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Original Article

Psychological consequences and predictors of adverse events in the first 5 years after predictive testing for Huntington's disease

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The promise of genetic medicine is to provide information, based on genotype, to persons not yet sick about their risk of future illness. However, little is known of the long-term psychological effects for asymptomatic persons learning their risk of having a serious disease. Predictive genetic testing for Huntington's disease (HD) has been offered for the longest time for any disease. In the present study, the psychological consequences of predictive testing were assessed prospectively in individuals at risk for HD during seven visits over 5 years. Questionnaires of standard measures of psychological distress (the General Severity Index of the Symptom Check List-90-Revised), depression (the Beck Depression Inventory), and general well-being (the General Well-Being Scale) were administered to the participants. A significant reduction in psychological distress was observed for both result groups throughout 2 years ($p < 0.001$) and at 5 years ($p = 0.002$). Despite the overall improvement of the psychological well-being, 6.9% (14 of 202) of the participants experienced an adverse event during the first 2 years after predictive testing that was clinically significant. The frequency of all defined adverse events in the participants was 21.8%, with higher frequency in the increased risk group ($p = 0.03$) and most occurring within 12 months of receiving results.

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The exponential growth in gene identification for specific diseases and new insights into genetic contributions to disease susceptibility have not been matched by an increased understanding of the impact of the application of these findings to individuals currently in good health but predicted with a very high likelihood of developing a particular disease. Huntington's disease (HD) was the first genetic disease for which such a test was developed and has continued to serve as a model for other predictive testing programs such as hereditary forms of breast, ovarian (1, 2), and colon cancer (3). Despite the fact that there is no cure for this late-onset neurodegenerative disorder, some at-risk individuals have welcomed a predictive test, to relieve the uncertainty and be able to plan for the future (4, 5). Initially, testing was performed through linkage analysis (6–8) and, since 1993, by direct testing for the HD mutation (9). Approximately 10–25% of persons at risk for HD have taken the predictive test (8, 10, 11).

The short-term (up to 1 year) psychological implications of predictive testing for HD have

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been previously described (7, 12–18). Although some individuals experience severe difficulties coping with the test results, the overall impression from these studies is that regardless of the test result, most test participants adapt to this new information and integrate it positively into their lives. Furthermore, there were no significant differences in psychological stress between participants who received an increased risk compared to those who received decreased risk (13, 16–18).

Little is known about the potential long-term effects of predictive testing. Tibben et al. (17) investigated the 3-year impact of predictive testing for HD by using a psychometric battery, showing less psychological distress compared to baseline for the decreased risk group (n = 29) but no change for the increased risk group (n = 20). Furthermore, a recent study by Decruyenaere et al. (19) reported on 5-year follow-up after predictive testing in Belgium (n = 57), showing a significant decrease of depression and anxiety for both carriers and non-carriers of the mutation, compared to baseline. Two other studies have reported anecdotal similar results (20, 21). The small number of individuals followed in each study, however, makes it difficult to know whether these patterns of response are representative of the broader predictive testing population.

The largest predictive testing cohort that has been studied regarding catastrophic events (severe adverse events) is the worldwide study of 4527 HD test individuals, where the frequency of suicide, suicide attempt, and psychiatric hospitalization following predictive testing was estimated to be 0.97% (22). It is noteworthy, however, that half of these individuals were in fact already symptomatic at the time of the catastrophic event. An increased risk result, psychiatric history prior to the predictive testing, and being unemployed were clearly identified as factors associated with an increased likelihood of a catastrophic event following predictive testing.

The goal of the present study was to examine prospectively the long-term (5 years) psychological impact of predictive testing in a large cohort (n = 202) and to identify the frequency, timing, and predictors of adverse events. The ability to predict disease onset is already far outpacing the development of appropriate interventions, which could alter the natural history of that illness. This is likely to increase as novel DNA changes are identified, which predict disease onset, severity, and response to therapy. The findings of this research are likely to be relevant as the nature of information provided by predictive medicine changes.

