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A Worldwide Assessment of the Frequency of Suicide, Suicide Attempts, or Psychiatric Hospitalization after Predictive Testing for Huntington Disease

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Summary

Prior to the implementation of predictive-testing programs for Huntington disease (HD), significant concern was raised concerning the likelihood of catastrophic events (CEs), particularly in those persons receiving an increased-risk result. We have investigated the frequency of CEs—that is, suicide, suicide attempt, and psychiatric hospitalization—after an HD predictive-testing result, through questionnaires sent to predictive-testing centers worldwide. A total of 44 persons (0.97%) in a cohort of 4,527 test participants had a CE: 5 successful suicides, 21 suicide attempts, and 18 hospitalizations for psychiatric reasons. All persons committing suicide had signs of HD, whereas 11 (52.4%) of 21 persons attempting suicide and 8 (44.4%) of 18 who had a psychiatric hospitalization were symptomatic. A total of 11 (84.6%) of 13 asymptomatic persons who experienced a CE during the first year after HD predictive testing received an increased-risk result. Factors associated with an increased risk of a CE included (*a*) a psychiatric history ≤5 years prior to testing and (*b*) unemployed status. The frequency of CEs did not differ between those persons receiving results of predictive testing through linkage analysis in whom there was only changes in direction of risk and those persons receiving definitive results after analysis for the mutation underlying HD. These findings provide insights into the frequency, associated factors, and timing of CEs in a worldwide cohort of persons receiving predictive-testing results and, as such, highlight persons for whom ongoing support may be beneficial.

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Introduction

During the past decade, molecular genetics research has led to the identification of an increasing number of disease-associated genes. Genetic testing is now available to assess whether an at-risk individual has inherited the DNA changes predictive of a clinical phenotype (predictive testing) and to confirm the diagnosis for symptomatic individuals (Miki et al. 1994; Nicolaides et al. 1994; Wooster et al. 1995; Reddy and Housman 1997). For Huntington disease (HD [MIM 143100]), an autosomal dominant neurodegenerative disorder with late onset, linkage analysis for predictive testing started in 1986, initially in Canada (Fox et al. 1989) and the United States (Meissen et al. 1988; Brandt et al. 1989) and then in many center around the world (World Federation of Neurology Research Group on Huntington's Disease 1993). Later, when the specific mutation associated with HD was identified, direct testing for the mutation became available (Huntington's Disease Collaborative Research Group 1993).

For many years, prior to the implementation of testing, serious concerns were raised as to whether it was ethical to offer predictive testing for a disease for which no treatment was available (National Institutes of Health 1977; Marsden 1981). It was feared that the test results could precipitate depression, anxiety, marital and family stress, survivor's guilt, and social stigmatization and discrimination in employment and insurance (Kenen and Schmidt 1978; Rosenfeld 1984; Wexler 1985). In addition, there was concern that individuals who learn that they will develop HD in the future may be at greater risk for catastrophic outcomes such as suicide, attempted suicide, or psychiatric hospitalization. This concern was based on higher suicide rates reported for HD patients compared with the general population (Hayden et al. 1980; Schoenfeld et al. 1984; Farrer 1986; Sørensen and Fenger 1992; Di Maio et al. 1993) and higher rates of psychiatric problems for persons at risk for HD (Oliver 1970; Kessler 1987). Furthermore, surveys of attitudes

toward predictive testing indicated that 11%–15% of at-risk individuals would contemplate suicide if they received an increased-risk result (Kessler et al. 1987; Mastromauro et al. 1987).

There have been a number of reports on the short-term psychosocial impact that predictive testing for HD has on individuals. The overall impression with regard to many tested individuals, in both the decreased- and the increased-risk groups, is that being informed of their genetic status relative to the mutation for HD is beneficial to them, although a significant proportion of individuals experience feelings of sadness, hopelessness, and depression (Nance et al. 1991; Bloch et al. 1992; Huggins et al. 1992; Tyler et al. 1992; Codori and Brandt 1994; Codori et al. 1997; Taylor and Myers 1997). Difficulties with coping with a new genetic status have also been described in case reports (Bloch et al. 1992; Huggins et al. 1992; Almqvist et al. 1997; Robins Wahlin et al. 1997). However, as a group, both decreased- and increased-risk individuals showed less psychological distress during the 1st year after testing, and this was particularly evident for those who either received a decreased-risk result or were informed that they had a normal CAG repeat length (Brandt et al. 1989; Wiggins et al. 1992; Decruyenaere et al. 1996; Tibben et al. 1997).

The frequency of adverse reactions (defined as suicidal ideation, psychiatric hospitalization, depression, relationship breakdown, substance abuse, or psychological distress) after the predictive-testing result was shown to be ~16% (15/95) among the tested individuals in a Canadian study, but no significant difference in frequency, between the increased- and the decreased-risk groups, was found (Lawson et al. 1996). Furthermore, Quaid (1993) reported on 4 (2.1%) of 189 individuals in a U.S. predictive-testing sample who were hospitalized after receiving the results (3 received an increased-risk result, and 1 received a decreased-risk result). However, these studies were in relatively small cohorts, and, until now, no estimates of the frequency of CEs in a large cohort of patients have been ascertained.

