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ORIGINAL RESEARCH

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 etiological 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.

Keywords Mild cognitive impairment · Alzheimer's disease · Diagnostic disclosure · Biomarker · Systematic review · Ethics

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Introduction

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, predementia, or even 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 monitor these patients better (Viloria Jiménez et al. 2013; Prvulovic and Hampel 2011). 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 (Le Couteur et al. 2013). 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 (Dworkin 1986; Fallowfield 1993; Rice and Warner 1994; Maguire et al. 1996; Heal and Husband 1998; Hirsh 1990; Holstein 1998; Daly 1999; Post 2000), rather less attention has been paid to the ethical aspects in mild cognitive impairment (MCI) and MCI due to AD. Mild cognitive impairment refers to the presence of an acquired objective cognitive deficit above the age of fifty 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 apnoea syndrome (Petersen et al. 2001). Mild cognitive impairment is further divided according to the cognitive domain that is mainly affected, most frequently episodic memory and executive function (Petersen et al. 2001). Mild cognitive impairment patients constitute a significant portion of patients consulting a memory clinic (Portet et al. 2006). Current estimates suggest that up to 50 per cent of MCI patients have underlying AD (Vandenberghe et al. 2013a).

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 (pAD). 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 (2014). According to McDougall, there has been interest in applying the techniques of systematic review to the bioethics literature (2014). 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 (McDougall 2014).

Literature Search

An initial search using "prodromal AD" 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 focusing 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 (Hirsh 1990; Holstein 1998; Daly 1999; Post 2000; Bamford et al. 2004). 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 (Strech et al. 2013). 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.

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 (McDougall 2014).

(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.

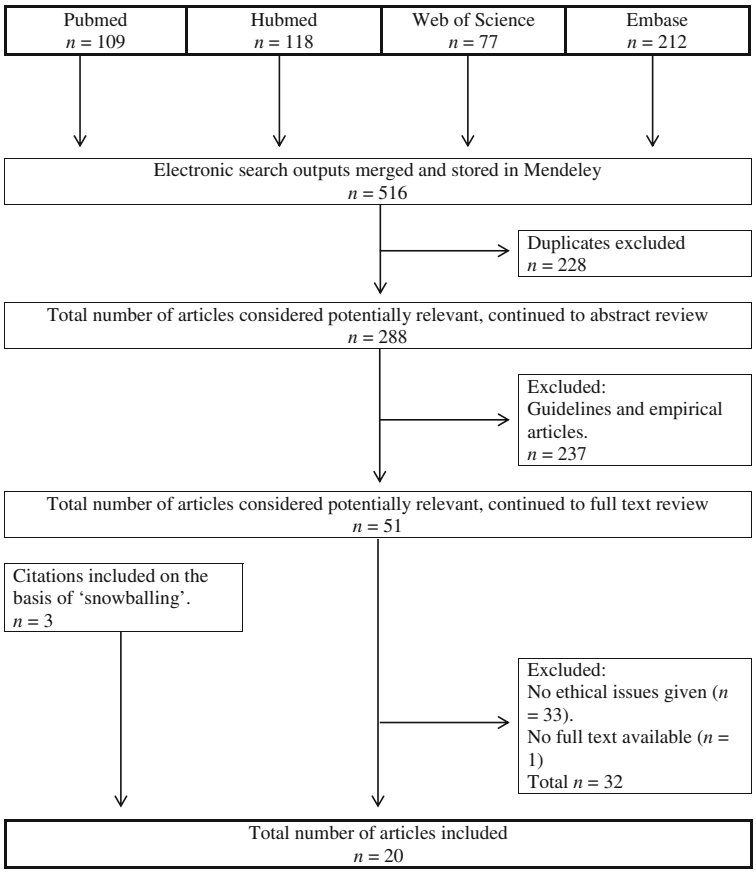

Figure 1 Results of the search algorithm in the electronic databases.

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

Results

A total of twenty articles were included for this systematic review: seventeen articles from the electronic databases and three articles based on snowball sampling. Table 1 (see online supplementary material) indicates which articles and type of articles were included, where they were published, and if the articles contain general AD literature or provide 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 (Strech et al. 2013; Viloria Jiménez et al. 2013).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 (Viloria Jiménez et al. 2013). This principle requires that the clinician does everything to prevent and avoid possible physical, emotional, or psychological damage to the patient (Viloria Jiménez et al. 2013), using, for example, an adapted, less harsh diagnosis such as "you have troubles remembering" (Viloria Jiménez et al. 2013). 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 (Mattsson et al. 2010)) 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 (Antoine and Pasquier 2013). 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 progress towards dementia may have the effect of placing "a dark cloud" over the remainder of the patient's life (Cornett and Hall 2008). 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 (Bamford et al. 2004).

