Recall of disclosed Apolipoprotein E genotype and lifetime risk estimate for Alzheimer's disease: The REVEAL Study

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Purpose: To determine whether individuals recall their apolipoprotein E genotype and numeric lifetime risk estimates after undergoing a risk assessment for Alzheimer's disease. **Methods:** One-hundred and four participants underwent Alzheimer's disease risk assessment that included disclosure of apolipoprotein E genotype and a numeric lifetime risk estimate. **Results:** At six weeks and one year post-disclosure, 59% and 48% of participants, respectively, recalled their lifetime risk estimate, and 69% and 63% recalled their apolipoprotein E genotype. Participants were more likely to remember their genotype than numeric lifetime risk estimate at one year ($P <$ 0.05). Apolipoprotein E ε4-positive participants had better recall of their genotype at both time points ($P < 0.05$). Participants were more likely to recall whether they carried the "risk-enhancing form of apolipoprotein E" than their specific genotype ($P < 0.05$). **Conclusions:** These data suggest that apolipoprotein E genotype, especially the presence of an ε4 allele, is more memorable than a numeric risk estimate for Alzheimer's disease. Participants recalled genotype information in a more simplified, binary form. Health professionals testing for complex disorders such as Alzheimer's disease must find an appropriate balance between communicating risk in an understandable format and addressing the probabilistic nature of the information. *Genet Med* 2006:8(12):746–751.

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Alzheimer's disease (AD) is a complex late-onset disease known to have a substantial genetic component.[1] There are three known genes associated with the early-onset autosomal dominant form of AD, but these genes account for <2% of AD cases.[2] The polymorphism associated with the much more common late-onset AD, the ε4 allele of the apolipoprotein E (*APOE*) gene,[3] is relatively common in the general population with approximately 25% of individuals carrying at least one ε4 allele.

At the present time genetic testing for late-onset AD is not widely performed or recommended because of the low predictive value of *APOE* genotyping and the lack of proven preventative options.[4–7] Genetic counseling and testing for complex disorders such as AD will become more widespread if additional susceptibility genes and effective preventative strategies are identified. A major aim of genetic counseling for complex disorders is to inform an individual of his or her probabilistic risk of developing a specific disease; therefore, an essential component of genetic counseling is risk communication. Risk perception and information recall are two measures that are commonly used to assess the effectiveness of risk communication. Although studies have explored perceived risk of AD in our study population,[8,9] little is known about how people recall risk estimates that are associated with genetic susceptibility testing for common disorders such as AD.

The vast majority of studies on risk information recall have been carried out in breast cancer genetic testing and counseling. The risk information presented in genetic counseling and testing for breast cancer is necessary for the health practitioner and patient to make informed medical decisions regarding appropriate risk management; this scenario may also apply to AD in the future if preventative strategies are identified. Studies examining the recall of risk information in breast cancer populations have shown that recall is poor and accuracy of risk recall varies widely.[10–12] One reason recall accuracy varies in the literature is that investigators have used different stringency criteria to define accuracy.[13] In addition, there is no consistency in the format in which risk figures are presented.[14,15] Studies have likely used different formats to present risk figures because women have expressed different preferences in how

risk information is presented.[16] A consensus for the most effective method of communicating risk information has not been reached. There is a need for more research in this area, specifically on how to communicate complex risk information for common diseases. We present the first study on recall of risk information in genetic susceptibility testing for Alzheimer's disease.

The REVEAL Study (Risk Evaluation and Education for Alzheimer's Disease) is the first multi-center randomized controlled trial to evaluate the impact of a risk assessment program using *APOE* genotyping and disclosure for nondemented adult children of people diagnosed with AD. For this paper, we assessed the recall accuracy of participants who received both *APOE* genotype as well as a lifetime risk estimate of developing AD. We hypothesized that 1) considering the amount of information presented in the study protocol, accurate recall of the specific genotype and numeric risk estimate would be poor with over 25% of the participants not able to accurately recall the information at one year; 2) based on previous REVEAL reports describing the impact of genetic testing on risk perception,[8–9] genotype information would be more accurately recalled than lifetime risk information and; 3) participants would be more likely to recall their ε4 status than their specific APOE genotype. Previous studies on hereditary breast cancer found that baseline worry about the disease,[17] family history,[18] and education[19] were associated with both risk perception and recall, thus, we were also interested in determining whether these factors along with gender influenced accurate recall for an AD risk assessment.

