ORIGINAL ARTICLE

22 years of Predictive Testing: The Experience of the UK Huntington's Prediction Consortium.

Baig SS[1*], Strong M[2], Rosser E[3], Taverner N[4], Glew R[5], Miedzybrodzka Z[6], Clarke A,[3] Craufurd D[7], UK Huntington's Disease Prediction Consortium, Quarrell OWJ[8*]

* These authors contributed equally towards this work.

Author Affiliations:

(1) Academic Foundation Doctor, Sheffield Teaching Hospitals NHS Foundation Trust.
(2) School of Health and Related Research, University of Sheffield
(3) Department of Clinical Genetics, Great Ormond Street Hospital
(4) Institute of Cancer & Genetics, University of Cardiff
(5) tbc
(6) School of Medicine, Medical Sciences & Nutrition, University of Aberdeen
(7) Institute of Human Development, University of Manchester
(8) Department of Clinical Genetics, Sheffield Children's Hospital

Word Count (excluding abstract, legends, tables and references) = 3901
(Word Limit = 6000 words)

ABSTRACT

Introduction: Huntington's disease (HD) is an inherited progressive neurodegenerative condition. Predictive direct mutation testing of at-risk individuals has been available since 1993.

Methods: The UK Huntington's Prediction Consortium collected anonymised data on all UK predictive tests, annually, from 1993-2014. Using the HD prevalence figure of 12.3 per 100 000, we determined the cumulative uptake of predictive testing in the at-risk population.

Results: From 1993-2014, 9407 predictive tests were performed in 23 UK centres. Where gender was recorded, 4077 participants were male (44.3%) and 5122 were female (55.7%). The median age of participants was 37.7 years. The most common reason for predictive testing was to reduce uncertainty (70.5%). Of 8441 predictive tests on individuals at 50% *apriori* risk, 4629 (54.8%) were reported as gene negative, 3790 (44.9%) were gene positive with 22 (0.3%) uninterpretable. The cumulative uptake of predictive testing in the 50% at-risk UK population from 1994-2014 was estimated at 17.4% (95% CI: 16.9-18.0%).

Discussion: Here we present the largest study ever conducted on predictive testing in HD. Our findings indicate the vast majority of individuals at-risk of HD (>80%) have not undergone predictive testing. Future therapies in HD will likely target pre-symptomatic individuals, therefore characterising the at-risk population whose gene-status is unknown is of significant public health value.

Keywords: Huntington's disease, Predictive Testing, Pre-symptomatic Testing, Prevalence

(Maximum 200 words for abstract); currently 214.

INTRODUCTION

Huntington's disease (HD) is a slowly progressive and ultimately fatal autosomal dominant inherited neurodegenerative disorder characterised by development of abnormalities in movement, cognitive decline and behavioural disturbances (1). The disease is caused by an expanded CAG repeat in the first exon of the *HTT* gene which encodes an abnormal polyglutamine expansion in the huntingtin protein resulting in selective neuronal degeneration (2).

In addition to the symptomatic population with an expanded allele, there are several-fold more individuals at risk of developing the condition (3). Predictive testing for HD first became available in 1986 with linkage analysis (4, 5) and was superseded by direct mutation analysis in 1993. The advent of optional pre-symptomatic testing in HD has profoundly influenced the lives of this at-risk population and has become a paradigm for predictive testing for genetic disorders as a broader clinical entity. Individuals at-risk are able to establish, with near certainty, whether they will develop HD or not. This clearly has implications on an individual level (personal wellbeing, relationships, family planning, employment and finances) (6) and on a societal level (targeted healthcare and social service provision). Given the significance of a positive result and the current paucity of disease modifying medical interventions, guidelines recommend a comprehensive programme consisting of genetic counseling and generally restrict access to those aged 18 and over (7).

