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Ethics Review

Perspectives on Communicating Biomarker-Based Assessments of Alzheimer's Disease to Cognitively Healthy Individuals

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Abstract. In clinical trials which target pathophysiological mechanisms associated with Alzheimer's disease, research participants who are recruited based on biomarker test results should be informed about their increased risk of developing Alzheimer's dementia. This paper presents the results of a qualitative focus group study of attitudes and concerns toward learning information about biomarker-based risk status among healthy research participants in the United Kingdom and Spain and people with dementia and their supporters/caregivers from countries represented in the European Working Group of People with Dementia of Alzheimer Europe. The study identified expectations related to learning risk status and preferences related to the content, quality, and follow-up of the disclosure process. The latter emphasize distinctions between risk and diagnoses, the importance of clear information about risk, and suggestions for risk reduction, as well as expectations for follow up and support. The implications of these preferences for practice are discussed. Providing details of research participants' experience and views may serve as a guide for the development of processes for the responsible disclosure of Alzheimer's disease biomarkers.

Keywords: Biomarkers, disclosure, focus groups, ethics, qualitative research

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INTRODUCTION

Research in Alzheimer's disease increasingly focuses on identifying risk statuses indicated by biological markers of pathological changes associated with later dementia, notably levels of amyloid-β in cerebrospinal fluid or on PET brain imaging. However, although significant research is ongoing, the clinical validity and value of biomarker information for asymptomatic individuals is still open to question [1]. The communication of biomarker information to people without symptoms of dementia thus presents an ethical challenge for researchers and, should such approaches translate into clinical practice, for clinicians [2, 3]. Routine communication of risk information to people without symptoms in clinical practice is currently not recommended [4, 5] considering the lack of robust individualized prediction [6] and the potential psychosocial harms caused by learning one's risk status in the absence of effective preventive or therapeutic options [7]. Attention has also been drawn to the potential of broader testing and screening programs associated with earlier stages of Alzheimer's disease to result in premature diagnoses and over-treatment of age-related cognitive change [8].

Nevertheless, in research settings there are two reasons why it may be acceptable or appropriate to communicate biomarker information related to Alzheimer's dementia risk to people without symptoms [9]. Some participants will want to know their estimated risk status, and communicating these individual research results may be an expression of respect for their autonomy and a form of reciprocity in some circumstances [10, 11], even if this information is not currently actionable and the exact meaning of risk prediction and specific biomarkers within risk prediction in an individual is unknown. It has been estimated that between 50% and 90% of people are interested in knowing the results of a 'predictive' or 'reliable' test of their risk of developing dementia, with numbers varying across countries [12–17]. However, when people's understanding of the current uncertainty and limited generalizability and clinical validity associated with biomarkers increases, their interest in learning about the biomarker wanes [15]. In fields where tests are predictive rather than probabilistic, experience suggests that actual uptake may be lower than anticipated, particularly in the absence of treatment [18]. It is thus likely that levels of public interest in learning Alzheimer's disease risk are overestimated.

A more compelling reason for disclosure relates to recruitment for clinical trials. Clinical trials are currently ongoing which target pathology in a population of relatively younger, asymptomatic individuals identified as being at 'high risk' of developing Alzheimer's dementia on the basis of family histories, genetic information, and biomarker tests [19, 20]. Within these studies, prospective research participants should know why they have been invited to take part in a study in order to make informed decisions about research participation [21] as part of a transparent recruitment process [22].

There is a small but growing body of evidence related to the impact of disclosure which suggests that learning that one is at elevated risk of developing Alzheimer's dementia in the absence of symptoms of dementia does not cause significant psychological or social harm [23]. However, although the immediate psychological impact of risk disclosure seems limited, there is an increase in test-related distress, and adverse psychological effects occur in a subgroup of research participants. Results from the Risk Evaluation and Education for Alzheimer's Disease (REVEAL) studies suggest risk disclosure may have implications in relation to long-term care insurance and possibly to health-related behavior changes [24]. Although not directly comparable, there is also evidence that diagnoses of mild cognitive impairment and mild Alzheimer's disease dementia are associated with lower quality of life [25]. Recent studies suggest a low risk of psychological harms associated with disclosure of Alzheimer's disease biomarkers [26, 27].

