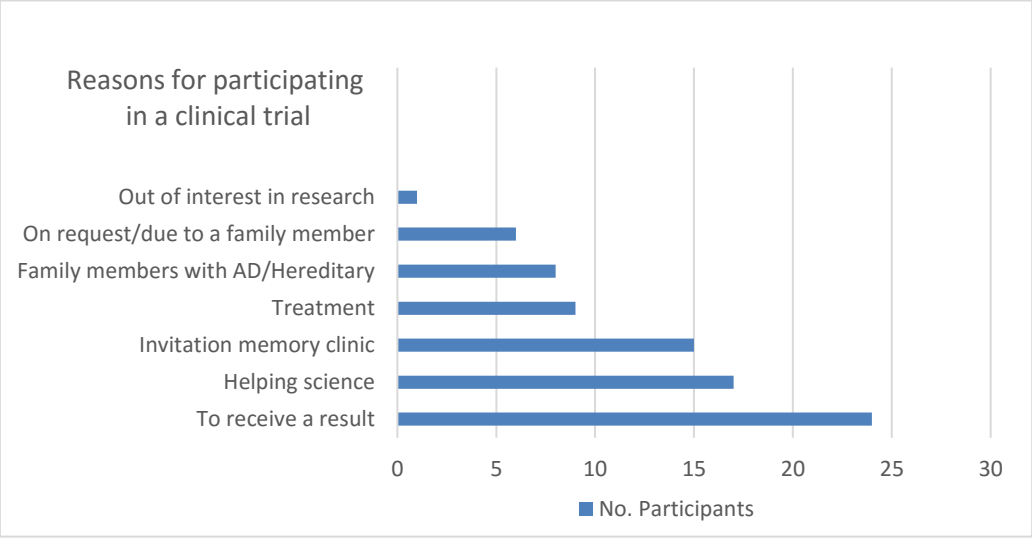

Figure 1. Specific reasons patients cited for wanting to participate in a clinical trial.

These seven reasons will be considered in more detail in the following section. We present quotes of the patients that serve to illuminate these reasons. The first reason was *having an interest in research*. One participant mentioned how he has always been interested in research. For him, this interest alone provided him with enough incentive to volunteer in the clinical study. The second reason cited by some participants for enrolling in the trial was because *family members encouraged them* to do so. Mostly the participant's partner, and often together with their children, noticed increasing forgetfulness in the participant. Family members not only advised the participants to go to the memory clinic for medical advice but also prompted them to volunteer in this trial.

> *"But I wouldn't have come on my own, but my husband wanted me to. But yes, he perhaps experiences it better […]. But I think my memory is not the same as in the past because I used to know everything, and now I have to look up [things] sometimes."* (Woman, 72 years old)

The third reason for enrolling in the trial was *having a family member with AD*. Of all participants, one-quarter had one or more family members who were diagnosed with some form of dementia or likely AD. These participants wanted to get an idea whether they too might develop the condition. Since they have witnessed firsthand how AD affected their relatives, they are well aware of its impact, and this provided them with the motivation to volunteer and to undergo testing for

AD. Some participants mentioned that dementia was highly prevalent in their family, indicating that this could be hereditary. For some participants the occurrence of the disease within their family also led to fear:

> *"Because in my family, there are many demented. So that scares me. It really scares me."* (Woman, 72 years old)

The fourth reason was the *desire to receive treatment*. Many participants were hoping to receive medication that would delay or slow down the progression of their disease. One participant even referred to the information brochure about the clinical trial, stating that in the event of a positive amyloid PET scan result, cholinesterase inhibitors would be administered. Although most participants were aware that at present AD is incurable, they did have some expectations about treatment:

> *"I expect that they can stop this. […] that I can get a treatment for that. So that I won't end up like my brother."* (Man, 74 years old)

The fifth reason was being *invited by memory clinic personnel to participate* in the trial after their recent follow-up at the memory clinic or during their first clinical consultation. Two participants mentioned that they discussed the invitation with their general practitioner (GP), and one participant indicated that his GP advised him to go the memory clinic, where he was invited to participate.

The sixth reason for volunteering for the trial was the desire to *contribute to science* and medicine. Some participants indicated that without their participation, research could not make medical progress. Another participant mentioned that, due to his current memory complaints, he might be an interesting case for scientists to investigate. However, most participants stated they enrolled in the trial not only to contribute to scientific research but also to find out what is going on with their health. We observed that the participants did not volunteer for purely altruistic reasons, as shown in the following quote: *"Yes absolutely, it is not just for myself, well a big part for myself* [laughs]*."* (Woman, 67 years old)

The seventh and most frequently mentioned reason for participating in the trial was *to receive a medical test result*. For many of the participants, it was very important to find out what caused their subtle memory complaints. One participant stated that AD is a common topic of discussion today, and just hearing discussions about AD can cause one to wonder whether one will develop AD in the future.

"[...] *But since this has been in my head for many years, I think it's important to know, because you think about that a lot. There is a lot, a lot spoken and said about [AD] and so I want to know it."* (Woman, 69 years old)

Some participants stated that, by participating in the trial, they were hoping to receive more information about their current health situation, and that this in turn, would help them understand more about their medical health situation.

"[...] *I think that I will learn something more. And I want to know where I stand. What it is exactly."* (Woman, 68 years old)

"Because again it was to find out why and at the moment, […] you know, at least if you know the amount of amyloids there [is] or not, that is, you are sure or relatively sure." (Man, 66 years old)

Perceived clinical trial advantages

After exploring what motivated participants to enroll in a clinical trial, we investigated whether participants perceived any advantages or benefits to participating in a clinical trial. First, a minority of participants spontaneously reported that there were no advantages to volunteering in a clinical trial. However, two participants subtly qualified their answer without hesitation:

"No, not directly. No, I don't see… except with the results to know what's going on. For the rest, I personally do not see any real advantages." (Man, 73 years old)

However, other participants did perceive certain advantages when participating in a trial, as described next.

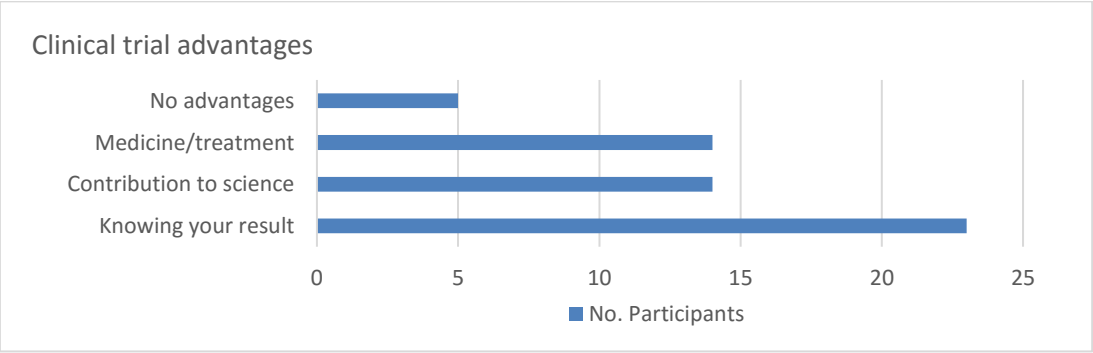

Figure 2. Clinical trial advantages perceived by participants.

Participants mentioned three advantages associated with participating in a clinical trial. First, medication and treatment were perceived as an advantage. When participants used the word "medication," they were referring to medicine that could delay or stop the disease. When

participants used the word "treatment," this suggested a broader connotation and did not solely refer to medication use. Participants also viewed "treatment" as the monitoring or following up of the disease. Some of the participants were eager to learn their test results and believed that the sooner they received them the sooner treatment could start:

> "[...] *If they find something, they can help me sooner, so I can be independent for as long as possible. I have seen it with my mother. She has been taking pills for two years now. Now it doesn't start to work that well, but it has still kept her at home for two, three more years. And yes, yes, I think that is certainly an advantage for me."* (Woman, 61 years old)

One participant stated that it is better to participate, because if something were wrong with her health, she at least had the option to receive treatment. She described her feelings about participating as follows:

> "[...] *So participating is always the best option, it is the best chance I have."* (Woman, 63 years old)

The second advantage of participating in a clinical trial that was mentioned, was to help science, which was also one of the reasons participants gave for participating. For some participants, the idea of being able to assist in advancing science not only served as their motivation to participate in the trial, but also as an advantage that could lead to medical improvements. Other participants provided a more nuanced response, stating that their participation would mainly benefit themselves, but that helping to advance science is a positive consequence. This sentiment is reflected in the following quote:

> "[…] *Yes, to help others, but I say it again. […] I'll be straightforward with you, I'm quite selfish. I am trying to save my own skin here […] I put it quite bluntly, but you can understand me."* (Woman, 63 years old)

The third advantage of participating in a clinical trial was that participants would know their test result. Some participants expected to receive all information related to their health status: *"Ah yes, because you'll know everything [...], when something's wrong."* (Woman, 76 years old)

Other participants expected to receive more information than what they believed they would receive during a regular doctor's office visit:

> *"I don't know if, well, with a normal diagnosis that it is always very fast. And the professor take one quick look [at you], and then he is back off again. [In a clinical trial] you'll receive more information."* (Woman, 66 years old)

This quote is consistent with the experience of one participant, who noted that clinicians were often under time pressure.

Perceived clinical trial disadvantages

We also sought to determine whether participants perceived any disadvantages related to participating in a clinical trial. Eighteen out of 38 participants spontaneously reported that there were no disadvantages related to participating in a trial. To explore the possibility that these participants were hiding their true feelings and were just providing socially desirable answers, the interviewer asked them additional auxiliary questions. After this line of questioning, we were able to determine that these participants felt that the advantages of participating in the trial outweighed any possible, albeit minor, disadvantages. The frequency of possible disadvantages perceived by the participants is shown in Figure 3.

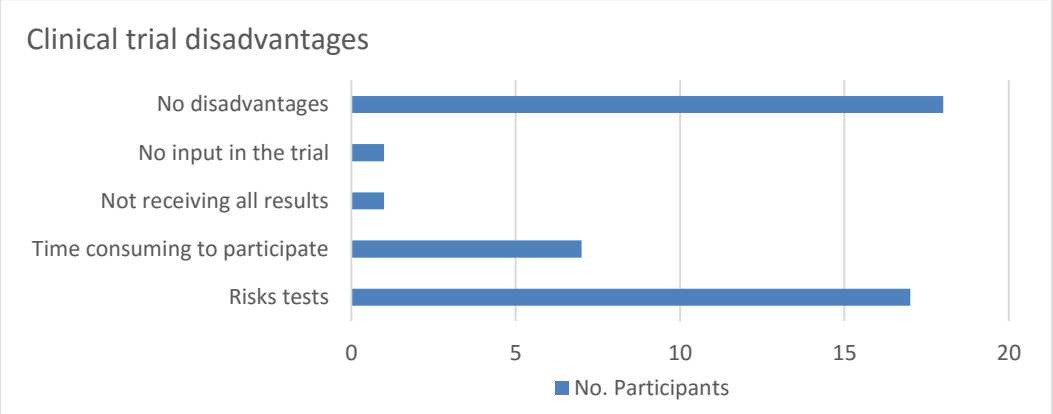

Figure 3. Clinical trial disadvantages perceived by the participants.

The participants mentioned four disadvantages of participating in the trial. The first was that participants did not have any influence on the design of the clinical trial. One participant stated:

> *"But the question is: you have no input into the trial. So, no, I don't like being involved in things that I cannot control."* (Man, 66 years old)

The same participant brought up another disadvantage: Not receiving all his personal data from this trial.

The third disadvantage was that trial participation is too time consuming. Participants viewed the trial as being too time consuming, because they had to visit the hospital several times in order to undergo a series of trial-related tests, such as neuropsychological investigation, MRI, PET scan, lumbar puncture (LP), and interviews. Most participants viewed these tests as only a minor inconvenience.

The fourth and last disadvantage mentioned was that trial participation is associated with certain risks. Most of the participants were aware of the risks involved with LPs and with amyloid PET scans, which require participants to receive an injection of a radioactive tracer. One participant stated that healthy people should not participate in a trial because of the possibility of exposing themselves to certain unnecessary risks:

> *"Well, it's a bit like, it's a simple lumbar puncture, but there are lots of ways. Just going to a hospital exposes you to more germs. And then, having a small procedure could be risky. Which, you know, I think it's different when you know there's something wrong with you and they say: 'Well, we need to examine you more thoroughly.' That's different than having to put yourself at risk if you don't need to."* (Man, 66 years old)

For a few of the participants who mentioned possible risks as a disadvantage to trial participation, it was not very clear to them how these risks could affect them. Others checked the information brochure, asked questions, and informed themselves about potential risks by asking others, such as their GP, for advice. Risks associated with the trial sometimes caused participants to question whether they had made the right choice. One participant, a 66-year-old woman, stated that the LP "*has made me think twice* [...]" about participating in the trial. Although most participants were concerned about the possible risks of participating, other participants immediately downplayed the risks, indicating that they viewed these to be minimal compared to those associated with more invasive trials or experimental trials that test medications. Most participants trusted the innovative techniques and the capabilities of the researchers, which contributed to the view that the risks were minimal. However, one participant did question the capabilities of some researchers. This particular participant demanded that his LP would be performed by professional healthcare staff, not by an intern. In general, only a minority of the participants expressed slight hesitation about some of the procedures associated with the trial. This was because a previous LP did not go well for them or because they were afraid of the pain might be caused by possible complications.

Family support

The option of participating in a trial was discussed by most participants in advance with their partner, and often with their children as well. This situation depended on their familial background, as some participants were divorced, widowed, or had little contact with their children and/or other family members. There were some participants who did not discuss this with their partner or children, since they believed it was a personal decision.

Most participants felt that their partner supported their choice to participate in a trial and their decision to know their IRR. One participant rarely discussed trial participation with his wife, and it bothered him that she rushed him before the interviews, so they could leave on time and do other things. He found this to be difficult. He stated that his wife found it unpleasant to join him when he had to be at the hospital, yet she wanted to do all of this for him. Another participant also experienced such mixed messages from his wife:

> *"Yes and no, in a sense, she thinks there's nothing wrong with me. You know, when we say that there are two types of people: people who want to know, and people who are the complete opposite."* (Man, 66 years old)

The last reason mentioned by patients revealed two other findings in our study. First, participants were not always certain whether their partner would volunteer in a trial and whether they would opt to know their IRR. They came to these conclusions because they believed that their partner would find it emotionally difficult to cope with bad news, had the disposition of not easily seeking medical advice or help, or had a resigned attitude: *"Whatever happens, happens."* Second, some participants indicated that when they were talking to others (partner, family members, and close friends) about their clinical trial participation, they frequently received the following reaction: *"Why are you participating? There is nothing wrong with you?"* This reaction was often difficult for the participant to accept because they felt that their memory problems were minimized or perceived as symptoms of normal aging.

Discussion

The current study aimed to gain insight into what motivates research participants to enroll in a clinical trial and their expectations about trial participation and complements an earlier report on amyloid PET disclosure [6]. The major strength of this qualitative research is the in-depth interviews with patients, as these face-to-face interviews provide researchers with the opportunity to delve into subjects' answers in-depth, clarify them, and check their opinions. This resulted in concrete motivational reasons (e.g. to receive a result, helping science, based on invitation of memory clinic, and so on) and perceived trial advantages (e.g. to know your result, treatment, and so on) and disadvantages (e.g. risks when undergoing tests, time consuming to participate, and so on) as mentioned by our study population. Based on our study results, we will comment and raise additional thoughts on five findings;

Individual research results

Most of the participants believed that it was common sense that they would receive their research results, since they participated in a clinical trial. In other words, they had a sense of ownership of any results that derived from their volunteer participation. This finding highlights the difficulties some participants had in understanding the differences between a clinical and research setting [11][12]. For example, most research subjects may be unaware that the main goal of research is to produce new general knowledge in a particular field of inquiry, not to produce and return individual bits of knowledge to a research participant [13][14]. This blurring of the boundary between clinical practice and research in the minds of research participants is often mentioned in the literature as an argument against the disclosure of these results [11][15]. Yet, there are also counter-arguments, such as the return of the IRRs would make research more transparent for society, who ultimately benefits and often funds the research [16]. Transparency may enhance public understanding and increase participants' willingness to contribute to future research studies [11][15][16][17]. However, it is understandable that participants perceive the disclosure of the IRR as common sense and that there is a blurring of the boundary between clinical care and the research setting. This may be due to the many clinical therapeutic trials where the line between research and clinical care is often blurred and in which, for example, a positive amyloid PET scan result is part of the inclusion criteria. In this case, participants become aware—although maybe implicitly—of their research result once they are accepted into the therapeutic clinical trial. This is different with regard to a non-disclosure policy in the research setting, which is not linked to therapeutic clinical trials. The implicit disclosure in therapeutic trials also raises several ethical concerns, as these results are usually

not actively disclosed. For example, what if the participant is not aware of this implicit disclosure and does not wish to know the result? Is the implicit disclosure of a result accurately understood by the participant? How do researchers and clinicians handle follow-up, counseling and guidance after an implicit disclosure of a positive amyloid PET scan result to the participant?

Limited efficacy of current treatment options

We hypothesized that participants would mention the limited efficacy of current treatment options as a disadvantage of trial participation as this is often described as an ethical issue in the available literature on AD [18][19]. As of yet, there is no treatment available to prevent or cure Alzheimer Disease [20]. There is the possibility to use drugs, such as acetylcholinesterase inhibitors (AChE-1) and memantine which can provide symptomatic relief, delay progression and possibly improve the quality of life of the patient [21].

When we asked participants whether limited efficacy of current treatment options is a disadvantage, they stated that they already knew before the start of the study no cure was available or that available medication could only delay the progression of the disease. They perceived the latter as a better option than receiving no medication at all. Most participants maintained strong hope that in the near future this will change and that history has shown how medical research rapidly evolves in the direction of providing new curative medicines.

Risks related to tests

In the present study, the majority of participants viewed the risks associated with certain tests, such as LP (headache, pain) and amyloid PET scan (radiation exposure), as a disadvantage of their trial participation. To address such concerns, the guidelines of GCP require that all possible risks are explained in the research study information brochure and that the researcher must clearly explain the study protocol to potential research participants [8]. As indicated in the results, a minority of our participants mentioned the possibility of risks, yet stated that it was not very clear what these risks could imply for them. This finding reveals that it is difficult to ensure that all participants will clearly understand all aspects of a trial that may or may not affect them as described in the information brochure. This finding underscores that obtaining informed consent from research participants should be an active information process, during which the researcher devotes sufficient time to explain the study and informed consent in an understandable manner. Although we are aware that this is a time-consuming process for the researcher, our study findings indicate how

necessary and beneficial this process is for the participant. In addition, if participants clearly know and understand what the clinical trial procedure implies, what they can expect, and what risks they might face, this may contribute to a reduction in dropouts through the course of the trial.

Trial participation is time consuming

In our study, we tried to conduct several tests in one visit at the hospital to maximize test opportunities and to minimize the burden for the patient by doing too many different visits with single tests. Yet, one in five participants still perceived that their participation was time consuming, although this was considered a minor disadvantage. A similar finding was reported by the clinical study of Christensen *et al* [22]. They indicated that the desire to contribute to AD research was rated highly and seen as a benefit by participants, but after completing a 12-month follow-up and after receiving their ApoE status, their rating was lower when asked about this desire to participate in research [22]. The authors stated that it is possible that study participants' initial eagerness at enrollment became tempered somewhat after realizing the many practicalities of research participation, such as administration tasks and regular follow-ups [22]. To overcome this problem, two practical steps seem to be important for researchers to take: (1) Before and throughout the study, clearly explain to the participant what their participation consists of, what will happen, and how long approximately each visit will be. (2) Cluster together as many tests as is feasible during each visit to the hospital. Doing this may help avoid subject dropout through the course of the trial. However, certain questions still need to be answered: Is it practically feasible to carry out several tests in one hospital visit? Will combining tests in one clinical visit influence or bias the results? Will a longer session with multiple tests be too burdensome; is it bearable for the participant?

Family support

Finally, this study demonstrates that a majority of participants feel supported and influenced by their family members regarding their trial participation. Although family support is a positive finding, caution is warranted in order to avoid a situation in which participants feel pressured by their family members to volunteer in a trial. Voluntary participation is also a requirement in the guidelines of GCP [8].

Limitations

One limitation is that the views expressed here are based on a relatively small population of aMCI patients in Belgium. This potentially limits the generalizability of our findings to other research contexts and other study populations. Different findings might emerge when an investigation takes place in a different country and when testing a different population, such as healthy elderly volunteers screened for preclinical AD or patients with mild cognitive complaints who have not undertaken steps to receive medical consult at the memory clinic. In addition, the interviews were part of a non-therapeutic trial. Different reasons for volunteering may emerge as part of a therapeutic clinical trial. Also, some individuals were given the option to enroll in a clinical trial, yet were not willing to participate. Some reasons were known, yet we do not have insight in all reasons of individuals who declined the possibility to volunteer. Future research could focus on the hesitation or refusal reasons from individuals who wish not to enroll in a clinical trial. Lastly, the interviews took place in Dutch, and used quotes were translated in English, which means that some of the interviewee's nuances may be lost. Despite these limitations, we believe that the present findings are an important first step in arriving at a better understanding of research subjects' motivations, will be useful beyond the context of this AD biomarker research, and will guide the design of future clinical trials.

Appendix

Appendix 1: Inclusion and exclusion criteria for participation in the BioAdaptAD study.

Inclusion criteria	Exclusion criteria
Patients must meet all of the following inclusion criteria to participate in the study: • Patient is male or female and between ≥ 55 and ≤ 85 years of age on the day of signing the consent form. • If female, patient is not of reproductive potential (i.e., two years post-menopausal or surgically sterile). • Patient has a subjective memory concern, as reported by patient, study partner, or clinician. • Patient has memory impairment, documented by scoring below the education-adjusted ranges on the AVLT total learning or delayed recall percentage (≥ -1 SD). • Patient has a Global Clinical Dementia Rating score of 0 or 0.5. • In the opinion of the investigator, the patient is in stable medical condition and willing and able to perform study procedures. • Patient has at least six years of education, or sufficient work history to exclude mental retardation, in the investigator's opinion.	Patients will be ineligible for participation in this study if they meet any of the following exclusion criteria: • Patient has a history of or current evidence for a neurological disorder that, in the opinion of the primary investigator, may contribute to the subject's cognitive impairment, including, but not limited to: o Large-vessel stroke, o epilepsy, o Parkinson's disease, o progressive supranuclear palsy, o Huntington's disease, o amyotrophic lateral sclerosis, o multiple sclerosis, o CNS infection, o significant head trauma with loss of consciousness, o Normal pressure hydrocephalus • Patient has a history of large-vessel stroke, or evidence of a large-vessel infarction or other focal lesions, on baseline MRI scan that may contribute to the memory impairment, in the opinion of the investigator. • Patient has received an examination over the past year involving more than 10 mS ionizing irradiation • Patient has a history, within 6 months prior to screening visit, or current evidence of a psychotic disorder or a major untreated depressive disorder. • Patient has a history of malignancy ≤5 years prior to signing informed consent, except for patients who have undergone potentially curative therapy with no evidence of recurrence for 1 year, and who are deemed at low risk for recurrence by her/his treating physician. • Patient has a history or current evidence of any potentially known clinically significant condition therapy, lab abnormality, or other circumstance that, in the opinion of the investigator, might confound the results of the study or interfere with the patient's participation for the full duration of the study, such that it is not in the best interest of the patient to participate. • Patient currently uses specific psychoactive medications (neuroleptics, chronic anxiolytics, tricyclic antidepressants, antiepileptics, anticholinergics etc.). Stable dose trazodone, mirtazapine or low dose benzodiazepines prescribed for mild insomnia is allowed.

	• Patient currently uses antithrombotics, with the exception of acetyl salicylic acid (exclusionary for lumbar puncture). • History of alcohol or substance abuse, or dependence within the past 2 years (DSM IV criteria) • Patient is currently participating or has participated in a study with an investigational compound or neuropsychological measures within 30 days of signing informed consent. • Subject has any magnetizable metal prostheses, implants or foreign objects that could pose a hazard during MRI scans.

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Chapter 4 Amnestic MCI patients' perspectives toward disclosure of amyloid PET results in a research context

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Abstract

Background: Researchers currently are not obligated to share individual research results (IRR) with participants. This non-disclosure policy has been challenged on the basis of participants' rights to be aware and in control of their personal medical information. Here, we determined how patients view disclosure of research PET results of brain amyloid and why they believe it is advantageous or disadvantageous to disclose.

Method: As a part of a larger diagnostic trial, we conducted semi-structured interviews with patients with amnestic Mild Cognitive Impairment (aMCI). Participants had the option to receive their brain amyloid PET scan result (i.e., their IRR). Interviews were conducted before they received their amyloid PET scan result.

Results: A total of 38 aMCI patients (100% of study participants) wanted to know their amyloid PET scan result. The two most frequently mentioned reasons for choosing amyloid disclosure were to better understand their brain health status and to be better able to make informed decisions about future personal arrangements (e.g., inheritance tax, moving into a smaller house, end-of-life decisions, etc.). Emotional risk was mentioned as the primary disadvantage of knowing one's amyloid PET scan result. On the other hand, non-disclosure was considered to be emotionally difficult also, as patients would be uncertain about their future health condition.

Conclusion: Many patients diagnosed clinically with aMCI want to know their brain amyloid test results, even though this knowledge may be disadvantageous to them. Knowing what is going on with their health and the ability to make informed decisions about their future were the two principal advantages mentioned for obtaining their amyloid PET results. Because of the overwhelming consensus of aMCI patients was to disclose their brain amyloid PET scan results, researchers should strongly consider releasing this information to research subjects.

Background

Biomarkers are biological indicators that can gauge the presence of a disease and can be used to support clinical diagnosis [1]. One of the biomarkers used to support a diagnosis of Alzheimer Disease (AD) is based on brain amyloid, which can be visualized *in situ* by positron emission tomography (PET) and radiotracers that have a high affinity for binding to beta-amyloid plaques *in vivo*. PET imaging of beta-amyloid plaques in the brain has been approved for diagnostic purposes in cognitively impaired patients who are being evaluated for AD [2][3]. Besides being useful for clinical situations, PET imaging of beta-amyloid plaques is also being used in brain research on AD.

Little is known about patients' motivations, opinions, and experiences in relation to their clinical trial participation and the disclosure of their result. In a research context, the degree to which individual research results (IRR) are shared with study participants varies, as the researcher is not obligated to do so [3][4]. Reasons to support the non-disclosure policy mostly relate to differences between the research and clinical context, the limited efficacy of current treatments, the experimental nature of certain types of data, and the limitations of lay participants to objectively and reasonably interpret the results [5][6]. On the other hand, some reasons to support disclosure are the right of participants to know and be in control of information about their medical condition, it affords participants the opportunity to make informed lifestyle changes and practical personal and family arrangements, and it opens up the possibility for participants to enroll in (early) medical interventions [5][7][8]. The previously mentioned reasons are based on the available theoretical literature and are mostly used by researchers to support or withhold disclosure. Yet, what are the concrete reasons and motivations of research participants? Thus, the following questions arise. Why would participants opt for the possibility to be informed about their IRR? What do participants perceive as possible advantages and disadvantages of knowing their IRR? Clear answers to these questions will help guide researchers and experimental subjects in deciding which option— disclosure or non-disclosure—to choose.