Subjects and methods

The methods of recruitment and criteria for eligibility in the Canadian Collaborative Study and descriptions of the research protocol are described in detail elsewhere (13). In the present study, however, we included only those individuals who entered the collaborative study with a 50% chance of having inherited the gene for HD and who received an informative result from DNA testing based on linkage analysis. The Canadian Collaborative Study was originally designed to include follow-up assessments at 1–2 weeks, 2 months, 6 months, 1 year, and 2 years after disclosure. A subsequent extension of the study enabled the addition of a long-term assessment at about 5 years after disclosure.

Psychological measures

A variety of frequently used, well-validated instruments were used to assess psychological mood before and at each follow-up after disclosure of predictive test results. Psychological distress was chosen *a priori* to be the primary psychological outcome measure for the study, as assessed using the General Severity Index (GSI) from the Symptom Check List-90-Revised (SCL90-R), with scores $\geq$63 indicating psychological distress in the clinical range (23), and is based on the premise that a major life event such as predictive testing could cause psychological distress and reduce one's sense of well-being. Secondary measures included the Beck Depression Inventory (BDI), with scores $\geq$10 reflecting clinical depression (24), and the General Well-Being Scale (GWB) (25), as measured by the Mental Health Index, were used to assess psychological mood.

Assessments of adverse psychosocial events

An assessment of adverse events was performed using information from the test individuals' follow-up questionnaires (n = 202), as well as from clinical chart notes and a separate questionnaire filled out by the clinical counselor (n = 140). This latter questionnaire covered only the 2-year follow-up portion of the study and was based on the counselors' review of the clinical charts including notes on the timing of the event. An adverse event was defined as clinically significant if the participant (i) was diagnosed with clinical depression, (ii) had a psychiatric hospitalization, (iii) attempted suicide, (iv) committed suicide, (v) showed marked increase in alcohol consumption (i.e. a three-fold increase compared to consumption when results were given and which was

sustained for more than one follow-up), (vi) planned suicide, or (vii) had a breakdown of a marriage or common-law relationship which had negative consequences for the test individual. We also used psychological measures to detect adverse events, defined as psychological distress or depressive mood (measured by an increase of greater than equal to five points into or within the clinical range on either GSI or BDI scores from one follow-up to the next). If more than one adverse event occurred, the most severe event was counted.

Statistical analysis

Associations between predictive test outcome (increased risk or decreased risk) and between the presence and absence of adverse events and the categorical characteristics of having children, belief about inheritance of the HD mutation, sex, education, employment, life insurance, and marital status were investigated using Fisher's exact test. Additional Fisher's exact tests were performed comparing the adverse event groups and risk status, history of adverse events, and religious attendance.

Fisher's exact test, independent sample *t*-test, Mann–Whitney test, and multivariate analysis of variance (MANOVA) were used to investigate baseline differences between the increased and decreased risk groups (or between participants having or lacking adverse events) and patients' age as well as each of the three psychological measures. *t*-tests were also performed between the 'adverse events' group and the 'no adverse events' group concerning life satisfaction index, the size of the social support network (number of persons who provide support), and the participants' satisfaction with their social support.

Changes in the mean responses obtained by each of the study groups (increased risk and decreased risk) at each follow-up for the three different psychological measures (GSI, BDI, and GWB) were investigated using the total cohort ($n = 202$). The data contained missing values, supposed to be at random. The variables GSI and GWB were analyzed using the procedure Mixed in SAS® (26). The model was set up as a repeated measure design. Different covariance pattern models were tested: compound symmetry, first-order autoregressive, and toeplitz (general autoregressive model [26]). The covariance structure with the smallest value of the Akaike's information criterion was considered most desirable. Study group, time, and study group × time effects were fitted as fixed effects. Study group effect was the between factor (increased risk and decreased risk), and time effect was the within factor with seven time points. Differences between levels of the time factor were evaluated by post-hoc contrasts. In case of a significant interaction, simple effects were examined, i.e. effects of one factor holding the other factor fixed. The variable BDI was dicothomized (<10 and ≥ 10) and was analyzed by analysis of variance (ANOVA) for repeated measures for binary response (Procedure GENMOD in SAS® [27]). Study group, time, and study group × time effects were fitted as fixed effects. Study group effect was the between factor (increased risk and decreased risk), and time effect was the within factor with seven time points. The predicted probability of clinical depression, ≥ 10, was estimated from the ANOVA model, for the two study groups at different time points.

