www.ep-ad.org

European Prevention of Alzheimer's Dementia Consortium

Grant Agreement nº115736

D8.3 Report on Research participant Panel

WP8 – Ethical, Legal and Social Implications

V2.0

Final

Lead beneficiary: *UCAM*
Date: *21/06/2016*
Nature: *Report*
Dissemination level: *Public (PU)*

TABLE OF CONTENTS

DOCUMENT INFORMATION

Grant Agreement Number	115736	**Acronym**	EPAD
Full title	Prevention of Alzheimer's Dementia Consortium		
Project URL	www.ep-ad.org		
IMI Project officer	Elisabetta Vaudano (elisabetta.vaudano@imi.europa.eu)		

Deliverable	D8.3	**Title**	Report on Research participant panel
Work package	WP8	**Title**	Ethical, Legal and Social Implications

Delivery date	**Contractual**	Month 15	**Actual**	21/06/2016
Status	Current version / V2.0		Draft ☐	Final ☒
Nature	Report ☒ Prototype ☐ Other ☐			
Dissemination Level	Public ☒ Confidential ☐ Other ☐			

Authors (Partner)	University of Cambridge			
Responsible Author	Richard Milne		**Email**	Rjm231@cam.ac.uk
	Partner	UCAM	**Phone**	+44 (0)1223 761912

Description of the deliverable	This deliverable reports on work with potential EPAD participants to develop recommendations related to the disclosure of Alzheimer's risk; and the establishment of mechanisms for future participant involvement.
Key words	Participants; risk; disclosure; PPI; involvement

DOCUMENT HISTORY

NAME	DATE	VERSION	DESCRIPTION
Richard Milne, Eline Bunnk, Ana Diaz, Dianne Gove	07/04/2016	1.0	First draft
Dianne Gove, Shirlene Badger, Edo Richard, Carol Brayne, Luc Truyen, Marianne Maman, Maartje Schermer, Krista Tromp,	11/05/2016 - 21/06/2016	1.1	Internal review
Richard Milne, Eline Bunnk		1.2	Review and changes
Dianne Gove, Marianne Maman		1.3	Review and changes
EPAD review		1.4	Review and comments
Richard Milne	21/06/2016	2.0	Final version

DEFINITIONS

- Partners of the EPAD Consortium are referred to herein according to the following codes:

- **Janssen**. Janssen Pharmaceutica NV (Belgium)
- **UEDIN**. The University of Edinburgh (United Kingdom)
- **UOXF.** Masters and Scholars of the University of Oxford (United Kingdom)
- **BBRC.** Barcelonabeta Brain Research Center (Spain)
- **SYNAPSE.** Synapse Research Management Partners S.L (Spain)
- **KI.** Karolinska Institutet (Sweden)
- **VU-VUMC.** Stichting VU-VUmc (Netherlands)
- **UCAM.** Masters and Scholars of the University of Cambridge (United Kingdom)
- **MRC.** Medical Research Council (United Kingdom)
- **BERRY.** Berry Consultants LLP (United Kingdom)
- **UNIGE.** Université de Genève (Switzerland)
- **RUMC.** Stichting Katholieke Universiteit (Netherlands)
- **CU.** Cardiff University (United Kingdom)
- **CHUT.** Centre Hospitalier Universitaire de Toulouse (France)
- **QUINTILES.** Quintiles, Ltd (United Kingdom)
- **AE.** Alzheimer Europe (Luxemburg)
- **EMC.** Erasmus Universitair Medisch Centrum Rotterdam (Netherlands)
- **APHP.** Hôpital de la Salpêtrière (France)
- **INSERM.** Institut National de la Santé et de la Recherche Médicale (France)
- **ULEIC.** University of Leicester (United Kingdom)
- **IXICO.** IXICO Technologies Ltd (United Kingdom)
- **ARACLON.** Araclon Biotech S.L (Spain)
- **FRAUNHOFER.** Fraunhofer-Gesellschaft zur Förderung der angewandten Forschung e.V. (Germany)
- **Eisai.** Eisai Inc (United States)
- **SARD.** Sanofi-Aventis Recherche & Développement (France)
- **NOV.** Novartis Pharma AG (Switzerland)
- **BI.** Boehringer Ingelheim International GmbH (Germany)
- **Eli Lilly.** Eli Lilly and Company Ltd (United Kingdom)
- **HLU.** H. Lundbeck A/S (Denmark)
- **Takeda EU.** Takeda Development Centre Europe Ltd (United Kingdom)
- **AC Immune.** AC Immune SA (Switzerland)
- **Biogen**. Biogen Idec, Inc (United States)
- **Amgen.** Amgen NV (Belgium)
- **Pfizer.** Pfizer Limited (United Kingdom)
- **UCB.** UCB Biopharma SPRL (Belgium)
- **ARIDHIA.** Aridhia Informatics Ltd (United Kingdom)

- **Grant Agreement.** The agreement signed between the beneficiaries and the IMI JU for the undertaking of the EPAD project (115736).
- **Project.** The sum of all activities carried out in the framework of the Grant Agreement.

- **Work plan.** Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in Annex I to the Grant Agreement.
- **Consortium.** The EPAD Consortium, comprising the above-mentioned legal entities.
- **Project Agreement.** Agreement concluded amongst EPAD participants for the implementation of the Grant Agreement. Such an agreement shall not affect the parties' obligations to the Community and/or to one another arising from the Grant Agreement.

EXECUTIVE SUMMARY

This deliverable reports on the activities conducted in involving potential EPAD participants in the development of the project and plans for the establishment of the EPAD Participant Panel. The work builds on the review of the ethical issues associated with EPAD presented in D8.1. The purpose of this deliverable is threefold:

1) To report work with potential EPAD participants conducted to inform the development of EPAD ethics guidance and practice. This involved qualitative work conducted in 2015/16 with current research participants, involved in Alzheimer's disease (AD) studies in the UK and Spain, and the Alzheimer Europe European Working Group of People with Dementia, to examine concerns related to the communication of the risk of AD.

2) To report recommendations on the disclosure of AD risk approved by potential EPAD participants to inform the disclosure and education process that will accompany participant recruitment from the EPAD Longitudinal Cohort Study to a Proof of Concept trial.

3) To set out recommendations and plans for involving EPAD participants in decision making throughout the research process. The aim of this work is to draw on participant experience to improve and develop the EPAD project, and to reciprocate the contribution of these participants to EPAD. It includes establishing mechanisms for participant representation at the local and project level. Key recommendations include that:

    a. Each local TDC should establish a local participant panel consisting of 6-8 participants.
    b. From each local participant panel, one participant will represent the local participant panel in the central EPAD Participant Panel,
    c. From the central Participant Panel, participants should take turns to represent the Panel at a project management level – advice on the implementation of this should be developed by WP5.

