Received: 7 April 2023 | Revised: 1 June 2023 | Accepted: 6 July 2023

DOI: 10.1002/alz.13410

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

REVIEW ARTICLE

Impact of sharing Alzheimer's disease biomarkers with individuals without dementia: A systematic review and meta-analysis of empirical data

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Funding information
ZonMW, Grant/Award Number: #73305095007; Health~Holland, Topsector Life Sciences & Health, Grant/Award Number: #LSHM20106; YOD-MOLECULAR, Grant/Award Number: #KICH1.GZ02.20.004

Abstract

Introduction: We conducted a systematic literature review and meta-analysis of empirical evidence on expected and experienced implications of sharing Alzheimer's disease (AD) biomarker results with individuals without dementia.

Methods: PubMed, Embase, APA PsycInfo, and Web of Science Core Collection were searched according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Results from included studies were synthesized, and quantitative data on psychosocial impact were meta-analyzed using a random-effects model.

Results: We included 35 publications. Most personal stakeholders expressed interest in biomarker assessment. Learning negative biomarker results led to relief and sometimes frustration, while positive biomarkers induced anxiety but also clarity. Meta-analysis of five studies including 2012 participants (elevated amyloid = 1324 [66%], asymptomatic = 1855 [92%]) showed short-term psychological impact was not significant (random-effect estimate = 0.10, standard error = 0.23, $P = 0.65$). Most professional stakeholders valued biomarker testing, although attitudes and practices varied considerably.

Discussion: Interest in AD biomarker testing was high and sharing their results did not cause psychological harm.

KEYWORDS
Alzheimer's disease, amyloid, biomarkers, diagnosis, disclosure, ethics, preclinical, prodromal, risk, tau

Highlights

- Most personal stakeholders expressed interest in Alzheimer's disease biomarker assessment.
- Personal motivations included gaining insight, improving lifestyle, or preparing for the future.
- There was no short-term psychological impact of sharing biomarker status, implying it can be safe.
- Most professional stakeholders valued biomarker testing, believing the benefits outweigh the risk.
- Harmonized guidelines on biomarker testing and sharing results are required.

1 | BACKGROUND

The pathophysiological hallmarks of Alzheimer's disease (AD) start accumulating 20 to 30 years before the onset of cognitive decline.[1–3] Decades of fundamental research and technological innovations have enabled in vivo detection of these protein changes in cerebrospinal fluid (CSF) and using positron emission tomography (PET) scans. This has led to a shift toward a biological definition of AD, by characterizing individuals based on the presence of AD-associated pathology. The "ATN" (amyloid/tau/neurodegeneration) research framework denotes AD as the combination of abnormal amyloid and abnormal tau, meaning persons with this profile have the disease, even if they don't fulfill criteria for dementia (yet).[4] While the construct was introduced for research purposes, the approval of disease-modifying therapies,[5,6] increase of prognostic accuracy,[7–9] and advancements in blood-based biomarkers[10–13] suggest biomarker testing may move into clinical practice to improve diagnostic accuracy, and therapeutic decision making.[14]

At the same time, this has fueled a heated and ongoing debate in the field. When patients without substantial cognitive deficits visit a memory clinic, is it ethically acceptable to conduct AD biomarker assessments and communicate the outcome? Learning whether amyloid or tau pathology is present in the brain may offer a chance to improve one's health, prepare for the future, and optimize quality of life.[15–17] Yet, being aware of living on the AD continuum may also involve risks of emotional burden, stigma, and discrimination.[18–20] As such, clinicians have a duty to do no harm, but also to provide good care, whereas individuals have a right to (not) know their test results.[21–23] Previous reviews indicate that disclosing amyloid PET results does not pose immediate psychological harm to asymptomatic research participants, but little is known about social and behavioral implications and the impact in cognitively impaired populations.[24,25]

To address these issues, we recently conducted a systematic review of theoretical data, and identified 26 diverse and contradictory considerations related to a clinical, personal, and societal context.[26] A next step is to examine how these, and perhaps other, aspects are perceived by stakeholders, including the general public, patients, families, and health-care professionals. In this study, we therefore aimed to provide an overview of empirical data on expected and experienced implications of sharing AD biomarker results with individuals who do not have dementia (yet).

2 | METHODS

A systematic literature search was conducted (by J.C.F.K. and J.v.d.S.) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement guidelines.[27] Our query combined synonyms and spelling variations on the terms "Alzheimer's" AND "disclos*" OR "diagnos*" AND "predementia" AND "biomarkers," using controlled standardized keywords as well as free text terms (Material S1 in supporting information). We searched PubMed, Embase, APA PsycInfo, and Web of Science Core Collection from inception up to November 10, 2021. Additional records were identified through other sources, for example, reference lists.

To be included, publications had to present empirical data (quantitative or qualitative) on expected or experienced implications of disclosing amyloid and/or tau results to cognitively normal (CN) individuals or those with subjective cognitive decline (SCD) or mild cognitive impairment (MCI; corresponding to clinical stages 1–3 in the ATN

framework).[28] Data could be collected from any perspective, including patients, family members, clinicians, and so forth. The scope was limited to scientific articles written in English for which the full text was available (no editorials, commentaries, conference proceedings or [sections of] books). Studies on later stages and other types of dementia or neurodegenerative diseases were not included, as well as those primarily focused on trial design or genetic risk.

Two authors (J.v.d.S. and W.M.v.d.F.) independently screened all titles and abstracts. Articles marked as potentially relevant were assessed for eligibility based on full text. In case of discrepancy, arguments for inclusion and exclusion were discussed while re-examining the contents and criteria. In all cases consensus was reached.

Included articles were grouped according to design (qualitative, quantitative), study population, and timing (i.e., expectations before or experiences after disclosure). Content was analyzed inductively, by identifying and categorizing main findings. We summarized the results narratively by the most common themes emerging from the data.

Studies reporting sufficient quantitative data on the psychological impact of biomarker disclosure were included in a meta-analysis. From these we extracted pre- and post-disclosure measurements and calculated standardized mean differences in test scores of anxiety, depression, stress, or suicidality. A random-effects model was used to synthesize effect sizes. In case of multiple follow-up assessments within a single study, we selected the measurement closest to 3 months after disclosure, as this was the most common follow-up time across publications. Two corresponding authors of studies included in the meta-analysis were contacted for additional information, and both responded. Risk of bias was assessed by two authors (J.v.d.S. and C.G.) independently using the Risk Of Bias In Non-randomised Studies—of Interventions (ROBINS-I) tool (Material S2 in supporting information).[29]

RESEARCH IN CONTEXT

1. **Systematic Review**: We searched PubMed, Embase, APA PsycInfo, and Web of Science Core Collection for articles on disclosing Alzheimer's disease (AD) biomarker results to individuals without dementia. As a biological definition of AD is increasingly used in research, and a small but growing body of evidence has emerged, we conducted a systematic review of the broad implications of early biomarker testing.
2. **Interpretation**: Personal stakeholders' high interest in biomarker assessment was motivated by gaining insight, reducing dementia risk, or preparing for the future. Those testing positive reported changing their lifestyle and plans, yet some worried about stigmatization. Most understood the meaning of biomarker results. The majority did not regret being informed. Attitudes among professional stakeholders were positive, but practices varied.
3. Future Directions: There is a need of developing guidelines and recommendations for how to incorporate biomarker testing and sharing results in diagnostic work-up, particularly considering the imminent advancements in disease-modifying treatment.

3 | RESULTS

The flow diagram in Figure 1 shows that our database search, complemented with additional records identified through other sources, and after removing duplicates, yielded 8046 records. Two reviewers independently screened all titles and abstracts, by consensus excluding 7853 for not addressing the topic of interest. Subsequently, 193 full-text records were examined for eligibility. After applying selection criteria, we included 35 articles.