Baseline scores as well as alcohol consumption and previous psychiatric history were used in logistic regression analysis to develop a model for the prediction of adverse events. Variables were selected for entry into the equation using forward stepwise selection with a cutoff value of 0.05.

Results

Demographic characteristics

A total of 239 individuals at 50% risk received an informative predictive test result by linkage analysis. Of these, 37 individuals were excluded due to no follow-up visits after the result session or after 1- to 2-week visit ($n = 23$, 11 at increased risk and 12 at decreased risk) or a receipt of diagnosis of HD within the first year of follow-up ($n = 14$). The final study cohort therefore comprised of 202 asymptomatic individuals, of whom a total of 106 individuals (52.5%) were followed for 5 years after receiving the test results (Table 1). Of the remainder ($n = 96$), 63 participants had not reached their 5-year follow-up at the time of the closure of data collection, 17 were lost to follow-up, 10 withdrew, four were diagnosed with HD during follow-up (data were excluded 1 year before diagnosis), and two had received a revised risk estimation after the 2-year follow-up. Because of the potential confounding effects of a risk reversal (28), as well as of a diagnosis of HD on psychological mood (29), these individuals were excluded.

Table 2 summarizes the characteristics of the study cohort at their baseline assessment. The mean age of the cohort was 37.4 ± 10.9 years (range 19–68 years), and 123 of 202 (or 60.9%) of the study participants were female. The mean age of the increased risk group was significantly lower than that of the decreased risk group ($p = 0.01$), but no other significant differences in baseline characteristics were detected between the

Table 1. Length of follow-up after predictive testing by test results

Length of follow-up	Decreased risk		Increased risk		Total	
	n	%	n	%	n	%
Baseline	134	100.0	68	100.0	202	100.0
1–2 weeks	134	100.0	68	100.0	202	100.0
2 months	134	100.0	68	100.0	202	100.0
6 months	126	94.0	67	98.5	194	96.0
1 year	119	88.8	62	91.2	182	90.1
2 years	101	75.4	48	70.6	150	74.2
5 years	75	56.0	31	45.6	106	52.5

two groups. Furthermore, a comparison of mean scores on the baseline set of psychological measures failed to reveal any differences ($p = 0.4$) between the increased and decreased risk groups (Table 2). A total of 134 individuals (66.3%) received a decreased risk and 68 individuals (33.7%) received an increased risk result (Table 2).

Comparisons between the 5-year cohort ($n = 106$) and the remainder group ($n = 96$) did not differ with regard to baseline scores of psychological measures (data not shown) and demographics, except for gender, age, and education. The 5-year cohort was older (39.6 years *vs* 35.0 years, $p = 0.002$), had more education (79.25% had completed high school or greater *vs* 34.7%, $p < 0.001$), and comprised of more women (68.9% *vs* 52.1%, $p = 0.01$).

The impact of predictive testing on psychological well-being

The primary outcome measure of psychological well-being was the GSI score of the SCL90-R. A significant and sustained reduction in psychological distress (GSI) was observed over time for both risk groups throughout the 5-year follow-up period compared to baseline (up to 2 years follow-up, $p < 0.001$ and at 5 years, $p = 0.002$, Fig. 1).

A total of 32 participants (of 202 or 15.8%) scored in the clinical range of psychological distress (GSI) at baseline. Fifteen of these individuals were later given an increased risk and were slightly over-represented in this group ($n = 68$), representing 22.1% (15 of 68) compared to those who received a decreased risk result (17 of 134 participants or 12.7%, $p = 0.1$). The GSI at baseline provided some prediction of later adverse events.