In this study, we focused on the reasons why patients with amnestic mild cognitive impairment (aMCI) were either in favor of or against the disclosure of their brain amyloid PET results. The experiences and opinions of these aMCI patients can differ from those of healthy individuals being screened for AD [9]. We also focused on the disclosure of brain amyloid PET scan results, because these biomarker findings have been approved by the FDA (Food and Drug Administration) and EMA (European Medicines Agency) for clinical use in patients with a

cognitive deficit [10][11][12]. Our findings are based on interviews with aMCI patients before they received their IRR.

Methods

Recruitment

Recruitment took place between June 2015 and June 2016 after approval of the study by the Ethics Committee, University Hospitals Leuven. All participants provided written informed consent in accordance with the Declaration of Helsinki.

The study cohort consisted of a consecutive series of aMCI patients [13] recruited via the memory clinic of the University Hospitals Leuven. The interview was part of a sub-study of the BioAdaptAD study, an investigator-driven longitudinal study of aMCI. The primary objective of the BioAdaptAD study (EUDRACT no. 2013-004671-12) was to evaluate the predictive value of baseline amyloid biomarker measurements for tracking longitudinal cognitive change over a two-year period. When candidate subjects met the inclusion criteria (see Appendix 1) of the BioAdaptAD study, they were given the option to participate in a sub-study investigating the opportunities to receive their IRR and the ethical challenges associated with it. More specifically, this sub-study provided the participants with the option of receiving their amyloid PET scan (binary visual read or positive/negative for brain amyloid) results that were obtained within the context of the BioAdaptAD study. We conducted semi-structured interviews with participants who agreed to take part in the sub-study in order to better understand their motivations, opinions, and experiences about the disclosure of their IRR.

Before the start of the sub-study, an informed consent brochure was given to candidate subjects. The content of this brochure was based on the E6 Guideline of Good Clinical Practice and contained background information about the study, study objectives, the interview process, and research subjects' rights. Before the scheduled interview, the interviewer orally repeated the content of the informed consent brochure and asked the candidate whether they had any further questions. If they hesitated or had doubts about participating, the interview was re-scheduled to a later time to give the candidate sufficient time to decide.

Data collection and analysis

The interview guide was developed by GV, KD, and RV, and its content was based on findings in the literature on the topic of IRR. The first two interviews constituted a pilot study, which was used to evaluate the interview guide and make needed adjustments. The interview questions covered three content areas. The first part of the interview consisted of questions intended to help us better understand how patients describe and experience their current memory problems.

Although patients' description of their memory complaints were not intended to be part of the result section of this manuscript, these exploratory questions were used as opening questions for the interview and to provide the interviewer with some concrete patients' experiences regarding their memory complaints. The second part consisted of open-ended questions about why they want to know their amyloid PET scan result and what they perceive as possible (dis)advantages of their amyloid PET scan disclosure. The third part consisted of hypothetical questions about how the patient thinks he would respond to a set of possible situations, such as: 'What if the researcher informs you that you have a positive amyloid PET scan result? How do you think you will respond to this news? Several interview techniques were used, such as rephrasing part of the participant's answer, asking yes or no questions, to briefly check whether the interviewer understood the participant's answer correctly. Supplementary questions were also asked to get more in-depth information from the participant.

After a short introduction of what the research was all about and what to expect in the interviews, patients were invited to sign the informed consent form (IC) and then to complete the sociodemographic information form. Completion of the IC form indicated that the patient understood that his/her results and interview records would remain confidential, that participation in the interview was voluntary, and that it would have no impact on his/her participation in the general study or on any other medical intervention he/she might undergo at the hospital. Participants were informed that results of the study would be published in a scientific journal and that a lay description of results from the interviews would be provided to them after completion of the study.

The interviews were recorded on tape with the consent of the interviewee. A mixed-method approach was used to analyze the interviews.

(1) Transcripts were analyzed using QSR International's Nvivo 10 software and was performed according to qualitative conventional content analysis methodology [14][15]. In the first phase, the interviewer (GV) coded the interviews three separate times, with an interval of a few weeks between each coding session. Letting time pass between each session and re-coding allows one to check whether new interpretations might be attributed to the content that could have been missed in just one coding session. To protect against bias, in the second analysis phase, we had five interviews independently coded by a second researcher. In the final phase, we compared the codes assigned by the interviewer and those done by the independent researcher (KD), working to reach a consensus on the final codes to be used.

(2) In addition, we used a quantitative approach to analyze the reasons, benefits, and disadvantages of receiving an IRR, as provided by the participants.

Interviews were conducted in Dutch, with the exception of one, which was conducted in English. For this interview, the patient preferred to speak in his native language, English. Quotations of patients presented here have been translated into English.

Results

Study population

The study population consisted of 38 aMCI patients who met the inclusion criteria of the study. Table 1 summarizes the demographic information and scores of the neuropsychological evaluation of the study population.

Characteristics	Number
Mean Age 71 ± 6.5 y (range: 55-83 y)	-
Gender Male Female	 22 16
Highest educational level attained Primary school Secondary school Professional bachelor Academic master	 7 17 6 8
Marital status Married Widow/widower Divorced	 30 4 4
≥1 Children	36
Neuropsychological evaluation	**Mean score**
Global Clinical Dementia Rating scale	0.5
MMSE (/30)	27.8 (range: 25-30)
AVLT: Total Learning (/75)	36.2 ± 10.2
AVLT: long term % recall	61.7% ± 29.6%

Table 1: Demographic Characteristics and neuropsychological evaluation scores of the study population of aMCI patients.

Reasons for wanting to know brain amyloid PET scan result

The results presented here are based on participants' answers in the interview *before* receiving their amyloid PET scan result. We decided to conduct the interviews in this order so that we could get unbiased answers as to why patients might want to know their result. All participants expressed the desire to know their individual brain amyloid PET scan result. Although one participant initially did not want to know his result, after thinking more about it, he changed his mind. Overall, nine reasons were mentioned by the participants for wanting to know their amyloid PET scan result. Some participants mentioned two or three reasons (Figure 1). These reasons will be considered in turn and elaborations will be provided in participants' quotes.

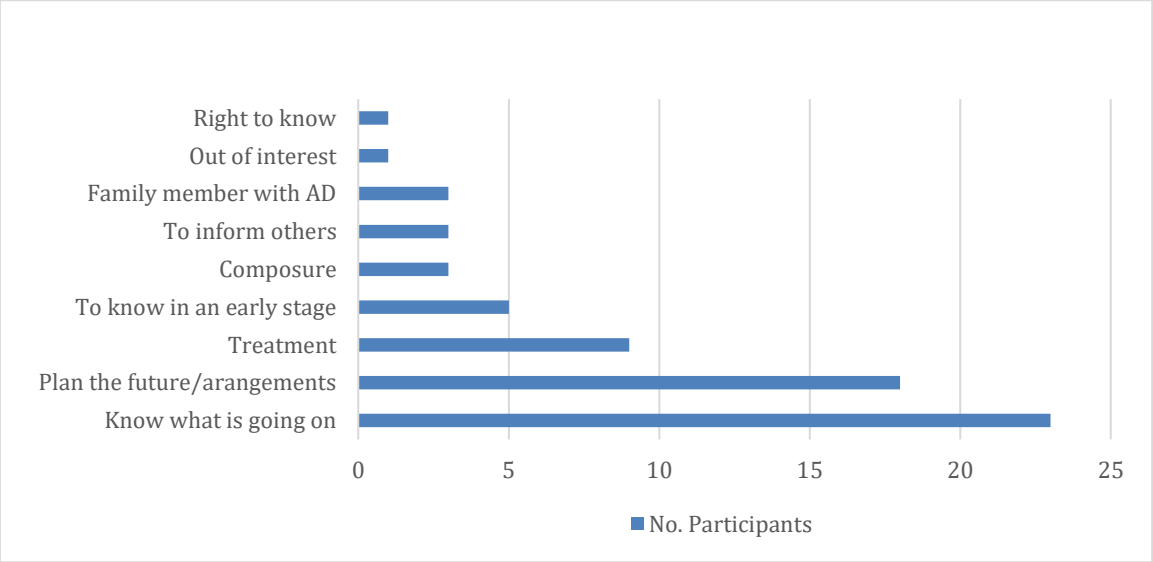

Figure 1. Frequency of reasons participants mentioned for wanting to know their brain amyloid PET scan result (i.e., IRR).* Some participants mentioned more than one reason.

(1) The patient's right to know their personal medical information was mentioned as one reason. As one participant described it, "*I think I have that right. It is from me; it is my body. And I know that I would rather know, otherwise it is useless to participate, I think [...]*" (Woman, 63 years old). This reason was the least frequently mentioned.

(2) Another reason mentioned was that participants were simply curious. One participant indicated that he was fascinated but did not elaborate on what he found interesting or fascinating about knowing his result.

(3) Another reason participants mentioned was that some had one or more family member(s) with dementia or who were diagnosed with AD. Since they had witnessed relatives who had AD, they knew firsthand what the disease does to a person, and this motivated them to volunteer for the

study and to opt in for receiving their amyloid PET scan result. This reason was mentioned more frequently than the first two reasons.

(4) The fourth reason was to get information so that they could inform others about their current health situation and discuss with them how their health might change in the near future. Participants mostly referred to their partner, children, relatives, or sometimes the close environment, like their neighbors, as "others." Participants viewed this reason for wanting to know their result as being an advantage. This aspect of knowing one's result will be discussed more in a subsequent section.

(5) Not knowing what was going on led to certain doubts, questions, and sometimes even anger, when forgetting something repeatedly. They hoped that getting their amyloid PET scan result would ease their mind, helping them to regain their composure and not get so visibly upset. This reason was mentioned as frequently as reasons 3 and 4 for wanting to know their IRR.

(6) Five participants mentioned that they considered it a better option to receive the possibly bad "news" contained in their result at an early, beginning stage of a disease than to receive it at a later, advanced stage.

(7) One of the most frequently mentioned reasons for participants desiring to know their result related to possible treatments (Figure 1). That is, if they knew their result, they might be able to make better choices about treatments for the symptoms they were experiencing. Treatment was described in two ways. On the one hand, participants talked about medication that might slow down the progression of the disease and thus possibly prolong their quality of life. On the other hand, they referred to treatment as making renewed health-related lifestyle changes. For example, a participant said that he would stop his weekly habit of drinking a pint of beer, and another participant was considering taking food supplements, if this was recommended by clinicians to treat their symptoms.

(8) Making informed future life decisions was the second most mentioned reason for wanting to know one's amyloid PET scan result. Participants referred to the opportunity of making arrangements or planning for the future, as they wanted to arrange their affairs before their memory problems became worse. Some participants clearly indicated that they had always made their own decisions, so they wanted to continue doing such, so they could avoid becoming a burden to others. The nature of this reason was diverse and could be divided into five general topical areas (Figure 2). These will be considered in turn (a-e, below).

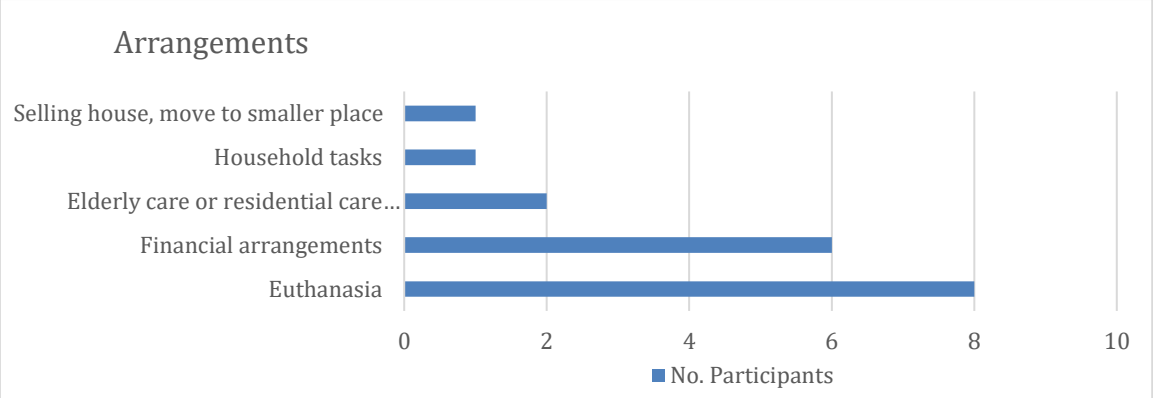

Figure 2. Frequencies of topical references made in relation to IRR affording the opportunity for making arrangements or planning for the future.

Topical area (a). This area was related to making lodging accommodations. One participant mentioned how he was currently considering selling his house and moving into a smaller house or apartment.

Topical area (b). This area was related to rearranging household tasks. Areas (a) and (b) were mentioned equally as often.

Topical area (c). The importance of arranging for elderly residential care in advance was another topic related to making advanced arrangements. One participant explained this by describing the difficulties related to "placing" or "forcing" elderly people to go to an elderly care center against their own wishes.

Topical area (d). Another given arrangement was to make financial decisions, such as donations to avoid inheritance taxes, or to find a person who can help with finances when the patient is no longer capable of caring for it by himself.

Topical area (e). The most frequently mentioned topical area related to making arrangements about euthanasia. Participants said this was mostly because they wanted to relieve the burden placed on their partner and children for caring for them in a demented condition. They also did not want "*to live like a plant,"* as they often described it. While some participants had already discussed this with their partner, and sometimes with their children, some participants stated that they would discuss this only when the result was known. The participants who had already talked about this felt understood and supported by their partner and/or children. This was nuanced in two different ways.

The first nuance related to a clarification that the request for euthanasia was not just to relieve them and their family of the consequences of AD, but also for other diseases that are legally accepted conditions according to the euthanasia law in Belgium.

The second nuance emerged from a statement by another participant, who said that receiving a positive brain amyloid PET scan would not result in panic and the immediate consideration of euthanasia. In addition, we noticed that most of the participants were unaware of the explicit details of Belgium's Euthanasia law and the various types of documents required for early care-planning and end-of-life decisions. This lack of information resulted in participants describing euthanasia in general terms and referring to "the document" without further clarification. Only one participant clearly described how he had all the necessary documents ready, as he had already consulted the Levens Einde Informatie Forum (LEIF).[1] LEIF is a national forum supported by the Belgian government concerning end-of-life decisions and dignified dying. While some participants had clear ideas about which specific arrangements they would make, other participants talked in general terms about making future arrangements. When asked to elaborate, they did not know yet which arrangements they would make.

(9) Finally, the most frequently mentioned reason of our participants for desiring to know one's result was to be informed about what was going on with one's health (Figure 1). In this vein also, participants often talked about future perspectives. If they could know what was going on, then they might know a little bit more about whether their symptoms could become worse or not.

Perceived advantages of knowing one's amyloid PET scan result

While we wanted to better understand why participants want to know their brain amyloid PET scan results, we also wanted to know what advantages or benefits participants perceived for disclosure of brain amyloid PET imaging.

A minority of participants pointed out that there were no advantages, or at least none that they could not think of, for knowing their result. A participant wondered more specifically whether receiving a positive amyloid PET scan result could be perceived as advantageous. As she explained, *"[…] will there be any advantages? That's the problem. If it is bad, is it actually, maybe disadvantageous that I know it"* (Woman, 81 years old). The majority of participants reflected on the advantages of getting

[1] Translated as, "Before You Go."

their IRR. Eight advantages were mentioned, as indicated in Figure 3. These will be considered in turn.

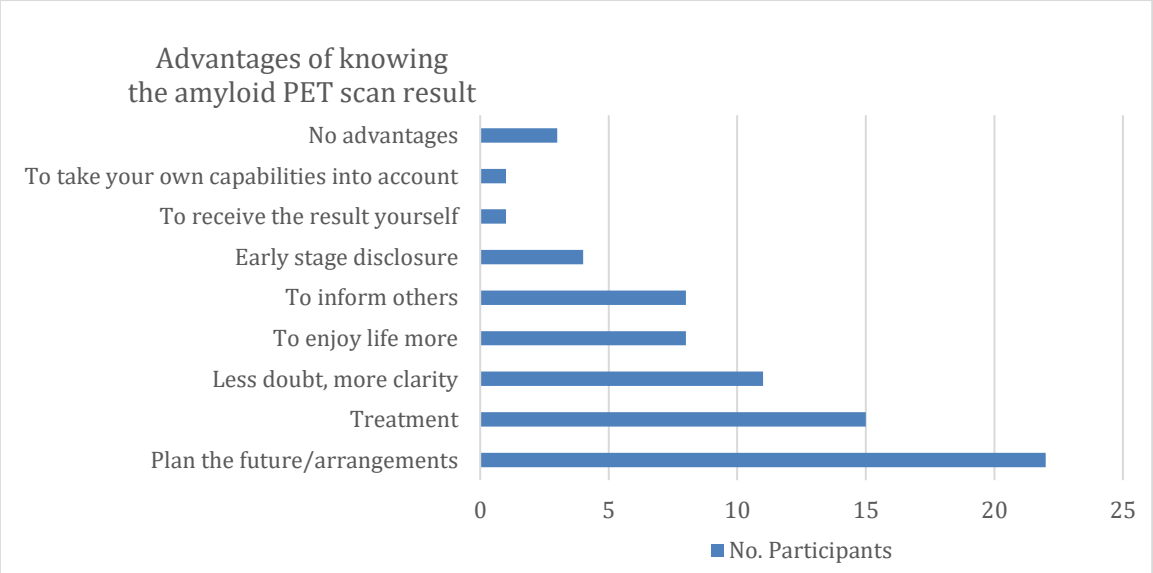

Figure 3. Frequencies of perceived advantages of knowing the amyloid PET scan result by participants.

(1) Knowing the result implies that one can take stock of one's own capabilities and then determine what is still possible to do or not to do, according to one's current health situation. Few participants mentioned this advantage.

(2) Receiving the result yourself rather than a family member, who may or may not disclose it. One participant mentioned that if the result were disclosed to her son, for example, she was afraid that he might not give her the complete information. When asked why this would be the case, she said that her son might phrase the news in a softer way to spare her emotionally. However, she wanted to know her situation firsthand, not filtered through a third party (e.g., caregiver or family member). That is why she perceived this as an advantage, whereby the researcher-neurologist would directly and completely disclose the news to her.

(3) Participants said that it would be advantageous to know the result at an early stage, so that they could benefit from an early intervention of treatment or imposition of health-related lifestyle changes. The difference between this advantage and the advantage of treatment (i.e., Advantage 7, below) is that participants specifically referred to the benefit of knowing this result at an early stage.

(4) Compared to just giving a reason for disclosure (i.e., previous section on informing others), more participants mentioned "informing others" as an advantage for knowing their result. While some participants focused on just informing their partner and children, other participants would also involve close friends. The benefit of informing others about their result is that they can take your new situation into account in personal interactions. One patient clearly indicated how she

would tell her partner and children, but not tell anyone else. She explained, *"No, you often think that you have friends, but behind your back […]. Nowadays, people are so dastardly"* (Woman, 72 years old). By contrast, one patient expressed that she was not sure whether to inform her children, because she was afraid of hurting them. As she described it, *"Yes, I don't even know whether or not I would tell that to my children. No, because that must be devastating if they know that their mother within 5 years... Yes, I believe I would not say it"* (Woman, 63 years old). We have to be clear that she did not refer to this aspect as an advantage or a disadvantage for knowing her amyloid PET scan result. This contrasting reaction does reveal how other participants can have different motivations for choosing not to inform others.

(5) Some participants stated that with the knowledge of their brain amyloid status they could enjoy life more. For example, they could travel more and do the things they had wanted to do in the past but had to postpone. Although, it was not immediately clear for every participant what he would enjoy in life more. They thought this would become clear and more obvious once they know the result. One participant already started to enjoy life more since he started to experience subtle memory complaints. As he described it:

> *"On the contrary, if you know something, you become more aware of this fact. Buddy, you need to enjoy life more. You know what we did? We reserved three city trips for this year. I found that; thank you, Alzheimer [laughs] […]"* (Man, 68 years old).

(6) With new knowledge about their health, participants felt doubt was removed about what was causing their memory problems. A positive brain amyloid test result implied for some that they had achieved more clarity about their current situation:

> *"*[…] *An advantage is, I think personally, you are with this in your mind [whether you have brain changes leading to AD]; you doubt"* (Man, 66 years old).

Sometimes, one's doubt is amplified when others comment on your memory problems:

> *"I know that something is going on, but what? Is it Alzheimer? Is it dementia? Or is this normal with age? Yes, then they say: 'Yes, but those people are also so old and they know more.' But I think that it is not the same with everyone. I don't know. It is a big question mark for me, and that's why I want to know it"* (Woman, 68 years old).

For some patients, no result could even lead to them losing composure, making them angry or frustrated every time they forget something.

(7) The possibility of being eligible for treatment. Patients did not only refer to treatment as a kind of medication or lifestyle changes but also to the advantageous consequences of receiving treatment, specifically follow-up medical consultations.

(8) The last advantage relates to being better prepared to plan for the future and make personal arrangements should they receive a positive result (Figure 4).

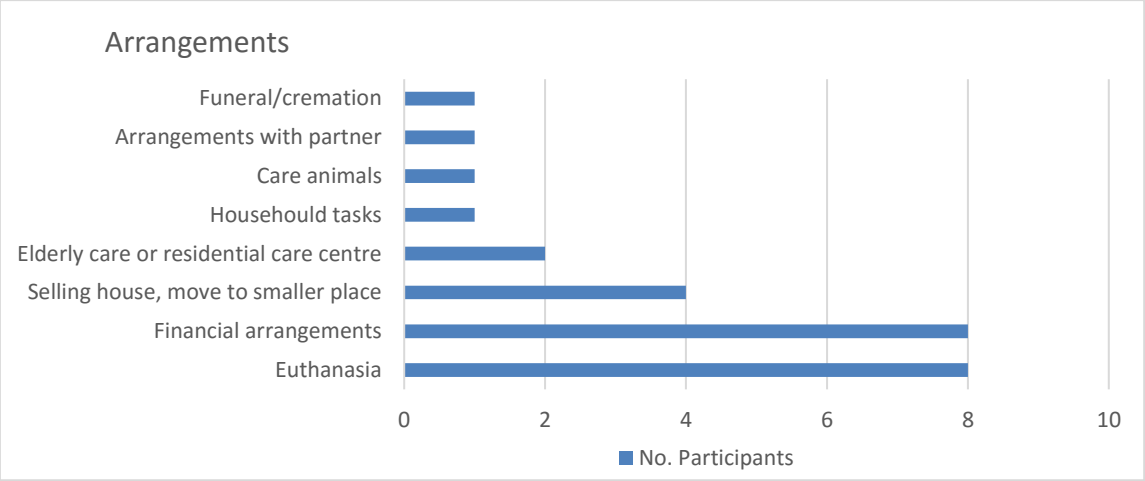

Figure 4. Frequencies of arrangements related to advantages mentioned by participants.

New practical arrangements were expressed by the participants that were not mentioned earlier as reasons for wanting to know their amyloid PET scan result. First, arranging for one's funeral or cremation was mentioned: *"How I want my funeral or cremation and so on. These kind of things"* (Woman, 68 years old). Another participant referred to making arrangements with their partner about creating schedules and stable places to make life easier in case her symptoms became worse. For example, she wanted to arrange for a consistent place to leave her keys and money. Another final arrangement one participant mentioned was finding appropriate care for her pets, as she is currently living alone.

One participant had a different opinion of what sort of future arrangements she should make if she knew her amyloid PET scan result. Although she described making arrangements for the future as being an advantage for knowing one's results, unlike other patients, euthanasia and arranging her funeral were not included as part of her arrangements. This example shows how patients can have different ideas about what sorts of things to consider when planning for their future. For one patient, planning for one's funeral, for example, is an absolute necessity, while for another patient, it is not so important. This sentiment is reflected in the following quote from this woman:

> *"And yesterday, yes, that's maybe, I don't know, all the children were there, and then I told them. So, if the time comes that I have Alzheimer's, and that they will investigate now, then I don't want*

> *euthanasia. I have already told that to them. I want to stay in this world. I don't know if that is an unhappy world. My mother [who had dementia] cried a lot. That won't be so easy. But still, I don't want euthanasia. And they can place me in the same department in that elderly care house where my mother was. Like that we talked about it. And yes, they didn't seem surprised. But now I won't talk about it anymore. That was that one time. But with that I know, because death and arranging your funeral, that not, that I won't do"* (Woman, 63 years old).

In the previous section, participants talked about requesting euthanasia because they did not want to become a burden for their family or because they did not want to live in a vegetative state. While this participant indicated that having AD is most likely not an easy thing to experience, she felt that having AD does not necessarily mean that one would be living in an "*unhappy world.*"

Perceived disadvantages of knowing one's amyloid PET scan result

Next, we sought to determine whether participants perceived any disadvantages in knowing their result. Half of the participants spontaneously stated that there were no disadvantages related to receiving an amyloid PET scan result. Some indicated that disadvantages likely exist, but the advantages of knowing the results outweigh all possible disadvantages. Participants did bring up, however, five specific disadvantages associated with knowing one's amyloid PET scan result (Figure 5).

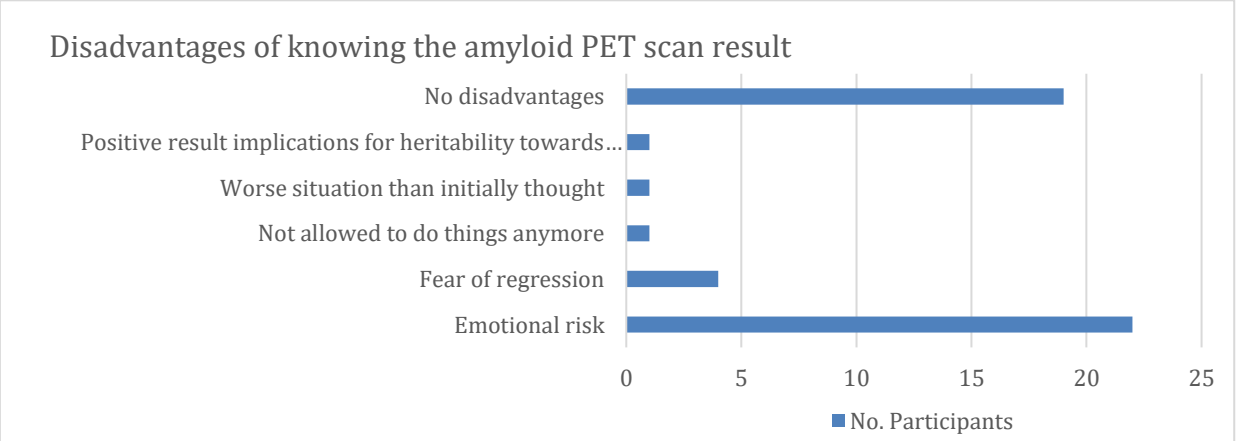

Figure 5: Frequencies of perceived disadvantages of knowing the amyloid PET scan result by participants.

(1) One disadvantage had to do with the hereditability of AD and how it would affect relatives. One participant clarified this, stating that a positive test result could be disadvantageous for her son. However, she also elaborated on this aspect, stating that it is always better to know these things in advance.