The goal of this survey was to determine the worldwide frequency of CEs after predictive testing for HD and to study factors that might influence its occurrence. These factors might help to identify individuals at highest risk for CEs, toward whom strategies of support may be directed, in order to prevent these serious adverse reactions. These data may also prove useful for other predictive-testing programs for late-onset hereditary diseases.

Subjects and Methods

A total of 175 centers in 26 countries that have offered predictive testing for HD were identified through contact with the International Huntington Association (a lay organization for HD) and professionals from participant lists from the World Federation of Neurology Research Group on HD. All centers were invited to participate in the present survey by completing a questionnaire (questionnaire 1A) providing demographic data and test results on all participants who had received predictive-testing results at their center. Diagnostic tests for symptomatic participants suspected of having HD were not included in the survey.

For those test candidates who had experienced a CE after the predictive-testing result, an additional questionnaire (questionnaire 1B) was completed. A CE was defined as (i) suicide, (ii) suicide attempt, or (iii) psychiatric disorder requiring hospital admission. Information concerning the CE—including when it occurred relative to the time of receipt of the predictive-testing results, clinical status at the time of the CE (in which the status, as rated by the test center, was asymptomatic, possibly affected, probably affected, or diagnosed HD), and direction of predictive-testing results—was provided. Demographic data—including gender, age, marital status, and employment status—were documented. A positive psychiatric history $\leqslant 5$ years prior to predictive testing was assigned if a suicide attempt, psychiatric hospitalization, or treatment by medications for psychological or psychiatric reasons had occurred. The protocol for the center's predictive-testing program was also attached.

In addition, we inquired that all participating centers provide information on the date of the predictive-testing result and the last follow-up contact, either in person or via letter or phone call, on all tested participants (questionnaire 1C). On the basis of these data, we estimated the length of follow-up after the predictive-testing results, for all persons.

Ascertainment

The generalizability of such a study is influenced significantly by the level of ascertainment. A potential source of bias and underascertainment of CEs could result from centers that had a higher frequency of CEs but that did not wish to participate in the survey. Therefore, an additional short questionnaire (questionnaire 2) was sent to centers that did not participate in this survey, requesting the total number of predictive-testing results provided at the center, as well as the number and type of CEs that had occurred.

Statistical Analyses

A Student's *t*-testing was used to assess differences in mean age. Fisher's exact test was used for 2×2 comparisons, and χ^2 analyses were used for other comparisons, to examine the differences, in demographic data,

between the group of participants with a CE and either the group of participants without a CE or, when the latter group was not available, a worldwide sample comprising pooled demographic data from published papers on HD predictive-testing participants. Because of differences in reported demographic data in these papers, the total number of tested participants varies for each demographic factor: (i) marital status includes data from Simpson et al. (1992), Holloway et al. (1994), Codori et al. (1997), Decruyenaere et al. (1997), Taylor and Myers (1997), Tibben et al. (1997), and E. Almqvist, M. Hayden, unpublished data; (ii) employment status includes data from Codori et al. (1997), Decruyenaere et al. (1997), Tibben et al. (1997), and E. Almqvist, M. Hayden, unpublished data; and (iii) previous psychiatric history includes data from Lawson et al. (1996) and E. Almqvist, M. Hayden, unpublished data.

Results

A total of 100 centers in 21 countries from five continents participated in this study (see the Appendix). These 100 centers reported that a total of 4,527 participants had received a predictive-testing result—via either linkage analysis (n = 741 [16.4%]), direct testing of the CAG repeat in the HD gene (n = 3,786 [83.6%]), or both (n = 241 [5.3%]) (table 1)—and were followed after receiving the predictive-testing results. A total of 1,817 participants (40.1%) received either an increased-risk result or an expanded CAG repeat >35; 2,601 participants (57.5%) received either a decreased-risk result or normal CAG length; 30 participants (0.7%) received an uninformative result from linkage analysis; and 70 participants (1.5%) had an intermediate-sized allele (table 1). The mean age at disclosure of the test result was 37.4 years, and the sample consisted of 40.7% males and 59.3% females (table 2).

An additional 441 tested participants from these centers received the predictive-testing results but were not included in this survey, because of the absence of follow-up (441/4,968 participants [8.9%]). Of these 441, 119 (27%) received an increased-risk result, 313 (71%) received a decreased-risk result, and 9 (2%) received either an uninformative result or an intermediate allele.

CEs

Frequency.—Of the 4,527 participants, 44 (0.97%) were reported to have experienced a CE after receiving the predictive-testing results (table 1): 5 participants, all women, committed suicide; 21 (13 women and 8 men) attempted suicide, and 18 (13 women and 5 men) were hospitalized for psychiatric reasons. All participants with a CE, irrespective of its apparent relationship with the predictive-testing result, were included.

