



Published in final edited form as:

Alzheimers Dement. 2008 November ; 4(6): 406–413. doi:10.1016/j.jalz.2008.04.007.

Comparing test-specific distress of susceptibility versus deterministic genetic testing for Alzheimer's disease

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Abstract

Background—Genetic risk for Alzheimer's disease (AD) may be conferred by the susceptibility polymorphism apolipoprotein E (APOE), where the $\epsilon 4$ allele increases the risk of developing late-onset Alzheimer's disease but is not a definitive predictor of the disease, or by autosomal dominant mutations (e.g., the presenilins), which almost inevitably result in early-onset familial Alzheimer's disease. The purpose of this study was to compare the psychological impact of using these two different types of genetic information to disclose genetic risk for AD to family members of affected patients.

Methods—Data were compared from two separate protocols. The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study is a randomized, multi-site clinical trial that evaluated the impact of susceptibility testing for Alzheimer's disease with APOE in 101 adult children of Alzheimer's disease patients. A separate study, conducted at the University of Washington, assessed the impact of deterministic genetic testing by disclosing presenilin-1, presenilin-2, or TAU genotype to 22 individuals at risk for familial Alzheimer's disease or frontotemporal dementia. In both protocols, participants received genetic counseling and completed the Impact of Event Scale (IES), a measure of test-specific distress. Scores were analyzed at the time point closest to one year post-disclosure at which IES data were available. The role of genetic test result (positive vs. negative) and type of genetic testing (deterministic vs. susceptibility) in predicting log-transformed IES scores was assessed with linear regression, controlling for age, gender, and time from disclosure.

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The authors have no conflicts of interest to disclose.

Results—Subjects from the REVEAL Study who learned that they were positive for the susceptibility gene APOE $\epsilon 4+$ experienced similar, low levels of test-specific distress compared to those who received positive results of deterministic testing in the University of Washington study ($p=0.78$). APOE $\epsilon 4+$ individuals in the susceptibility protocol experienced more test-specific distress than those who tested $\epsilon 4-$ in the same study ($p=0.04$); however, among those receiving deterministic test disclosure, the subjects who received positive results did not experience significantly higher levels of distress when compared to those who received negative results ($p=0.88$).

Conclusions—The findings of this preliminary study, with limited sample size, suggest that the test-related distress experienced by those receiving positive results for a deterministic mutation is similar to the distress experienced by those receiving positive results from genetic susceptibility testing, and that the majority of participants receiving genotype disclosure do not experience clinically significant distress as indicated by IES scores one year after learning of their test results.

Keywords

genetic susceptibility testing; deterministic testing; Alzheimer's disease; APOE; genetic counseling

1. INTRODUCTION

Alzheimer's disease (AD) is unique in that both susceptibility and deterministic genes may confer risk for the disorder. The apolipoprotein E (APOE) gene is a susceptibility polymorphism for late-onset AD, the most common form of AD and the most common dementia in the aging population. The APOE $\epsilon 4$ allele increases the risk of developing AD but is neither necessary nor sufficient to cause AD, and genetic testing for APOE cannot be interpreted as a definitive predictor.¹ In contrast, early-onset familial AD has been linked to the genes presenilin-1 (PS1) and presenilin-2 (PS2), both of which, though quite rare, are nearly 100% penetrant and are thus considered deterministic.² As such, individuals carrying a mutation at the disease locus will almost inevitably develop the condition with typical onset in the 4th to 7th decade. Keeping in mind the different ages of onset for its subtypes, AD is the only neurodegenerative disease that has both testable deterministic gene markers and a testable susceptibility gene marker, presenting a unique opportunity to compare the psychological impact of disclosing the results of different types of genetic testing within the same disease. AD may also serve as a paradigm for understanding the implications of susceptibility and deterministic genetic testing for other neurological diseases.

