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PERSPECTIVE

Facing the new diagnostic and treatment options of Alzheimer's disease: The necessity of informed consent

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Abstract

With advances in biomarker-based detection of Alzheimer's disease (AD) and new treatment options with disease-modifying treatments (DMTs), we are heading toward a new conceptualization of diagnostics and therapy in the early stages of AD. Yet consensus guidelines on best clinical practices in predictive AD diagnostics are still developing. Currently, there is a knowledge gap regarding counseling and disclosure practices in early symptomatic disease stages, its implications for dementia risk estimation, and DMTs with associated risks and benefits. The crucial feature is the capacity of patients with (mild) cognitive impairment, eligible for DMTs, to consent. This perspective aims to (1) discuss the current challenges in assessing capacity to consent and (2) highlight the importance of a supported (informed) decision-making process. Measures to facilitate informed decision-making of patients constitute an ethical approach to enhancing the quality of care in this evolving therapeutic landscape.

KEYWORDS
anti-amyloid therapy, biomarkers, capacity to consent, communication, dementia risk estimation, early diagnosis, informed consent, supported decision-making

Highlights

This perspective:

- Explores biomarker-based early symptomatic AD detection and the implications for patient care.
- Emphasizes supported decision-making in DMTs for MCI and dementia patients.
- Discusses the need for standardized tools to assess the capacity to consent.
- Aligns diagnostic and treatment approaches with ethical care standards.
- Enhances patient autonomy in the evolving AD therapeutic landscape.

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1 | INTRODUCTION

Advances in the early detection of Alzheimer's disease (AD) and new therapeutic pathways have resulted in an increased awareness of the timely diagnosis of AD in the population while at the same time putting expert institutions, such as memory clinics, in increasing higher demand. Thus, a paradigm shift is emerging in the healthcare system and society, where soon easily accessible predictive measures, such as blood-based biomarker testing, and individualized therapy will be a realistic scenario.[1,2] Weighing up the costs and benefits, for a long time AD biomarker testing was (partially) considered to offer no additional clinical utility.[3] Moreover, it has been argued that AD detection in early symptomatic stages, such as the stage of mild cognitive impairment (MCI), may lead to psychological distress and stigmatization in patients and result in an economic burden for the healthcare system due to uncertainty about reimbursement for biomarker testing. Meanwhile, empirical evidence supports the psychological safety of AD diagnosis in early symptomatic disease stages and improvements in clinical management in people with MCI.[4–6] In the scientific and medical discourse the concept of "timely diagnosis" has emerged.[7] This term refers to a time of diagnosis that allows for the best treatment options and quality of care for patients. It also implies that a diagnosis should be made when patients will derive the most benefit from effective therapy, in terms of improving symptoms or delaying disease progression. With cognitive decline, decision-making abilities may be increasingly reduced over time, which underscores the particular importance of supported decision-making (SDM) for patients with marginal decision-making capacities.[8] A timely diagnosis may therefore extend the time frame in which patients may make their own informed decisions regarding future life planning (eg, advance care planning). Eventually, the right time to learn one's biomarker status and whether or not to start treatment with disease-modifying treatments (DMTs) is a very personal decision up to each patient,[9] and clinicians should be supportive along the personal decision-making path.