(2) A second disadvantage was linked to one's own perception of memory loss. This notion is in line with what another participant stated: Knowing the results might be disadvantageous if your results are worse than how you perceived your own subtle memory complaints to be and to how you thought your health situation was.

(3) A third disadvantage mentioned was that knowing one's results could limit one's freedom to do certain things, like drive a car, one activity that would likely be disallowed. As one participant described it:

> *"[...] Or [that] you cannot drive the car anymore, because they recently said: 'Do you have troubles with that? Do you sometimes forget your way? Don't you forget where you are? […] I can still do that, but I would not drive to the South of Spain. […] I would, but I don't think my wife would like to drive with me anymore [laughs]"* (Man, 67 years old).

Furthermore, this man indicated that if his driver's license were taken away, this would have serious implications for his and his wife's mobility, and this would force them to live somewhere else.

(4) The fear of regression was also perceived as a disadvantage of knowing one's amyloid PET scan result. That is, the fear you get when you receive a positive test result, that your cognitive decline will become worse. Not knowing how long it will take before the progression will accelerate, leads to fear and questions for these participants.

(5) A final disadvantage mentioned was the emotional risk and impact of receiving an amyloid PET scan result. Participants used phrases such as, "*to shed a tear, feeling worried, fear and more frustration,*" to describe the emotional impact of receiving a positive brain amyloid PET scan result. For example, one participant described it as: *"Of course it would be a shock if you heard it: You've got Alzheimer's or the chance is very high that soon you will develop Alzheimer's"* (Man, 81 years old). One participant also indicated that receiving this news may lead to internal confrontation:

> *"Well, in a sense, if you don't know what the result is, then you don't have to make any plans. Once you know the result, then you always got the personal, because you start to think: "Well, how long, why, what can I do about this and this." So, there is more stress and pressure than before [getting the result]"* (Man, 66 years old).

Others indicated that it is never a pleasant thing to hear bad news, but the only way to deal with this news is to accept it and to move on with life. This last reaction indicated that many participants were aware of the possible emotional difficulties connected to knowing one's result. They expressed that they do feel capable of dealing with this information (i.e., the amyloid PET scan result). Some participants provided more subtle answers; for example, how knowing the result can

be simultaneously advantageous and disadvantageous: *"[...] The advantage is to know it, yes. If you know it, then it is a disadvantage that you have to accept it as it is, that you cannot say, yes, I don't want to know"* (Woman, 55 years old). In addition, not knowing the news, can be emotionally difficult too, as expressed by one participant:

> *"Yes, it won't be a pleasant thing […]. If it is bad, then it is not fun. Then your world collapses; I know that too, but, does that weigh up against walking around at home and feeling bad, because you forget everything, and it is not going anymore, and you are plodding? Well, I don't know it [...]"* (Woman, 67 years old).

Although the news can be emotionally difficult, some participants argued that it is still better to know the result now at an early stage of the disease so one can still take actions, from starting therapy to making personal arrangements:

> *"You have to, you have to be able to absorb that information of course, but if you get that now, preventive or early, you get that information next year or within 5 years, that does not matter. Sooner or later, it will come out as positive so rather sooner than later is better, because then you can still do something about it"* (Man, 63 years old).

Participants' understanding of an amyloid PET scan result

Confusion about the meaning of the amyloid PET scan result: a positive test result means good news, right?

Throughout the interviews it was clear that the terminology researchers used to label a positive or negative brain amyloid PET scan result sometimes confused participants. A positive test result was perceived as good news by some participants. In a similar way, a negative test result was perceived by some patients as bad news. Rather than indicating the presence or absence of amyloid, some participants thought 'positive' or 'negative' referred to the emotional valence attached to the result. To be clear, a positive brain amyloid PET scan indicates the presence of higher levels of amyloid than age-normal, and an increased likelihood that the aMCI patient would progress to AD.

Limited predictive value

No participant spontaneously mentioned the limited predictive value of brain amyloid PET scans as a disadvantage of knowing one's result. We specifically asked participants about this, how they thought about their result in terms of a high or low probability of developing AD. We also related this to the less-than-100-percent certainty of the result (i.e., risk of false positive and false negative) and the uncertainty about how the disease progression might occur.

Participants indicated that in medicine, it is not uncommon for clinicians to speak in terms of high or low chances, or use terms of percentage risk. Some participants referred to familial breast cancer for context, in which the clinician spoke of x-percentage of risk based on family history of breast cancer, x-chance of relapse, etc. In fact, participants often indicated that medicine never uses terms of absolute certainty.

Overall, participants indicated that being told they have a high chance of their current memory problems being due to early AD was already perceived as information they would like to receive, instead of knowing nothing about their current condition. They referred to possible advantages of knowing this result, such as the possibility of early intervention and disease monitoring:

> *"I continue to say that the earlier something like this disease is diagnosed, even if it is not 100 percent certain, it is still better that they do everything to prevent it than to cure it afterwards"* (Man, 63 years old).

However, three subtleties were expressed in these views. (a) Some participants mentioned that if one receives the result about progressing towards AD, yet this process turns to go slower than researchers expected it would, this was perceived as a good thing. (b) A participant mentioned that there could be a disadvantage with this type of result. He described it: *"[...] The danger could possibly exist that you, of course, start with medication, while this was not necessarily required. But I don't know if I am estimating that correctly"* (Man, 74 years old). (c) There was another participant who clearly indicated that she would like her result and her medical condition to be told as it is, without the clinician "beating around the bush."

Other participants thought differently about the limited predictive value of the amyloid PET scan result. One participant indicated that it is better not to think about the limited predictive value of the result and to have a 'wait-and-see' attitude towards what might unfold. Another participant felt that it was better that the researchers did not speak in terms of 100 percent certainty, as she found this to sound very negative. She explained that if the result is a 100 percent certain, this takes her hope away that her situation can still turn out positively.

Expected reactions after receiving a positive brain amyloid PET scan result

We asked participants how they thought they would respond if they were to receive a positive PET scan result, implying the chances were high that in a few years they might convert to AD. Different responses, depending on the coping strategy of the participants, emerged. For some participants, they stated that it was difficult to anticipate how they would respond to this news, whilst others had no difficulties and immediately indicated that they would be emotional, leading to tears, or that this news could have a negative impact on their state of mind. Some participants indicated that they would feel somehow shocked after receiving this news. As one participant described it: *"Yes, certainly a bit shocked, because you always expect that you won't get it"* (Woman, 68 years old). As some participants presume they will receive good news, others assume, or are convinced, that they already have AD: "*Sad. Although I realize that I'm regressing, I know it"* (Woman, 81 years old). Others saw a positive PET scan result as a confirmation of their current memory problems they are experiencing.

Most participants reacted to a positive result by responding in a solution-oriented way, which was interpreted in a broad sense by them. More specifically, they imagined solutions ranging from starting therapy to making lifestyle changes to making practical arrangements.

While most participants described their own reaction to the disclosure of a positive result, some participants were more concerned about their partner' and children's reaction:

> *"I would find that very bad for my wife, for my children, for myself also, but yes, for myself, for myself I would find that rather sad. Do you understand the difference?"* (Man, 67 years old).

Although most participants indicated that a positive brain amyloid PET scan is unpleasant news to receive, they concluded that it is better to receive this news rather than to know nothing and have lingering doubt about their own health situation. One participant indicated that it was better to receive a positive result rather than a negative result:

> *"*[...] *then you've got something to plan for and you've got something, you know. Because it's sometimes more worrying than if they say there is nothing there, because then, what's my problem due too?"* (Man, 66 years old).

Expected reactions after receiving a negative brain amyloid PET scan result

Patients' reactions to a negative brain amyloid PET scan result were less diverse and can be clustered into two types of hypothetical reactions. On the one hand, some participants were happy and relieved after receiving a negative result. These participants responded either extremely enthusiastically: *"Thank you! Well, is there any champagne? [laughs][...]"* (Man, 80 years old). Whilst others responded more subtly:

> *"Relieved, logically […]. But still, yes, I would keep in the back of my mind that, [inarticulate] it eventually is still possible to happen in the far future. Maybe I'm already gone by then"* (Man, 73 years old).

On the other hand, many participants were left with the question: "What is causing my symptoms?" This lead to questioning the value of the result or of further investigation:

> *"Yes, then I would ask myself, how it is that I'm forgetting that much [laughs]. I would ask: 'Is everything correct?'"* (Man, 67 years old).

Discussion

In this study, we sought to document and to better understand the perspective of aMCI patients regarding the disclosure of their amyloid PET scan results. The two most frequently mentioned reasons for choosing amyloid PET scan disclosure were to better understand their own brain health status and to be able to make informed decisions about future personal arrangements they might have to make if their PET scans were consistent with the development of AD. Emotional risk was mentioned as the primary disadvantage of knowing one's result.

In the field of AD research, not a lot of research on amyloid PET scan disclosure has been done. However, a number of studies focused in particular on the desire of participants to opt for genetic AD risk assessment [16][17][18]. For example, a telephone survey in a community-recruited sample concluded that 79% of respondents expressed interest in predictive genetic testing for AD [18]. Another recent survey in cognitively normal older adults by Gooblar *et al.* indicated that 97% of participants had a strong interest in obtaining their research results, including those related to the detection of the molecular pathology of AD, such as amyloid imaging [19]. In all previously mentioned studies only a minority of participants preferred not to know their result. In our study, all 38 of the aMCI patients (i.e., 100% of participants) wanted to know their brain amyloid PET scan result. Our sample was quite diverse demographically, varying in age from 55-83 years (mean 71 years; 58% men), most being married with children, and most finishing secondary school or higher. An important limitation is that all 38 aMCI patients were recruited via the memory clinic and already took first initiative to receive medical advice.

Although all of our participants wanted to know their result, two caveats should be mentioned about these results. One participant initially did not want to know his result but later on changed his mind. Another participant stated that he did not want to know his result but said that his wife really wanted to know. In this case, we explained to him and his wife together what this would mean practically and how they might deal with the situation in which one spouse knew the results and the other did not. With additional time to reflect, this participant decided that he wanted to know the results. We carefully queried this participant's reasoning to determine whether he was "pushed" into his decision for amyloid PET scan disclosure by his wife, or whether he made the decision independently.

This high percentage of aMCI patients wanting to receive their amyloid PET scan result suggests that in the near future more participants might be open to participating in research if they have the possibility of receiving their result. However, researchers should be aware that if the release of amyloid PET scans to subjects and patients were to become commonplace, it might

attract people with subjective mental complaints or hypochondriacs to volunteer for research studies, which would then negatively affect not only recruiting criteria and the recruiting process but also research results. Thus, more research is needed on how participants might volunteer for a clinical trial, but opt out of receiving their result. Although in most studies, this group is smaller than the group of participants who do want to know, insight into the opinions and perspectives of the people who opt out of wanting to know is equally important for the disclosure/non-disclosure debate.

The predictive value of amyloid PET scans of aMCI patients for progression to AD in the next years has certain limitations. This is an ethical issue being debated in the general literature about disclosure [20][21][22] and is a point highlighted in our information brochure. Our hypothesis was that the limitations of the predictive value of amyloid PET scans would be perceived as a disadvantage by participants for wanting to know this particular type of result. No participants mentioned this as a disadvantage, even though they presumably read about it in the brochure. To temper the possibility that participants were providing socially desirable answers, we asked more in-depth follow-up questions about this limited predictive value. Still, it was clear that participants did not perceive this as a disadvantage. Participants with aMCI still perceived that it was better to know if they had a high or low risk of developing AD than to remain completely "in the dark" about their current health situation. In addition, our results indicate how some participants perceived this uncertainty as a positive aspect, since it leaves open the possibility for hope. Nevertheless, accurate and clear information about the amyloid PET scan and its associated limited predictive value remains important in order to prevent patients from misunderstanding this information.

Another hypothesis we had was that participants would mention the limited efficacy of current treatment options as a disadvantage of knowing their result. This hypothesis was based on published reports suggesting that available treatment options are perceived as an ethical issue [8][20][22]. This was not mentioned as a disadvantage by any of our participants. When asked, participants answered that they already knew before the start of the study that there is no cure available for AD, or that there is medication available but that it can only delay progression of the disease. The latter was perceived as a better option than receiving no medication at all. Some participants referred to the situation of cancer and its treatment, in which medicine can already do a lot, but is not always able to cure the disease. Most participants maintained strong hope that in the near future the situation will change for early treatment of AD, whereby researchers can rapidly make medical progress.

The concept of therapeutic misconception is important to consider when trying to understand participants' decisions in choosing disclosure/non-disclosure of their amyloid PET scan result. This concept, which is often mentioned by the general literature about IRR disclosure [5][6][23][24], refers to the situation in which patients often fail to distinguish between clinical care and the research setting. Participants believe the researcher is a physician who has two core ethical obligations: (1) endeavor to avoid non-maleficence (no harm), and (2) work toward beneficence (doing well). "Doing well" can be understood as taking care of the health and well-being of the patient by providing necessary therapy and drug treatments [23][25]. In this case, patients who become participants in clinical trials often expect or have high hopes that they will receive treatment. As described in our findings, participants do perceive the option for treatment as a reason to know their amyloid PET scan result. Thus, the therapeutic misconception also occurred in our study. Two nuances should be addressed. First, described in the informed consent brochure as mandatory by the International Guidelines of Good Clinical Practice (ICH GCP) [26] and explained by our researchers to the study participant, was that participants would receive cholinesterase inhibitors if they had a positive amyloid PET scan. Thus, this knowledge likely would affect a participant's decision about their amyloid PET scan disclosure. For a negative amyloid PET scan, this medication would not be prescribed, because it is less effective when the underlying pathology is not related to AD. Second, the concept of treatment was interpreted widely by participants and was not limited to medication. Follow-up, disease monitoring, and imposition of health-related life style changes (e.g., taking food supplements, cessation of drinking, etc.) were also thought of as treatment. This broad understanding also likely affected participants' decisions about their amyloid PET scan disclosure.

The majority of our participants reflected on planning for the future as an advantage of knowing their result. This finding is in line with other AD studies, such as the Risk Evaluation and Education for Alzheimer's Disease study (REVEAL) who reported on the importance of making arrangements for the future [16][27][28]. In our study, almost one-in-five participants also mentioned end-of-life decisions as playing a prominent role in their reasoning about amyloid PET scan disclosure, more specifically the request for euthanasia, given a positive brain amyloid result. The participants who mentioned this possibility in our study might have been influenced by ongoing legal discussions in Belgium. First since 2002, euthanasia can be legally requested in Belgium under strict circumstances (Belgian Euthanasia Act, 28th of May 2002) [29]. These circumstances, imply that: (1) the patient is legally competent and conscious at the moment of making the request; (2) the request is voluntary, well-considered and repeated, and is not the result of any external pressure; (3) the patient is in a medically futile condition of constant and unbearable

physical or mental suffering that cannot be alleviated, resulting from a serious and incurable disorder caused by illness or accident (section 3, §1) [29]. Second in past years, there has been a growing awareness in Belgium that healthcare institutions bear the responsibility for translating these legal regulations into optimal care for patients requesting euthanasia. For example, enhancing communication toward patients and their relatives about end-of-life decisions and early care planning [30][31]. To properly compare the situation in Belgium with that in other countries, research is needed to evaluate whether euthanasia might be considered as a reason for wanting to know one's amyloid PET scan result, and if this would lead to an increase in euthanasia requests.

aMCI participants in our study mentioned euthanasia as a practical arrangement; two ethical concerns emerged from this. First, most participants explained how they do not want to become a burden to their family members. Thus, euthanasia was perceived as a solution, whereby family members would not be burdened with a beloved one who has AD. A person's source of "burden awareness" is an important consideration: In a euthanasia request, did the patient independently arrive at the awareness that he may become a burden, or did he become aware of it by discussions with relatives? According to the Belgian Act on Euthanasia, the request needs to be voluntary, well considered, and not the result of any external pressure [29].

Although there is a worldwide increase in the burden of caring for people with dementia, the solution for this problem should not be euthanasia but proper help throughout the care process from the perspective of both patients and caregivers. Government and healthcare regulations ought to (a) invest in damping down the perception that patients feel they are or will become a burden to their family members and in lifting the actual burden family members currently experience; and (b) maximize proper care that enhances the capabilities of patients and provide respite to ensure that the life of caregivers is not put "on hold" because they are providing care for their beloved one with dementia.

A second ethical concern that relates to aMCI participants in our study mentioning euthanasia as a practical arrangement is that participants feared living in a vegetative state, not wanting to "end up living like a plant." This indicates how there is a negative perception or stigma about AD. Only one participant indicated that having AD does not necessarily mean that they will be living in an unhappy world.

Our findings also reveal how our participants are unclear about the legislation on end-of-life decisions in Belgium. This resulted in the use of the term euthanasia in general terms and showed that they were unaware of the different types of documents Belgian legislation provides. In Belgium, there are five different documents regarding advanced-care planning and end-of-life

decisions [32]. Three of these documents are important, and our participants appear to be confused about them. The first one addresses negative advance declaration about the refusal of certain treatment options; the second addresses the stipulation that advance declaration regarding euthanasia is a document that has to be prepared in advance and has to be renewed every five years. Euthanasia will only be performed in case of irreversible coma, which excludes dementia. The third addresses an active request for euthanasia [32]. The above-mentioned criteria of the Belgian Euthanasia Act also need to be followed. It is clear that our participants confuse issues germane to these three documents. Many participants think that the advance declaration regarding euthanasia is sufficient if they receive an AD diagnosis. In reality, if a patient with an AD diagnosis wants euthanasia to be performed, he has to declare an active request for euthanasia when he is still capable of expressing his wishes. This implies that the patient actively chooses to shorten his life by certain good months/years before cognitive deterioration becomes worse.

There was also confusion among some participants about the terminology used for positive and negative amyloid PET scans. Some patients understood a positive scan to be good news, a report with a favorable outcome for future brain health. Although the correct terminology was explained in the informed consent brochure and throughout the information session when the researcher explained the content of the trial face-to-face with the patient, we noticed that throughout the interviews, patients misused or misunderstood the terminology. If the interviewer noticed that a participant misunderstood the terminology, she elaborated on the point with the aim of avoiding the situation in which the interviewee and interviewer were talking about "different" results. Thus to clarify the terminology, we compared the amyloid test to an alcohol test: Having too much alcohol in the blood results in a positive alcohol test. In the same way, having too many amyloid plaques in your brain results in a positive amyloid test. Most of our participants understood this comparison. For patients to understand this type of research result, it is imperative to explain it clearly in a simple and correct way.

Limitations

The current study aimed to gain insight into the motivations and opinions of patients with regard to the disclosure the amyloid PET scans in a research context. The strength of this qualitative sub-study was its in-depth patient interviews, which enabled us to better understand their motivations, opinions, and experiences. Face-to-face interviews provide researchers the opportunity to go beyond numerical quantitation, which can overlook the real reasons behind a subject's answers; interviews allow researchers to get a correct understanding of the interviewee's opinions [33]. A limitation with all qualitative research, however, is that participants are always embedded in a certain cultural or societal setting, which can influence the results [33]. For example, the widely discussed views on euthanasia in Belgium could have affected our results. The views of participants presented here are based on a small population of aMCI patients in Belgium who were recruited via the UZ Leuven memory clinic. It is possible that somewhat different findings may emerge when investigating this topic in a different country or when recruiting a different study population. For example, subjects with minor memory complaints who have not undertaken the first steps to receive medical advice from the memory clinic or healthy adults being evaluated for preclinical AD. We do believe that the findings are important beyond the context of this research and can be of use for further clinical trials.

Appendix

Inclusion criteria	Exclusion criteria
Patients must meet all of the following inclusion criteria to participate in the study: • Patient is male or female and between ≥ 55 and ≤ 85 years of age on the day of signing the consent form. • If female, patient is not of reproductive potential (i.e., two years post-menopausal or surgically sterile). • Patient has a subjective memory concern, as reported by patient, study partner, or clinician. • Patient has memory impairment, documented by scoring below the education-adjusted ranges on the AVLT total learning or delayed recall percentage (≥ -1 SD). • Patient has a Global Clinical Dementia Rating score of 0 or 0.5. • In the opinion of the investigator, the patient is in stable medical condition and willing and able to perform study procedures. • Patient has at least six years of education, or sufficient work history to exclude mental retardation, in the investigator's opinion.	Patients will be ineligible for participation in this study if they meet any of the following exclusion criteria: • Patient has a history of or current evidence for a neurological disorder that, in the opinion of the primary investigator, may contribute to the subject's cognitive impairment, including, but not limited to: o Large-vessel stroke, o epilepsy, o Parkinson's disease, o progressive supranuclear palsy, o Huntington's disease, o amyotrophic lateral sclerosis, o multiple sclerosis, o CNS infection, o significant head trauma with loss of consciousness, o Normal pressure hydrocephalus • Patient has a history of large-vessel stroke, or evidence of a large-vessel infarction or other focal lesions, on baseline MRI scan that may contribute to the memory impairment, in the opinion of the investigator. • Patient has received an examination over the past year involving more than 10 mS ionizing irradiation • Patient has a history, within 6 months prior to screening visit, or current evidence of a psychotic disorder or a major untreated depressive disorder. • Patient has a history of malignancy ≤5 years prior to signing informed consent, except for patients who have undergone potentially curative therapy with no evidence of recurrence for 1 year, and who are deemed at low risk for recurrence by her/his treating physician. • Patient has a history or current evidence of any potentially known clinically significant condition therapy, lab abnormality, or other circumstance that, in the opinion of the investigator, might confound the results of the study or interfere with the patient's participation for the full duration of the study, such that it is not in the best interest of the patient to participate. • Patient currently uses specific psychoactive medications (neuroleptics, chronic anxiolytics, tricyclic antidepressants, antiepileptics, anticholinergics etc.). Stable dose trazodone, mirtazapine or low dose benzodiazepines prescribed for mild insomnia is allowed. • Patient currently uses antithrombotics, with the exception of acetyl salicylic acid (exclusionary for lumbar puncture).

	• History of alcohol or substance abuse, or dependence within the past 2 years (DSM IV criteria) • Patient is currently participating or has participated in a study with an investigational compound or neuropsychological measures within 30 days of signing informed consent. • Subject has any magnetizable metal prostheses, implants or foreign objects that could pose a hazard during MRI scans.

Appendix 1. Inclusion and exclusion criteria for the BioAdaptAD study.

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Chapter 5 Amnestic MCI patients' experiences after disclosure of their amyloid PET result in a research context

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Abstract

Background: Biomarkers, such as amyloid imaging, are increasingly used for diagnosis in the early stages of Alzheimer disease. Very few studies have examined this from the perspective of the patient. As of yet, there is only limited evidence about how patients experience and value disclosure in an early disease stage.

Method: Semi-structured interviews were carried out in 38 amnestic Mild Cognitive Impairment (aMCI) patients as a part of an investigator-driven diagnostic trial in which participants could opt to know the binary outcome (positive/negative) result of the amyloid PET scan. Verbatim transcripts of the interviews were analyzed via qualitative content analysis and by using the Nvivo 11 software.

Results: Eight out of 38 patients received a positive amyloid PET scan result and the remaining 30 patients received a negative amyloid PET scan result. After disclosure of the result, we interviewed each patient twice: (1) Two weeks after disclosure and (2) six months after disclosure. Patients had difficulties in repeating the exact words used during disclosure of the amyloid PET scan result by the neurologist, yet could recall the core message of the result in their own words. Some patients were confused by the terminology of an amyloid-positive/negative test result.

After six months, 2/8 patients with a positive amyloid PET experienced emotional difficulties (sadness, feeling worried). 3/30 patients with a negative amyloid PET started to doubt whether they received the correct result. Patients reported that they experienced advantages after the disclosure, such as information about their health status, the possibility of making practical arrangements, medication, to enjoy life more and a positive impact on relationship. They also reported on disadvantages following disclosure, such as having emotional difficulties, feeling worried about when symptoms will deteriorate, the risk of a more patronizing attitude by relatives and the possibility of a wrong diagnosis.

Conclusion: This exploratory study has shown that the majority of patients can accurately recall the information received during disclosure. The experienced advantages and disadvantages reported by our patients depends on the outcome of the result (positive or negative) and the time interval of the conducted interview (two weeks or six months post amyloid PET disclosure). Discrepancies were found between patients' expectations according to the interview prior to amyloid PET disclosure (Vanderschaeghe G. et al., Neuroethics, 2017) and their actual experiences after their amyloid PET disclosure.

Background

In the early, predementia stage of Alzheimer's Disease (AD), clinical, neuropsychological and MRI characteristics may not suffice for a reliable AD diagnosis. Especially in the early phases of the disease, biomarkers of the underlying amyloid pathology play an increasingly important role in the recommendations for diagnostic guidelines, in particular in a clinical research setting [1][2][3]. In most current clinical trials of potentially disease-modifying drugs in AD, biomarker positivity is considered an essential criterion for inclusion of patients.

Several questions remain before amyloid PET can be recommended for application in routine clinical practice in amnestic Mild Cognitive Impairment (aMCI) [4][5]. These questions relate, among others, to the prediction of the individual timeline of cognitive decline and the psychological consequences of amyloid PET disclosure [6][7][8][9]. There is also limited knowledge on how to best disclose amyloid PET scan results to the tested individual [10][11][12][13].

A key perspective that has been relatively under-represented until now, is the perspective of the patients themselves [14][15][16]. One study explored the views of patients and caregivers on amyloid PET imaging [17]. In that study, the views of the 23 caregivers outnumbered the views of the nine included patients (7 patients with an amyloid-positive and 2 with an amyloid-negative PET scan) [17]. In addition, the diagnosis in the patient population (n = 26) was heterogeneous (e.g. MCI, atypical presentation of AD dementia, young-onset cognitive impairment,…) [17]. A number of previous studies have examined the degree to which study participants wish to be informed about the outcome of tests, but these have been mainly performed in cognitively intact individuals. An academic memory clinic based study in 2015 reported that 45.5 % of cognitively normal (95/209) participants in a longitudinal aging study were extremely interested in knowing their biomarker result, although this proportion slightly decreased after an education intervention [18]. A review by Bemelmans *et al* covered fourteen studies of disclosure of genetic AD biomarkers [19]. For example, the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study investigated the preferences for undergoing genetic Apolipoprotein E (APOE) susceptibility testing for AD in healthy adults who have at least one relative with AD [20][21]. For amyloid PET, far less studies have reported on the perspective of study participants towards the disclosure of the result.

A suitable research methodology for gaining insight into patients' perspectives and experience is qualitative research [22][23]. Hence, we have conducted an explorative study in 38 patients with aMCI that may provide novel qualitative data on how patients with a MCI perceive and experience amyloid PET scan disclosure in a research setting. The current study was performed

as an optional substudy of a longitudinal observational cohort study about the predictive value of amyloid PET in aMCI. Subjects were offered the possibility to receive their amyloid PET scan result.

Methods

Recruitment

Recruitment took place between June 2015 and June 2016 after approval of the study by the Ethics Committee, University Hospitals Leuven. All participants provided written informed consent in accordance with the Declaration of Helsinki.

