Disclosure of APOE Genotype for Risk of Alzheimer’s Disease

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ABSTRACT

BACKGROUND
The apolipoprotein E (APOE) genotype provides information on the risk of Alzheimer’s disease, but the genotyping of patients and their family members has been discouraged. We examined the effect of genotype disclosure in a prospective, randomized, controlled trial.

METHODS
We randomly assigned 162 asymptomatic adults who had a parent with Alzheimer’s disease to receive the results of their own APOE genotyping (disclosure group) or not to receive such results (nondisclosure group). We measured symptoms of anxiety, depression, and test-related distress 6 weeks, 6 months, and 1 year after disclosure or nondisclosure.

RESULTS
There were no significant differences between the two groups in changes in time-averaged measures of anxiety (4.5 in the disclosure group and 4.4 in the nondisclosure group, P=0.84), depression (8.8 and 8.7, respectively; P=0.98), or test-related distress (6.9 and 7.5, respectively; P=0.61). Secondary comparisons between the nondisclosure group and a disclosure subgroup of subjects carrying the APOE ε4 allele (which is associated with increased risk) also revealed no significant differences. However, the ε4-negative subgroup had a significantly lower level of test-related distress than did the ε4-positive subgroup (P=0.01). Subjects with clinically meaningful changes in psychological outcomes were distributed evenly among the nondisclosure group and the ε4-positive and ε4-negative subgroups. Baseline scores for anxiety and depression were strongly associated with post-disclosure scores of these measures (P<0.001 for both comparisons).

CONCLUSIONS
The disclosure of APOE genotyping results to adult children of patients with Alzheimer’s disease did not result in significant short-term psychological risks. Test-related distress was reduced among those who learned that they were APOE ε4-negative. Persons with high levels of emotional distress before undergoing genetic testing were more likely to have emotional difficulties after disclosure. (ClinicalTrials.gov number, NCT00571025.)
K
owledge of the results of genetic-susceptibility testing may cause anxiety, depression, and other types of distress. Nevertheless, gene variants that are associated with risks of common diseases are being rapidly discovered, and genetic testing is now marketed to consumers.\textsuperscript{1-3} A variant of the gene APOE, which encodes apolipoprotein E, is associated with an increased susceptibility to Alzheimer’s disease,\textsuperscript{4} and we thought that testing for the presence of this gene would be useful for evaluating the effect of genetic-risk assessment.\textsuperscript{4} By consensus, APOE testing is not currently recommended for asymptomatic persons; a major concern is the emotional effect of risk disclosure.\textsuperscript{5-8}

In the Risk Evaluation and Education for Alzheimer’s Disease (REVEAL) study, we hypothesized that persons who learned about their APOE genotype through an education-and-disclosure protocol would not have greater symptoms of anxiety, depression, or test-related distress than those not receiving such information.

\section*{Methods}

\subsection*{Study Population and Instruments}
We recruited adult children of a living or deceased parent with Alzheimer’s disease through self-referral or telephone calls to families in research registries.\textsuperscript{9} As part of the screening process, we interviewed the subjects and administered standardized tests to evaluate their cognitive ability, academic achievement, and levels of anxiety and depression. We excluded subjects who scored 1.3 SD below norms on the Repeatable Battery for the Assessment of Neuropsychological Status or the Wide Range Achievement Test 3; higher than 20 on the Beck Anxiety Inventory (BAI), which ranges from 0 to 63, with higher scores indicating greater anxiety; or higher than 26 on the Center for Epidemiological Studies Depression Scale (CES-D), which ranges from 0 to 60, with higher scores indicating greater depression. Ancestry was determined by self-report obtained through a multiple-choice question, with the following options: white, American Indian, Asian, black, and Hispanic; we pre-specified the designation of “other” in the event that a subject selected more than one option.