1.1 | The diagnostic shift in early AD

With the advent of approved DMTs, a fundamental turn has emerged in the medical field.[2] As of now, AD biomarker assessment in clinical practice needs to be conducted to identify people at early symptomatic stages of AD eligible for DMT, such as people with MCI or early-stage dementia. In the case of MCI in particular, patients, relatives, and physicians are additionally confronted with the question of dementia risk stratification and prediction of the course of the disease. People with MCI have objective cognitive impairment, while activities of daily living can still be maintained.[10] The MCI stage is associated with an increased risk of progressing to dementia; however, not all people with MCI will ultimately develop dementia.[11,12] The prognosis of MCI patients depends on the underlying etiology, as MCI itself is a heterogeneous condition and only about 50% of MCI patients have neuropathological correlates of AD.[13] While biomarker-based prognostic models predict a 5-year dementia risk of 10% in MCI with a normal AD biomarker profile, the 5-year dementia risk increases to >90% in MCI patients with a full AD profile (amyloid and tau pathology).[14,15] Therefore, a timely and accurate diagnosis of MCI may help patients and their relatives to make important arrangements for the future, start preventive measures, such as lifestyle modifications, and, if eligible, decide in favor of or against DMTs. It will also help physicians select patients that most likely benefit from DMTs. In the near future, prognostic models may assist clinicians in predicting the individual progression of cognitive decline. Currently, risk prediction can only be estimated at the group level; therefore, in the case of exclusively biomarker-based risk prediction, the specificity for individual prediction is limited, as further important clinical data, such as age and gender, are not included in the prognosis calculation. For example, the relationship between age, cognitive decline, and amyloid pathology is not linear but reaches saturation in old age.[16] However, timely disease detection may also empower healthcare professionals to improve diagnostics toward precision medicine, eventually leading to a more individualized treatment pathway.

From an ethical and societal perspective, arguments in favor of or against AD biomarker testing in predementia stages were analyzed by Smedinga et al. within an ethical framework, based on the four principles of medical ethics (non-maleficence, beneficence, respect for autonomy, and justice).[3] With regard to non-maleficence, arguments against AD biomarker diagnosis may comprise the risk of self- and external stigmatization, discrimination, overdiagnosis, psychological harm, and the burden of the testing itself.[3] However, the literature also indicates that the impact of AD biomarker disclosure on individuals with MCI may not necessarily be negative. Vanderschaeghe et al. reported that individuals appreciated having more information about their brain health status and experiences of positive social support, as having the chance to develop a new personal and social role ascription.[17] Relating to beneficence, AD biomarker testing in people with cognitive impairment may increase diagnostic certainty and improve personal and social future planning, such as better health status and well-being. However, the benefits of AD biomarker testing in people without cognitive impairment may be limited, as the certainty of developing dementia at all is not given in these cases. The principle of respect for autonomy stresses the importance of an individual's right to know or not to know the personal AD biomarker status, and the risk of developing dementia. With regard to justice, the arguments of high costs and limited availability of AD biomarker testing should be considered, especially in the light of scarce healthcare resources. The availability of DMTs in early symptomatic AD stages will significantly impact healthcare costs, as prudent diagnostics are a requirement for decision-making regarding treatment and safe monitoring during ongoing therapy. This is where the challenge of health equity moves to the fore, as it is essential to ensure that diagnostic and treatment options are accessible to a broad population.[18] To conclude, predictive medicine implies better possibilities of diagnosis and personalized therapy; however, it also has a direct impact on the individual, the social environment, and the healthcare system.

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1.2 | Challenges in counseling practices

Given the complexity of risk prediction, accurate communication about the diagnosis, prognosis, diagnostic opportunities, and, finally, the therapeutic measures and risks, is essential to enable patients to make informed decisions.[19] Difficult decisions have to be made by healthcare workers, for example, whether, which, and how many biomarkers assessments should be used, which patients to test, and determining the right time for diagnosis and therapy along the patient journey. Also, the expected gain of information for change of clinical management, from an economic point of view, must be considered.[5,20] Furthermore, understanding health-related risk information is known to be challenging for physicians and patients alike.[21–23]