Of these, 19 presented quantitative data,[30–48] 1 mixed methods research,[49] and 15 qualitative data.[50–64] As the designs varied considerably, we classified them in three categories, according to population and timing. Twenty-seven articles reported on perspectives of personal stakeholders, that is, members of the general public, research participants, study partners, patients, caregivers, or relatives.[32–34,36–38,40,41,44,46–57,59–64] Thirteen of these assessed expectations before (hypothetical) testing (Table 1),[33,34,36,40,44,46,50,51,56,57,60–62] and 14 addressed actual experiences after disclosure of results in a research setting (Table 2).[32,37,38,41,47–49,52–55,59,63,64] The remaining eight represented attitudes and practices of health-care professionals, including general practitioners, neurologists, and dementia specialists (Table 3).[30,31,35,39,42,43,45,58]

3.1 | Personal stakeholders' perspective: expectations

Thirteen publications featured results from studies on personal stakeholders' expectations regarding (hypothetical) biomarker testing, before receiving the results (see Table 1).[33,34,36,40,44,46,50,51,56,57,60–62] Authors reported on (hypothetical) interest, comprehension, and implications regarding various types of biomarker testing in individuals without dementia. Six articles described quantitative[33,34,36,40,44,46] and seven qualitative data.[50,51,56,57,60–62]

3.1.1 | Interest

All but one study gauged personal stakeholders' wish to (not) learn biomarker levels.[33,34,36,40,44,50,51,56,57,60–62] A randomized controlled survey among 219 CN research participants, who had undergone blinded biomarker assessments, found that 95% wanted to learn their results.[36] When posed as a hypothetical scenario, 72% to 75% CN

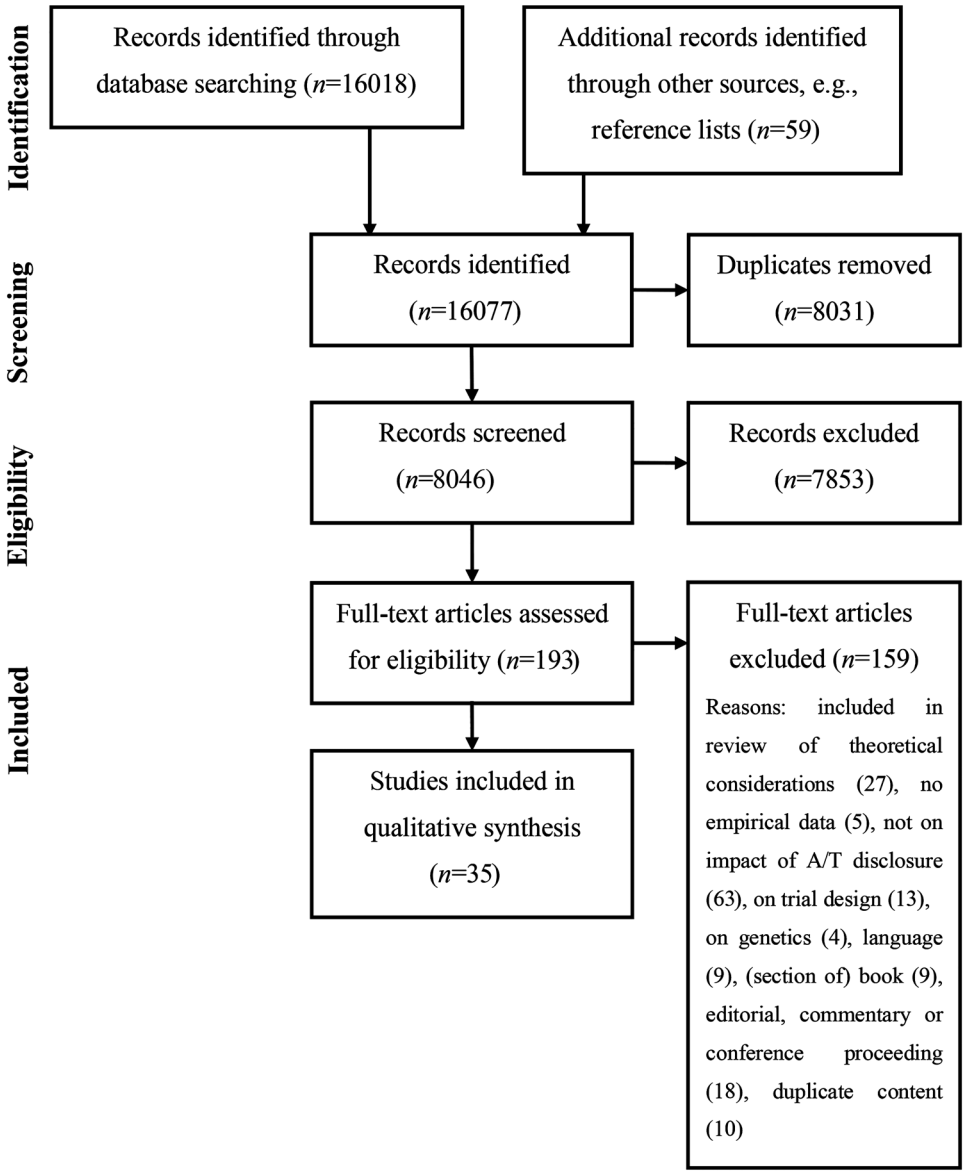

FIGURE 1 Flow diagram of study selection.

research participants expected they would want to take a test,[34,44] versus 80% to 81% of (mostly) CN at-risk individuals involved with an AD prevention registry.[33,40] Similarly, most or all research participants with MCI in two semi-structured interview studies opted to receive their predetermined amyloid status.[60,62] Three studies in (mostly) CN populations found that a family history and/or high perceived susceptibility predisposed for a higher desire for testing,[33,36,40] yet in one, a survey among 164 at-risk participants, having an affected parent was inversely related[40] and according to a fourth study among 874 community-dwelling older adults self-rated risk was irrelevant.[44] "Extreme interest" was lower in a survey among members of the general population (55.1% vs. 12.5%).[36] Likewise, qualitative studies found the majority of individuals were open to predictive testing.[50,51,56,57,60,61]

3.1.2 | Comprehension

Seven studies reported on personal stakeholders' knowledge and comprehension of biomarker tests and results.[33,36,40,56,57,60,62] In a randomized controlled survey among 219 CN research participants interest decreased after an educational intervention on benefits and limitations, except in participants with high subjective risk, family history, and low attendance to research meetings.[36] Another study among 164 (mostly) CN at-risk participants found desire to learn test results was not associated with factual knowledge about amyloid brain imaging.[40] In a survey among 4036 visitors of a prevention website 33% of respondents did not recognize that elevated biomarkers (CSF and amyloid PET) in a mildly symptomatic person reflected "either increased risk for or presence of AD."[33] Qualitative studies

TABLE 1 Publications on personal stakeholders' expectations before (hypothetically) learning biomarker results.

Quantitative						
Authors (year)	**Design (determinants)**	**Population (cohort)**	**Scenario**	**Outcome measures**	**Results**	**Conclusion**
Stites et al. (2022)[46]	Randomized controlled survey with vignettes of no/mild/moderate symptoms, 'positive'/'negative' biomarkers, and with/without disease-modifying treatment	1817 members of general public (national panel, US)	Appraising a hypothetical person with preclinical biomarker diagnosis	Stigma (FS-ADS)	Vignettes with asymptomatic persons evoked weaker reactions of stigma than those with mild/moderate dementia (all $P < 0.001$). Positive biomarker results yielded harsher judgments on all but one stigma domains, compared to negative outcomes (all $P < 0.001$). Availability of a disease-modifying treatment had no significant effect ($P > 0.05$).	Dementia stigma spills over into preclinical AD, regardless of treatment.
Gooblar et al. (2015)[36]	Randomized controlled survey (educational intervention: $n = 119$, placebo presentation: $n = 100$; predictors of interest); survey with vignette	219 CN research participants; 1418 members of general public (KADRC; TAPS, US)	Learning actual biomarker (CSF and amyloid PET), genetic (*APOE*) and cognitive test results	Interest, implications	95% of research participants wanted to learn their actual research results. An education intervention lowered this (81%), except in those with high subjective risk, family history, and low research involvement. "Extreme interest" was lower in members of the general public (55% vs. 13%), yet strongest in those likely to participate in research and with family history (44%).	Interest is increased by AD experience and somewhat tempered by education.
Caselli et al. (2014)[33]	Survey	4036 CN visitors of AD prevention website (APR, US)	Taking a hypothetical preclinical biomarker and genetic test	Interest, knowledge, implications	80% would want biomarker testing. Interest was related to male sex, education level, and family history. 33% did not recognize that results reflect risk or presence of AD. If at high risk, 91% would pursue a healthier lifestyle, 77% would obtain long-term care insurance, and 19% would spend all their money for pleasure, but 10% would also seriously consider suicide.	Interested individuals should be educated and psychologically screened.
Caselli et al. (2015)[34]	Survey (predictors of high risk for suicidal ideation)	287 CN research participants (Arizona APOE cohort, US)	Taking a hypothetical preclinical biomarker and genetic test	Interest, suicidal ideation	72% would want biomarker testing. If diagnosed with preclinical AD, 6% thought they would consider suicide. These participants were more likely to feel unsupported but did not differ in cognitive or depression scores. Both interest and endorsement of suicidal ideation were substantially lower in this research cohort than in previously reported website cohort (see publication number 3)[33]	Suicidal ideation is not associated with depression, or cognitive decline.