The BAI\textsuperscript{10,11} is a 21-item scale designed to distinguish symptoms of anxiety from those of depression and to be sensitive to change. This test is based on self-reported severity of a given anxiety symptom during the previous week, with a clinical cutoff score of 16 (moderate anxiety). The CES-D\textsuperscript{12,13} measures depressive symptoms in studies of nonclinical populations, with a clinical cutoff score of 16 to 20.\textsuperscript{14,15} We estimated that 5-point differences on either the BAI or the CES-D would be a sensitive indicator of clinically meaningful change and that with a sample of 46 persons per group, the study would have a statistical power of 80% to detect this difference on either scale. The Impact of Event Scale (IES) is a 15-item self-report instrument assessing test-related distress\textsuperscript{16,17} that is commonly used in genetics research. The scores range from 0 to 75, with higher scores indicating greater distress.\textsuperscript{18-25} A total score of 20 to 40 may indicate significant distress, and a 5-point difference is a conservative measure of clinically meaningful change. We also developed a series of original questions to gauge changes in risk perception, positive and negative effects of the genetic disclosure, and whether the subject would make the same decision again to undergo genetic testing.

\subsection*{Study Design}
The REVEAL study group — an interdisciplinary team of experts in clinical trials, neurology, genetics, genetic counseling, health psychology, biostatistics, and bioethics — designed the study, drawing on surveys conducted with relatives of patients with Alzheimer’s disease.\textsuperscript{26-28} We created risk curves for the disclosure process that were specific for age and sex, showing the lifetime cumulative incidence of Alzheimer’s disease and the remaining risk of Alzheimer’s disease for each subject (cumulative incidence from current age to the age of 85 years).\textsuperscript{29}

The study was conducted from 2000 through 2003 at sites in Boston, Cleveland, and New York. It was approved by the institutional review board at each center and was coordinated by a board-certified or board-eligible genetic counselor at each site. Informed consent was obtained first by telephone, then in writing (Fig. 1, and the Supplementary Appendix, available with the full text of this article at NEJM.org). A 90-minute, semiscripted group session that was led by the genetic counselor described the limitations of APOE testing, the absence of a medical benefit of such testing, and the format for communication of the risk. All subjects later met individually with the genetic counselor for the drawing of blood samples, which were sent to Athena Diagnostics for APOE genotyping. Subjects
Disclosure of APOE Genotype for Risk of Alzheimer's Disease

Subjects in the nondisclosure group were individually shown two charts: one showing the incidence of Alzheimer's disease in the general population according to age and another showing the sex- and age-specific incidence of the disease among first-degree relatives of patients with Alzheimer's disease. Subjects in the disclosure group were shown the same curves with an additional line for their genotype-specific risk (Fig. 1 in the Supplementary Appendix). They also received their lifetime cumulative incidence risk by the age of 85 years. Subjects were told their APOE genotype and were given written reports of their lifetime cumulative incidence risk and remaining incident risk.

Outcome Measures
The prespecified primary outcomes were changes in subjects' anxiety and depression symptoms, as measured by the BAI and the CES-D, respectively. The prespecified secondary outcome was test-related distress, as measured by the IES.

We administered the BAI and the CES-D before randomization and 6 weeks, 6 months, and 1 year after disclosure or nondisclosure of risk. We administered the IES at 6 weeks, 6 months, and 1 year. The primary analysis compared the two randomized groups. A secondary analysis compared the subgroup of subjects in the disclosure group who were informed that they carried at least one e4 allele, which is associated with an increased risk of Alzheimer’s disease (the e4-positive subgroup), with either a subgroup of subjects who were informed that they did not carry an e4 allele (the e4-negative subgroup) or with the nondisclosure group.

Safety Monitoring
Throughout the study, genetics counselors monitored all subjects for adverse psychological effects. We created an independent external ethics and safety board to review the protocol, monitor study progress, and establish criteria for the reporting of adverse events to the institutional review board at each site. For example, subjects whose BAI or CES-D scores were more than 16 or increased by more than 15 points were immediately interviewed, with referral as appropriate. The chair of the ethics and safety board reviewed the results annually to screen for adverse or unanticipated events.