Table 2. Demographic characteristics and scores on psychological measures at baseline

	Decreased risk (n = 134)		Increased risk (n = 68)		
	n	%	n	%	p-value (two-sided)
Children					
Have no children	54	40.3	27	39.7	
One or more children	80	59.7	41	60.3	1.00[a]
Marital status					
Married/common law	103	76.9	46	67.6	
Single/divorced/widow	31	23.1	22	32.4	0.18[a]
Sex					
Female	77	57.5	46	67.6	
Male	57	42.5	22	32.3	0.17[a]
Belief about inheritance of mutation (n = 189)					
Do not believe have the gene	105	84.7	50	76.9	
Believe have the gene	19	15.3	15	23.1	0.23[a]
Employment					
Employed	110	82.1	50	73.5	
Unemployed/homemaker	24	17.9	18	26.5	0.20[a]
Life insurance					
Have life insurance	91	67.9	45	66.2	
No life insurance	43	32.1	23	33.8	0.87[a]
Education (n = 201)					
High school or greater	77	57.9	40	58.8	
Incomplete high school	56	42.1	28	41.2	1.00[a]
Age at testing	38.8 ± 11.1[d]		34.8 ± 10.0[d]		0.01[b]
Psychological measures					
GSI	51.2 ± 10.5[d]		53.5 ± 11.3[d]		0.15[b]
GWB	105.3 ± 14.3[d]		102.6 ± 14.3[d]		0.21[b]
BDI	3[e]	1–6[f]	5[e]	1–7[f]	0.16[c]

[a]Fisher's exact test.
[b]Independent sample *t*-test.
[c]Mann–Whitney test.
[d]Values are mean ± SD.
[e]Median values.
[f]Q_{25}–Q_{75} values.

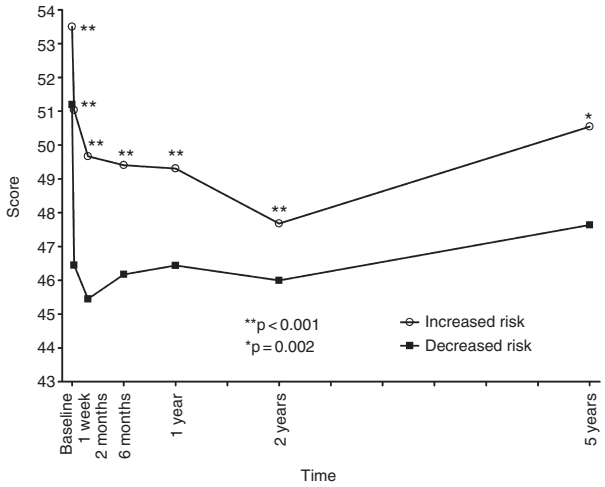

Fig. 1. Repeated measure analysis on the General Severity Index (GSI) scores using all data for the total cohort (n = 202, Table 1). Of these, 75 individuals had complete data on all follow-up visits. Lower scores indicate less psychological distress. There was no significant difference in scores over the 5-year follow-up between the two result groups. The GSI scores improved significantly throughout 2-year follow-up ($p < 0.001$) and at 5-year follow-up ($p = 0.002$) compared to baseline for both result groups.

Fifteen individuals (of 32 or 46.9%, increased risk n = 9 and decreased risk n = 6) with evidence of psychological distress at baseline experienced an adverse event some time during the 5-year follow-up period. This proportion was significantly higher than the proportion of those with a normal GSI at baseline who experienced an adverse event (29 of 170 or 17.1%, $p < 0.001$).

A total of 170 of 202 (84.2%) participants had normal GSI scores (i.e. <63) at baseline. Of these, 28 participants (16.5%) scored in the clinical range of psychological distress some time during follow-up with comparable frequencies between the test result groups (11 of 53 or 20.8% of the increased risk group and 17 of 117 or 14.5% of the decreased risk group, $p = 0.4$).

In regard to the BDI scores, no significant change over time was observed within the results groups ($p = 0.81$, Table 3). However, the mean score over time as significantly higher in the increased risk group ($p = 0.05$). A total of 22 participants (of 202 or 10.9%) had BDI scores in the clinical range for depression (i.e. ≥10) at baseline. Of these, 10 persons were from the group that later was given an increased risk (10 of 68 or 14.7%) and 12 persons were those who later received a decreased risk result (12 of 134 or 9.0%, $p = 0.24$). The scores improved into the normal range for 10 (or 45.5%) of these individuals during follow-up (three participants received an increased risk and seven a decreased risk result).