(Continues)

TABLE 1 (Continued)

Quantitative						
Authors (year)	**Design (determinants)**	**Population (cohort)**	**Scenario**	**Outcome measures**	**Results**	**Conclusion**
Sheffrin et al. (2016)[44]	Survey (predictors of interest in and completion of advance directives)	874 CN research participants (HRS, US)	Taking a hypothetical free and definite predictive test	Interest, completion of advance directives	75% of respondents would want predictive testing. Those willing had similar race and education levels but were more likely to be ≤75 years old and less likely to have completed an advance directive. Interest did not differ by subjective risk or perceived memory. If certain to develop AD, 87% would discuss health plans with loved ones and 81% would complete an advance directive.	Older adults are very interested to engage in advance care planning.
Ott et al. (2016)[40]	Survey	164 participants of AD registry, CN or with MCI (RIPR, US)	Taking a hypothetical biomarker (amyloid PET) and genetic (*APOE*) test	Interest, knowledge, implications	81% would want amyloid testing. Interest was related to perceived risk and inversely related to having an affected parent, but not to knowledge. > 70% answered at least four out of six amyloid PET questions correctly. Motivations included arranging personal affairs (74%), participating in research (73%), preparing family (60%), and ending their life once symptomatic (12%).	Individuals are very interested in amyloid testing to assist in making life plans.
Qualitative						
Authors (year)	**Design**	**Population (cohort)**	**Scenario**	**Themes**	**Results**	**Conclusion**
Milne et al. (2018)[57]	Focus groups	48 CN research participants (PREVENT, UK; BBRC/ALFA, Spain)	Taking a hypothetical biomarker (amyloid PET) and genetic (*APOE*) test	Interest, implications	Most were interested in testing. Willingness and comprehension were shaped by certainty, actionability, and family history. Participants would take action to reduce risk, improve quality of life, and manage the future, but also expected anxiety, (un)welcome vigilance from themselves and others, and loss of social status. The altered time perspective would also change priorities.	Living with risk is likely to be a complex, long-term, and social phenomenon.
Milne et al. (2018)[56]	Focus groups	48 CN research participants (PREVENT, UK; BBRC/ALFA, Spain), 6 dementia patients and 4 caregivers (EWGPWD, Europe)	Taking a hypothetical preclinical biomarker test	Interest, implications	Participants were interested in testing, motivated by personal utility. Given family history and perception of high risk, they did not expect additional psychological harm, but some mentioned suicide to avoid suffering. Long-term effects included hypervigilance of their own cognition and being second-guessed by others, which was both perceived as valuable and worrying.	Interest depends on personal utility and more on long- than short-term effects.

(Continues)

TABLE 1 (Continued)

Qualitative						
Authors (year)	**Design**	**Population (cohort)**	**Scenario**	**Themes**	**Results**	**Conclusion**
Vanders-chaeghe et al. (2019)[61]	Focus groups	40 CN stakeholders (10 healthy elderly, 9 informal caregivers, 6 nursing staff, 8 researchers, and 7 clinicians) (stakeholder group, Belgium)	Taking a hypothetical (amyloid PET) biomarker test	Interest, implications	Most would want to know their own results, to have clarity, inform relatives, make arrangements, change lifestyle, and enjoy life more. Arguments con included fear and anxiety, lack of treatment, and risks of tests. Some consequences were classified as both pro and con. They reported a need for information and support, and anticipated patronization and stigmatization.	Individuals are interested, but reasons are diverse, and views differ.
Vanders-chaeghe et al. (2017)[60]	Semi-structured interviews	38 research participants with MCI (BioAdaptAD, Belgium)	Learning actual (amyloid PET) biomarker results	Interest, implications	All participants wished to know their actual research results, to learn what is going on, make future plans, and optimize their health. Half saw no disadvantages, others mentioned emotional impact and fear of regression. Most indicated elevated results would be unpleasant but preferred to know. Terminology of "positive" and "negative" results was sometimes confusing.	Individuals want to know what is going on and to make informed decisions.
Lingler et al. (2022)[62]	Semi-structured interviews	30 research participants with MCI, 19 caregivers (ADRC, US)	Learning actual (amyloid PET) biomarker results	Interest, knowledge, implications	Interest was high: 24 patients wished to know their actual research results, 4 were still undecided, 2 declined. Most demonstrated adequate understanding of biomarker limitations. Most dyads were motivated by gaining insight in the etiology and prognosis of MCI, to plan ahead or for knowledge's sake. Mention of drawbacks, including negative psychological impact, was minimal.	Individuals are focused on benefits and should be educated on limitations.
Alpinar-Sencan et al. (2021)[50]	Focus groups	28 patients with mild neurocognitive disorder, 20 relatives, 40 caregivers (various settings, Germany, Israel)	Taking a hypothetical preclinical biomarker test	Interest, motivation, implica-tions, cultural differences	Participants were evenly split pro or con testing. Moral motivation comprised of personal utility for well-being, prospective responsibility for their families, self-determination to control their future, and personal notions of a good life. German participants tended to be more concerned about test validity, more focused on autonomy and more open about suicide.	Attitudes are related to perceived personal utility of the information.

(Continues)

TABLE 1 (Continued)

Qualitative						
Authors (year)	**Design**	**Population (cohort)**	**Scenario**	**Themes**	**Results**	**Conclusion**
Arias et al. (2015)[51]	Semi-structured interviews	17 family members of patients with MCI/dementia (memory clinics, US)	Taking a hypothetical preclinical biomarker test	Interest, implications	Most participants reported a positive perspective on testing. Potential benefits included making lifestyle changes, seeking treatment, and preparing for cognitive decline. Risks comprised psychological burden, adverse life decisions, and social harms. Consequences were reported to depend on an individual's (unspecified) personality or traits.	Individuals are interested and reported non-clinical benefits and harms.

Abbreviations: AD, Alzheimer's disease; ADRC, Alzheimer's Disease Research Center; ALFA, Alzheimer's and Families; APR, Alzheimer's Prevention Registry; BioAdaptAD, Biomarker-Based Adaptive Development in Alzheimer's Disease; BBRC, BarcelonaBeta Brain Research Centre; CN, cognitively normal; CSF, cerebrospinal fluid; EWGPWD, European Working Group of People with Dementia; FS-ADS, Family Stigma in Alzheimer's Disease Scale; HRS, Health and Retirement Study; KADRC, Knight Alzheimer Disease Research Center; MCI, mild cognitive impairment; PET, positron emission tomography; RIPR, Rhode Island Alzheimer's Prevention Registry; TAPS, The American Panel Survey; US, United States.

provided more insight. According to focus groups with mainly CN research participants, interpretation of biomarker status was shaped by family history.[56,57] In two interview studies, patients with MCI demonstrated adequate understanding,[62] but were sometimes confused by the use of contra-intuitive terminology, mistakenly believing that a "negative" result would be the "unfavorable scenario" and vice versa.[60]

3.1.3 | Implications

All studies inventoried personal stakeholders' expected implications of learning their biomarker status.[33,34,36,40,44,50,51,56,57,60–62]

In quantitative and qualitative studies most frequently anticipated positive implications among all groups included preparing for cognitive decline by arranging medical, financial, legal, and personal affairs;[33,36,40,44,50,51,57,60–62] adopting a healthier lifestyle to reduce risk;[33,36,50,51,56,57,61] obtaining early access to care or medication;[40,50,51,56,57] contributing to research;[36,40,51,62] and revising life plans and priorities to enjoy the time left.[33,40,50,51,56,57,60,61] Studies among patients with MCI of mixed populations also reported gaining insight or clarity.[51,60–62] Those more sceptic doubted the clinical validity, the prognostic certainty, and the medical utility.[40,50,51,56,61] A lack of need or benefit was only reported by studies among (caregivers or family members of) patients with MCI.[50,51,62]

If found to be at high risk of cognitive decline, participants anticipated stress, anxiety, and depression.[40,50,51,56,57,60–62] Qualitative research among patients with MCI and their caregivers or family members also reported worry about consequences for their loved ones.[51,56,60] Several studies examined thoughts about suicide and euthanasia, which individuals mentioned as both benefit and harm.[33,34,36,40,50,56,57,60–62] They found 10% to 12% of individuals involved with a prevention registry reported expected thoughts of ending one's life,[33,40] compared to 6% in AD research participants,[34] and <0.01% among those whose biomarkers had been measured but not communicated.[36] Focus groups with participants from Germany and Israel found cultural variation in openness to discussing assisted dying.[50]

Most CN individuals would share the presence of AD biomarker evidence with their spouse, but only half with their friends,[33] and few anticipated feeling comfortable disclosing their risk to their employer or health insurance company.[36] Informing others was perceived both as a benefit and liability.[56,57,60,61] Although being monitored by physicians and loved ones was appreciated, it was also feared to turn into surveillance or second-guessing, loss of social and professional status, or the freedom to drive a car.[56,57,60,61] Indeed, a vignette-based randomized controlled trial among members of the general population suggested the stigma of dementia spills over into preclinical AD, irrespective of treatment availability.[46]

3.2 | Personal stakeholders' perspective: experiences

Fourteen publications presented results from studies on personal stakeholders' actual experiences after receiving biomarker results (see Table 2).[32,37,38,41,47–49,52–55,59,63,64] Authors reported on motivation, comprehension, and implications regarding amyloid PET biomarker testing in individuals without dementia. All biomarker results were disclosed in a trial setting, to 6419 CN research participants,[32,37,41,54,55,63,64] 53 with SCD,[48,49] 62 with MCI,[38,59] 70 caregivers/family members,[52,53] and 166 in mixed groups.[37,47] Six articles described quantitative studies,[32,37,38,41,47,48] one mixed methods research,[49] and seven qualitative data.[52–55,59,63,64]

TABLE 2 Publications on personal stakeholders' experiences after learning biomarker results.