Direction of the test result.—Of the 44 participants who had experienced a CE, 37 (84.1%) either had received an increased-risk result via linkage analysis

Table 1

Direction of Predictive-Testing Results and Frequency of CEs

Test and Result	No. (%) of Participants			
	Without a CE[a]	With a CE[b]	P[c]	No. (%) of CEs in Cohort
Linkage analysis:				
Increased risk	251 (34.3)	6 (66.7)	Not significant	6/257 (2.3)
Decreased risk	451 (61.6)	3 (33.3)		3/454 (.7)
Uninformative result	30 (4.1)	0 (0)		0/ 30 (0)
Total	732 (100)	9 (100)		9/741 (1.2)
Direct test:				
Mutation carrier	1,529 (40.8)	31 (88.6)	<.0001	31/1,560 (2.0)
Normal CAG length	2,143 (57.1)	4 (11.4)		4/2,147 (.9)
Intermediate allele	79 (2.1)	0 (0)		0/ 79 (0)
Total	3,751 (100)	35 (100)		35/3,786 (.9)
Totals for both linkage analysis and direct testing:				
Increased risk/mutation carrier	1,780 (39.7)	37 (84.1)	<.0001	37/1,817 (2.0)
Decreased risk/normal CAG length	2,594 (57.9)	7 (15.9)		7/2,601 (.3)
Uninformative result by linkage analysis	30 (.7)	0 (0)		0/30 (0)
Intermediate allele	79 (1.8)	0 (0)		0/ 79 (0)
Grand total	4,483 (100)	44 (100)		44/4,527 (.97)

[a] Participants who underwent both linkage analysis and direct testing (235 [5.2%] of all those without CE) are included in the direct-testing group.

[b] For the six participants with a CE who underwent both linkage analysis and direct testing, test results are reported with respect to the test after which the CE occurred.

[c] Data are for comparisons between the participants with a CE and those without a CE, in the increased-risk group versus the decreased-risk group.

Table 2

Predictive-Testing Participants, by Age and Sex

Age (years)	No. (%) of Men[a]	Women[b]	Total[c]	Participants with a CE
16–19	23 (1.2)	58 (2.2)	81 (1.8)	0 (0)
20–29	428 (23.2)	687 (25.6)	1,115 (24.6)	8 (18.2)
30–39	670 (36.4)	904 (33.7)	1,574 (34.8)	17 (38.6)
40–49	417 (22.7)	640 (23.8)	1,057 (23.3)	17 (38.6)
50–59	199 (10.8)	278 (10.3)	477 (10.5)	2 (4.5)
60–69	78 (4.2)	87 (3.2)	165 (3.6)	0 (0)
70–79	20 (1.1)	26 (1.0)	46 (1.0)	0 (0)
80–90	1 (.05)	4 (.1)	5 (.1)	0 (0)
Unknown	5 (.3)	2 (.07)	7 (.2)	0 (0)
Total	1,841 (100)	2,686 (100)	4,527 (100)	44 (100)
Total by sex	1,841 (40.7)	2,686 (59.3)		

[a] Mean Age ± SD =37.6 ± 12.4 years.
[b] Mean Age ± SD =37.3 ± 11.5 years.
[c] Mean Age ± SD =37.4 ± 11.9 years.

($n = 6$) or were HD mutation carriers ($n = 31$). This represented 37/1,817 (2%) of the cohort receiving increased-risk results, which was significantly greater than the frequency of CEs in those receiving decreased-risk results (7/2,601 [0.3%]; $P < .0001$ [see table 1]). There were two participants in this CE sample who received a risk estimate, via linkage analysis, that was revised from decreased risk to increased risk. The corrected risks were used in the computation of the test-results data. No significant difference in frequency of CEs was seen between the linkage-analysis group (9/741 participants [1.2%]) and the direct-testing group (35/3,786 participants [0.9%]) (table 1).

Clinical status.—A total of 24 (54.5%) of those who experienced a CE were already symptomatic at the time of the CE—that is, were either diagnosed ($n = 8$) or rated as probably ($n = 7$) or possibly ($n = 9$) affected (tables 3 and 4). The eight affected persons experienced their CEs at varying times (0–28 mo) after diagnosis (table 5). In particular, all who committed suicide were symptomatic (four were diagnosed, and one was probably affected) at the time of the CE. Of those with an increased risk, 24 (64.8%) of 37 were symptomatic at the time of the CE.

Timing of the CE.—The mean incidence of CEs was 0.44%/year (range 0.35%–0.65%/year) (table 3). No significant variation in frequency of CEs over time was seen relative to time of receipt of the predictive-testing result. There was at least one follow-up contact with all participants during the first 6 mo after testing, and 0.35% (16/4,527) experienced a CE during this period, and three of these CEs occurred ⩽1 mo after receipt of the results. For subsequent follow-up periods, the frequencies were as follows: 6–12 mo after testing, 0.37% (10/2,679); 1–2 years after testing, 0.45% (9/1,992); 2–3 years after testing, 0.65% (or 7/1,074); and 3–4 years after testing, 0.37% (2/540) (table 3 and fig. 1).

The majority (4/7 [57.1%]) of those who received a decreased-risk result experienced the CE >1 year after receiving the result, in contrast with the increased-risk group, in which most (23/37 [62.1%]) participants experienced a CE during the 1st year. The numbers, however, are small in both of these groups.

The mean time interval for occurrence of the CE after receipt of predictive-testing results was 14.4 ± 12.6 mo (range 0.5–42 mo) for symptomatic participants, whereas it was 10.1 ± 8.8 mo (range 0.5–29 mo) for asymptomatic participants (not significant). The mean time interval for those who committed suicide was 18 ± 12.9 mo (range 3–35 mo); for those who attempted suicide, 9 ± 8.7 mo (range 0.5–29 mo); and, for those who were hospitalized, 14.9 ± 12.4 mo (range 0.5–42 mo) (not significant).

