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ORIGINAL RESEARCH

Should Doctors Offer Biomarker Testing to Those Afraid to Develop Alzheimer's Dementia?

Applying the Method of Reflective Equilibrium for a Clinical Dilemma

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Abstract An increasing number of people seek medical attention for mild cognitive symptoms at older age, worried that they might develop Alzheimer's disease. Some clinical practice guidelines suggest offering biomarker testing in such cases, using a brain scan or a lumbar puncture, to improve diagnostic certainty about Alzheimer's disease and enable an earlier diagnosis. Critics, on the other hand, point out that there is no effective Alzheimer treatment available and argue that biomarker tests lack clinical validity. The debate on the ethical desirability of biomarker testing is currently polarized; advocates and opponents tend to focus on their own line of arguments. In this paper, we show how the method of reflective equilibrium (RE) can be used to systematically weigh the relevant arguments on *both* sides of the debate to decide whether to offer Alzheimer biomarker testing. In the tradition of RE, we reflect upon these arguments in light of their coherence with other argumentative elements, including relevant facts (e.g. on the clinical validity of the test), ethical principles, and theories on societal ideals or relevant concepts, such as autonomy. Our stance in the debate therefore rests upon previously set out in-depth arguments and reflects a wide societal perspective.

Keywords Bioethics · Alzheimer's disease · Risk testing · Clinical ethics · Biomarkers

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Introduction

Increasingly, people without dementia seek medical attention for concerns about their memory (Gruters et al. 2019). Many of them are afraid that their forgetfulness will worsen into Alzheimer's disease (AD) dementia—currently listed as the most feared disease after cancer (Alzheimer Europe and Harvard School of Public Health 2011). The number of "memory clinics" has grown exponentially over the last twenty years to accommodate for this increasing demand for medical advice (Le Couteur et al. 2013).

A diagnosis of AD used to be preserved for those who have a severity of cognitive worsening that interferes with the ability to perform daily activities, i.e. dementia (McKhann et al. 1984). According to some recent clinical guideline proposals, however, AD can now also be diagnosed earlier, in people who have mild cognitive impairment, by using biomarker tests (Johnson et al. 2013; Shaw et al. 2018; Guerra et al. 2015). These biomarker tests involve a brain scan or a lumbar puncture that aim to measure protein levels in the brain that are alleged precursors for AD dementia (Dubois et al. 2007). Clinicians have also reported using biomarker tests in people who do not have dementia for

the purpose of ruling out or confirming AD (Somers et al. 2016; de Wilde et al. 2019). The use of Alzheimer biomarker testing in people without dementia is defended and encouraged by an appeal to the importance of offering an earlier and more specific diagnosis of AD, improving disease management, and enabling people to decide themselves whether they want to undergo biomarker testing, out of respect for their autonomy (Frisoni et al. 2017; Rodriguez-Gomez et al. 2019).

These arguments are undermined, however, by the fact that Alzheimer biomarkers provide only limited certainty about *if* or *when* someone will develop AD dementia (Martinez et al. 2017b, a; Richard et al. 2013). An individual's risk to develop dementia depends on many factors, including for instance the presence of cerebrovascular disease. If Mrs. Smith would undergo Alzheimer biomarker testing and her results turn out positive, there is a possibility that she may never develop dementia. Vice versa, despite negative results, she may still develop dementia. Moreover, there are no proven effective prevention or treatment strategies to offer to those without dementia who have positive biomarker results. The American Academy of Neurology, for instance, does therefore not recommend biomarker testing (Petersen et al. 2018).

Discussions of the desirability of AD biomarker testing in people without dementia in the biomedical and bioethical literature are usually held in general terms; authors tend to offer either arguments in favour of or against biomarker testing. However, AD biomarker testing is likely neither *always* nor *never* a good idea. Rather, the weighing of arguments depends on the specific context in which biomarker testing is considered (Smedinga et al. 2018). The benefit of having increased planning possibilities, for instance, may be different for an 85-year-old than for a 51-year-old. Also, the question whether to offer an amyloid PET scan is only relevant in specialized clinical settings within high-income countries in which these scans are available.

