

## To Know or Not to Know: An Update of the Literature on the Psychological and Behavioral Impact of Genetic Testing for Alzheimer Disease Risk

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Alzheimer disease (AD) is a genetically heterogenous disorder; in rare cases autosomal dominantly inherited mutations typically cause early-onset familial AD (EOAD), whereas the risk for late-onset AD (LOAD) is generally modulated by genetic variants with relatively low penetrance but high prevalence, with variants in apolipoprotein E (*APOE*) being a firmly established risk factor. This article presents an overview of the current literature on the psychological and behavioral impact of genetic testing for AD. The few studies available for presymptomatic testing for EOAD showed that only a very small proportion of individuals had poor psychological outcomes as a result. Initial interest in testing for EOAD decreases significantly after identification of a specific mutation in a kindred, suggesting that interest and potential for knowledge may not translate into actual testing uptake. The majority of individuals from both the general population and those with a family history of AD had positive attitudes towards, and were interested in, susceptibility testing for *APOE*. Motivations for genetic testing included to provide information for future planning and to learn about one's own and one's children's risks of developing AD. Although susceptibility testing for *APOE* genotype is not currently recommended due to the lack of clinical utility, this review demonstrates that there is interest in testing and no obvious adverse psychological effects to those who have been tested.

### Introduction

**A**LZHEIMER DISEASE (AD) is the most common form of dementia amongst older people, with estimates that 1 in every 85 people will be living with the disease by 2050 and a worldwide prevalence of 106 million (Brookmeyer *et al.*, 2007). AD is typically divided into early onset AD (EOAD), where onset is typically before 60 to 65 years, and late-onset AD (LOAD), where onset is thereafter (Bekris *et al.*, 2010). Our understanding of AD has progressed significantly over the last 20 years, leading to the identification of mutations in three causative genes for EOAD that follow an autosomal dominant pattern of inheritance, one major (apolipoprotein E [*APOE*]) and several minor susceptibility genes that are associated with increased risk for LOAD.

### Genetic testing for autosomal dominant AD

Autosomal dominantly inherited AD accounts for ~1%–5% of all cases (Bertram and Tanzi, 2005). Families with dominantly inherited AD are characterized by multiple cases of the disease across several generations. Mutations in three genes have been identified as causing autosomal dominant EOAD, namely, *APP*, *PSEN1*, and *PSEN2* genes, causing onset of symptoms from as young as 30 years (Bekris *et al.*, 2010). Each of the known AD genes is considered to play a role in the production and clearance of beta amyloid peptides, fibrillar forms of which are important constituents of senile plaques in the brain (Tabaton and Tamagno, 2007). It is likely that there are additional genes that cause dominantly inherited AD, as mutations have not been identified in all affected families

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(Campion *et al.*, 1999). The penetrance of mutations in the *PSEN1* and *APP* genes has been shown to be 100% and can thus be considered predictive for AD, while *PSEN2* shows 95% penetrance (Tanzi *et al.*, 1996). These discoveries have made possible genetic testing for mutations associated with dominantly inherited AD in individuals with a strong family history of AD; in unaffected individuals such testing will hereafter be referred to as "predictive testing" and as "diagnostic testing" in people who appear symptomatic. Predictive and diagnostic genetic testing for dominantly inherited AD is now well-established and the potential benefits of genetic testing include definitive diagnosis in affected individuals and the option of predictive testing in at-risk relatives, including the possibility of pre-implantation genetic diagnosis (PGD) in families with identified mutations.

### APOE susceptibility testing

The vast majority of AD cases are LOAD. The risk for LOAD is largely modulated by genetic variants with relatively low penetrance but high prevalence (Betram *et al.*, 2007). Of the three alleles,  $\epsilon 2$ ,  $\epsilon 3$ , and  $\epsilon 4$ , of the apolipoprotein E gene (*APOE*), the  $\epsilon 4$  allele is a firmly established risk factor for AD. Compared with individuals with no  $\epsilon 4$  alleles, individuals with one  $\epsilon 4$  allele are three times more likely, and those with two  $\epsilon 4$  alleles are up to 15 times more likely to develop AD (Farrer *et al.*, 1997; Betram *et al.*, 2007). There are other recently identified genetic variants associated with LOAD, although each of these variants confers much lower relative risks than the *APOE* gene (Harold *et al.*, 2009; Lambert *et al.*, 2009; Jun *et al.*, 2010). As there are no indications as yet for genetic testing using these low-risk variants, this review will focus on the *APOE* gene as a firmly established and well-researched risk factor for which genetic testing is already available.