Previous psychiatric history.—A total of 15 (38.5%) of 39 participants with a CE had a psychiatric history ⩽5 years prior to the predictive testing (for 5 participants, status was unknown), which is a significantly greater frequency than that in the predictive-testing comparison group ($P < .0005$; see table 4): 2 of these participants had attempted suicide ⩽5 years prior to entering the predictive-testing program; 12 of these participants were treated, by medication, for depression; and 1 was hospitalized for other major psychiatric problems prior to predictive testing.

Other demographic characteristics.—The CE group comprises participants from nine countries (Australia, Belgium, Canada, France, Germany, the Netherlands, Sweden, the United Kingdom, and the United States). Age, gender, and marital status did not influence the likelihood of a CE, compared with the likelihood ob-

Table 3

Follow-up Period after Predictive-Testing Results, and Timing of CE

Length of Follow-up	No. (%) of Participants	No. of Participants with a CE (% of Total)	No. of Participants (% of CE Group) Who Are		
				Asymptomatic	
			Symptomatic	With Increased Risk	With Decreased Risk
.5–6 mo	4,527 (100)	16 (.35)	8 (50.0)	6 (37.5)	2 (12.5)
6–12 mo	2,679 (59.2)	10 (.37)	4 (40.0)	5 (50.0)	1 (10.0)
1–2 years	1,992 (44.0)	9 (.45)	6 (66.7)	2 (22.2)	1 (10.0)
2–3 years	1,074 (23.7)	7 (.65)	4 (57.1)		3 (42.9)
3–4 years	540 (11.9)	2 (.37)	2 (100)		
4–5 years	375 (8.3)				
5–6 years	245 (5.4)				
6–7 years	130 (2.9)				
7–8 years	70 (1.5)				
8–9 years	23 (.5)				
9–10 years	1 (.02)				
10–11 years	1 (.02)				
Total		44 (.97)	24 (54.5)	13 (29.5)	7 (15.9)

served in the combined worldwide predictive-testing sample (table 4). In contrast, employment status was significantly related to the frequency of CE, with 23 (52.3%) of 44 such persons being unemployed versus 43 (14.3%) of 300 in the combined predictive-testing sample ($P < .0001$; see table 4).

Ascertainment.—We received complete information (questionnaires 1A, 1B, and C) from 100 (57.1%) of the 175 centers. In an effort to determine whether we might have underascertained the frequency of CEs, and whether centers with more CEs were less likely to complete the questionnaires, we specifically inquired, of those centers that did not provide complete information (on either questionnaires 1A and 1B or questionnaire 2 only), as to the number of tested participants and CEs in their center. We received information from 47 additional centers, providing an ascertainment of the frequency of CEs from a total of 147 (84%) of the 175 centers. These additional 47 centers reported that 11 (0.4%) of 2,985 tested participants had experienced a CE. This number was significantly lower ($P < .004$) than that seen in the initial cohort, which suggested that underascertainment of CEs in the centers that did not fill out all the questionnaires was not likely to have undermined the scientific integrity and validity of this study.

Discussion

Bundey (1997, p. 4) recently has proclaimed that predictive "genetic testing for HD is a success story, and the few adverse effects should be put into context of the many thousands of individuals who have been relieved of the anxiety of not knowing whether or not HD would develop." Although the present survey of CEs worldwide could be interpreted as supporting that view—in that, over varying periods of follow-up, only 0.97% of all tested participants experienced a catastrophic reaction to predictive testing—this frequency is still high and, in fact, represents a minimum frequency, despite attempts to achieve as high an ascertainment rate as possible. Furthermore, since the time of ascertainment varied among patients, with 59% being followed up ⩽1 year after receiving results, longer-term follow-up would be likely to reveal additional instances of CEs with respect to predictive testing in this cohort.

Even though ascertainment was relatively high for this study, with follow-up data collected from 84% of centers participating in predictive testing, one potential concern still remains—that is, that CEs may be higher in those persons who had no follow-up. One way to address this is to assess whether persons with no follow-up were more likely to have received an increased-risk result. In this group with no follow-up, 27% received an increased-risk result, and 71% received a decreased-risk result, compared with 40.1% and 57.5%, respectively ($P < .00001$), in the group with follow-up, suggesting that lack of follow-up in this small proportion of patients is unlikely to have altered the findings of this study.

It is also important to note that the frequency of CEs reported in the present study is based on reports from established predictive-testing centers that essentially follow protocols recommended by the World Federation of Neurology, Research Committee, Research Group on Huntington's Chorea (1989). It is possible that those centers not following such protocols would have an increased frequency of serious side effects.