Quantitative								
Authors (year)	**Design (determinants)**	**Population**	**Determinant**	**Assessment time points**	**Scenario**	**Outcome measures**	**Results**	**Conclusion**
Ryan et al. (2022)[41]	Longitudinal study	4327 CN research participants (A4, US)	Amyloid PET status (elevated: $n = 1280$, not elevated: $n = 3047$)	Baseline and after disclosure	Learning actual (amyloid PET) biomarker results	Motivation (VPAI)	Participants rated altruism and contributing to research as most important motivations. Before disclosure those with elevated amyloid endorsed confirming or assuaging perceived risk more strongly, which disappeared after adjusting for subjective memory concerns. After disclosure all scores increased across both groups.	Participants are mostly motivated by altruism and contributing to research.
Grill et al. (2020)[37]	Longitudinal study	1705 CN research participants (A4, US)	Amyloid PET status (elevated: $n = 1167$, not elevated: $n = 538$)	Before, at, 1–3 days, and mean of 42/57 days after disclosure for elevated/non-elevated groups	Learning actual (amyloid PET) biomarker results	Anxiety (STAI), depression (GDS), suicidality (CSSRS), concern (CAADS), future time perspective (FTPS), and impact of events (IES)	Participants with elevated amyloid were no more likely to experience short-term increases in depression, anxiety, or suicidality. They did have increased concern about AD ($P < 0.001$). Individuals with a negative result experienced a slight increase in future time perspective ($P < 0.001$).	Participants do not experience short-term negative psychological sequelae.
Burns et al. (2017)[32]	Longitudinal study	97 CN research participants (APEX, US)	Amyloid PET status (elevated: $n = 27$, not elevated: $n = 70$)	Before, at, 6 weeks, and 6 months after disclosure	Learning actual (amyloid PET) biomarker results	Anxiety (BAI), depression (CES-D), test-related distress (IGT-AD)	Depression was stable over time and did not differ between groups. A small increase in anxiety at disclosure ($P = 0.03$) was not sustained over time. Distress was slightly higher in the elevated group at 6 weeks ($P < 0.001$) and 6 months ($P < 0.015$), which was predicted by baseline anxiety and depression.	Disclosure to CN participants appears to be safe and well tolerated.

(Continues)

TABLE 2 (Continued)

Quantitative								
Authors (year)	**Design (determinants)**	**Population**	**Determinant**	**Assessment time points**	**Scenario**	**Outcome measures**	**Results**	**Conclusion**
Wake et al. (2020)[48]	Longitudinal study	42 research participants with SCD (memory clinic, Japan)	Amyloid PET status (elevated: $n = 10$, non-elevated: $n = 32$)	Pre, 6, 24, and 52 weeks post-disclosure	Learning actual (amyloid PET) biomarker results	Anxiety (STAI), depression (BDI-II), impact of events (IES-R)	Anxiety, depression, and distress were well within cut-off scores and did not change over time within or between the groups, except at 52 weeks distress was higher in participants with non-elevated amyloid ($P = 0.04$). This was correlated with baseline anxiety in individuals with normal ($P = 0.02$), but not with abnormal results.	Disclosure to SCD individuals does not cause psychological risk.
Lim et al. (2016)[49]	Mixed methods: longitudinal study; semi-structured interviews	11 research participants with SCD (memory clinics, trials matching service, US)	Amyloid PET status (elevated: $n = 4$, not elevated: $n = 7$), psychoed-ucational intervention (yes: $n = 6$, no: $n = 6$)	Baseline and 9 or 18 months after disclosure	Learning actual (amyloid PET) biomarker results	Anxiety, depression, stress (DASS), depression (GDS), impact of events (IES-R), memory complaints (MAC-Q)	Disclosure did not affect mood, subjective memory impairment, or perceived risk of AD, nor caused distress, regardless of status. Those with normal results felt relief, those with elevated amyloid were not surprised, given their family history, and more likely to make lifestyle changes. Education did not alter perceived risk.	Disclosure to SCD individuals appears to be safe and tolerable.
Mattos et al. (2019)[38]	Longitudinal study	24 patients with MCI (ADRC, US)	Amyloid PET status (elevated: $n = 12$, not elevated: $n = 12$)	12 daily contacts over 2 weeks after disclosure	Learning actual (amyloid PET) biomarker results	Anxiety and depression (PHQ-2), mood and suicidal ideation (EMA)	No significant effects of amyloid status, time, or interaction were found. Patients with an elevated result had more variability in anxiety from day to day ($P = 0.047$), and a trend of more variability in depression ($P = 0.056$) compared to peers with a normal scan outcome.	Ecological momentary assessment is effective for adverse event monitoring.

(Continues)

TABLE 2 (Continued)

Quantitative								
Authors (year)	**Design (determinants)**	**Population**	**Determinant**	**Assessment time points**	**Scenario**	**Outcome measures**	**Results**	**Conclusion**
Taswell et al. (2018)[47]	Longitudinal study	99 patients with MCI and 34 with AD (memory clinics, Australia)	Amyloid PET status (elevated: $n = 104$, not elevated: $n = 29$), age (< 70: $n = 58$, > 70: $n = 75$), diagnosis (MCI: $n = 99$, AD: $n = 34$)	Median of 35 before and 57 days after scan	Learning actual (amyloid PET) biomarker results	Anxiety (STAI, HADS-A), depression (HADS-D, CES-D, GDS)	Patients reported no change in anxiety or depression before versus after disclosure, overall or in the subgroups. Those with non-elevated outcomes experienced a slight increase in STAI ($P = 0.040$) and GDS ($P = 0.050$) based on the Gosset *t* test, but not Wilcoxon's, so the authors considered this a Type I error.	Disclosure to patients with MCI/AD causes no short-term psychological harm.
Qualitative								
Authors (year)	**Design**	**Population**	**Amyloid PET status**	**Assessment time points**	**Scenario**	**Themes**	**Results**	**Conclusion**
Largent et al. (2019)[63]	Semi-structured interviews	80 CN research participants (A4/LEARN, US)	Elevated: $n = 50$, not elevated: $n = 30$	4–12 weeks and 12 months after disclosure	Learning actual (amyloid PET) biomarker results	Implications	Two thirds of participants reported not thinking of physician-assisted death, several were ambivalent, and 1 in 5 stated pursuing this upon deterioration. Proportions were roughly equivalent in those with negative results, when asked to consider being positive.	Learning results does not change attitudes toward physician-assisted death.
Largent et al. (2020)[54]	Semi-structured interviews	80 CN research participants (SOKRATES [A4/LEARN], US)	Elevated: $n = 50$, not elevated: $n = 30$	4–12 weeks and 12 months after disclosure	Learning actual (amyloid PET) biomarker results	Comprehension, implications	Most participants understood their results. Those with elevated amyloid viewed the test as serious, given its implications for sense of self and stigma. They reported more changes in health behavior and future plans than those with normal status, who were relieved and reinterpreted their memory concerns.	Participants with elevated amyloid make more changes to health and future plans.