*APOE* genotyping differs in many respects from predictive/diagnostic testing for the high-risk disease-causing gene mutations associated with dominantly inherited AD in that it provides much less certain risk information, but applies to a much larger proportion of the population (Roberts *et al.*, 2005). Due to these characteristics, the term "susceptibility testing" will be used hereafter in the context of *APOE* testing.

Although diagnostic *APOE* testing of individuals exhibiting symptoms of AD is already being used in clinical practice, susceptibility testing for unaffected at-risk individuals is currently not recommended for several reasons (Goldman *et al.*, 2011). In contrast to the causative genes associated with dominantly inherited AD, the presence of the *APOE*  $\epsilon 4$  allele is neither necessary nor sufficient to cause the disease (Betram, 2009). As for "predictive testing," clinical utility of *APOE* testing is limited given that currently no proven and clinically applicable strategies exist to delay the onset of AD, although many studies are underway to examine the short- and long-term efficacy of potentially preventative strategies for people at increased genetic risk of AD (Neugroschl *et al.*, 2009).

*APOE* genotyping is already commercially available and marketed worldwide direct-to-consumer (DTC) among other personal genomic tests, thus allowing consumers to potentially bypass genetic counseling (McGuire and Burke, 2008). Companies offering DTC genetic testing are coming under increasing regulatory scrutiny; in the United States, the Food and Drug Administration (FDA) has recently initiated a Molecular and Clinical Genetics Panel Meeting in March 2011 to

discuss and make recommendations on scientific issues concerning DTC genetic tests that make medical claims (Brice, 2011). The challenges of regulating the internet DTC market have been acknowledged; for this reason some jurisdictions are looking to alternative approaches, such as the Human Genetic Commission's initiative for the establishment of a code of conduct for companies operating in this market (Human Genetics Commission, August 2010). The emergence of such DTC susceptibility tests highlights a need to understand how users appraise them and their experiences of the testing process.

As genetic testing for AD susceptibility becomes increasingly accessible, a better understanding of the previous experiences and psychosocial and behavioral outcomes of those who have already had testing for AD risk can be used to inform and improve testing protocols and procedures. The purpose of this review therefore is to examine the available evidence on the experiences and attitudes of individuals towards genetic testing for AD, either as predictive or diagnostic testing for dominantly inherited AD or *APOE* susceptibility testing.

### Methods

A systematic review of studies published between January 1990 and October 2011 was conducted. MEDLINE, EMBASE, and CINAHL databases were searched using the following key words individually and in combination: *Alzheimer disease*, *familial Alzheimer disease*, *early onset Alzheimer disease*, *genetic testing*, *genetic screening*, *susceptibility testing*, *predictive testing*, and *presymptomatic testing*. The reference lists accompanying all identified publications were hand searched for additional studies, and retrieved by searching bibliographic databases and electronic journals. Searches were also conducted for key authors in this field.

### Inclusion criteria

Studies were included if they (i) were published in a peer-reviewed journal in English; (ii) included human subjects; and (iii) evaluated the perceived risk, psychological, and/or behavioral impacts of genetic testing for either autosomal dominantly inherited AD or *APOE* susceptibility testing. Both qualitative and quantitative studies were included for this review. Outcomes of interest were perceived risk, affective outcomes (e.g., distress and anxiety), attitudes, and behavioral outcomes (e.g., lifestyle changes). Publications were excluded from the review if they were lectures, single case reports, or conference abstracts.