MATERIALS AND METHODS

Overview

The REVEAL Study's methods have been described in detail in previous publications.[8,9,20,21] Briefly, the study protocol was developed by a multidisciplinary team of experts in the fields of AD, neurology, genetics, genetic counseling, psychology, and bioethics. Development of the protocol was overseen and approved by a study External Advisory Board, as well as institutional review boards at each of the three study sites. All participants gave written informed consent.

Participants and procedures

All REVEAL study participants were adult children of a living or deceased individual diagnosed with late-onset AD (age of onset ≥60 years) and were referred to the study through systematic ascertainment from AD research registries or self-referral. All participants underwent neuropsychological screening and were judged to be cognitively intact. Participants were randomized to either an Intervention or Control Arm in a 2:1 ratio, respectively, after blood was drawn for genetic testing. Participants in the Intervention Arm received both *APOE* genotype and a lifetime risk estimate based on family history, genotype, and gender. The Control Arm did not learn their *APOE* genotype but did receive a lifetime risk estimate based on gender and family history. For the purposes of this paper,

we focused on information recall among the Intervention Arm participants (N = 104) only because we were interested in comparing correct recall of *APOE* genotype and a numeric lifetime risk estimate.

The study protocol consisted of five stages: 1) A telephone interview in which demographic and family history information was obtained; 2) a group education session which provided a description of the study, an overview of genetic principles and the genetics of AD; 3) a blood drawing session in which neuropsychological screening, specifically the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[22] was administered along with individualized genetic counseling; 4) a disclosure session in which a risk assessment was provided as well as *APOE* genotype; and 5) follow-up sessions at six weeks, six months and one year post-disclosure in which questionnaires were self-administered. In an effort to focus on initial and long-term recall of the information, we analyzed questionnaire responses from the six-week and one-year post-disclosure sessions.

Information provided during counseling

During the educational session, the genetic counselors provided information about the study protocol, AD, and genetics via a standardized slide show. A printout of the presentation was given to each participant. The genetic counselors presented statistics on the prevalence of AD as well the general population lifetime risk of developing AD. An overview of genetic principles was presented, and the genetic counselors discussed familial AD and the associated genes. A significant portion of the educational session was devoted to *APOE*: specifically, the three different alleles, the six possible genotypes, the frequency of *APOE* genotypes in the general population, and statistics to demonstrate that the ε4 allele is a susceptibility gene that is neither sufficient nor necessary to cause AD. Participants had the opportunity to ask questions about the information presented during the educational session and during the individualized genetic counseling session.

During the disclosure session, participants in the Intervention Arm received three pieces of risk information: A lifetime risk estimate which was defined as the risk from birth to age 85; a remaining risk estimate which was defined as the risk from the participant's current age to age 85; and their *APOE* genotype. Participants were also informed of the general population lifetime risk of developing AD as well as risk to all first-degree relatives for comparative purposes. The lifetime risk estimates ranged from 13% to 57% depending on an individual's gender and *APOE* genotype. Risk estimates were formulated using data from a multi-center AD genetic epidemiology studies based at Boston University.[21] The risk estimates were presented in oral, visual, and written formats and included in a take-home letter provided to participants. *APOE* genotype was not provided in the letter in order to minimize the possibility of genetic discrimination by disclosure to an unintended third party. The risk estimate was presented as a percentage and although it was stressed that an individual's specific risk may vary according to other unknown risk factors, a range of risk

was not offered. Risk curves tailored to a participant's genotype and gender were generated. The risk curves included a line representing the general population lifetime risk, a line representing risk to all first-degree relatives, and a line representing the individual's lifetime risk based on family history, gender, and genotype (Fig. 1). The risk curves were not taken home by the participants.

Measures

At six weeks and twelve months after disclosure, participants were asked a series of written survey questions designed to assess their perceptions of AD risk, the impact of the risk and genotype information, and their recollection of the information presented during the disclosure session. All questionnaires were self-administered onsite, although in rare instances, the questionnaire was mailed to the participant if he or she was unable to come to the site. Questions regarding a participant's information recall at six weeks post-disclosure were as follows (response options in parentheses): 1) "What is the percentage you were given as your lifetime risk of developing AD?" (open-ended); 2) "What were your *APOE* genetic test results?" (I don't remember, $\varepsilon2/\varepsilon2$, $\varepsilon2/\varepsilon3$, $\varepsilon2/\varepsilon4$, $\varepsilon3/\varepsilon3$, $\varepsilon3/\varepsilon4$, $\varepsilon4/\varepsilon4$). At one year post-disclosure, participants were asked the above questions as well as the following: 1) "What form (allele) of *APOE* is the risk-enhancing form?" ($\varepsilon2$, $\varepsilon3$, $\varepsilon4$, I don't remember); 2) "Do you have the risk-enhancing form (allele) of *APOE*?" (Yes: one copy, Yes: two copies, No, I don't remember).