Both survey data^{3–5} and clinical research^{6–9} have shown that many persons at risk for AD are interested in seeking their own genetic profiles. One national survey indicated that 79% of respondents would take a hypothetical predictive genetic test for AD, and 45% would take the test even if it were only partially predictive.⁴ At-risk individuals who pursue testing in a research environment perceive many advantages to disclosure of risk estimates, including preparing one's family for AD and guiding decisions on advance directives and long-term care insurance.^{8,10} However, there is a concern that providing genotype information may create distress as well as legal and financial complications for the patient. For these reasons, and because genetic susceptibility testing does not have definitive predictive value, several consensus statements were published in the 1990's arguing against the clinical use of APOE genotyping for predictive purposes in clinical settings.^{11–15} A consensus statement in regard to the use of deterministic genetic testing for familial Alzheimer's disease has also been published, which argues for judicious use of this type of genetic testing in research settings, but cautions against widespread clinical introduction.¹⁶

The psychological sequelae of providing these two types of genetic testing for AD have never been systematically compared. Such information becomes especially important as prophylaxis

and treatments for AD are developed, making accurate early identification of those at risk increasingly vital to prevention and patient care, and as patients become increasingly interested in the technology. Towards this end, the present study examined psychological distress in the aftermath of both susceptibility and deterministic genetic testing for AD.

2. MATERIALS AND METHODS

Data were collected in the context of two separate, individually designed protocols. The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) Study, based at Boston University School of Medicine, was conducted to assess the impact of providing genetic susceptibility testing to first-degree relatives of patients with late-onset AD.^{6,8,9,17} A separate group at the University of Washington collected similar data as to the impact of deterministic genetic testing for early-onset familial AD and frontotemporal dementia.⁷

2.1 Susceptibility Testing Protocol

The REVEAL Study protocol is a multi-site randomized controlled trial, and has been described in previous publications.^{6,8,9,17} In brief, 92% of research participants at three sites were adult children of a person with clinically diagnosed or autopsy confirmed AD. The remaining 8% of participants were siblings of a person with AD. Of the participants included in analyses for this study, 74 were self-referred after hearing of the REVEAL Study in memory assessment clinics, public presentations, or the media, and 27 were systematically ascertained through research registries at the study site. Following an education session with a genetic counselor, participants were genotyped for APOE and received both genotype disclosure and a risk estimate for AD (range: 13–57%) derived from genotype, age, gender, and family history. At follow-up time points (approximately 6 weeks, 6 months, and 12 months post-disclosure; actual date determined by participant availability and receipt of questionnaires) the Impact of Event Scale (IES) was one of several outcome measures administered to each participant in the form of a mailed-in survey.¹⁸ This scale is described in detail below.

2.2 Deterministic Testing Protocol

The protocol to assess the impact of deterministic testing for AD was conducted at the University of Washington, and has also been previously detailed.⁷ Briefly, families have been identified with detectable mutations in the genes PS1, PS2, and TAU, which confer a 95% lifetime penetrance for Alzheimer dementia (PS1, PS2) and for frontotemporal dementia (TAU).² Members of these identified pedigrees were contacted by mail with a letter describing the availability of genetic testing and providing a contact for further information. Those who responded were then phoned and provided a booklet describing genetic testing in detail and discussing the risks and benefits of such testing. Individuals who enrolled in the study were provided with genotype disclosure and genetic counseling, with subsequent long-term follow-up. A support person, such as a spouse or friend, was included in the genetic counseling sessions as an emotional and social resource when the subject received genetic test results. IES and other data were collected immediately following genotype disclosure, at approximately 6 months post disclosure, at approximately 12 months post disclosure, and at yearly intervals thereafter via mailed-in surveys. However, because some IES surveys were not returned, these data were not available at every time point for each individual participant.

Because there were insufficient numbers of individuals with specific familial deterministic mutations (PS1, PS2, TAU), we could not analyze the outcome of genetic testing for each mutation separately. Results for the deterministic group therefore represent the impact of deterministic genetic testing in a cohort at risk for either inherited AD or inherited frontotemporal dementia. As these disorders are both dementias and both are inherited in an

autosomal dominant fashion, we considered the implications of genotype disclosure to be similar enough to pool both groups together in analyses.