In between conflicting recommendations for biomarker testing in clinical practice, a push from research for wider clinical use and critique on its potential adverse societal consequences, there remain situations like those of Mrs. Smith (see Table 1) that still need moral examination: Should she be offered biomarker testing for AD?

In this paper, we answer this question by weighing all the main arguments in favour of and against biomarker testing within its specific clinical context. We do so using the method of reflective equilibrium (RE), which is known as the preferred method of medical-ethical inquiry (Arras et al. 2017), even though it is rarely explicitly applied (with a few exceptions [Ismaili M'hamdi and de Beaufort 2018; Van Thiel and Van Delden 2016]). By answering an urgent moral question within clinical practice using the method of RE, we aim to demonstrate its added value in answering concrete (clinical) moral questions.

The hypothetical clinical scenario described in this paper is set within the Netherlands. Here, biomarker tests are employed in some (specialized) memory clinics, even though the national guideline recommends not to apply them in routine medical care (Gruters et al. 2019).

A similar case study has been examined from an ethical perspective once before, in a more concise manner, when the scenario of a patient asking for a biomarker test was mostly hypothetical (Baum 2016). In the meantime, however, it has become a reality for many medical experts working in memory clinics, fed by media attention for Alzheimer biomarkers and new evidence on their prognostic value. Moreover, the structuring the arguments through the method of RE may serve as a basis for the moral examination of cases similar to that of Mrs. Smith.

Table 1 Example case of a moral question in hypothetical clinical scenario

Mrs. Smith, a 75-year-old retired English teacher, is visiting a neurology practice. She is worried about her memory; worried that she will develop Alzheimer's disease (AD). For a few weeks, she has been forgetting appointments and losing things around the house. Next to her sits her daughter, confirming that her mother has lately seemed more disordered.

At the general practitioner's, Mrs. Smith did a memory test. The memory test results confirmed that her memory is worse than average for her age, which made her even more anxious. She has always been afraid to await the same future as her father, who had AD.

In the newspaper, Mrs. Smith read that AD can now be detected many years before symptoms appear by testing so called "Alzheimer biomarkers" via a lumbar puncture or an amyloid positron emission tomography (PET) brain scan. The biomarker measures are believed to reflect the biological process that eventually causes Alzheimer's dementia and starts years before symptoms begin. Mrs. Smith knows that there is no treatment available. Still, if she has AD or is going to develop it, she wants to know. She would be able to stop worrying and prepare for the future. She visits the neurologist today, because she wishes to have an "Alzheimer biomarker test."

Should the neurologist offer an Alzheimer biomarker test to Mrs. Smith?

The Method of Reflective Equilibrium

John Rawls coined the term RE for his method to answer his moral inquiry into the meaning of justice (Rawls 1971). There are many different theoretical interpretations of the method of RE, but it has sparsely been applied to concrete moral inquiries (other examples include: Ismaili M'hamdi and de Beaufort 2018; Van Thiel and Van Delden 2016). Here, we use RE as a method for moral reasoning that includes considered moral judgements, ethical principles, facts, and background theories on moral concepts or societal ideals. It involves systematically categorizing these argumentative elements as such, reflecting upon their credibility, and adapting them in light of their mutual coherence. The credibility of each of the elements increases, the more they are mutually supportive and coherent with other elements in the RE.

When applying the method of RE, we first categorize the arguments that play a role in the current debate on the desirability of Alzheimer biomarker testing as being "considered moral judgements" (CMJ) (see Table 2). The arguments are "moral judgements" in the sense that they describe a reason to prescribe or prohibit an action—i.e. offering Mrs. Smith an Alzheimer biomarker test. We selected the most relevant arguments by reviewing the biomedical and bioethical literature on the desirability of biomarker testing (reported elsewhere (Smedinga et al. 2018) and by interviewing clinicians on their views (Tromp et al. 2021) (Table 2).