### Results

Articles that met the inclusion criteria were evaluated, and data from these articles were extracted (B.R.). The included articles were checked by B.M. to determine if they met the inclusion criteria. A search of electronic databases generated 841 citations as potentially relevant. After reviewing these, 31 articles were selected for detailed review using the inclusion criteria described previously. Of these, 18 articles related to two randomized controlled trials undertaken in the United States that assessed the impact of *APOE* susceptibility testing in asymptomatic individuals who were at increased risk of developing AD because of a family history; the acronym for these studies is REVEAL (Risk Evaluation and Education for



Alzheimer disease). Eleven articles emerged from the REVEAL I study, and seven from the REVEAL II study. In REVEAL I, all participants ( $n=160$ ) had *APOE* susceptibility testing and were randomly assigned either (i) to receive the results of their own *APOE* genotyping as well as a lifetime risk based on race, gender, and testing result (disclosure group) or (ii) to only receive a lifetime risk estimate based on family history, race, and gender but not receive their personal genotype result (non-disclosure group). Participants ( $n=293$ ) in REVEAL II received *APOE* genetic testing but were randomly allocated to receive information regarding *APOE* genotype and AD risk either through a brochure or an extended counseling protocol.

Tables 1 and 2 show the articles that were reviewed in detail. More detailed descriptions of the findings can be found in the Supplementary Tables S1–S8 (Supplementary Data are available online at [www.liebertonline.com/gtmb](http://www.liebertonline.com/gtmb)).

#### Attitudes and motivations toward genetic testing for AD

Genetic testing for autosomal dominantly inherited AD. Three studies assessed attitudes and motivations towards testing for EOAD in family members with multiple relatives with AD across several generations (Tibben *et al.*, 1997; Marcheco *et al.*, 2003; Marcheco-Teruel and Fuentes-Smith, 2009). The main motivations cited in these studies were to prepare for the disease and satisfy curiosity about genetic status (Marcheco *et al.*, 2003), and to help research, relieve uncertainty, inform children, and plan for the future (Tibben *et al.*, 1997).

In one study, members of a large family ( $n=56$ ) at risk of EOAD were surveyed regarding their attitudes toward predictive testing (Marcheco *et al.*, 2003; Marcheco-Teruel and Fuentes-Smith, 2009) and followed up in a later study after a family-specific mutation had been identified (Marcheco-Teruel and Fuentes-Smith, 2009). The same items were used in both studies to assess interest in genetic testing, with only the hypothetical scenarios modified according to the current scope of genetic testing. In this latter study, 69% were interested in predictive testing, compared with 100% in the original study. The authors conclude that the modification in attitudes may have been caused by the shift from a hypothetical genetic test to an actual genetic test and an increased understanding of the lack of treatment or preventive strategies for AD (Marcheco-Teruel and Fuentes-Smith, 2009).

*APOE* susceptibility testing. Three articles examined the attitudes of the general population to susceptibility testing for AD (Frost *et al.*, 2001; Neumann *et al.*, 2001; Hips *et al.*, 2003), and five studies assessed attitudes in individuals with a family history of AD (Cutler and Hodgson, 2003; Roberts *et al.*, 2003; Bassett *et al.*, 2004; Moscarillo *et al.*, 2007; Christensen *et al.*, 2011). Generally these attitudinal studies show high levels of interest in hypothetical testing for *APOE*; for example, Bassett *et al.* (2004) found that 72% of individuals with a family history of AD would choose to have a genetic test if it was offered to them. Interestingly, no significant differences in interest were observed between individuals with (68%) and without a family history of AD (62%) (Cutler and Hodgson, 2003). Several factors have been identified as being associated with interest in genetic testing: memory concerns (Cutler and Hodgson, 2003), desire to prepare family members for AD (Roberts *et al.*, 2003), being aged below 60 years, higher educational level (Roberts *et al.*, 2004), holding positive attitudes toward the test, and knowing someone with AD (Frost *et al.*, 2001). Also, level of interest in testing has been found to increase with the degree of certainty imparted by a hypothetical test. Specifically, in two studies of participants sampled from the community, 64% (Hips *et al.*, 2003) and 79% (Neumann *et al.*, 2001) would opt to have a fully predictive test for AD, while 30% (Hips *et al.*, 2003) and 45% (Neumann *et al.*, 2001) would be interested in a partially predictive test. Despite the interest shown in genetic testing for AD, it is important to note that interest may not necessarily translate to actual uptake in testing, as has been seen with predictive testing for Huntington's disease (Craufurd *et al.*, 1989; Quaid and Morris, 1993).