The study cohort consisted of a consecutive series of 38 aMCI patients recruited via the memory clinic of the University Hospitals Leuven. The interviews were part of the BioAdaptAD study, which is an investigator-driven diagnostic trial in aMCI. The primary objective of the BioAdaptAD study (EUDRACT no. 2013-004671-12) was to evaluate the predictive value of baseline amyloid biomarker measurements for longitudinal change over a 2 years' period. When participants met the inclusion criteria (see appendix 1 for all in- and exclusion criteria) of the BioAdaptAD study, participants were given the option to participate in the substudy investigating the ethical opportunities and challenges regarding the return of their amyloid PET scan result.

All participants who agreed to volunteer in the substudy had the possibility to be informed of their amyloid PET scan result. Therefore, no protocol was needed to determine who would learn their amyloid PET scan result. This option was favored for two reasons by the research team: first, in order to respect the individual decision making of the patients. Second, in order to investigate how many of the participants would choose to learn their amyloid PET scan result. The substudy consisted of three semi-structured interviews which were conducted with the aim of getting insight into: (a) participants' motivations and expectations before the disclosure of their result (findings reported in Vanderschaeghe G. *et al* [15]) and (b) participants' experiences after the disclosure of their result. This manuscript focuses on the findings of the two interviews (two weeks and six months) after the amyloid PET disclosure.

Before the start of the substudy, an informed consent brochure on the general and the sub study was provided to the participant. This informed consent brochure was based upon the E6 guideline of Good Clinical Practice [24] and contained background information, objectives, interview process and participant's rights. Additional time before the first scheduled interview (pre-amyloid PET scan disclosure) was provided whereby the interviewer orally repeated the content of the informed consent brochure and asked the participants if they had any additional questions. During the two interviews after the amyloid PET scan disclosure, the researcher repeated the participants' rights and the interview process.

Participants were asked to complete the socio-demographic form and to sign the informed consent form (IC). The latter indicated that they understood the following: that their result and interview recording were to remain confidential, that their participation was voluntarily, that withdrawal from the substudy would have no impact on their participation in the BioAdaptAD study nor on the ability to receive any other medical intervention at the hospital. Participants were informed that the results of this study would be published in a scientific journal and that general findings from our interview study would be provided to them after completion of the substudy.

Diagnostic consult for amyloid PET disclosure

The disclosure of the amyloid PET scan result was performed by the study physician who was a neurologist (RV or RB). The disclosure happened two to three weeks following acquisition of the amyloid PET scan in a semi-standardized fashion. First, the physician explained that the visit was a study visit to communicate the amyloid PET result since the person had provided informed consent to the disclosure substudy. Second, the physician explained in general terms what an amyloid PET scan measures and that a scan can show either an increased level of amyloid or a normal level. The physician explained that an increased level (or positive amyloid PET scan result), meant in practical terms that the memory problems were caused by a very early stage of AD and that this also meant that over time there was a high chance that the memory problems would further deteriorate. The physician explained that in case of a normal level (or a negative amyloid PET scan result), this meant in practical terms that the memory problems were not due to AD. Third, the physician disclosed the amyloid PET result of the individual patient using the same terminology. In case of a positive amyloid PET scan the physician emphasized that an amyloid PET scan can already show increased amyloid levels in cognitively intact subjects before clinical symptoms appear. Fourth, in case of a positive amyloid PET scan, the physician advised to start treatment with a cholinesterase inhibitor and went on to provide the standard explanation regarding the effect and possible side effects. In particular, it was mentioned that a cholinesterase inhibitor could help stabilize the symptoms for a longer period of time although it could not be predicted at the individual level for how long. Note that the use of a cholinesterase inhibitor in MCI is off-label use, as it is only clinically approved in clinically probable AD. In case of a negative amyloid PET scan, the physician informed the patient that this did not mean that the memory problems were discarded as being unimportant: further follow-up was still advisable since there may be other causes than AD. Fifth, the physician asked whether the patient or the family had any remaining questions. Following this visit, a study visit report was written which mentioned the amyloid PET

scan result, the interpretation of the result, the fact that the result was communicated to the patient and the planned course of action. This report was sent to the family physician.

Data collection and analysis

Visual assessment of amyloid PET scans

^{18}F-Florbetaben (or product name Neuraceq, Piramal Imaging) amyloid PET-scan were obtained during a period of 30 minutes between 90 – 120 min post injection (p.i) on a Siemens Biograph PET/CT scanner (Siemens, Erlangen, Germany). This acquisition window was based on the Neuraceq EMA brochure, which recommends the acquisition of a 20-minute PET scan starting at approximately 90 minutes after intravenous injections of ^{18}F-Florbetaben. From 90 minutes p.i., the tracer concentration reaches a plateau in healthy controls and AD patients and an acquisition window of 30 minutes can be expected to further increase the signal to noise ratio if tolerated by the patient [25]. Visual assessment of summed ^{18}F-Florbetaben amyloid PET image in subject space was performed by three independent, blinded and certified (Neuraceq training by Piramal Imaging) readers. According to the Neuraceq visual assessment guidelines, the following brain regions were assessed for elevated amyloid levels: lateral temporal lobes, frontal lobes, posterior cingulate/precuneus and parietal lobes. The ^{18}F-Florbetaben amyloid PET-scan was classified as amyloid-positive (+) or amyloid-negative (-) if at least one of these brain regions showed increased amyloid levels. According to the literature, visual assessment of ^{18}F-Florbetaben amyloid PET has a sensitivity of 98% and a specificity of 89% compared to the histopathological standard of truth [26].

Interviews and data analysis

The interview guide was developed by GV, KD and RV and consisted of four main content areas: recall of one's result, emotional well-being after the disclosure of the result, experienced advantages and disadvantages of knowing one's amyloid PET result and feedback of the trial and interviews. These content areas were based on the existing literature and findings from our previous study before patients' amyloid PET disclosure [15]. A pilot study, which consisted of the first two interviews, was used to evaluate the interview guide [22].

The interviews were recorded on tape following consent of the interviewee. The verbatim transcripts were analyzed using the Nvivo 11 software and via the qualitative conventional content analysis methodology [27][28][29]. In a first phase, the interviewer (GV) used the pencil and paper method as described in the Quagol [30]. GV coded the interviews at three different times, leaving

an interval of a few weeks in between the coding process. Leaving interval times and re-coding provides the possibility to check whether new meanings can be attributed to the transcript, increases rigor and minimizes subjective interpretation [30]. In a second phase, five interviews were separately coded by an independent researcher (KD). In a final phase, a comparison was made between the codes by the interviewer and the independent researcher and finally consensus upon the codes was reached. Only after consensus of the codes, transcripts were inserted in the qualitative analysis software of Nvivo 11, which provided the researchers with an additional check-up [30].

For the two weeks post-interview, saturation for the negative amyloid cases was reached after 23/30 interviews. There was no saturation of amyloid-positive cases in both two weeks and six months post-interview due to the limited number of positive cases as part of this clinical trial [31].

For the six months post-interview, saturation for the negative amyloid cases was reached after 20/27 interviews. Although saturation for the negative cases was reached before we conducted all interviews, we continued the process of the interviews until the deadline of the substudy. The rationale behind the continuation of the interviews was, to provide each participant with the same discourse as part of the general clinical study. However, three six months post-interviews were not conducted because of the difficulty in finding an interview date that was suitable for the patient as well as before the deadline of the substudy. Nonetheless, this did not affect the data due to the data saturation mentioned above.

Interviews were conducted in Dutch, with the exception of one patient who preferred the interview to be conducted in his native language, English. In this publication, all transcribed excerpts from the interviews are translated into English.

Results

Study population

Sixty-seven patients were invited to participate in the BioAdaptAD study; 26 of them decided not to participate, and three other patients quitted the study after the first neuropsychological screening visit. These 26 MCI patients were not significantly different in terms of age (t = -1.67, p = 0.10, mean age 73.5 ± 5.4, range 62-82 years), nor were there any differences in gender (chi-square (1) = 0.86, p = 0.36, 14 women/12 men) compared to the group of 38 aMCI patients that decided to participate in the full study. Most of these individuals did not provide a reason or explanation for their decision not to volunteer, yet some referred to the burden of caring for a partner or to a lack of motivation. For the three patients who dropped out of the study, the following three reasons were mentioned; a lack of motivation, disagreement of the partner and an inability to schedule a new appointment that best suited the patient. This resulted in a study population that consisted of 38 aMCI patients who met the inclusion criteria (Appendix 1) of the BioAdaptAD study [15][32]. All aMCI patients agreed to participate in the additional substudy in order to obtain their amyloid PET scan result.

Eight ^{18}F-Florbetaben amyloid PET-scans were classified as amyloid-positive and 30 ^{18}F-Florbetaben amyloid PET-scans were amyloid-negative. Table 1 summarizes the demographic information and the performance on the conventional neuropsychological tests.

Demographic characteristics	**Amyloid-positive (*n* = 8)**	**Amyloid-negative (*n* = 30)**	***P value***
Age (years): mean + SD (range)	74.8 ± 4.8 (66-81)	69.8 ± 6.6 (55-83)	0.057
Gender (*n*)	♀: 3 ♂: 5	♀: 13 ♂: 17	/
Years of education: mean + SD (range)	13.4 ± 3.4 (8-19)	13.1 ± 3.8 (8-22)	0.679
Neuropsychological evaluation	**Amyloid-positive Mean + SD (range)**	**Amyloid-negative Mean + SD (range)**	
Global Clinical Dementia Rating (CDR)	0.5	0.5	/
Cornel Depression Rating Scale (CSDD)	1.5 + 1.3 (0-3)	3.6 + 3.1 (0-13)	0.066
Mini Mental State Examination (MMSE) (/30)	27.0 ± 2.0 (25-30)	28.5 ± 1.2 (25-30)	0.047
Auditory Verbal Learning Test (AVLT) Total Learning (/75)	29.1 ± 4.1 (23-33)	38.1 ± 10.5 (21-62)	0.011
AVLT long term % delayed recall	45.9 ± 47.7 (0-133.3)	65.9 ± 21.9 (11.1-111.1)	0.062

Table 1: Demographic characteristics, neuropsychological evaluation and visual assessment read amyloid PET scores

Recall of the individual amyloid PET scan result

Two weeks after disclosure, the amyloid-positive cases had difficulties in repeating the exact words used during disclosure by the neurologist, yet were able to recall the core message of the result in their own words. Patients added that they received their result in an early phase, even though this result does not necessarily imply that their memory problems will decline in the near future.

> *"Explanation, amyloid tissue in the brain. I don't know anymore what exactly has been said."* (Woman, 66-years old).

Patients who received a negative amyloid PET scan result, described that the neurologist clearly communicated the result. They described how the neurologist first re-explained the trial, including the tests that had been done. Some of the patients mentioned the fact that the neurologist had stated that no amyloid plaques on the scan were found; or that their current memory complaints were not due to AD. Patients also mentioned that their result or cognitive health status could be different within 5 to 10 years.

A general finding in both groups was that some patients confused the terminology of a positive/negative amyloid PET scan result. For example, some participants found it confusing that the neurologist spoke of a positive amyloid PET scan result even though this was interpreted as 'bad news' for the patient. Vice versa, the negative cases reported they received a positive result.

After six months, no differences were noticed compared to the two weeks post-result interview.

Emotional aspects associated with amyloid PET scan disclosure

Two weeks after disclosure

Overall, the amyloid-positive cases responded that they did not feel surprised by the news as they already experienced some memory complaints, yet receiving bad news is never a pleasant thing. Some individual reactions were, for example, how a participant said he did not allow that this news controlled his life in a negative way. Another example, describes how a patient initially cried after receiving the news, yet has come to accept it; *"At that time, I cried for a moment, silently. But yes, what can you do about it? Can I now sit down in my sofa and cry the entire day? That is not possible.* (Woman, 72-years old). Another patient described her emotional difficulties in accepting and coping with the news as she labelled the result as a type of '*verdict'* whereby she just has a few more years where she would still function well.

The amyloid-negative cases mostly responded with feelings of relief that their memory complaints were not due to an underlying AD pathology. A minority replied in more neutral words by indicating that they would not cheer or celebrate because they have received a negative test result. Other patients reported that their initial reaction was '*mixed*'. On the one hand, they were happy that AD was not detected on the scan. On the other hand, they were wondering what was causing their memory problems. One of them described it as: *'I think that if I don't have Alzheimer's disease, then I have something else."* (Woman, 63-years old).

Six months after the disclosure

Patients who received a positive amyloid PET-scan result mostly responded not feeling surprised to the news due to the memory complaints they already experienced. However, some differences were noticed compared to their initial feelings two weeks after the disclosure. For example, the patient who initially cried, yet accepted the news, described feeling *'unhappy'* after six months. This resulted into a mixed feeling: On the one hand, the patient mentioned how she only agreed to come to the memory clinic in the first place because her husband and children asked her to. On the other hand, the patient explained that it might be good to know the news now, although she found it difficult to know that her symptoms are due to AD while she experienced her symptoms as '*not that badly'* and was initially not too concerned about her memory problems. This is in contrast with another patient who was grateful for the news. This result changed his perspective and view on life. Despite the memory complaints, he now felt more self-confident. As he explained it: *"I think good. Yes, I have more self-confidence again […] I feel it in my daily life, in the daily approach with others. […]"* (Man, 74-years old). One patient described at both post-interviews that she had emotional difficulties to accept and cope with the news.

No major differences were noticed in the patients who received a negative amyloid PET scan result. Most of the patients said they were not thinking of their result anymore. A patient clarified that in the previous interview, he felt angry about the received result because he was constantly worried and thinking of his memory complaints, which made him angry when the researcher explained his complaints were not due to AD. After six months, he described how he could understand his negative result better now compared to the previous interview two weeks after the disclosure of the result.

Informing others, or not?

Two weeks after the disclosure

The amyloid-positive cases mostly informed their children and close family members of the news. In most of the cases, the partner of the patient was present at the moment of disclosure. Patients indicated that their partner and children were not surprised about the news since most of them already noticed the memory complaints of the patient. Two patients who received a positive amyloid PET scan result still had to inform their children because they did not have enough time yet to see their children or had doubts about informing their children out of fear of putting a burden on them.

When asked whether patients with a positive amyloid PET scan result had already informed others (friends, neighbours, and so on), reactions were twofold:

(1) The majority of the positive cases indicated that time was too short to inform others, but that they did not have any problems to talk about the news with others. To inform others about their news was perceived as useful based upon several reasons as indicated in Table 2.

Reasons to inform others (by majority of amyloid-positive patients)	**Reasons *not* to inform others (by large group of amyloid-negative patients)**
• Other people would know what is going on with them. • Other people can help the patient and take the patient's situation into account. • Sooner or later other people will notice what is going on with the patient. • Because it can do the patient well to talk to other people who can understand their problem.	• The decision was made together with the partner before the disclosure of the amyloid PET scan result about whom they would inform once the result is known. • Once you inform others, you have no control of the information. This could result in people who start to perceive the patient differently or that others start to generalize that the patient already has dementia. • Some people do not know how to respond to bad news. In particular, for younger people it might be difficult to understand the memory complaints of the participant. • The amyloid PET scan result is your personal and thus private information. • It is uninformative news to tell due to the negative amyloid PET scan result. If they would have a positive test result, they would have informed their inner circle of family and friends.

Table 2: Reasons (not) to inform others

(2) A minority of patients with a positive amyloid PET scan result were not planning to inform others beyond their inner circle of family and friends. For example, a patient described the fear

that once you have disclosed the result, there is no control of how people interpret and spread this news to others;

> *"And I do know that it is not something that stays with the people but that will be told to others and before you know it, you get a name glued on you that is much worse than what is going on. Then I think you gradually become shut down from groups you work with, the people you are busy with and so on. I do not live alone in society. I still live together with a few people around me and I have a bit fear that there is too much chatting about that"* (Man, 79-years old).

A large group of the amyloid-negative cases said they only informed their partner, children and some close family members. In addition, they were not planning on informing many others, nor on making the news public according to the following reasons as stated in Table 2.

A minority of patients who received a negative amyloid PET scan result had no problems on informing others. For example, a patient stated that she does not care about how others respond to the news. Therefore, she had no problem with talking about her trial participation and her received result.

Six months after the disclosure

All patients informed their partner and children about the result. The same notion as described in the first follow-up interview, whereby some patients were reluctant to inform others about their result (both positive and negative) was noticed in the second follow-up interview. For example, a participant who received a positive amyloid PET scan result described how she found it difficult to talk to others about the news out of fear of receiving negative reactions or comments. This resulted in the attitude of hiding her symptoms and received IRR:

> *"I still find it very difficult to tell it to strangers or to talk about it with people. With the children it is okay, but with other people I still have the feeling: I want to hide it as long as possible"* (Woman, 66-years old).

Although the previous mentioned citation refers to the fear of negative responses when informing others, no negative reactions of others commenting on their amyloid PET result were reported by our patients (in both positive and negative cases).

Experienced advantages

Two weeks after the disclosure

Patients who received a positive amyloid PET scan result mentioned five experienced advantages two weeks after the disclosure (Table 3).

Patients with an amyloid-positive test result	Patients with an amyloid-negative test result
Two weeks after disclosure: (1) More contact with family (2) Early diagnosis (3) Practical arrangements (4) Medication (5) Clarification/to know what is going on with their health **Six months after disclosure:** (a) Similarities: (1) Early diagnosis (2) Medication (3) Clarification / to know what is going on with their health (4) Practical arrangement: Tricks for memory complaints (b) New mentioned advantages: (1)To enjoy life more (2)More and closer follow-up (3)Better for relationship (4)Reassurance / Relief (c) Not mentioned after 6 months: (1) More contact with family	**Two weeks after disclosure:** (1) To know the news as early as possible (2) To resume normal lifestyle (3) To enjoy life more (4) Planning arrangements in the long term (5) To accept memory complaints better (6) Clarification/to know what is going on with their health (7) Reassurance/relief **Six months after disclosure:** (a) Similarities: (1) To know the news as early as possible (2) To resume normal lifestyle (3) Clarification, to know what is going on with their health (4) Reassurance / Relief (5) To plan ahead / to plan the future (b) New mentioned advantages: / (c) Not mentioned after 6 months: (1) Enjoy life more (2) To accept memory complaints better

Table 3: Patients' experienced advantages two weeks and six months after the amyloid PET disclosure.

(1) More contact with family. For example, a patient indicated how he experienced more contact with his family since he has informed them about the result. He had the impression that they wanted to help him, which he perceived as a positive change. However, he nuanced that this helping attitude should not change into patronizing him.

(2) Early diagnosis was perceived by a minority of patients as an advantage, whereby symptoms are still minor and whereby AD is detected at a very early stage.

(3) Ability to make practical arrangements. Half of the patients who were either thinking of or already started to make practical arrangements mentioned this as an advantage. Examples given were: to move to a smaller place, financial arrangements, household help, creating order in

practicalities such as creating a good agenda and creating fixed places for objects, such as: keys, wallet, and so on. In addition, one patient started to think of an elderly care setting as it takes time to find and to arrange a proper place. Yet, he said he was not ready to live in an elderly care setting as he is still capable of doing most things by himself.

(4) The option to start medication that can possibly delay symptoms. Although no cure is available, patients described feeling satisfied that some medication was available to stabilize their symptoms.

(5) To know now what is going on with one's health. Patients have received a clarification for the symptoms they are experiencing.

A minority of patients with a negative amyloid PET scan experienced no advantages two weeks after their IRR disclosure. Since they did not receive 'bad news' as they often described it, life just goes on as before the disclosure of the result. However, others mentioned several advantages after the IRR disclosure (Table 3):

(1) Regardless of the outcome of the result, knowing the news as soon as possible, in an early stage, was perceived as an advantage.

(2) Ability to resume a normal lifestyle. A patient described how before the disclosure of the result, the fear that something might be wrong, determined his life. This resulted in doing only the important (practical things) and suspending non-urgent and non-necessary habits, such as a daily walk and a monthly visit to the theatre.

(3) Ability to enjoy life more. For example, a patient mentioned that before the disclosure, she would always postpone certain activities, such as, travelling. However, the negative amyloid PET scan result, made her realize that her news was good, yet other diseases or accidents could always occur. She gained the insight that she needed to do the things she wants to enjoy now without (further) postponing these activities again.

(4) Ability to make long-term plans. As described by a patient, the negative amyloid PET result gave her more time to plan and arrange things for the future in a better way, yet without rushing things now. A positive result would have implied that she urgently needed to make, for example, financial arrangements.

(5) Ability to better accept/cope with memory-loss and other AD symptoms. As a patient described it:

"I have to live with that now [referring to symptoms]. That is not always easy, but I can accept it better now because it is not from dementia, so I can accept it better and it is easier for me […]" (Woman, 61-years old).

(6) Knowledge and increased clarity about their health situation. Before the disclosure, patients were in doubt, not knowing what is going on. The negative amyloid PET scan result provided them with a clarification and with the opportunity to '*exclude the worst [disease]'* as they would often describe it. For some, to know what is going on resulted in the fact that they stopped comparing their symptoms with, for example, another family member who suffers from AD, as they now know their symptoms are not due to AD.

(7) Reassurance or relief. The majority of patients who had received a negative amyloid PET scan result mentioned this advantage due to their fear of getting AD. As a patient described it:

"Yes, it's a relief. […] There was a heavy burden, because you think, misery is about to happen and lots of suffering will come to you. Maybe that is over now. Well, you never know, but nobody knows that […]" (Woman, 68-years old).

Six months after the disclosure

Six months after the disclosure, we investigated whether patients experienced any advantages of knowing their result. This resulted in several findings as displayed in Table 3.

After six months, patients who received a positive amyloid PET scan result experienced three similar advantages compared to the interview two weeks after the initial disclosure. These advantages were: the use of medication, to know what is going on with their health and the fact that they received the news in an early, still beginning phase. This time, only external aids to deal with their memory complaints were mentioned as a practical arrangement, such as writing things down on paper, keeping track of their agenda, and so on. Patients referred to four new advantages six months after the disclosure of their result:

(1) Ability to enjoy life more than before the disclosure of the result.

(2) Regular follow-ups and close monitoring of patients' memory complaints were an advantage of knowing the result.

(3) Better for relationship. A minority of patients said that the result improved their relationship and led to a better understanding from their partner's perspective. Their partner stopped complaining about their memory complaints. In addition, one patient said that in the past, he would have never admitted that he had memory problems. Due to the received result, he now accepts and

admits he has memory problems, which for him had a positive impact on his relationship with his wife.

(4) Feeling of reassurance and relief. For example, a patient said that the result positively influenced his self-confidence. Before the result, he felt in constant doubt.

Patients who received a negative amyloid PET scan result reported similar experienced advantages compared to the interview two weeks after the initial disclosure (Table 3). These similarities were: Clarification, to resume normal lifestyle, to know the news as early as possible and the feeling of relief. To plan the future was mentioned again, yet without explicitly referring to planning in the long term as was described in the interview two weeks after the initial disclosure.

Experienced disadvantages

Two weeks after the disclosure

A minority of patients who received a positive amyloid PET result stated how their awareness about their experienced memory complaints did not result into the feeling of being shocked or surprised after the disclosure of their result. Due to this awareness, they experienced no disadvantages. However, other patients mentioned different experienced disadvantages after the disclosure of the result (Table 4).

Patients with an amyloid-positive test result	**Patients with an amyloid-negative test result**
Two weeks after disclosure: (1) Emotional difficulties (2) Worse situation than initially expected (3) Patronized by partner/children (4) Question: Will my symptoms become any worse. If so, when?	**Two weeks after disclosure:** (1) No access to all clinical trial data (2) Question: What is causing my memory complaints?
Six months after disclosure: (a) Similarities: (1) Emotional difficulties (2) Question: Will my symptoms become any worse? If so, when?	**Six months after disclosure:** (a) Similarities: (1) Question: What is causing my memory complaints?
(b) New mentioned disadvantages: (1) Driver's license	(b) New mentioned disadvantages: (1) Wrong diagnosis?
(c) Not mentioned after 6 months: (1) Worse situation than initially expected (2) Patronized by partner/children	(c) Not mentioned after 6 months: (1) No access to all clinical trial data

Table 4: Patients' experienced disadvantages two weeks and six months the amyloid PET scan disclosure

(1) Emotional difficulties coping with the news, such as crying.

(2) Worse situation than initially expected. For example, a patient described how she initially experienced her memory complaints as minor complaints. Due to the result, she realized her complaints were more severe.

(3) Experience of a patronizing attitude on behalf of the patients' partner or children. The feeling that others are taking over practical things while patients are still capable of doing things by themselves. For example, a patient described how he understood that his children were most likely just trying to help him. Therefore, he mentioned it as a current minimal concern, yet as something he wanted to be aware of in case his children would become too patronizing. One of the patients really feared losing her independence and control of her own life. She would find it difficult if her children would start to check the things she did and would take over.

(4) The hope that their current memory complaints would remain stable without becoming any worse, was mentioned by half of these patients. Yet, after the disclosure of the result, the question: 'Will my symptoms become worse and if so, when?' occurred in their mind. Although one participant described the difficulty to predict the time course of cognitive decline:

> *"Yes, I hope for the best. It will definitely evolve. I don't think it will stay like that, but is that within five years? Is that already next year? It's possible, that by next year I'm already completely from the map. Is it within ten years if I'm still alive by that time? I don't know. As far as I know, there is no fixed rule for that, I think"* (Man, 81-years old).

The majority of the negative amyloid PET patients experienced no disadvantage two weeks after the disclosure of their result, since the majority of these patients perceived their news as '*good news'*. As a patient who received a negative amyloid PET scan explained: *"Disadvantages no. No. On the contrary, it is good news, so it can only bring advantages"* (Woman, 69-years old). However, a minority of patients experienced two disadvantages after receiving their negative amyloid PET result (Table 4).

(1) A patient described that it is a disadvantage they only received their amyloid PET scan result, whilst they did not have access to all data about the trial and about all the conducted tests.

(2) While most of the patients with a negative amyloid PET scan result perceived clarity as an advantage of knowing their result, some were left with the question: 'What is causing my memory complaints as I still forget a lot?' This unanswered question stayed on these patients' mind two weeks after the disclosure of the negative result. Two patients described it in the following way:

> *"Then I ask myself, there must be something different that they cannot find or where no research has yet been done"* (Man, 73-years old).

"[…] You are happy and still you think, damn, I forget so much. I would better be sick than not being sick" (Man, 67-years old).

For some patients, a positive amyloid PET scan result was considered better than receiving a negative result. A positive result provided them with more clarity compared to a negative result whereby unanswered questions were left.

Six months after the disclosure

Half of the group of patients who received a positive amyloid PET scan result experienced no disadvantages six months after the disclosure of their result. However, the other half of the group did report some experienced disadvantages (Table 4).

(1) Emotional difficulties to accept and cope with the news remained an experienced disadvantage of knowing their result. One patient described how she started to feel worried. She said it would be better that she would pass away before her husband would die. For her, the disclosure of a positive amyloid PET scan made her anxious about the future: What will happen to her if she is suddenly alone and her partner is no longer around to help her in case her memory complaints become worse? When asked whether she discussed this with her partner, she replied her husband is very caring, yet not very communicative. He is also very sensitive. Therefore, she found it difficult to express her concern to him without emotionally harming him.

(2) A patient referred to the disadvantage of driving the car. She was temporarily not allowed to drive the car due to another medical problem. Yet, she was afraid that her positive amyloid PET scan result would turn this into a fixed problem.

(3) The question whether their symptoms will become worse, remained a perceived disadvantage six months after the disclosure.