However, the evidence remains limited: there has been little analysis of the impact of risk disclosure in relation to non-genetic biomarkers and there is sparse evidence on disclosure outside the United States despite geographical variation in interest in knowing [16] and important differences across countries in long-term care provision. Published work on ApoE genetic testing concentrates on individuals who are first-degree relatives of a person with Alzheimer's dementia [28], who may already perceive themselves to be at increased risk due to this history [29]. Further, there is potentially important variation in the experience of family history, notably between cases in which dementia occurs late in life and close to death rather than earlier in life [30, 31]. In sum, the impacts of biomarker disclosure on healthy research participants remain to be studied. Importantly, the impact of disclosure is also likely to be affected by the manner in which information about amyloid biomarkers

is presented to the research participant. Careful attention is needed to determine whether people want to learn information about biomarkers for Alzheimer's dementia, what this information should include, and when and how it should be communicated [32].

There are no current shared guidelines for communicating amyloid biomarkers, and a small number of descriptions of current practice have been published to date. The most detailed of these are those elaborated in clinical research settings for the communication of amyloid PET imaging to asymptomatic individuals [27, 33] and to those with mild cognitive impairment [34]. Clinical communication models focus on shared decision-making with regard to amyloid testing and standardized language to describe the clinical significance of amyloid biomarkers [35–37].

The disclosure process described by Harkins et al. [33] is the most clearly elaborated and detailed approach within a research setting published in the literature to date. It was developed for initial use in the Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease (A4) study [20] (NCT02008357), which recruits participants based on positive results on amyloid PET imaging. It draws on a Delphi consultation with experts in genetic testing and neuroimaging.

The A4 disclosure process starts with education in the form of an information brochure provided in advance of the initial consent visit. This sets out the state of knowledge about amyloid imaging, the range of possible results, and their implications. The information in the brochure is then discussed in detail during the consent process, along with the motivations of potential participants to join the study. Comprehension of the brochure is then assessed, and potential participants are screened for anxiety and depression to establish their suitability to receive amyloid biomarker results. The actual PET imaging takes place at a second visit, and disclosure at a third visit. Prior to the disclosure of results, study staff again ascertain a participant's willingness to learn the results, their mood, and whether they have had recent life stress. Harkins et al. emphasize the importance here of involving staff who are skilled in communicating and recognizing distress. Disclosure itself occurs using standardized language which reflects that used in the information brochure and is accompanied by written information and with a family member or friend present if desired. Comprehension of the results is then assessed. Participants are followed up by phone three days after disclosure to assess well-being, distress, and the impact of disclosure, with a follow-up plan created based on responses. Finally, participants are followed up over the course of the study. The approach described by Burns and colleagues [27] for the Alzheimer's Prevention Through Exercise (APEX) study (NCT02000583) is similar. Notable characteristics are an emphasis on the probabilistic nature of both 'elevated' and 'nonelevated' amyloid results, a policy not to share scan results with the participant's physicians or enter them into the medical record, and follow-up by phone or e-mail at six weeks and six months.

The approach developed by Lingler et al. [34] focuses on the disclosure of amyloid status to people with mild cognitive impairment. Their guidance starts from guidance on genetic counselling and an iterative expert consultation, and was then tested and refined with mild cognitive impairment patients and caregivers. This approach also emphasizes the importance of pre-disclosure counselling and post-disclosure assessments of comprehension and the value of involving family or friends in the disclosure process. It also contributes important points on the content of information—highlighting the possible value of using brain images and the importance of clear graphics, as also increasingly recognized in the communication of genetic risk [38]. Finally, participants in the study by Lingler and colleagues expressed a desire for seamless communication with primary care providers.

The research reported in this paper was conducted to inform the development of the risk disclosure process during recruitment to trials within the European Prevention of Alzheimer's Dementia (EPAD) project [39, 40], a longitudinal cohort study and clinical trial platform for the secondary prevention of Alzheimer's dementia. The paper examines the perspectives of individuals with no symptoms of dementia, people with dementia, and caregivers on the communication of Alzheimer's dementia risk. No biomarker information has been communicated to these individuals, and the paper briefly describes their expectations related to the implications of learning information related to Alzheimer's disease risk status. The paper then sets out the preferences of participants related to the content, process, and follow-up of biomarker-based risk disclosure in research settings. These preferences are intended not to be prescriptive, but to reflect qualities of Alzheimer's disease risk communication considered important by those who may be involved in it in the future, and which should be engaged with by researchers and clinicians in the development of disclosure processes.

