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Predictive Genetic Testing for Alzheimer's Disease: Impact upon Risk Perception

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The aim of this study was to determine the impact on risk perceptions of disclosing genetic test results used to estimate the risk of Alzheimer's disease (AD). Adult children ($n = 149$) of people with AD were randomized to one of two groups—Intervention group: lifetime risk estimates of AD based on age, gender, family history, and Apolipoprotein E (APOE) genotype; Control group: lifetime risk estimates of AD based on the same risk factors excluding APOE genotype. Perceptions of personal risk (PPR) for AD were assessed six weeks after risk assessments. PPR were correlated with actual lifetime risk estimates ($r = 0.501$; $p < 0.0001$). After controlling for lifetime risks communicated to participants, age, and number of affected relatives, PPR scores among those with an $\varepsilon 4$-positive test result (the test result associated with increased AD susceptibility) (adjusted mean: 3.4 (*SD*: 0.7)) were not different from the PPR scores in the Control group (adjusted mean: 3.4 (*SD*: 0.7) ($F_{(1,91)} = 1.98$; $p = 0.162$). Again, controlling for lifetime risk estimates, age, and number of affected relatives, the PPR score of those receiving an $\varepsilon 4$-negative test result was significantly lower (adjusted mean: 3.1 (*SD*: 0.8)) than those in the Control group (adjusted mean: 3.4 (*SD*: 0.7) ($F_{(1,95)} = 6.23$; $p = 0.014$). Perceptions of risk of developing AD are influenced by genetic test disclosure in those receiving $\varepsilon 4$-negative, but not those receiving $\varepsilon 4$-positive test results. Despite the reduced perceptions of risk in the former group, there was no evidence of false reassurance (i.e., perceiving risks as equal to or lower than population risks of AD), although this possibility should be assessed in other testing contexts.

KEY WORDS: Alzheimer's disease; genetic testing; risk perception

1. INTRODUCTION

One of the key challenges in translating the results of the Human Genome Project into clinical settings is to understand how people perceive genetic risks.[1] This is particularly important as developments in genetics begin to encompass susceptibility testing for common complex diseases. Unlike genetic tests for some Mendelian conditions for which the presence of a particular genotype invariably leads to the disease (such as Huntington's disease, familial autosomal dominant Alzheimer's disease (AD), or familial adenomatous polyposis), susceptibility genetic testing for complex conditions provides estimates of the likelihood of developing the condition. We present here the results of the first study to assess the psychological impact of susceptibility testing for Alzheimer disease that includes disclosure of Apolipoprotein E (APOE) genotype.[2]

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The APOE gene on chromosome 19 has three alleles, designated $\varepsilon 2$, $\varepsilon 3$, and $\varepsilon 4$. The $\varepsilon 4$ allele has a frequency of about 15% in the general population and is felt to be responsible for roughly half of the genetic risk for AD.[3] The presence of a single $\varepsilon 4$ allele increases risk of AD approximately three-fold, while two copies of the $\varepsilon 4$ allele increase this risk 15–30-fold, in comparison to other APOE genotypes, and more precise risk estimates utilizing gender and age have been generated.[4] Yet, the $\varepsilon 4$ allele is neither necessary nor sufficient to cause the disease, and is, therefore, considered a susceptibility or risk gene. To date, APOE genotyping for risk assessment has not been used clinically because of uncertainty about the impact of disclosing this information.

In risk assessment using genetic susceptibility testing, it is important that those undergoing the genetic test understand that those with the gene variant associated with an increased risk are not necessarily destined to develop the disease. Also important is the understanding that those without the gene variant are not necessarily destined to be disease free. Failure to understand this can result in false reassurance with a failure to engage in preventative behaviors. Of interest is how the disclosure of a genetic test in a risk-assessment package affects risk perceptions.

It is now widely acknowledged that epidemiologically derived probabilities may have only a small impact upon risk perceptions.[5] The characteristics of the health threat in question play an important role in influencing these perceptions. Slovic and colleagues have identified two broad dimensions that affect perceptions of risk.[5] The first concerns the extent to which the threat is dreaded and the second concerns the extent to which the threat is perceived as familiar. Threats that evoke the greatest dread are those that are perceived as being the most uncontrollable. Based on this analysis, risks derived from genetic testing would be expected to be perceived as higher than similar but nongenetically related risks, given that genetically conferred risks are generally perceived as uncontrollable[6,7] and unfamiliar.