Table 4

Demographics of Participants with a CE versus Those without a CE

	No. (%) of Participants						
	With a CE						
	Suicide[a]	Suicide Attempt[b]	Psychiatric Hospitalization[c]	Total[d]	Without a CE[e]	Predictive-Testing Comparison Group	*P*[f]
Sex:							
Female	5	13	13	31 (70.4)	2,656 (59.2)	321 (59.1)	NS[g]
Male	0	8	5	13 (29.6)	1,827 (40.8)	222 (40.9)	
Total	5	21	18	44 (100)	4,483 (100)	543 (100)	
Predictive-testing results:							
Increased risk/mutation	5	17	15	37 (84.1)	1,780 (39.7)	Not available	<.0001
Decreased risk/normal	0	4	3	7 (15.9)	2,594 (57.9)		
Intermediate allele	0	0	0	0 (0)	79 (1.8)		
Uninformative (linkage analysis)	0	0	0	0 (0)	30 (.7)		
Total	5	21	18	44 (100)	4,483 (100)		
Time (after receipt of results) when CE occurred:							
0–6 mo	1	10	5	16 (36.4)	Not applicable	Not applicable	
6–12 mo	1	5	4	10 (22.7)			
1–2 years	1	3	5	9 (20.4)			
2–3 years	2	3	2	7 (15.9)			
3–4 years	0	0	2	2 (4.5)			
4–5 years	0	0	0	0 (0)			
5–6 years	0	0	0	0 (0)			
6–7 years	0	0	0	0 (0)			
Total	5	21	18	44 (100)			
Clinical status when CE occurred:							
Asymptomatic	0	10	10	20 (45.5)	Not applicable	Not applicable	
Possibly affected	0	4	5	9 (20.4)			
Probably affected	1	4	2	7 (15.9)			
Diagnosed	4	3	1	8 (18.2)			
Total	5	21	18	44 (100)			
Marital status:							
Married or common-law man and wife	2	11	12	25 (56.8)	Not available	371 (68.3)	NS[h]
Single or equivalent	3	10	6	19 (43.2)		172 (31.7)	
Total	5	21	18	44 (100)		543 (100)	
Employment status:							
Employed	0	10	11	21 (47.7)	Not available	257 (85.7)	<.0001[h]
Unemployed	5	11	7	23 (52.3)		43 (14.3)	
Total	5	21	18	44 (100)		300 (100)	
Psychiatric history ⩽5 years prior to predictive testing:							
Present	2	7	6	15 (38.5)	Not available	15 (12.6)	<.0005[h]
Absent	2	12	10	24 (61.5)		104 (87.4)	
Total	4	19	16	39 (100)[i]		119 (100)	

[a] Mean age ± SD =36.6 ± 10.1 years (range 21–47 years).
[b] Mean age ± SD = 37.3 ± 9.7 years (range 24–55 years).
[c] Mean age ± SD = 36.7 ± 6.4 years (range 27–47 years).
[d] Mean age ± SD = 37.0 ± 8.3 years (range 21–55 years).
[e] Mean age ± SD =37.4 ± 11.9 years (range 16–90 years).
[f] NS = not significant.
[g] Comparison of total no. of participants with a CE versus total no. of participants without a CE.
[h] Comparison of total no. of participants with a CE versus predictive-testing comparison group (pooled data; see Subjects and Methods).
[i] For five participants, psychiatric history was unknown.

Certain demographic features of this cohort are interesting, particularly in view of the fact that it is the largest cohort of predictive-testing subjects ever studied. Worldwide, the mean age at predictive testing is 37 years (range 16–90 years), again indicating that, worldwide, predictive testing often is being undertaken after persons have made reproductive decisions. In addition, as reported elsewhere (Holloway et al. 1994; Lawson et al. 1996; Codori et al. 1997; Tibben et al. 1997), the majority (59%) of participants are female. In addition, there was a trend toward an excess of female participants who experienced a CE (70.4% [31/44] of women, vs. 29.6% [13/44] of men; $P = .18$).

Numerous issues with clinical implications emerged from this study. Fully 54.5% of persons with a CE were symptomatic at the time of the event, clearly highlighting the vulnerability of this particular group of increased-risk participants who begin manifesting with signs and symptoms. Prior to the advent of predictive testing, the time around the onset of HD has been recognized as a time of high risk for suicide, since persons aware of the course of the illness are still able to both plan and implement a suicide strategy. Although predictive testing cannot definitively be invoked as contributing to these persons' CEs, predictive testing in all likelihood played a significant role in the CE of asymptomatic persons. The majority (11/13 [84.6%]) of asymptomatic participants who experienced a CE ≤12 mo after receiving results, received an increased-risk result. By contrast, after 1 year the majority (4/7 [57.1%]) of CEs occurred in persons who received a decreased-risk result. However, the longer the time after results, the more likely it is that factors either other than or in addition to the results contributed to the CE.

This study has helped to identify those factors that might be associated with an increased frequency of suicide, suicide attempt, or psychiatric hospitalization after predictive testing. Awareness of these risk factors may be extremely important, since it allows for identification of a subset of persons for whom increased counseling and support may be helpful.