Data analyses

Descriptive statistics were used to characterize the sample in terms of its demographics and information recall. Responses were analyzed to examine the extent to which participants recalled lifetime risk information and genotype at six weeks and at one year following the disclosure session. Based on definitions of recall accuracy in previous reports,[11,14,23] some leeway was given in determining accurate recall of lifetime risk, which we defined as within five percentage points of the estimate provided during the disclosure section. Accurate recall of genotype was defined as the correct recall of both *APOE* alleles. McNemar's χ^2 analysis was employed to compare the accuracy of recall of specific genotype and numeric risk estimates. Correlative and regression analyses were utilized to assess factors

associated with accurate recall of both types of information (genotype and lifetime risk estimates) at six weeks and one year; variables assessed included gender, education, number of relatives affected with AD, and baseline worry about developing AD.

RESULTS

Demographic characteristics of the study sample (N = 104) and genotype breakdown are shown in Table 1. All participants underwent neuropsychological screening and formal memory testing was within normal limits for all participants. Descriptive statistics indicate that at the six-week follow-up, 61 participants (59%) accurately recalled the numeric risk probability they were given, 24 (23%) incorrectly recalled their risk and 19 (18%) indicated that they did not remember the information. Of the 24 individuals who did not accurately recall their numeric risk probability, 7 (29%) overestimated and 17 (71%) underestimated their risk. Seventy-two (69%) correctly recalled their *APOE* genotype, 13 (13%) incorrectly recalled their genotype, and 19 (18%) did not remember the information (Table 2).

At the one-year follow-up, 50 participants (48%) accurately recalled the numeric risk probability they were given, 37 (36%) did not accurately recall their risk, and 17 (16%) indicated that they did not remember the information. Of the 37 individuals who did not accurately recall their numeric risk probability, 12 (32%) overestimated and 25 (68%) underestimated their risk. Sixty-three participants (63%) correctly recalled their *APOE* genotype, 10 (10%) were incorrect in their recall of genotype and 28 (28%) indicated they did not remember (Table 2). A detailed breakdown of correct recall of lifetime risk for 6 weeks and 12 months post-disclosure shows that 59% of the participants were correct within 5 points of the risk estimate given and 71% were correct within 15 points of the risk estimate given (Table 3). Although it was not a focus of the study, an analysis of the Control Arm recall showed that there was no significant difference for accurate lifetime risk recall between the Intervention Arm and the Control Arm.

At the one-year follow-up, all participants were asked whether they knew the risk-enhancing form of *APOE*. Sixty-
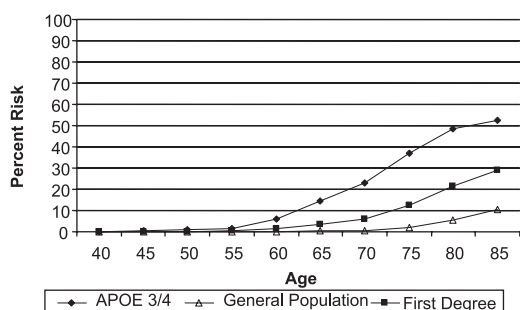

Fig. 1. Example of an Alzheimer's disease (AD) risk curve presented to participants.

Table 1
Demographic characteristics of the sample (N = 104)

Mean Age, years (SD)	51.3 (9.7)
Gender (F/M)	73/31
Mean years education (SD)	16.6 (2.1)
APOE genotype, N (%)	
3/3	51 (49)
3/4	43 (41)
2/3	4 (4)
4/4	3 (3)
2/4	3 (3)

Table 2
Number of participants accurately recalling lifetime risk estimate, APOE genotype and possession of risk-enhancing gene (ε4 allele)

	Number correct (%)	
	6 Weeks	1 Year
Lifetime risk estimate	(N = 104)	(N = 104)
Accurate	61 (59%)	50 (48%)
Incorrect	24 (23%)	37 (36%)
Didn't recall	19 (18%)	17 (16%)
Genotype	(N = 104)	(N = 100)[a]
Accurate	72 (69%)	63 (63%)
Incorrect	13 (13%)	10 (10%)
Didn't recall	19 (18%)	28 (28%)
Possession of ε4 allele	N/A[b]	(N = 100)[a]
		76 (76%)

[a]Missing data.
[b]Participants were not asked this question at this timepoint.