INTRODUCTION

Patients and the public feature at several points in the EPAD research process, most prominently as research participants. However, they also play a role in two further activities, commonly defined as engagement and involvement. The first activity involves work specifically aimed at raising awareness of research, sharing knowledge or engaging and creating a dialogue with the public – in EPAD such work is often the responsibility of WP6 or the TDCs. The second involves creating and maintaining a relationship with participants within EPAD. It indicates input which shapes the research process itself; often described as carrying out research *with* members of the public, rather than solely *on* or *about* the public[1]. The value of patient, public and participant involvement in research is increasingly recognised[1] as providing practical benefits for the research process and as important in establishing an ongoing relationship with research participants that reciprocates their contribution.

Mechanisms for involving participants are well-established or under development in some EPAD parent cohorts, including the PREVENT and ALFA cohorts. They provide the basis for a two-way interaction with EPAD research volunteers, and a means of making meaningful the description of these individuals as 'participants', with a role in influencing the design, conduct and reporting of research [2,3], and shifting the relationship towards that of collaborators rather than subjects.

Figure 1: The aim of the EPAD Participant Panel is to move participants from a role as passive subjects to active partners in the EPAD project

There are two main arguments for participant, patient and public involvement (PPPI) in health research. Moral arguments suggest that involvement is a right, so that the citizen can have a voice in publicly funded research, and that individuals have the right to be involved with any research intervention potentially being done 'to' them. PPPI activities thus establish a reciprocal relationship between researchers and participants that recognises the contribution and interest of participants in the study. They also establish accountability and transparency between the study goals and the study population, and provide an opportunity for researchers to respond to participants' concerns.

A methodological argument suggests PPPI leads to higher-quality research with greater impact. Participant involvement can provide a valuable set of insights into the research process. Potential positive impacts relevant to EPAD include the development of user-friendly and user-focussed research objectives, questions, and study information, improved consent procedures, questionnaires and interview schedules and enhanced implementation and dissemination of study results[4]. Participant involvement may also enable the adaptation of study logistics and documentation to specific local contexts and sensibilities, facilitate the introduction of new test modalities and/or study requirements and aid in the identification and resolution of ethical concerns.

This report consists of two sections. The first describes work conducted with potential EPAD participants to inform the development of EPAD ethics guidance and practice. It focusses on the background, methods and main findings of the Approaches to the Communication of Alzheimer's disease Risk (ACAR) study, led by WP8. Focus groups explored potential EPAD participants' views on potential benefits, risks and implications of AD risk disclosure in the context of research, their preferences with regard to AD risk disclosure, and their responses to different types of risk information (i.e. genetic, imaging, or lifestyle information). The study developed recommendations for the communication of AD risk with research participants. These were approved by all participants.

In the second section, WP8 outlines its plans for establishing ongoing participant panels within EPAD. As a large-scale and leading European research project, EPAD should support high standards of research conduct at all stages. This includes involving research participants at all levels of research organisation. The proposed model involves the establishment of local EPAD participant panels at each TDC. A central EPAD Participant Panel will be formed from representatives of local participant panels. These proposals were presented and discussed at the EPAD General Assembly.

This deliverable leads to follow-on work which will involve developing guidelines for participants and TDCs outlining expectations for participant involvement, and working with WP5 to identify how participants will be incorporated into project governance. In addition, WP8 will develop a programme of research building on the empirical work conducted within the ACAR study and a systematic review around disclosure.

SECTION I: INVOLVING POTENTIAL EPAD PARTICIPANTS IN EXPLORING ETHICAL ISSUES AND STUDY DESIGN

WP8's initial work with EPAD participants consists of involving potential EPAD participants in scoping the ethical issues associated with the project. These resulted in recommendations which will feed into the design of later stages of EPAD, notably related to the disclosure of Alzheimer's disease risk. This work was conducted under the auspices of the Approaches to the Communication of Alzheimer's disease Risk (ACAR) study.

1. The Approaches to the Communication of Alzheimer's disease Risk (ACAR) study

1.1. Introduction

As discussed in detail in deliverable 8.1, disclosure of biomarker-based Alzheimer's dementia risk status will occur during recruitment to PoC trials within the EPAD project. The implications of disclosing information related to Alzheimer's disease risk have been discussed in the clinical and scientific literature for two decades [5,6]. This conversation has primarily focussed on the communication of genetic susceptibility genotypes, notably APOE4. Existing research has explored the implications of, and procedures for, risk disclosure [7–9] by building on the model developed for the communication of genetic test results. This literature suggests that there are few if any long-term implications for anxiety and depression among those who receive risk disclosure[10] (see D8.1 Annex for a summary of this work). However, these studies have important limitations in terms of their geographical focus and scope.

Firstly, existing research has concentrated on the USA. As such, it inevitably reflects US attitudes towards risk, Alzheimer's disease, healthcare and clinical research. Importantly, research by Alzheimer Europe[11] along with a small body of existing comparative work[12–14] suggests that attitudes to AD risk may vary significantly between and potentially within countries, including between the USA and Europe. By providing a European perspective on disclosure, this research aimed to deepen our understanding of how and why this is the case, adding to the evidence on how understandings of AD risk vary cross-culturally. Secondly, existing research concentrates on the disclosure of genetic-based risk information and disclosure approaches based around the model of counselling for genotype disclosure. This reflects the prominence of APOE genotype in thinking about AD risk. However, in the context of EPAD there is a need to explore whether such trait information, which may make only an incremental contribution to individuals' knowledge of their future health in the context of well-understood family histories[15], differs from state information, such as the results of PET imaging or CSF sampling [16].

The empirical research undertaken for this deliverable thus aimed to investigate what people think about the disclosure of the risk of developing Alzheimer's dementia and to contribute to guidance on whether and how to communicate risk status in Alzheimer's research.

1.2. Summary of key findings

- Hypothetically, the majority of the participants would want to know their Alzheimer's risk status.
- Information on risk was seen as useful to facilitate planning, for taking action to reduce risk and to help obtain early diagnosis in the event symptoms emerge in the future.
- The uncertainty of risk information significantly reduced its value and appeal, as did the lack of effective treatments or clear approaches to risk reduction.
- The implications of risk were significant for families, because of heritability and the potential future care responsibilities of partners and children.
- Most would tell partners and children about their risk status, but some were concerned about its effect on these relationships
- There were no major differences in discussions between different types of risk information.
- The most important feature of any disclosure is its ability to provide clear, concrete information.
- Discussions of biomarker and lifestyle-based risk scores placed more emphasis on the causes of elevated risk, and on responsibility for this.
- The research led to the development of recommendations on the disclosure of AD risk which were approved by all participants. These will inform the disclosure and education process that will accompany participant recruitment from the EPAD Longitudinal Cohort Study to Proof of Concept trial.