Next, CMJs are linked to four basic principles of medical ethics: beneficence, non-maleficence, respect for autonomy, and justice (see Table 2) (Beauchamp and Childress 2001). Depending on the moral inquiry, other relevant ethical principles can be added, such as the principle of subsidiarity, according to which benefits must be achieved through the least invasive methods. Also, depending on the specific sociocultural context in which the inquiry presents itself, these principles may be interpreted and weighed differently. Medical professionals are committed to these basic ethical principles within their professional role (Ismaili M'hamdi and de Beaufort 2018), and since our moral inquiry is set from the clinician's professional perspective, we adopt these principles by default. In this step, it becomes explicit why the incorporated CMJ's matter *morally*. Potential healthcare benefits resulting from biomarker testing matter *morally*, for example, because of a consensus within our healthcare system (if not wider society) that health professionals should promote people's health and well-being. This consensus is represented in the ethical principle of beneficence (Beauchamp and Childress 2001).

Linking CMJs to ethical principles also reveals which arguments are in fact not really justified by ethical

Table 2 Considered moral judgments, ethical principles, relevant facts, and background theories which are brought "in RE"

Considered Moral Judgements (CMJ)	Background Theories (BT)	Ethical Principles* (P)	Relevant Facts (RF)
CMJ1: People have a right to receive a specific or early diagnosis CMJ2: Biomarker testing should be offered because it enables anticipation of one's future health CMJ3: Alzheimer biomarker testing will lead to health benefits	BT1: Concepts of health and disease BT2: Respect for autonomy BT3: Justice and healthcare priorities	P1: Respect for autonomy P2: Beneficence P3: Non-maleficence P4: Justice P5: Subsidiarity	RF1: Cognitively healthy people who receive positive Alzheimer biomarker results adjust their life planning RF2: Alzheimer biomarker and memory test results together can correctly predict the development of dementia within three years in around 64 per cent of the cases RF3: There is no effective treatment for Alzheimer's Disease for people without dementia RF4: People who received negative biomarker results may feel relieved RF5: The prognostic value of AD biomarkers is highly dependent on age, especially in people older than 75 years, because many other factors related to ageing could cause dementia

principles (Arras, Childress, and Adams 2017). In case a CMJ is incoherent with an ethical principle, it may be reconsidered, or, vice versa, if ethical principles lead to undesirable practical outcomes, they may be revised. Contrary to a more deductive or inductive approach, all argumentative elements used within a RE are provisional; they are considered to be valuable or true until their incoherence with other (more convincing) argumentative elements forms a strong reason to judge otherwise. An equilibrium where CMJs and ethical principles are mutually supportive is called a narrow RE (Rawls 1975).

Third, as a separate category of argumentative elements, relevant facts are included to evaluate the extent to which the CMJs, linked to ethical principles, are supported by evidence. Results from research on health benefits of biomarker testing would, for example, be categorized as "relevant facts."

Fourth, to lower the risk of circularity between moral intuitions and ethical principles, relevant background theories on morally relevant concepts, such as disease or autonomy, or societal ideals can be added to the RE (see Table 2) (Daniels 1979). This step widens the equilibrium (wide RE) and avoids ending up with a set of mutually coherent CMJs and ethical principles that are incoherent with other generally upheld views, for instance, on the desired role of medicine in our society or on the meaning of autonomy.

Involving the four basic principles of medical ethics in a narrow RE, like ours, may create discussion or doubt about the right interpretation of either of these principles. If so, in this fourth step, the RE should be widened by involving corresponding background theories. When adopting a specific interpretation of an ethical principle based on particular background theory, this interpretation should also be defensible in other clinical scenarios, to safeguard external coherence.