Figure 1. Enrollment and Outcomes.
Of the 21 subjects who were excluded before randomization, 7 had low neurocognitive scores, and 2 had high depression scores. The other 12 subjects withdrew from the study for other reasons.
STATISTICAL ANALYSIS

We used two-sided t-tests or chi-square tests to compare baseline variables between the two initial randomization groups (the disclosure group and the nondisclosure group) and between the nondisclosure group and the ε4-positive and ε4-negative subgroups. We compared the rate of withdrawal from the study among the groups. Prespecified primary analyses compared scores on the BAI and the CES-D in the disclosure group with those in the nondisclosure group and included data from all time points, with the use of longitudinal analysis of mixed-effects models that were adjusted for age, sex, years of education, time, and baseline outcome score (if available). In the intention-to-treat analysis, missing values were calculated with the Markov chain Monte Carlo method of multiple imputation with the use of PROC MI statistical software, version 9.1 (SAS Institute).

To assess trends over time, we added interaction terms between group and time as covariates to longitudinal models. The model for the primary analysis was also run separately for each time point. This process was repeated for the IES scores. All three outcomes were then examined in the same manner for the two disclosure subgroups and the nondisclosure group. Although the study was not originally powered for equivalence testing, equivalence was demonstrated post hoc when a confidence interval for a group difference did not include 5 points in either direction. We examined raw changes in scores on each outcome measure to calculate the percentage of subjects whose changes in scores exceeded clinically significant thresholds (Fig. 3 in the Supplementary Appendix).

RESULTS

SUBJECTS

Of the subjects who participated in the informational interview and educational session, 61% and 84%, respectively, underwent phlebotomy (Fig. 1). Twelve subjects withdrew from the study after phlebotomy and before randomization, and seven subjects with low neurocognitive scores and two subjects with high depression scores were excluded. The remaining 162 subjects were randomly assigned in a 2:1 ratio to either the disclosure group (111 subjects) or the nondisclosure group (51 subjects) (Table 1).

After randomization, 14 subjects withdrew from the study, citing study-related reasons. Of the variables listed in Table 1, only the baseline BAI score showed a trend toward an association with withdrawal from the study (i.e., those who were less anxious were more likely to withdraw; P=0.07). Some subjects in the nondisclosure group were dissatisfied at not receiving their genotyping results; of these subjects, 8 (16%) withdrew, as did 6 subjects (5%) in the disclosure group (P=0.04). Of the 53 subjects in the ε4-positive subgroup, 3 (6%) withdrew from the study, as did 3 of 58 subjects (5%) in the ε4-negative subgroup. Of the 111 subjects in the disclosure group, 3 (3%) had the ε4/ε4 genotype, 46 (41%) had the ε3/ε4 genotype, 53 (48%) had the ε3/ε3 genotype, 5 (4%) had the ε2/ε3 genotype, and 4 (4%) had the ε2/ε2 genotype; none of the subjects had the ε3/ε4 genotype. Subjects with the ε4/ε4 genotype were given a higher risk estimate but were included in the ε4-positive group in analyses. Data that were collected after randomization but before withdrawal were included in the analyses.

For the end points of scores on the BAI and the CES-D, adjusted group means for the disclosure and nondisclosure groups did not differ significantly either with the use of the time-averaged longitudinal model or at any individual time point (Table 2). Changes from baseline in time-averaged scores for anxiety and depression did not differ significantly between the two groups: for the anxiety score, 4.5 in the disclosure group and 4.4 in the nondisclosure group (P=0.84); and for the depression score, 8.8 and 8.7, respectively (P=0.98).

Interaction analyses indicated that between-group differences in scores were stable over time. We designed the prespecified analyses to allow detection of significant differences, and observing none, we then carried out a post hoc analysis for equivalence by examining 95% confidence intervals. All the confidence intervals excluded a difference of 5 points or more for scores on both the BAI (within 3 points) and the CES-D (within 2 points). Post-disclosure scores on the BAI and the CES-D were strongly associated with respective baseline scores on these measures (P<0.001 for both comparisons).