Table 3
Participant recall of lifetime risk (N = 104)

Lifetime risk recall	6 Week post-disclosure number (%)	1 Year post-disclosure number (%)
Exact	28 (27%)	20 (19%)
Within 5 points	33 (32%)	30 (29%)
Within 6 to 10 points	7 (7%)	10 (10%)
Within 11 to 15 points	6 (6%)	11 (11%)
Within 16 to 20 points	5 (5%)	3 (3%)
>20 points	6 (6%)	13 (12%)
Don't remember	19 (18%)	17 (16%)

Accurate recall defined in text as within 5% of the numeric risk estimate disclosed to participants.

four participants (62%) correctly indicated that ε4 is the risk-enhancing *APOE* gene. All participants were also asked whether they carried the "risk-enhancing form of *APOE*." The question was worded so that individuals would not be required to know that the ε4 allele is the risk-enhancing form, but only whether they possessed zero, one or two copies of the gene that increased AD risk. Seventy-six participants (76%) correctly recalled how many copies of the risk-enhancing allele they possessed. There were three ε4 homozygotes in the study sample and all three correctly recalled that they possessed two copies of the risk gene.

McNemar's χ^2 analyses revealed that at one year after disclosure, participants were significantly more likely to recall their specific genotype than their numeric risk estimate (Table 2; $P < 0.05$). No difference was seen at six weeks. χ^2 analyses demonstrated that participants who were ε4-positive were

more likely to correctly recall their genotype at 6 weeks ($P < 0.05$) and one year ($P < 0.05$) than those participants who were ε4-negative. χ^2 analyses also showed that participants were significantly more likely to recall whether they possessed a copy of the risk gene than to recall their specific genotype ($P < 0.05$). There was a trend suggesting that participants who were worried about developing AD at baseline were more likely to recall their genotype at six weeks ($P = 0.07$), but this association was not apparent at one year. Logistic regression revealed that *APOE* genotype predicted accurate recall of genotype information ($P < 0.05$) with ε4-positive participants more likely to recall their genotype than ε4-negative individuals one year after disclosure. None of the other study variables entered into the model (gender, education, baseline AD worry, and number of affected relatives) significantly contributed to genotype recall. No significant predictors were found for recall of lifetime risk at one year or for either type of information at six weeks.

DISCUSSION

This study is the first to examine whether participants correctly recall their APOE genotype and numeric risk estimates after undergoing a risk assessment for AD. Genetic counseling studies have shown that accurate recall of numeric risk estimates for cancer vary widely with a range of 31%[24] to 81%,[14] although a lack of standardization in how risk was presented (odds or percentages) and in how recall accuracy was defined likely contributed to this large range.[25] Our data fall within this previously reported range with 59% recall accuracy of the numeric risk estimate (defined as within 5%) at six weeks post-disclosure and 48% accuracy at one year. Our study is also unique in that we were able to analyze recall of genetic test results because there are six possible genotypes for APOE as opposed to either a mutation positive or negative result in genetic testing for hereditary cancer.

In our study, a sizable number of people could not remember or did not accurately recall risk information. Six weeks after the risk assessment and disclosure, 41% of the participants did not accurately recall their risk estimate and 31% did not accurately recall their genotype. Inaccurate recall increased at one year post-disclosure when 52% of the participants could not correctly recall their risk estimate and 47% could not accurately recall their genotype. In addition, at the one-year follow-up 38% of the participants were not able to identify which *APOE* allele increased risk and 24% of participants were not able to recall how many copies of the risk-enhancing gene they possessed. A primary reason for the poor recall may have been information overload. During the disclosure session, the general population lifetime risk, the risk to all first-degree relatives of AD patients, genotype specific lifetime risk, remaining risk, and *APOE* genotype were presented; this amount of information may have been confusing or difficult for an individual to process and recall. Also, as in genetic counseling for cancer, the information presented in AD genetic counseling is complex. For example, to stress the fact that AD is multifactorial and that age is a risk factor, we presented prevalence statistics showing

that 50–60% of people in their nineties suffer from dementia, most of which is AD. It is possible that some study participants may have confused such general information with their own personal risk information. Alternatively, the general information may have played a role in how an individual perceived and recalled his or her personal risk, such as believing his or her lifetime risk was 50% because approximately 50% of individuals in their nineties suffer from AD. Previous studies have described the intermingling of general information and personal risk information[26] and credited it to the large amount of information presented during genetic counseling sessions.[15] In the future, it may be worthwhile to simplify the general information presented with a handout prior to individualized counseling to allow the counselor to spend less time on formal education and more time on interpersonal counseling.