To minimize bias, one should make an effort to find opposing elements to include in a RE rather than gather evidence to support one's initial view. This can be done, for example, by including (qualitative) empirical research that gathers various (conflicting) CMJs on the topic of interest to avoid potential blind spots (De Vries and Van Leeuwen 2010). Similar to the falsification principle in science, testing the RE against opposing views will strengthen its justificatory power (Daniels 1979).

The moral justification of the RE derives from the internal coherence between the elements. After going

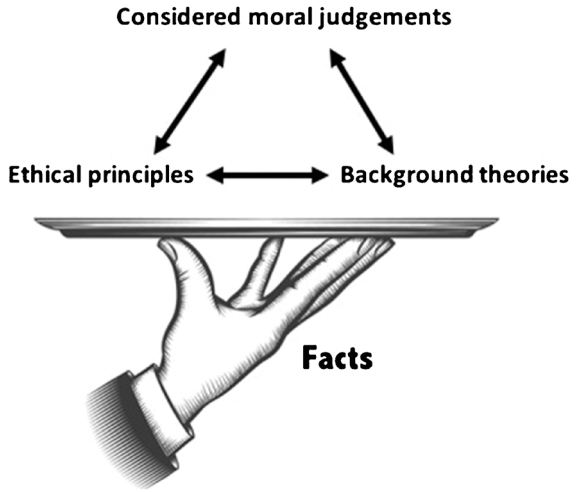

Fig. 1 The process of RE

"back and forth" between any incoherencies, one reaches the most comprehensive set of coherent and mutually supportive arguments. In this stage, the arguments are said to be "in RE" (illustrated in Figure 1). The term RE thus refers both to a method for moral reasoning and to its end-point. In practice, this end-point serves as an ideal. The "equilibrium" is provisional and should always be receptive for new relevant facts, arguments, or ethical principles, and be changed accordingly (Arras et al. 2017).

The Method of Reflective Equilibrium Applied

First Round: Considered Moral Judgements, Relevant Facts, and Ethical Principles

In the first round of applying the method of RE, we are formulating a narrow RE for our moral question.

CMJ1: People Have a Right to Receive a Specific or Early Diagnosis

One of the most prominent arguments in favour of testing biomarkers in the literature states that biomarker testing can increase *diagnostic certainty* about AD and that people have a right to receive a specific or early diagnosis (CMJ1) (Smedinga et al. 2018; de Wilde et al. 2019). According to recently introduced research criteria for AD, the disease is defined by the presence of biomarkers, not symptoms (Jack et al. 2018).

Following this definition, biomarkers would thus indeed, by definition, improve diagnostic certainty.

Knowing the (exact) cause of one's cognitive decline may enable patients to give meaning to their symptoms and support coping (Vanderschaeghe et al. 2017). For this reason, CMJ1 can be linked to the ethical principle of beneficence.

CMJ2: Biomarker Testing Should be Offered because it Enables Anticipation of One's Future Health

The value of prognostic information on AD is knowing what one's future may be like and having the possibility to anticipate what lies ahead (Van der Laan 2016). Enabling and supporting individual choice in making life plans is coherent with the ethical principle of respect for autonomy (P1). Research shows that the majority of cognitively healthy individuals who received positive AD biomarker results, and were told to have an uncertain but increased risk for AD dementia, indeed adjusted their life plans or considered this (Largent et al. 2020). They decided, for example, to go travelling or to downsize or sell their property (RF1).

To check whether the coherence of CMJ2 with P1 is supported by evidence, we would ideally incorporate clear-cut facts on the prognostic value of biomarker tests for Mrs. Smith; their capacity to predict *if* she will develop dementia and *when*. However, long-term studies including 75-year-old research participants have yet to establish this information. In its absence, experts have interpreted existing studies (that lack generalizability) very differently.