The following motivations for pursuing *APOE* genotyping for AD have been described: to provide information for future planning and the arrangement of personal affairs, to contribute to research/altruism, to organize long-term care, and to learn about one's own and children's risks (Roberts, 2000; Cutler and Hodgson, 2003; Roberts *et al.*, 2003). A qualitative study showed that gaining knowledge for its own sake was a major motivation for *APOE* testing. Specifically, knowledge about one's genetic status was described as fulfilling a "need to know" (REVEAL I; Hurley *et al.*, 2005), and as allowing participants to "feel in control" of their health (Gooding *et al.*, 2006).

TABLE 1. ARTICLES ON PRESYMPTOMATIC TESTING FOR EARLY ONSET FAMILIAL ALZHEIMER DISEASE

Country	Authors	Study design	Sample size	Measurement time points	Main outcome measures
Cuba	Marcheco <i>et al.</i> (2003)	Prospective	$n=56$	N/A	Individual risk, attitudes to testing
Cuba	Marcheco-Teruel and Fuentes-Smith (2009)	Prospective	$n=52$	N/A	Individual risk, attitudes to testing
Spain	Molinuevo <i>et al.</i> (2005)	Prospective	$n=9$	Baseline, 2 weeks, 3 months, 6 months	Anxiety and depression
United States	Steinbart <i>et al.</i> (2001)	Prospective	$n=21$	6–36 months	Anxiety, depression, test-related distress
The Netherlands	Tibben <i>et al.</i> (1997)	Cross-sectional	$n=21$	N/A	Uptake and attitudes toward presymptomatic testing

N/A, not applicable.

TABLE 2. ARTICLES ON SUSCEPTIBILITY TESTING FOR APOLIPOPROTEIN E

Study/country	Authors	Study design	Sample size	Measurement time points	Main outcome measures
REVEAL II/ United States	Ashida <i>et al.</i> (2009)	RCT/prospective	n=271	6 weeks	Communication of APOE results
REVEAL II/ United States	Ashida <i>et al.</i> (2010)	RCT/prospective	n=293	Baseline, 6 weeks, 12 months	Anxiety, depression, test-related distress
United States	Basset <i>et al.</i> (2004)	Prospective	n=518	N/A	Knowledge and interest of APOE testing
REVEAL I/ United States	Cassidy <i>et al.</i> (2008)	RCT/prospective	n=123	12 months	Distress
REVEAL I/ United States	Chao <i>et al.</i> (2008)	RCT/prospective	n=147	12 months	Changes to diet, exercise, medication/vitamins
REVEAL II/ United States	Christensen <i>et al.</i> (2011)	RCT/prospective	n=293	Baseline, 12 months	Perceived pros and cons of testing
United States	Cutler and Hodgson (2003)	Prospective	n=258	N/A	Testing intentions, decision making, memory functioning, personal concern, mastery
United Kingdom	Frost <i>et al.</i> (2001)	Prospective	n=449	N/A	Positive attitudes, beliefs, subjective norms, anticipated regret, perceived risk, testing intentions
REVEAL I/ United States	Gooding <i>et al.</i> (2006)	Qualitative	n=60	N/A	N/A
REVEAL I/ United States	Green <i>et al.</i> (2009)	RCT/prospective	n=162	6 weeks, 6 months, 12 months	Anxiety, depression, test-related distress
United States	Hipps <i>et al.</i> (2003)	Prospective	n=452	N/A	Testing interest, anticipated consequences, testing beliefs
REVEAL II/ United States	Hiraki <i>et al.</i> (2009)	RCT/ cross-sectional	n=293	Baseline	Family history, risk perception
REVEAL I/ United States	Hurley <i>et al.</i> (2005)	RCT/prospective and qualitative	n=60	12–18 months	N/A
REVEAL I/ United States	LaRusse Eckert <i>et al.</i> (2006)	RCT/prospective	n=104	6 weeks, 12 months	Information recall: numeric lifetime risk vs. APOE genotype
REVEAL I/ United States	LaRusse <i>et al.</i> (2005)	RCT/prospective and qualitative	n=66	6 weeks	Impact of risk assessment information
REVEAL II/ United States	Linnenbringer <i>et al.</i> (2010)	RCT/prospective	n=246	Baseline, 6 weeks	Perceived personal risk
REVEAL I/ United States	Marteau <i>et al.</i> (2005)	RCT/prospective	n=149	6 weeks, 6 months, 12 months	Perception of AD risk
United States	Moscarillo <i>et al.</i> (2007)	Prospective	n=67	N/A	Knowledge of AD, knowledge of genetic testing for AD
United States	Neumann <i>et al.</i> (2001)	Prospective	n=314	N/A	Public attitudes about genetic testing for AD
United States	Roberts (2000)	Prospective	n=203	N/A	Test intentions
REVEAL I/ United States	Roberts <i>et al.</i> (2003)	Cross-sectional	n=206	N/A	Reasons for pursuing susceptibility testing
REVEAL I/ United States	Roberts <i>et al.</i> (2004)	RCT/prospective	n=289	N/A	Demographic predictors of study participation
New Mexico	Romero <i>et al.</i> (2005)	Prospective	n=76	4 weeks, 4 months, 10 months	Depression, worry, relief
REVEAL II/ United States	Taylor <i>et al.</i> (2010)	RCT/prospective	n=276	Baseline, follow-up (time point not given)	Changes to long-term care insurance
REVEAL II/ United States	Vernarelli <i>et al.</i> (2010)	RCT/prospective	n=272	6 weeks	Health behavior changes
REVEAL I/ United States	Zick <i>et al.</i> (2005)	RCT/prospective	n=293	6 weeks, 6 months, 12 months	Changes to health, life, and disability insurance

