Fifteen years of experience in predictive testing for Huntington disease at a single testing center in Victoria, Australia

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Purpose: This retrospective study describes 15 years of experience in predictive testing for Huntington disease at a single center in Victoria, Australia. **Method:** Data collected on 756 participants included age, gender, family history, prior risk and the age at which this risk became known, exposure to Huntington disease, number of children, and proximity to the testing center. **Results:** Some 57.8% of participants were female, and 88.8% had a 50% risk of developing Huntington disease. The mean age at entry was 40.4 years and was gender-independent. Of all completed tests (n = 648), 37.5% gave high-risk results, and 3.2% were in the zone of reduced penetrance. The 14.3% who withdrew from testing tended to be younger and childless, lacked exposure to severe Huntington disease, and more often at 25% or less risk. Some 32.4% of candidates presented for testing within 1 year of becoming aware of their risk, and most of these individuals had little or no exposure to severe Huntington disease. Those whose exposure was considerable waited on average for more than 13 years. Among the most inexperienced candidates were a group of "adoptees" (raised away from their biological family). Maternal transmission was the source of risk for 19 of 20 adoptees. **Conclusion:** This study illustrates the significance of exposure to Huntington disease and its impact on the timing of testing. *Genet Med* 2006:8(11):673–680.

Huntington disease (HD) is an autosomal dominant neurodegenerative disorder in which the main sites of pathology are the basal ganglia and cerebral cortex. It is characterized by cognitive and motor impairment (typically chorea), and is often accompanied by psychiatric and/or personality affliction. Symptoms most often develop in adult life, leading to dementia and death on average 15 to 20 years after onset.[1,2]

Testing of the genetic status of asymptomatic at-risk individuals became possible following the discovery in 1983 of a tightly linked marker (G8) that localized the HD gene to chromosome 4.[3] The first predictive test results worldwide were given in 1987[4] and in the state of Victoria (Australia) in 1989.[5,6] Because of the necessity of obtaining blood samples from multiple family members, the uninformative nature of some family pedigrees, and the possibility of recombination between the markers and the gene, linkage analyses were not suitable for all those at risk requesting testing.[4] In 1993 the mutation associated with HD was characterized as an unstable CAG repeat within exon 1 of the *IT15* gene.[7] Measurement of the number

of CAG repeats by direct mutation analysis obviated the need for obtaining DNA samples from other family members, thus enhancing the autonomy and privacy of individuals seeking to know their genetic status and providing them with a definitive predictive test.

This study was designed to analyze the first 15 years of HD predictive testing in Victoria to the end of 2004 and to compare our experience with other studies. Counseling, neurologic assessment, and genetic analyses were coordinated through the Genetic Health Services Victoria (known before 2001 as the Victorian Clinical Genetics Service), leading to a standardized approach and consistency and completeness in recording not possible in many studies.

MATERIALS AND METHODS

Predictive testing program

Victoria's only testing center services a population of approximately 5 million. The program is free of charge and centered in metropolitan Melbourne, a large city located centrally but in the southern part of the state. Components of the program include a number of counseling and genetic consultations, a neurologic/neuropsychiatric assessment, and a DNA test.[8] For the purposes of this study, entry into the program was defined as face-to-face consultation with a counselor and/or neurologist associated with the program. Thus, phone contact seeking preliminary information did not constitute entry. The number of predisclosure consultations was generally approxi-

mately three or four, although the range was wide, and follow-up contacts were as needed and thus variable in number. Two consultations in a single day at the metropolitan center, phone counseling, and attendance at nonmetropolitan outreach clinics were measures adopted to meet the needs of rural candidates. Asymptomatic status was not always clinically confirmed because some candidates declined the neurologic examination that was offered to all; however, predictive testing proceeded if the candidates believed themselves to be asymptomatic. Completion of testing was defined as the candidate having received the result of the DNA test. When the candidate chose not to receive the result, the test was defined as incomplete and the candidate was deemed to have withdrawn. The stage reached before withdrawal was recorded. Those cases considered to be ongoing at the end of 2004 for whom a result was likely to be given in the near future were excluded from this study, because they were neither complete nor had the candidates withdrawn from testing. The minimum age for predictive testing in Victoria is usually 18 years.