1.3. Methods

Focus groups were held in London and Barcelona between November 2015 and January 2016. Spanish participants were recruited through the BBRC (Barcelonaβeta Brain Research Centre) database of volunteers. The BBRC is the research centre of the Pasqual Maragall Foundation and many of the group participants were also participants in the ALFA longitudinal study of Alzheimer's disease[17]. UK participants were recruited through the PREVENT study based at West London Mental Health Trust[18]. Both ALFA and PREVENT focus on dementia prevention in mid-life and none of the participants in the London and Barcelona groups had dementia. Participants in studies such as these are likely to be among those contacted to take part in EPAD. As such, while their views may not be representative of the population as a whole, they are more likely to capture the concerns of participants in research and as such, have more immediate relevance. In addition, one group discussion was held with Alzheimer Europe's European Working Group of People with Dementia (EWGPWD) to obtain the perspective of people with dementia. The study was approved by ethics committees in Cambridge and Barcelona.

Four groups were held at each site, three with people with a first generation relative with Alzheimer's dementia, one with people without this family history. A total of 51 people participated, 32 in Spain, 19 in the UK. The Spanish groups consisted of 20 women, 12 men, with a median age of 61. These groups were facilitated in Spanish by Ana Diaz (AE). The UK groups included 10 women and 9 men with a median age of 55. These groups were facilitated in English by Richard Milne (UCAM). The EWGPWD group included six people with dementia and four partner caregivers. It was facilitated in English by Richard Milne.
The groups were conducted according to the same protocol. In advance of the groups, participants were provided with a short background information document on the shift in Alzheimer's disease research to a focus on prevention and early intervention (see Annex). The discussions started by establishing how this new information fitted with participants' background knowledge and their own and familial experiences with Alzheimer's and other forms of dementia. It then moved into a broader discussion of whether participants would want to learn their Alzheimer's disease risk and what the implications of this would be. In the second part of the discussion, three short vignettes were introduced (see Annex). These described three forms of risk information – genetic testing for ApoE, PET amyloid scanning and a 'combined risk score' based on lifecourse and lifestyle factors. Each of these vignettes was discussed. Participants were asked whether the nature of the test affected their previous discussion of risk, and if or how such information might be useful or harmful. Finally, participants were asked for their views on how the disclosure of Alzheimer's disease risk should occur, drawing on the own experience and the group discussion.

Following the group meetings, the findings and recommendations were written up as a report for participants. This was circulated by email to the participants in Spain and the United Kingdom for comment. The participants from Alzheimer Europe's EWGPWD discussed and reviewed the recommendations in a face-to-face meeting. The findings and recommendations have been revised in response to all feedback provided.

1.4. Results

1.4.1. Background knowledge

The majority of participants at both ACAR sites had family members with AD or other forms of dementia. This included all but four participants in Barcelona and three of the four groups in the UK. In reflecting on their own knowledge and experience of dementia a key theme among those with a family history across both sites and the EWGPWD was the difficulty they or their family members had encountered in receiving a diagnosis, and the lack of support associated with a diagnosis. In Spain, participants described a lack of awareness of dementia on the part of GPs and in society more broadly. In the UK, participants described how it had been difficult to obtain a formal diagnosis of dementia.

1.4.2. Attitudes to disclosure

The majority of participants in both the UK and Spain expressed an interest in knowing their own risk status. A number of reasons were given for wanting to know. Significantly, a number of people with a parent with Alzheimer's or another dementia already felt they were at high risk. Participants in the Barcelona groups also mentioned that other people, including colleagues or friends, also assumed they were at higher risk because they had a family member with AD. As such, participants suggested that learning AD risk status might provide only an incremental change in knowledge.

While there was overall interest in learning AD risk status, there was also an acknowledgement that this might not be the case in practice. A discussion in one of the London groups is particularly illuminating in this regard, in which participants described being at a research meeting where they thought someone was about to be described as being 'at risk', their "stomach just sort of went into my boots" leading them to think that "when you're actually faced with it I'm sure it's going to be very different".

1.4.3. Perceived benefits of learning risk information

One important driver of the desire to know was clearly the experience of seeking a diagnosis – either for themselves or relatives – and the hope that being identified as 'at risk' might lead to earlier detection of symptoms, earlier diagnosis and potentially earlier access to care.

The value of learning risk information was described at both sites in terms of its implications for practical planning, including setting up advance directives or establishing power of attorney. Some participants with a family history also mentioned that it would allow them to accept their risk and prepare themselves, including potentially enabling them to have conversations with family members that they wished they had had with their own parents.

Participants also suggested that knowing they were at higher risk would enable them to take action to reduce their risk, although they were also sceptical about whether this would happen.
Finally, in the Spanish groups, one perceived possible advantage of learning risk status was that, as it became more widespread, it might contribute to increasing societal knowledge about dementia, and shifting attitudes.

1.4.4. Concerns about learning risk information

Concerns about learning AD risk status emphasised the lack of effective treatment or of anything 'definite' that could be done to reduce risk or delay the onset of dementia. As one participant in the EWGPWD described:

> *…. if 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? 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…*

Furthermore, they suggested that there is currently little benefit to knowing as the information itself is uncertain and consequently of limited value. As UK participants described after considering the case study vignettes:

> *C – But it's interesting getting me thinking with what I've gone through before, you know, would I … if I left here today and I was approached like, 'Do you want to go to genetic testing and the amyloids at this stage?' and just thinking about it I probably wouldn't. You know, why …*
> *A – You're not going to gain any information from it.*
> *C – Yeah.*

Finally, participants were concerned that some people might be told they are at risk but never develop dementia. This would lead to unnecessary stress and anxiety for people and their families

1.4.5. Implications of knowing

Participants described a number of expected implications of knowing that they were at elevated risk. Firstly, they suggested that whilst initially it could be difficult to learn about risk, these initial consequences would pass, and they would learn to deal with the information. But they suggested other people may not want or be able to do this.

Participants described the potential implications for their families, either because the information would be genetic and therefore shared between family members, or because of the knowledge that family members might become carers in the future. A number of participants in the groups in Spain and the UK then emphasised that they did not want their children to have to look after them in the same way they had cared for their own parent.

The provision of risk information was seen as a potential opportunity to institute changes in lifestyle or, as one Spanish group described, to review life values. As one UK participant put it, introducing lifestyle changes would mean that you would know "you gave it your best shot as well." However, in both UK and Spanish groups, there was scepticism about how realistic or durable lifestyle change would be.