2.3 Impact of Event Scale

The IES is a well-validated, 15-item scale that anchors distress to a specific event (in this case, disclosure of genetic risk information) and quantifies the symptoms of distress into two categories: intrusion and avoidance.¹⁸ Intrusion is described by Horowitz as “unbidden thoughts and images, troubled dreams, strong pangs or waves of feelings, and repetitive behavior” in regard to the psychologically significant event, and is assessed on the IES instrument with questions such as “I thought about it when I didn’t mean to.” Avoidance is described as “ideational constriction, denial of meanings and consequences of the event, blunted sensation, behavioral inhibition or counterphobic activity, and awareness of emotional numbness” in regard to the psychologically significant event, and is assessed on the IES with questions such as “I tried to remove it from my memory.” For each item, participants are asked to indicate the occurrence of an intrusion or avoidance event. Specifically, the instructions on the IES instrument used in our study read: “Recently we told you the results of your risk assessment for Alzheimer Disease. Below is a list of comments made by people after they have experienced similar events. Please circle each item, indicating how frequently these comments were true for you DURING THE PAST SEVEN DAYS. If they did not occur during that time, please mark the “not at all” column.” Scoring was calculated by the following scale: never = 0; seldom = 1; sometimes = 3; often = 5. The intrusion subscale consists of seven items with a maximum score of 35, and the avoidance subscale is eight items with a maximum score of 40, giving a total maximum score of 75. There is no baseline score for the IES because it is given after and in response to a specific event (in this case, genetic disclosure).

While initially constructed as a measure of the response to trauma, the IES has been successfully used to assess the impact of genotype disclosure in other genetic testing studies.^{19–22} Furthermore, the reliability of the IES has been validated and its psychometric properties verified in the literature, with the conclusion that this instrument is a legitimate measure of distress after a range of significant events.²³

2.4 Statistical Analyses

Total IES scores and subscale scores were evaluated at the time point closest to one year at which IES data were available for the susceptibility protocol (mean 12.9 ± 1.4 months, range: 7 – 16 months from disclosure) and for the deterministic protocol (mean 16.6 ± 8.9 months, range: 6 – 36 months from disclosure). We controlled for the disparity in time points by including a time from disclosure variable in a linear regression model. Linear regression analysis included variables for type of genetic test, result, gender, age, and time from disclosure (in months), to assess their predictive importance to log-transformed IES scores on each subscale. IES scores were log-transformed in the linear regression model due to non-normal distribution of the raw scores. Mean IES scores in each group were compared using ANOVA. Using standard convention of $\alpha = 0.05$ and $\beta = 0.80$, we calculated that this study was powered to reliably detect a difference of 5.3 in mean IES scores between two groups. SAS computer software was used in all analyses.

We also analyzed IES outcomes according to cutoff points indicative of possible clinical significance. While there is no universally accepted score to indicate clinically significant distress on the IES, previously published work has established score ranges that may be suggestive of clinical distress.^{21,24,25} Although these studies have used different cutoff points, we considered individuals with values of ≥ 13 for avoidance, ≥ 15 for intrusion, and ≥ 28 in total as being potentially significantly distressed. These cutoff points fall in the range established by other reports.

3. RESULTS

Demographic characteristics for the two sample populations are shown in Table 1. Of the participants included in our analyses, 49 were APOE $\epsilon 4+$, 52 were APOE $\epsilon 4-$, nine tested positive for a deterministic genotype, and 13 tested negative for a deterministic genotype. In the deterministic group, nine individuals were tested for PS1 (four positive, five negative), six individuals were tested for PS2 (three positive, three negative), and six individuals were tested for TAU (two positive, four negative). Study participants in both susceptibility and deterministic protocols were predominantly white, with no significant difference in race distribution between the two protocols ($p=0.311$). There was a greater representation of women than men among both sample populations (71.3% female in the susceptibility protocol, 59.1% in the deterministic protocol); there was no significant difference in gender representation between the two protocols ($p=0.262$). Mean age was 51.9 years in the susceptibility protocol and 40.7 years in the deterministic protocol ($p<0.0001$).