When candidates presented with a risk of 25%, every effort was made to offer their at-risk parent testing first (if still living). Most of the group at less than 25% risk were only distantly related to an affected person, presenting different counseling issues to those directly descended from an affected person.

Data collected

Ethics approval for this study was obtained from the Ethics in Human Research Committee of the Royal Children's Hospital, Melbourne.

Data on 756 entrants into the program were drawn from genetic files, counseling files, and laboratory records held at Genetic Health Services Victoria and compiled into an anonymous database. The data included gender, age, prior risk and the length of time the risk had been known, level of prior exposure to HD, family history (including gender, CAG repeat number and the age of onset of HD in affected relatives, and whether or not the candidate was raised by their biological family), outcome of any neurologic testing, and geographic proximity to the testing center. The level of prior exposure to HD was categorized according to whether the candidate had none, had been exposed only to the early symptoms of the disease, or had observed the advanced stages and/or death of a family member. On the basis of postcode data, participants were assigned to one of four geographic localities in relation to the testing center: less than 20 km, 20 to 100 km, 100 to 300 km, or more than 300 km.

Before 1993, linkage analysis of markers linked to the HD mutation within a candidate's family was used to provide a modified risk. The final risk was calculated, allowing for the probability of recombination events, using the MLINK component of the LINKAGE computer program (obtained from Lathrop et al.[9]). A CAG repeat number derived from direct mutation testing of 40 or more indicates the presence of an HD allele with full penetrance and defines a gene-positive result. A zone of reduced penetrance, where some individuals remain asymptomatic, corresponds to alleles with 36 to 39 CAG repeats. Alleles with 35 or less repeats define a normal or gene-negative result.[10]

Data analysis

Data were entered into a Microsoft Access database (Microsoft Corp., Redmond, WA). Descriptive analysis was undertaken using Microsoft Excel and the Statistical Package for the Social Sciences (version 12.0, SPSS Inc, Chicago, IL). Data are presented as means and standard deviations (SDs) for continuous variables and proportions for categoric variables. The statistical significance of differences in mean levels of continuous variables was assessed using t tests for independent samples for comparisons between two groups and one-way analysis of variance for comparisons across three groups. Differences in proportions between groups were assessed for statistical significance using the chi-square test for association. To test whether observed proportions in a single group followed the expected distribution, for example, a 50:50 gender distribution, the chi-square goodness-of-fit test was used. The criterion for statistical significance was P less than .05.

RESULTS

The predictive testing program in Victoria began in 1987. The annual entry since then is detailed in Figure 1A, reaching a peak of 87 entrants in 1994 shortly after the introduction of direct DNA mutation analysis. In total, 756 people commenced testing; 95 started when testing was done by linkage analysis and the remainder since that time. In 648 cases, the testing and counseling process was completed and a result was given. Figure 1B shows the annual distribution of these completed tests.

DEMOGRAPHIC DATA FOR PROGRAM ENTRANTS

Age and gender

Demographic data for the study cohort are presented in Table 1. There were 437 females (57.8%) and 319 males (42.2%) who entered the program, with a mean age at testing of 40.4 years (SD = 14.4). Analysis of age by gender shows means of 40.5 years for females and 40.2 years for males, and a similar age distribution (Fig. 2). One candidate, who underwent testing of her own volition, received a result at 17½ years because of family planning intentions. The remainder of the results were given to individuals aged 18 years or more.