For the sake of the argument, we incorporate the strongest evidence available on the numeric prognostic value of AD biomarkers. First, the prognostic value is highly dependent on age, especially in people older than 75 years, because, as said, many other factors related to ageing could cause dementia (RF5) (Richard et al. 2013; Martinez et al. 2017). Depending on the study cohort, around 5-15 per cent of 75-year-olds who have concerns about their memory and score relatively low on a memory test, like Mrs. Smith, will develop dementia per year (Heister et al. 2011) and 15 per cent will revert to normal cognitive functioning (Koepsell and Monsell 2012). Overall, 55 per cent will test positive on AD biomarkers (Jansen et al. 2015). Biomarker and memory test results together can correctly predict the development of dementia within three years in around 64 per cent of the cases (RF2) (Richard et al. 2013). However, biomarkers were found to have no *added* prognostic value for dementia prediction over a short memory test (Richard et al. 2013). The latter is less invasive and cheaper and therefore preferable in light of the ethical principle of subsidiarity (P5). The negative predictive value of biomarkers is slightly better but also worsens with increasing age (van Maurik et al. 2019).[1] Genetic testing for ApoE-ε4, which indicates an increased risk for AD dementia, is rarely applied in clinical practice in the Netherlands.

The dementia risk information conveyed by biomarkers is thus highly uncertain, especially for people who are older than 75 years. Several reviews from the Cochrane review board, an institute that provides the highest level of evidence through comprehensive meta-analyses, concluded that the prognostic value of biomarkers is in general too poor to be used in clinical practice (Martinez et al. 2017b, a; Martinez et al. 2017), as did the American Academy of Neurology (Petersen et al. 2018). The Alzheimer's Association, among others, take a slightly more positive stance towards the prognostic value of biomarkers. Their endorsement of clinical use is however primarily based on its advantages other than prognostic value (Shaw et al. 2018; Johnson et al. 2013).

Individuals may differ in the normative value they attach to risk information. People may start to live in anticipation of future dementia after receiving positive biomarker results and, as said, have even reported to (consider) selling their house (Largent et al. 2020). Basing such far-reaching decisions on such highly uncertain predictions would, in our view, be awfully risky and unwise. Negative consequences as a result of misinterpretations of dementia risk status are incoherent with the ethical principle of non-maleficence (P3).

CMJ3: Alzheimer Biomarker Testing Will Lead to Health Benefits

The impact of amyloid PET scanning on "patient management" of mild cognitive impairment has been a central argument in favour of its clinical use (CMJ3) (Barthel and Sabri 2017). Amyloid PET scan results were found to motivate clinicians to initiate AD treatment or to offer enrolment in clinical trials (de Wilde et al. 2019; Zwan et al. 2017; Rabinovici et al. 2019). If this impact would benefit a patient's health, the argument (CMJ3) would be coherent with the ethical

[1] Notably, there is a small difference in pre- and post-test probability because dementia is a relatively common disease

principle of beneficence (P2). However, there is no effective AD treatment for people who have no or only mild cognitive impairment (RF3); none of the numerous clinical trials over the last twenty years have resulted in an approved AD treatment (Anderson et al. 2017). The currently approved AD medication that stems from before that time, is only effective in people who have dementia. This suggests that the health benefit of treatment or trial participation will presumably be limited or absent. Hence, AD biomarkers will not allow for changes in disease management that will benefit Mrs. Smith's health.

They might, however, alleviate the burden of being worried about developing AD dementia, which can be considered a health benefit and therefore in line with the ethical principle of beneficence (P2). People with subjective cognitive complaints who received negative biomarker test results felt relieved and started to interpret their memory complaints as a result of normal ageing (RF4) (Largent et al. 2020; Vanderschaeghe et al. 2017). Given the poor prognostic value of AD biomarkers for people with Mrs. Smith's characteristics, however, there is a substantial risk that such feelings of relief may be based on false beliefs.[2] Moreover, negative biomarker test results have also shown to bring up new concerns and questions, about whether the results were correct or about the cause—if not AD—of one's memory complaints (Vanderschaeghe et al. 2017). Potential negative consequences of false reassurance are incoherent with the ethical principle of non-maleficence (P3). On the other hand, there is no evidence that disclosing positive biomarker results causes severe psychological reactions (de Wilde et al. 2018).