Cumulative uptake of predictive testing has classically been expressed as the number of predictive tests performed as a proportion of those estimated to be at 50% risk in the population (8). This methodology is problematic as it ignores the fact that, as new cases of HD are diagnosed, the number of individuals known to be at-risk of HD in a given population (the denominator in the equation) increases over time; as such, previous studies have overestimated the cumulative uptake of predictive tests. In the absence of a national, comprehensive HD population registry with detailed information on family pedigrees, establishing the at-risk population is difficult. To overcome this

problem, Tassicker *et al* (9) have proposed a method to determine the cumulative at-risk population over time which accounts for the changing at-risk population and disease duration. This method has been applied by smaller, centrally organised centres in Victoria, Australia (9) and Northern Ireland (10) and has provided measures of cumulative uptake of predictive testing in HD that are more consistent with observations made by HD Counsellors and Clinical Geneticists (9).

Here, using the UK Huntington's Prediction Consortium's (UK HPC) data from 1993 – 2014, we update our previous study (8) and report on the largest study ever conducted on the experience of predictive testing for HD.

METHODS

Data Recording

The UK HPC was launched in 1989 to systematically collect anonymised data on all completed pre-symptomatic tests for HD in the UK and to provide a forum for the evolving discussion of issues pertaining to predictive testing (8). Forms were completed by nominated participants at each centre and were entered into a central database by the Consortium Coordinator. All 23 centres in the UK offering predictive testing have participated contemporaneously from the outset giving near complete coverage of data.

Data recorded included the testing centre, gender, age of testee, prior genetic risk, details of the type of genetic test and final result. From 1993-2006, the test results were characterised as being normal/unaffected (<36 CAG repeat length on largest allele) or abnormal/affected (≥ 36 repeat length on the largest allele). From 2007, centres also began to report on intermediate alleles (28-35 CAG repeat length on the largest allele) and reduced penetrance alleles (36-39 CAG repeat length on the largest allele). In later years, information on the ethnicity of testees, maternal/paternal origin of mutation and reasons for predictive testing were also recorded.

Descriptive analysis was performed on all predictive tests performed from 1993 - 2014. The calculation of the cumulative uptake of predictive testing was determined from predictive tests performed from 1994-2014 which represents 21 complete years of testing.

Calculations for Cumulative Uptake of Predictive Testing (1994-2014)

The inclusion criteria for the cumulative uptake analysis were as follows:

(1) Age 18 or over. The rationale for this is that those under 18 are not eligible for predictive testing[i] although some tests have been carried out for exceptional circumstances related to planning health and social care interventions. This will be the subject of a future publication.

(2) Family history of confirmed Huntington's disease and an a priori risk of 50% at conception (first degree relative affected or a carrier).

(3) Completed testing protocol with the final result available.

The exclusion criteria for the cumulative uptake were as follows:

(1) Prenatal testing for Huntington's disease.

Data on predictive tests were available for 23 testing centres for the period 1993 to 2014. Because predictive testing only became available towards the end of 1993, this year was excluded from the analysis. Within each year, tests were included for those who were 18 years and over, and who were identified as being at 50% risk. There were 483 centre-level data collection periods in total (i.e. 21 years multiplied by 23 centres). Ten centres did not report data for one or more years, which resulted in 26 of the 483 (5.4%) of the centre-level data collection periods having missing data. We assumed missing data were missing at random ('MAR') and used multiple imputation based on predictive mean matching to impute plausible values based on year and centre (11).

The cumulative uptake of predictive testing over the study period was determined using the formula described by Tassicker et al (9):

Uptake (%) = (T/D) x 100

Where:

T = Cumulative number of predictive tests performed on eligible participants (≥ 18 years old) with a prior risk of 50% over the study period.

D = Cumulative number of eligible individuals at 50% risk of HD over the study period

= *P +*

P = Number of individuals at 50% risk who are eligible for testing at the start of the study (prevalence in the adult population x 4.2).

The cumulative number of individuals at 50% risk (P) of HD is the sum of the eligible individuals at 50% risk at the start of the study and those individuals who become eligible over the course of the study. In order to calculate reliably the population at 50% risk, accurate estimates of the prevalence of HD in the general population are required. This is itself a contentious issue (see Discussion). In the present study, the prevalence figure of 12.3 per 100 000 in adult population was used to calculate the cumulative uptake of predictive testing over the study period.