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 (Antoine and Pasquier 2013). 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 (Cornett and Hall 2008). 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 (Viloria Jiménez et al. 2013; Cornett and Hall 2008).

In the case of an early diagnosis, the awareness and the capabilities to understand the diagnosis is mostly preserved (Antoine and Pasquier 2013). 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 (Howe 2013). Based upon this right to know, some patients could feel dissatisfied or upset if they found out that the clinician adapted this information (Antoine and Pasquier 2013). 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 (Howe 2013). 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 (Cornett and Hall 2008). According to Cornett and Hall (2008), 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." 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 (Antoine and Pasquier 2013).

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 (Le Couteur et al. 2013; Bamford et al. 2004; Howe 2013). 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 (Le Couteur et al. 2013; Antoine and Pasquier 2013; Howe 2013). For example, these patients may believe that they would lead a better life not knowing whether they have or will develop AD (Howe 2013). 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 (Howe 2013).

The Uncertainty and 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 (Prvulovic and Hampel 2011; Antoine and Pasquier 2013; Porteri et al. 2010). These tests may give "guidance," as described by Werner and Korczyn (2008), 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 due to AD will convert towards dementia due to AD (Chiu and Brodaty 2013; Werner and Korczyn 2008). 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 (Chiu and Brodaty 2013; Porteri and Frisoni 2014). 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 (2008) state that it would be erroneous to view MCI automatically as "very mild AD." This may only be the case once it is known that the underlying pathology in MCI is AD (Werner and Korczyn 2008).

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's wishes, preferences, and capabilities to comprehend medical information (Antoine and Pasquier 2013). Awareness on how clinicians feel when communicating this uncertain diagnostic information was also mentioned in the literature (Antoine and Pasquier 2013). 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 (Antoine and Pasquier 2013).

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 (Visser et al. 2012). 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 (Werner and Korczyn 2008), and information on the presence of biomarkers may, according to Visser et al. (2012), cause stress to patients and their family.

It is necessary to keep the rate of a false-positive biomarker diagnoses at a minimum to avoid potential negative emotional reactions, such as fear and feeling worried, in subjects that are not affected by a neurodegenerative disease (Viloria Jiménez et al. 2013; Prvulovic and Hampel 2011). Since a false-positive diagnosis will most likely result in a treatment, any harmful side effect is, according to Mattsson, Brax, and Zetterberg (2010), "a serious infringement" on the basic ethical principle of non-maleficence. 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 (Mattsson, Brax, and Zetterberg 2010).

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 (Viloria Jiménez et al. 2013).

Treatment

There is currently no treatment available to prevent or cure Alzheimer's disease (Prvulovic and Hampel 2011; Cornett and Hall 2008; Howe 2013). There is the possibility to use drugs, such as acetylcholinesterase inhibitors (AChE-1) and memantine (Prvulovic and Hampel 2011). 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 (Prvulovic and Hampel 2011). Unfortunately, this will only be of help for some patients and does not imply guaranteed success for every patient (Viloria Jiménez et al. 2013; Porteri et al. 2010, b).

Despite the limited efficacy of drug treatment, patients can adjust their lifestyle through physical, mental, and social activities (Howe 2013; Chiu and Brodaty 2013), 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 (Chiu and Brodaty 2013).

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 (Prvulovic and Hampel 2011). 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 (Viloria Jiménez et al. 2013). 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 (Prvulovic and Hampel 2011). 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 (Viloria Jiménez et al. 2013; Antoine and Pasquier 2013).

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 (Howe 2013; Werner and Korczyn 2008). 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" (2013, p.308). These decisions can be, for example, about financial, legal matters, and future care (Prvulovic and Hampel 2011; Antoine and Pasquier 2013; Visser et al. 2012; Draper et al. 2010). 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?" (Antoine and Pasquier 2013). For this purpose, it is important to anticipate daily aspects that in the near future will become difficult for the patient (Antoine and Pasquier 2013).

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 (Viloria Jiménez et al. 2013). 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 (Viloria Jiménez et al. 2013).

The review by Draper et al. (2010) describes how there are patients who refuse to receive any type of treatment that can unnecessarily prolong their life with Alzheimer's Disease. 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 (Draper et al. 2010).

Currently it is unknown how many patients with mild cognitive impairment would consider euthanasia. Draper et al. (2010) and Davis (2014) 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.

However, 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 (Draper 2015).

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 a patient's employment situation. This can occur if a patient's medical records are not protected and an employer gains access to their personal information (Antoine and Pasquier 2013; Visser et al. 2012; Karlawish 2011). 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 (Le Couteur et al. 2013).

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 (Leuzy and Gauthier 2012; Wright et al. 2009; Snyder 2005; Carr and Ott 2010). On the one hand, this restriction is a measure to prevent car crashes—a safety protection for the patient and society. On the other hand however, patients may feel that this is a violation of their autonomy (Leuzy and Gauthier 2012; Snyder 2005). 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 (2010, p. 1634) indicate that "a diagnosis of dementia should not be the sole justification for the revocation of a driver's license." 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 licence (Snyder 2005). 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 (Viloria Jiménez et al. 2013; Leuzy and Gauthier 2012; Snyder 2005). 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 (Carr and O'Neill 2015).