A Narrow Reflective Equilibrium

Based on the first round of considering CMJs in light of ethical principles and relevant facts, we can conclude that the alleged advantage of offering a specific diagnosis through biomarker testing (CMJ1) and, therewith, increased planning possibilities (CMJ2) would be coherent with the ethical principle of beneficence (P2), if it was not for the fact that biomarkers have a poor prognostic value in cases like Mrs. Smith's. In the second round, we nuance this narrow equilibrium.

Second Round of Moral Reasoning: Background Theories and Societal Ideals

BT1: Concepts of Health and Disease

The argument that biomarker testing will improve "diagnostic certainty" in the case of suspected AD (CMJ1) only applies when following the *biological* definition of AD which defines the disease by the presence of biomarkers. This definition was introduced for research purposes focused on understanding the pathophysiological process underlying Alzheimer's dementia (Jack et al. 2018), which is characterized by a long asymptomatic stage. The argument is illogical if one were to adhere to a traditional, *clinical* definition of AD as a form of dementia (McKhann et al. 1984). The latter is generally (still) upheld in clinical practice and in the general media (Smedinga et al. 2021).

In order to safeguard CMJ1 within the RE, the biological definition of AD would need to be adopted within clinical practice. This would however involve a substantial expansion of the number of people "having" AD, from those who have dementia to those who have positive biomarker results but only mild or no clinical symptoms. As pointed out earlier, around 55 per cent of the people of Mrs. Smith's age with mild cognitive impairment will have positive AD biomarkers and would therefore qualify for a biological definition of AD while not meeting its clinical diagnostic criteria.

For Mrs. Smith, receiving an AD diagnosis based on biomarkers cannot end any uncertainties about her future health. Still, she may start to see herself as "sick" and be treated as such by others; the diagnosis may change her social relationships and her societal role (Alzheimer Europe 2017). As previously argued by Schermer and Richard, receiving a "diagnosis of AD" based on biomarker results may therefore do more harm than good, especially for those who will never develop dementia (Schermer and Richard 2019).

Accordingly, out of medical-philosophical considerations and in line with societal ideals that eschew overdiagnosis, the clinical definition of AD should continue to be favoured over the biological definition in clinical practice. Mrs. Smith should not receive an AD diagnosis

[2] One could argue that feelings of relief or a confirmation of worries would be simply misplaced in response to receiving a (uncertain) *risk* status. In the context of clinical practice, however, making a prognosis and assumptions about future health based on risk information would be the exact purpose of testing these biomarkers and is therefore hard to avoid.

based on biomarker results. If she would be offered biomarker testing, the results should be framed as prognostic, not diagnostic information.

BT2: Respect for Autonomy

The ethical principle of respect for autonomy denotes the importance of fostering an individual's ability to make life-choices according to personal values (P1). Threats to this decision-making process, such as misguidance, an overload of information or triggers of irrational fears, should be avoided. The ethical principle involves a right to refuse medical care but not a right to claim it (Beauchamp and Childress 2001). Despite the lack of treatment options, knowing that one is soon going to develop a severe disease like AD dementia may be valuable information that may foster one's autonomy when planning retirement, for example, or a visit to a loved one abroad. However, as previously argued by Bunnik et al., when biomarker results lack clinical validity, they cannot offer any valuable insights that could foster her life-choices (Bunnik et al. 2018). Respecting the autonomy of Mrs. Smith would therefore not entail (simply) meeting her wish to undergo biomarker testing.