As an example of how to improve best clinical practices, the Dutch research project Alzheimer's Biomarkers in Daily Practice (ABIDE) developed a biomarker-based prediction model and a guidance to support clinicians, patients, and care partners in the context of early symptomatic AD biomarker detection. The aim is to facilitate the counseling and disclosure practices of AD biomarker test results and support clinicians to engage patients in the decision-making process.[24] Meanwhile, the effects of AD biomarker test results disclosure on patients in asymptomatic and symptomatic predementia stages and their care partners continue to move into scientific focus.[4,25–31] Data from asymptomatic individuals with pathological amyloid positron emission tomography (PET) results showed that approximately two-thirds of them understood their biomarker results correctly, while psychological safety and health behavior changes aimed at improving brain health were noted.[27,28] Data on amyloid PET results disclosure on people with MCI and mild dementia revealed mixed emotional findings and no major psychological risks in connection with psychometric evaluation on short-term outcomes.[25,32] Results from a randomized controlled trial of amyloid PET results disclosure in MCI confirmed no risks. Assessing for depressive and anxiety disorders, but higher levels of distress after disclosure among amyloid-positive tested dyads.[4] Similar results were found in a study on disclosing apolipoprotein E (APOE) genotypes and communicating AD risk to individuals with MCI and their study partners.[33] Despite these scientific efforts, practical consensus guidelines for counseling and disclosure of biomarker test results remain poorly developed, and structured national and international recommendations for the early diagnostic work-up of cognitive impairment are under development.[19,34–37] Even with algorithms and risk prediction models emerging to assist physicians during this process, the actual communication of the individual dementia risk and the uncertain prognosis of the patient remain a challenge.[14,38] This leads to equivocal recommendations and increases uncertainty for everyone involved.

With the advent of DMTs in clinical practice, even more uncertainties arise as to how to counsel, how to engage patients and their care partners to promote informed consent, and, finally, how to determine the clinical meaningfulness of the therapy from the point of view of patients and society.[39] When discussing the impact of potential side effects, transparent and clear information and communication are essential, and the risk of side effects under treatment must be weighed against the potential benefits, such as delaying disease progression for a certain amount of time. Important dose-dependent side effects of DMTs are amyloid-related imaging abnormalities (ARIAs). While ARIA-E (edema) is described by magnetic resonance imaging (MRI) as evidence of vasogenic edema, which involves brain swelling, ARIA-H (hemorrhage) is defined by MRI evidence of hemosiderin deposits, which involves brain bleeds. Clinically, ARIAs are mostly asymptomatic or mildly symptomatic and reversible.[39] The risk of radiographic and symptomatic ARIAs is higher among individuals with an APOE ε4 genotype, especially among homozygous gene carriers, compared to non-carriers.[40] Although ARIAs can be serious, in the majority of cases they can be managed effectively, so these side effects need to be weighed against the prognosis of a progredient neurodegenerative disease.[39,40] The risk for ARIAs is highest in the early treatment phases, so the potential benefit might be higher in the course of treatment duration. Taken together, potential risk factors for ARIAs, such as APOE ε4 gene carrier status, must be taken into account when counseling patients and care partners. Therefore, the current appropriate use recommendations for lecanemab suggest APOE genotyping before treatment starts as this will help in carrying out a personalized risk-benefit evaluation and determine the appropriateness of treatment in collaboration with patients and care partners. This, conversely, adds more complexity to the counseling process, as patients and care partners need to effectively weigh probabilistic risk information in already challenging decisions. Also, APOE genotyping has implications not only for patients but for all first-degree relatives, who may also be affected by the predisposition gene, such as adult children. This in turn might have implications for people in young to midlife stages and so, for example, with insurance decisions (eg, long-term care and disability insurance).[41] Treatment decision processes regarding DMTs require further elaboration of practice guidelines, highlighting the necessity of training for clinicians, patient education, and the development of patient decision aids. Therefore, patients and care partners should be empowered to navigate through the vast amount of information to enable them to make competent decisions in line with their health preferences. Ideally, the information on precautionary measures and a safety plan during treatment should be embedded in a shared informed decision process, defined by a collaborative process through which clinicians support patients (and care partners) in deciding about their health status.