Two weeks after the disclosure, patients with a positive amyloid PET result, described the disadvantage of patronizing. Six months after the disclosure, patients did not spontaneously mention this as a disadvantage anymore. Patients who initially mentioned this disadvantage two weeks after the disclosure, were asked to indicate what their current view on this aspect was. They responded that they no longer feared being patronized or that they had thus far not experienced being patronized by others.

Half of the group of patients who received an amyloid-negative PET scan result reported no experienced disadvantages of knowing one's IRR. The other half described two disadvantages (Table 5). One of these disadvantages was already mentioned at the interview two weeks after the disclosure, which was the following question: What is causing the memory complaints? One new disadvantage occurred after six months, whereby a minority of patients doubted their result due to the remaining memory complaints these patients experienced. For example, a patient thought the researcher mistakenly confused her result with the result from another patient. Another patient talked about false positive and false negative results;

> *"No, it's always a faint chance that there's something wrong, a false negative or something, or maybe for some reason on that day you are better. There's a faint chance that it could be a wrong diagnosis"* (Man, 66-years old).

Patient feedback on the trial

We asked patients at the six months post-interview to evaluate the study and the interviews as part of this trial. Overall, patients responded that everything went smoothly throughout their clinical trial participation. Based on the reactions from the patients, two recommendations for future trials emerged:

(a) A patient said he would change future trials by letting patients be more involved in the design of the study. As he described it:

> *"So maybe you should talk to patients first and ask them what they would want to know and then design the study, if you understand what I mean"* (Man, 66-years old).

(b) A second recommendation was to receive their result in a written report or document which they could show to relatives. This document was intended for the patient himself and may not be confused with the written report, which was provided to the patient's general practitioner.

Most patients mentioned that the interviews were an added value to the trial as they felt it gave them the desired guidance and follow-up. Additionally, they thought it was an opportunity to talk to researchers who understood their complaints about memory-loss. A small number of participants described some interview questions as slightly confronting. They said it was confronting to talk about their memory-loss even though they also added they positively experienced the fact that these questions made them think about their health situation. This included all the patients who received a positive amyloid PET scan and most of the patients who received a negative amyloid PET scan. The latter mentioned that in case of a positive amyloid PET

scan result, they would have found it beneficial to talk about their 'bad news' and to receive some follow-up counseling.

Before the follow-up interviews in our study, a minority of participants who received a negative amyloid PET scan result doubted whether or not they would continue these interviews since they have received *'good news',* as they described it. In addition, the same patients said that these follow-up interviews were not necessary to implement in future clinical trials.

Regret of their initial choice?

Six months after the disclosure, we asked whether participants would reaffirm their choice to participate in the study and to know their result if they could turn back time. From the eight patients who received a positive amyloid PET scan result, seven patients answered that they would make the same decision regarding their trial participation and the option of being informed of their result again. The patient who had mixed feelings six months after the disclosure answered that she doubted whether she would make the same decision again. The patient who had emotional difficulties at both follow-up interviews, replied that she would make the same decision again, yet that it is not easy to emotionally accept and cope with the news.

All patients who received a negative amyloid PET scan result would reaffirm their participation and their option of being informed about their amyloid PET scan result. They clarified that everything went smoothly for them. Overall, they were pleased with the result. For them, this resulted in feelings of reassurance, less doubt and more clarity about their health situation.

Discussion

The current qualitative report provides important first-hand and in-depth information from aMCI patients themselves about how a positive or negative amyloid PET-scan result is received over a time course of two weeks to six months. Since the goal of this study was to explore the patients' views and experiences on amyloid PET disclosure, we used the methodology of qualitative content analysis and data saturation. Hence, we did not provide a quantitative analysis for two reasons: (a) there are methodological difficulties to quantify personal views and experiences, and (b) the study was not powered for quantitative statistical analyses. However, the results allow us to raise additional thoughts on the following five findings;

Understanding one's amyloid PET scan result

Literature on result disclosure often refers to the difficulties of study participants to interpret and understand their result For example, in the field of genetics, it is not uncommon that participants misunderstand their genetic risk disclosure [33][34]. In the field of AD, the REVEAL study has indicated that asymptomatic adults with a parent that has AD understand that their risk is higher or lower according to their genotype [20]. Our study is in line with the findings from REVEAL as aMCI patients were able to understand the core message of their result, yet often had trouble in using the scientific terminology (positive/negative amyloid PET scan) of their result. Amnestic MCI patients often used the word 'positive' to describe their 'good news', and vice versa for the negative result. Although some patients misused the terminology, most reported that their result was clearly explained and could recollect the core message of their result.

The following two recommendations could help to avoid misinterpretion by patients regarding their amyloid PET scan result:

(a) Firstly, as mandatory according to international guidelines of good clinical practice (ICH GCP), the information brochure prior to disclosure should clearly explain the possible types of outcome (positive/negative) of the test in a style that is easy to understand by the participant [24]. In addition, it might be useful and lead to less confusion of the terminology of a positive/negative test result when the researcher provides an example, which is comparable to the amyloid PET scan. This recommendation is based on the study conducted by Vanderschaeghe *et al* before the amyloid PET disclosure for which the researcher provided a simple example of an alcohol test to clarify the correct use and interpretation of a positive and negative test result [15].

(b) Secondly, in our current study, patients provided feedback after six months about the trial and amyloid PET disclosure. This resulted into a practical recommendation mentioned by one of our patients' to provide a written document about their received result.

Emotional risk after one's amyloid PET disclosure

Literature reports on the diversity of emotional reactions, such as fear, stress, depression, and the possibility of an increased risk for suicidal behaviour, as an ethical challenge after the diagnostic disclosure of a dementia diagnosis [35][36][37][38]. In our study, most aMCI patients responded well to their amyloid PET scan result. From the patients who received a positive amyloid PET scan result, two out of eight (25%) described having emotional difficulties (sadness, feeling worried) after six months, with no suicidal ideation being reported. Our findings are in line with studies, such as, the REVEAL study [8][20], and more recently with the findings published by Grill *et al* [17]. The latter study concluded that learning their amyloid status, can cause sadness and despair for some patients and caregivers, yet also resulted in relief and satisfaction [17]. However, the small sample size of our study, limits the precision of this given estimate. Therefore, more quantitative studies in larger populations are needed before generalizing this particular finding.

It is possible that the risks of developing suicidal behaviour did not occur in our study due to the following two study limitations: First of all, only eight patients were amyloid-positive. Secondly, the interviews were conducted within a timeframe of six months after the disclosure of the IRR. Literature recommends how a longer timeframe for follow-up is necessary to generalize a particular finding [8][39]. For example, the study of Timman *et al* about predictive testing for Huntington Disease stated that psychological outcomes 7 to 10 years after predictive testing are worse than in the 2 to 3 years after testing [39]. The rationale behind the longer follow-up would be that individuals are closer to the likely age of disease onset, which could lead to more distress levels [39]. Although 7 to 10 years is long in the case of aMCI patients, we do recommend longer follow-up for at least several years.

Patient' reactions toward their amyloid PET disclosure versus patient' expectations

In our study, a majority of aMCI patients who tested positive reported not feeling surprised about their positive amyloid PET scan result and these patients explained how the result was a confirmation of their experienced memory complaints. This confirms that positive test results are not always perceived as overwhelming if the test results match patients' expectations [7].

The overall majority of patients who received a negative amyloid PET scan result were happy with their 'good news' of being amyloid-negative. However, a minority (three out of thirty) of amyloid-negative patients reported six months after the IRR disclosure that they started to doubt whether they had received the correct test result. Due to the limited study population of amyloid-negative cases in Grill's study [17], our study findings establish the 'potential dichotomy' (between the perception of amyloid-negative as 'good news' or as 'clinical uncertainty') and the need of further research with more amyloid-negative patients as described by Grill *et al* [17]. Possible explanations for these differentiated reactions within the amyloid-negative patients are:

(a) Patients who received a negative amyloid PET scan result, most likely expected to have received a positive test result due to their experienced memory complaints. After six months, the continued experience of their memory complaints, led them to doubt their result. Some patients even concluded that a positive test result would have been better than their received negative result. This positive result would probably match better with their experienced memory complaints.

(b) Another explanation is derived from the study conducted by Linnenbringer *et al* [40]. The latter study concluded that from participants (healthy adults with at least one relative with AD) who did accurately recall their risk information, nearly one third of these patients perceived their personal risk to develop AD to be higher than the actual communicated risk by the researcher [40]. This finding highlights that participants may accurately understand their received information, but may still perceive it slightly different depending on, for example, their personal coping strategy and experienced memory complaints in our study population [40][41][42].

Advantages and disadvantages of knowing one's result

The study by Grill *et al* reported on several mentioned advantages and disadvantages of amyloid imaging from patient and caregiver's point of view [17]. For example, the advantage of making informed care decisions and the benefit that the patient now has a diagnosis [17]. Our study population described several pros and cons of knowing one's IRR, which are in line with, yet cannot

be limited to the described advantages and disadvantages from Grill *et al.* More importantly, we noticed in our study four modifiers of the given pros and cons as described by our patients. These modifiers were:

Firstly, the outcome of the result – a positive or negative amyloid PET scan result – had an impact on the experienced (dis)advantages. For example, to start medication and to have more contact with family members were mentioned as two advantages (two weeks after the disclosure) of patients with a positive amyloid PET scan, yet did not occur with the patients who received a negative amyloid PET scan result.

Secondly, the time interval of the conducted interviews – two weeks or six months after the disclosure of one's result – also had an impact on the experienced advantages and disadvantages. For example, a positive impact on the relationship with their partner was mentioned as an advantage at the interview six months after the disclosure, yet was not mentioned two weeks after the disclosure (with patients who received a positive amyloid PET scan result). Vice versa, patronizing was perceived as a disadvantage two weeks after amyloid PET disclosure in case of a positive amyloid PET scan result, yet was not mentioned again after six months. When this issue was re-addressed to the patients who mentioned this disadvantage after two weeks, they replied they did not (or no longer) experience this issue. Possible explanations are, for example, the initial reactions or coping strategies of some partners and children to deal with the received information. It is a possibility that some family members misinterpreted the positive test result as meaning that the patient already has dementia [29][30].

Thirdly, differences were noticed between patients' expectations before the disclosure of one's amyloid PET result and their concrete experiences after the disclosure. For example, making practical arrangements for the future, and in particular the request for euthanasia, was the advantage of knowing one's result in the interview study that was most frequently mentioned by the aMCI patients before their amyloid PET disclosure [15]. Results of our current study reveal how arranging for the future was still mentioned, yet experienced less as a disadvantage of knowing their IRR. In addition, most aMCI patients do no longer have a sense of urgency to make certain arrangements due to their negative amyloid PET scan result. The study of Gooding *et al* about genetic susceptibility testing for AD stated that planning for the future is important for all elderly people, not excluding people who learned they were not at increased genetic risk for AD [43]. The same notion is applicable to our study in case of aMCI patients who tested negative on the amyloid PET scan.

Fourthly, our findings reveal how patients' experiences may not be limited to the expected risks and benefits as described in: (a) general literature on amyloid PET disclosure [44][14][7][45][10], individual research result disclosure [46][47][48] and (b) in the information brochure of the clinical trial as part of the ICH GCP guidelines [24].

Family support and family pressure

Family support is an important aspect when patients volunteer in a clinical trial and opt for the disclosure of their amyloid PET result. Our findings showed how patients mostly felt supported by their family members. However, after six months, one specific patient who received a positive amyloid PET scan result described her doubts about participating and opting for her IRR disclosure. This patient talked about mixed feelings; it was clear that she would not have participated and come to the memory clinic in the first place if her husband and children did not ask her to do so. Although it might be advantageous to know this news in an early stage, the option of being informed of the result should be made by the patient who is still capable and autonomous to make this personal decision, yet without the influence of family pressure. This specific case indicates how there is a blurry line between support and pressure and how difficult it may be for external people, such as researchers, to distinguish whether the study participant is supported or pressured by his family members. In addition, what study participants may perceive as family support before disclosure, can be interpreted differently after disclosure of the result and depending on the outcome of the conducted test(s).

Limitations

The strength of this qualitative research is the in-depth interviews, face-to-face interviews with patients as this provides the researchers with the opportunity to go in-depth, clarify and check the opinions of the interviewees. We have to acknowledge several limitations of this exploratory study. A first limitation is that participants are always embedded in a certain cultural or societal setting, which can reflect in the results. The views expressed here are based upon a small population of patients with aMCI in Belgium who were recruited via the UZ Leuven Memory Clinic complaints and was based upon eight patients who received a positive amyloid test result. The total number of amyloid-positive MCI cases was relatively low (8 out of 38) and this may be due to the fact that amnestic MCI patients were recruited regardless of the duration of prior follow-up. Patients who had converted to AD in the months and years following a diagnosis of amnestic MCI would not be eligible for the current study. As a consequence, the sample may have been enriched for non-AD causes of amnestic MCI cases. Different findings can occur when investigating in a different country and when recruiting for a different population, such as, patients with subjective memory complaints, patients with minor memory complaints who have not been to the memory clinic to receive medical advice and healthy adults being evaluated for preclinical AD. Lastly, the used quotes for this paper were translated into English, whereby some of the participants' nuances may be lost. We do believe that the findings are of importance beyond the context of this research and can be of use for future studies.

Appendix

Inclusion criteria	Exclusion criteria
Patients must meet all of the following inclusion criteria to participate in the study: • Patient is male or female and between ≥ 55 and ≤ 85 years of age on the day of signing the consent form. • If female, patient is not of reproductive potential (i.e., two years post-menopausal or surgically sterile). • Patient has a subjective memory concern, as reported by patient, study partner, or clinician. • Patient has memory impairment, documented by scoring below the education-adjusted ranges on the AVLT total learning or delayed recall percentage (≥ -1 SD). • Patient has a Global Clinical Dementia Rating score of 0 or 0.5. • In the opinion of the investigator, the patient is in stable medical condition and willing and able to perform study procedures. • Patient has at least six years of education, or sufficient work history to exclude mental retardation, in the investigator's opinion.	Patients will be ineligible for participation in this study if they meet any of the following exclusion criteria: • Patient has a history of or current evidence for a neurological disorder that, in the opinion of the primary investigator, may contribute to the subject's cognitive impairment, including, but not limited to: o Large-vessel stroke, o epilepsy, o Parkinson's disease, o progressive supranuclear palsy, o Huntington's disease, o amyotrophic lateral sclerosis, o multiple sclerosis, o CNS infection, o significant head trauma with loss of consciousness, o Normal pressure hydrocephalus • Patient has a history of large-vessel stroke, or evidence of a large-vessel infarction or other focal lesions, on baseline MRI scan that may contribute to the memory impairment, in the opinion of the investigator. • Patient has received an examination over the past year involving more than 10 mS ionizing irradiation • Patient has a history, within 6 months prior to screening visit, or current evidence of a psychotic disorder or a major untreated depressive disorder. • Patient has a history of malignancy ≤5 years prior to signing informed consent, except for patients who have undergone potentially curative therapy with no evidence of recurrence for 1 year, and who are deemed at low risk for recurrence by her/his treating physician. • Patient has a history or current evidence of any potentially known clinically significant condition therapy, lab abnormality, or other circumstance that, in the opinion of the investigator, might confound the results of the study or interfere with the patient's participation for the full duration of the study, such that it is not in the best interest of the patient to participate. • Patient currently uses specific psychoactive medications (neuroleptics, chronic anxiolytics, tricyclic antidepressants, antiepileptics, anticholinergics etc.). Stable dose trazodone, mirtazapine or low dose benzodiazepines prescribed for mild insomnia is allowed. • Patient currently uses antithrombotics, with the exception of acetyl salicylic acid (exclusionary for lumbar puncture).

	• History of alcohol or substance abuse, or dependence within the past 2 years (DSM IV criteria) • Patient is currently participating or has participated in a study with an investigational compound or neuropsychological measures within 30 days of signing informed consent. • Subject has any magnetizable metal prostheses, implants or foreign objects that could pose a hazard during MRI scans.

Appendix 1: In –and exclusion criteria of the BioAdaptAD study.

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Chapter 6: Stakeholders' views on early diagnosis for Alzheimer's Disease, clinical trial participation and amyloid PET disclosure: a focus group study

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Abstract

Background: Detection of Alzheimer's Disease (AD) in an early stage is receiving increasing attention for a number of reasons, such as the failure of drug trials in more advanced disease stages, the demographic evolution, the financial impact of AD, and the approval of amyloid tracers for clinical use. A number of reasons can be put forward in favour of an early clinical diagnosis and in favour of disclosing individual research results, yet the views of several stakeholders on this topic has not been explored in a systematic fashion.

Method: Via the methodology of purposive sampling, five focus group (FG) interviews with stakeholders (e.g. healthy elderly, informal caregivers, nursing staff, researchers and clinicians) were conducted. A semi-structured format was used by presenting three scenarios to the stakeholders, in combination with documents that the participants were invited to fill out. The verbatim transcript were analysed via the Nvivo 11 software.

Results: Participants reflected on several topics; from the difficulties to interpret first memory signs, toward their views on obtaining their amyloid PET scan result and the perceived advantages and disadvantages of knowing this particular result. Overall, most stakeholder groups wanted to know their own amyloid PET scan result. However, differences occurred between FG groups, as two groups (informal caregivers and researchers) all wanted to know, whilst in the three other groups (healthy elderly, nursing staff and clinicians) FG members opted not to know or were still in doubt about their decision. Stakeholders provided insight into their reasons for wanting to know their amyloid PET scan result (e.g. the need for clarity, to inform relatives, to make arrangements, and so on), not wanting to know their result or why they were in doubt about their decision (e.g. fear for AD, not wanting to burden the environment, and so on). Furthermore, several advantages (e.g. to know what is going on with their health, to plan for the future, to enjoy life more, etc.) and disadvantages (e.g. absence of a disease modifying treatment, risks when undergoing tests, etc.) were mentioned as part of knowing their amyloid PET scan result. Certain considerations were clustered in a grey zone, in between advantage and disadvantage, such as the emotional and psychological consequences.

Conclusion: Several studies have reported on high numbers of individuals who want to know their result. However, our study showed more diversity (e.g. FG members who were in doubt or preferred not to know) in answers. The presented results also show how advantages and disadvantages of knowing the result were viewed differently depending on personal views/values and/or coping strategy. To conclude, clinicians, researchers and policy makers ought to be aware of the diversity of reasons for (not) wanting to know their result, and how possible benefits and

risks can be viewed differently. The current findings are of importance for future early diagnosis and disclosure of results in the research setting.

Background

Today, many clinicians, researchers, pharmaceutical companies, health care- and dementia organisations emphasize the importance of detection of Alzheimer's Disease (AD) in an early pre-dementia or even preclinical phase. This idea has gained considerable momentum for several reasons: Novel treatment may have a better outcome when initiated in an early stage before irreversible brain damage has occurred due to AD. Given the failure of many recent trials in AD in a more advanced stage of dementia, clinical trials have started to target individuals earlier in the disease course at the stage of mild cognitive impairment (MCI) before the onset of dementia and before significant functional impairment [1]. Detection of Alzheimer in these early stages has only become possible thanks to the development of biomarkers. These are biological indicators that can gauge the presence of a disease and can be used to detect abnormalities at an earlier, pre-dementia or even at a preclinical stage [2]. One of the biomarkers used to support a diagnosis of AD is brain amyloid, which can be visualized by positron emission tomography (PET) [3]. Besides being potentially useful for clinical practice, PET imaging of beta-amyloid plaques is also being used in brain research on AD [3][4][5]. Research to validate biomarkers for clinical use and to develop new AD biomarkers is ongoing [6]. The Food and Drug Administration (FDA) and the European Medicine Agency (EMA) have approved three amyloid radiotracers that have high affinity for binding to beta-amyloid plaques (flutemetamol, florbetapir, and florbetaben labelled with (18)F for PET imaging) for diagnostic purposes in cognitively impaired patients who are being evaluated for AD [7][8][9][10]. In a research setting, the FDA and EMA approval along with the Appropriate Use Criteria for Amyloid PET have been put forward as arguments pro-disclosure in the debate whether or not to return individual research results (IRR) to the study or research participant [11][12][7]. To date, the degree to which IRR's are disclosed varies depending on the trial, as there is no legal obligation for the researcher to return IRR's [13][14].

These and other elements have been put forward in favour of an early detection of AD and hence early disclosure of an AD diagnosis, yet several ethical questions emerge: What are the ethical benefits and risks of an early disclosure? Would people want to know an early diagnosis or an IRR as part of a clinical trial when current treatment options are still limited? Whether and how should the researcher disclose the IRR? Is the road of early disclosure the road clinicians and researchers want to take?

To our knowledge, only a few qualitative studies have been conducted in the past, such as interviews with patients and/or their carers on the topic of amyloid PET disclosure [7][8]. With regard to published focus group interviews, these were often limited to a specific topic, such as the

diagnostic disclosure of dementia and the emotional impact of dementia diagnosis. Hence, they were mostly conducted from one or two perspectives, such as the views from patients, carers, or general practitioners (GP) [15][16][17][18][19].

However, little is known about stakeholders' (patients, relatives, informal caregivers, clinicians, researchers, patient- and dementia organizations, and healthy elderly who are often perceived as an at-risk group for getting AD) views and experiences on the following topics: How early would individuals seek medical consult from a general practitioner or at the memory clinic? What would attract or withhold individuals from seeking medical advice? What are the motivations to enroll in a clinical trial? Why would stakeholders opt for the disclosure of their amyloid PET scan result and what do they perceive as risks/benefits from the this disclosure? The views of these stakeholders are vital as all these groups are either involved in or concerned about the ethical issues in the above mentioned topics. Exploring the views, experiences and concerns of stakeholders will allow us to enhance early diagnostic disclosure, trial recruitment and participant follow-up, as these items will be based on the expectations, needs and concerns from these stakeholders.

Therefore, we sought to explore these issues from a multiple perspective by conducting focus group interviews with several stakeholders.

Methods

Recruitment

After ethical clearance from the Social and Societal Ethics Committee of the University of Leuven (SMEC, Belgium, study number G-2015 05 250) focus group (FG) interviews with stakeholders were conducted between December 2015 and February 2017. Recruitment was done through one contact person belonging to the stakeholder group. This methodology was best suited, as people volunteered within a group that consisted of the same characteristics and via the network of the contact person, most people within the group, knew each other before the interview took place. This created an open atmosphere for discussing and reflecting on the topic. We aimed for five to ten participants per FG [20]. Via the contact person, an invitation letter and information brochure was handed over to or e-mailed to the participants before the FG interview took place.

Before the start of the FG interview, the interviewer (GV) provided each participant with a printed information brochure and orally explained the procedure of the FG, participants' rights, the fact that the FG will be recorded and that subsequent data was used for scientific publications. Participants were assured that all personal data would remain confidential. Participants were then invited to sign the informed consent form (IC) and to complete the socio-demographic form. In addition, participants could fill in their contact details on the IC if they wished to be informed about the general results after the completion of the study.

An hour and a half was allotted to each FG. A moderator and observer were always present. A location and time were chosen that best suited the participants. After completion of the FG interview, participants received a small token (box of chocolates) for their willingness to collaborate in this study.

Data collection and analysis

Focus groups were used to explore participants' views and experiences and to provide insight into the addressed topic [21]. A semi-structured format for the FGs was favoured by using the same scenarios for each FG. The used scenarios (see Table 3, 4 and 5) were designed by the authors (GV, KD and RV) and based upon ethical issues addressed in the available literature published on this topic. The used scenarios were presented to the SMEC ethics commission as part of retrieving ethical clearance.

The analysis of the collected data was done in two steps:

(1) The data from the collected socio-demographic forms is presented in Table 1. In the appendix 1 – 3, we present additional data collected throughout the FG interviews. Appendix 1 represents the chosen positions (wife, husband and general practitioner as part of scenario 1) as chosen by the FG members. Appendix 2-3 represents the rationale for wanting to know or not to know the IRR (scenario 2, exercise A) and the clustered advantages and disadvantages of knowing the IRR (scenario 2, exercise B) as written down by the participants. For scenario 3, no additional tools, with the exception of the scenario, were used. Hence, no additional data is available in the appendix regarding scenario 3.

(2) Content analysis was used for the verbatim transcripts and by using the qualitative software of NVIVO 11 [20][22][23]. This was done in 4 phases: (a) An initial coding by GV of all FG transcripts separately. (b) Two – three weeks after the initial coding process, all FG transcripts were separately coded a second time. (c) The codes from the second coding process were then compared with the codes from the initial coding process. (d) Lastly, all codes were double-checked by another researcher (KD) to avoid misinterpretation.

All of the FG interviews were conducted in Dutch. Citations used in this article were translated into English. Due to privacy reasons, mentioned names will be replaced in the used quotes as 'X' or 'Y'.

Results

Demographics of the study population and structure of the results

In total, 40 individuals participated in five FG, conducted between December 2015 and February 2017. The demographics and recruitment strategy of each focus group are listed in Table 1.

Focus group (FG) (+ if of added value: current job position)	**Recruitment method ***	**Duration of FG**	**Gender of participants**	**Age category of participants**	**Educational level of participants**
Healthy elderly	Contact person via a Flemish organization for Elderly/retired people that organizes social activities.	2 hours	Woman: *n* = 8 Man: *n* = 2	50 – 60 years: *n* = 2 60 – 70 years: *n* = 1 70 – 75 years: *n* = 4 75 plus: *n* = 3	Primary school: *n* = 5 Secondary school: *n* = 4 Professional bachelor: *n* = 1
Informal caregivers (Mostly partners) of patients with AD	Contact person via an elderly care home specialized in dementia care.	2 hours	Woman: *n* = 5 Man: *n* = 4	40 – 50 years: *n* = 1 50 – 60 years: *n* = 2 60 – 70 years: *n* = 4 70 – 75 years: *n* = 1 75 plus: *n* = 1	Secondary school: *n* = 3 Professional bachelor: *n* = 3 Academic master: *n* = 3
Nursing staff of elderly residential care setting specialized in dementia. (head)nurse, care coordinator, ergo therapist, director)	Contact person via an elderly care home specialized in dementia care.	1h30	Woman: *n* = 5 Man: *n* = 1	18 – 25 years: *n* = 1 30 – 40 years: *n* = 2 40 – 50 years: *n* = 2 60 – 70 years: *n* = 1	Professional bachelor: *n* = 5 Academic master: *n* = 1
Researchers (Global trial managers, clinical pharmacist, lab technicians, chemical scientist)	Contact person via a pharmaceutical company.	1h30	Woman: *n* = 5 Man: *n* = 3	30 – 40 years: *n* = 1 40 – 50 years: *n* = 3 50 – 60 years: *n* = 3 60 – 70 years: *n* = 1	Professional bachelor: *n* = 1 Academic master: *n* = 7
Clinicians (Neurologist, GP, Director dementia organization)	Contact person via a Dementia organization /institution	1 hour	Woman: *n* = 0 Man: *n* = 7	30 – 40 years: *n* = 1 40 – 50 years: *n* = 4 50 – 60 years: *n* = 1 60 – 70 years: *n* = 1	Professional bachelor: *n* = 1 Academic master: *n* = 6

Table 1: Recruitment strategy and demographic details of FG participants.

*For privacy reasons, the name of the contact person nor of the organization/institution was not mentioned. The results do not represent the viewpoints from an institution/organization, yet represent the personal views and experiences from recruited stakeholders.