Mrs. Smith explains her wish to receive biomarker testing as a means to end her uncertainties about her future health, so that she can make plans for the future or stop worrying. When taking these wishes and hence her autonomy seriously, the neurologist should explain why biomarker tests are unfit for this purpose and consider alternative ways to achieve them. For example, by starting a conversation about her worries. Is she concerned that she will not receive the right (medical) support once she develops dementia? Planning routine check-up appointments with her general practitioner, or setting up advanced directives, may help to provide relief (Miller et al. 2019).

BT3: Justice and Healthcare Priorities

In coherence with the ethical principle of justice (P4), according to which like cases should be treated alike (Beauchamp and Childress 2001), Mrs. Smith should not be treated differently from others in clinically similar scenarios. This means that if AD biomarker testing would be offered to Mrs. Smith, it should also be offered to the increasing number of other individuals without dementia who seek medical help for their memory concerns (Gruters et al. 2019; Le Couteur et al. 2013). This would require a substantial financial shift of (already scarce) healthcare resources (Wimo 2018). The costs of an amyloid PET scan, for example, starts from around USD$3000 (Alzheimer Association 2020). In current circumstances, in which diagnostic or prognostic value of biomarker tests is lacking, there is no ground for such investment, when a short memory test is an equally reliable and less costly alternative.

Coming to a Decision for Mrs. Smith

We evaluated the main arguments in favour of and against biomarker testing to facilitate early diagnosis of AD in people with memory complaints, like Mrs. Smith, using the method of RE. We conclude that the neurologist should refrain from offering biomarker testing for either diagnostic or prognostic purposes.

The advantages of biomarker testing in this clinical scenario are limited. First, if one adheres to a clinical definition of AD—which is desirable as it helps to avoid the negative consequences of overdiagnosis—biomarker tests cannot offer (more) "diagnostic certainty." That is, a biomarker test will not be able to answer to Mrs. Smith's desire to know if and when she will develop dementia. Second, there is no AD treatment available for Mrs. Smith, and so biomarker testing will not benefit her health. Third, a biomarker-based AD prognosis is currently poorly reliable. If one were to disagree with this *normative* judgement about the *numeric* prognostic value, it would still be desirable to use a short memory test instead, which provides equally prognostic information, is less invasive against lower costs. Mrs. Smith may find relief after receiving negative test results. The goal of alleviating her worries to develop AD dementia and supporting her wish to prepare for the future might also be achieved through other, subsidiary alternatives. The burden of undergoing biomarker testing and the potential harmful consequences of misinterpreting the complex meaning of its outcome may seem small. Given the high number of people who are concerned about their memory at older age, however, on a population-scale they may become substantial—as may the financial costs.

The conclusion that the neurologist should refrain from offering biomarker testing to Mrs. Smith only applies to her hypothetical clinical scenario because, as

said, the desirability of AD biomarker testing depends on specific clinical context in which testing is considered.

Shifting the Equilibrium

The equilibrium may shift with changes in circumstances because, as said, the weight on the different arguments depends on the clinical context. If Mrs. Smith would have been 58 years of age, for example, and had depression and a family history of AD, her biomarker test results would most likely have had a better negative predictive value for AD dementia. This would become relevant in this case, because her cognitive impairment might be due to another disease causing dementia, or burn-out or depression. Negative biomarker results would then make it more likely that her memory impairment is related to her depression, suggesting that it may improve when her depression clears.

The contextual factors that influence the desirability of biomarker testing in a clinical scenario go far beyond the individual patient. In the future, biomarker testing may become more desirable if the test becomes cheaper or more reliable, for example, or if effective treatments become available. Today, the question whether biomarker testing is desirable is, for a start, only relevant to (high-income) healthcare systems in which PET scans are available. Within those systems, the desirability will then again depend on the (financial) organization of the healthcare system, among other things, such as whether the test is to be paid out of public or private means, or on the sociocultural norms that are upheld in the dynamic between patients and clinicians when the decision about testing is made. Thus, technical, organizational, and sociocultural features of healthcare systems will influence which dilemmas clinicians will face, when, and where.