A further consequence of learning risk status was seen as the potential to become hyper-aware of changes in cognition. Thus in the Spanish ACAR groups one participants described how "I would monitor myself closely, so I could see any early changes" while in the UK, another described how

> *"it could be that if you've been assessed as having a higher risk and then you've got 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."*

Interestingly, the discussion in the group without family history in the UK took a slightly different direction. As the conclusions above suggest, discussion in the majority of groups focussed on the nature of dementia, and the need for care. However the discussion among this group focussed much more abstractly on 'risk' and its meaning, drawing on broader understandings of disease risk, including related to heart disease and cancer, and concentrating much less on the implications of learning *dementia* risk per se.

1.4.6. Who to tell?

Almost all participants indicated that they would tell their partners if they were told they were at increased risk of developing Alzheimer's dementia. They emphasised that it was not necessarily information they saw as significant, as it is only a risk status, and its implications are unclear. However, some participants in the EWGPWD group said that they would keep it to themselves for some time.

Most participants suggested they would tell their children. There were concerns that children would become worried, but participants also suggested they would be able to tell their children not to care for them. Few participants indicated they would tell their friends - although some suggested they would tell a close group of friends, while one Spanish participant commented that "It should be treated like a risk for any other illness/disease". Nobody felt they would inform their employer or insurance company unless they had to. Participants in both countries argued that it was not information that would be relevant to employers, while in the UK groups it was also suggested that the information could potentially prove damaging in a competitive work environment; perhaps leading to being overlooked for promotion. Some EWGPWD members described receiving good post-diagnosis support provided by employers but felt that, in contrast, knowledge of risk status might damage opportunities for employment and progression and that it was information that should be protected.

While almost everybody said they would tell somebody about their risk status, there was concern in all the groups about the consequences of this, including subsequently feeling like they were being monitored by their family or losing authority within the family. As one participant in London described:

> *"I wouldn't want people second guessing me. So if you've told somebody that and then you do say something really stupid [laughs], or they find your keys in the fridge, right, they think, oh, that's what it is then".*

For some, this lead to a preference not to tell anyone, at least initially. As one Barcelona participant commented:

> *"people would treat me different, they would be trying to find signs of dementia. I would monitor myself, I would not like others telling me what to do, or "observing" me".*

1.4.7. Risk domain vignettes

In the second part of the group discussion, participants considered specific forms of risk information. Three examples were presented: genetic testing, PET amyloid imaging, and a 'combined risk score' based on lifestyle and other factors. Of the three, participants generally saw no significant difference between the genetic and amyloid risk information. The defining factor at all three sites was the detail and predictive accuracy of the information provided, rather than the domain of the information. Nevertheless, discussion of amyloid status did move the groups towards considering the causes of pathology, while the genetic information was seen as more clearly causal in its own right. Discussion of causes and prevention then expanded significantly in discussion of the third vignette, around

lifestyle risk scores. The overall narrative in all contexts was that this was more useful information, in that it was enabling and provided participants with a course of action.

APOE

The distinctive feature of genetic testing was that it makes risk a concern for families as well as participants. In addition, in the UK groups it was seen as having implications at an early stage in the lifecourse, as it could influence whether or not people chose to have children. This created a quandary in terms of when the information would be most pertinent. On the one hand, "if you knew early enough" people may decide not to pass on the gene. On the other hand, participants said that they would not want to know in their 20s and "carry that burden" for 40 or 50 years, particularly if the gene is not predictive of likely age of onset. Similarly, in the EWGPWD discussion, one participant described how knowing that she had a gene would "hamper" her life, while another said that he would like to know at his age, in his late 60s, but would not have wanted to know previously.

Given the probabilistic nature of the APOE gene, some participants described it valuable as part of an overall picture of risk. As one described "I'm trying to sort of paint a picture of what I, my understanding of this, because we have to have an individual understanding of what we think it is and how it relates to us I suppose."

PET Amyloid

For most participants, PET amyloid imaging was discussed in the same terms as APOE genetic testing. Again, the most important feature of any information was its ability to accurately quantify risk, and to provide a course of action. Nevertheless, there was some discussion of how, while APOE was predictive, PET amyloid provided evidence of actual brain changes. As one UK participant put it ""you know, there is something there, not just a predisposition because of genetics but they're actually tracing something". However, the relevance of this information alone was not clear. In the EWGPWD discussion, participants focussed on the fact that some people with dementia do not have significant amyloid deposits. As one group discussion in London described:

> *E – I'm not going to come out going, 'Oh my God! Amyloids!'*
> *D – But unless they can tell you what's causing the amyloids or what you've got to do to get rid of the amyloids …*
> *A – No that's right.*
> *D – … what do you gain from it?*

As the extract above suggests, discussion of PET amyloid did start to move the focus towards the perceived causes of brain changes. As one Spanish participant put it "What I would like to know is what is causing these deposits, not the fact that I have them". Similarly, a UK

participant described how the value of the test would come when "you knew what was causing the amyloids and what you could stop doing to stop the build-up."

Combined risk score

The final example of risk information, the combined score, was discussed with more enthusiasm in the groups, despite not providing more detail about the actual level of risk. This was due to the perceived ability of participants to do something in response to the information. As one London participant described "Well I think it's quite valuable, actually, because that means that there is something almost straightaway that you could do". In the EWGPWD the combined, lifestyle-based risk score fitted well with discussions of why people felt they had developed dementia – including lifestyle factors, stress and depression as well as head injuries.

There was comparatively little discussion of the nature of this type of information. However, in one of the UK groups, one participant described the combined risk score as "… a softer diagnosis let's say than … you know, you've got that wrong with your brain or you've got that wrong with your genes." For some, this meant that the information was less convincing. As another UK participant described, contrasting it with amyloid imaging, "you can't, you can't fabricate or deny an amyloid in the brain or a protein in the brain, you can't deny one of these tangles, whatever they look at, it's more, it's more factual".

While the overall perception of the combined risk score was as useful information, there was some disappointment in both the UK and Spanish groups that the likely prescribed courses of action – dietary change, exercise – were the same as the general advice provided for healthy living. Similarly, an EWGPWD member suggested that the usefulness of the information depends on how specifically it can be linked to dementia. Concerns were also raised in the Spanish groups about whether family and friends would pressurise people to make lifestyle changes in response to the information, and whether it was fair to make people make changes without being certain of the benefits. Similarly, in one of the London groups, it was felt that the lifestyle score pointed more clearly to individual 'guilt' and responsibility in relation to dementia risk.

1.5. Conclusions

The ACAR and EWGPWD group discussions suggest that there is interest in risk information but that this is tempered by an awareness of the poor predictive quality of the information. The desire to know or not is also shaped by participants' own experiences, understandings and attitudes towards Alzheimer's dementia. The few groups with participants without family histories suggest that without this experience, discussion focusses more on the generic or abstract nature of disease risk.