Table 3. Fraction of normal Beck Depression Inventory (BDI) scores (<10) and in the clinical range (≥10) during follow-up for both result groups

	Decreased risk (%)		Increased risk (%)	
Length of follow-up	BDI <10	BDI ≥10	BDI <10	BDI ≥10
Baseline	91.0	9.0	85.3	14.7
1–2 weeks	93.3	6.7	81.0	19.0
2 months	91.0	9.0	82.8	17.2
6 months	89.9	10.1	84.2	15.8
1 year	87.5	12.5	86.0	14.0
2 years	90.8	9.2	86.0	14.0
5 years	93.3	6.7	74.2	25.8

A total of 180 of 202 (89.1%) participants had normal BDI scores (i.e. <10 points) at baseline. Thirty-six (of 180 or 20.0%) had scores in the clinical range of depression some time after the test results, of whom 14 (of 180 or 7.8%) had scores that were considered an adverse event (i.e. an increase of greater than equal to five points and resulting in a score of clinical depression). No significant difference in number between the two results groups was seen (14 of 58 or 24.1% in the increased risk group compared to 22 of 122 or 18.0% in the decreased risk group, $p = 0.5$).

For the increased risk group, the GWB score did not change significantly during follow-up compared with baseline levels (data not shown). A significant change was only seen for the decreased risk group which improved the scores at 1 week ($p < 0.001$) and slightly improved at 2 months ($p = 0.043$).

Frequency of adverse events (by risk status)

A total of 14 individuals (of 202 or 6.9%) experienced adverse events as clinically defined (Table 4). The proportion of individuals in the increased risk group with a clinical adverse event (seven of 68 or 10.3%) was two times greater than the decreased risk group (seven of 134 or 5.2%, $p = 0.24$, Table 4).

The most frequent clinically significant adverse event was diagnosed clinical depression requiring antidepressants (six of 202 participants or 3.0%). Three (of 202 or 1.5%) participants attempted suicide, and two participants (1%) had a breakdown of a serious relationship, with negative consequences for the test participants. Psychiatric hospitalization, sustained, increased use of alcohol during the follow-up period, or development of a suicide plan was seen in one person in each group (0.5%, Table 4).

We also employed the psychological measures to detect adverse events, defined as greater than five-point increase into or within the clinical range for psychological distress (GSI) or depressive mood (BDI). Additionally, 30 of 202

Table 4. Frequency and type of adverse events by predictive test results during follow-up after predictive testing

Type of adverse event	Decreased risk (n = 134)		Increased risk (n = 68)		Number of adverse events in the total cohort	
	n	%	n	%	n	%
Clinical adverse events						
Diagnosed clinical depression	2	9.1	4	19.0	6	3.0
Suicide attempt	3	13.6	0	0	3	1.5
Psychiatric hospitalization	1	4.5	0	0	1	0.5
Relationship breakdown	0	0	2	9.5	2	1.0
Suicide plan	0	0	1	4.8	1	0.5
Marked increase in alcohol use	1	4.5	0	0	1	0.5
Subtotal	7		7		14	6.9
Adverse events based on psychological measures						
Increased scores on GSI or BDI	16	69.6	14	66.7	30	14.9
Total	23	100	21	100	44	21.8

participants or 14.9% had adverse events by these criteria only. Six (four with an increased risk and two with a decreased risk) had elevated scores at baseline, but during the follow-up, the scores increased by at least another five points, which was considered as an adverse event.

Taken together, the total frequency of adverse events was 21.8% (44 of 202 individuals). The proportion of individuals in the increased risk group with an adverse event (21 of 68 or 30.9%) was significantly higher than in the decreased risk group (23 of 134 or 17.2%, $p = 0.03$, Table 4).

Case reports of attempted suicides

Three participants who received a decreased risk attempted suicide during follow-up. One person had slightly elevated GSI score (65 points) and BDI score (11 points) at baseline, which improved into the normal range during the first year of follow-up. Four years after predictive testing, this individual was diagnosed with chronic fatigue syndrome, the employment was terminated, and shortly thereafter attempted suicide. This individual felt that the problems at this time were due to the chronic fatigue syndrome and not related to the predictive test results.