There were 17 individuals in the susceptibility protocol who had family members involved in the study. Of these, seven families had two siblings and one family had three siblings. In three families, both siblings tested $\epsilon 4+$. In three other families, both siblings tested $\epsilon 4-$. There was a single family in which one sibling tested $\epsilon 4+$ and the other tested $\epsilon 4-$. For the single family with 3 siblings, one tested $\epsilon 4-$, and two tested $\epsilon 4+$. The 22 individuals in the deterministic study represent 11 distinct families, with four sibling pairs. In two of these sibling pairs, both siblings tested positive. In the other two sibling pairs, one sibling was positive and one sibling was negative. Members of other families were more distant relatives.

In the susceptibility protocol, the overall response rate to IES questionnaire was 88.3%. There was no difference in response rate between subjects testing $\epsilon 4+$ and those testing $\epsilon 4-$ ($p=0.607$). In the deterministic protocol, the overall response rate to mail-in questionnaires was 75%. For those testing positive, the response rate was 73%. For those testing negative, the response rate was 77%. One individual testing positive asked not to be re-contacted, so no questionnaires were sent to this subject.

Comparing the impact of susceptibility versus deterministic testing, we found no significant differences in mean total IES scores between individuals positive for the susceptibility gene and those positive for a deterministic gene (mean IES=8.1, SD=8.7 vs. mean IES=9.1, SD=14.8, $p=0.78$, see Table 2). However, individuals who tested negative in the deterministic protocol scored significantly higher on the IES intrusion scale than individuals who tested negative in the susceptibility protocol (mean IES=5.8, SD=8.9 vs. mean IES=2.0, SD=4.9, $p=0.045$).

In the susceptibility protocol, mean total IES score at one year post-disclosure for APOE $\epsilon 4+$ individuals was significantly higher than the mean IES score for individuals who received disclosure of APOE $\epsilon 4-$ genotype (mean IES=8.1, SD=8.7 vs. mean IES=4.4, SD=8.8, $p=0.035$, see Table 2). Higher total IES scores among APOE $\epsilon 4+$ individuals compared to the APOE $\epsilon 4-$ group were driven by high mean scores on the avoidance subscale of the IES in particular (mean=5.2, SD=5.9 vs. mean=2.4, SD=4.7, $p=0.009$). In contrast, after deterministic testing, individuals who received negative disclosure results experienced approximately as much distress as those who tested positive, with mean scores of 8.2, SD=11.4, and 9.1, SD=14.8, respectively ($p=0.88$).

A linear regression model (Table 3) with log-transformed IES score as outcome measure and variables for test result (positive vs. negative), type of genetic testing (susceptibility vs. deterministic), age, gender, and time from genotype disclosure (in months) revealed no significant predictive value of time from disclosure on IES scores, lending validity to the comparison of disparate time points necessitated by this analysis. The genetic test result

(negative or positive) was predictive of total IES, with individuals who received a positive result scoring 56.8% higher than the negative group when adjusting for all other variables in the model ($p=0.01$). Test result was also predictive of the IES avoidance subscale scores, with the positive group scoring 54% higher than the negative group ($p=0.005$). Result was not a significant predictor of IES intrusion subscale scores. Type of genetic testing (susceptibility or deterministic) was not significantly predictive of total IES score, nor was it a significant predictor of the subscale IES scores when adjusting for other variables. Neither age nor gender played a predictive role in IES scores.