Differences between types of risk information are secondary to the perceived predictive value of the information itself. While no major differences emerged between genetic and biological markers, discussion of the former emphasised the relevance of the information to family members, and treated it as static information of different utility at different stages of life. In contrast, the latter directed attention much more towards individualised causes of pathology. This discussion then developed further in relation to the lifestyle risk score. This final source of information was seen by participants as providing more options for action than the first two, and thus as potentially more useful information to receive.

The findings of the ACAR work, and the recommendations produced, represent the first stage in the empirical work of WP8. They are pilot qualitative findings, aimed at elaborating key areas for further research. Such research will explore the generalisability of the discussions and recommendations introduced here, and will, where possible, involve EPAD research participants as collaborators to explore the experience and implications of EPAD participation.

2. Recommendations related to the EPAD disclosure process

The ACAR research produced to a number of recommendations related to the disclosure, within research settings, of the risk of developing Alzheimer's dementia. The recommendations will be used to inform the development of EPAD educational materials and the disclosure process, alongside existing best practice.

The recommendations assume an individual has already chosen to learn their risk status, and the implementation of each recommendation should reflect individual preferences around disclosure where possible. The recommendations concentrate on the nature of the communication process, and the content and consistency of the information. However, they also suggest that the disclosure of risk status has the potential to become the start of a pathway that ultimately cumulates in diagnosis. Given the uncertainties around AD risk information, and the potential implications of formal and informal monitoring associated with risk status, the value and impact of this journey needs careful consideration. Follow-up work will explore this post-disclosure journey, and expand work with people without family histories.

RECOMMENDATIONS ON THE DISCLOSURE PROCESS FROM ACAR PARTICIPANTS
Information should be provided by experts with the necessary skills and knowledge to help people make sense of the information.
Participants emphasised that not everybody would know how to make sense of the risk information. They suggested that it was important that the person responsible for disclosure have sufficient depth of knowledge to help people understand the information and its implications.
The risk disclosure process should make it clear that this is a risk status, not a diagnosis.
Participants were concerned to make it clear that their discussion was not about receiving a diagnosis of Alzheimer's dementia, but a risk status. It is important that this distinction is emphasised.
Consistent and clear information should be provided on what higher risk means.
One of the most important themes in the group discussions was the importance of being able to explain what exactly is meant by higher risk. Participants would ideally want detailed – ideally numerical – information on what their actual risk was of developing Alzheimer's dementia. This should be provided in writing, to allow people to review and reflect on the

information.

Information about risk should be adapted to the person receiving the information.

Participants suggested that not everybody would either understand or interpret information in the same way, and that the disclosure process should account for this.

The process of disclosure should take place face to face in a dedicated, quiet setting.

Participants felt that they would rather learn their risk status face to face rather than by telephone or letter. The environment in which face-to-face risk disclosure occurs should be appropriate.

People should have the opportunity to ask questions during and after the disclosure process.

The disclosure process should allow time for discussion and for questions. As not all questions may occur to people at the time, they should be able to raise questions after disclosure as well.

The information and its interpretation should be consistent whether communicated by researchers or in medical practice, including by GPs

Participants were concerned that while they would be given a clear interpretation of risk information by clinicians involved in research, their GPs may not give them the same interpretation in subsequent conversations. They were concerned that this could lead to potentially conflicting and confusing messages.

The risk disclosure process should involve psychological and emotional support.

Participants suggested that for some people, the impact of learning risk status would be significant, and emphasised that support should be available to people if they would like it. They also suggested that the process should make people aware of the other sources of support that are available.

Communicating risk status should be accompanied with the best available information on how to reduce risk.

One important reason for wanting to know risk status was that it might enable people to take action to reduce their risk. Providing this information as part of the disclosure process provides people with a course of action.

People should be monitored and supported after disclosure.

Participants expected that there would be some kind of follow-up after people learn their risk status if they would like it. This would involve making psychological and emotional support available in the longer term and potentially a regular check-up with a doctor.

In the future it is important that people have equal access to information about risk

Although the discussions focussed on the communication of risk within a research setting, concerns were also raised about who would have access to risk information in the future, and whether testing would be equally available and affordable to all. This may be particularly pertinent in the case of genetic and amyloid testing.

2.1. Implementing the recommendations in EPAD

The recommendations for AD risk disclosure developed within the ACAR study will be translated into the EPAD research context. In setting up procedures for the disclosure of the AD biomarkers, EPAD researchers should consider and accommodate the following recommendations:

During disclosure:

- Disclosure of an AD biomarker should ideally take place face-to-face in a private, quiet room. This implies that the TDC must make rooms available for this purpose.
- There should be sufficient time for research participants to ask questions.
- The disclosure discussion should be conducted by an expert who provides clear and consistent information and has the skills to help participants understand the meaning and implications of a positive biomarker for AD, each at their own level of understanding.
- The expert should focus on informing participants that a positive AD biomarker is a risk factor, not a diagnosis. Ideally, the expert should be able to accurately quantify the participant's AD risk, although this may not be feasible on the basis of available evidence. In this case, the uncertainties associated with the information should be made clear
- The expert should point out whether there are any strategies to reduce AD risk that have proven effective. Given that conclusive evidence is limited in this area, participants should be provided with information based on the best available evidence.

After disclosure:

- Participants should receive written information materials about the meaning and implications of a positive biomarker for AD, and about established strategies to reduce AD risk.
- In order to improve participants' access to relevant information, EPAD may make information available online, outlining the state of knowledge around AD biomarkers and dementia risk reduction. In its newsletters, it can refer to up-to-date information posted online.
- Participants should be given written information they can bring to their GPs, treating physicians, or other healthcare professionals, providing scientific references to explain the significance (or lack of significance) of the finding to them and ensure a consistent healthcare approach.
- Those who may need psychological support, should be referred by EPAD researchers. This implies that EPAD researchers should make prior arrangements with psychological care professionals in the region.

Disclosure will take place in various TDCs in various countries by various researchers in various languages. In order to assess the psychological, behavioural and social effects of AD risk disclosure, and to facilitate comparison across EPAD sites, the disclosure processes will ideally be standardised. This underlines the importance of the Education Task Force, which will provide information and educational materials for research participants, and form part of the ongoing training of EPAD investigators on how to inform, communicate and/or disclose information about EPAD.

SECTION II: ESTABLISHING PROCESSES FOR ONGOING INVOLVEMENT OF EPAD PARTICIPANTS

3. The participant panel

The aim of the ongoing EPAD participant panel is to enable research participants and patients to make a meaningful contribution to the direction of the EPAD study, to reciprocate their contribution to research and to obtain feedback about their experience of participation. Though the everyday interactions in the TDCs in the various regions should involve active inquiry into the welfare and the experiences of research participants, formal mechanisms for involvement will be put in place through the creation of a central EPAD Participant Panel formed from members of the EPAD longitudinal cohort study.