In this analysis, relatively much weight is put on the diagnostic and prognostic value of AD biomarker testing. The lack of an effective clinical treatment on itself may, by some, be considered enough reason to refrain from biomarker testing. Nevertheless, in current clinical practice, biological testing for untreatable diseases is sometimes considered acceptable or even required based on its prognostic or diagnostic value. Huntington's disease, for example, is an untreatable autosomal dominant genetic disorder. A genetic test for Huntington's disease is however offered in clinical practice. In an asymptomatic stage, the results may be considered relevant to provide valuable information, for instance for reproductive decisions. In early symptomatic stages, positive results can explain symptoms and sets an outline for a probable disease course. As discussed in this paper, it is questionable whether AD biomarkers can provide either, on top of the lack of a treatment option.

Applying the Method of RE in Practice

The method of RE as set out in the paper can, in our view, be useful to clinicians and others for two purposes. First, it might be applied by clinicians or others who face recurring clinical dilemmas in their medical clinic to improve practice. Since it requires going through the effort of making explicit the arguments that drive their clinical decision-making and systematically analysing and weighing these in light of relevant facts and ethical principles, it is not fit for day-to-day clinical practice. Applying the method to recurring clinical dilemmas, however, might provide insight into potential information gaps, inconsistencies, or the cause of disagreements with patients or colleagues. It may also provide a more profound justification for one's decisions. Second, the method of RE might also have an added value for those involved in policy-making, such as members of clinical guideline committees or those working for health insurance or health authorities, having to decide for which patient groups a certain diagnostic test or treatment would be appropriate. Applying the method of RE may help gaining support for such decisions by leaving room for CMJs of those involved in the particular practice—similar to the way in which clinicians' views are incorporated in the argument above.

Conclusion

The conclusion that our hypothetical neurologist should not offer biomarker testing to Mrs. Smith contradicts an increasing number of guidelines for the use of biomarker tests in clinical practice issued by, among others, the Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association and ongoing efforts to endorse them (Johnson et al. 2013, Frisoni et al. 2017). There are several explanations for this difference. First,

the guidelines and the (research) strategies that endorse offering Alzheimer biomarker testing to people without dementia who have cognitive impairment are principally grounded on its added value of improving "diagnostic certainty." As discussed, this argument only holds within a conceptual paradigm that is currently dominant in AD research, which defines the disease in purely biological terms. The clinical use of this (new) definition of AD, however, is undesirable, as argued elsewhere (Schermer and Richard 2019). Researchers might not be aware of these conflicting definitions and their ethical implications. Second, these guidelines and research papers focus on arguments in favour of biomarker testing but generally leave aside arguments against its use. The advantage of applying the method of RE is that it forces us to include arguments both in favour and against, next to relevant facts and ethical principles to come to a well-considered assessment. Third, as illustrated above, some of the arguments are not based on an in-depth understanding of the principles they claim to pursue, such as respect for autonomy, which have been examined in previous work (Bunnik et al. 2018). Such gaps are revealed by applying the method of RE. Fourth, there might be motivations to pursue AD biomarker testing, such as commercial interests of industrial enterprises, that have not been made explicit or taken into account here as the dilemma is approached from the clinician's professional perspective, in which commercial interests (should) have no place.

The RE can always be refined with new information. For example, if a preventive treatment for AD would become available, the equilibrium may shift in favour of using biomarker tests. This should be seen as a strength, not a weakness, of RE. Another advantage of applying the method of RE is that, through its systematization, those who disagree with the conclusion can point out particular aspects within the argumentation that they question and those that they agree with. The debate on the desirability of AD biomarker testing in clinical practice is currently polarized and conducted in general terms. Instead, a systematic weighing of the given arguments for a specific context by use of the RE, as illustrated here, can be a constructive manner to nuance and advance the debate.

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Declarations

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