A further factor that influences perceptions of risk concerns the processing of probabilistic information. There is good evidence that people typically simplify and summarize complex information and extract the gist.[8] Lippman and colleagues observed that in the context of genetic consultations, individuals often perceived probabilities in a binary form, as reflected in a frequently expressed view: either I will or I will not develop the condition.[9] While self-evidently true, this captures the numerator of a given probability expression to the neglect of its denominator.

Genetic test results are usually reported in binary form, i.e., the mutation or polymorphism is reported as present or not present, although the risk conferred may be probabilistic, as is the case for APOE testing and AD. It is therefore possible that the use of genetic tests may reinforce a more binary perception of risks than results of tests assessing biological markers that are continuous in nature, such as age or cholesterol. Given this, we hypothesized that including APOE disclosure in a risk-assessment protocol and receiving a negative test result (absence of the $\varepsilon 4$ allele) would lead to lower perceptions of personal risk (PPR) than provision of a similar lifetime risk estimated without APOE disclosure. Similarly, we hypothesized that receipt of a positive APOE test result (presence of the $\varepsilon 4$ allele) would lead to higher PPR than a similar lifetime risk estimated without the use of APOE disclosure. This second hypothesis is also predicted from the evidence reviewed above suggesting that genetically associated risks will be received as more threatening, i.e., higher.

We have already reported data that support the first of these predictions. Comparing perceptions of risk among 66 women with identical lifetime risks of developing AD, those who were randomized to receive genetic testing as part of their risk assessment and who then received an APOE $\varepsilon 4$-negative test result, perceived their risks as lower than women whose identical lifetime risks were communicated without APOE disclosure.[10] We report here data on a larger sample, comprising men as well as women, comparing responses in three subgroups: those with APOE $\varepsilon 4$-positive test results, as well as those with $\varepsilon 4$-negative test results, and those who did not receive APOE test results (controls). In addition, we are testing the study hypotheses using a different analytic approach to control for lifetime risk, age, and number of affected relatives, which differ between the three subgroups.

2. METHOD

2.1. Overview

The Risk EValuation and Education for ALzheimer's (REVEAL) study is a multicenter, randomized, controlled trial of a risk-assessment procedure for Alzheimer disease, with and without genetic susceptibility testing and disclosure of APOE. The study protocol was developed by a multidisciplinary

team of experts in the fields of Alzheimer disease, neurology, genetics, genetic counseling psychology, and bioethics. Development of the protocol was overseen and approved by a four-member external advisory board, as well as institutional review boards at each of the three study sites, and genetic data were protected by a certificate of confidentiality. All participants gave written informed consent.

2.2. Participants and Procedures

All REVEAL study participants were adult children of a living or deceased person with AD. Participants were referred to the study either through systematic ascertainment from AD research registries ($n = 47$) or self-referral ($n = 115$). Participants interested in the REVEAL study were invited to attend a formal education session conducted by the site's genetic counselor. At the education session, the genetic counselor provided information about AD and the study protocol via a scripted slide show presentation. In this session, the genetic counselor stressed the distinction between susceptibility and deterministic testing for AD and discussed the possible benefits and limitations of susceptibility testing with APOE disclosure. Benefits included information to guide future planning and increase awareness of candidacy for potential future treatments, while limitations included the imperfect nature of test information, the lack of treatment options to prevent or cure AD, and the potential for genetic discrimination once APOE genotype was known to the participant. Following the education session, interested participants progressed to the counseling/blood draw stage of the study, where individualized genetic counseling occurred and where blood was drawn for APOE genotyping prior to randomization. While all participants were tested, those in the Control group did not receive their test results. At this stage, potential participants were also screened with regard to their cognitive functioning and psychiatric status, using the Repeatable Battery for the Assessment of Neuropsychological Status,[11] Center for Epidemiological Studies-Depression Scale,[12] and Beck Anxiety Inventory.[13]