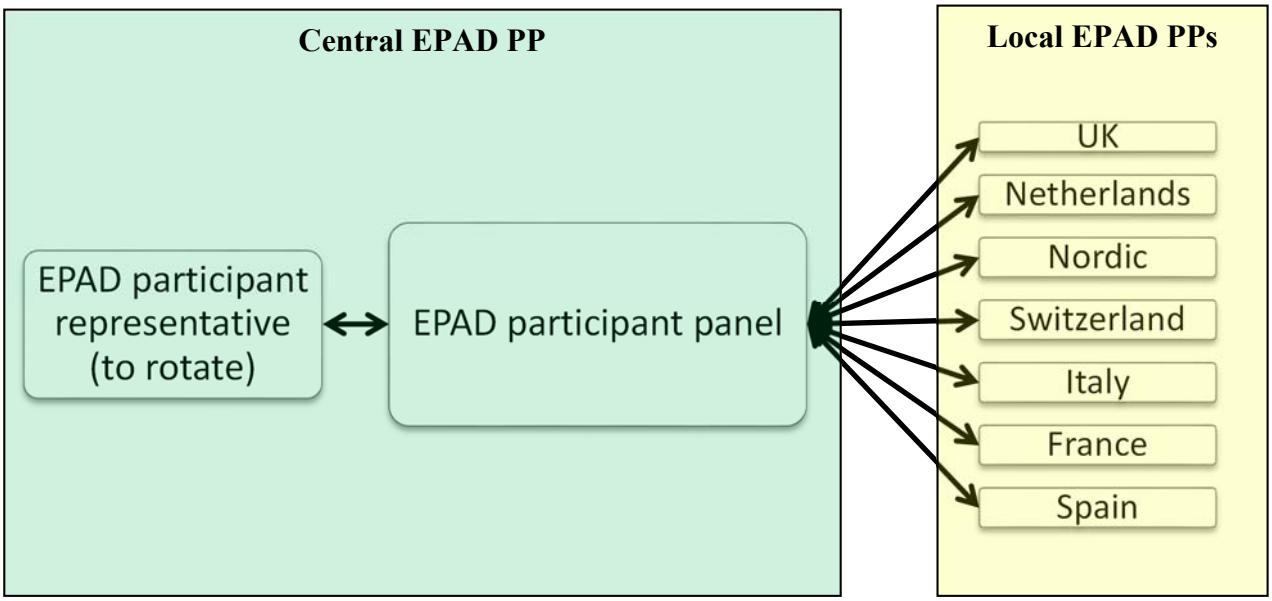
3.1. The panel structure

The EPAD Participant Panel should represent participants at a local TDC and at the wider/whole project level.

Each local TDC should establish a local EPAD Participant Panel consisting of 6-8 participants. In local panels, participants can discuss their experiences in their native languages, and raise issues that may be specific to the TDC, to the local healthcare system or to the cultural context of the TDC. Establishing local representation will enable recommendations that result from local panel discussions to be directly implemented at the TDC. The group will meet at least once a year in person at the TDC.

From each local EPAD Participant Panel, one participant will represent that panel in the central (English-speaking) EPAD Participant Panel. Every year, the central EPAD Participant Panel will meet once physically at the General Assembly, and once virtually, through an online communication tool. This meeting will be facilitated by WP8.

From the central Participant Panel, one participant should represent the Panel at a project management level – advice on the implementation of this will be developed with WP5.



3.2. Panel recruitment

Through either the first newsletter to be sent to EPAD LCS participants and study partners, or at the first repeat LCS visit, all participants should receive a notice explaining the aims and structure of the local and central participant panels. Participants will be asked to contact the TDC if they would like to take part in their local participant panel. They will then be provided with information on what taking part in the panel involves, including the loss of confidentiality and anonymity associated with being identified as a research participant.

One member of this panel should be willing to attend the central EPAD participant panel, and the TDC should endeavour to ensure that this person can speak sufficiently fluent English to participate in the central panel discussion.

If this approach leads to few responses, additional approaches must be considered (e.g. a notice on the EPAD website, a flyer at the TDC, a brief oral introduction of the participant panel by EPAD investigators, etc.). WP8 will provide a template for the notice(s) in English, which TDC coordinators can translate into the local languages of the various TDCs.

If the newsletter announcement leads to a significant response, the TDC should attempt to ensure that the panel is as representative of a range of views and experience among the study population as possible. The TDC should also consider establishing a waiting list of participants who replace members of the panel who chose to cease this role, or who reach the end of a fixed term.

3.3. Content of discussions

Participant panel discussions will provide for reflection on existing study experience; discussion of future plans for EPAD, such as those related to the establishment of collaborative agreements with other studies or the introduction of new testing modalities; and focussed discussions on issues that would benefit from the direct attention of participants, such as reviewing study documentation or reviewing questionnaires for assessing the experience of EPAD participation for both participants and study partners.

3.4. Ensuring the success of the panel

The success of the panel requires a clear articulation of the responsibilities of both participants and researchers. A number of core values associated with the panel should be agreed, including respect for the confidentiality of discussions and for the opinions of panel members. Participants should make a commitment to be present at one or two meetings a year, to prepare for these meetings and to act as a point of contact for other participants if necessary. For one participant at each TDC, their commitment will also involve effectively representing the local group at the EPAD General Assembly. TDCs should make a commitment to respect the input from the participant panel, be willing to make changes to practice to reflect their recommendations, and ensure that participant panel members' experience of taking part in EPAD research is not affected (negatively or positively) by their involvement in the panel.

Research suggests that successful lay representation in research studies relies on an effective working relationship between the local study team and participant representatives[1]. It is thus essential that the participant panel is reviewed and fostered locally. One key element is identifying a named contact with whom participants feel comfortable liaising, ideally someone independent of the core study team.

3.5. Monitoring the effectiveness of participant involvement

One key weakness of existing work in PPI has been the difficulty in assessing the impact of such activities. Consequently, TDCs and participant representatives should work together to record their input at TDC level and associated outcomes. This will enable the review, assessment and refinement of the EPAD Participant Panel over time.