We have structured the result section of this article based on the topics as discussed in our FG discussions. This format is well suited as it provides a clear representation of the FG discussions. Table 2 presents an overview of the structure of the result sections and where to find additional information in the appendix.

In each presented topic in our result section, we cover the general findings where all FG groups agreed on. Where possible we refer to the FG differences at the end of the presented result section.

Presented scenario	Implementation in result section of the article	Additional information available in appendix
# Scenario 1 (Table 3)	• To seek medical advice after recognition or experience of memory complaint	Appendix 1
# Scenario 2 (Table 4) ➔ Exercise A: write down reasons (not) to know IRR	• Reasons to know or not to know the amyloid PET scan result	Appendix 2
➔ Exercise B: Cluster possible (dis)advantages of knowing your IRR	• (Dis)advantages of knowing the amyloid PET scan result.	Appendix 3
# Scenario 3 (Table 5)	• Post disclosure	/

Table 2: Overview of the structure throughout the result section.

To seek medical advice after recognition or experience of memory complaints?

In the first presented case (Table 3), we explored how participants thought about seeking medical advice after recognizing or experiencing first memory complaints, which attitude or position they would adhere to (cf. the position of the wife, husband or general practitioner (GP)) in the presented case and which difficulties may emerge throughout that process. The summary of the elements discussed under this case are presented in appendix 1.

Scenario 1: A man of 63 starts to experience first memory complaints, yet minimalizes these problems: 'Every one forgets something and especially at this age'. His wife is more concerned and pushes her husband to seek medical advice from the general practitioner (GP). GP thinks the problem is stress and due to overload of work causing the problems and advices to come back in 3 months if the situation has not changed. The wife is still concerned and wants her husband to go for further testing to memory clinic, yet the man is in doubt: Do I already want to know if there is something wrong with me? I am 63 and still working. Which of the three positions (wife, husband, GP) would you take?

Table 3: Description of presented scenario 1 and opening question.

The right (not) to know of the patient versus family pressure and burden

Most participants' opted for the position of the wife to seek medical advice and to know what is going on. The pushy attitude of the wife was also perceived by most FG participants as a good attitude; *"He starts to doubt under impulse of his wife, thank God maybe, what possibly facilitated his diagnosis* (Clinician, man)*."* For other participants' the attitude of the wife can only lead to increased levels of uncertainty and stress with the patient as it is his decision to know or not to know what is going on;*"[…] That would be my biggest concern. What quality of life will I give to him when suggesting him to seek medical advice? To make him doubt? That would be important for me* (Nursing staff, woman)."

Some participants mentioned that it is understandable that some patients opt not to know and prefer to remain in ignorance as there is currently no disease modifying treatment available or due to anxiety for AD.

The FG group of informal caregivers and nursing staff also pointed to the impact of a patient's decision to know or not to know as both decisions have implications for the partner. On the one hand, not knowing can be difficult for the partner who often notices these changes first and who often stimulates the patient to seek for medical advice. On the other hand, knowing the news affects both patient and family members;

> *"So I personally think that if you get the diagnosis, and I have told that to the professor 'X' [cfr. Caregiver referred to the consulted neurologist who is also professor] last time, then I actually think they should also inform the partner that their life completely changes, because the person himself does not know it, for 'Y' it is normal way of life, but in one year time my life has enormously changed. Not just in that one year since we know [cfr. The diagnosis of husband], but from that moment onwards it has really changed. […]"* (Carer, woman)

GPs role

Most FG members found that the GP in the presented scenario should have taken the memory complaints more serious, should have provided more information about possible next steps and should have referred the patient to the memory clinic for further testing. However, two nuances were reported. Firstly, a few individuals (addressed in the FG of the researchers, health care staff and healthy elderly) stated that the advice of the GP to give it a few more months to see how the memory complaints evolve, was perceived as a good attitude as the GP was not causing immediate stress and concern towards the patient. Secondly, the group of healthy elderly reported that there is no blame toward the GP' decision to wait and see, as there is no cure available for AD.

Furthermore, FGs reflected on the difficulties for GPs to recognize these symptoms of cognitive decline. An element mentioned in all FG's was the GPs perceived lack of experience with AD and dementia patients as it was thought that they often only have a few of these cases per year. Certain FGs addressed difficulties for the GP to recognize these symptoms of cognitive decline. For example, informal caregivers stated that via their own concrete experiences, some patients deny or hide their symptoms and act in a social desirable way in front of their GP, family members and friends. As they described it:

> *"It is a very lonely period because 'Y' succeeded to behave in a desirable way in social situations toward friends, with the GP, with professor 'X'. Every time again and again […].* (Carer, woman)

The FG of clinicians reported on another difficulty for the GPs, whereby they are often not aware about new diagnostic possibilities to detect the disease and that GPs often become 'selectively blind' as they follow-up and know some patients for a long period of time;

> Participant 1: *Of course, and that is also another problem, that is that they become selectively blind due to the fact they follow their patient for a long time. You become part of the furniture of their house, well, this is something GPs also admit, that sometimes a fresh look at the case can give a few new insights.*
> Participant 2: *Indeed, but if the GP knows the family well and knows the reliability of the wife of the patient who notices something and reports this […].*
> Participant 3: *[…] That is because we already receive a referred to and selective population. I think that it is not easy for a GP to refer everybody just like that. They see many people with vague complaints that may possibly be cognitive.*
> Participant 1: *What you are saying is that the GP could also dig a bit deeper. He could take a mini mental state, could also perform a blood test.*
> Participant 3: *Yes, the simple things that don't demand too much time.*
> (Dialogue between three clinicians, all men)

Clinicians and researchers referred to the importance of a more in-depth consultation by conducting a few simple tests, such as the Mini-Mental State Examination (MMSE) and the necessity of patient referral to the memory clinic. Yet, clinicians admitted that it is not always easy to refer a patient to the memory clinic especially when cognitive symptoms are not being detected

Reasons to know or not to know the amyloid PET scan result

The second case (Table 4) presented the possibility of enrolling in a clinical trial and the option of being informed of the amyloid PET scan result.

Scenario 2: A woman of 68 has received a diagnosis of MCI at the Memory Clinic and was provided with the option to participate in a clinical trial, where she can opt for the disclosure of her amyloid PET scan result. This amyloid PET scan result could reveal to the participant that het MCI is due to AD. She is doubting whether or not to know the result as according to her, there are several advantages and disadvantages when knowing this result.

Table 4: Description of presented scenario 2.

In appendix 2 we present the chosen positions (to know, not to know or in doubt) and the provided rationale to support their decision as written down by our FG participants as part of the first exercise of scenario 2.

In the group of the informal caregivers and the researchers, there was a strong tendency toward opting for their amyloid PET scan result. In the group of healthy elderly, nursing staff and clinicians, a mix between the participants was noticed as some opted to know and others preferred not to know or were still in doubt about their decision.

Rationale in favour of opting for amyloid PET disclosure

The following three reasons were mentioned the most amongst all FGs:

(1) The need for clarity about their health condition; Participants wrote down sentences, such as; *'I know what is going on. To know if there is a risk to get AD. Desire for clarity and not to remain in doubt.'*

(2) To inform partner, children and other family members about the result; Informing family members implies that they can understand the patient's situation and anticipate future cognitive decline and character or personality changes.

(3) To make arrangements for the future while the person is still capable to do so; Arrangements about finances, quality of social relationships, but also advance directives and end-of-life decisions were discussed. In particular, euthanasia was mentioned by many participants amongst the different FGs as part of arranging their future. Addressed by members within the groups of informal caregivers, health care staff and clinicians was the difference between thinking of euthanasia and the actual implementation of euthanasia. For example, a clinician described it in the following way:

> *"I would be tempted to say, or I can imagine that I would choose for euthanasia in such circumstances. But on the other hand, I have already seen many people firmly deciding that if they would get Alzheimer's during their life, they would want euthanasia, but the moment they become ill, they change their mind. So I don't dare to stick my hand in the fire that I would choose for euthanasia in this situation, but it is a possibility that I would keep open for myself, I think […]" (Clinician, man)*

Another reason that was often simultaneously given with the rationale of planning for the future was to enjoy life more, by creating a bucket list or by doing the things now while the patient is still capable of doing so, such as travelling.

A stakeholder difference in the rationale of knowing their IRR was noticed. To enrol and participate in clinical trials were brought up by the group of researchers and clinicians, yet was not expressed by the other FGs.

Rationale for not wanting to know the amyloid PET scan result or for doubting what to decide

Two common reasons were mentioned amongst the FG members who wished *not to know* or who were still *in doubt* about their decision for the situation as presented in scenario 2 (Table 4). These were:

(1) Fear or anxiety for AD. Participants used word such as; '*Fear for what can happen. I would become anxious, etc.'*

(2) The fact that currently no disease modifying medication is available for AD provided many FG members with an argument to doubt whether they would want to know or to opt for not knowing the result; *"Yes, if they can provide effective help or cure. No, if they cannot provide effective help or cure, I don't want to know* (Healthy elderly, woman)."

A stakeholder difference regarding the rationale for not knowing the IRR was noticed. The burden of medical investigation and risks when undergoing tests were mentioned by healthy elderly and nursing staff as a reason for not opting for the result, yet did not occur among the other groups. In the group of researchers, one researcher expressed the opinion that PET scans are not invasive, so there is no burden regarding these type of tests.

Advantages and disadvantages of knowing the amyloid PET scan result

The second exercise as part of the second scenario (Table 4) aimed to explore how FG members classify possible advantages and disadvantages of knowing their result, which is different from exploring their motivation and rationale to know or not to know the result.

In concrete, FG members were provided with an envelope that contained several small sheets of paper with advantages and disadvantages written on them. The sheets addressed the following aspects: No cure for AD, emotional/psychological consequences, no absolute certainty with the result, more clarity/to know what is going on with health, to plan for the future, to inform others, to start early treatment/intervention, to enjoy life more, to change lifestyle, risks when undergoing tests. Participants also had the possibility to write down any other possible advantages and disadvantages they were thinking of.

This resulted into the schedule as presented in appendix 3, where the advantages and disadvantages of knowing their IRR were categorized per group and according to the frequency of how many participants within the group used an advantage/disadvantage/grey zone in their schedule.

The most common perceived advantages in all FGs were; to know what is going on with their health, to plan for the future, to change their lifestyle and to enjoy life more. Another frequently mentioned advantage was to inform others about the received result.

The most common perceived disadvantages between all FGs were: the absence of a disease modifying treatment for AD and the risks of undergoing tests. A few participants in the FG group of healthy elderly added additional elements to the risks associated with tests. These were the fear for undergoing the tests, the burden of going to the hospital and the burdensome process of

undergoing many tests before receiving a diagnosis. The lack of absolute certainty about the test result was also mentioned under the category of disadvantage.

The previous two paragraphs discussed the most common clustered elements under the category of advantage or disadvantage. However, a minority of FG members, classified a topic which was mostly classified under 'advantage' as a disadvantage, which indicates that for a minority of FG members, this specific topic was perceived in a different way compared to the majority of FG members. For example, to inform others was mentioned above as an advantage. However, informing others was also categorized by a minority of FG members under the category of disadvantage. On the one hand, informing others can be beneficial to receive practical support, and also to receive emotional support and understanding for the patients' and informal caregivers' situation. Some informal caregivers reported the difficulties about patient's decision not to inform others, as they cannot talk about the emotional difficulties and burden they are experiencing. On the other hand, the question was raised whether people will still treat the patient in the same way once they know the result.

Vice versa, some of the elements classified as a 'disadvantage' were clustered by a minority of FG participants as an advantage. For example, the absence of absolute certainty about the test result was mostly clustered under the category of disadvantage. However, a few participants from the four FGs (healthy elderly, informal caregivers, nursing staff and researchers) described this as an advantage. They elaborated that a high/low chance or risk perception is also meaningful information that provides more clarity about their health situation. Some participants stated that it is important that the result is disclosed as it is, which includes that also the risk perception and the lack of an uncertainty in the result needs to be addressed. In the FG of nursing staff and researchers discussed which percentage of risk they would like to receive themselves. These two FGs stated that it was not easy to attribute a number to the meaningfulness of a risk percentage, yet both groups agreed that the risk percentage should be at least 50 percent to have some valuable information concerning one's health.

Another example is the emotional and psychological consequences after receiving the result which was mostly mentioned under the category of disadvantage. Again, few participants described it as an advantage. These participants described that not knowing the result and remaining in doubt would be emotionally and psychologically burdensome too. Although it was mentioned that receiving bad news can be emotionally difficult at first, knowing the result provides these participants with the opportunity to cope and move on with life.

Also, some FG members classified elements in a 'grey zone'. This grey zone indicates that a topic could have both advantageous and disadvantageous aspects depending on the situation, whereby it is the viewpoint from these FG members that this element cannot be categorized strictly as either an advantage or a disadvantage. The 'grey zone' was only used by a few FG members of the informal caregivers and the nursing staff. All other groups clustered the elements under either advantage or disadvantage. Aspects mentioned in the grey zone were, for example, to inform others, to enjoy life more and psychological and emotional consequences.

Post disclosure

The third presented scenario (Table 5) aimed at exploring how participants would respond to possible difficulties after the disclosure of the result.

Scenario 3: A man of 76 with MCI participated two years ago in a clinical trial where he opted to be informed about his amyloid PET scan result. He received a positive amyloid PET scan result. After two years his memory complaints are still stable and did not become worse. After the disclosure of the result, his wife reacted over-concerned, taking over his household tasks, not allowing him to drive the car. In addition, his neighbours started to look at him as if he already has AD. He regrets his decision of opting for the disclosure of the result two years ago. In his opinion, not knowing the result would have provided less consequences. What do you think of the man's decision based on his experienced consequences?

Table 5: Description of the presented scenario 3 and opening question.

Need for adequate information and follow-up after disclosure

If clinical trials and research settings provide participants with the option of IRR disclosure, than a consensus of all FG members was that research participants should know beforehand what the implications of IRR can be and what the possible consequences can be after the disclosure. Especially they agreed that the risk perception and the limited predictive value should be explained to the research participant.

The FG group of researchers and clinicians added two nuances. Firstly, researchers and clinicians referred to the difficulty to estimate in advance how the psychological strength and coping capabilities of participants are in order to deal with this information.

Secondly, they reported that it is often difficult to explain this limited predictive value to the research participant. Even when the limited predictive value is well explained, it is likely that participants misinterpret these findings or regret their decision of being informed;

> Participant 1, man: *That is very difficult.*
> Participant 2, man: *You cannot give a clear message.*
> Participant 1, man: *You can give the message of the risk exactly, but you cannot determine what the perception of the individual is.*

Participant 3, woman: *That is another problem.*
Participant 2, man: *Also, you cannot say what the likelihood is.*
Participant 1, man: *Imagine that you could do that, even then? What does that mean for? That perception?*
Participant 3, woman: *The period. Seventy percent within ten year of within twenty years? (Dialogue between three researchers)*

Besides the need of adequate information, all FG members reported on the need of more communication, support and follow-up. This should not be limited to clinical trials, yet is also of importance in the clinical setting when disclosing a clinical diagnosis to the patient. Psychosocial support should in their opinion not be restricted to the patient, but should also include support for partners and informal caregivers. Support and counselling is important to explain to the participant/patient and their relatives how to interpret this result, the possibilities of cognitive rehabilitation and to stimulate the capabilities the patient can still do well. This is considered to be a task of both researchers and GPs.

Who to inform and what to say about the result?

FG members discussed two concrete consequences that may occur after informing others, more specifically stigmatization and patronizing whereby family members take over, for example, practical tasks:

Patronizing: Most participants reflected that they would not like to be patronized themselves. However, some informal caregivers reported that it is a very recognizable situation to take over from the patient. Informal caregivers clarified that it is often meant '*to do well*', yet that for the patient this patronizing attitude may work counterproductive. Some FG members said it is also up to the patients themselves to clearly communicate about the things they still can do well. This is especially important for people at an early and often (very) mild stage of the disease.

Stigmatization: The FGs of informal caregivers and nursing staff provided several experienced situations with stigmatization and reported that it is not always easy to inform others as people either have a negative perception about AD or do not know how to respond to the news. The need was raised to inform society more about what AD is and to make AD discussable.

> *"So from the moment onward that we disclosed, you get, 'x' got immediately labelled and that is really a stigma. People look at him like: 'He is about to do something whereby I will see that he has got Alzheimer.' While there are moments that there is nothing going on with him. […] And what 'y' also said, that evasive behaviour where people address me while he is standing next to me. I always have to say: 'Ask him? He is standing there, so ask him? It doesn't mean that he cannot do anything.' So you have to constantly educate people […]."* (Carer, woman)

Based on these two consequences, FGs discussed the importance of first communicating with partner and family about who to inform and what to tell. Especially in the case of receiving a positive amyloid PET scan result, the FG of researchers and clinicians referred to the importance that others should be aware that this result does not imply that the patient already has AD.

Discussion

This focus group study aimed, as first of its kind, at exploring multiple stakeholders' views on early diagnosis, clinical trial participation and disclosure of amyloid PET scan results. The strength of this study is that several perspectives, from informal caregivers to clinicians, were explored. This enables us to get in-depth insight into the views from one specific group and to compare between stakeholder groups. Here, we will raise additional ethical insight and comment to the following findings:

Difficulty of recognizing first symptoms of AD

Many participants in our FG study referred to the difficulties of recognizing first symptoms of AD by their GP. Firstly, it became clear throughout the FD discussions that there is no consensus on what a first symptom for AD might be. While for some, forgetting groceries would be a first sign, for others this was not the case. Actual triggers for seeking medical advice were the urgency and the feeling of worriedness of the participants. Secondly, throughout the FG discussions, especially with the informal caregivers, it became clear that many patients act in a socially desirable way, or in denial, and try to hide their memory complaints. The combination of the lack of clarity of a first symptom, and the denial or socially desirable attitude, can make it more difficult for the GP to interpret the complaints as early signs or triggers for AD.

Our findings confirm the surveys that have reported on the difficulties for GPs in diagnosing AD, whereby recognizing symptoms was mentioned as one of these struggles [17][18][24]. Although these difficulties were reported in general AD literature, they are possibly of increasing interest when moving toward earlier diagnosis. For example, GPs might overlook the first symptoms of MCI and misinterpret these symptoms as signs of a burn-out or stress [17]. Research also describes how it can take up to two years between the first consultation and the disclosure of the diagnosis [17][25]. This can be problematic as in many cases the GP is mostly the first clinician to be contacted by the patient or even the only clinician involved in making the diagnosis [18][43].

To know or not to know?

In the FG of informal caregivers and researchers, all members opted for knowing their result, whilst in three other groups (healthy elderly, nursing staff and clinicians) there was a mix between the members who wanted to know, did not want to know, or were still in doubt. The findings from

this FG study provide a more nuanced answer to the recently published studies that reported high numbers of respondents expressing the desire to know their genetic risk result for AD [26][27][28]. For example, all of the MCI participants who enrolled in a longitudinal observation amyloid PET study opted for disclosure of their amyloid PET scan result, but it remains unclear to which degree this can be generalized to a wider population [29].

Only limited research has been performed that explored the views of individuals who prefer not to know their result. The current study can provide insight into the rationale of the people who would prefer not to know or who are in doubt about their decision. Reasons for not wanting to know or for doubting were: fear and anxiety for AD once the result is known; feeling worried, stressed or depressed; not wanting to burden the close environment and the lack of a treatment for AD.

Early or timely diagnosis?

In the current study, most FG members reflected on the topic of 'early diagnosis'. Only one FG member, more specifically a clinician, explicitly referred to the concept of 'timely diagnosis' and favoured this concept above an 'early diagnosis'. 'Timely' diagnosis seems to be a clinically highly relevant concept in AD diagnostics that raises a number of questions; how does a timely differ from an early diagnosis and how do we define an early diagnosis? For some, MCI and MCI due to AD is already an early pre-dementia diagnosis. For others, early refers to a-symptomatic preclinical AD. Dubois et al define a 'timely' diagnosis as: "*a diagnosis at the stage when patients come to the attention of clinicians because of concerns of changes in cognition, behavior or functioning and can be still free of dementia and functionally independent"* [35]. According to this definition, a timely diagnosis is made at the right time for the individual patient, irrespective of the disease stage and is therefore not expressed in chronological terms [30][31][32]. This means that a timely diagnosis does not exclude an early diagnosis. An early and timely diagnosis both occur after exploring the patient's wish about testing for and knowing the result. However, a timely diagnosis gives the impression to respect the decision-making process of the patient more compared to a society and industry moving towards earlier diagnosis and eventually resulting in 'overdiagnosis' and screening for a disease in healthy individuals.

Furthermore, a study conducted by Dhedhi *et al* reported on the following two findings [30]; (a) Their study shows that GPs favoured timely above an early diagnosis. (b) They also concluded that the failure of making a diagnosis does not point to GPs lack of awareness or training skills [30]. According to them, the policy focus on education and training to improve the awareness of

GPs toward the benefits of early diagnosis, may be misguided [30]. Dhedhi *et al* state that it would be better to focus on supporting GPs in managing the complexity and uncertainty of the disease and in helping GPs with the dilemmas about providing family support after the diagnosis [30]. However, in our FG study participants often expressed the opinion that there was a lack of training and experience amongst GPs. In addition, the FG group of informal caregivers, nursing staff and clinicians mentioned the long duration of the diagnostic process. Most of these FG members used an earlier diagnosis as a term, with only one clinician who explicitly favoured the term 'timely diagnosis'. This highlights that although the concept of a timely diagnosis is beneficial and respects the decision-making of patients, for other groups, and especially mentioned in the FG of informal caregivers, an early diagnosis was not only perceived as important, yet also training and education for GPs would be recommended to enhance and facilitate the diagnostic process. This way, the current study with multiple stakeholders, provides additional insight to the views of GPs as described in the study by Dhedhi *et al* [30].

Impact of the news on both patient and relatives

Our FG with informal caregivers showed how the decision to know or not to know affects both patients and their relatives. Informal caregivers also argued that the GP needs to inform the partner that his/her life will change after the disclosure of the news to the patient. This finding is in line with previous reported literature that addressed the burden of a diagnosis on the patient and his family members, and in particular the carer [33][34][35][36].

Based on the Patients' Rights, it is a standard procedure in many countries that only the patient first is informed of the results. If the patient agrees, in a second step relatives may be informed of this news. On the one hand, the Patient's Rights focus on the perspective of the patient, whereby it is up to the patient himself to decide whether to undergo testing and whether to be informed of this result. This view ignores the difficulties and impact of the patients' decision on their relatives. On the other hand, it is important that patients can take this decision voluntarily, without being pushed or pressured by relatives who wish to know what is going on with their family member.

Advantages and disadvantages of IRR disclosure

Our FG study reported on several advantages (e.g. to plan for the future, to inform others, etc.) and disadvantages (e.g. absence of a disease modifying treatment, etc.) of knowing an IRR. These findings are in line with previously reported studies. For example, the REVEAL study reported via a survey the views from asymptomatic adults on the disclosure of their genetic APOE status [28]. The interview study from Grill et al [36] focused on both patient and carer views, whilst the previous study explicitly focused on the views from aMCI patients [32].

However, our study differs from the previously mentioned studies as multiple stakeholders' views were explored on this topic using the same scenarios. Also, our FG study indicates how certain advantages and disadvantages were put in 'the grey zone' by some FG members. This reveals how individuals can interpret and perceive these elements in different ways depending on, for example, personal views, personal values and/or coping strategy. A concrete example was the emotional and psychological consequences of knowing the result, which is often described in the literature as an ethical challenge and as a disadvantage of knowing an early diagnosis or IRR. Here, the emotional implications were clustered under both advantage and disadvantage, and has been put forward by some FG members as a topic in the grey zone. This finding highlights that researchers need to explain all possible risks/benefits as they are, and let the participant decide whether these elements are perceived by their own personal views and values as benefits/risks or elements in the grey zone.

Different interpretation on the notion of 'risk' depending on stakeholders' viewpoint

Our FG study with several stakeholders revealed how a given FG can assign their own important nuances to a discussed topic. For example, the burden of going to the hospital, the fear for undergoing medical tests and the burdensome process of undergoing multiple medical examinations and tests before receiving a diagnosis, provided another interpretation to the word 'risk' mentioned specifically and only by the group of healthy elderly. This result is also in line with a previous study, which concluded that 'risks' as perceived by researchers can be viewed differently from the patient's perspective [32]. Additionally, the FG finding refers to the importance of clearly explaining to the patient, prior to the testing, which tests and how many tests are needed to establish a diagnosis.

No absolute certainty and the unpredictability of the disease progression

The absence of absolute certainty about the received result was mentioned in our FG study under the category of disadvantage. However, as described in the results, some FG members pointed out that a high/low chance or risk is also meaningful information about their health. Two FG groups, nursing staff and researchers, discussed the topic of 'which percentage of risk' would be meaningful to them. Both groups indicated that any test percentage above 50 percent contains valuable information. This was lower than the value that we had expected a priori, as the lack of absolute certainty and the limited predictive value of an AD diagnosis is often mentioned as an ethical concern in the literature [25][37][38][39][40][41]. However, the mentioned 50 percent by the two FG groups, might indicate that adequate information about the limited predictive value and the risk perception is perhaps more important than the exact 'percentage' of risk.

The risk estimation and the unpredictability of the progression was at first only mentioned by a few FG members in our study as a reason to doubt or opt for not knowing the result. Only when FG members were asked to categorize predefined elements as either a perceived advantage or as a disadvantage, this element was mentioned more as a concern. This reveals that, at first, many individuals are not aware of these issues. Again, this shows the importance of informing individuals about the risk estimation and about the unpredictability of possible disease progression prior to any testing.

'The then self' and 'the now self' in the quest for euthanasia

In the FG groups of informal caregivers, nursing staff and clinicians, the request for euthanasia was mentioned under the category of making arrangements for the future. However, it was nuanced that there is a difference between '*thinking of*' and '*the actual implementation'*.

In the literature on advance directives and end-of-life decisions there are similar reflections available. In particular the difference between '*the then self*' and '*the now self*' [42][43][44][45][46]. The *then self* refers to the person making the necessary arrangements prior to the onset of dementia. The *now self* refers to the same person with the onset of dementia. This process should not be perceived as two separate decision-making processes, or as a dichotomy, yet rather as Gastmans wrote: *"both past and present views of the person with dementia should be considered* [47]*"*. The idea behind this is that one may plan and make certain decisions before the onset of a disease, yet this can change throughout the disease course.

Limitations

The strength of this qualitative study was the in-depth focus group interviews with stakeholders, which enabled us to better understand and explore the different opinions, experiences and perspectives about this topic. Qualitative research provides researchers with the opportunity to go beyond numerical quantitation, and is very suitable to uncover the reasons behind participants' answers.

A limitation within the used recruitment strategy of purposive sampling was that we used contact persons from specific settings, such as a pharmaceutical company. In addition, the FGs of healthy elderly, informal caregivers and nursing staff consisted of participants from the same province in Belgium, which implies that somewhat different findings may emerge when recruiting in a different province of Belgium. This is combined with a limitation part of all qualitative research studies, namely that participants are always embedded in a cultural and societal setting, which can influence the results. For example, the mentioned euthanasia arrangement in our study is understandable due to the Belgian legislation on euthanasia, yet would be unlikely in countries where euthanasia is forbidden. Another limitation is the absence of certain stakeholders, such as patient and dementia organizations, GPs or family members.