RCT, randomized controlled trial; AD, Alzheimer disease; APOE, apolipoprotein E.

#### Psychological impact of genetic testing for AD

Six articles described the psychological impact of genetic testing for AD risk, two in the context of predictive testing for dominantly inherited AD (Steinbart *et al.*, 2001; Molinuevo *et al.*, 2005), and four in that of APOE susceptibility testing

(Romero *et al.*, 2005; Gooding *et al.*, 2006; Green *et al.*, 2009; Ashida *et al.*, 2010).

Genetic testing for autosomal dominantly inherited AD. Only two studies are available that assessed the psychological impact of genetic testing for autosomal dominantly inherited



AD; both also dealt with frontotemporal dementia, another progressive, neurodegenerative disease that often shows autosomal dominant inheritance (Steinbart *et al.*, 2001; Molinuevo *et al.*, 2005). In a retrospective study, Steinbart *et al.* (2001) found that of the 12 asymptomatic individuals who had predictive testing for AD and received their results, three had moderately high anxiety levels (one with positive and two with negative test results), and one had moderately high depression levels following testing (negative test result but past history of depression) (Steinbart *et al.*, 2001). A prospective study by Molinuevo *et al.* (2005) assessed people at risk for dominantly inherited AD ( $n=5$ ); only two individuals who were at risk for dominantly inherited AD and were mutation positive were included. These individuals had contrasting reactions, in that one participant experienced an increase in anxiety during the first-month post-result disclosure before returning to normal levels, while the other had decreased anxiety levels immediately after receiving his results.