3.6. Future directions for the EPAD Participant Panel

Current plans for the EPAD Participant Panel will be revised over time in collaboration with members of the panel themselves, with the long-term aim of developing a truly participatory approach to research. Particular areas of interest include but are not limited to:

- Planning for meaningful participant involvement in EPAD clinical trials
- Contributing to the development of procedures for assessing study experience for both participants and study partners
- Expanding mechanisms for participant involvement beyond the scope of the panel
- Establishing opportunities for participant partnership in follow-on research proposals from EPAD
- Identifying gaps in participant representation within EPAD

ANNEXES

Annex 1: Materials provided to ACAR participants

CONTENTS

1. Approaches to the Communication of Alzheimer's disease Risk (ACAR) Information Booklet – provided to all participants in advance of the study
2. Vignettes on different testing domains

ACAR Background Information Booklet

Approaches to the Communication of Alzheimer's disease Risk (ACAR)

Information booklet

The changing definition of Alzheimer's disease

There are more than 10 million people with dementia across Europe. Dementia has a range of causes and affects everyone differently. It includes a group of associated symptoms, from memory loss to difficulties with thinking, problem-solving or language, and sometimes changes in mood or behaviour. Dementia is progressive, becoming more pronounced over time.

Dementia affects people's ability to do a range of activities of everyday life and to maintain their independence. It may have social, physical and psychological effects, which may be due to the effects of dementia, but also to frustration and worry or the attitudes and behaviour of other people. With support, it is possible to live well with dementia.

Alzheimer's disease is the most common cause of dementia, accounting for around 70% of cases. Until recently, it has been identified by changes in people's memory and behaviour. However, doctors and researchers working on Alzheimer's disease have produced a new definition of the disease. They hope that changing how we think about Alzheimer's will allow a better understanding of what happens in the disease and lead to new drugs becoming available.

Changing criteria for Alzheimer's disease

The new definition of Alzheimer's disease builds on research that has helped produce a clearer picture of what is going on in the brain over time. It suggests that early changes in the brain happen as much as 20 years before the first symptoms show. During this stage, people may have no symptoms, but deposits of proteins called amyloid plaques and tau tangles start to form throughout the brain.

These protein deposits are the characteristic signs of Alzheimer's disease. As they form, nerve cells in the brain stop functioning, lose their connections with other nerve cells, and die. It is however important to note that not all people with plaques and tangles go on to develop the disease.

Understanding how the brain changes

Current research aims to better understand the biological changes in these early stages – what the new definition calls 'preclinical' or 'asymptomatic' Alzheimer's disease. Understanding how the brain changes before symptoms appear might allow doctors to accurately estimate an individual's risk of developing dementia. This would be important because it is thought that drugs or other therapies to stop or slow the changes would be most effective at these early stages.

At the moment it is impossible to predict with any certainty whether an individual will develop Alzheimer's dementia in the future, except in people who have rare genetically

inherited forms, which account for between 1% and 5% of cases. Research suggests that for most people a large number of genetic and lifestyle factors increase or decrease the risk of developing Alzheimer's dementia in the future.

Much is still unknown about the course of Alzheimer's disease, and many people who have the early changes associated with Alzheimer's disease never develop symptoms of dementia. There is no agreed standard for what is a significant change in tests for markers, and different tests can give differing results. Finally, while current treatments are effective at treating symptoms, there are no medicines scientifically proven to prevent, stop or slow the progression of the disease. Because of this the new criteria are not currently used by doctors in clinical practice.

Using the criteria

In the last 25 years, only four drugs for Alzheimer's disease have been introduced, despite research on many medicines that were thought to be promising. Now, many researchers think that past trials failed because they were aiming too late in the disease when the damage to the brains of participants was already too far advanced. They want to use markers to find people, potentially before symptoms appear, for inclusion in drug trials to prevent or slow the disease process. However, recruiting people for this research may mean telling people who are currently healthy that they are in a high risk group for Alzheimer's dementia. It's not clear what the implications of this for individuals and their family and friends would be.

Glossary

Preclinical: The first stage of the new Alzheimer's disease classification. It covers a (possibly long) time period when the biological changes associated with Alzheimer's may be seen in the brain, but there are no symptoms. It is a definition intended to be used in research, not in clinical practice.

Biomarker: A biomarker is something in the body that can be measured which reliably indicates whether disease is present or not, or the risk of later developing a disease. Commonly used examples include blood sugar levels for diabetes, or cholesterol levels for heart disease.

Amyloid: A protein in the brain. 'Plaques' of amyloid in the brain are a classic sign of Alzheimer's disease. In the past it has only been possible to see them after death, but they can now be seen with new brain imaging technologies.

Tau: A protein in the brain. 'Tangles' of tau are thought to kill nerve cells and are one of the characteristic features of Alzheimer's disease.

Optional further reading

Introductions to Alzheimer's disease

The Alzheimer's Society (UK) introduction to Alzheimer's disease
http://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=133

Alzheimer Europe introduction to Alzheimer's disease
http://www.alzheimer-europe.org/Dementia/Alzheimer-s-disease

'Alzheimer's basics' from the National Institute of Ageing (USA)
https://www.nia.nih.gov/alzheimers/topics/alzheimers-basics

For more information on the new definition of Alzheimer's disease

Description of the new diagnostic criteria from the Alzheimer's Association (USA)
http://www.alz.org/research/diagnostic_criteria/

And their Frequently Asked Questions
http://www.alz.org/documents_custom/Alz_Diag_Criteria_FAQ.pdf

For any questions about the booklet, please contact

Dr Richard Milne
01223 761912
rjm231@cam.ac.uk

Institute of Public Health
University of Cambridge
2 Wort's Causeway
Cambridge
CB1 8RN

ACAR Vignettes

Genetic testing

Scientists have so far identified several genes implicated in the most common, late onset form of Alzheimer's disease. The gene with the strongest influence on risk is called APOE. It has three forms called ε2, ε3 and ε4. People who carry the ε4 form have an increased risk of developing Alzheimer's disease.

A blood test can identify which forms of APOE a person carries. However, it cannot predict with certainty whether they will or will not develop Alzheimer's disease. This is because a number of other factors influence whether or not somebody will develop Alzheimer's disease.

Genetic testing is widely used in research, to help understand the factors associated with an increased risk of developing Alzheimer's. However, it is currently not recommended by doctors.

*If you learned you were at increased risk of Alzheimer's disease from **a genetic test,** what would the implications be?*

Figure 2: A genetic test would be done on a blood or spit sample

Amyloid Imaging

One of the distinctive signs of Alzheimer's disease in the brain is the presence of abnormal build-ups of a protein called amyloid. For a long time, it was only possible to see these after people had died. In the last few years, a new brain imaging technology called amyloid-PET has been developed. It allows scientists to detect amyloid in the brain while people are alive.

Not everybody with a build-up of amyloid will go on to develop Alzheimer's dementia. Some people with amyloid build-up have no cognitive problems. In addition, some people without amyloid will have other forms of dementia. However, research suggests that older people with evidence of raised levels of amyloid in the brain may be at higher risk of Alzheimer's dementia. Scientists do not yet know *which* people with normal cognition and higher levels of brain amyloid will develop dementia.