(Continues)

TABLE 2 (Continued)

Qualitative								
Authors (year)	**Design**	**Population**	**Amyloid PET status**	**Assessment time points**	**Scenario**	**Themes**	**Results**	**Conclusion**
Largent et al. (2021)[55]	Semi-structured interviews	80 CN research participants (SOKRATES I [A4/LEARN]/SOKRATES II, US)	Elevated: $n = 50$, not elevated: $n = 30$	4–12 weeks and 12 months after disclosure	Learning actual (amyloid PET) biomarker and (*APOE ε4*) genetic results	Sharing results with others	Participants found it burdensome to decide whom, why, and how to tell others. All with elevated amyloid shared this with at least one person close to them, half with friends, and almost none at work. Reasons pro were receiving emotional and future support. Reasons con were avoiding stigma and discrimination.	Decisions about sharing are complicated by stigma and discrimination.
Largent et al. (2021)[53]	Semi-structured interviews	70 family members of CN research participants (REVEAL-SCAN, US)	Elevated: $n = 27$, not elevated: $n = 43$	1.8–33 months after disclosure	Learning actual (amyloid PET) biomarker results	Motivation, comprehension, implications	Interviewees understood (83%) and valued (75%) the test results. Favorable outcomes evoked happiness and relief; increased risk led to disappointment and sometimes vigilance of memory. While noting a lack of medical utility, a third described changes in health behaviors and future plans.	Family members value information but could take on a pre-caregiver role.
Mozersky et al. 2018[64]	Semi-structured interviews	50 CN research participants (SOKRATES [A4], US)	Elevated: $n = 50$	4–12 weeks and 12 months after disclosure	Learning actual (amyloid PET) biomarker results	Comprehension	62% interpreted their results as increased but uncertain risk of developing AD. Understanding of the probability varied considerably. Some requested more information on the degree of amyloid elevation. 54% expected their results, due to family history or subjective complaints.	Most participants understand the meaning of elevated results.

(Continues)

TABLE 2 (Continued)

Qualitative								
Authors (year)	**Design**	**Population**	**Amyloid PET status**	**Assessment time points**	**Scenario**	**Themes**	**Results**	**Conclusion**
Vanders-chaeghe et al. (2017)[59]	Semi-structured interviews	38 patients with MCI (BioAdaptAD, Belgium)	Elevated: $n = 8$, not elevated: $n = 30$)	2 weeks and 6 months after disclosure	Learning actual (amyloid PET) biomarker results	Comprehension, implications, regret	Most patients could recall their results, some were confused about "positive"/"negative." Two (A+) had emotional difficulties, three (A−) questioned their outcome. Reported advantages and disadvantages were modified by expectations, biomarker status, and assessment time. One (A+) doubted her decision.	MCI patients' reactions are related to expectations, test results, and time.
Grill et al. (2017)[52]	Semi-structured interviews	10 patients with SCD/MCI/deme and 23 caregivers (memory clinic, US)	Elevated: $n = 18$, not elevated: $n = 2$, no scan: $n = 6$	234 ± 176 days after scan	Learning actual (amyloid PET) biomarker results	Motivation, comprehension, implications, regret	Participants were mainly motivated by learning the cause of cognitive impairment. They commonly expressed relief upon learning the result, regardless of the scan outcome. Nearly all would make the same decision again, although some had unrealistic expectations of diagnostic confidence.	Participants value information but should be counseled on limitations.

Abbreviations: A4, Anti-Amyloid Treatment in Asymptomatic AD; ADRC, Alzheimer's Disease Research Center; APEX, Alzheimer's Prevention through Exercise; *APOE*, apolipoprotein E; CN, cognitively normal; BAI, Beck Anxiety Index; BDI-II, Beck Depression Inventory-II; BioAdaptAD, Biomarker-Based Adaptive Development in Alzheimer's Disease; CAADS, Concerns About Alzheimer's Disease Scale; CES-D, Center for Epidemiologic Studies Depression; CSSRS, Columbia Suicide Severity Rating Scale; DASS, Depression; Anxiety, and Stress Scale; EMA, ecological momentary assessment; FTPS, Future Time Perspective Scale; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scales; IES, Impact of Events Scale; IES-R, Impact of Events Scale Revised; IGT-AD, Impact of Genetic Testing for Alzheimer's Disease; LEARN, Longitudinal Evaluation of Amyloid Risk and Neurodegeneration; MAC-Q, Memory Assessment Clinic questionnaire; MCI, mild cognitive impairment; PET, positron emission tomography; PHQ, Patient Health Questionnaire; REVEAL-SCAN, Risk Evaluation and Education of Alzheimer's Disease: The Study of Communicating Amyloid Neuroimaging; SCD, subjective cognitive decline; SOKRATES (I), Study of Knowledge and Reactions to Amyloid Testing; SOKRATES II, Study of Knowledge and Reactions to APOE Testing; STAI, State-Trait Anxiety Inventory; US, United States; VPAI, Views and Perceptions of Amyloid Imaging questionnaire.

TABLE 3 Publications on professional stakeholders' attitudes and practices regarding biomarker testing.

Quantitative						
Authors (year)	**Design (determinants)**	**Population**	**Scenario**	**Outcome measures**	**Results**	**Conclusion**
Armstrong et al. (2019)[30]	Survey (subgroups)	114 clinicians (dementia specialists, neurologists), 107 patient stakeholders (patients, caregivers, and advocates) (AAN; various settings, US)	Doing (amyloid PET) biomarker testing in CN persons and patients with MCI or dementia.	Attitudes	Compared to clinicians, patient stakeholders judged it more important to test asymptomatic individuals ($P < 0.001$). They also placed more value on the quantity of amyloid and prognosis of cognitive decline ($P < 0.001$). The only topic they rated lower than clinicians was the harm of a false positive diagnoses ($P < 0.001$). No differences were found between other subgroups.	Patients place more value on a diagnosis and testing asymptomatic individuals.
Bertens et al. (2019)[31]	Survey	102 clinicians (EAN/EADC, EU)	Doing biomarker testing for diagnosing AD in patients with MCI	Attitudes, practices	< 25% routinely performed CSF and less than 5% amyloid PET testing. 68% used research criteria for diagnosing prodromal AD, for increased certainty, counseling, and follow-up. 32% did not for lack of standards, treatment, and implications. > 80% agreed diagnosing AD was helpful, these patients were more often counseled on follow-up, risk, and advance planning ($P = 0.0001$).	Diagnosing AD in MCI patients has clinical utility, but standardization is needed.
Frederiksen et al. (2020)[35]	Survey	110 physicians (EADC, EU)	Doing biomarker testing for diagnosing AD in patients with MCI	Attitudes, practices	91.8% had access to CSF and 50.9% to amyloid PET biomarker testing. 85.7% most found them useful. 85.7% always or usually discussed the decision to test with patients. Pre- and postbiomarker counseling varied across centers, as did practices for referral to support groups and advice on preventive strategies. 47% reported discussing driving and advance care planning.	The variability in practice calls for better counseling and communication.
Mormont et al. (2020)[39]	Survey	26 clinicians (BeDeCo, Belgium)	Doing biomarker testing for diagnosing AD in patients with MCI or dementia	Attitudes, practices	> 60% recommended CSF biomarker testing to patients with MCI, in case of abnormal results, nearly all disclosed a diagnosis of AD. 88% believed benefits outweigh risks for patients, 31% observe it is sometimes harmful and 12% often. 92% rarely or never learn patients regret being informed. 92% would want to know their own diagnosis, regardless of the stage.	Diagnosing AD in patients with MCI and abnormal biomarkers is recommended.
Sannemann et al. (2020)[42]	Survey	343 general practitioners (MOPEAD, Spain, Sweden, Germany, Slovenia, the Netherlands)	Doing biomarker testing for diagnosing AD in patients with MCI or early dementia	Attitudes, practices	74% of general practitioners valued an early diagnosis, most thought benefits outweigh risks for patients (58%) and relatives (71%). Barriers included lack of confidence, time, and reimbursement of procedures, with significant differences across countries. If a disease-modifying treatment were available, 59% would change their implementation of early diagnosis.	Early diagnosis requires education and time for diagnostic procedures.

(Continues)

TABLE 3 (Continued)

Quantitative						
Authors (year)	**Design (determinants)**	**Population**	**Scenario**	**Outcome measures**	**Results**	**Conclusion**
Schweda et al. (2018)[43]	Survey	108 physicians (hospitals/memory clinics, Germany)	Doing biomarker testing for diagnosing AD in CN persons and patients with MCI	Attitudes, practices	In case of elevated biomarkers 88% disclosed risk or diagnosis to patients with MCI and 53% to subjects with SCD. Practiced differed between university and general hospitals ($P < 0.0001$). 75% always communicated biomarker results, most expected benefits for future planning (75%), but also psychological stress (82%) and self-stigmatization (70%). 86% required medical guidelines.	There is considerable heterogeneity, and a need for standards and guidelines.
Shulman et al. (2013)[45]	Survey	159 investigators (clinicians, physicians, coordinators; ADNI, US)	Disclosing (amyloid PET) biomarker results to CN research participants or those with MCI	Interest, attitudes, practices	Although 60% of respondents received requests from research participants with MCI and 55% from CN subjects, 90% never returned amyloid PET results to participants with MCI and 94% to CN subjects. If the FDA approved florbetapir, the majority would inform participants with MCI (73%) or CN subjects (58%) but emphasized a need for guidance on disclosure and research on the impact.	Returning research results is supported but guidance and research are needed.
Qualitative						
Authors (year)	**Design (determinants)**	**Population**	**Scenario**	**Outcome measures**	**Results**	**Conclusion**
Tromp et al. (2020)[58]	Semi-structured interviews	15 physicians (5 general practitioners, 6 geriatricians, 4 neurologists; various settings, the Netherlands)	Doing biomarker testing for diagnosing AD in CN persons patients with MCI	Attitudes	There was large variability in knowledge and terminology. Considerations in favor but mostly against diagnosing AD in CN persons or patients with MCI included respecting patients' characteristics and wish to (not) know; (lack of) diagnostic validity and clinical utility; risk, cost, and burden of testing; changing definition of AD; and fear or medicalization.	Diagnosing AD in CN persons or patients with MCI conflicts with views of good care.