Several previous studies have reported that participants who do not accurately recall their risk tend to overestimate[15–17,27] and that overestimation has been associated with worry about developing the disease.[17,28–30] However, we did not observe these phenomena among the participants in our study. Of the participants who did not accurately recall their risk, 71% and 68% underestimated their risk at six weeks and one year postdisclosure, respectively. It is possible that this underestimation served as a defense against potentially threatening information, which has been described in other health behavior studies.[31,32] Although there was a trend toward significance in the association between worry at baseline and correct recall of risk at six weeks, there was no such association between baseline worry and recall of risk information at the one-year follow-up.

Our findings suggest that *APOE* genotype, specifically possession of an ε4 allele, may be more memorable than numeric estimates of lifetime risk of AD. At one year after disclosure, participants were significantly more likely to recall their specific genotype compared to the risk estimate and ε4 positive individuals were significantly more likely to recall their genotype six weeks and one year after disclosure. The influence and impact of disclosing *APOE* genotype as part of an AD risk assessment has also been observed in other REVEAL studies examining the effect of genetic test result disclosure on risk perception.[8,9]

There are several possible explanations for the association between *APOE* genotype disclosure and accurate information recall. A methodological consideration is that participants were asked about *APOE* genotype recall in a multiple choice format while they were asked about lifetime risk in a more challenging open-ended format. The nature of the risk information itself may have also influenced recall. Study participants may have been motivated to participate in the study because of the potential of receiving genetic test results and thus may have focused more on *APOE* genotype, especially the possession of the allele that increases AD risk. The way that the numeric risk estimate was presented may have also contributed to poorer recall of this information. Participants were informed that the numeric risk estimates were based on population studies, thus *APOE* genotype may have been perceived as more personalized and more memorable information when

compared to the risk estimate. In addition, the risk estimate was presented as a probability and the range of possible risk estimates was 13–57%. Therefore, the risk estimate was midrange and typically less than the usual probabilities associated with genetic testing, specifically Mendelian disorders. The study participants, despite their high education level, may have been uncomfortable with mathematical concepts and probabilities, which have been reported elsewhere.[32–34] Also, it is possible that some participants might have shown better recall if the risk estimates had been presented in a different format, such as odds or in a more descriptive and discrete format, such as high or low.[16,33]

Participants were significantly more likely to remember the more general information of whether they carried the risk gene than to recall their specific genotype. These findings support previously documented observations that individuals often dichotomize risk and thus perceive the risk in a binary form, such as "I will or won't get the disease," or "I do or don't possess the risk gene."[35] These findings as well as the fact that 59% of participants recalled the risk estimate within 5 percentage points and 71% of participants recalled lifetime risk within 15 percentage points of the actual risk disclosed (Table 3) are also congruous with the belief that individuals simplify complex information and extract the gist.[7,36,37] Although it is beneficial for an individual undergoing genetic testing and counseling for a complex disorder to correctly recall the essential information communicated, especially if preventative measures are identified, it is also important that they understand that the risk is probabilistic. A probabilistic risk of developing AD may be an important tool in deciding whether an at-risk individual should undergo preventative measures that have side effects and more studies are needed to develop effective ways to communicate the concept of probabilities.

There are some limitations to this study. Our participants are not representative of the general population at risk for AD, given that they are predominantly White, female, and have a high level of education. Although the education session presentation was standardized, the questions asked during the education session as well as the content of the individualized genetic counseling sessions both before and during disclosure were appropriately not standardized. In addition, the genetic counselors likely had different counseling styles and may have emphasized different issues in accordance with the questions and concerns of the participants. It is possible that the accuracy of information recall and risk perception also reflects the skills of the health professional providing the counseling, but studies have been inconclusive on this point.[38,39] Future REVEAL studies will analyze the individual counseling sessions and relate counseling process variables to various outcomes such as risk perception and recall. In addition, the participants in REVEAL will be followed for an additional eight years beyond the disclosure session which will allow us to assess risk information recall and perception along with other variables over a much longer period.

This is the first study to assess information recall in genetic counseling and testing for late-onset Alzheimer's disease. Not only are the findings significant for risk communication in AD,

they are also relevant for cancer counseling and for genetic counseling for other complex diseases, especially as more susceptibility genes and effective preventative strategies are found. The data imply that individuals are more likely to accurately recall discrete information, such as genotype, than probabilistic information, such as the risk estimate. Furthermore, participants recalled the genotype information in a more simplified format than it was presented. Considering the complexity, magnitude, and probabilistic nature of the information presented in AD genetic counseling, additional research identifying effective risk communication is clearly needed.

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