In the disclosure/randomization stage, interested and eligible participants were randomized to either the Intervention or Control arm of the study in the ratio of 2:1 in order to achieve similarly sized groups who tested positive and negative for the presence of an APOE $\varepsilon 4$ allele in the Intervention arm. Participants randomized to the Intervention arm received genetic counseling and risk assessment based on their age, gender, family history of AD, and APOE genotype, along with APOE genotype disclosure, while those randomized to the Control arm received genetic counseling and risk assessment based only on their age, gender, and family history, and did not receive APOE genotype disclosure. Participants were followed with measurements of several outcomes for a year after the disclosure session, with data collection points at 6 weeks, 6 months, and 12 months.

2.3. Measures

Perceived personal risk (PPR) of developing AD was assessed using a single-item measure: "According to the risk assessment you were given, would you say your risk for developing Alzheimer disease is . . . ," with response choices ranging from 1 = very low to 5 = very high.

Perceived personal risk of developing AD compared to those without a family history (PPR-FH) was assessed using a single item: "How would you compare your risk for developing Alzheimer disease with someone who does not have a close relative with Alzheimer disease? Would you say that your risk is . . . " 1 = much lower to 5 = much higher.

This measure was used to characterize "false reassurance" as described below.

Cumulative lifetime risk estimates ranged from 18% to 57% depending on participant's age, gender, and APOE genotype. Risk estimates were estimated using data from a multicenter genetic epidemiology studies of AD based at Boston University[3,14,15] and presented via risk curves in which the participant's lifetime risk was shown along with curves representing the risk of first-degree relatives in general, and individuals not selected for a family history of AD. Development of risk estimates and curves for the REVEAL study is described in greater detail elsewhere.[4] As expected, risk estimates were higher among those with one or two $\varepsilon 4$ alleles.

False reassurance was defined as perceiving the probability of developing AD to be the same or lower than the general population, assessed using PPR-FH. The general population risk of developing AD was communicated to participants during the education session as being between 10% and 15%. All the participants in the REVEAL study were first-degree relatives, and received lifetime risk estimates of 18% or higher. In addition, all participants were shown risk curves for persons like themselves that were explicitly

shown to be higher than comparison curves representing the general population.

Demographic characteristics in the analysis included age, gender, ethnicity, years of education, marital status, number of relatives affected by AD or related memory problems, and income. Each was assessed by self-report.

2.4. Data Analysis

Descriptive statistics were used to characterize the study sample in terms of its demographic features. Pearson's correlation coefficient was used to assess the association between the estimated lifetime risk that was communicated to the participant and the PPR of developing AD. Analysis of covariance was used to control for lifetime risk communicated to the participant in order to assess the extent to which disclosure of APOE contributed to PPR beyond the contribution it made to estimates of lifetime risk. Age and number of affected relatives were also controlled for, given differences in these variables between the three subgroups.

3. RESULTS

Participants in the Intervention and the Control arms were similar in their demographic characteristics. To test the study hypotheses, the Intervention arm was divided into those who were positive for the presence of at least one APOE $\varepsilon 4$ allele and those who were not. The three comparison groups (i.e., the two Intervention subgroups and the Control arm) were similar in all the demographic characteristics, except for age and number of affected relatives: those in the Control arm were significantly older than those in the Intervention arm who were found to be $\varepsilon 4$ positive (Table I), and those found to be $\varepsilon 4$ positive had more affected relatives than those in the $\varepsilon 4$-negative subgroup.

The mean lifetime risks of those in the three study groups differed ($F_{(2,146)} = 179.61$; $p < 0.00001$) (Table II). Those in the Intervention arm who were $\varepsilon 4$ positive were, by definition, given significantly higher lifetime risks than both those in the Intervention arm who were $\varepsilon 4$ negative and those in the Control arm.

Following disclosure of lifetime estimates, few participants scored their PPR as either very low ($n = 2/150$) or very high ($n = 7/150$), with most perceiving their risks as average or above average (118/150) (Fig. 1). PPR was positively associated with the communicated lifetime risk ($r = 0.51$; $p < 0.0001$).