Classically, the ratio of the number of symptomatic individuals (prevalence) to individuals at 50% risk of developing HD in a population has been described as being, on theoretical grounds, 1:5 (3). Tassicker *et al* (9) revised this to a ratio of 1:4.2 based on their own empirical data from multiple source ascertainment of at-risk individuals in Victoria, Australia; this revised ratio is similar to the empirical data from Northern Ireland (10). A ratio of 1:4.2 was used to calculate the cumulative uptake as it is based on empirical evidence. Discrepancies in the estimated prevalence of HD and the ratio of symptomatic individuals to individuals at 50% risk in the research literature were accounted for by performing a sensitivity analysis to calculate multiple uptake figures based on several different parameter estimates.

Disease duration, from onset of symptoms to death, was taken as being 18.8 years based on the average of the reported median disease duration in two large cohort studies (15, 16). Mid-year population estimates for those 18 and over were obtained for the UK for each year in the period

1994 to 2014 (17).

Statistical Analysis

Descriptive analysis was carried out using SPSS Statistics software (Version 22*).* For the main results, point estimates and 95% confidence intervals are reported. In order to calculate confidence intervals observed counts were assumed Poisson distributed. Imputation of missing data was via predictive mean matching based on centre and year. The imputation of missing data was carried out using the `mice` package in R (Version 3.2.2).

RESULTS

Demographic information and apriori risk

Between 1993 and 2014, 9407 predictive tests for Huntington's disease were performed in 23 centres in the United Kingdom. The demographic information and *apriori* risk of participants are summarised in **Table 1.**

There were slightly more females than males who undertook predictive testing (54.4% vs 43.3%). Data on gender was not available for 208 individuals (2.2%). The median age for undergoing predictive testing was 37 years (interquartile range: 29-47 years).

The majority of participants undergoing predictive testing had an *apriori* risk of 50% (89.7%). For a minority of participants (3.3%), the apriori risk could not be determined because of one of the following reasons: the risk estimate was missing from the dataset; expressed as a figure determined from a life-risk table; described in qualitative terms rather than an *apriori* risk; or the risk was determined to be very low and the predictive testing protocol was being carried out as part of the pre-implantation genetic diagnosis protocol as they had a gene-positive partner.

Predictive Testing by Year

Predictive testing by direct mutation testing became available part-way through 1993. In the later years of the study the response rate from participating centres was not complete, therefore, minimal missing data was imputed using the standard procedure described in the Methods. In the initial years of predictive testing (1994-1998), the mean number of tests performed annually on those ≥18 years old with a 50% apriori risk, after imputation of missing data, was 535 (SD 2.9). From 1999-2014, the corresponding figure had fallen to 362 (SD 1.9).

Reasons for Testing

Patient-reported reasons for undergoing testing were not recorded uniformly for all centres or consistently throughout the study. Reasons for predictive testing were recorded for 4743 (50.4%) participants and we can report on the number of responses recorded for the five most common reasons for predictive testing (summarized in Table 2). Participants were allowed to cite multiple reasons for predictive testing and this is reflected in the results. The most common patient-reported reasons for undertaking predictive testing were to "reduce uncertainty " (70.5% of responders) and for "future-planning" (57.7%). Other reasons included "to provide information to relatives" (38.3%), "reproductive decision making" (23.0%) and the "hope for future treatments" (9.6%). Rarer reasons for predictive testing included: testing as part of the assisted reproduction protocols, insurance/mortgage purposes, "curiosity," patient-reported symptoms, the absence of prior genetic confirmation in families with a clinical diagnosis of HD and to plan social care in individuals with pre-existing learning or physical disabilities.

Test Outcomes

9372 tests (99.6%) were performed by direct mutation analysis characterizing the CAG repeat length. 27 tests (0.3%) were performed by linkage analysis and 8 participants had both tests (0.1%). The majority of linkage tests (93%) were carried out before 1994.

Of the 8441 predictive tests performed on individuals with an *apriori* risk of 50% from 1993-2014, 4629 (54.8%) were reported as gene negative (CAG repeat length <36) whilst 3790 (44.9%) were reported as gene positive (CAG repeat length ≥36). 22 results (0.3%) were missing or uninterpretable.