METHODS

Focus groups were held in London and Barcelona between November 2015 and January 2016, and in Brussels in December 2015. Spanish participants were recruited through the BarcelonaBeta Brain Research Centre (BBRC) of the Pasqual Maragall Foundation [41]. Participants in the United Kingdom were recruited through the Prevent cohort study [42]. The group discussion held in Brussels was comprised of participants recruited from within Alzheimer Europe's European Working Group of People with Dementia[1] (EWGPWD). The aim of this latter group was to obtain the perspective of people with dementia. This allowed the investigators to explore further the relationship between the diagnostic and risk disclosure processes. The study was approved by ethics committees in both Cambridge (NHS REC Reference 15/EE/0381 and University) and Barcelona.

Four groups were held in both London and Barcelona, three with people with a first-degree relative with Alzheimer's dementia, one with people without this family history. In total, 48 people participated, 32 in Spain and 16 in the UK. Group sizes ranged from 3 to 10. The participants included 30 women and 18 men, all of whom identified as Caucasian. 34 of the participants (71%) had a family history of dementia. Further details are given in Table 1. The EWGPWD group included 6 people with dementia (4 women, 2 men, median age 64.5) and 4 partner caregivers (2 men, 2 women, median age 66.5). Demographic data other than age were not collected from this group.

The individuals recruited for the focus groups in London and Barcelona were purposively sampled to be indicative of the likely future population for Alzheimer's disease clinical trials involving risk disclosure. They are research-engaged individuals, who are more likely to have a family history of dementia. While their views may not be representative of the population, they have immediate relevance to questions regarding the development of responsible disclosure processes in research. The participants from the EWGPWD, as members of a pre-existing, established group, represent a convenience sample.

Table 1
Participant characteristics

	London	Barcelona
Number of participants	16	32
Female	10	20
Male	6	12
Family history of AD dementia	12	22
Median age	55 (43–59)	61 (48–76)
Median years education	17 (13–22)	15 (8–18)

The groups were conducted according to the same protocol at the sites in London and Barcelona (see Supplementary Table 1). An adapted protocol was used for the EWGPWD. Participants were provided with short background information on biomarker-oriented research into Alzheimer's disease. The structured protocol then asked a series of questions related to 1) this background information; 2) participants' interest in learning their Alzheimer's disease risk, and the implications of this information, 3) how this differed for different types of risk information, and 4) preferences related to disclosure. This paper reports focuses on findings related to sections 2 and 4.

The focus groups were recorded and transcribed verbatim. Groups in London and the EWGPWD were conducted in English, while the Barcelona groups were conducted in Spanish and translated into English as part of the process of analysis. A coding framework was developed and used by RM and AD to identify key themes in the transcripts at each site. Data coded to these themes was then shared and used in further iterations of coding and analysis. Following an initial discussion of the themes emerging from the data at each site which identified comparable results, data from both sites was analyzed together.

The investigators identified preferences related to disclosure from initial analysis of the discussions in section 4 of the protocol related to the process of disclosing Alzheimer's disease risk information. These were collated by RM and AD and written up for participants. This report was circulated by email to the participants in Spain and the United Kingdom for comment and respondent validation [43]. The participants from the EWGPWD reviewed and agreed upon the report in a face-to-face meeting.

The study has a number of limitations. First, the findings relate to expectations of the disclosure process, rather than reflections on experiences of disclosure. As such it involves some elements of conjecture on the part of participants. Focus groups

[1] In 2012, Alzheimer Europe set up a Working Group of People with Dementia (EWGPWD). The EWGPWD is composed of 10 people with dementia from different countries and with different types of dementia. The EWGPWD works to ensure that the activities, projects and meetings of Alzheimer Europe duly reflect the priorities and views of people with dementia. The group operates independently, with its own Board and agenda of activities. The Chairperson of the EWGPWD also sits on the Board of Alzheimer Europe.

are particularly well suited for these types of questions, as the focus on interaction enables people to draw on both their own experience and that of others as discussions develop. However, focus group methods also have limitations, not least the limited generalizability of the results and the difficulty and limited value of quantifying perspectives which emerge during group interaction. In the current work, it was also necessary to develop the protocol, facilitate the groups, and analyze the data while working across languages and cultures. This required a more structured approach to facilitation and protocol design to enable the production of comparable data than might have been adopted in a single-language setting, and further detailed work is needed to explore cultural differences related to disclosure and attitudes to dementia risk. Nevertheless, the current work provides a set of preferences related to disclosure generated and reviewed by participants which represent a starting point for consideration and further exploration.