A strength of this study is the in-depth insight granted by the semi-structured methodology of presenting scenarios or cases and by using a starting question. This however limits the attention to other possibly interesting themes. Due to the large amount and richness of collected data, the presented results were limited to the most common addressed themes and important differences between FGs. However, the appendix 1-3 represents all data based on the concrete exercises participants filled out. This provides readers with the opportunity to have insight into the findings and smaller details of the data. Lastly, the discussions took place in Dutch, and used citations were translated in English, which means that some of the participants' nuances may be lost.

Appendix

Appendix 1 Scenario 1: Chosen position (Wife, husband and GP) and arguments as mentioned by participants. *Not all participants within each FG presented their chosen position. **It is possible that arguments were mentioned for a certain position, although the participant did not favour this position.

Focus group	Which position?	Chosen by how many participants? *	Arguments mentioned for the position**	Important nuances/difficulties addressed within certain position
FG 1: Healthy Elderly (*n* = 10)	Wife	2	- Better to test in an early phase. - To start medication	- The pressure of the wife on the partner to seek medical advice, can lead to more stress and complaints.
	Husband	3	/	- Understandable that the man doubts about seeking medical advice and knowing diagnosis, cfr. doubt and fear. - Fear of going from one medical investigation to the other, not knowing how long this process will take. - Recognizable that patients initially deny symptoms.
	GP	2	- Better to give it some more time to exclude other factors such as stress.	- The GP did not give wrong medical advice. Since there is no medication available, the outcome remains the same. - Does the GP have enough experience with this? How has the GP been educated/trained to deal with these circumstances? ←→ If GP does not know what is going on, better to refer to other clinician straight away.
FG 2: Informal caregivers (*n* = 9)	Wife	9	- Partner can estimate well the symptoms of person (s)he is living with.	- Difficult to confront your partner with symptoms (initial denial of symptoms, and leading to pressure on relationship and discussions).
	Husband	0	/	- Position of man is understandable out of fear for what might happen and the difficulty to face with the symptoms.
	GP	0	- Difficulty to notice first symptoms (confusion with depression for example).	- Recognizable situation: Many participants within this FG experienced the same scenario as presented in the case and referred to minimalizing the symptoms by their GP and a long diagnostic process. - Is the GP trained and suited for dementia diagnosis (lack of experience?) ←→ Should refer to other clinician.

Focus group	Which position?	Chosen by how many participants? *	Arguments mentioned for the position**	Important nuances/difficulties addressed within certain position
FG 3: Nursing staff (*n* = 6)	Wife	4	- The wife that 'pushes' the husband to seek medical advice is good to make the husband aware of the situation. - Concerned about situation of husband. - To intervene before something bad, for example, an accident has happened.	- "To push", yet the husband needs to agree and feel comfortable in seeking medical advice (Maybe he prefers not to know). - Concerned to 'harm' and 'burden' the partner when confronting about noticing first memory problems.
	Husband	1	- It is the decision of the husband/patient himself. He needs to be ready to take this step. - What is the benefit, the value of knowing? What are possible consequences?	- Recognizable situation: Fear for the disease.
	GP	1	- Good attitude from the GP not to create immediately fear or anxiety about possible AD, but to give it some time and follow situation up.	- Recognizable situation: Many of the nursing staff indicate to have been confronted with patients who experienced a long and difficult diagnostic process. - GPs lack of expertise and knowledge about AD. - GPs should inform patients in a broader sense, refer to specialist and not minimalize situation.
FG 4: Researchers (*n* = 8)	Wife	3	- When there is doubt/uncertainty, better to find out and test. - Early diagnosis or risk is useful to start cognitive enhancers and memory exercises. - At least you know what is going on. - Opportunity to plan ahead.	- Then you know the diagnosis or risk, and then what? There is no effective curing medication available. - Since there is no effective treatment available, not good to 'push' someone to seek testing. Respect person's decision to know or not to know.
	Husband	1	- It is a slow process of becoming aware and accepting situation. - Mentality of it should be very severe before going to GP.	- Recognizable situation: Participant responded he would probably also respond with: 'Ah, everything will be all right.'
	GP	3	- Not bad to give it a bit more time to see whether or not situation becomes worse. - Better not to make hasty conclusions.	- Consultation at the GP is approximately 15 minutes. This is too short to perform enough investigations and to make proper diagnosis. - Important that GP provides information about possible next steps to come and what they can expect regarding, for example, guidance, treatment options, etc.

Focus group	Which position?	Chosen by how many participants? *	Arguments mentioned for the position**	Important nuances/difficulties addressed within certain position
FG 5: Clinicians (*n* = 7)	Wife	7	- Nothing to lose if you continue to test. Can lead to more clarity and can take the worry away. - Early diagnosis provides more possibilities, such as participating in clinical trials.	- Better to speak of timely diagnosis instead of early diagnosis. What is early? Timely also respects the decision making of patient more to undergo testing. Also, there early diagnosis is nice for clinicians, but in reality, we can't offer that much more to patient with early diagnosis.
	Husband	0	- Patient also has the right not to know.	- The right not to know of patient, can cause big burden for partner and society.
	GP	0		- Recognizable situation: For neurologists difficult to address GPs if they have waited to long for patient referral or did not notice the symptoms. - GP can do more basics tests first, such as mini-mental state examination to get more insight into patients' problems instead of waiting a few months to see if situation 'improves/declines'. In case of doubt, refer to specialist. - GPs often lack knowledge and experience: o On the contrary, they are not confronted with so many dementia cases compared to neurologists. o GPs often know medical history of their patient, yet often becomes selectively blind if he knows patient too long.

Focus group	Which position?	Mentioned by how many participants? *	Reasons
FG 1: **Healthy Elderly**	To know IRR	4	- Clarity - To know if there is a risk to get AD. - Plan / arrangements for the future - Processing time/coping time close environment - Maybe there is a solution? - To be aware about possible consequences of the disease.
	Not to know IRR	3	- Fear/anxiety to live with the disease if the result is known. - I do not want to lie to my children who are precious to me. - If you have positive result, you might constantly think about it. So I would rather not know and enjoy life for a few more years.
	Doubt	1	- Yes, if they can provide effective help or cure. No, if they cannot provide effective help or cure, I do not want to know.
FG 2: Informal caregivers	To know IRR	6	- Plan / arrangements for the future o To arrange things now while I'm still capable o To communicate with family about end-of-life care - To do things now that later on I cannot do anymore, such as travelling. - To test is to know. - Desire for clarity and not to remain in doubt / feeling worried. - What can I do about it myself? - Which medications available?
	Not to know IRR	0	/
	Doubt	1	- Yes, because you can rearrange your live, talk about euthanasia, and because every time I would forget something I think I have AD. No, because there is a risk error with the test result.

Appendix 2: Scenario 2: To opt for IRR and mentioned reasons as described by participants in their tool A. *Results are completely presented as they are based on the participants within each group who handed over their filled out paper to the moderator.

Focus group	Which position?	Mentioned by how many participants? *	Reasons

FG 3: Nursing staff	To know IRR	2	- To prepare myself and others to what will happen. This can have positive impact on my quality of life.
			- Support throughout the disease
			- To make arrangements:
			  o Communication about end-of-life decisions
			  o Quality of social relationships
			- The hope that the result will be normal/negative. If the result is positive, the hope to remain stable for a few more years.

	Not to know IRR	1	- I am afraid that if the result is positive, I would become depressed or anxious.
	Doubt	2	- Yes, if there is the necessary support. No, how will my future look like? Scared to know this. Fear that society responds negative to your disease and the fear that they will leave you behind. - Yes, to have an answer, to have more clarity. No, fear for the result, the burden of medical investigations, and to have more questions after knowing the result.

FG 4: Researchers	To know IRR	6	- To plan / make arrangements for future:
			  o Treatment plan
			  o End-of-life decisions
			- I know what is going on, what can happen.
			- To inform family / others
			- To enjoy life while you are still in good health.
			- The possibility to participate in clinical trials.
			- Relief, also in case of positive test (would take doubt away).
			- These PET scans are not invasive, no burden for person undergoing the test.
			- Although no certainty, amyloid PET scan reveals big risk to get AD.
			- If deciding to enroll in a clinical trial, then also the desire to know the results.

	Not to know IRR	0	
	Doubt	2	- Yes, because you can plan in the short and long term and maybe there are some options to delay AD or improve symptoms. No, maybe there is nothing than can be done, anxiety and nobody is 100% certain about how life will turn out. - Yes, because you know what is going on, you can arrange for the future and participate/help out science. No, the fear for what can happen, stress.

Focus group	Which position?	Mentioned by how many participants? *	Reasons

FG 5: Clinicians	To know IRR	4	- To have insight in the disease
			- To plan / make arrangements for the future
			  o Plans with partner and close environment
			  o Financial arrangements
			  o Advance directives
			- Not knowing if you will get the disease is worse than to know your diagnosis.
			- To know what is going on is reassuring: '*I'm not crazy'.*
			- To inform family
			- Possibility for further follow-up
			- Possibility to start in clinical trials.

	Not to know IRR	0	
	Doubt	3	- Yes, to plan my life as long as I still can. No, I do not want to live my remaining life in the shade of my diagnosis, without the possibility of being cured. - Yes, to inform partner, children and environment, to make arrangements (financially and about end-of-life/advance directives). No, because there is no treatment possible, I do not want to burden my close environment, confrontation with whom you will become which can lead to depression. - Yes, to have diagnostic certainty, to make arrangements (financially and end-of-life/advance directives), to enjoy life (bucket list), possibility to start in clinical trials. No, lack of effective treatment (but maybe possibility via therapeutic clinical trials).

Appendix 3: Scenario 2: Tool 2 where participants were asked to cluster elements according to what they perceive as (dis)advantages as part of their decision-making process.

Focus group	Category	Which elements mentioned under each category? (n = number: how many times mentioned under this category) (cursive letters = new elements which were spontaneously mentioned/added by participants as (dis)advantages to their schedule)
FG 1: Healthy Elderly	Advantages	• More clarity/to know what is going on (n = 10) • To enjoy life more (n = 9) • To change lifestyle (n= 9) • Start early treatment/intervention (n = 8) • To plan / arrange for the future (n = 7) • To inform others about result (n = 6) • No absolute certainty, but high or low risk to get AD (n = 3)
	Disadvantages	• No effective treatment or cure for AD (n = 9) • Risks of undergoing tests (n = 9) o *Burden of undergoing tests/going to hospital* (n = 1) • Emotional/psychological consequences (n = 9) o *Stress* (n = 1) • No absolute certainty, but high or low risk to get AD (n = 7) • To inform others about result (n = 3) • To plan / arrange for the future (n = 2) • Start early treatment/intervention (n= 2) • To change lifestyle (n = 1)
	Grey zone	/
FG 2: Informal caregivers	Advantages	• Start early treatment/intervention (n = 9) • To change lifestyle (n = 9) • To plan / arrange for the future (n = 9) • To enjoy life more (n = 8) • To inform others about result (n = 8) • More clarity/to know what is going on (n = 7) • No absolute certainty, but high or low risk to get AD (n = 3) • Emotional/psychological consequences (n = 1) • *To know is to be more in control* (n = 1)
	Disadvantages	• No effective treatment or cure for AD (n = 7) • Risks of undergoing tests (n = 7) • Emotional/psychological consequences (n = 5) • No absolute certainty, but high or low risk to get AD (n = 5) • To inform others about result (n = 1) • *Stigma + society looks at you in different way* (n = 1) • *Unpredictability of the deterioration* (n = 1)
	Grey zone	• Emotional/psychological consequences (n = 1) • To enjoy life more (n = 1) • *Living with dementia is also a meaningful way of living* (n = 1)
FG 3: Nursing staff	Advantages	• To plan / arrange for the future (n = 5) • More clarity/to know what is going on (n = 4) • To inform others about result (n = 4) • Start early treatment/intervention (n = 4) • To enjoy life more (n = 3) • To change lifestyle (n = 3) • No absolute certainty, but high or low risk to get AD (n = 1) • Emotional/psychological consequences (n = 1)
	Disadvantages	• Risks of undergoing tests (n = 4) • Emotional/psychological consequences (n = 4) • No effective treatment or cure for AD (n = 3) • No absolute certainty, but high or low risk to get AD (n = 3) • To change lifestyle (n = 1) (Nuance: Participant changed it in to: 'To *have to* change lifestyle').

	Grey zone	• To inform others about result (n = 1) • To change lifestyle (n = 1) • To enjoy life more (n = 1) • More clarity/to know what is going on (n = 1)
FG 4: Researchers	Advantages	• More clarity/to know what is going on (n = 8) • To inform others about result (n = 8) • Start early treatment/intervention (n = 8) • To plan / arrange for the future (n = 8) • To change lifestyle (n = 7) • To enjoy life more (n = 7) • No absolute certainty, but high or low risk to get AD (n = 2)
	Disadvantages	• No effective treatment or cure for AD (n = 8) • Emotional/psychological consequences (n = 8) • Risks of undergoing tests (n = 5) • No absolute certainty, but high or low risk to get AD (n = 5)
	Grey zone	/
FG 5: Clinicians*	Advantages	/
	Disadvantages	/
	Grey zone	/

*This exercise was not performed with this group due to the following two reasons: (a) Group already mentioned in the previous exercise a lot of these (dis)advantages as part of their decision-making about being informed, and (b) due to limited/restricted time.

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Chapter 7: From information to follow up: ethical recommendations to facilitate the disclosure of amyloid PET scan results in a research setting

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Abstract

In the field of Alzheimer disease research, the use of biomarkers such as amyloid Positron Emission Tomography (PET) has become widespread over a relatively brief period of time. There is an increasing tendency in research studies and trials to switch from no disclosure under any condition towards a qualified disclosure of individual research results, such as amyloid PET scan results.

This perspective paper aims to evaluate the possible need for a modification of the available recommendations on amyloid PET scan disclosure, based on recent empirical evidence obtained within the field of amyloid PET. This paper also applies the International Guideline of Good Clinical Practice (ICH-GCP) to the field of amyloid PET disclosure. Hence, we propose several recommendations (abbreviated as the IDT CRP method) to facilitate amyloid PET disclosure while minimizing possible risks of amyloid disclosure in a research context.

Background

There is currently no obligation for the researcher to disclose individual research results (IRR) to the research participant. No one favours full disclosure under all circumstances or no disclosure under any condition [1]. In the field of Alzheimer disease (AD) research, the use of biomarkers such as amyloid Positron Emission Tomography (PET) has become widespread over a relatively brief period of time.

There is an increasing tendency to switch from no disclosure under any condition towards a qualified disclosure of IRR. This switch has been guided partly by the Appropriate Use Criteria of Amyloid Imaging and the Health Authorities approval of amyloid PET imaging in patients with a clinically defined memory impairment [2][3][4][5][6][7]. Grill *et al* showed how disclosure of amyloid status is not a barrier to the recruitment of participants in clinical trials [8]. A qualified disclosure policy implies that disclosure may take place if the result is in line with particular criteria. These criteria take into account the proof of clinical utility of the result and the actionability of the result (e.g. possibility to provide a treatment, symptomatic relief, etc.) [1][9]. Disclosure of results will also vary depending on three other factors: The first factor concerns the issue of active versus passive disclosure. Passive disclosure only takes places after explicit request of the research participant, whilst an active disclosure refers to a process whereby researchers actively offer results to the participant [1]. The second factor concerns the result itself: there is a difference between disclosing an aggregate group result, an incidental finding or an individual research result [1]. The content of the data also make a difference, e.g. a standard blood value results or disclosure of a genetic risk factor. The third factor concerns the study population: There is a fundamental difference between disclosing information to cognitively healthy participants, participants who have a cognitive deficit or participants who are already in a more severe stage of AD.

To our knowledge, four studies have developed recommendations about the disclosure of amyloid PET results. The recommendations from Porteri *et al,* Lingler *et al* and Grill *et al* focus on Mild Cognitive Impairment (MCI) patients, whereby the recommendations by Harkins *et al* targeted the disclosure of results to cognitively normal adults [10][11][12][13]. Three out of four recommendations [10][11][13] focused on the disclosure of amyloid PET results, while one recommendation [14] pertains to biomarker-based information more generally. Relatively few empirical studies have explored the viewpoints of patients, carers and stakeholders regarding amyloid PET disclosure [15][16][17][18][19].

This paper aims to evaluate the possible need for a modification of the previously mentioned available recommendations [10][14], based on recent empirical evidence and the perspective of

patients themselves [15][16][20]. This perspective paper applies the International guideline for Good Clinical Practice (ICH-GCP) to the field of amyloid PET disclosure in a research context taking into account recent empirical evidence obtained within the field of amyloid PET. The review also takes into account relevant elements that have arisen from recent empirical studies of genetic AD risk disclosure [21]. We propose several recommendations to facilitate amyloid PET disclosure while minimizing possible risks of amyloid disclosure in the research context. Although this article focuses on the use of amyloid PET scans in research, the criteria set forward in this article may also be of interest for clinicians when using amyloid PET scans as part of the clinical diagnostic evaluation of their patients with cognitive problems.

From information to follow-up

Disclosure of results is associated with multiple ethical challenges. Based on the article of Porteri *et al* [12] that describes multiple important aspects of the informed consent process, we suggest a six steps recommendation to facilitate disclosure and to minimize possible risks of amyloid PET disclosure. These recommendation result in six concrete steps: Information (I), Decision (D), Testing (T), Confirmation (C), Return of result (R) and Post-guidance (P). These are abbreviated as the IDT CRP recommendations (Figure 1).

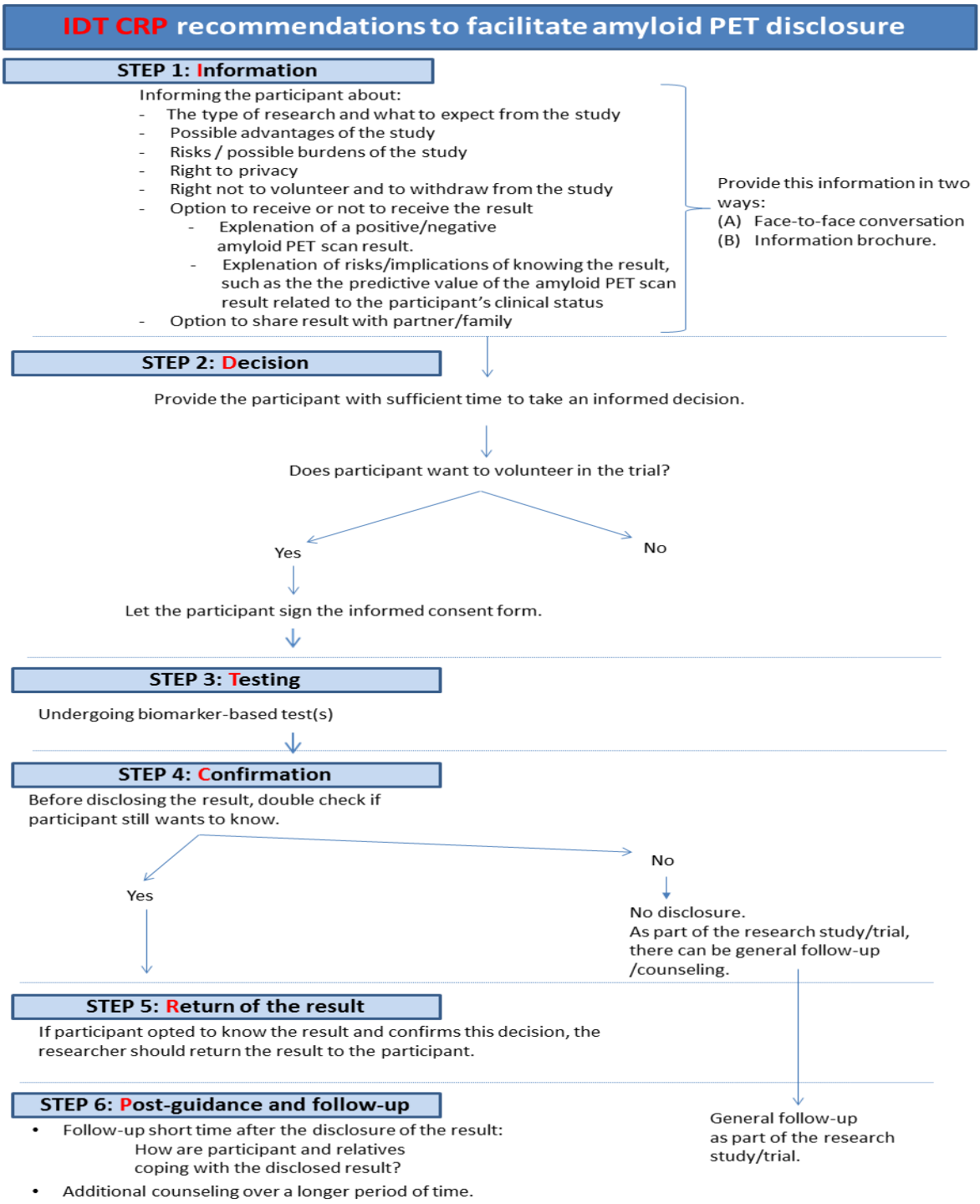

Figure 1: IDT CRP recommendations. This figure is based on the amyloid PET recommendations from Porteri et al [14] and Harkins et al [10]. However, this figure has been designed by the authors of this publication with the purpose of providing an overview schedule of the recommendations.

(1) Information

Prior to testing, it is of key importance to provide accurate, clear, and easily understandable information to the participant [10][12][21]. Participants with diverse educational backgrounds might have difficulties to understand the complexity of the research design and the type of individual research result they may opt for [1][22][23]. For instance, interviews prior to amyloid disclosure showed how some participants misused the terminology of a positive and negative amyloid PET scan result, whereby the word 'positive' was used by participants to describe 'good news' and vice versa [15]. The REVEAL study and a recent study with MCI patients after IRR disclosure highlighted that most participants understood the 'take-home-message', yet many participants could not recall the specific wording of the result as explained by the study physician [16][24]. Hence, the provided information should not be restricted to a written information brochure. It should also include the opportunity to have a face-to-face conversation with a researcher or study clinician to address any questions and concerns about the study design and the option of being informed of their amyloid PET scan result. The added value of an oral conversation and question moment was mentioned by participants and their carers in the study conducted by Lawrence *et al*, and received positive feedback from amnestic MCI patients in a clinical trial prior to the amyloid PET disclosure [15][25].

Information provided to the participant

Prior to trial participation, the following topics need to be explained to the participant [12]: voluntary decision to participate, the right to withdraw throughout the study without having to provide a reason, and to change their mind about being informed of the result [12]. There are two important nuances. First, the participant does not need to provide a reason for altering his/her mind. While the reason for withdrawal as provided by the participant sometimes provides additional insight and feedback for the research team about the ongoing trial, it can also benefit the research team when designing, setting up and recruiting for a new trial. Second, participants may change their mind about disclosure up to the moment of disclosure. Participants need to know that once the result has been disclosed, that this is an irreversible process. Conversely, if the participant initially opted not to know, he can still change his decision later on.

In table 1, we represent benefits and risks as reported by previously conducted studies regarding disclosure of results [15][16][17][18][25][26][27][28][29][30]. Table 1 can provide researchers with an overview of possible benefits and risks, which can be explained to the

participant. The benefits and risks should not be limited to the elements mentioned in table 1, as research is still ongoing to explore more participants' views and concrete experiences on this topic.

Benefits and risks can be interpreted differently by participants compared to the views of researchers [16]. For example, emotional and psychological consequences may be perceived as a compelling reason against disclosure of results. However, studies have reported that not all participants respond negatively to the disclosed result, even when it indicates pathology instead of a normal state. For example, knowing the result can also lead to the feeling of relief and less anxiety [16][17][31][32]. A recent study concluded that the disclosure of amyloid PET scan results to cognitively normal adults had no effects on depressive symptoms. However, anxiety symptoms peaked at a low level on the day of amyloid PET scan disclosure but this was not sustained at 6 weeks or 6 months post disclosure [33]. Furthermore, test-related distress was slightly higher in participants with elevated amyloid compared with participants with normal amyloid levels [33]. This can indicate that after a certain amount of time to reflect and cope with the news, most participants may respond better to the news than is indicated in the literature as arguments against disclosure.

Advantages/benefits	**Disadvantages/risks**

- The opportunity of receiving the result in an early stage of the disease course.
- The ability to inform others
- The ability to enjoy life more consciously
- The ability to make lifestyle changes (healthier lifestyle)
- Knowledge about the underlying cause of the memory problems
- The possibility to participate in AD drug trials
- The ability to make arrangements for the future, such as::
  o Financial arrangements
  o Legal arrangements
  o Life insurance
  o Advance directives
  ▪ Future care and treatment options
  ▪ Arranging elderly care or residential care centre
  ▪ Depending on legislation: euthanasia request
  o Household tasks
  o Move to a smaller place/house
	- Emotional risk of knowing the result
	- The lack of an effective disease modifying treatment
	- Risks of undergoing tests
	- Trial participation is time consuming
	- The possibility of an equivocal test result
	- The cost of tests
	- The fear of future cognitive decline
	- Negative stigma/label
	- The possibility of being patronized by others, such as by relatives and friends.

Table 1: Reported advantages and disadvantages of knowing amyloid PET result. (Table 1 is based on the advantages and disadvantages as reported in the following studies: [14][15][16][17][25][26][27][28][29][30])

In particular, the following two disadvantages, consequences or risks need to be addressed and explained in-depth to the participant:

Uncertainty and limitations of the predictive value: The correct meaning of a positive and negative amyloid PET scan needs to be explained to the research participant prior to any disclosure and this information needs to be tailored to the clinical status of the subject, both content-wise as well as regarding the way in which the information is explained [10][12]. For example, in case of MCI, if the amyloid PET scan is positive, this indicates an elevation of the detected amyloid plaque levels in the brain, which implies that the underlying pathology of MCI is due to AD, yet this does not imply that the participant will progress toward AD dementia in the near future. Due to the difficulty of individual timelines, it is hard to predict which participants will convert to AD dementia over which time period, who will remain stable over the following years or who will develop a different neurodegenerative disease [28][29]. In addition, age is an important factor as it is associated with a higher prevalence of a positive amyloid PET scan [34]. To avoid false reassurance in case of a negative amyloid PET scan result, the participant needs to be aware that a non-AD cause can be the underlying pathology causing their memory complaints [29]. A negative amyloid PET scan result implies that at the moment of the conducted scan, there was no elevation of amyloid plaques detected. For MCI patients with a negative amyloid PET scan, in a few years, there may be a conversion from a negative to a positive amyloid PET scan, in particular when values are at an intermediate level. Despite the limitation of the predictive value, the information which individuals will most likely progress to clinical AD is of importance and has great relevance for the participant [13][29]. For example, MCI patients stated that receiving a high or low risk of having underlying AD based on the amyloid PET scan was already perceived as valuable information [15].