It is important to note that intermediate and reduced penetrance alleles were not reported on uniformly and consistently from the outset of the study so the raw figures from 1993-2014 cannot

be used to quantify reliably the frequency of these alleles in the 50% at-risk population. To assess this more accurately, a subgroup analysis was performed on the predictive tests performed from 2010 onwards, by which point the vast majority of centres had begun to report on intermediate and reduced penetrance alleles. From 2010-2014, 77 results were reported as intermediate alleles (4.2%) and 82 results were reported as reduced penetrance alleles (4.5%). The outcomes of predictive testing are summarised in **Table 2.**

Cumulative Uptake of Predictive Testing

From 1994-2014, after imputation of minimal missing data, 8113 predictive tests performed on participants aged ≥ 18 and with an *apriori* risk of 50% were recorded in the database. After imputation of minimal missing data, an estimated 8382 predictive tests were performed in the same group. **Figure 1** illustrates the selection criteria for cases for the analysis of the cumulative uptake of predictive testing.

Cumulative uptake of predictive testing over the study period (1993-2014) was calculated using the Tassicker formula described in the Methods:

Uptake (%) =

= 17.4%

The calculated cumulative uptake of predictive testing in the eligible population at 50% risk of HD from 1993-2014 is 17.4% (95% CI 16.9%, 18.0%). This is based on a prevalence figure in adults of 12.3 per 100 000 and on the ratio of symptomatic HD cases to population at 50% risk of developing HD as being 1:4.2. **Figure 2** illustrates the cumulative uptake of predictive testing in the 50% at-risk population from 1994-2014 over time. **Table 3** shows the cumulative uptake estimates assuming alternative prevalence figures and ratios of symptomatic individuals: 50% at risk individuals.

DISCUSSION

Main Findings

The data presented here represents the largest study ever conducted on the uptake of predictive testing for Huntington's disease in a single population. Over a 22 year period from 1993-2014, 9407 predictive tests were recorded and the estimated cumulative uptake of predictive testing for the UK population at 50% risk of developing Huntington's disease from 1994-2014 was 17.4% (95% CI 16.9%, 18.0%).

Several previous studies of predictive testing in Huntington's disease have overestimated the cumulative uptake of tests by the at-risk population by not correcting for the fact that the at-risk population is dynamic and increases over the study period. Our group previously reported a similar cumulative uptake figure of 18% after only four complete years of predictive testing (1993-1997) (8); this represents an overestimation of the uptake of predictive testing in 1997 as the former study used a lower prevalence of 7.5 per 100 000 and does not correct for the increasing at-risk population over time.

Table 4 summarises the key features of other studies of the uptake of predictive testing in Huntington's disease. Our estimated uptake of 17.4% is comparable to figures of 12.3-14.6% in Northern Ireland (10) and 15.4% in Victoria, Australia (9) where the Tassicker formula (9) was applied. In the remaining studies, the reported uptake of predictive testing varies from 5% - 44.7%, however, it is imperative to note that there are major methodological differences in the approaches to these uptake calculations that invalidates a direct comparison with our findings. For instance, in Slovenia, where an uptake figure of 44.7% was reported, the authors included tests performed on those at *apriori* risks <50% and expressed uptake as the fraction of tests performed on those identified at-risk from their registries and medical records rather than the estimated at-risk population (18); using this method, any incomplete ascertainment of at-risk individuals will lead to

an overestimate of cumulative uptake. The sources of variation in uptake measurements are summarised in **Table 5.**

A low uptake of predictive testing in Huntington's disease has been consistently reported in several different populations. Broadly, this may be explained by factors related to autonomous decision making by individuals or by issues related to accessing services. The individual choice to undertake predictive testing may be affected by the absence of disease modifying treatments, anxiety about an abnormal result, the financial implications of an abnormal result, personal experiences caring for relatives with Huntington's disease or perceived stigma associated with the condition. Barriers to accessing predictive testing may include the travel requirements required to access counselling and testing services, the stress of travelling, opportunity costs of missed work or time with family members, the inflexibility of the testing process and difficulty in accessing support (19). Furthermore, many at-risk individuals may not necessarily be aware that a relative has been diagnosed with the condition and, therefore, will not be able to access testing services; this may be more true of individuals with an *apriori* risk of <50%. In the United Kingdom, 23 centres offer predictive testing so the geographic barriers to testing may be less influential in determining the uptake rate.