RESULTS

The first section presents the results of the group discussions related to why participants would be interested in or willing to learn their Alzheimer's disease risk status, and what they saw as the potential limitations and concerns associated with doing so. Results from the EWGPWD group discussion are based on slightly reformulated questions as the participants already have dementia. Consequently, in this section, the views expressed by this group should be interpreted not on the basis of how they are affected but rather on how they would have been affected in the past.

Section two presents the preferences related to disclosure processes in research settings.

The potential benefits of knowing

Participants were interested in learning their risk of developing Alzheimer's dementia, primarily because of the perceived personal utility of the information:

> "*Information is good, it puts the problem on the table, if you do not have more risk, great, and if you do then you can remedy it.*" *(SP1)*

The most prominent discussion was whether the information was valuable for acting to reduce risk. However, the link between knowledge and action was seen as problematic given the uncertain predictive value of risk information and the lack of proven options for risk reduction:

> "*[I]f the probability was uncertain, I would also want to know it, but surely I would be less interested, because I do not know if I can use this much to make decisions.*" *(SP2)*

> "*[I]f you told me that I was at a high risk I would certainly want to have, um, advice. How do I go on from here, what can I do to prevent it from getting any worse, or developing into a full-scale thing?*" *(EWGPWD supporter/caregiver)*

Information about risk status is thus seen as valuable when it has personal utility. Where this is absent, the perceived benefits are diminished.

The potential harms of knowing

The provision of information in the absence of available courses of action raises concerns about the short and longer-term impact of knowing for individuals and their families. As the participant quoted above continued:

> "*Otherwise I don't think I would like you to tell me, because what could I do? And why should I carry this worry, and why should I burden my family with this kind of worry?*" *(EWGPWD supporter/caregiver)*

Focus group discussions introduced two forms of impact which might be considered harmful: short-term psychological effects and longer-term hypervigilance.

Short-term effects

Participants rarely described expecting effects on their mood or anxiety following risk disclosure. This absence is important for understanding how people comprehend risk information, and reflected the role of family history in shaping risk perceptions:

> "*Even if I didn't do any of this [testing] I feel my risk is high. Therefore, would it affect me if somebody actually quantified it?*" *(UK1)*

However, when risk information was seen to be highly predictive and the development of dementia imminent a small group of participants suggested that they would consider using this information to inform suicide or assisted suicide to avoid the suffering they expected to result from Alzheimer's dementia:

"*I want to know immediately, that is, even a risk of 80%, not 99%, to make my own decisions, because I will not go through what happened to my father, I am very clear. Bump me off before I get to be like [that].*" *(SP2)*

This expectation was based upon personal experiences with the disease (e.g., in one or more first-degree relatives). Equally commonly however, participants referred this reaction to others, suggesting that although *they* would find the information useful, as discussed above, *other* people who were told they were at risk might mis- or over-interpret its significance.

Longer-term effects

Participants' main discussions of the effects they expected to be associated with learning their biomarker status relate to the longer-term. Participants focused on how risk information could change their perception of their own cognition, leading to hypervigilance with regard to possibly dementia-related symptoms:

"*it could be that if you've been assessed as having a higher risk and then you've gone a couple of days, and twice you've come down without the thing you went up for . . . That could then make you think, ah, this is the beginning of it.*" *(UK2)*

This was seen by some as a drawback of learning about one's Alzheimer's disease risk status. Moreover, this group further suggested that the revelation of dementia risk could affect their relationships with their families, including leading to their decisions or views being "second-guessed" (UK2). This ongoing consideration might make people reconsider their long-term plans:

"*I think it's the practical side of it that would worry me, I guess. Would it make me think differently about where I lived and how I moved*" *(UK1)*

While this was worrying for some participants, it was also seen as potentially valuable in terms of accessing earlier assistance from health and social services. This assessment contributed to participants' preferences related to the disclosure process and follow-up.