Abbreviations: AAN, American Acedemy of Neurology; AD, Alzheimer's disease; ADNI, Alzheimer's Disease Neuroimaging Initiative; BeDeCo, Belgian Dementia Council; CN, cognitively normal; CSF, cerebrospinal fluid; EADC, European Alzheimer's Disease Consortium; EAN, European Academy of Neurology; EU, European Union; FDA, Food and Drug Administration; MCI, mild cognitive impairment; MOPEAD, Models of Patient Engagement for Alzheimer's Disease; PET, positron emission tomography; SCD, subjective cognitive decline; US, United States.

3.2.1 | Motivation

Three studies addressed personal stakeholders' motivation to be informed of biomarker status.[41,52,53] Despite differences in design, results suggest that individuals at (perceived) risk were primarily driven by the wish to confirm or assuage subjective memory concerns. A questionnaire among 4327 CN participants identified altruism/contributing to research as the most important reasons. However those who (unknowingly) had elevated amyloid scored higher on motivations of perceived risk, and this association was mediated by perceived cognitive problems.[41] Similarly, family members of CN participants with at least one first-degree relative with AD were mostly interested in learning their relatives' predisposition, either to be reassured or make plans accordingly.[53] In addition, semi-structured interviews with patient–caregiver dyads in various (pre)dementia stages showed the majority was compelled by wanting to receive a definite (etiological) diagnosis, learn more about the condition, and follow their physician's recommendation to undergo the scan, while reasons for

opting out of testing included costs, insurance coverage, or lack of benefits.[52]

3.2.2 | Comprehension

Six studies evaluated personal stakeholders' comprehension of the test results,[49,52–54,59,64] three of which reported on results from the SOKRATES study (Study of Knowledge and Reactions to Amyloid Testing).[53,54,64] When sharing amyloid status after pre-disclosure education, most CN participants and most family members understood that elevated levels implied "an increased but uncertain risk of developing AD dementia," although their understanding of the probability varied considerably and some requested information on the degree of amyloid elevation.[53,54,64] Half of those with normal readings and the majority of family members knew their chances were decreased.[53,54] Yet overall, some participants felt the information was ambiguous or insufficient.[49,53,54] Patients with MCI who tested positive could not recall the exact message after disclosure, like their amyloid-negative peers did, although they were able convey the essence in their own words.[59] A few (mostly less involved) family members misinterpreted the results, and some patients with MCI were confused by the terminology, struggling with the notion that a "positive" outcome was "bad."[59]

3.2.3 | Implications

The impact of disclosing test results to personal stakeholders was measured in 11 studies.[32,37,38,47–49,52–54,59,63] Seven of these presented quantitative data. In the largest study, 1705 CN and pre-scan educated participants were informed of their results according to a specified protocol, and psychologically assessed before, at, and after disclosure.[37] Individuals with elevated amyloid levels (n = 1167) were no more likely to experience short-term negative psychological consequences than those with normal results (n = 538). However, the positive group did have increased concern about AD, whereas the negative reported a slight improvement in future time perspective. One study among 97 CN participants found distress was slightly higher in the elevated group,[32] while another with 42 participants with SCD reported higher distress in those with normal results,[48] both associated with baseline levels of anxiety or depression. Research with 24 patients with MCI measured more variability in anxiety from day to day in those with elevated results compared to those with normal scan outcomes.[38] None of the other studies found sustained effects or significant differences between groups or over time.

Five studies provided sufficient data on pre- and post-disclosure measurements of anxiety, depression, stress, or suicidality to be included in a meta-analysis. These assessed CN participants,[32,37] those with subjective decline,[48,49] or MCI/mild AD,[47] with follow-up times ranging from 6 weeks to 1.5 years. Meta-analysis of the standardized mean outcome difference (pre-disclosure vs. 3 months post-disclosure) revealed no significant psychological impact when considering all participants (random-effect estimate = 0.10, standard error [SE] = 0.23, P = 0.65), nor when considering individuals with negative biomarkers (estimate = 0.19, SE = 0.32, P = 0.55), or positive biomarkers (estimate = 0.01, SE = 0.33, P = 0.97) separately (see Figure 2). These forest plots further show this is consistent across outcomes and studies. Thus, our synthesis of results across quantitative studies indicates that disclosure does not infer short-term psychological harm.

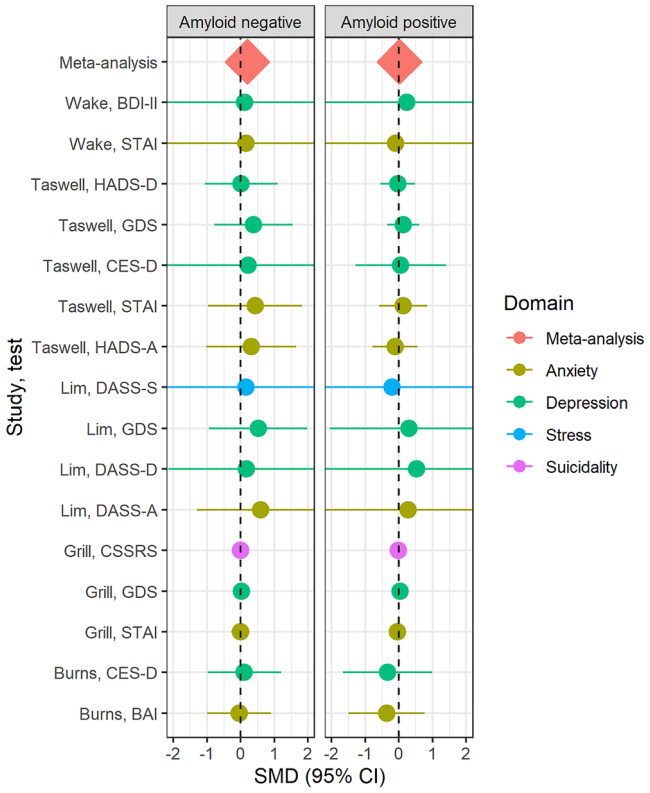

FIGURE 2 Forest plots of the psychological impact of sharing AD biomarkers results with individuals who do not have dementia. Forest plots of the short-term psychological impact of sharing AD biomarker results with individuals who do not have dementia, before versus 3 months after disclosure, are shown using a random effects model, considering all participants (random-effect estimate = 0.10, SE = 0.23, P = 0.65), only biomarker-negative individuals (left plot, magenta: random-effect estimate = 0.19, SE = 0.32, P = 0.55) and only biomarker-positive individuals (right plot, magenta: random-effect estimate = 0.01, SE = 0.33, P = 0.97). AD, Alzheimer's disease; BAI, Beck Anxiety Index; BDI-II, Beck Depression Inventory-II; CES-D, Center for Epidemiologic Studies Depression; CSSRS, Columbia Suicide Severity Rating Scale; DASS, Depression; Anxiety, and Stress Scale; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scales; SE, standard error; SMD, Standardised Mean Difference; STAI, State-Trait Anxiety Inventory.