It is important to note that the majority of participants in both protocols scored well below clinical cut-offs in response to genetic testing (Table 2). In the susceptibility protocol, 5.8% of those testing $\epsilon 4-$ scored in the range of potential clinical significance, while 4.1% of those testing $\epsilon 4+$ scored in that range. In the deterministic protocol, 7.7% of participants who tested negative scored in the clinically significant range, while 11.1% (one individual out of nine) of those testing positive scored in that range.

4. DISCUSSION

Our primary finding is that there was no significant difference in distress as measured with the IES instrument between those who underwent susceptibility testing and those who underwent deterministic testing. We also found that both susceptibility and deterministic genetic testing appeared to be well-tolerated using disclosure protocols that provided screening, education, counseling and follow-up. Of interest, individuals who tested positive for the APOE $\epsilon 4$ allele in the susceptibility protocol experienced more test-specific distress over the first year post-disclosure than those who tested negative, while individuals who tested negative for autosomal dominant dementia in the deterministic protocol experienced approximately the same degree of distress as those who tested positive.

Despite the lack of significant difference in mean IES scores between positive and negative groups in the deterministic protocol, our linear regression model showed that test result was the only significant variable in predicting the total and avoidance IES score outcome measure when controlling for other variables. Indeed, the linear regression model showed that the type of genetic testing did not play a significant predictive role in IES outcome, nor did age, gender, or time from disclosure. This suggests that the type of genetic testing may not greatly influence post-disclosure distress, despite the very different genetic implications of susceptibility versus deterministic testing.

Our results showed a statistically significant difference in IES scores between those who tested positive for APOE $\epsilon 4$ and those who tested negative for the genotype. However, it remains unclear whether this difference in distress as reflected by quantitative IES score is indicative of clinically perceivable differences in qualitative distress. While statistically significant, the numerical disparity between total IES score means of the APOE $\epsilon 4+$ and $\epsilon 4-$ groups was only 3.7 points on a scale that ranges from 0 to 75. Furthermore, both groups showed mean IES scores in the low range of the scale. It is therefore difficult to interpret how the differences between the APOE groups detected by this study might be manifested clinically.

We were surprised to observe that those receiving negative test results with deterministic testing had average IES total scores that were nearly as high as those testing positive. These results may be considered in light of the fact that subjects presenting for deterministic testing are more likely to have witnessed siblings and multiple family members affected by the disease, potentially resulting in “survivor guilt” even if they are spared a positive result upon predictive testing.²⁶

Most participants in both protocols appeared to tolerate genetic testing well, with only a small minority of individuals having IES scores above a cut-off that could be considered clinically significant, and none of the participants in either study reporting severe adverse events such as suicide attempts. These observations are consistent with studies on the impact of disclosure in HD, breast cancer, and colon cancer,^{20, 26–40} along with more limited studies of other autosomal dominant diseases,^{22, 41} which have reported an overall ability of subjects to cope successfully with genetic test results when provided in the context of a formal genetic counseling and education protocol. HD studies are particularly relevant as this is a neurodegenerative disease for which there is worldwide experience. While initial surveys of anticipated responses and anecdotal reports on the impact of HD testing suggested the possibility of severe psychological risks,^{42–48} systematic studies are more reassuring. With respect to suicide after HD testing, a world-wide survey of catastrophic events among those who received testing for HD did not suggest that suicide was more common than the general population among persons receiving positive test results who were truly pre-symptomatic.⁴⁹ With respect to the emotional toll of testing, there is extensive evidence and remarkable consensus that with appropriate screening, education, and counseling, individuals testing positive for HD may experience modestly increased anger, despair or distress in the first weeks or months after disclosure. However, in the longer term, they are not emotionally more distressed than they were before being tested. There is also evidence that those who receive a negative test experience substantial emotional relief.^{26–28, 30, 33, 34, 40, 50, 51}