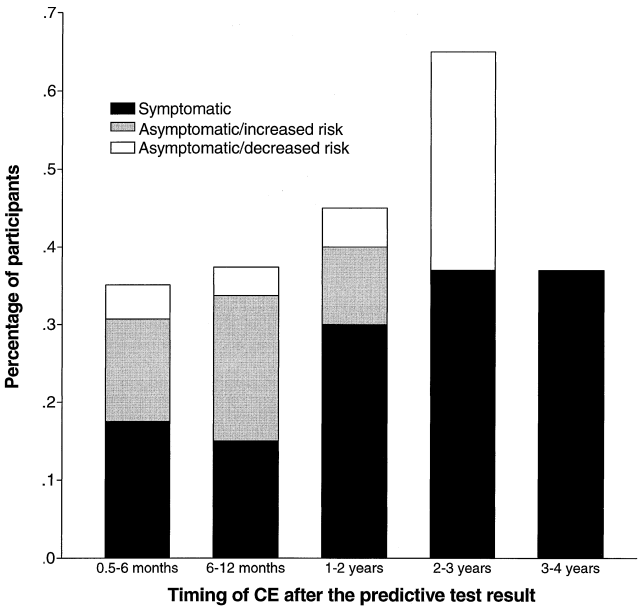

Figure 1 Proportion of participants, in the total group, who had a CE, with regard to timing of CE after receipt of predictive-testing results. Participants who were rated by the predictive-testing center as diagnosed, probably affected, or possibly affected are included in the category of "Symptomatic" participants.

In this study, 38.5% of persons with a CE had a psychiatric history ≤5 five years after entering the predictive-testing program. In addition, more than half of those with a CE, as well as all those who committed suicide, were unemployed. Unemployment has previously been shown to be a significant risk factor for suicide, but, clearly, those participants who are most seriously depressed are likely to be unemployed at that time (Platt 1984).

Clinical status was also an important predictor of a

Table 5

Timing of CE and HD Diagnosis after Predictive-Testing Result

Participant	Type of CE	Time, after Predictive Testing Result, of (mo)		Time, after HD diagnosis, of CE Occurrence (mo)
		CE Occurrence	Diagnosis[a]	
1	Suicide attempt	1	0	1
2	Suicide	3	3	0
3	Psychiatric hospitalization	3	1.5	1.5
4	Suicide	8	0	8
5	Suicide attempt	12	0	12
6	Suicide attempt	24	12	12
7	Suicide	25	0	25
8	Suicide	35	7	28

[a] 0 = diagnosis at the same time that predictive-testing results were received.

CE in this study; for example, 54.5% of all persons who had a CE were possibly, probably, or recently diagnosed with HD. Indeed, four of the five persons who committed suicide had recently been diagnosed with this illness. This provides further evidence that the risk of suicide is elevated during the period immediately after the delivery of a diagnosis of HD. Of the 21 suicide attempts, 11 were by persons who also were symptomatic at the time (table 4). Similarly, the risk for suicide attempts is increased at the time of onset of the disease. Individual case reports of the vulnerability of these patients have been presented elsewhere (Bloch et al. 1993). Taken together, 54.5% of all CEs in this cohort occurred in persons with some signs and symptoms of the illness.

The majority (37/44 [84.1%]) of the CE participants who experienced a CE had received a predictive-testing result indicating an increased risk of development of HD in the future. Approximately 2% of all persons with an increased-risk result had a CE, which was significantly higher than the frequency of in the decreased-risk group ($P < .0001$; see table 1). What is notable, however, is that ~0.3% (7/2,601) of participants in this sample who either received a decreased-risk result or were informed that the they had a normal CAG length in the HD gene also had a CE, comprising four suicide attempts and three psychiatric hospitalizations.

Although we and others (Nance et al. 1991; Bloch et al. 1992; Huggins et al. 1992; Tyler et al. 1992; Codori and Brandt 1994; Codori et al. 1997; Taylor and Myers 1997) have reported that adverse events may occur in both the increased- and decreased-risk groups, this is the first report of a CE in persons ($n = 7$) who have been told that they will not develop HD. These seven persons had other factors that may have contributed to their risk for a CE. Three of these seven participants had a previous psychiatric history; these included psychiatric problems during adolescence, and, in one instance, the participant became depressed and developed significant ballistic movements and was diagnosed as HD, despite the decreased-risk result. Direct testing was performed, which confirmed the normal CAG length. However, this was followed by a suicide attempt by this participant.

Another question that has been raised previously (Mattsson and Winnberg Almqvist 1991; Babul et al. 1993) concerns the possibility that persons who have received a direct-testing result may do less well than persons who have received linkage-analysis results, since in the latter of case the results would, because of the possibility of recombination between the marker and the gene, be less definitive. It has been suggested that the possibility that this result could be incorrect might have offered some hope to persons receiving an increased-risk result. The role that this uncertainty played in maintaining hope in these participants has not been previously assessed. The results of this study clearly show that CEs occurred with equal frequency in participants after linkage analysis and in those who received a definitive result with regard to the presence or absence of the mutation for HD. This suggests that the uncertainty conferred by linkage analysis did not offer any added comfort for at-risk participants previously participating in predictive testing. Furthermore, direct assessment with regard to the mutation did not eliminate hope for the future and did not result in a significant increase in the frequency of CEs in the population receiving definitive results concerning future risk.