Children

Before testing, 67.3% of candidates had one or more children (Table 1), and four were pregnant at the time of entry. The relative proportion of the group seeking testing before having children has not changed significantly since the inception of testing; in the period before the introduction of the direct mutation test, 38.8% of candidates were childless compared with 35.3% since that time (P = .53).
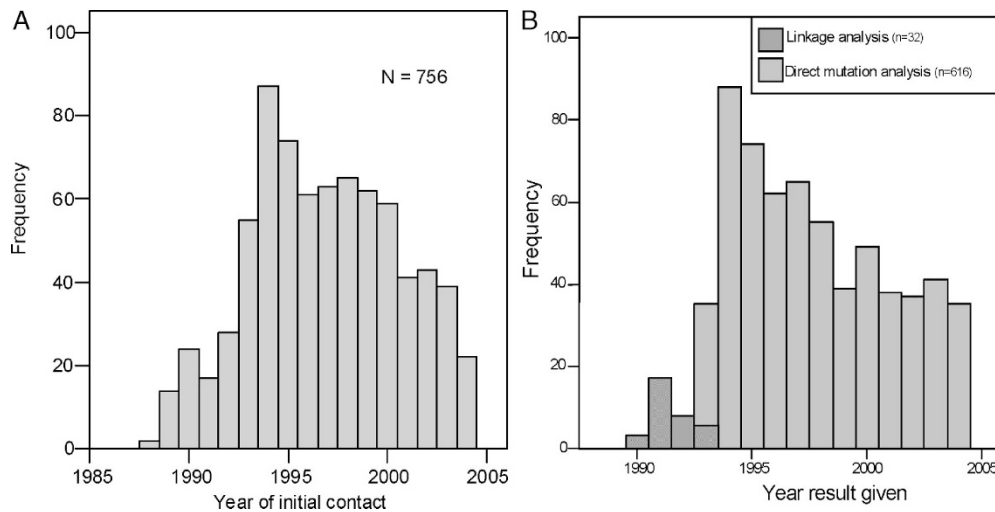
Fig. 1. A. The number of candidates entering into the predictive testing program for HD per year. B. The number of tests completed in any given year and the method of analysis used.

Family history

In 83.3% of cases an affected parent (or one with an expanded HD allele) was directly identified. In an additional 8.1%, the at-risk parent could be implied from diagnoses in maternal or paternal relatives. A maternal family history of HD was significantly more common than a paternal one (54.8% vs. 36.5%, $P < .001$). There were 65 cases (8.6%) with no clearly documented family history of HD before the current generation. Most of these candidates became aware of their risk after the diagnosis of HD in a sibling (53 cases) or a child (6 cases).

Prior risk

In total, 88.8% cases had a prior genetic risk of 50%. One person presented with a 75% prior risk because both parents were affected, and 8.1% presented with a risk of 25% and required particularly careful exploration and multistaged counseling. In eight cases, the parent with a prior risk of 50% subsequently chose to be tested first, and the candidate's prior risk of 25% was modified during the testing process. Three candidates, whose risk was nullified by their parent receiving a gene-negative result, withdrew. Two of the five whose parents tested gene positive, and whose risk was modified to 50%, also withdrew.

Proximity to the test center

Australian Bureau of Statistics figures for June 2004 indicated that 24% of Victoria's 4.98 million residents live more than 100 km from the center of Melbourne,[11] as do 25.3% of program participants. Although we do not know the precise distribution of the at-risk population it would seem that distance from the testing facilities does not impact the rate of presentation for testing ($P = .42$). However, living more than 100 km from the testing center affects the rate of completion, with 35.1% of those who withdrew and 23.8% of those who completed testing living in this region ($P = .024$).

Prior exposure to Huntington disease

A person's prior exposure to HD was categorized as none (14.6% of cases in whom data were available); having observed only the early symptoms (34.7%); or having observed severe illness and/or death of family members with HD (50.7%). Because of the retrospective nature of this study, such information was not available for 97 of 756 candidates.