Another person had BDI scores suggestive of a mild depression (14 points) at baseline and attempted suicide while waiting for results. The risk of having inherited HD was estimated at 23% by linkage analysis. Eighteen months later, this individual returned for a refined risk calculation, prompted by a pregnancy. The risk of having inherited the HD mutation was decreased to 3%, and an immediate improvement of the BDI score was observed. However, she became severely depressed again 2 months after receiving the revised test results and 5 months after the result session attempted suicide again. This person had a psychiatric history prior to entering the predictive testing program, and a family history of suicide attempts.

The third individual, with normal scores on all of the psychological measures at baseline, attempted suicide unexpectedly on the same day after receiving the decreased risk of having inherited the mutation for HD. This reaction was clearly related to the test results, as the test candidate and the spouse both stated that they were expecting bad news and this result came as a shock (30).

Timing of the adverse event

The majority of all the adverse events occurred in the first year after receiving the test results (32 of 44 or 72.7%, $p < 0.001$, Fig. 2). This was particularly obvious for persons receiving an increased risk result (18 of 21 or 85.7% during the first year *vs* three of 21 or 14.3% after the first year, $p < 0.001$). Increased scores of greater than equal to five points on GSI or BDI were predominant adverse events for both groups during the first year compared to the clinical adverse events that occurred more evenly throughout the follow-up period (Fig. 2). The earliest clinical adverse events occurred within a week of receipt of the test results: a suicide attempt and marked increase in alcohol use in two separate individuals who received a decreased risk. No other individuals with a decreased risk had a clinical adverse event during the first year after testing.

Predictors of adverse events

In an attempt to develop a way to prospectively identify individuals who may be vulnerable to difficulties with coping with knowledge of their genetic status, a number of baseline variables that may predict adverse events were analyzed (Table 5). Five variables clearly discriminated

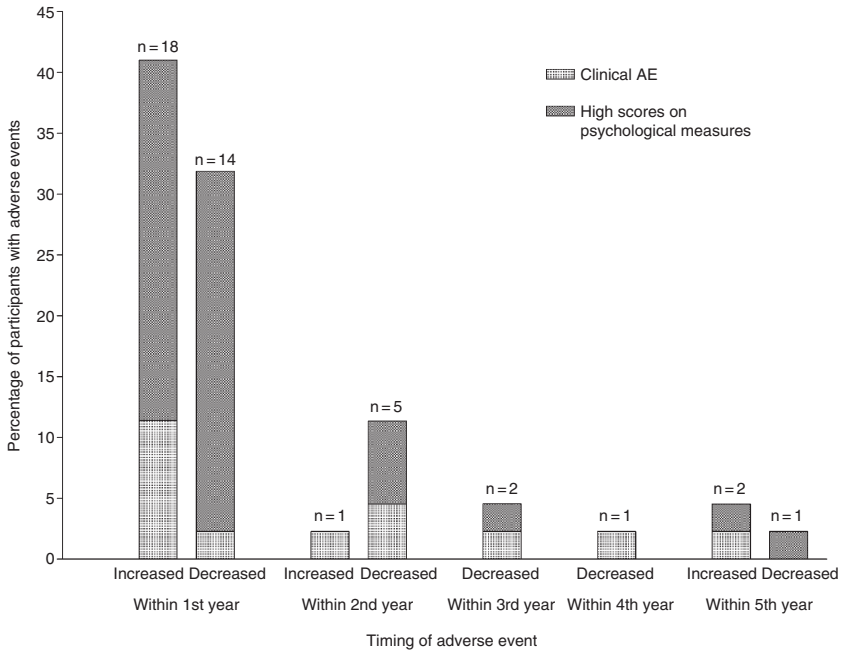

Fig. 2. Timing of adverse events (AEs). The number of participants with clinical adverse events (subset of AEs defined as high scores on the psychological measures is identified in bar graph) for the increased and decreased risk groups are shown related to when the event occurred. Most adverse events occurred in the first year of follow-up ($p < 0.001$).

between those participants who experienced an adverse event and those who did not. These were a history of adverse events prior to predictive testing ($p = 0.01$), scores in the clinical range on BDI (scores classified as <10 and ≥ 10, $p = 0.007$) and GSI ($p < 0.001$), lower scores on GWB ($p < 0.001$), and an increased risk result ($p = 0.03$).