Of the 9199 predictive tests where the gender was recorded, 55.7% of the participants were female. This is consistent with the majority of studies of uptake in predictive testing where there is a slight female preponderance among those tested (18, 20-26). Several theories have been proposed to explain this finding; it may be that females are more likely to address questions relevant to reproductive planning and may feel better equipped to cope with an abnormal result (27).

The median age for participants who underwent predictive testing was 37. This is slightly higher than Greece (21), Slovenia (18) and France (20) but slightly younger than the figures of 39.3 and 41

reported in Canada (24) and Victoria (25), respectively. An interesting finding was that 6.2% of tests were performed on participants aged >60 years old. As life expectancies increase, there may be a trend towards the presentation of Huntington's in later life. Interestingly, the frequency of reduced penetrance alleles in the 50% at-risk group > 60 years old was 6.4% compared to 4.5% for all age groups at 50% risk.

Of the predictive tests performed on participants with an *apriori* risk of 50%, 54.8% were gene-negative whereas 44.6% were gene positive. The tendency to acquire slightly more normal results when the expected frequencies would be 50:50 is a phenomenon that is consistent with other studies (18, 20, 22, 24, 26). This may be explained by the fact that the 50% risk of developing Huntington's disease is the risk at birth and those who are asymptomatic in adult life when they present for testing have a slightly reduced risk by virtue of the fact that they have not developed symptoms thus far. In keeping with this, we observed a lower frequency of abnormal results in the higher age groups (data not shown).

Genotypes with intermediate alleles (IAs) and reduced penetrance (RP) alleles were recorded consistently from 2010 onwards with their observed frequencies in the 50% at-risk population being a minimum of 4.2% and 4.5%, respectively. Sequeiros *et al* assessed CAG repeat length in the general population in Portugal and determined the frequency of genotypes with intermediate alleles (IAs) and reduced penetrance (RP) alleles to be 6% and 0.1%, respectively (28). In Canada, the corresponding figures were 5.8% and 0.4%, respectively (29).The current study demonstrates a higher proportion of reduced penetrance alleles in the predictive testing population and is in keeping with Sequeiros' figure of 4.8% in the Portugese predictive testing population (28). Furthermore, the current study only reports on the largest allele size; therefore, it may underestimate the presence of an additional IA/RP allele in genotypes where a larger CAG expansion was present.

The participant-reported reasons for undergoing predictive testing were recorded for 4743 (50.4%) individuals. Decreasing uncertainty was the most commonly cited reason for having the predictive test with future and family planning also being important factors. It is important to note that whilst an abnormal predictive test informs the testee they will develop the disease, it does not predict the age of onset, thereby introducing a different type of uncertainty. Furthermore, a result demonstrating a reduced penetrance allele once more maintains a level of uncertainty. These reasons are similar to those given by participants when predictive testing was first introduced (30). One can anticipate that the development of effective disease-modifying therapies targeted at those in the pre-symptomatic phase of the disease would provide a major reason for at-risk individuals to undergo predictive testing.

Limitations of the current study

In the current study, basic information on participants undergoing predictive testing was collected annually from 23 centres over a 22 year period. Over the course of the study, some centres did not provide data for every year of predictive testing (overall, a maximum of 5.4% of yearly centre-level reports were missing; therefore, imputation of missing data was required to calculate more reliably an estimate of cumulative uptake of predictive testing. In some instances, there was incomplete or uninterpretable information on prior risk, gender and test results recorded on the database. A further issue is that the codes of practice were not standardised across the 23 centres and multiple laboratories; for example, in some centres, individuals who presented as being at risk may have had neurological signs of HD but still went through a predictive testing protocol rather than diagnostic testing.