Waiting period

The waiting period was defined as the number of years an individual had known of his or her own at-risk status before presenting for predictive testing. The mean waiting period calculated from 629 valid cases was 9.7 years (SD = 9.3) (Table 2). Those at 50% prior risk waited significantly longer than those at 25% or less risk before testing (on average 10 vs. 6.5 years, $P = .006$). The group who waited longest were those who had prior exposure to severe HD (13.4 years). This compares with 4.0 years for those with no exposure and 5.4 years for those having only experience of the early symptoms in their relatives ($P < .001$).

The age at which candidates first learned of their risk and their level of exposure to HD are also related. Those exposed to severe HD learn at a mean age of 23.8 years compared with 36.2 years for those less experienced ($P < .001$).

In 204 of 629 of cases (32.4%), testing occurred within 1 year of the risk becoming known (Fig. 3). The female:male ratio in this group was identical to that of the total cohort (57.8%: 42.2%). The propensity to test "immediately" (i.e., within 1 year) was considerably higher among those whose experience of HD was very limited (70.2% of those with no exposure, 52.6% of those exposed to early symptoms only, and 11.3% of those with substantial experience).

Adoption

A subgroup referred to as "adoptees" was composed of individuals who were raised away from their biological family

Table 1
Demographic profile of program participants

|	Total cohort n = 756 (%)	Testing completed n = 648 (%)	Withdrew from testing n = 108 (%)
Gender			
Female	437 (57.8)	373 (57.6)	64 (59.3)
Male	319 (42.2)	275 (42.4)	44 (40.7)
Age (y)			
Mean ± SD	40.4 ± 14.4	41.0 ± 14.6	36.4 ± 12.4
(range)	(16–87)	(16–87)	(17–68)
Children			
None	241 (31.9)	193 (29.8)	48 (44.4)
≥1	509 (67.3)	452 (69.8)	57 (52.8)
Pregnant at testing	4 (0.5)	3 (0.5)	1 (0.9)
Family history			
Maternal[a]	415 (54.8)	359 (55.3)	56 (51.9)
Paternal[a]	276 (36.5)	233 (35.9)	43 (39.8)
Other[b]	65 (8.6)	57 (8.8)	8 (7.4)
Proximity to test center			
<20 km	282 (37.9)	244 (37.7)	38 (39.2)
20–100 km	274 (36.8)	249 (38.4)	25 (25.8)
100–300 km	150 (20.2)	125 (19.3)	25 (25.8)
>300 km	38 (5.1)	29 (4.5)	9 (9.3)
Prior risk			
50%	671 (88.8)	584 (90.1)	87 (80.6)
25%	61 (8.1)	42 (6.5)	19 (17.6)
Other[a,c]	24 (3.2)	22 (3.4)	2 (1.9)
Prior exposure to HD			
No prior exposure	96 (14.6)	81 (14.5)	15 (18.3)
Early symptoms only	229 (34.7)	193 (33.4)	36 (43.9)
Severe disease/death	334 (50.7)	303 (52.5)	31 (37.8)
Raised outside family	24 (3.2)	21 (3.2)	3 (2.8)

SD, standard deviation; HD, Huntington disease.
[a] One person had HD on both sides of the family and was at 75% risk.
[b] Indicates no family history before the current generation, for example, risk due to diagnosis in a sibling or offspring.
[c] Twenty-three patients with a risk of less than 25%, generally based on the affected person being a distant relative with a proven or probable diagnosis, in whom the most direct line of risk often had been broken by the death of undiagnosed individuals. In several cases the family history was unclear because of an extended lack of contact.