**APOE susceptibility testing.** In the REVEAL I study, Green *et al.* (2009) found that disclosure of APOE genotype did not lead to significant short-term psychological risks. In a qualitative component assessing a sub-sample of the same cohort, participants ( $n=29$ , 48%) reported feelings of relief after APOE result disclosure, including four participants who received  $\epsilon 4$ -positive results (Gooding *et al.*, 2006). This result confirms the findings from another prospective study of 76 asymptomatic individuals with a family history of AD (Romero *et al.*, 2005). Participants in this study reported feeling reassured by receiving their genotype results, regardless of the result itself. None of the participants in the low-risk ( $\epsilon 4$ -negative) group in this study reported symptoms of depression post-result disclosure; however, a small number of participants ( $n=4$ ) from the high-risk group ( $n=27$ ) were still depressed 10 months after result disclosure (Romero *et al.*, 2005). Similarly, in the REVEAL II study, 9% of participants who had low levels of depression at baseline reported clinically significant levels after 12 months. An increase in concern about developing AD was associated with an increase in depressive symptoms and anxiety levels 12 months later (Ashida *et al.*, 2010).

Data are also available to allow comparisons between genetic testing for dominantly inherited AD and APOE susceptibility testing. A REVEAL I study compared the psychological impact of predictive testing for dominantly inherited AD ( $n=22$ ) with that of APOE susceptibility testing ( $n=101$ , REVEAL I study participants) and found that there were no statistically significant differences in test-related distress between individuals who were identified as mutation positive in predictive testing and those who received  $\epsilon 4$ -positive results from APOE susceptibility testing (Cassidy *et al.*, 2008). Test-related distress was low in both groups, and few participants in either group experienced distress levels that suggested a need for clinical intervention.

#### *Impact of genetic testing on risk perception*

No studies were found that assessed risk perceptions following genetic testing for dominantly inherited AD, while five studies were identified that described risk perceptions following APOE testing (LaRusse *et al.*, 2005; Marteau *et al.*, 2005; LaRusse Eckert *et al.*, 2006; Hiraki *et al.*, 2009; Linnenbringer *et al.*, 2010).

**APOE susceptibility testing.** In a cross-sectional study of REVEAL II participants, individuals with more than one relative with AD had significantly higher risk perceptions than those with only one affected relative prior to testing (Hiraki *et al.*, 2009). A strong belief in genetics as an AD risk factor was also found to be a significant predictor of higher perceived risk. Participants from REVEAL I who received  $\epsilon 4$ -negative results perceived their risk of developing AD as significantly lower compared with other participants, while those who were  $\epsilon 4$  positive showed no significant changes in their perceived risk (Marteau *et al.*, 2005). In another substudy of REVEAL I, participants either received a lifetime risk estimate based on family history and gender only (family history group), or an  $\epsilon 3/\epsilon 3$  genotype result (genotype group). All participants in both groups received the same lifetime risk estimate of 29% for developing AD (LaRusse *et al.*, 2005). Participants who received their genetic test information reported lower perceived risk and less anxiety than those who only received a risk estimate, although they were at the same risk of developing the disease.

#### *Impact of genetic testing on health behaviors*

No studies were identified that assessed health behaviors following genetic testing for dominantly inherited AD, while four studies examined the impact of APOE gene testing on health behaviors (Zick *et al.*, 2005; Chao *et al.*, 2008; Taylor *et al.*, 2010; Vernarelli *et al.*, 2010).

**APOE susceptibility testing.** A REVEAL I study aimed to gain insight into the relationship between APOE genetic testing for AD and life insurance purchasing behavior (Zick *et al.*, 2005). Long-term care insurance was the only domain where there was a significant change; 17% of participants who tested positive for  $\epsilon 4$  changed their long-term care insurance coverage in the year after receiving their results, compared with 2% who were  $\epsilon 4$  negative. Similarly, it was shown that individuals with at least one  $\epsilon 4$  allele were significantly more likely to have increased, or planned to increase, long-term care insurance than those with two  $\epsilon 3$  alleles (Taylor *et al.*, 2010).

The impact of receiving APOE  $\epsilon 4$  results on diet, exercise, medication, and vitamin intake was measured by Chao *et al.* (2008; REVEAL I). Participants who were  $\epsilon 4$  positive were significantly more likely to make AD-specific health behavior changes than those who were  $\epsilon 4$  negative. Changes in dietary supplement use were strongly associated with having received  $\epsilon 4$ -positive results. The most commonly reported supplement changes were increases in the use of vitamin E and/or botanicals, such as ginkgo biloba and green tea (Vernarelli *et al.*, 2010; REVEAL II).