One pitfall of this study is the absence of a direct comparison group of untested at-risk persons who have been followed over time and have not participated in predictive testing. Therefore, the relative estimated frequency of CEs in the present study cannot be fully appreciated until the occurrence of suicidal behavior or psychiatric hospitalization among either nonparticipants at risk or a comparable general population is known. Prior estimates of suicide frequency in families with HD with rates have been four to eight times that seen in the corresponding general population in which the study was undertaken (Schoenfeld et al. 1984; Farrer 1986; Sørensen and Fenger 1992; Di Maio et al. 1993). Suicide attempts were seen in ~25% of all HD patients assessed (Farrer 1986). These studies focused primarily on affected patients, but the few studies of at-risk persons also indicated rates that were at least two times greater than those seen in the general population (Sørensen and Fenger 1992; Di Maio et al. 1993). It is noteworthy that, worldwide, there were no instances of suicide in men in the predictive-testing program but that there were five suicides in women. Although the suicide rate of the predictive-testing population is lower for men and higher for women than what is seen in similar-age cohorts in the Canadian general population (Health Canada 1994, p. 36–42), both the absence of a comparable control group and the size of the cohorts in the present study limit the usefulness of such comparisons. Whether this reflects a true lower rate of CEs among males than might be expected for persons at risk for HD or, rather, is an indication of self-selection of persons in predictive-testing programs who may be psychologically better equipped with good coping skills is unknown (Codori et al. 1994; Decruyenaere et al. 1995).

It is of interest that the frequency of CEs in the cohort as a whole is constant over time. This suggests that other factors, independent of the predictive-testing result, continue to make a significant contribution to the likelihood of a CE in families with HD (fig. 1).

Overall, these results indicate that predictive testing for HD may have serious risks, even though the frequency of CEs may be lower than previously feared. These findings emphasize both the importance of long-term availability of support for persons receiving either

an increased- or decreased-risk result and the times at which each of these groups may be most vulnerable—that is, the presence of increased risk ⩽1 year after receipt of results and when the participants begin to manifest with signs and symptoms. In contrast, persons receiving a decreased-risk result are at low risk for having a CE close to the time of receipt of results, but they probably return to their baseline risk after the impact of this information have been incorporated into their lives and other factors are more prominent in influencing psychological well-being. The study also highlights features in the clinical history that may serve to alert the clinician to the need for the most vigilant ongoing psychological support.

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Appendix

Participating Centers with Follow-up Data (no. of individuals tested)

Australia (n = 646):
- J. Conaghan, Hunter Genetics, Waratah, New South Wales
- C. Hempel, Flinders Medical Centre, Bedford Park, South Australia
- T. Liebeck and C. Connor, Selby Centre, Shenton Park, Western Australia
- F. Richards, The New Children's Hospital, Parramatta, New South Wales
- I. Simpson and Dr. A. Waugh, Aspley Community Health Services, Queensland
- S. Taylor, Launceton General Hospital, Launceston, Tasmania

Austria (n = 9):
- Dr. H. Aschauer, University Hospital Psychiatry, Vienna

Belgium (n = 190):
- Drs. A. De Paepe and A. Van Tongerloo, Universitair Ziekenhuis, Gent
- Dr. G. Evers-Kiebooms, Universitaire Ziekenhuizen, Leuven
- Dr. C. Verellen, Universite Catholique de Louvain, Brussels
- Dr. A. Verloes, Centre Hopital Universitaire, Liege

Canada (n = 641):
- Drs. E. Almqvist, M. Bloch, and M. Hayden, UBC Hospital, Vancouver
- Dr. S. Bamforth, University of Alberta's Hospital, Edmonton
- S. Cardwell, Royal University Hospital, Saskatoon
- M. Crowley and Dr. E. Ives, Janeway Child Health Centre, St. John's, Newfoundland
- S. Dufrasne, McGill University, Montreal
- D. Eisenberg and Dr. D. Whelan, McMaster University Medical Centre, Hamilton, Ontario
- A. Fuller, IWK Grace Health Centre, Halifax, Nova Scotia
- C. Gillies, Thunder Bay District Health Unit, Thunder Bay, Ontario
- Dr. C. Greenberg, Children's Hospital, Winnipeg
- H. Hare, Sudbury & District Health Unit, Sudbury, Ontario
- M. Johnstone, Oshawa General Hospital, Oshawa, Ontario
- R. Lokkesmoe, Queen's University, Kingston, Ontario
- Dr. P. MacLeod, Victoria General Hospital, Victoria, British Columbia
- C. Prevost, Hôpital de Chicoutimi, Chicoutimi, Quebec
- F. Robert, North Bay District Health Unit, North Bay, Ontario

Czech Republic (n = 1):
- Dr. J. Zidovska, Teaching Hospital of Charles University, Prague

Finland (n = 13):
- Dr. M. Peippo, The Family Federation of Finland, Helsinki

France (n = 178):
- Dr. A. Durr, Hopital de la Salpetriere, Paris
- Dr. M.-C. Malinge, Centre R. Debre CHU d'Angers, Angers
- Dr. H. Pison, Service de Cytogenetique, Grenoble
- Drs. H. Plauchu, E. Ollagnon, and T. d'Amato, Hôpital Hôtel Dieu, Lyon
- Drs. F. Tison and D. Lacombe, Hopital Pellegrin, Bordeaux
- Dr. J. Yaouanq, Hopital Pontchaillou, Rennes

Germany (n = 124):

Drs. J. Epplen, A. Riess, and O. Riess, Ruhr-Universität, Bochum
Drs. D. Nolte and U. Mueller, Institute of Human Genetics, Giessen
Drs. Schwinger and U. Zühlke, Institut für Humangenetik, Universität Lübeck, Lübeck