If you learned you were at increased risk of Alzheimer's disease from ***a brain scan,*** *what would the implications be?*

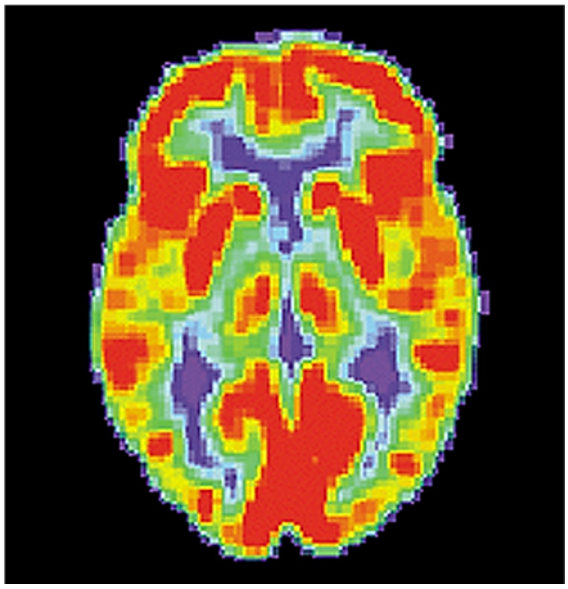


Figure 3: An example of a PET amyloid scan

Combined Risk Score

The biggest risk factor for the development of Alzheimer's disease is age. Other factors associated with a higher risk include a family history of Alzheimer's disease, high cholesterol, high blood pressure, diabetes, smoking, obesity and a lack of physical activity. There are also characteristics associated with a lower risk of developing Alzheimer's disease, including higher levels of education, being more socially active, and taking part in mental activities.

Information about many of these risk factors is collected routinely by doctors. It can be combined to develop a 'risk score' that might enable doctors to identify individuals who may have a higher risk of developing Alzheimer's disease. However, it is not able to predict with certainty who will and who will not develop Alzheimer's disease.

*If you learned you were at increased risk of Alzheimer's disease from **a combined risk score,** what would the implications be?*

Figure 4: An example score from a risk calculator app

REFERENCES

1. Wilson P, Mathie E, Keenan J. ReseArch with Patient and Public invOlvement: a RealisT evaluation-the RAPPORT study. *Heal Serv …*. 2015. https://kar.kent.ac.uk/50495/. Accessed September 22, 2015.
2. Williamson C. The challenge of lay partnership. It provides a different view of the world. *BMJ*. 1999;319(7212):721-722. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1116582&tool=pmcentrez&rendertype=abstract. Accessed May 26, 2016.
3. Corrigan O, Tutton R. What's in a name? Subjects, volunteers, participants and activists in clinical research. *Clin Ethics*. 2006;1(2):101-104. doi:10.1258/147775006777254524.
4. Brett J, Staniszewska S, Mockford C, et al. Mapping the impact of patient and public involvement on health and social care research: A systematic review. *Heal Expect*. 2012:637-650. doi:10.1111/j.1369-7625.2012.00795.x.
5. Post SG, Whitehouse PJ, Binstock RH, et al. The clinical introduction of genetic testing for Alzheimer disease. An ethical perspective. *JAMA*. 1997;277(10):832-836. http://www.ncbi.nlm.nih.gov/pubmed/9052715. Accessed August 10, 2015.
6. American College of Medical Genetics/American Society of Human Genetics Working Group on ApoE and Alzheimer disease. Statement on use of apolipoprotein E testing for Alzheimer disease. *JAMA*. 274(20):1627-1629. http://www.ncbi.nlm.nih.gov/pubmed/7474250. Accessed August 10, 2015.
7. Green RC, Roberts JS, Cupples LA, et al. Disclosure of APOE genotype for risk of Alzheimer's disease. *N Engl J Med*. 2009;361(3):245-254. doi:10.1056/NEJMoa0809578.
8. Harkins K, Sankar P, Sperling R, et al. Development of a process to disclose amyloid imaging results to cognitively normal older adult research participants. *Alzheimers Res Ther*. 2015;7(1):26. doi:10.1186/s13195-015-0112-7.
9. Cassidy MR, Roberts JS, Bird TD, et al. Comparing test-specific distress of susceptibility versus deterministic genetic testing for Alzheimer's disease. *Alzheimers Dement*. 2008;4(6):406-413. doi:10.1016/j.jalz.2008.04.007.
10. Heshka JT, Palleschi C, Howley H, Wilson B, Wells PS. A systematic review of perceived risks, psychological and behavioral impacts of genetic testing. *Genet Med*. 2008;10(1):19-32. doi:10.1097/GIM.0b013e31815f524f.
11. Alzheimer Europe. *The Value of Knowing: Findings of Alzheimer Europe's Five Country Survey of Public Perceptions of Alzheimer's Disease and Views on the Value of*. Luxembourg; 2011. https://scholar.google.co.uk/scholar?hl=en&q=alzheimer+europe+value+of+knowing&btnG=&as_sdt=1%2C5&as_sdtp=#2. Accessed July 30, 2015.
12. Binetti G, Benussi L, Roberts S, et al. Areas of intervention for genetic counselling of dementia: cross-cultural comparison between Italians and Americans. *Patient Educ*

Couns. 2006;64(1-3):285-293. doi:10.1016/j.pec.2006.03.008.

13. Justiss MD, Boustani M, Fox C, et al. Patients' attitudes of dementia screening across the Atlantic. *Int J Geriatr Psychiatry*. 2009;24(6):632-637. doi:10.1002/gps.2173.
14. Hipps YG, Roberts JS, Farrer LA, Green RC. Differences between African Americans and Whites in their attitudes toward genetic testing for Alzheimer's disease. *Genet Test*. 2003;7(1):39-44. doi:10.1089/109065703321560921.
15. Chilibeck G, Lock M, Sehdev M. Postgenomics, uncertain futures, and the familiarization of susceptibility genes. *Soc Sci Med*. 2011;72(11):1768-1775. doi:10.1016/j.socscimed.2010.01.053.
16. Roberts JS, Dunn LB, Rabinovici GD. Amyloid imaging, risk disclosure and Alzheimer's disease: ethical and practical issues. *Neurodegener Dis Manag*. 2013;3(3):219-229. doi:10.2217/nmt.13.25.
17. Molinuevo JL, Gramunt N, Gispert JD, et al. The ALFA project: A research platform to identify early pathophysiological features of Alzheimer's disease. *Alzheimer's Dement Transl Res Clin Interv*. March 2016. doi:10.1016/j.trci.2016.02.003.
18. Ritchie CW, Ritchie K. The PREVENT study: a prospective cohort study to identify mid-life biomarkers of late-onset Alzheimer's disease. *BMJ Open*. 2012;2(6). doi:10.1136/bmjopen-2012-001893.