1.3 | Capacity to consent in people with MCI and dementia

Assessing capacity to consent is an essential part of health care, ensuring that patients understand and appreciate the implications of medical decisions. Capacity to consent involves key decision-making skills: understanding relevant information, appreciating personal consequences, reasoning about treatment options, and expressing choices. In people with MCI, these abilities are often already significantly impaired. A meta-analysis shows that people with MCI have distinct

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deficits in their ability to understand due to impaired episodic memory and executive functions; appreciation is compromised by deficits in working memory, processing speed, and episodic memory; and reasoning is constrained by limitations in working memory and executive functions.[42] Moreover, people with mild to moderate dementia have additional impairments in making treatment decisions, particularly those with moderate disease symptoms who are often unaware of their symptoms, prognosis, or diagnosis.[43]

A patient-centered approach to counseling should include information on the disease itself, the diagnostic opportunities, and the different symptomatic and DMTs strategies. A more paternalistic approach that withholds DMTs would deny patients the possibility of potential benefits or, conversely, impose a therapy that is not in line with patient wishes. Given the potential side effects, initiation of therapy can only be justified if patients make an informed and autonomous decision to do so. This is crucial since findings show that people with dementia tend to have an impaired capacity to consent when making high-risk decisions.[44] However, the capacity to consent within the target population for biomarker-based AD detection and DMTs, which includes people with MCI and early dementia, is often uncertain. A self-determined, informed, and freely made decision may therefore not always be possible. Thus, it has been shown that the prevalence of incapacity to consent in people with MCI is around 20% and increases to 54% in people with dementia, which is significantly higher than in the general population (0.3%).[45] In light of this, measures to enable individuals with cognitive impairment to actively and meaningfully participate in their treatment decisions are crucial. This aligns with the principles outlined in the United Nations Convention on the Rights of Persons with Disabilities (CRPD), which emphasizes the right to individual autonomy of Persons with Disabilities (Article 3). Persons with Disabilities are defined as having "long-term physical, mental, intellectual or sensory impairments which in interaction with various barriers may hinder their full and effective participation in society on an equal basis with others," which includes cognitive impairment (Article 1). According to Article 12, paragraph 3, states must take appropriate measures to provide the support – both formal and informal – needed to exercise their legal capacity. Against this background, various guidelines advocate for adequate information and involvement of people with MCI and dementia in decision-making processes.[46–48] For a detailed discussion of the tools and methods used to assess these capabilities, including the challenges and ethical dilemmas associated with such assessments, see Section 1.4 on Capacity assessment.

The capacity to consent serves as the gatekeeper for the right to autonomous decision-making regarding medical treatment. Acting as a gateway to autonomy rights, SDM can be employed for individuals "at the margins of autonomy."[49] SDM is a model of decision-making in which adults with marginal capacity receive support in making their own informed decisions.[50,51] The model of SDM emphasizes the avoidance of unnecessary deprivation of personal autonomy.[49] SDM is legally anchored differently internationally and varies in its concrete implementation (for more information on the US understanding and implementation of SDM and the special challenges it faces there, see Peterson et al.[49]; for an ethical discussion of SDM as derived from the UN-CRPD, see Scholten and Gather[52]).

A common thread among different international implementations is that SDM involves supporting individuals at the boundaries of decision-making capacity through a trusted individual.[50,51] While in some countries and states, "trusted individuals" (supporters) explicitly include persons other than guardians and in addition to physicians (eg, variation in SDM legislation in US states in Ref. 53), in other countries, the mandate to provide support for enabling autonomous decision-making does not end with the establishment of guardianship, so trusted persons who support decision-making may – besides informal supporters and physicians – be guardians. In such interpretations, guardians avoid representation as much as possible and instead empower persons under their guardianship to make decisions for themselves whenever feasible. Here, the dynamics at the margins of capacity to consent are understood more broadly, and it is explicitly the guardian's responsibility to empower the already assisted person to make self-determined decisions.[54] In what follows, we refer to SDM as the use of decision aids by (formal or informal) trusted persons to facilitate the decision-making process of persons at the margins of capacity to consent while avoiding undue influence.