(adopted or raised in other forms of care). Of this group of 24 individuals (Table 1), 14 were female; the mean age at presentation was 38.5 ± 12.5 years, 18 were at 50% risk, and 9 had no children, although one was pregnant. Where the family history could be traced (in 20/24 cases), the HD risk was maternal in all but one case. Only five "adoptees" recorded substantial prior exposure to HD, and three more had been exposed to early symp-
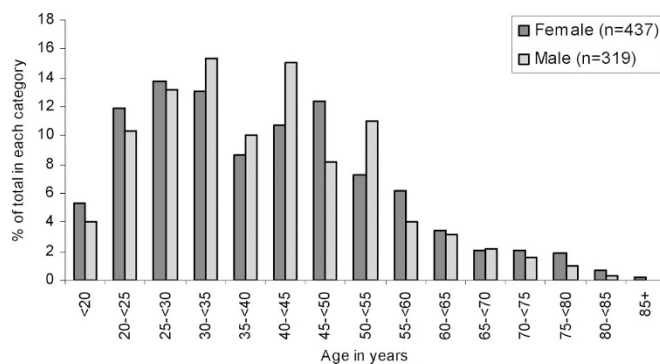
Fig. 2. Age distribution of males and females at the time of their initial contact with the HD predictive testing program.

toms. Although the mean waiting period for the "adoptee" group was 6.1 years (Table 2), 57% had known their at-risk status for less than 1 year before seeking testing. These data form a subset of the data in Figure 3.

Incomplete tests

The demographic profile of the 108 people who withdrew from testing is presented in Table 1. This accounts for 14.3% of program entrants. Features that most clearly differentiate this group from those who completed testing include the following: younger age (36.4 vs. 41.0 years, $P = .002$); childlessness (44.4% vs. 29.8%, $P = .002$); lack of exposure to severe HD (62.2% vs. 47.5%, $P = .013$); being at 25% or less risk (19.5%

Table 2
Years of knowledge of "at-risk" status before initial contact with the predictive testing program (waiting period)

	Average age when risk became known	Waiting period	Valid cases[a]
Total cohort	30.0 ± 15.3 y	9.7 ± 9.3 y	629
Gender			
Female	30.1 ± 16.0 y	9.9 ± 9.5 y	359
Male	29.8 ± 14.5 y	9.3 ± 9.1 y	270
Prior risk			
50%	29.2 ± 14.7 y	10.0 ± 9.3 y	569
25%	32.4 ± 15.3 y	6.5 ± 8.3 y	42
Other	48.3 ± 21.7 y	6.4 ± 9.5 y	18
Prior exposure to HD			
No prior exposure	40.2 ± 19.2 y	4.0 ± 6.2 y	84
Early symptoms only	34.5 ± 14.9 y	5.4 ± 6.8 y	196
Severe disease/death	23.8 ± 11.4 y	13.4 ± 9.5 y	291
Adoptees	34.3 ± 13.9 y	6.1 ± 8.0 y	21
Test completion			
Complete	29.8 ± 15.3 y	10.2 ± 9.5 y	567
Incomplete	31.5 ± 15.3 y	5.2 ± 6.5 y	62

[a] Data were limited to those in whom *both* years at risk and age at first contact were known.
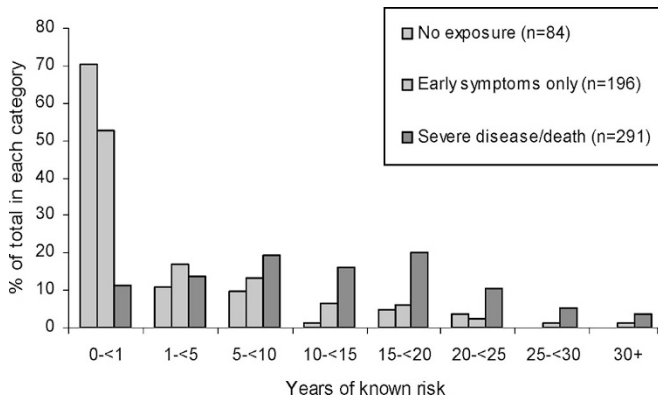
Fig. 3. The effect of prior exposure to HD on the timing of testing. *Note the uneven scale on the X-axis.*

vs. 9.7%, *P* = .004), and having known of their risk status for a lesser time (5.2 vs. 10.2 years, *P* < .001). The gender of the candidate or of the family carrier did not significantly differ from the overall cohort.