There were no significant differences between the nondisclosure group and the two disclosure subgroups (ε4-positive and ε4-negative) in the overall model on the BAI or the CES-D at any time point (Tables 3 and 4), with all 95% confidence intervals excluding a difference of 5 points or more. We observed no significant differences between
Table 1. Characteristics of the Subjects at Baseline.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Randomization Groups (N = 162)</th>
<th>Disclosure Subgroups (N = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nondisclosure Group (N = 51)</td>
<td>Disclosure Group (N = 111)</td>
</tr>
<tr>
<td>Age — yr</td>
<td>Mean 55.3±9.0</td>
<td>52.0±10.0</td>
</tr>
<tr>
<td></td>
<td>Range 37–78</td>
<td>30–76</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>40 (78)</td>
<td>77 (69)</td>
</tr>
<tr>
<td>White race — no. (%)</td>
<td>46 (90)</td>
<td>106 (96)</td>
</tr>
<tr>
<td>Education — yr</td>
<td>Mean 16.8±2.5</td>
<td>16.7±2.2</td>
</tr>
<tr>
<td></td>
<td>Range 10–22</td>
<td>12–22</td>
</tr>
<tr>
<td>Currently married — no. (%)</td>
<td>31 (61)</td>
<td>74 (67)</td>
</tr>
<tr>
<td>BAI score‡</td>
<td>4.6±4.5</td>
<td>4.2±5.0</td>
</tr>
<tr>
<td>CES-D score§</td>
<td>5.2±4.9</td>
<td>6.7±5.6</td>
</tr>
<tr>
<td>Site — no. (%)</td>
<td>Boston 17 (33)</td>
<td>39 (35)</td>
</tr>
<tr>
<td></td>
<td>New York 18 (35)</td>
<td>37 (33)</td>
</tr>
<tr>
<td></td>
<td>Cleveland 16 (31)</td>
<td>35 (32)</td>
</tr>
<tr>
<td>Self-referred to study — no. (%)</td>
<td>35 (69)</td>
<td>80 (72)</td>
</tr>
<tr>
<td>More than 1 relative with Alzheimer’s disease — no. (%)</td>
<td>35 (70)</td>
<td>70 (63)</td>
</tr>
<tr>
<td>Caregiver for relative with Alzheimer’s disease — no. (%)¶</td>
<td>40 (78)</td>
<td>82 (75)</td>
</tr>
<tr>
<td>Age at onset of Alzheimer’s disease in affected parent — yr‖</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Mean 74.6±9.0</td>
<td>70.8±8.6</td>
<td>68.8±7.7</td>
</tr>
<tr>
<td>Range 55–90</td>
<td>55–91</td>
<td>55–83</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ±SD.
† Race was self-reported.
‡ Scores on the Beck Anxiety Inventory (BAI) range from 0 to 63, with higher scores indicating greater anxiety.
§ Scores on the Center for Epidemiological Studies Depression Scale (CES-D) range from 0 to 60, with higher scores indicating greater depression.
¶ In this category, the denominators were 110 in the disclosure group and 52 in the ε4-positive subgroup.
‖ The age at onset was known for 44 (86%) of subjects in the nondisclosure group, 97 (87%) in the disclosure group, 48 (91%) in the ε4-positive subgroup, and 49 (84%) in the ε4-negative subgroup.

the nondisclosure group and the ε4-positive group over time using the longitudinal model or at any time point. Adjusted means were very similar to unadjusted means. (Tables show only adjusted means; raw means are shown in Figure 2 in the Supplementary Appendix.) Adjusted mean IES scores for the disclosure and nondisclosure groups did not differ significantly at any time point or over time (6.9 in the disclosure group and 7.5 in the nondisclosure group, P=0.61). All 95% confidence intervals excluded clinically meaningful differences of 5 points or more, except for the scores at 6 months, which showed a trend toward less distress in the disclosure group. Adjusted IES scores in the ε4-negative subgroup were lower than those in the nondisclosure group at 6 months (P=0.01), with a similar trend over time (P=0.09) (Table 4). A comparison of IES scores in the ε4-negative group with those in the ε4-positive group showed significant differences over time (4.8 in the ε4-negative group vs. 8.5 in the ε4-positive group, P=0.01) and at 6 weeks (P=0.02) and 6 months (P=0.01), with a marginally significant difference at 12 months (P=0.06).