Psychosocial implications were further examined in seven interview studies with (a)symptomatic individuals and/or relatives,[49,52–55,59,63] including three in the SOKRATES study.[53–55] The majority of participants were reassured, relieved, or happy upon receiving normal test outcomes,[49,52–55,59] although in patients with MCI this was sometimes tempered by not having an explanation for concerns or symptoms.[52,54,59] CN individuals tended to reinterpret previous

"memory lapses" as normal aging,[53,54] those with MCI resumed previously suspended "normal" activities and plans.[59]

Conversely, upon learning amyloid levels were elevated, participants felt sadness, worry, or despair,[49,52–54,59] although they also indicated they appreciated knowing the cause of the cognitive complaints, having more certainty, and better follow-up and monitoring of health and symptoms.[49,52,54,59] Compared to those with normal biomarkers, they were more likely to make lifestyle changes to improve physical and cognitive health;[49,54] adapt future plans, including practical, medical, financial, and legal affairs;[49,52–54,59,63] and reevaluate priorities to enjoy time left and optimize quality of life.[53–55,59] One interview study among CN participants found that two thirds of interviewees with elevated amyloid reported not thinking of physician-assisted death, several were ambivalent, and approximately one in five stated pursuing this upon deterioration. Proportions were roughly equivalent in those with negative results, when asked to consider being positive.[63]

Some participants with SCD were satisfied with the level or social support,[49] and patient with MCI experienced improved relationships, due to more openness and understanding.[59] Others described uncertainties about the future and becoming aware or paranoid of cognitive slips.[54,59] Family members acknowledged watching them more closely,[53] to the point where patients with MCI felt that monitoring turned into patronizing attitudes.[59] In addition, participants struggled to decide whom to confide in, as well as why and how to tell others about their test results, for fear of negative reactions, losing control of the information, and worries about stigma and discrimination.[55,59] As such, amyloid imaging was considered different from other medical tests,[53,54] partially because of the unique relationship to their identity as perceived by themselves and others.[54]

Even so, upon reflection most interviewees stated they would make the same decision again,[52,59] but cautioned others to reflect on their desire and capacity to learn such sensitive information about themselves.[53]

3.3 | Professional stakeholders' perspective: attitudes and practices

Eight studies presented professional stakeholders' perspectives on biomarker testing (see Table 3).[30,31,35,39,42,43,45,58] Authors reported on attitudes and practices regarding amyloid PET testing in individuals without dementia. Seven described quantitative,[30,31,35,39,42,43,45] and one qualitative, data.[58] Six queried health-care providers from Europe,[31,35,39,42,43,58] and two from the United States.[30,45]

3.3.1 | Attitudes

Regarding the quantitative data, three studies among European health professionals found that 58% to 88% believed the benefits outweighed the risks of detecting AD in patients with MCI.[31,39,42] In addition, a survey among 26 European physicians found that 12% often observed harm. Furthermore, 92% rarely or never learned their patients regretted being informed.[39] One survey on attitudes regarding predementia biomarker testing in the United States reported that, compared to patient stakeholders, clinicians placed more value on the harm of false positive results, but judged it less important to test asymptomatic individuals.[30]

In contrast, qualitative data from an interview study among 15 Dutch physicians led to the conclusion that a predementia biomarker diagnosis did not fit with their views on good care, regardless of the absence or presence of symptoms, for lack of medical utility.[58]

3.3.2 | Practices

Data on current practices were quantitative and mostly from European studies.[31,35,39,42,43,45] A survey among 110 physicians from 42 centers found that 92% had access to CSF and 51% to amyloid PET testing.[35] However, another questionnaire revealed that <25% of clinicians routinely performed lumbar punctures or amyloid imaging.[31] Practices on disclosure and terminology differed. According to two other studies, in the case of abnormal results nearly all Belgian clinicians disclosed a diagnosis of AD to patients with MCI,[39] whereas 88% of German physicians communicated an increased risk for dementia to patients with MCI and 53% to persons with SCD.[43]

In a survey among 159 Alzheimer's Disease Neuroimaging Initiative investigators from the United States, most never returned amyloid PET results to research participants with MCI (90%) or CN subjects (94%), although after the US Food and Drug Administration's approval of florbetapir the majority would return them to those with MCI (73%) or even CN individuals (58%) upon request.[45]

Reasons for performing biomarker testing included increasing diagnostic certainty, providing counseling, starting medical intervention, facilitating follow-up planning, and selecting research participants.[31] Barriers were lack of: validity, standards, time, confidence, clinical utility, knowledge about the impact on patients and relatives, as well as cost, risk, and burden of the procedures.[30,31,42,45,58]

In addition, practices on counseling, disclosure, referral to support groups, and advice on preventive strategies, as well as information on driving and advance care planning varied across countries and between centers,[35,42,43] illustrating room for developing, harmonizing, and educating testing standards and disclosure protocols.[43,45]

4 | DISCUSSION

In our systematic review of the impact of sharing AD biomarker results with individuals who do not have dementia, from different stakeholders and perspectives, we found that the vast majority of individuals was interested in biomarker testing, learning their results was well tolerated, and this information was perceived as actionable. Although most professional stakeholders valued biomarker assessments, their attitudes and practices varied considerably, illustrating the importance of developing guidelines and

recommendations for how to incorporate biomarker testing in diagnostic work-up.

Upon comparing these results to our previous systematic review of theoretical data on this topic, from which we synthesized 26 diverse and opposing considerations, related to a clinical, personal, or societal context, we noticed three things. First, the empirical studies almost exclusively addressed clinical and personal implications; only one examined a societal consequence, that is, how biomarker results affect the stigma related to AD.[46] Second, authors of theoretical literature tended to focus on risks, whereas participants of empirical studies were prone to highlight benefits. Third, patients and relatives identified new nuances and concepts, which were not addressed as extensively in theoretical literature, including the influence of subjective risk and family history; the dynamic among monitoring, vigilance, and paranoia; and the impact on quality of life. These findings identify gaps in knowledge and starting points for future research. We believe the discrepancies should not be interpreted as contradictory but rather as complementary, as they capture different aspects: the theoretical data are more reflective of ethical acceptability in general, while empirical data are closer to social acceptance, and both are relevant.[65] It is important to consider how both perspectives can be integrated in a comprehensive moral evaluation.[66,67]

Among personal stakeholders, interest in biomarker information was high. Nearly all (80%–94%) participants who had been tested in a research setting wished to receive their results,[36,60,62] the vast majority (72%–81%) of persons involved with AD studies would hypothetically want to learn their biomarker status,[33,34,40,44,51,56,57,61] while diverse samples more representative of the general population were about evenly split pro and con.[36,50] These results are consistent with public interest in genetic testing for AD in the general population, which ranges from 51% to 75%.[68–70] Interestingly, several surveys in our review found associations with subjective risk and a family history,[33,36,40] but in one, having an affected parent actually lowered desire for biomarker assessment,[40] and in another no relation with perceived susceptibility was found.[44] An explanation for these contradictory findings could be that persons with substantial concerns about their cognitive health may be a self-selected target population for biomarker assessment in pursuit of insight and control of their future. However, similar to pre-symptomatic testing for pathogenic mutations of AD,[71,72] for some a high likelihood and more caregiving experience may deter them from wanting to be confronted with their disposition for an incurable and fatal disease.

One of the main concerns of sharing biomarker results with individuals who do not have substantial symptoms is the emotional burden of knowing one's status.[73,74] Our meta-analysis found that in a protocol with pre-scan education the short-term psychological impact of disclosure was not significant when considering all participants, nor when examining those with positive or negative biomarker separately. This supports the emerging consensus that the psychological risk of sharing biomarker results to individuals without dementia does not reach the threshold for clinical concern.[75] Some studies in our review reported a (trend toward) more variability,[38] or a slight increase in distress, anxiety, or depression,[32,47,48] in all subjects or either subgroup, even exclusively in those with normal biomarkers.[47,48] In addition, qualitative data indicate that while "clean" scans generally evoked reactions of relief or reassurance, lack of an explanation for concern also gave disappointment or frustration, and although evidence of AD pathology typically led to stress or anxiety, it provided insight and clarity too. These ambivalent responses to both "good" and "bad" news suggest that the degree of concerns and symptoms (including those too subtle to be picked up by neuropsychological tests) shapes the expectations of individuals and their families, which may in turn modify their reactions to the test outcomes. This hypothesis is supported by recent findings that when scan results confirm care partners' suspicions of elevated amyloid, they tend to report relief and gratitude rather than distress.[76] More personal and contextual factors may influence the nature of responses, which emphasizes the importance of pre-test counseling and psychological screening.[77]

Another matter of extensive debate is the actionability of sharing biomarker data, in terms of personal utility.[78] Several of the included studies in CN participants or individuals with SCD reported that those with elevated amyloid were more likely to actually make changes to their lifestyle, by adjusting their diet, exercising more, challenging their minds, or considering trial participation, to remain cognitively healthy and to delay or prevent cognitive symptoms.[49,53,54] In addition, they were more likely to actually prepare for the future, by changing financial, legal, and medical plans, as well as their living arrangements. Last, they were more likely to actually improve quality of life, by adapting their use of leisure time.[53,54] This is consistent with research showing that disclosing genetic risk information to asymptomatic individuals is associated with changes in health behaviors and preparations for cognitive decline.[69,79,80] However, although some participants reported sharing their biomarker status with their significant others improved relationships and social support, others struggled to decide whom to confide in and mentioned patronizing, stigmatizing, and discriminating attitudes.[55,59] More research is needed into these social aspects, the dynamics between benign and adverse implications, and their development in the longer term.