#### **Discussion**

Although susceptibility testing for APOE genotype is not currently recommended due to the lack of clinical utility, preventative strategies, and treatments, this review shows that knowledge of APOE genotype may be of benefit particularly in terms of making health behavior changes and/or long-term care insurance decisions. Any potential benefits, however, must be weighed against psychological costs, if any.



### Genetic testing for dominantly inherited AD

We identified only two studies that examined the psychological impact of genetic testing for at-risk individuals; these studies were limited by small sample sizes and/or a retrospective study design (Steinbart *et al.*, 2001; Molinuevo *et al.*, 2005). The paucity of literature available in this area may reflect the rarity of families with dominantly inherited AD (Bekris *et al.*, 2010). The psychosocial impact of genetic testing for dominantly inherited AD may also be understudied because the impact may arguably be similar to that of Huntington's disease; the psychological impact of genetic testing for Huntington's disease has been well studied by comparison following the identification of the mutation responsible for the disease in the late 1980s (Meiser and Dunn, 2000).

### APOE susceptibility testing

The results of LaRusse *et al.* (2005) (REVEAL I) showed that participants who received APOE genotype results ( $\epsilon 3/\epsilon 3$  genotype) had lower perceived risk and anxiety than participants who received an AD risk estimate only, despite both groups being given identical lifetime risk figures of 29% for developing AD. This finding suggests that receiving a "reassuring" genotype result (i.e.,  $\epsilon 4$ -negative genotypes) may have provided a sense of certainty, which in turn led to a reduction in anxiety and perceived risk (LaRusse *et al.*, 2005). The results of this study have important implications; they support the importance of genetic testing for AD not only to provide information but as a means to reduce uncertainty for at-risk individuals. Uncertainty can affect an individual's sense of control over the danger, in this case the risk of developing AD, and can thereby increase feelings of helplessness and stress (Baty *et al.*, 2006). However, the challenge facing individuals who choose to have genetic testing is that genotyping may provide increased certainty as to their risk of developing a disease, but it is a disease where there are no proven preventative measures or treatment options to halt its progression. The desire for certainty is also reflected in the studies that measured interest in genetic testing or willingness to take a genetic test for AD. Studies found that the majority of participants would have testing if it was 100% accurate or fully predictive, while only a small number of participants would be interested in testing that was only partially accurate or predictive (Neumann *et al.*, 2001; Hipps *et al.*, 2003).

Knowledge of APOE genotype was also found to impact health behaviors. Individuals who received  $\epsilon 4$ -positive genotypes were more likely to increase their use of dietary supplements, despite the current lack of evidence on the efficacy of such supplements in preventing AD or delaying its onset (Zick *et al.*, 2005; Vernarelli *et al.*, 2010). While such behaviors may provide reassurance to individuals and give them a sense of control, the reassurance may be false. Further, the use of dietary supplements comes at a monetary cost and is not always without adverse effects.

Long-term care insurance was also affected by knowledge of APOE genotype status, with individuals who were  $\epsilon 4$  positive more likely to increase their long-term care insurance coverage. Genetic testing and insurance has been a contentious issue for a number of years. Fear of discrimination from insurers and employers based on results of genetic testing led to the introduction of a federal law in 2008 in the United States, the Genetic Information Nondiscrimination Act