With the diagnostic shift in early AD and patients facing complex health-related decisions, including new therapeutic agents, measures for supporting patients' decisions to meet the aforementioned guidelines are gaining more importance. Studies have indicated that people with mild to moderate dementia can make independent decisions with appropriate decision support.[55–57] These findings highlight the potential of SDM interventions to improve the capacity to consent of people with dementia. As such, the German consensus-based guidelines for informed consent in people with dementia strongly endorse the use of written and visual aids for decision support.[51] However, due to small sample sizes and the use of combined supporting interventions without a separate evaluation for each method, the empirical evidence for the effectiveness for SDM remains too small.[37] Furthermore, this lack of evidence is not confined to Germany but is also recognized internationally. For instance, while the NICE guidelines in the UK recommend SDM, they do not provide evidence for its effect on capacity to consent.[58] In the USA, the National Resource Center for Supported Decision-Making recognizes the urgent need for empirical evidence to understand the impact of SDM on autonomy.[59] This emphasizes the necessity for further research with larger sample sizes.

1.4 | Capacity assessment

Clinicians often face significant challenges in assessing the capacity to consent of people with dementia,[60] with research indicating only about 56% agreement in borderline cases.[61] In addition, clinicians tend to overestimate patients' capacity to consent in their clinical judgments.[62] Conversely, tools such as the MacArthur Competence Assessment Tool-Treatment (MacCAT-T) tend to underestimate the capacity to consent.[63,64] This dynamic reflects a significant ethical dilemma: overestimation of capacity to consent may lead to neglecting

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duties of clinical care, while underestimation violates the individual's right of self-determination.[54,65] The MacCAT-T evaluates a patient's competence to consent by assessing understanding, reasoning, appreciation, and the ability to communicate a choice. It measures the ability to understand medical conditions and treatments, weigh up treatment options, and recognize how information applies to the patient personally using a semi-structured interview format. Despite the thoroughness of the MacCAT-T, its average administration time of more than 20 min[66] makes it inappropriate for routine clinical use. A survey of psychiatrists reported that only 4% use the MacCAT-T in clinical practice.[67] Awareness and application of the widely accepted four abilities[68] – understanding, appreciation, reasoning, and expressing a choice – can improve the accuracy of the assessment of capacity to consent.[69,70] Evidence suggests that the accuracy of outcomes is improved when practitioners are aware of these criteria[71,72] or when they use standardized instruments that are integrated in accordance with the guidelines of the American Bar Association/American Psychological Association. The latter underscore that these standardized instruments are supplemental to, but not a substitute for, clinical judgment, thereby increasing the reliability of the assessment while still preserving the value of clinician expertise.[73]

When assessing capacity to consent, screening tools are essential for identifying individuals with MCI or early dementia who are at risk of not being able to consent, while simplifying the assessment process for those who are found to be able to consent. The University of San Diego Brief Assessment of Capacity to Consent (UBACC)[74] has been validated in the context of research consent for this population, specifically in relation to the MacArthur Competence Assessment Tool-Clinical Research (MacCAT-CR). However, this underlines the lack of a similarly validated tool for treatment decision-making. In contrast, the Bedside Capacity Assessment Tool (BCAT),[75] which is used in clinical settings, has not been validated against an established standard such as the MacCAT-T but has been compared informally with clinical judgment. This gap highlights the need for the development and validation of a brief tool specifically designed to assess the capacity to consent in a clinical context.

In response to the complexities of capacity assessment in dementia care, we integrate the model proposed by Scholten and Haberstroh,[54] which optimizes the decision-making process and support provided to patients (Figure 1). The process begins by establishing an appropriate ambiance and room design specifically tailored to people with cognitive impairment. A comprehensive evaluation then identifies the areas of capacity to consent that are impaired. Based on these findings, targeted SDM strategies are implemented. The effectiveness of these interventions is continually monitored, and if they prove inadequate, there is a directive to revise and refine the support strategies. The workflow culminates in a determination of whether the capacity to consent has been effectively established, allowing for self-determined treatment decisions. If capacity is not established, the model calls for the involvement of surrogate decision makers. This approach delivers guidance for clinical practitioners and highlights the importance of an adaptive, iterative process in enhancing patient autonomy and ensuring that individuals with cognitive impairment are actively involved in their care decisions.