Outcome of testing

The outcome of testing is shown in Table 3. The results have been given to 85.7% (648/756) of those entering the program.

Linkage analysis

The results based on linkage analysis were given over the period 1989 to 1993. All 35 candidates who underwent testing had been at 50% prior risk, 57% were female, and the mean age at first contact was 35.7 years (SD = 13.5). After testing, 23% had their risk of inheriting HD modified to high (88%–99%) and 69% to low (2%–16%); the remaining 8% withdrew because their family analyses were uninformative. Twelve candidates (2 who had withdrawn, 4/8 "high-risk" candidates, and 6/24 "low-risk" candidates) subsequently had direct mutation analysis. The 10 cases of previously implied status were all confirmed. The time elapsed until the direct test was taken aver-

aged 31 months for the "high-risk" group and 55 months for the "low-risk" group.

Direct DNA test

Of 648 completed tests (including the linkage tests), the relative frequency of genotypes was 37.5% gene positive, 3.2% in the zone of reduced penetrance, and 59.3% gene negative. The range of CAG repeats in the gene-positive category was 40 to 54, with a peak at 42 to 43 accounting for 42.4% of cases (complete data not presented).

The group at 25% prior risk might be expected to have a lower proportion of gene-positive results compared with the 50% risk group; however, the observed difference was not significant (31.0% vs. 38.9%, *P* = .301). A gene-positive result for an individual at 25% risk inevitably revealed the gene status of his or her at-risk parent, although data were not always available on whether the parent was alive. In the small group whose risk was less than 25%, only 14.2% (3/21) were gene positive, in line with expectations.

Of the group found to carry a reduced penetrance allele, 13 of 21 (62%) were aged more than 50 years, including seven (33%) aged more than 70 years. In eight cases testing was prompted by the diagnosis of HD in a sibling or child rather than a parent. This is the only group among those tested in whom the transmitting parent was more often the father (11/17 in whom the family history was clear).

There was considerable disparity between genotype and mean age at presentation: gene positive = 37.1 years, gene negative = 42.6 years, and reduced penetrance = 55.4 years (*P* < .001). Figure 4 shows the relationship between test outcome and age group (in decades). The ratio of negative/positive results was not heavily skewed in favor of negative results except in the group of those aged 50 years, and the peak for outcomes in the zone of reduced penetrance actually occurred in the group of those aged more than 70 years.

Table 3
Outcome of predictive testing for all completed tests

Completed tests[a]	Total	Gene positive CAG >39 n (%)	Reduced penetrance CAG 36–39 n (%)	Gene negative CAG <36 n (%)
Total	648	243 (37.5)	21 (3.2)	384 (59.3)
Gender				
Female	373	130 (34.8)	12 (3.2)	231 (61.9)
Male	275	113 (41.1)	9 (3.3)	153 (55.6)
Prior risk				
50%	584	227 (38.9)	21 (3.6)	336 (57.5)
25%	42	13 (31.0)	—	29 (69.0)
Other[b]	22	3 (13.6)	—	19 (86.4)
Age at initial contact Mean (range)	41.0 ± 14.6 y (16–87)	37.1 ± 11.7 y (16–80)	55.4 ± 18.3 y (25–87)	42.6 ± 15.3 y (17–84)