Two analyses of covariance were conducted to test the hypotheses regarding the impact of genetic testing on PPR. The first analysis compared Control arm participants with those receiving APOE $\varepsilon 4$-positive test results, while the second compared Control arm participants with those receiving APOE $\varepsilon 4$-negative test results. In addressing the first hypothesis, an $\varepsilon 4$-positive result did not significantly affect the mean PPR score when compared with the mean PPR score of Control arm participants, controlling for reported lifetime risk estimate, age, and number of affected relatives ($F_{(1,91)} = 1.98$; $p = 0.162$). Mean PPR score unadjusted and adjusted for lifetime risk is shown in Table II. In addressing the second hypothesis, those receiving a test result negative for APOE $\varepsilon 4$ perceived their risks of developing AD as significantly lower than did Control arm participants, controlling for reported lifetime risk estimate, age, and number of affected relatives ($F_{(1,95)} = 6.23$; $p = 0.014$).

Table I. Demographic Characteristics of Study Participants

	Intervention Group		Control Group	
Demographic Characteristic	APOE $\varepsilon 4+$ ($n = 49$)	APOE $\varepsilon 4-$ ($n = 55$)	Controls ($n = 45$)	Total ($n = 149$)
Mean age (years, *SD*)	49.3 (7.7)	53.1 (11.0)	54.7 (8.5)	52.3 (9.4)
Range	34–69	30–76	37–78	30–78
Gender (no. of females)	39 (79.6%)	34 (61.8%)	36 (78.3%)	109 (72.7%)
Race/ethnicity (no. of white)	46 (93.9%)	53 (96.4%)	41 (89.1%)	140 (93.3%)
Years of education (*SD*)	16.8 (2.0)	16.4 (2.2)	16.8 (2.3)	16.6 (2.2)
Range	12–21	12–22	12–22	12–22
Marital status (no. of married)	35 (71.4%)	33 (60%)	29 (63%)	97 (64.7%)
Mean number of affected relatives (*SD*)	2.5 (1.3)	1.9 (1.0)	1.8 (1.0)	2.1 (1.3)
Range	1–7	1–5	1–5	1–5
Median income bracket	$70K–99,999	$70K–99,999	$70K–99,999	$70K–99,999

Table II. Cumulative Lifetime Risk (Mean (*SD*, Range)), Perceived Personal Risk (Mean (*SD*)) (a) Unadjusted for Lifetime Risk and (b) Adjusted for Lifetime Risk, Age, and Number of Affected Relatives, by APOE ε4 Status

	Cumulative Lifetime Risk	Perceived Personal Risk	
		(a) Unadjusted	(b) Adjusted
APOE ε4+	47.8 (9.6, 25–57)	3.9 (0.7)	3.4 (0.7)
APOE ε4–	24.1 (5.5, 18–29)	2.9 (0.8)	3.1 (0.8)
Controls	26.8 (4.4, 18–29)	3.2 (0.7)	3.4 (0.7)

To assess the extent to which the information provided by an APOE ε4-negative test result might have been falsely reassuring (i.e., led people to perceive their risks as the same or lower than the general population) PPR-FH scores were compared across the three comparison groups. Any response depicting risk to be the same or lower than the general population was considered as evidence of false reassurance. Thirty-one of the 149 participants were classified on this basis as being falsely reassured (31%), with those receiving an APO4 ε4-positive test result being least likely to show such a response (4/49 or 8%) compared with those with an APOE ε4-negative test result (17/55 or 31%) and those in the Control arm (10/45 or 22%). These latter two groups were not significantly different (difference: 9%; 95% CI: −8.26) (Fig. 2).

4. DISCUSSION

As we contemplate the discovery and dissemination of genetic risk markers, an important clinical question is how risk information using genetic testing can be communicated effectively. It has been theorized that risk perceptions are influenced not only by the lifetime risk estimates generated and communicated to an individual, but also by the binary result of a genetic test used in the assessment. In this study, receiving an APOE ε4-positive disclosure as part of the risk-assessment protocol had no influence on risk perceptions beyond that conferred by the lifetime risk estimate reported to the participant. However, receiving an APOE ε4-negative disclosure result led to a perception of risk that was, on average, lower than that following the provision of an equivalent lifetime risk estimate assessed without using a genetic test.