On the IES, we could not demonstrate equivalence to within 5 points with 95% confidence at
any time point for comparisons between the non-disclosure group and the ε4-negative subgroup or between the ε4-positive subgroup and the ε4-negative subgroup. A comparison of the nondisclosure group with the ε4-positive subgroup showed no significant differences over time or at any time point. A difference of 5 points could be excluded with 95% confidence at 6 months, 12 months, and over time but not at 6 weeks, when scores for distress were higher in the ε4-positive subgroup. The results of all intention-to-treat analyses were similar to the results of analyses that included only subjects for whom scores at all time points were available (data not shown).

There was no significant change in our findings after adjustment for race, years of education, marital status, study site, referral source, family history, caregiver status, or mean age of the affected parent at the onset of disease. A difference of 5 points could be excluded with 95% confidence at 6 months, 12 months, and over time but not at 6 weeks, when scores for distress were higher in the ε4-positive subgroup. The results of all intention-to-treat analyses were similar to the results of analyses that included only subjects for whom scores at all time points were available (data not shown).

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scores, combined with prespecified safety criteria, triggered an assessment of adverse psychological effects in 13 subjects: 3 in the nondisclosure group, 4 in the ε4-negative subgroup, and 6 in the ε4-positive group (4 with the ε3/ε4 genotype and 2 with the ε4/ε4 genotype). None of the subjects attributed their psychological state to concern about disclosure but instead cited personal events or experiences, such as family illness and job-related stress, that were not related to the study.

### DISCUSSION

Subjects who were randomly assigned to undergo risk assessment with APOE disclosure did not have greater anxiety, depression, or test-related distress than those who were assigned to undergo risk assessment without APOE disclosure. Post hoc equivalence within 5 points was demonstrated at all visits over time for all outcomes, with the exception of the 6-month time point for the secondary outcome of the IES score, which showed a trend toward less distress in the disclosure group.

Subjects who learned they were ε4-positive and were therefore at increased risk for Alzheimer’s disease showed no more anxiety, depression, or test-related distress than those who did not learn their genotype, although strict equivalence could not be demonstrated for test-related distress at 6 weeks, which reflected, in part, transient test-related distress among ε4-positive subjects at this time point. The comparison of subjects in the ε4-positive subgroup with those in the ε4-negative subgroup revealed significant but not clinically meaningful differences on test-related distress, driven by reduced distress among ε4-negative subjects at 6 months and 12 months. The change in the IES score from baseline to 6 weeks also differed significantly between the ε4-positive subgroup and the ε4-negative subgroup, which we partly attributed to an increase in distress in the ε4-positive group. On all outcome measures, mean scores in the two disclosure subgroups and the overall disclosure group were well below clinical thresholds for concern. Subjects with outcome scores above prespecified safety thresholds were evenly distributed among the nondisclosure group and the ε4-positive and ε4-negative subgroups, and these subjects did not cite genotype disclosure as contributing to their psychological distress.

Additional questions about risk perception and the effect of testing 6 weeks after disclosure suggested that subjects understood that their risk was higher or lower according to their genotype, and they had the expected negative or positive feelings about this news. Thus, subjects were not immune to the negative implications of learning that they had an increased risk, but these feelings were not associated with clinically significant psychological distress.

These data support the psychological safety of disclosing data regarding genetic-counseling protocols to screened adult children of patients with Alzheimer’s disease who request such information, despite the frightening nature of the disease and the fact that disclosure has no clear medical benefit. Larger studies that follow subjects for more than 1 year will be required to detect uncommon and long-term effects, such as delayed emotional repercussions and injudicious life decisions.