[a] Results for 32 tests done by linkage analysis are included as positive (= high risk) or negative (= low risk), even though in 22 cases a follow-up direct DNA mutation analysis was not performed. The 10 candidates who were tested by both methods have only been counted once.
[b] One had a 75% risk; all others had less than a 25% risk.
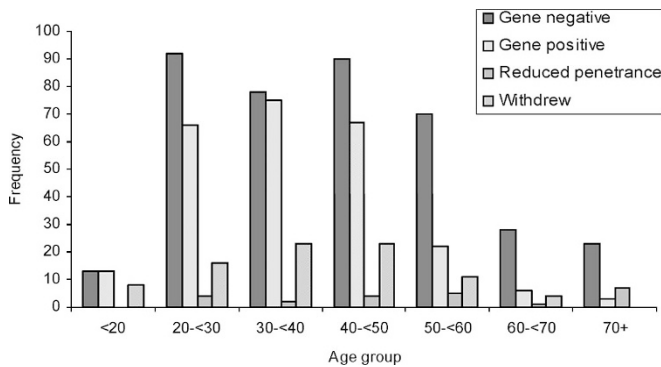
Fig. 4. Distribution by age group and test outcome for 756 individuals presenting for predictive testing for HD.

Data relating to the testing process

Although all candidates were offered a neurologic examination as part of the predictive testing program, 211 of 756 (28%) of the total cohort chose not to be assessed. Among those who received a gene test result, 20.4% declined the offer. There was no gender bias among those choosing not to be examined.

Postdisclosure contacts were provided on a needs basis, averaging 3.4 per candidate. In general, the number varied according to the nature of the result given: the means were 6.0 for a gene-positive result, 2.0 for reduced penetrance, and 1.8 for a gene-negative result. The program of follow-up contacts was not compromised by distance, although a higher proportion of contacts were made by telephone for those living further from the testing center.

DISCUSSION

In this article we describe the outcomes of 15 years of predictive testing at a single testing center. As with most other large studies, approximately 90% of candidates came with a prior unmodified risk of 50%.[12–15] The finding that 57.8% of candidates were female is also consistent with international observations, which generally range from 54% to 63%.[12,14–22] Exceptions have only occurred where numbers were small (e.g., 50% in the study of Kromberg and colleagues[23]) or where testing was done anonymously (38%).[24] A recently published study showed clear gender differences in attitude toward predictive testing, with females having a higher perception than males of their own ability to cope with an adverse result than males and a greater likelihood of disclosing their genetic status to others.[20]

We also found that it was significantly more common for the HD mutation to be carried maternally (60%) in the families of those presenting for testing.[13,25–27] A possible reason that this figure may be skewed is that paternally transmitted HD shows greater average expansion of the CAG repeat number than maternal transmission with a concomitant tendency for earlier onset, thus reducing the opportunity for presymptomatic testing.[13,28–32]

An interesting subset of candidates were those raised away from their biological family, who accounted for 3.2% of the total cohort. Within this group, 95% were found to be at risk of inheriting the expanded allele from their mother (compared with 60% for the total cohort). One possible reason for this extreme skewing is that children are more likely to be raised outside the family when the affected parent is the mother. Kessler states "when the mother is affected it appears to have a greater impact on effective family functioning than when the father is affected."[33] Another possible explanation is that it may be easier for an adoptee to find details of his/her biological mother than his/her biological father on public record.

The distance a candidate lives from the testing center affected the likelihood of completing testing. Although the DNA test continues to be done in Melbourne, efforts are being made to accommodate the needs of distant candidates by co-scheduling multiple consultations to reduce visits to the center and providing alternative means for some of the pre- and post-test counseling. The options include the use of local community health professionals, the HD Association, an increasing number of outreach genetics clinics, and telephone counseling with the metropolitan-based counselor. A similar situation is described by Benjamin and colleagues,[34] relating to testing in British Columbia, where counseling services within the local community have been developed with appropriate support from the genetics center to help overcome the tyranny of distance.

The timing of testing is a complex issue that seems to be influenced by a number of interrelated factors. These include proximity to the mean perceived age of onset,[26,35,36] prior exposure to and knowledge of HD, level of risk, and length of time the individual's own risk has been recognized.

In certain respects our findings closely parallel the Canadian experience, where the overall mean age was 39.3 years (compared with our 40.4 years) and 64.7% already had children (compared with 67%).[14,18] However, we observed two peaks in the age distribution curve both for males and females, one in the late 20s to early 30s and the other in the late 40s. This may suggest that there are different age-related motives for testing: one a reproductive risk decision and another to clarify the risk for their children.