Israel ($n = 16$):
Dr. M. Frydman, Sheba Medical Centre, Tel Hashomer

Italy ($n = 53$):
Dr. G. Campanella, University Federico II, Naples
Drs. M. Frontali and A. Jacopini, Istituto Medicina Sperimentale CNR, Rome

Mexico ($n = 12$):
Dr. E. Alonso Vilatela, Instituto Nacional de Neurologia y Neurocirugia, Col. La Fama

The Netherlands ($n = 566$):
Dr. J. Cobben, Gröningen University, Gröningen
N. Knoers, University Hospital, Nijmegen
Drs. A. Maat-Kievit and M. Vegter-van der Vlis, Academisch Ziekenhuis, Leiden
Dr. R. Richard, Academic Medical Centre, Amsterdam
Dr. A. Tibben, Erasmus University, Rotterdam

New Zealand ($n = 110$):
Dr. W. Cambourn, Wellington Hospital, Wellington
Dr. A. Macleod, Psychiatric Consult. Services, Christchurch Hospital, Christchurch
Dr. I. Winship, J. Giles, Northern Regional Genetic Services, Auckland

South Africa ($n = 55$):
Dr. J. Greenberg, UCT Medical School, Cape Town
Drs. A. Krause, J. Kromberg, University of Witwatersrand, Johannesburg
Dr. M. Marx, University of Stellenbosch, Tygerberg
Dr. W. Winship, University of Natal Genetic Clinic, Durban

Spain ($n = 45$):
Dr. J. Garcia de Yebenes, Universidad Autonoma de Madrid, Madrid
Dr. M. Ramos-Arroyo, Hospital Virgen del Camino, Pamplona

Sweden ($n = 55$):
A. Haegermark, Drs. M. Anvret and A. Lundin, Karolinska Hospital, Stockholm
Dr. U. Kristoffersson, University Hospital, Lund

United Kingdom: U.K. Huntington's Prediction Consortium ($n = 1{,}017$):
C. Benjamin and Dr. A. Fryer, Royal Liverpool Children's Hospital, Liverpool
Dr. D. Craufurd, St. Mary's Hospital, Manchester
R. Glew and Dr. S. Huson, Oxford Radcliffe Hospital Trust, Oxford
J. Haydon and Dr. S. Bundey, Birmingham Women's Hospital, Birmingham
Dr. S. Holloway, Western General Hospital, Edinburgh
A. Howick and Dr. M. Patton, St. George's Hospital, London
A. Kershaw and Dr. J. Yates, Cambridge University, Cambridge
A. Lashwood, Guy's Hospital, London
E. McGhee, Dr. S. Raeburn, City Hospital, Nottingham
Dr. P. Morrison, Northern Ireland Genetics Services, Belfast
C. Patch and Dr. N. Dennis, The Princess Anne Hospital, Southampton
B. Smith, D. Guthrie Institute of Medical Genetics, Glasgow
Dr. R. Trembath, Leicester Royal Infirmary, Leicester
Dr. G. Turner, St. James's University Hospital, Leeds
G. Garner and Dr. P. Turnpenny, Royal Devon & Exeter Hospital, Exeter

United States ($n = 796$):
P. Allinson, University of Virginia Medical Center, Charlottesville
Dr. H. Bass, Kaiser Permanente Medical Group, Panorama City, CA
B. Baty, University of Utah Health Sciences Center, Salt Lake City
R. Bennett and Dr. T. Bird, University of Washington Medical Center, Seattle
G. Brookshire, Children's Medical Center, Dallas
M. Earnhart, Marshfield Clinic, Marshfield, WI
C. Evers, University of Iowa, Iowa City
L. Godmilow, University of Pennsylvania, Philadelphia
D. Goodwin, Thomas Jefferson University, Philadelphia
C. Gray, University of Kansas Medical Center, Kansas City
C. Haverkamp, Kaiser Permanente, Denver
V. Hannig, Vanderbilt University Medical School, Nashville
Dr. J. Johnson, Shodair Hospital, Helena, MT
Dr. R. Jones, Emory University School of Medicine, Atlanta
K. Kovak, Oregon Health Sciences University, Portland
K. Leonard, Baylor College of Medicine, Houston
C. Ludowese, Hennepin County Medical Center, Minneapolis
Dr. G. Mengden, Southwest Genetics, San Antonio
Dr. T. Mueller, University of South Florida, Tampa
Dr. K. Quaid, Indiana University, Indianapolis
E. Otto, University of Missouri Hospital and Clinics, Columbia

N. Potter, University of Tennessee Medical Center, Knoxville
Dr. F. Schaefer, Chapman Institute, Tulsa
Dr. C. Schramke, Veterans Affairs Medical Center, Pittsburgh
Dr. K. Shannon, Rush-Presbyterian/St. Luke's Medical Center, Chicago
G. Suter, Donald J. Allen Memorial HD Clinic, Wichita
Dr. D. Yim, Kaiser Permanente Medical Group, Honolulu
A. Zanko, University of California Medical Center, San Francisco

Electronic-Database Information

The accession number and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for HD [MIM 143100])

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