APOE is the most robust risk marker available for Alzheimer’s disease; it is also associated with impaired memory among persons without dementia and with progression to Alzheimer’s disease among persons with mild cognitive impairment. Surveys indicate that the public is interested

### Table 3. Measures of Anxiety, Depression, and Test-Related Distress in the Nondisclosure Group and in the Two Disclosure Subgroups with Known APOE ε4 Status.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Nondisclosure Group (N=51)</th>
<th>ε4-Positive Subgroup (N=53)</th>
<th>ε4-Negative Subgroup (N=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAI score†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 wk</td>
<td>4.4±0.7</td>
<td>5.2±0.7</td>
<td>4.5±0.6</td>
</tr>
<tr>
<td>At 6 mo</td>
<td>4.6±0.6</td>
<td>4.6±0.6</td>
<td>3.9±0.6</td>
</tr>
<tr>
<td>At 12 mo</td>
<td>4.2±0.6</td>
<td>4.4±0.6</td>
<td>4.2±0.6</td>
</tr>
<tr>
<td>CES-D score‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 wk</td>
<td>9.3±1.0</td>
<td>9.0±1.0</td>
<td>8.5±0.9</td>
</tr>
<tr>
<td>At 6 mo</td>
<td>8.7±1.0</td>
<td>9.6±1.0</td>
<td>8.9±1.0</td>
</tr>
<tr>
<td>At 12 mo</td>
<td>8.0±0.9</td>
<td>8.3±0.9</td>
<td>8.5±0.9</td>
</tr>
<tr>
<td>IES score§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At 6 wk</td>
<td>6.7±1.4</td>
<td>9.4±1.3</td>
<td>5.2±1.3</td>
</tr>
<tr>
<td>At 6 mo</td>
<td>8.9±1.3</td>
<td>8.6±1.2</td>
<td>4.2±1.2</td>
</tr>
<tr>
<td>At 12 mo</td>
<td>7.7±1.5</td>
<td>8.5±1.3</td>
<td>5.1±1.2</td>
</tr>
</tbody>
</table>

† Scores on the Beck Anxiety Inventory (BAI) range from 0 to 63, with higher scores indicating greater anxiety.
‡ Scores on the Center for Epidemiological Studies Depression Scale (CES-D) range from 0 to 60, with higher scores indicating greater depression.
§ Scores on the Impact of Event Scale (IES) range from 0 to 75, with higher scores indicating greater distress.
in APOE genotyping and that 15% of primary care physicians who treat patients with Alzheimer’s disease have already received requests for genotyping. If APOE genotyping is discovered to predict treatment efficacy or a risk of side effects, the level of interest is likely to increase.

Although visions of personalized medicine suggest that genetic risk markers will empower patients to improve their health through preventive practices and early interventions,36 there is concern that the understanding of risk among both the lay public and medical professionals is exceedingly poor,37 that genetic tests offering probabilistic estimates for risks of common diseases in the absence of a family history or environmental risks may be misunderstood, and that the psychological harm of such misunderstanding may outweigh the benefits, particularly with disorders such as Alzheimer’s disease, for which no medical interventions are available.38-40 These concerns are amplified by the recent emergence of companies offering direct-to-consumer genetic testing, with most of them evaluating single-nucleotide polymorphisms that indicate the APOE genotype,1-3 in the absence of guidelines for deciding which associations between genes and disease have sufficient clinical validity and usefulness to justify disclosure and with no gauge of the effect of such disclosure. Caution is thus warranted, and empirical data are valuable.

Our study is limited in that it concerns a single polymorphism that is robustly associated with Alzheimer’s disease. In addition, most of the subjects were of fairly homogeneous and similar ancestry. If APOE genotyping had been provided without genetic counseling or to subjects who had no family history of Alzheimer’s disease, the results might have been different. In addition, the