The length of time people wait before presenting is strongly influenced by the level of their prior exposure to HD and the age at which they first knew of their risk. These two factors are interrelated, because the risk is learned earlier in families in whom individuals are exposed to advanced HD. Despite knowing of their risk from a relatively early age, individuals in this group wait on average for 13.4 years to present for testing, with many waiting in excess of 20 years (Fig. 3). Although being older when they learn of their risk, the majority of those with little or no exposure to HD sought testing within 1 year. This suggests a more spontaneous and perhaps less considered response to learning of their risk, possibly influenced by a lack of information. Exploration of issues during counseling may lead to a reassessment of the desire to know, with a consequently higher withdrawal rate in this group. Further support for this hypothesis comes from the "adoptee" group. They learned of their risk late (mean age 34.3 years), only one third

of them reported any direct exposure to HD, and 57% were tested within 1 year. The level of prior knowledge for those inheriting alleles of reduced penetrance is also often minimal because the disease in such families tends to be of later onset.[32,37,38] They represent the oldest group, presenting for testing at a mean age of 55.4 years. This study serves to illustrate the significance of the candidates' exposure to HD and the impact it has on the timing and completion of testing.

Of individuals receiving a result, 37.5% were gene positive, which is in line with most other reports reporting a range from 31.5% to 45%.[12–15,17–22] This is to be expected because 11.3% of candidates were at less than 50% risk, and individuals born at 50% risk and who present for testing as adults have a significantly lesser risk the longer they remain asymptomatic.[39,40] The fact that a proportion of the at-risk population become symptomatic and thus ineligible for predictive testing is likely to account for the gene-positive group being younger (mean age 37.1 years) than the gene-negative (42.6 years) or "reduced penetrance" candidates (55.4 years).

A number of studies have looked at the reasons why "at-risk" individuals choose not to participate in predictive testing.[41–45] However, few have considered those who commence testing but withdraw without learning their genetic status, except in relation to the testing of those at 25% risk.[15,45–48] Although we cannot specifically address the reasons for withdrawal because of the retrospective nature of the study, we attempted to profile the members of this group. The overall rate of withdrawal in this study is 14.3% (108/756), which is low by international standards; 51% withdrew in an Italian study,[49] 25% of those at 50% risk withdrew in the United Kingdom,[34] and 23% withdrew in Leiden, The Netherlands.[15,48]

The stage in the process at which withdrawal occurred varied. By definition, all had at least one session of face-to-face counseling. Almost half (45%) proceeded with blood collection and/or neurologic or neuropsychiatric assessment, together with multiple counseling sessions. In 19% of cases all clinical consultations were undertaken, but the candidate chose not to receive their result.

The data gave a picture of those most likely to withdraw as being relatively young (especially if female) and childless, lacking significant knowledge of or exposure to severe HD, and having knowledge of their own risk for a relatively short period. Those at 25% or less risk were overrepresented in this group. It may be that the dynamic process of the program prompted reassessment of their desire to know their genetic status, realizing the severity and inevitability of the disease. Factors that did not seem to be relevant include the gender of either the candidate or the family carrier, and whether or not the candidate was raised away from his or her biological family.

In summary, data from our study are broadly in keeping with international observations with respect to parameters such as age at presentation, "at-risk" status, gender balance, family history, and distribution of genotypes. The major contribution of this study centers on the timing of predictive testing within an individual's life experience. We have identified two interrelated experiential factors that strongly influence the length of time people wait once aware of their own risk status before they present for testing and the subsequent likelihood that testing will be followed through to completion. These factors are their level of prior exposure to HD and the age at which they became aware of their own risk status. Those with little knowledge or exposure to HD are significantly more likely to rush into testing and ultimately less likely to elect to receive their results.

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