Preferences related to the disclosure process

The considerations of value, limitations and impact were used to outline a series of preferences related to the risk disclosure process in research. These cover the process of communicating Alzheimer's disease risk information, from the framing and the content of the information, to the conduct of disclosure, and the follow-up.

1. The communication process should make it clear that it relates to a risk rather than a diagnosis.

"*It should also be emphasized that it is not a diagnosis, it is a suggestion that you are at high risk. So therefore you could calm the situation down a bit.*" *(EWGPWD, participant with dementia)*

The first preference expressed by participants was that the communication of biomarker test results should highlight the appropriate framing of risk information and distinguish it from the communication of a diagnosis.

2. Information should provide clear details on risk level.

"*A diagnosis is certain, but what about risk? If they tell me that I have a 10% or 80% possibility it is not the same. If it is 80% or more then I want to know, but if not, why [would I]? And the when also, whether it is tomorrow that I could develop it, in 2 or 3 years and within 20, because if it is in 20 years I will have already died and what would all the stress be for, for all this. For me the key is in the information, in the type of information.*" *(SP1)*

Participants recommended that information should detail and quantify the level of risk described wherever possible. As this quote illustrates, this information would give detail beyond a simple increase in risk, but an idea of the time to which it refers.

3. Information should be accompanied with suggestions for action.

"*If they tell you, or if you want to know, they have to put the cards on the table and say, 'You are in this situation, but you have this, this and this you can do.'*" *(SP3)*

This expectation that risk information would be accompanied by information about risk reduction reflects the central reason that our respondents were

interested in knowing their Alzheimer's disease risk status, that it might enable them to act to reduce this risk.

4. Information should be provided by experts with the necessary knowledge and skills.

"*P1: Well that was my concern, is somebody telling me information very casually, and I would want somebody that's really interested and has the time . . .*

P2: And an encyclopedic knowledge of this." *(UK1)*

Participants emphasized that individuals with an appropriate level of expertise and an ability to communicate sympathetically should be responsible for communicating information related to risk.

The precise identity or professional role of the individual responsible for communicating risk information was not specified by group participants, and indeed may vary between settings. Some referred to a combination of "medical and social experts who might give advice as to what one might and might not do" (SP3).

5. Information should be provided face-to-face.

"*Face to face, definitely. I mean not if, if the answer's, 'No, you're just at an average risk,' then fine, you know. An email or a letter would be fine. But if the answer is that you're identified as being at high risk then I think that should be a face to face conversation.*" *(UK4)*

The preference among participants in this research was for disclosure of risk status to occur in a face-to-face meeting. This conclusion was supported by examples of experiences with brusque or inappropriate disclosure of diagnoses or clinical information in the past. While this discussion may evolve as Alzheimer's disease risk information becomes more commonplace, it suggests that research participants prefer that disclosure in research settings starts from face-to-face encounters.

6. Time should be allowed for questions before, during and after disclosure.

"*I think if you're going to, you know, if you're going to tell people about this kind of stuff they'll be like, OK, fine, but what does it mean to me, and where can I go with this information? So you can give me lots of information but can I have a conversation with somebody one-to-one about the implications of that for me personally?*" *(UK2)*

Participants expected that time would be made for discussion of the likely meaning of test results before receiving them and for interpretation of the results themselves. Also, they suggested that they would expect research teams to be available after disclosure for further and follow-up questions.

7. Communication should occur consistently across settings.

"*I'm cautious of the role of my GP, the GP. So I would like to have some information [on] what I can tell him, or a piece of paper, so that he can get it in his own vocabulary, not through me as an amateur.*" *(EWGPWD, caregiver/supporter)*

The preference for expert-led disclosure has implications for the portability of risk information, i.e., the use and interpretation of test results outside the research study. A concern raised by participants was that, as Alzheimer's disease risk markers are not routinely used in healthcare, non-expert clinicians including primary care physicians might provide alternative interpretations.