Lack of an effective disease modifying treatment: Most individuals are aware that there is currently no treatment for AD. The lack of a cure or prevention for AD may withhold some participants from opting for their amyloid PET scan disclosure. Therefore, the study physician or researcher should clarify the current state of the art in AD therapy and which actions (e.g. lifestyle interventions, medication, etc.) the participant may undertake based on the received result [29]. To avoid therapeutic misconception, whereby participants mistakenly assume they will receive treatment as part of the clinical trial, information prior to trial participation is again of high essence. It may be that participants volunteer in the trial out of a sense of personal urgency to gain access to otherwise unavailable interventions [28].

Who to inform about the result

Presence of a relative

Prior to any disclosure, it is beneficial to ask the participant who needs to be informed of the test result. For some participants, the presence of a trusted relative or close friend can provide the necessary support in case of a positive amyloid PET scan result. It can also allow the participant's family to understand their situation and to assist in any type of financial, legal, health care, or other arrangements [12]. Others may not want to burden their relatives, or may depending on the familial situation or due to privacy reasons, prefer not to involve others in this disclosure process. This is in line with the recommendations by Grill *et al*, who stated that an informant should be present as the informant can provide social/emotional support [11]. However, Grill *et al* also mentioned that the preference of MCI patients who refuse bringing an informant should be respected [11].

Deciding on informing others after disclosure of the result

In advance, it is better to address if the participant and trusted relative want to inform others of the disclosed result and, if so, who they will inform. If they decide to inform others, what message will they provide to them? It is important to avoid a situation whereby the participant is confronted with outsiders who have been informed without explicit consent of the participant, with misinterpretation of the received result and with a possible situation of stigmatization.

(2) Decision

Participants need to decide themselves on volunteering for the trial, undergoing biomarker-based tests and whether or not to be informed about the study results. As described in the ICH GCP guidelines, this decision should be made voluntarily and without external pressure (e.g. research team, relatives, and so on) [21]. It was reported that most MCI patients felt supported by their family members in their decision to volunteer in the trial and to opt for their amyloid PET scan result, yet that there is a thin line between family support and family pressure [20]. Researchers should check whether the participant has made the decision himself freely and what the motivation is to enrol and to opt in for disclosure.

In reality, including family members may create challenges [11]. For example, they might disagree with each other or the patient might feel pushed by the relative to know the result. To avoid a situation whereby the patient feels pushed or pressured by a relative's decision, the researcher can possibly resolve this problem by using one of the following techniques;

(a) Addressing the question first to the patient and by listening to the patient's questions and decision. In a second step, the researcher addresses the same questions to the relative or informant who is present.

(b) The first option is not always feasible. For example, the relative may take over the conversation, or the patient may not feel comfortable to freely express his/her opinion in the presence of a relative or due to certain familial tensions. When one or more of these difficulties are noticed, the researcher may ask to discuss the above mentioned topics first with the patient alone. After this private face-to-face conversation, the relative may then be asked to share his/her opinion and thoughts.

In case of doubt or clear discordance between the views of the patient and the relative, the researcher should address with both of them together what the impact of the discordance may be. For example, the impact on their relationship when the partner or relative wants to know the result, while the participant clearly feels that he/she is not ready to be informed of this result.

The following studies have provided insight into possible motivational reasons to enrol and to opt for disclosure [15][17][20][30]. We have clustered these motivational reasons in table 2 as this can provide researchers with an insight into the views of participants.

Motivational reasons to volunteer in trial	**Motivational reasons to opt for IRR disclosure**
- Out of interest in research - To help science - Treatment - On request/due to a family member - Family history of AD - Received invitation by, for example, the memory clinic to volunteer - To receive individual research results	- Right to know this information - To know what is going on with health - Out of interest, curiosity - Family history of AD - Fear for AD - To know in an *early stage* whether or not AD is the cause. - To plan for the future, make arrangements - Treatment

Table 2: Reported motivational reasons for trial volunteering and for opting to know their result (Table 2 is based on the following publications that have reported on trial volunteering [16][18][26][27]).

The notion of 'knowledge is power' and the need for information was addressed. In the REVEAL study participants mentioned the need for information in order to make informed health care decisions [32]. Information could also fulfil psychological rather than practical needs [30].

(3) Testing

Conducting tests

After consent of the participant to undergo testing, it is important to describe each step of the test procedure.

Studies have also reported on the issue of trials being time consuming due to the many tests being conducted [17][20]. To reduce the disadvantage of trial participation as time consuming and to avoid drop-out throughout the trial, it is recommended to inform participants prior to consent about the estimated time/amount of visits and to cluster several tests into one hospital visit. However, clustering as many tests as possible into one hospital visit needs to remain feasible for the researchers and the research setting, should not burden the participant, nor affect the quality of the obtained research data [20].

For the participants who opted to know their result, additional information about the estimated timeline for test analysis, can provide them with insight when to expect the disclosure of their result.

Analysis and validation of the amyloid PET scan

For the visual read of the amyloid PET scan, it is of vital importance that the read is performed in a reliable manner.

In case the amyloid PET result is equivocal, waiting with disclosing the amyloid PET scan result until more information is available from other biomarker tests such as cerebrospinal fluid results, is recommended. The participant should then be informed about this delay in a proper manner.

(4) Confirmation

It is important to assess whether the participant still wants to be informed about the result during a confirmation moment prior the actual disclosure [16][33]. This can be an opportunity to repeat the purpose of the amyloid PET scan, the classification and interpretation of an amyloid positive and amyloid negative PET scan result. This confirmation moment has two concrete benefits: (1) to answer remaining questions and concerns and (2) to minimize the possibility that the participant afterwards misinterprets this information.

(5) Return or disclosure of the result

Disclosure by a trained and skilled researcher/clinician

The Amyloid Imaging Task Force (AITF) provides criteria for prescribing and disclosing amyloid PET result. They stated that the disclosure should be done by a dementia specialist who devotes at least 25% of their patient contact time to the evaluation and care of adults with cognitive impairment or dementia [6][7].

The terminology of the disclosed result

The terminology used throughout the disclosure process and how these words could impact the participants and his relatives, is an ethical challenge in amyloid disclosure. The amyloid PET scans is most commonly classified as positive/negative, yet alternative terms have been used, such as: elevated/nonelevated levels, presence or absence of amyloid, build up or no significant build up, normal/abnormal levels of amyloid plaques in the brain [10][11][13]. Researchers ought to be aware that some of the used terminology may be misinterpreted by the participant or may have a negative emotional connotation for the participant. For instance, an amyloid PET scan classified as abnormal does not imply that the participant is abnormal, yet implies that the level of amyloid detected in the brain is outside the normal range.

Hence, the use of easy-to-understand examples, pictographic and visual information can provide additional clarification for the participant and may enhance their capabilities to accurately recall and interpret their result. Showing the scan (visual read) to the participant may help for some participants to understand the result, yet researchers ought to be aware that for some patients, scan images with the visual appearance of elevated amyloid levels in the brain, might trigger emotional reactions [28]. Checking beforehand with participants if they would like to see the scan and by explaining that this might be confrontational for some participants can be seen as a preventive measure. However, it does not guarantee that the participant will not emotionally respond to these viewed images.

The disclosed result with the correct interpretation of the amyloid PET scan result should also be provided in a written document to the patient and to the patient's general practitioner (GP) [11][16]. This information should explain the imaging technique and in particular what the amyloid PET scan measures, how the amyloid PET scan result needs to be interpreted, what this result implies on the patient's level regarding the lack of good predictive individual timeline for future cognitive decline and possible treatment options.

After the disclosure, it is beneficial to provide the participant with the possibility of follow-up and counselling and to explain the purpose and benefit of follow-up. This can provide participants with a moment of reflection and a moment to receive an answer to any additional questions that may occur after disclosure.

(6) Post-guidance and follow-up

The available recommendations highlight the importance of follow-up after disclosure [10][12]. This practical need was also addressed in empirical studies [17][18]. The opportunity for counselling and follow-up may be valued more by the participant depending on the following three aspects:

(a) The outcome of the result. The disclosure of both amyloid positive and negative PET scans requires follow-up, as both can have implications. In case of a positive scan, the knowledge that one has an elevated level of amyloid in the brain, which Roberts *et al* described as 'viewable image of amyloid growing in the brain', might trigger different reactions [5]. Not knowing whether and when the individual will cognitively deteriorate, might provoke fear in these individuals.

Vice versa, persons who have received a negative amyloid PET scan result may be left with unanswered questions regarding the cause of their memory deficit or may feel overly reassured. The latter attitude may result in postponing arrangements for the future. This issue has been addressed in a qualitative study whereby some MCI patients did not feel a sense of urgency anymore to make practical arrangements for the future in light of their received negative amyloid PET scan result [16]. However, making arrangements for the future is important for anyone of advancing age, also for those who are not at increased genetic risk for AD [30].

Furthermore, the post-guidance phase can also provide an opportunity to ask how relatives and carers are coping with the news.

(b) The expectations of participants. If the test results match expectations, even positive results for severe disorders are not necessarily overwhelming. For example, studies reported on the feeling of 'relief' after receiving a positive amyloid PET scan result [16][17]. However, if the test results are unexpected (e.g. screening in healthy adult populations) the psychological consequences may be different [31][35].

(c) The perception of the disclosed result. Studies have reported that participants may accurately recall their disclosed risk information, yet not all participants match their perceived personal risk with the disclosed objective risk of a disease [36][37]. This may be the case in participants who have a memory deficit as they may be influenced by their own concrete memory experiences or via emotional experiences through family history of AD [16][31]. An interview study with amnestic

MCI patients revealed that some patients who had received a negative amyloid PET scan result, started to doubt the result due to their experienced memory complaints [16]. Another explanation for different perception of the disclosure was provided by the study of Linnenbringer *et al* whereby APOE ε4 positive individuals minimized their risk as a way to cope with unfavourable risk information. Counselling and follow-up may improve accuracy of participants' risk perception [37].

Furthermore, research is needed on the caregivers' perception after disclosure. We recommend assessing the perception of the relative in order to see how they are coping with the IRR results. This reflection moment with relatives can avoid possible misinterpretation and possible harm of undergoing 'unnecessary' arrangements after the disclosed news.

Discussion

In the field of genetics, disclosure of individual research results is a much debated and explored topic. In the field of AD therapeutic trials, disclosure of results is a domain that received far less research attention. Researchers may fear implementing disclosure as part of the trial design as disclosure could have a negative impact on the retrieved study data.

Based on the limited recommendations and research studies on amyloid PET disclosure, we can conclude that it is nonetheless feasible to disclose amyloid PET scan results to the research participant. Nevertheless, awareness of potential pitfalls and risks on amyloid PET disclosure is critical, such as the importance of a reliable amyloid PET scan read, the potential of causing emotional harm to the research participant and the limitations in predictive value of the result. Hence, the presented IDT CRP method can provide necessary insight and guidance for researchers and facilitate amyloid PET disclosure to the research participant in a proper manner.

Due to the novelty of disclosure in AD research, there are unexplored or under-investigated areas where future research should focus on. First, the need to further address the impact of amyloid PET disclosure on both the participant and the researcher/research setting. Second, the long-term impact (e.g. 5 – 10 years) of the disclosed result. Third, limited information is available on how a participant who received a negative amyloid PET scan responds to a positive amyloid PET scan conversion, nor on how a false positive/negative result was perceived by the participant. Fourth, awareness into how the result was disclosed is of utter importance (e.g. which words were used, which steps or disclosure procedures were followed,…) as this could impact the design of future trial-disclosures. Fifth, AD therapeutic trials commonly use an implicit disclosure design whereby a positive amyloid PET scan result is an inclusion criterion for trial participation. Research should explore whether this implicit disclosure is the way forward in therapeutic trials and whether participants are well aware of the meaning, implications and consequences of an implicit disclosure. Since studies have reported on the value of knowing the amyloid PET scan result by the patients, it would be interesting to explore the perspective and views of research participants towards the implicit disclosure policy in AD therapeutic trials.

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Summary and general conclusion

General conclusions and future directions

Throughout this doctoral dissertation, we have explored the key issues associated with the disclosure of biomarker information, and more specifically amyloid PET scan results, in the early stage of Alzheimer's disease (AD). As explained in the general introduction, this thesis was built upon three objectives. The first objective was to gain insight on the existing scientific literature on the ethical aspects of a biomarker-based results in the early stage of AD. The second objective was to analyse and compare the current ethos and moral attitudes of the patients and other stakeholders about early AD disclosure with the existing ethical literature. The third objective was to generate new ethical insights and reflection resulting in concrete recommendations to improve and facilitate disclosure of diagnostic information or research results. To achieve these three objectives, we have performed a literature study (e.g. objective 1), an empirical study (e.g. objective 2) and both studies were then integrated into ethical recommendations (e.g. objective 3). Here, we briefly summarize the main findings of the doctoral dissertation and address, were relevant, topics for future research.

Objective 1: To gain insight on the existing scientific literature.

Based on the literature study, we can conclude that research from an ethical point of view has focused less on the topic of mild cognitive impairment (MCI) compared to AD. In *chapter 1*, we systematically reviewed the available bioethics literature between 2003 and 2016 on the ethical issues of a biomarker-based diagnosis in the clinical setting [1]. Based on the twenty included articles, several ethical issues about the disclosure process of an early biomarker-based diagnosis emerged: the right (not) to know, the uncertainty and the limited predictive value of the diagnosis, and several issues that can occur after the diagnosis, such as the emotional implications of knowing a biomarker-based diagnosis. Using AD biomarkers in the clinical setting has several advantages, such as providing patients with the choice to receive an earlier diagnosis about what is going on with their health, letting patients plan their future, and so on. We further elaborated on the ethical issues as reported in the systematic review. For example, knowledge about an early diagnosis does not always equal power since current treatment options only have limited efficacy. Patients may also have difficulties to understand an MCI diagnosis as a risk estimation, because they often expect a straightforward diagnosis (e.g. 'yes, you have AD' or 'no, you don't have AD'). Hence, when using AD biomarkers in the clinical setting, it is important to communicate to the patients prior to testing about what a positive and negative amyloid PET scan implies, about the limited predictive value of these biomarkers and about possible risks or disadvantages. This is necessary to avoid the patient and society depriving the patient from, for example, medical insurance, based on an

incorrect interpretation of a positive amyloid PET scan result. Furthermore, additional ethical questions were raised. For example: *"Are patients aware of the predictive value of the biomarker-based diagnosis? What do patients expect from their diagnosis and what is perceived by patients as a proper diagnosis?"* These are questions where empirical research, both quantitative and qualitative, is necessary in order to get insight into the opinions and experiences from stakeholders, such as patients, family members, caregivers and clinicians [1].

In *chapter two*, we explored the ethical issues of disclosing biomarker-based information (e.g. amyloid PET scan results) to the research participant. These issues were clustered according to the four principles of Beauchamp & Childress [2]. In chapter two, we have learned that it is still uncommon practice in AD research to actively disclose results to the research participant. The lack of disclosure is due to the limited predictive value of amyloid PET scan results and based on the fear that disclosure may affect the research data and out of fear of emotionally harming the research participant. Despite the fact that disclosure is uncommon practice, chapter two concluded that in AD research, it is time to move toward a qualified disclosure policy, where individual research results should be returned when they meet particular conditions.

Objective two: to analyse and to compare the current ethos and moral attitudes in the patients and other stakeholders

Chapters three to five have provided significant contributions to the field of AD research as only limited research was available regarding the impact of an amyloid PET scan result from a patient's perspective. Hence, the findings as presented in chapter three to five are based on a qualitative empirical study with 38 amnestic MCI patients as a part of an investigator-driven diagnostic trial where participants could opt in for the disclosure of their brain amyloid PET scan binary visual read result. The presented results were based on semi-structured interviews at three different intervals; a pre-interview before the disclosure of the result, a first post-interview two weeks after the disclosure and a second post-interview six months after the disclosure of their amyloid PET scan result.

In *chapter three* valuable information for researchers on what motivates participants to volunteer in a trial was presented [3]. The two most frequently mentioned reasons for volunteering in a trial were to contribute to science and to receive an individual research result. The wish to make a contribution to science was not based purely on altruistic sentiments, but was a consequence of the participants' primary motivation of possibly receiving medical test results. Participants perceived several disadvantages of trial participation. This input may help researchers in the design of future trials. For example, the two most frequently mentioned disadvantages by

the patients were the possible risks related to certain tests done in the trial and the fact that volunteering was time consuming. The latter indicates that researchers might consider reducing the number of hospital visits perhaps by clustering several tests within one visit, as far as practically feasible and to the degree that this would not impact on data quality. The semi-structured interviews also revealed that most participants felt that their partner and/or children supported their decision to enroll in this study. However, researchers need to be cautious when recruiting participants for clinical trials by ensuring that participants truly desire to participate in the study and that they are not being coerced by family members [3].

Chapter four presented the motivations of amnestic MCI patients related to the option of knowing their amyloid PET scan result and what they perceive as possible advantages and disadvantages of knowing this result [4]. All 38 patients indicated the desire to know their amyloid PET scan result. The most frequently mentioned benefits were to achieve clarity regarding their deteriorating health, to start informed treatment options, and to plan for the future by making informed decisions about certain arrangements that may be required. Most of the participants mentioned the emotional risk as the main disadvantage, although most patients thought they would be able to cope with receiving bad news about a positive scan. Based on the reported literature, our hypothesis was that the limited efficacy of current treatment options and the limited predictive value of the amyloid PET scan would be mentioned by patients as possible disadvantages. However, based on the interviews both the limited efficacy of treatments and the limited predictive value were not perceived by patients as disadvantages. This is an important finding as it highlights that patients' interpretation of what is written in the informed consent as possible risks and benefits can differ from what was intended by researchers [4].

In *chapter five* we presented the reactions and the experienced advantages and disadvantages of the 38 aMCI patients who received their amyloid PET scan result [5]. From these 38 aMCI patients, eight received a positive amyloid PET scan result and thirty patients received a negative amyloid PET scan result. Key findings for researchers are that some patients confused the terminology of an amyloid positive/negative test result, and that no major emotional reactions were reported after the disclosure of the result. For example, most patients who received an amyloid positive PET scan result were not surprised by the news based on their experienced memory complaints. We noticed differences in experienced advantages and disadvantages depending on two factors. The first factor was the outcome of the result (positive or negative amyloid PET scan). The second factor was the time of the conducted interview (two weeks or six months after the disclosure). In addition, we compared the experienced consequences with the perceived consequences from the pre-interview. This comparison showed, for example, how patients still

mentioned planning for the future as an experienced advantage after the disclosure of the amyloid PET scan result, yet it was mentioned less frequently compared to the perceived advantages from the pre-interview. This reveals how, in light of a negative received amyloid PET scan result, patients do no longer have a sense of urgency to make practical arrangements. Based on our study findings as presented in chapter five, future research should incorporate longer duration of follow-up interviews after amyloid PET disclosure. This would allow an exploration of how the emotional reactions of patients change over time, as well as how patients with a positive amyloid PET scan result cope with cognitive deterioration [5].

In *chapter six,* we presented the second part of our empirical study, which was an exploratory focus group study that reported on the views of five stakeholder groups. This chapter revealed two educational implications in the field of AD. Firstly, this focus group study shows that many individuals favour an early diagnosis and desire to be informed about their health. However, there were individuals who were in doubt, or who preferred not to know this result. The mentioned rationale to support their decision were the fear for AD, not wanting to burden their environment, the lack of an effective treatment for AD, and so on. Hence, the chapter in this thesis indicates that researchers and clinicians may never assume that all patients and participants want to be informed of their result. Secondly, focus group members reflected on several advantages and disadvantages of knowing their result, while it became clear that some topics were categorized between advantage and disadvantage, resulting in a 'grey zone'. This indicates how possible consequences can be interpreted differently depending on personal coping strategies and personal views and values. For clinicians, researchers and policy makers, it is important to describe these consequences for the individual prior to testing and to let patients decide by themselves whether they consider these consequences as an advantage, disadvantage or as a consequence in the 'grey zone'. Based on our study findings as presented in chapter six, future research should focus on the three aspects. Firstly, views of stakeholders who wish not to know their amyloid PET scan result, as little insight is available in this matter. What are possible factors that may influence stakeholders to know or not to know their amyloid PET scan result? Secondly, what is the impact of knowing the amyloid PET scan result in the long term? Studies have mostly reported on the short term consequences of knowing this type of information. Thirdly, investigating the discrepancy of 'the then self' versus 'the now self'. Studies have reported on this discrepancy in the decision making process of the patient, yet only limited studies have investigated this topic from a qualitative matter. Qualitative studies with patients who have recently received an early diagnosis of AD, may help to clarify this matter.

Objective 3: to generate new ethical insights resulting in concrete recommendations to improve and facilitate disclosure of diagnostic information or research results.

Chapter seven presented the IDT CRP method, which is a six-phase method that we developed based on the findings from the available literature, (ethical) recommendations and empirical studies [6]. The IDT CRP method is an abbreviation for each phase of the method to facilitate amyloid PET scan disclosure. Within each phase, we made recommendations on attention points or 'points-to-consider' in the process of disclosing amyloid PET scan information to the patient or research participant. For example, in the information phase it is crucial to inform the patient on the limitations of the predictive value, the lack of an effective disease modifying treatment, but also the type of trial the patient has volunteered to (e.g. therapeutic or non-therapeutic trial to avoid therapeutic misconception). In the decision phase, we recommend several techniques to avoid that the patients feels pushed or pressured by a relative. Another recommendation was to cluster several tests into one hospital visit, without burdening the participant or affecting the quality of the obtained data. This recommendation was integrated in the testing phase from the IDT CRP method and was based on the findings from our qualitative study with aMCI patients. Based on our findings as presented in chapter seven, future research should explore the long-term impact of the disclosed result, participants' reactions to an amyloid PET scan conversion, and their reaction on a false positive or false negative result. Another point for future research attention is whether implicit disclosure, which is commonly used in AD therapeutic trials, is the way forward in therapeutic trials and whether participants are well aware of the meaning, implications and consequences of an implicit disclosure [6].

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Study limitations

Several considerations on the study limitations were mentioned throughout the doctoral dissertation. Here, we will describe a global summary of the study limitations. As presented in the general introduction of this thesis, our focus on ethics, mild cognitive impairment and biomarker-based information (in particular amyloid PET scan results) implies a limitation. For example, a focus on pre-symptomatic Alzheimer disease can reveal different results.

Chapter one and two of the literature study were written when interest in disclosing biomarker-based information in Alzheimer disease was beginning. Toward the end of this doctoral project, more and more research on disclosing biomarker-based information in AD is being published

As pointed out in chapters three to five of the exploratory empirical study, the interviews were based on a small sample size of 38 cases with amnestic mild cognitive impairment (30 amyloid negative cases and 8 amyloid positive cases). Although data saturation was reached for the interviewee's who received a negative amyloid PET scan result, more amyloid positive cases are needed to explore the impact of amyloid disclosure. There may be a subject selection bias within this interview study, as the data are based on those who agreed to participate in the clinical diagnostic trial. However, we do not have information on the participants who declined the option to participate in our study trial.

The focus groups, as presented in chapter six of this thesis, were based on a population of five groups. Including more groups, such as patients, Alzheimer communities and organizations, may result in additional and/or different findings. A methodology used to structure the focus groups was to use a scenario with an opening question. This approach may have limited the attention to other interesting and potentially unexplored themes.

For both the interviews and the focus groups, we have to point out to the specific setting. For example, the academic memory clinic at the UZ Leuven Hospital in Belgium for the semi-structured interviews. As stated in these specific chapters, it is likely that different findings may occur when conducting this research in, for example, another clinical context, such as geriatric or psychiatric hospitals.

The ethical recommendations presented in chapter seven were based on a few published recommendations and a few empirical studies that have investigated the viewpoints of patients and stakeholders on amyloid PET disclosure. It is likely, that future research on this topic may result in additional or altered ethical recommendations.

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Scientific abstract

This doctoral dissertation explores key ethical issues raised by the introduction and utilization of biological markers, and in particular, amyloid imaging, in the context of the early stage of Alzheimer's Disease (AD). The objectives of this dissertation are three-fold: 1) Gaining a comprehensive overview of the existing literature on the ethical challenges of a bioamarker-based result in the early stage of AD. 2) Exploring the views of patients and different stakeholders on early AD disclosure. 3) Generating new ethical insight resulting in concrete recommendations to improve and facilitate disclosure of biomarker-based results within the field of AD. To meet its first objective, this dissertation presents a comprehensive overview of the reported ethical challenges within biomarker-based diagnosis in the early stage of AD. In line with its second objective, this dissertation reports findings of a qualitative semi-structured interview study with patients with amnestic mild cognitive impairment and a focus group study with stakeholders (healthy elderly, family members/caregivers, nursing staff, clinicians and researchers with expertise in AD or dementia). The interview study with patients focuses on the rationale to volunteer in a clinical diagnostic trial, their rationale to opt for the disclosure of their amyloid PET scan result, their expectations before and their concrete experiences after the disclosure of the result. The focus group study explores stakeholders' views on early diagnosis, clinical trial participation and amyloid PET disclosure. In line with the third objective, recommendations to facilitate amyloid PET scan disclosure were developped, which were abbreviated as the IDT CRP method. For each objective, the doctoral dissertation discusses its main findings, contextualizes the results within the existing scientific literature and further elaborates on their implications.

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Personal contribution

Gwendolien Vanderschaeghe has contributed to this dissertation by writing the first draft of all eight chapters of this manuscript. She also actively participated in the methodological design, data collection and data analysis of the seven studies (chapters two to eight) described herein.

Conflict of interest statement

Gwendolien Vanderschaeghe has no conflict of interest to disclose.

Rik Vandenberghe has been principal investigator of the phase 1 and 2 studies with 18F-flutemetamol, one of the amyloid PET ligands approved for clinical use. Rik Vandenberghe has received consultance fees from GE Healthcare. Rik Vandenberghe and Rose Bruffaerts' institution has a clinical trial agreement with Merck, EliLilly, and Biogen (RV local PI). The authors declare no other conflicts of interest.

None of the other individuals who have co-authored papers included in this dissertation had conflicts of interest to disclose at the time of their publication.

About the author

Gwendolien Vanderschaeghe was born on 7 March 1990 in Bruges, Belgium. Gwendolien received her secondary education at the college 'Sint-Lodewijks' in Bruges, following which she pursued her academic bachelor and advanced master studies in theology and religious studies at the University of Leuven (2008-2013). Gwendolien joined the Center for Biomedical Ethics and Law in November 2013, where she has been doing research around the ethical issues in biomarker-based testing in the early phase of Alzheimer disease. After the end of the PhD scholarship in October 2017, Gwendolien started in November 2017 as a Health & Safety Specialist for HR Rail (the juridical and medical employer for the Belgian Railway Company). In addition, she continued to work as a voluntary academic staff member of the Center for Biomedical Ethics & Law in order to complete her doctoral dissertation.

List of publications

This doctoral dissertation was based on multiple scientific papers published in peer reviewed journals:

(1) Vanderschaeghe, G., Schaeverbeke, J., Vandenberghe, R., Dierickx, K., Amnestic MCI patients' perspectives toward disclosure of amyloid PET results in a research context, Neuroethics (2017) 10:281 - 297. Doi:https://doi.org/10.1007/s12152-017-9313-z.

(2) Vanderschaeghe, G., Schaeverbeke, J., Vandenberghe, R., Dierickx, K., Amnestic MCI patients' perspectives on volunteer participation in a research context, J Clin Res Bioeth (2017) 8:3. Doi: 10.4172/2155-9627.1000305.

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