Since genetic testing is not widely available, participants in genetic testing studies represent persons who have actively sought out these services within research protocols. Research reports have suggested that those responding and willing to participate in genetic testing studies are likely to be individuals who are well-prepared to receive results, have often known for years of their high-risk status, and therefore tend to cope well in the immediate aftermath of receiving genotype disclosure.^{52, 53} This may account, in part, for the fact that no differences in distress were observed between deterministic and susceptibility protocols. Because of the selection bias inherent to genetic testing research, the findings of this and other genetic testing studies may not be generalizable to the population at large. However, one study has compared the impact of genetic testing for hemochromatosis in high-risk groups to the impact of population-based genetic testing for the same disorder, and found similar levels of distress in both groups.⁵⁴ Although the disclosure for the hemochromatosis gene holds different health implications than might be expected in genetic testing for Alzheimer's disease, this study may suggest that population-based genetic testing could be as well-tolerated as that in more prepared high-risk groups.

Our study is limited by small sample sizes, particularly in the deterministic protocol, which may not have revealed differences in psychological impact between protocols due to low statistical power. Therefore, the results of this pilot study should be considered preliminary. While small, however, the data in the deterministic protocol represent the largest study of its kind and the best information on genetic testing for dominantly inherited AD and frontotemporal dementia currently available.

The differences in the protocol design between the two studies compared in this research are also limiting factors. In particular, the inclusion of a support person at the genetic counseling sessions in the deterministic protocol was not a feature of the susceptibility protocol design. This may have resulted in more emotional and social support in the deterministic group, which could have influenced IES scores in the post-test period. Also of note, the response rate to IES questionnaires was higher in the susceptibility group than in the deterministic group. One person testing positive in the deterministic group specifically requested not to be contacted in follow-up. These differences in response rates may impose some bias on the results of our study, as those who are more distressed might be less likely to return IES questionnaires. While

our small sample size necessitated considering the results of genetic testing for the TAU gene, which is related to frontotemporal dementia, as having similar psychological impact to disclosure of a deterministic genotype for AD, in reality these two dementias are not identical. As such, the impact of disclosure of the TAU genotype may in actuality have a different psychological impact that was not detected in our study, and may therefore have skewed the IES scores in the deterministic group.

The study population demographics may also introduce a limitation to our conclusions, as there was an overrepresentation of white, highly educated participants. These individuals are likely to be better equipped to understand the implications of complex genetic information than would less educated members of the general population. Additionally, there are other potentially significant factors influencing the individual response to genetic testing that were not accounted for in our analyses, such as baseline psychological functioning and social support.^{26, 55} Another limitation lies in the fact that we did not examine a broad range of psychological outcomes in this study, relying instead exclusively on the IES, which was the only validated measure common to both protocols. Finally, although the limited availability of data in the deterministic protocol necessitated comparison of IES outcomes at disparate post-disclosure time points, controlling for this variable in a linear regression model showed no significant impact of time from disclosure in prediction of IES scores.

Further research is needed on the long-term psychological impact of both susceptibility and deterministic testing for AD. Future studies should aim to analyze the consequences of genetic testing for potentially distressing diagnoses in larger clinical samples, and should attempt to elucidate the individual baseline psychological or demographic characteristics that may predict a poor response to genotype disclosure in candidates for genetic testing. Additional knowledge is also needed on the long-term impact of genetic testing for AD, to ascertain how distress may change as those who have received genotype disclosure progress closer towards the age of onset.

Clinical genetic testing paradigms to date have evolved from experiences with rare deterministic mutations such as HD. Yet, the future of genetic testing in clinical medicine is more likely to involve susceptibility testing in complex genetic disorders. Research on genetic testing in AD, where both types of genetic testing are available, may provide some insight into the changing parameters of genetic risk assessment in the future.

Acknowledgements

This research was supported by NIH grants RO1-HG/AG-02213 (The REVEAL Study), RO1-AG09029 (The MIRAGE Study), P30-AG13846 (Boston University Alzheimer's Disease Core Center), P50-AG05136-22 (University of Washington Alzheimer's Disease Center) and VA research funds.