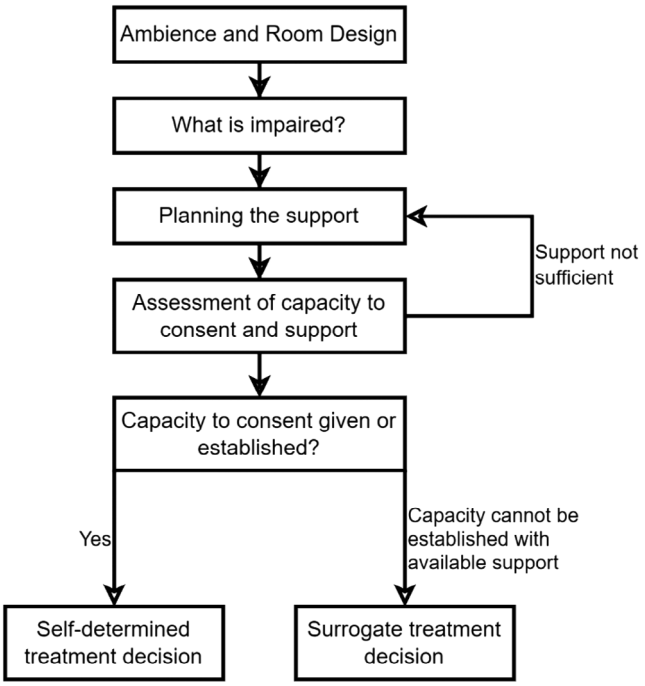


FIGURE 1 Model for enhanced SDM for individuals with cognitive impairment (adopted from Scholten and Haberstroh[54]). SDM, supported decision-making.

1.5 | Conclusion: A patient-centered approach to informed consent

Given the complex risk-benefit profile of DMTs, it is critical that patients take the lead in their treatment decisions, guided by their healthcare professionals. This patient-centered paradigm requires a robust SDM framework that ensures that patients, even in the early stages of cognitive decline, receive tailored support and comprehensive information to effectively navigate their diagnostic and treatment options. Such an approach should integrate specific materials and tools designed to clarify the complexities surrounding DMTs and empower patients to make informed choices that align with their values and preferences. Facilitating this level of engagement and autonomy not only upholds the principles of informed consent but also promotes a model of care that is transparent, respectful, and ethically grounded. This concerted effort will strengthen patient autonomy, improve the soundness of decision-making, and contribute to a healthcare environment that prioritizes ethical transparency and patient well-being.

Scholten et al.[76] have proposed a combined approach that integrates SDM with the assessment of capacity to consent, which seems particularly appropriate in this context. This method could provide a more holistic framework that allows for a comprehensive assessment of a patient's capacity to consent. By providing tailored support and ensuring that information is delivered in an accessible manner,

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clinicians can empower people with cognitive impairment to actively participate in their own care decisions.[57] To adhere to the combined approach proposed by Scholten et al.,[76] it is necessary to conduct thorough research to develop an economical assessment tool for evaluating capacity to consent in people with MCI and early dementia, potential eligibility for DMTs, and improve decision support tools. Such an assessment tool may allow a rapid yet comprehensive assessment that is suitable for clinical settings. The development and validation of evidence-based SDM tools specifically designed for the context of diagnosis and treatment of early AD is of crucial importance. Finally, advances in diagnostics and therapy must go hand in hand with advances in research and the application of assessment of capacity to consent, such as SDM tools, to facilitate autonomous decision-making by patients and ensure safety in clinical practice for healthcare professionals.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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