We next developed a model that discriminated at entry into the program as to whether an adverse event would occur. A history of adverse events, GWB score at baseline (the strongest variable of the psychological measures), and risk status were identified by logistic regression analysis using forward stepwise selection as variables for inclusion into such a model for prediction of adverse events. The model with these three variables correctly identified 103 of 106 participants (97.2%) who would not have an adverse event and 11 of 31 participants (35.5%) who in fact later had an adverse event. Models that included either BDI or GSI instead of GWB performed nearly as well (Table 6). A model with BDI substituted for GWB variables correctly identified 102 of 106 participants (96.2%) who would not have an adverse event and 12 of 31 participants (38.7%) who in fact later had an adverse event. Similarly, a model with GSI substituted for GWB variables correctly identified 101 of 106 participants (95.3%) who would not have an adverse event and 11 of 31 participants (35.5%) who in fact later had an adverse event. A model based on only the variables 'increased risk results' and 'a history of adverse events' correctly identified seven of 31 participants (22.6%) who later had an adverse event.

Discussion

The present study describes the psychological consequences of the largest known predictive testing cohort for the longest period upon receipt of predictive test results (up to 5 years). Our findings show that psychological distress was significantly reduced compared to baseline (mean values of GSI) for both groups after receiving predictive testing results.

Several hypotheses have been put forward to explain the lack of significant negative responses of the increased risk group. For example, a self-selection of individuals, more capable of coping with 'bad' news, is requesting predictive testing (31, 32). Pre-test expectation of receiving an increased risk (32) or activation of coping mechanisms such as denial or minimization due to severe stress reactions (17, 32) could also account for this finding. Another possibility is that although predictive testing is clearly an emotionally demanding process for participants, it is only one of many different experiences that impact on the way in which people experience their lives, at any given time. Frequently, the results have ramifications for the entire family, and even though a particular outcome may be perceived by others as positive or negative, such may not be the case for persons receiving the result due to their particular family and social context (20, 33–36). It is also possible that persons receiving linkage results, which are not definitive, may be clinging to the hope of misassignment and therefore do not experience adverse events as could be expected. However,

Table 5. Comparison of baseline variables of the group with and without adverse events

	No adverse event (n = 158)		Adverse event (n = 44)		
	n	%	n	%	p-value (two-sided)
Risk status					
Increased risk	47	29.7	21	47.7	0.03[a]
Decreased risk	111	70.3	23	52.3	
History of adverse events					
Yes	10	6.3	11	25.0	0.01[a]
No	96	60.8	20	45.5	
Children					
No children	64	40.5	17	38.6	
One or more children	94	59.5	27	61.4	0.86[a]
Marital status					
Married/common law	117	74.1	32	72.7	
Single/divorced/widow	41	25.9	12	27.3	0.85[a]
Sex					
Female	91	57.6	32	72.7	
Male	67	42.4	12	27.3	0.08[a]
Belief about inheritance of mutation (n = 189)					
Do not believe have the gene	124	78.5	31	70.5	
Believe have the gene	23	14.6	11	25.0	0.17[a]
Employment					
Employed	125	79.1	35	79.5	
Unemployed/homemaker	33	20.9	9	20.5	1.00[a]
Life insurance					
Have life insurance	103	65.2	33	75.0	
No life insurance	55	34.8	11	25.0	0.28[a]
Religious attendance					
Regular	28	17.7	5	11.4	
None	126	79.7	37	84.1	0.49[a]
Education (n = 201)					
High school or greater	92	58.2	25	56.8	
Incomplete high school	66	41.8	18	40.9	1.00[a]
Age	37.7 ± 11.3[d]		36.4 ± 9.2[d]		0.46[b]
Life satisfaction index (Q_1–Q_8)	5.6 ± 0.9[d]		5.2 ± 1.1[d]		0.39[b]
Size of social support network	4.6 ± 2.2[d]		4.1 ± 2.2[d]		0.18[b]
Satisfaction with social support	5.5 ± 0.6[d]		5.4 ± 0.7[d]		0.35[b]
Psychological measures					
GSI	50.4 ± 10.4[d]		57.5 ± 10.4[d]		<0.001[b]
GWB	106.8 ± 12.9[d]		95.8 ± 16.1[d]		<0.001[b]
BDI	3[e]	1–6[f]	5[e]	2–9[f]	0.007[c]

[a]Fisher's exact test.
[b]Independent sample *t*-test.
[c]Mann–Whitney test.
[d]Values are mean ± SD.
[e]Median values.
[f]Q_{25}–Q_{75} values.