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Table 1

Study Population Demographics

Demographic Characteristic	APOE ε4- (n = 52)		Susceptibility Protocol APOE ε4+ (n = 49)		All (n = 101)		Deterministic Protocol	
	Mean Age, years (SD); Range	APOE ε4- (n = 52) 30-76	Mean Age, years (SD); Range	APOE ε4+ (n = 49) 34-72	All (n = 101) 30-76	Negative (n = 13) 28-60	Positive (n = 9) 28-54	All (n=22) 28-60
Sex, # female (%)	32 (61.5%)	40 (81.6%)	32 (61.5%)	40 (81.6%)	72 (71.3%)	10 (76.9%)	3 (33.3%)	13 (59.1%)
Race, # White (%)	51 (98.1%)	46 (93.9%)	51 (98.1%)	46 (93.9%)	97 (96.0%)	11 (84.6%)	9 (100%)	20 (90.9%)
Mean years of education (SD); Range	16.5 (2.2); 12-22	16.8 (2.1); 12-21	16.5 (2.2); 12-22	16.8 (2.1); 12-21	16.6 (2.1); 12-22	15.5 (2.0); 12-18	15.8 (2.5); 12-20	15.6 (2.2); 12-20

Table 2

IES Scores by Type of Testing and Genetic Test Result

	APOE ε4- (n = 52)		Susceptibility Protocol APOE ε4+ (n = 49)		All (n = 101)		Deterministic Protocol Positive (n = 9)		All (n = 22)	
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range
Total IES Scores										
Mean (SD)	4.4 (8.8)*	0-41	8.1 (8.7)*	0-32	6.2 (8.9)	0-41	8.2 (11.4)	0-40	9.1 (14.8)	0-45
Range										
Number of persons scoring above clinical significance (%)	3 (5.8%)		2 (4.1%)		5 (5.0%)		1 (7.7%)		1 (11.1%)	2 (9.1%)
Intrusion Subscale IES Scores										
Mean (SD)	2.0 (4.9)**	0-25	3.0 (3.5)	0-13	2.5 (4.3)	0-25	5.8 (8.9)**	0-30	5.1 (10.6)	0-33
Range										
Number of persons scoring above clinical significance (%)	3 (5.8%)		0 (0.0%)		3 (3.0%)		2 (15.4%)		1 (11.1%)	3 (13.6%)
Avoidance Subscale IES Scores										
Mean (SD)	2.4 (4.7)***	0-24	5.2 (5.9)***	0-22	3.7 (5.5)	0-24	2.5 (3.3)	0-10	4.0 (5.8)	0-13
Range										
Number of persons scoring above clinical significance (%)	2 (3.9%)		6 (12.2%)		8 (7.9%)		0 (0.0%)		1 (11.1%)	1 (4.6%)

* significant difference, p = 0.035

** significant difference, p = 0.045

*** significant difference, p = 0.009

Table 3
 Linear Regression Analysis Predicting Log-Transformed IES Scale Scores*

Variable	Total IES			Intrusion IES			Avoidance IES		
	b	95% CI	p	b	95% CI	p	b	95% CI	p
Genetic Test (deterministic vs. susceptibility)	0.31	-0.33, 0.95	0.34	0.41	-0.04, 0.92	0.10	-0.003	-0.56, 0.56	0.99
Result (positive vs. negative)	0.57	0.14, 1.00	0.01	0.32	-0.02, 0.65	0.06	0.54	0.16, 0.91	0.005
Gender (male vs. female)	-0.39	-0.85, 0.05	0.07	-0.31	-0.67, 0.04	0.08	-0.29	-0.70, 0.11	0.16
Age (years)	0.004	-0.01, 0.02	0.69	0.01	-0.01, 0.02	0.42	-0.001	-0.01, 0.02	0.90
Time from disclosure (months)	0.01	-0.04, 0.07	0.67	0.02	-0.02, 0.06	0.31	-0.01	-0.06, 0.04	0.62

* Estimates are made with susceptibility testing, negative result, and female gender as reference variables.