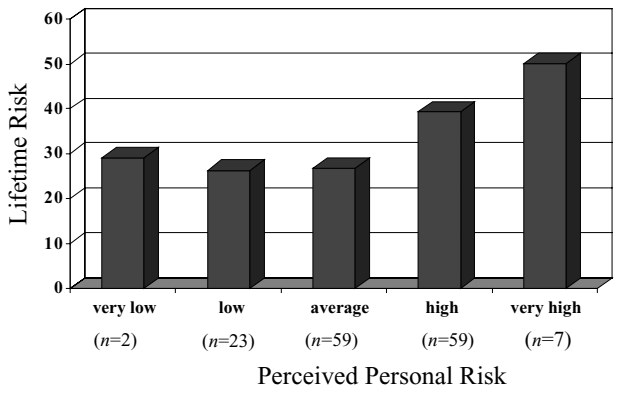

Fig. 1. Perceived personal risk and cumulative lifetime risk estimates for AD.

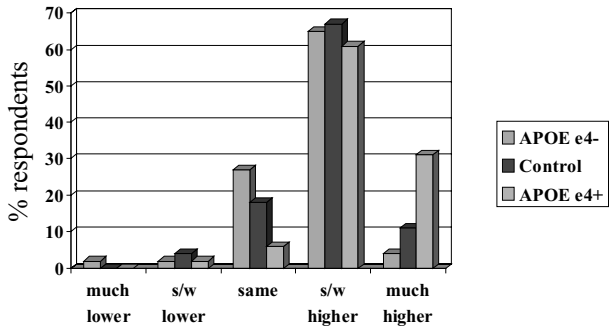

Fig. 2. Perceived personal risk compared with those without a family history of AD.

The results of this study provide partial support for fuzzy trace theory[8] in that responses to an APOE ε4-negative disclosure result may reflect the extraction of the gist associated with that test result (lower risk), leading to a lowered perception of risk following a risk estimate based in part upon this test result. The lack of a similar pattern in response to an APOE ε4-positive disclosure result suggests other factors are in play. Three possible explanations are considered below, although none of these is mutually exclusive. First, the pattern of results suggests that the processing of genetic risk information differs according to whether results are favorable or unfavorable. In other words, receiving a positive genetic test result does not affect risk perception, but receiving a negative result does have an effect, albeit a relatively small one. This may reflect the well-described emotional processes designed to minimize the impact of threatening information.[16,17] For example, in a recent study assessing the impact on risk perception of providing social comparison information, favorable comparisons (i.e., informing individuals that they had a lower than average chance of developing heart

disease) lowered risk perceptions, while unfavorable comparisons (i.e., informing individuals that they had a higher than average chance of developing heart disease) resulted in risk perceptions similar to those of individuals not given any social comparison information.[18]

Another possible explanation for the relative lack of impact of an unfavorable genetic test result is that an unfavorable test result may have been expected by the majority of those undergoing testing, perhaps reflecting their family histories of AD. Test results that meet expectations regardless of whether they are favorable or unfavorable have a less negative impact than test results that confound expectations.[19] It remains to be seen whether the same pattern of results might be obtained in those without family histories of AD who undergo APOE testing.

A third possible explanation for the imbalance in the impact of APOE ε4 test results concerns the way in which test results were communicated. It is possible that in preparing participants for testing and in presenting APOE ε4-positive test results counselors may have inadvertently expended more effort on anticipating responses to a positive test result, and when presenting such a result, presented it so as to reassure those who tested positive of the "susceptibility" rather than "deterministic" risk conferred by a positive result, thereby avoiding a marked impact on risk perception of an APOE ε4-positive test results. Similarly, counselors may have presented lifetime risk estimates derived in part from APOE ε4-negative test results more positively than risk estimates that did not include such a test. While all the counselors in the REVEAL study were trained to present information in a standard manner, the extent to which this was achieved in practice is unknown.