An additional consequence of 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 (Prvulovic and Hampel 2011; Leuzy and Gauthier 2012; Visser et al. 2012). 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 (Karlawish 2011).

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 (Mattsson, Brax, and Zetterberg 2010; Leuzy and Gauthier 2012). Cornett and Hall (2008) refer to qualitative study on patient and family experiences from Smith and Beattie (2001) and a questionnaire from Husband (2000) to indicate that people with AD often feel that they are observed by others as being less capable compared to persons without AD. 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 (Cornett and Hall 2008). 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 (Antoine and Pasquier 2013). Due to this negative stigma, society is often more afraid of having AD than dying from a heart disease, diabetes, or a stroke (Antoine and Pasquier 2013). 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 (Karlawish 2011; Gauthier et al. 2013). 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 (Karlawish 2011; Gauthier et al. 2013).

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 (Viloria Jiménez et al. 2013; Werner and Korczyn 2008; Visser et al. 2012; Draper et al. 2010). Howe (2013) describes how patients informed of their MCI diagnosis sometimes feel better because they now understand why they are having these subtle memory problems. 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 (Werner and Korczyn 2008). Serious fears include becoming or already being a burden for their partner and relatives and losing their own autonomy and capabilities (Antoine and Pasquier 2013). Receiving the diagnosis, in combination with the negative perception of society about AD, can have a negative impact on the patient's self-confidence and self-appreciation (Mattsson, Brax, and Zetterberg 2010; Leuzy and Gauthier 2012). The study by Cornett and Hall (2008) indicates that people with AD often feel ashamed compared to persons without AD. 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 (Howe 2013). 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 (Antoine and Pasquier 2013).

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 (Chiu and Brodaty 2013; Karlawish 2011; Gauthier et al. 2013). 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 (Mattsson, Brax, and Zetterberg 2010). 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 (Viloria Jiménez et al. 2013; Prvulovic and Hampel 2011).

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 (Antoine and Pasquier 2013; Cornett and Hall 2008). 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 (Antoine and Pasquier 2013). However, the option to fully disclose the diagnosis to others without allowing the patient to express their own opinion and preferences can result in the feeling of being held in ignorance and in a loss of trust in their relatives and in the clinician (Antoine and Pasquier 2013; Cornett and Hall 2008). Although the diagnosis is often seen as potentially harmful knowledge, a "conspiracy of silence," as Viloria Jiménez et al. put it, should also be avoided (Viloria Jiménez et al., 2013; Mattsson, Brax, and Zetterberg 2010; Karlawish 2011).

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 attention by genetic testing for Huntington disease (Wilson 2005; Bortolotti and Widdows 2011). 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 (Dierickx 1998). (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 (Dierickx 1998). 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" (Vandenberghe et al. 2013a, 506). 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 (van Hout et al. 2000). This is in contrast with the findings reported in empirical studies (van Hout et al. 2000; Turner et al. 2004; Cahill et al. 2008), 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 fully 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 (van Hout et al. 2000; Turner et al. 2004). A second struggle refers to the difficulty in recognizing the symptoms of AD. One GP in the survey conducted by Van Hout et al. (2000) indicated how rarely he noticed what was really going on during the consultation time but only afterwards he realized something was wrong. 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 (van Hout et al. 2000; Cahill et al. 2008). These difficulties were identified for a general AD diagnosis yet are of pressing concern in MCI and pAD. General practitioners might overlook the first symptoms of MCI and misinterpret these symptoms as signs of a burn-out or stress (Cahill et al. 2008). Literature describes how it can take up to two years between the first consultation and the disclosure of the diagnosis (Cahill et al. 2008). This can be problematic as in many cases the GP is the first clinician to be contacted by the patient or even the only clinician involved in making the diagnosis (van Hout et al. 2000).

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 healthcare systems (Witte et al. 2015). 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 and 100 per cent (Vandenberghe, Adamczuk, and Van Laere 2013b). However, the time course of decline is currently hard to predict at the individual level based on amyloid biomarkers alone (Vandenberghe, Adamczuk, and Van Laere 2013b). A negative amyloid PET does not exclude progression to dementia due to a non-AD cause (Vandenberghe et al. 2013a). 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 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 (Johnson et al. 2015). 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.

Conclusion

This review presented several ethical issues about the disclosure process of an early biomarker-based diagnosis. The following issues 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. 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 upholds and about the limited predictive value of these biomarkers. 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, are necessary in order to get insight into the opinions and experiences from stakeholders such as patients, family members, caregivers, and clinicians.

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