We found that the majority of professional stakeholders value biomarker testing, believing the benefits outweighed the risks.[31,39,42] However, as most studies examined attitudes and practices in European health-care professionals, and the majority involved patients with MCI, these findings may not be representative for all clinicians and populations. In addition, regional and conceptual variations were found. Differences in opinions on what abnormal biomarkers implied for individuals were strongly related to the desirability of testing and the communication of results. Dutch physicians believed such outcomes indicated an uncertain prospect, rather than the definite presence of a disease.[58] Whereas Belgian clinicians shared a diagnosis of AD,[39] German physicians disclosed an increased risk for dementia.[43] These inconsistencies may compound existing misconceptions in society.[81,82] Little is known about the implications of various framings, although one study reported not the label, but the prognosis, contributed to stigma and discrimination.[83] There is an urgent need for testing guidelines and communication protocols to be developed and harmonized for the implementation in memory clinic practice, especially as recent

evidence suggests that biomarker information not only improves diagnostic certainty and patient management, but also institutionalization and mortality.[84–86] The advance of disease-modifying treatments will further increase medical utility.[5,6]

Notably, empirical data on stakeholders' interest in learning their biomarker status were mostly based on CN research engaging individuals or members of the general public, while results on their experiences tended to include more patients with SCD or MCI, and findings on professional stakeholders' attitudes and practices mostly surveyed dementia specialists. This suggests a gap in data, as these are different situations. Implications of receiving amyloid and/or tau test results may differ depending on individuals' cognition (i.e., CN, SCD, or MCI), and the context in which this information is shared (i.e., as part of trial participation or in the memory clinic). Currently, the absence or presence of cognitive impairment determines whether disclosure of test results is only recommended in research settings or also permissible in clinical practice, although this may change once a preclinical diagnosis of AD becomes medically actionable. Still, our findings suggest subjective concerns and symptoms affect patients' anticipation of the results and thus the emotional impact of learning them, as elevated biomarkers may confirm or explain suspicions, while those without worries or unaware of signs may be less prepared to receive "bad news." Especially for the latter, pre-test screening, counseling, and education (on topics including uncertainty, stigma, and discrimination) are important. Conversely, to patients with MCI, biomarker results provide information on the underlying condition of a syndrome that has already been diagnosed, whereas negative biomarkers may create frustration over lack of insight into the cause. Furthermore, disclosure in a symptomatic phase may leave less time and opportunity to benefit from disease-modifying therapies, adopt a risk-reducing lifestyle, arrange personal affairs, and advance life plans, whereas the risk of for medicalization, stigmatization, and discrimination may be bigger in a preclinical stage. More research is needed to assess the motivation for and impact of biomarker testing in various cognitive stages and different settings. Previous research suggests that individuals come to memory clinics with specific motivations, which are not always stated and may differ from those of their caregivers.[87] As the evaluation of the risk and benefits is specific to the individual and their situation, this merits shared decision making and a personalized approach.

4.1 | Strengths and limitations

We supplemented our systematic review with a meta-analysis of several studies evaluating the impact of sharing biomarker results with persons who do not have dementia. Another strength is our extensive search strategy, which enabled us to synthesize data from both the personal and professional perspective, providing a comprehensive overview. We incorporated both quantitative and qualitative studies, which conveyed complementary information. In addition, there are some limitations which should be addressed in future research. First, there was considerable heterogeneity among study designs and quality, which complicated comparison of results. Some were based on small and specific populations. The concept of biomarker testing had diverse operationalizations, such as a hypothetical assessment, a combination of both biological and genetic markers, or amyloid PET imaging alone. Populations consisted of CN individuals or those with SCD or MCI and their relatives, and most were research participants rather than clinical patients, for whom biomarker testing might be most relevant. Due to the limited body of data and the variety in methods used for analysis in the included studies, it was not always possible to distinguish between these groups in our synthesis. Second, as few studies were available for meta-analysis and follow-up was relatively short, careful interpretation of the overall results is warranted and the long-term impact remains to be assessed. Third, the vast majority of studies included US and European participants, predominantly White and well educated. In most studies, individuals were psychologically screened and those with elevated levels of anxiety, depression at baseline, or a history of suicidal ideation were excluded. Several publications reported on different aspects of a single study or included participants from the same cohorts. These limitations severely constrain generalizability. There is a lack of research into people with more socioeconomic, ethnic, and racial diversity as well as those with lower psychological resources. Future research should be more inclusive, involve larger sample sizes, and include patient-centered outcomes in more biologically oriented studies, whether trials or biomarker validation.

5 | CONCLUSION

In conclusion, biomarker testing in individuals who do not have dementia is a topic of ethical debate. Based on the available empirical data on the impact of sharing results, our systematic review and meta-analysis found that interest among personal stakeholders is high, and sharing test results does not cause significant short-term psychological harm and offers actionability. Although most health-care professionals value biomarker testing, attitudes and practices varied considerably. Development and harmonization of testing guidelines and communication protocols are required, particularly in view of the imminent advancements in disease-modifying therapies.

ACKNOWLEDGMENTS

Research of Alzheimer Center Amsterdam is part of the neurodegeneration research program of Amsterdam Neuroscience. Alzheimer Center Amsterdam is supported by Stichting Alzheimer Nederland and Stichting Steun Alzheimercentrum Amsterdam. The clinical database structure was developed with funding from Stichting Dioraphte. The chair of Dr. Van der Flier is supported by the Pasman stichting. Jetske van der Schaar is appointed at ABOARD, which is a public–private partnership receiving funding from ZonMW (#73305095007) and Health~Holland, Topsector Life Sciences & Health (PPP-allowance; #LSHM20106). More than 30 partners participate in ABOARD. ABOARD also receives funding from Edwin Bouw Fonds and Gieskes-Strijbisfonds. Yolande Pijnenburg is recipient of YOD-MOLECULAR (NWO #KICH1.GZ02.20.004).

CONFLICT OF INTEREST STATEMENT

Jetske van der Schaar wrote a book for a layman's audience about the personal impact of dominantly inherited AD, for which she received grants or contracts from Aegon Nederland and Alzheimer Nederland and royalties from Uitgeverij Prometheus. She is a member of the advisory board for the National Dementia Strategy of the Dutch Ministry of Health, Welfare and Sport. Leonie Visser has been an invited speaker by the Schwabe Group; fees were paid to her institution. Her research has been funded by ZonMW, Alzheimer Nederland, Health~Holland, Topsector Life Sciences & Health, and the Amsterdam Public Health research institute. Philip Scheltens is a full-time employee of EQT Life Sciences (formerly LSP) and Professor Emeritus at Amsterdam University Medical Centers. He has received consultancy fees (paid to the university) from Alzheon, Brainstorm Cell, and Green Valley. Within his university affiliation he is global PI of the phase 1b study of AC Immune, phase 2b study with FUJI-film/Toyama, and phase 2 study of UCB. He is past chair of the EU steering committee of the phase 2b program of Vivoryon and the phase 2b study of Novartis Cardiology and presently co-chair of the phase 3 study with NOVO-Nordisk. Research programs of Wiesje van der Flier have been funded by ZonMW, NWO, EU-FP7, EU-JPND, Alzheimer Nederland, Hersenstichting CardioVascular Onderzoek Nederland, Health~Holland, Topsector Life Sciences & Health, stichting Dioraphte, Gieskes-Strijbis fonds, stichting Equilibrio, Edwin Bouw fonds, Pasman stichting, stichting Alzheimer & Neuropsychiatrie Foundation, Philips, Biogen MA Inc, Novartis-NL, Life-MI, AVID, Roche BV, Fujifilm, Eisai, and Combinostics. She holds the Pasman chair. She is recipient of ABOARD, which is a public–private partnership receiving funding from ZonMW (#73305095007) and Health~Holland, Topsector Life Sciences & Health (PPP-allowance; #LSHM20106). She has been an invited speaker at Boehringer Ingelheim, Biogen MA Inc, Danone, Eisai, WebMD Neurology (Medscape), NovoNordisk, Springer Healthcare, NovoNordisk, and European Brain Council. She is consultant to Oxford Health Policy Forum CIC, Roche, and Biogen MA Inc. She participated on advisory boards of Biogen MA Inc, Roche, and Eli Lilly. All funding is paid to her institution. She is a member of the steering committee of PAVE and Think Brain Health. She was associate editor of *Alzheimer, Research & Therapy* in 2020/2021. She is associate editor at *Brain*. The other authors have no conflicts of interest to declare. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

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

How to cite this article: van der Schaar J, Visser LNC, Ket JCF, et al. Impact of sharing Alzheimer's disease biomarkers with individuals without dementia: A systematic review and meta-analysis of empirical data. *Alzheimer's Dement*. 2023;19:5773–5794. https://doi.org/10.1002/alz.13410