8. People at increased risk should be monitored following disclosure.

"*I don't know what's out there but, um, that sense of responsibility lying on the patient's or the individual's head is quite onerous sometimes, and so if there were, right OK once every two years or once every year or whatever have a check-up, like you're in a system where you're held and contained and monitored, that would be good*" *(UK4)*

Participants suggested that people who are told they are at higher risk of developing Alzheimer's dementia would anticipate a regular check-up with a doctor, or at least some monitoring of their cognitive status.

9. Psychosocial support should be available.

"*I think if there is a test you give people the opportunity to know one way or the other, and then, the only thing is then if they decide to take that information is you have to provide them with the knowledge that they're susceptible, and you then have to have the support network.*" *(UK3)*

Finally, participants described the availability of longer-term psychological and emotional support,

not necessarily provided by clinicians or the research team. Discussions emphasized the potential value of establishing forums for broader support and discussion extending over a longer period.

DISCUSSION

Focus group participants' discussions of the likely benefits and harms associated with learning information related to Alzheimer's disease risk emphasize the perceived personal utility of the information. These findings correspond with those raised in similar research on both the hypothetical and actual impact of learning the results of biomarker tests related to Alzheimer's disease risk [14, 15, 17, 44]. In line with the findings of REVEAL and similar studies, they suggest the short-term psychological impact of risk information may not generally result in harm, but that there may be subgroups who experience significant negative impacts.

The discussions reported here do, however, draw attention to the longer-term impacts of risk information, not least the potential for hypervigilance and long-term monitoring among people who already feel they are at risk of developing dementia. Risk information should thus be considered in terms of its potential contribution to 'dementia worry' [45, 46] and the danger of introducing a diagnostic misconception, whereby people who undergo research diagnostic procedures come to see themselves and are seen by others as patients although they would not have received any diagnosis in a standard clinical setting [47]. This is important in considering the implications and assumptions involved in the preferences of research participants related to the disclosure process.

Preferences concentrate on the content of the information, the quality of communication, and the follow-up process. Discussions of content emphasize the importance of attending to the language used in discussions of biomarker test results, and distinguishing between risks and diagnoses. This reflects the potential difficulties which have been highlighted elsewhere [48] associated with using terms such as 'preclinical Alzheimer's disease' to refer to individuals who have no symptoms of dementia. In practice, it can be difficult for investigators to effectively communicate this distinction, and risk statuses do frequently become elided with diagnoses by both people at risk and clinicians [49]. For example, in studies involving the disclosure of mock PET results to people with mild cognitive impairment and care partners, even when researchers clearly stated that PET evidence of amyloid was not synonymous with a clinical diagnosis of Alzheimer's disease, this relationship was still presumed by recipients [50].

Attention is thus needed to effective communication of both risk and ambiguity. Guidance on risk communication is well developed in relation to genetic testing, where data on relative and absolute risks are more readily available. Research groups have effectively used pictographs and other visual presentations of risk (e.g., video) to help research participants understand relative and absolute risks conveyed by genetic susceptibility markers for dementia [38, 51]. However, the lack of precise information about the risk associated with non-genetic biomarkers of Alzheimer's disease (notably related to amyloid load), and the timescale to which the risk refers, makes such an approach difficult to implement. Research is ongoing to improve the accuracy of biomarker testing [39, 41, 42]. However, currently, this limitation should be addressed through the development within these studies of information or education materials to accompany disclosure processes [33, 40]. In line with the findings from qualitative work following amyloid disclosure, these may need to address how classifications of amyloid 'positive' or 'negative' are produced [32], and should also be transparent about the scientific uncertainties associated with biomarkers [52]. However, more work is also needed to inform the communication of scientific *ambiguity* or epistemic uncertainty [53] related to Alzheimer's disease, as well as in our understanding of the concept of Alzheimer's disease itself, given that the majority of individuals die with these pathologies in their brains and that, among the oldest old—the age of greatest risk for dementia—the risk of Alzheimer's dementia associated with these pathologies is attenuated [54, 55].