5. IMPLICATIONS

This is the first randomized study to directly compare the impact of risk assessment, with and without genotype disclosure, on risk perception. It should be noted that these findings contrast with the adverse effects of genetic predictive testing that some commentators had forecasted.[20] We have reported elsewhere that the Intervention arm participants, particularly those with an APOE ε4-negative test result, were more likely than Control arm participants to report that their risk assessment had had a positive impact.[21] In a similarly designed study of familial hypercholesterolemia (FH) aimed at assessing the impact of using genetic testing as part of a diagnostic package, use of genetic testing resulted in the diagnosis being seen as more accurate.[22] Genetic tests are relatively recent biological markers of disease, and their role in assessing disease susceptibility has engendered much discussion, but little use to date. This novelty of using genetic testing as part of risk perception may contribute to the more positive perceptions of genetic testing found in these studies.

There was no evidence in our study that receiving APOE ε4-positive disclosure affected risk perceptions beyond the risk estimates provided to the participants. In the short term, these results are consistent with those seen in predictive testing for other conditions in which the presence of a mutation associated with increased risk does not result in excess emotional distress.[23] Longer-term follow-up and inclusion of older individuals in such research protocols is warranted to ensure that as individuals approach the time when AD may develop, those who have undergone predictive testing do not experience more distress, a pattern that is being observed in long-term follow-up of those found to have a disease conferring mutation for Huntington's disease.[24]

While participants who received an APOE ε4-negative result perceived their risk estimates optimistically, there was no other evidence of false reassurance as defined and operationalized within this study. The pattern of results does, however, suggest that false reassurance is a possibility that needs to be assessed in other testing contexts, including testing in populations without a family history, and when less time is devoted to counseling testees. The one study to date assessing the impact of using gene testing to make a diagnosis, which was conducted for FH, reported that 24% of those who were mutation negative were falsely reassured by their result, assessed by agreement to the item: "Now that I don't have FH, my cholesterol can never be too high."[25] Those falsely reassured were less likely to have plans for testing their cholesterol levels in the future, suggesting that false reassurance could engender behavioral effects that increase an individual's risk of coronary heart disease. In the current study, those participating in the risk assessment were seen on several occasions both before and after being given their test results. The genetic counselors were trained to emphasize the nondeterministic nature of an ε4 test result in a seemingly successful attempt to avoid high anxiety and risk perceptions in those with ε4-positive results and, conversely, to avoid false reassurance in those who tested negative for this mutation.[21] The impact upon risk

perceptions of using briefer, more clinically feasible counseling protocols, is currently under investigation.

Finally, it should be noted that the results presented here compare the means of various groups. It will be important in future studies to consider not only the impact on groups as measured in the average scores, but also to consider individual responses to genetic testing.

6. STUDY STRENGTHS AND WEAKNESSES

This is the first randomized controlled study to assess how susceptibility genotyping affects risk perception. The results cast light on the possible advantages and disadvantages of doing so, and generate hypotheses to be tested in other contexts. The study was limited in two ways. First, risk perceptions were measured using single items, PPR and PPR-FH. While this is a common practice, it is a potentially unreliable means of measuring a higher-order construct. The second limitation was the study sample size. It was relatively small and hence lacked the power to detect small or medium effects. It was also unrepresentative of any general population because of high proportions of women, those with white ethnicity, and those with high socioeconomic status, although the current sample could reflect the characteristics of those who would come forward for such an assessment outside of a research context. Given that risk perceptions have been shown to vary by gender, ethnicity, and socioeconomic status in other contexts,[26,27] it remains to be seen whether the impact of APOE testing will differ in populations that better represent men, those with nonwhite ethnicity, and those with lower socioeconomic status.

7. CONCLUSION

Receiving an APOE ε4-positive disclosure as part of a risk-assessment protocol for AD had no influence on risk perceptions beyond that conferred by the lifetime risk estimate reported to the participant. However, receiving an APOE ε4-negative disclosure result led to a perception of risk that was, on average, lower than that following the provision of an equivalent lifetime risk estimate assessed without using a genetic test. Despite the reduced perception of risk in those who learned they were APOE ε4 negative, there was no evidence of false reassurance, although this possibility should be assessed in other testing contexts.

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