Table 6. Odds ratio for experiencing an adverse event related to risk status, history of an adverse event, and baseline scores of psychological measures

	Odds ratio for adverse event	95% CI	p-value
Model with GWB			
Increased risk	2.9	1.2–7.4	0.024
History of adverse events	3.1	1.0–9.6	0.046
Baseline GWB score (lower)	0.9	0.9–1.0	0.001
Model with GSI			
Increased risk	2.5	1.0–6.3	0.048
History of adverse events	3.65	1.2–10.9	0.02
Baseline GSI score in the clinical range	1.1	1.0–1.1	0.007
Model with BDI			
Risk status	2.8	1.1–6.7	0.025
History of adverse events	4.3	1.5–12.6	0.007
Baseline BDI score in the clinical range	3.1	0.9–10.4	0.068

this argument was not supported by the study of Almqvist et al. (22), which did not show any difference in the frequency of catastrophic events after predictive testing between those who received linkage results and direct test results. It must be, however, remembered that the individuals who have participated in studies evaluating the psychological consequences of predictive testing have received substantial support and counseling, not only in preparation for receiving the test results, but also for a considerable amount of time afterwards. How individuals who are seeking predictive testing outside such protocols are coping is not known.

This study also shows that some individuals will have considerable difficulty integrating the information from predictive testing into their lives, which is reflected by the frequency of clinically significant adverse events (6.9%). In particular, this is reflected by the individual who received a decreased risk and at the same day attempted suicide without any indications of previous or current psychological distress. A sudden crisis in identity could possibly explain such an unexpected event, which is extremely hard to predict and prevent. This is the sole report of such an event in the literature and therefore seems to be a very rare occurrence within established predictive testing programs for HD (37).

The frequency of catastrophic events (i.e. suicide, suicide attempts, and psychiatric hospitalization) in this study (1.98% or four of 202) was similar to the worldwide frequency (0.97% or 44 of 4527, $p = 0.3$) (22). Overall, the increased risk group showed significantly more adverse events compared to those receiving a decreased risk, although the most severe events (i.e. suicide attempts) were experienced solely by individuals who received a decreased risk. Not surprisingly, most adverse events occurred within the first year after receiving the results. The decline of adverse events over time is a common occurrence in predictive testing programs (38). Therefore, 1 year of counseling and support after receiving the test results should be considered for predictive genetic testing for HD.

To predict an adverse outcome of a predictive test result and possibly prevent an adverse event, others and we have assessed baseline parameters (15, 16, 22, 39–41). For example, elevated baseline scores for depression or psychological distress have been previously shown to increase the risk of depressive symptoms following testing (15, 16, 41), which was also observed in the present study. In addition, and similar to the worldwide study of catastrophic events (22), a history of adverse events prior to entering the predictive testing program and an increased risk result were identified in this study to be associated with an adverse event after testing. Although our model showed a good probability of identifying individuals who would not have an adverse event, it would likely misidentify 64.5% of the cases who would, showing that other yet unknown factors influence the occurrence of an adverse event. The difference in prognostic value of the model using any of the three psychological measures was small, reflecting the high correlation all three scores have with each other ($p < 0.001$).

Clearly, the evaluation of the test individuals' psychological profile at baseline can identify people who may be more vulnerable than others and for whom extra support may be necessary during both pre- and post-test counseling period. However, the identified predictors of adverse events in this study (increased risk result, scores in the clinical range for GSI and BDI, lower scores on GWB, and history of adverse events) are only one part of the knowledge of this complicated process of acquiring information on genetic status.

Importantly, however, this study clearly showed that for those persons receiving a decreased risk result, improvement in quality of life is significant and sustained for at least 5 years. For persons with an increased risk, initial reduction in anxiety and improvement in general well-being are sustained for 2 years but returns to baseline levels over 5 years. Little is known about how the quality of life changes, as these persons get closer to onset. This study provides support for inclusion of predictive testing for HD in medical practice within the context of availability of ongoing support and counseling.

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