(GINA), which prohibits discrimination in health coverage and employment based on genetic information (Department of Health and Human Services, accessed February 16, 2012). However, this law does not extend to long-term care insurance which is a life insurance product. Individuals who learn they are  $\epsilon 4$ -positive may be reluctant to disclose such results to insurers, for fear of discrimination by insurance companies that may deny them coverage or charge vastly increased premiums based on their genetic test results. This raises several ethical issues relating to genetic testing and life insurance. The commercial nature of the insurance application requires that both parties act in good faith. On the part of consumers, they are obliged, contractually and ethically, to disclose all they know at the time of the application relevant to the risk, including genetic test results. On the part of insurers, issues of concern are those of moral hazard and adverse selection. Moral hazard in the insurance context refers to changes in health behavior as a result of taking out the coverage so that there is less concern about developing a condition as their care is provided for. In terms of APOE testing, those individuals who test  $\epsilon 4$ -positive and take out insurance to cover their long-term care are doing so specifically because they know they are at risk. Similarly, adverse selection occurs when individuals with  $\epsilon 4$ -positive genotypes or who are at greater risk of developing AD, either increase their long-term care insurance coverage or take out a policy specifically because they are at greater risk than average without disclosing this risk to the insurer, contrary to their disclosure obligations. The usual approach of sharing the risk across the whole community is skewed to those who will make claims. If insurers do not have access to this knowledge, and as a result are unable to adjust their actuarial calculations, it will potentially lead to economic loss (Zick *et al.*, 2005). Insurance companies have no desire to deny coverage to a significant segment of the population; however, as their goal is to maximize profits, insurers need to avoid the possibility of adverse selection (Godard *et al.*, 2003). A balance needs to be found between reassuring and protecting individuals from unjustified discrimination, and the commercial viability of the provision of long-term care insurance policies.

### Limitation of available studies

This review identified a number of limitations of the studies available. Although there is interest in genetic testing for AD among both individuals at risk for AD and the general population, the extent to which interest in hypothetical testing may translate into actual testing uptake is unknown, given that no data are available on uptake rates amongst individuals offered testing. Another limitation of the studies identified on APOE susceptibility testing is that almost all articles published in this area stem from two large studies from the United States (REVEAL I and REVEAL II). The attitudes and impact of testing described are likely to be culture specific and influenced by the United States health care system and insurance context, and findings may therefore not be generalizable to individuals undergoing testing elsewhere. Further, a certificate of confidentiality was obtained specifically for participants in these two studies to ensure confidentiality of testing results. Thus, it is possible that outside the research setting individuals may be less inclined to opt for testing because of concerns about potential insurance discrimination. Finally, as part of the screening process, subjects were



administered standardized tests to evaluate their cognitive ability, academic achievement, levels of anxiety, and depression. Individuals with low functioning or high levels of distress were excluded from participation. The REVEAL studies also implemented a comprehensive counseling protocol. Therefore, the results may not be generalizable to settings where less strict eligibility criteria or less rigorous counseling protocols are used. In terms of the implications for policy, given the limitations of the research available, appropriate and thorough pre- and post-test genetic counseling using a multidisciplinary approach should always be provided to individuals and their families considering genetic testing for AD.

#### Suggestions for future research

Even though the majority of people who were tested experienced no measurable adverse psychological effects, the available studies show that a small percentage (about 10%) of individuals experience adverse psychological outcomes that are of clinical significance following APOE testing (Romero *et al.*, 2005; Ashida *et al.*, 2010). No data are available on the psychological risk factors for the development of distress specifically in this population; research should be prioritized to help identify individuals most at risk of negative outcomes and to plan appropriate interventions.

Research is also needed on the impact of testing where less-intensive counseling protocols are used; in particular, the impact of DTC APOE testing where genetic counseling may be bypassed altogether (McGuire and Burke, 2008). Also, no data are currently available on the impact of APOE disclosure in a general population sample. Given that presence of a family history of AD is not a good indicator of presence of the  $\epsilon 4$  allele (Slooter *et al.*, 1998), data on the psychological and behavioral impact of APOE genotyping in the general population are needed, particularly in light of the increasing availability and uptake of DTC personal genomic testing, including APOE genotyping (Bloss *et al.*, 2011).

#### Conclusions

The main findings of this review are consistent with those from the larger body of literature on the psychological impact of genetic testing for both single gene and complex disorders with onset in adulthood, including Huntington's disease (Meiser and Dunn, 2000), depression risk (Wilhelm *et al.*, 2009), and cancer risk (Meiser, 2005; Hamilton *et al.*, 2009). This literature shows remarkably few adverse psychological effects of testing and demonstrates that the best predictors of the psychological impact of genetic testing are pre-testing levels of psychological distress and past psychiatric history. It is therefore advisable to use validated screening measures to assess distress prior to genetic testing and refer those with high distress levels for an in-depth psychological or psychiatric assessment.

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