This emphasis on uncertainty is important in considering discussions related to providing information on risk reduction. In practice, it appears rare for research participants to use genetic risk information, including that related to Alzheimer's disease, to change their behaviors to reduce health risks [56]. Nevertheless, some individuals identified as being at higher risk *will* wish to act upon it [57]. Providing well-evidenced information on risk reduction as part of the disclosure process would recognize this perceived value and may also reduce the harms associated with learning about disease risks without having any actionable options available. However,

while there is consistent evidence of beneficial associations between mid-life physical activity and other exposures, healthy aging, and disease outcomes [58], the available evidence about prevention does not yet clearly point to the efficacy of particular activities or behaviors in preventing the onset of dementia [59]. As in the discussion of risk information, communication related to risk reduction should highlight the current state of the evidence and persistent uncertainties, and be updated as further evidence becomes available [60].

Concerns related to expertise and the consistent interpretation of results echo those of participants in relation to amyloid disclosure in mild cognitive impairment [34]. They suggest an education and liaison role for Alzheimer's disease researchers, healthcare professionals, and Alzheimer's associations to ensure that the existence of research diagnostic classifications for Alzheimer's disease [61] and associated technologies is recognized. The focus on education, follow-up, and in-person disclosure highlights the potential benefits of learning from the genetic counselling model, in line with the approach proposed by Harkins and colleagues [4]. In particular, such models highlight the importance of shared decision making and two-way communication [36, 62]. However, it is also important to remain cognizant of material differences between 'state' and genetic 'trait' information [28], notably the potential for levels of amyloid change over time, and the unclear nature of the relationship between amyloid load and the development of dementia. Importantly, this involves re-emphasizing the limits in the evidence base of biomarker-based Alzheimer's disease risk information in order to reduce the potential for over-treatment and the reification of a diagnostic misconception [63].

The preferences described here highlight the importance of considering the nature and extent of short and longer-term follow-up after the communication of biomarker status. Involving wider health professionals, particularly primary care clinicians, would enable participant preferences in relation to monitoring to be met, possibly providing reassurance in the context of hypervigilance. However, such monitoring could also intensify the impact of risk information, complicate its relationship with a clinical diagnosis and possibly impact on life insurance and employment status. Regular check-ups with medical specialists would start to blur the clear boundaries between 'research' and 'clinical' criteria proposed in the 2011 NIA-AA definitions. In such circumstances, it remains to be established that the potential harms associated with unnecessarily treating individuals who may never develop dementia outweigh the benefits to those who would. It would also have resource implications for healthcare systems, although the costs of monitoring, surveillance, and preventive treatment of asymptomatic individuals with increased risks of Alzheimer's dementia are difficult to estimate accurately [64]. As current research studies will not routinely refer at-risk participants to medical care, it is not expected that major financial effects on healthcare systems will occur imminently. However, research groups should be prepared to discuss and address expectations related to support and future care, rather than automatically introducing such monitoring with unknown consequences for participants, health systems costs, and harms through diversion of resources.

Risk communication should be a two-way process, supported through a clear procedure for dialogue, encouraging and responding to follow-up questions and identifying individual needs and concerns. Recommendations on disclosure emphasize the importance of short-term follow-up by the research team, for instance through a telephone call a few days post-disclosure [33, 34]. A member of the research team should be easily accessible for research participants post-disclosure, for instance by telephone. However, participants in this research also highlight the value of longer term follow-up, in line with the six week and six month contact described in the APEX study [27], and of broader support networks of family and friends [33, 34]. Again, though, this requires a careful approach which avoids reifying a risk status as a diagnosis, and emphasizes that people who learn they are at higher risk do not have any cognitive impairments, and are not and may never become Alzheimer's dementia patients.

CONCLUSIONS

Interest in learning risk information regarding Alzheimer's dementia seems common. Often, however, it is dependent on favorable estimations of the predictive value and personal utility of Alzheimer's disease biomarkers: interest is lower when people learn that biomarkers are not conclusive or informative and options to reduce risk of disease are limited or absent. Respondents' discussions dwelt more on the long-term implications of risk information and the production of hypervigilance than short-term effects.

Participants' preferences related to the process of learning risk information underline the need for careful, responsible risk disclosure processes in research settings. They have immediate implications for practice for researchers, clinicians, and Alzheimer's associations. Importantly, they highlight the fine line and inherent ambivalence in trying to offer an appropriate level of care and support and to avoid an over-interpretation of the clinical significance of biomarker-based risk information. Research groups should be careful to prevent the care and support they offer from reinforcing the diagnostic misconception and resulting in the harms and burdens associated with hypervigilance.

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SUPPLEMENTARY MATERIAL

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