<table>
<thead>
<tr>
<th>Measure</th>
<th>Difference between e4-Negative Group and Nondisclosure Group (95% CI)</th>
<th>Adjusted P Value</th>
<th>Difference between e4-Positive Group and Nondisclosure Group (95% CI)</th>
<th>Adjusted P Value</th>
<th>Difference between e4-Positive Group and e4-Negative Group (95% CI)</th>
<th>Adjusted P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAI score†</td>
<td>-0.1 (-1.4 to 1.1)</td>
<td>0.84</td>
<td>0.4 (-0.9 to 1.7)</td>
<td>0.55</td>
<td>0.5 (-0.7 to 1.7)</td>
<td>0.40</td>
</tr>
<tr>
<td>Longitudinal model</td>
<td></td>
<td></td>
<td>At 6 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(time-averaged)</td>
<td></td>
<td></td>
<td>-0.1 (-1.8 to 2.0)</td>
<td>0.92</td>
<td>0.8 (-1.1 to 2.7)</td>
<td>0.40</td>
</tr>
<tr>
<td>At 6 mo</td>
<td>-0.7 (-2.4 to 0.9)</td>
<td>0.38</td>
<td>-0.02 (-1.7 to 1.7)</td>
<td>0.98</td>
<td>0.7 (-0.9 to 2.3)</td>
<td>0.38</td>
</tr>
<tr>
<td>At 12 mo</td>
<td>0.02 (-1.6 to 1.7)</td>
<td>0.98</td>
<td>0.2 (-1.5 to 1.9)</td>
<td>0.80</td>
<td>0.2 (-1.4 to 1.8)</td>
<td>0.81</td>
</tr>
<tr>
<td>CES-D score‡</td>
<td>-0.1 (-2.1 to 1.9)</td>
<td>0.92</td>
<td>0.1 (-1.9 to 2.2)</td>
<td>0.89</td>
<td>0.2 (-1.7 to 2.2)</td>
<td>0.80</td>
</tr>
<tr>
<td>Longitudinal model</td>
<td></td>
<td></td>
<td>At 6 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(time-averaged)</td>
<td></td>
<td></td>
<td>-0.8 (-3.6 to 1.9)</td>
<td>0.55</td>
<td>-0.3 (-3.2 to 2.5)</td>
<td>0.81</td>
</tr>
<tr>
<td>At 6 mo</td>
<td>0.2 (-2.6 to 3.0)</td>
<td>0.89</td>
<td>0.9 (-2.0 to 3.7)</td>
<td>0.55</td>
<td>0.7 (-2.1 to 3.4)</td>
<td>0.63</td>
</tr>
<tr>
<td>At 12 mo</td>
<td>0.5 (-2.0 to 3.0)</td>
<td>0.71</td>
<td>0.2 (-2.3 to 2.8)</td>
<td>0.85</td>
<td>-0.2 (-2.7 to 2.3)</td>
<td>0.85</td>
</tr>
<tr>
<td>IES score§</td>
<td>-2.5 (-5.5 to 0.4)</td>
<td>0.09</td>
<td>1.4 (-1.7 to 4.4)</td>
<td>0.38</td>
<td>3.7 (1.0 to 6.5)</td>
<td>0.01</td>
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<td>Longitudinal model</td>
<td></td>
<td></td>
<td>At 6 wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(time-averaged)</td>
<td></td>
<td></td>
<td>-1.6 (-5.3 to 2.2)</td>
<td>0.41</td>
<td>2.7 (-1.2 to 6.5)</td>
<td>0.17</td>
</tr>
<tr>
<td>At 6 mo</td>
<td>-4.7 (-8.2 to -1.1)</td>
<td>0.01</td>
<td>-0.3 (-3.9 to 3.2)</td>
<td>0.85</td>
<td>4.3 (0.9 to 7.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>At 12 mo</td>
<td>-2.6 (-6.4 to 1.2)</td>
<td>0.17</td>
<td>0.8 (-3.1 to 4.7)</td>
<td>0.70</td>
<td>3.4 (-0.2 to 7.0)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* Mean scores were adjusted for age, sex, years of education, and baseline score if it was available (there was no baseline score for the measure of test-related distress). Missing values were calculated with the Markov chain Monte Carlo method of multiple imputation.
† Scores on the Beck Anxiety Inventory (BAI) range from 0 to 63, with higher scores indicating greater anxiety.
‡ Scores on the Center for Epidemiological Studies Depression Scale (CES-D) range from 0 to 60, with higher scores indicating greater depression.
§ Scores on the Impact of Event Scale (IES) range from 0 to 75, with higher scores indicating greater distress.
exclusion of subjects with low neurocognitive scores and high depression scores may have influenced the results. Within these constraints, our results suggest that disclosure of genotyping information provides a benefit to those who are negative for a susceptibility variant and causes transient, modest distress to those with a positive result.

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APPENDIX

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REFERENCES

Disclosure of APOE Genotype for Risk of Alzheimer's Disease


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