The Tassicker method for calculation of the cumulative uptake of testing relies on an accurate

measure of prevalence for Huntington's disease in the adult population and the ratio of symptomatic cases:population at 50% risk (9). Based on highest quality and most current evidence we estimated these to be 12.3 per 100 000 adults and 1:4.2, respectively. The UK prevalence of HD is a contentious issue: two recent studies calculating prevalence figures based on two different GP research databases in the UK gave vastly different estimates of 5.96 (from The Health Network Improvement database) (12) and 12.3 (from the General Practice Research Database) (13) per 100,000 of the population. This significant discrepancy can be explained, in part, by the fact that the former study looked at the prevalence in the whole population whereas the latter exclusively looked at the population over 20 years old (14); the significance of this is that the prevalence of cases under the age of 20 years is lower. In the present study, the figure of 12.3 per 100 000 in the over-20 population was used to calculate the cumulative uptake of predictive testing over the study period. The rationale for this is that, firstly, it is based on recent evidence and, secondly, the present study is principally interested in the prevalence in the adult population who can reliably give informed consent for predictive testing.

If our parameter estimates are inaccurate, then the estimated cumulative uptake figure will vary. However, as the sensitivity analysis shows, regardless of the probable parameter estimates used, less than 27% of individuals of individuals at 50% risk of HD have taken the predictive test and our best estimate is that the cumulative uptake of predictive testing is approximately 17.4% (95% CI 16.9% to 18.0%)

Another limitation of the Tassicker method is the assumption of a constant disease duration throughout the course of the study. We used the average disease duration from symptom onset to death as being 18.8 years based on the average of two large cohort studies, however, it may be argued that the disease duration has increased over the last 22 years with the provision of the direct mutation test giving earlier diagnoses and minor improvements in survival due to medical, nursing

and social care interventions.

Conclusion

The current study identifies that the vast majority of those at-risk of HD in the UK (more than 80%) have not participated in the predictive testing program. This is likely to be due to a combination of factors including the reluctance to undertake testing in the absence of disease-modifying or neuroprotective therapies and barriers to testing and accessing appropriate services. There are a number of clinical trials which are currently enrolling and ongoing (31). If even a single study agent shows a neuroprotective effect in Huntington's disease, then an awareness of size of the at-risk population who have not yet had their gene status confirmed is necessary in order to optimally plan intervention in the pre-symptomatic phase of the illness.

TABLES

Table 1
Demographic information and apriori risk of participants undergoing predictive testing (1993-2014)

Variable	
Gender	
Male	4077 (43.3%)
Female	5122 (54.4%)
Missing information	208 (2.2%)
Total	9407
Age	
< 18	68 (0.8%)
18-30	2776 (29.5%)
31-40	2681 (28.5%)
41-50	2001 (21.3%)
51-60	1151 (12.2%)
> 60	586 (6.2%)
Missing information	144 (1.5%)
Total	9407
Median age (IQR)	
Male	37 years (29-47)
Female	37 years (29-48)
Overall	37 years (29-47)
Apriori risk of Huntington's disease	
12.5%	13 (0.1%)

25%	642 (6.8%)
50%	8441 (89.7%)
Other/missing information	311 (3.3%)
Total	9407

Table 2
Results of predictive testing for individuals with an apriori risk of 50%

Outcome	
1993-2014	
Negative (<36 repeats)	4629 (54.8%)
Positive (≥ 36 repeats)	3790 (44.9%)
Result missing/uninterpretable	22 (0.3%)
Total	8441
2010-2014	
Normal (0-27 Repeats)	857 (46.9%)
Intermediate Alleles (28-35 repeats)	77 (4.2%)
Reduced Penetrance Alleles (36-39 repeats)	82 (4.5%)
Affected (40+ repeats)	812 (44.4%)
Total	1828

Table 3
Alternative calculated figures of of cumulative uptake of predictive testing based on alternative parameter estimates

UK Prevalence of HD (per 100 000 adult population)	Ratio of symptomatic individuals to individuals at 50% risk of developing HD.	Calculated Cumulative Uptake (95% CI) (%)
8	1:4.2	26.8 (25.9 – 27.6)
8	1:5	22.3 (21.6 – 23.0)
10	1:4.2	21.4 (20.7 – 22.1)
10	1:5	17.8 (17.3 – 18.4)
12	1:4.2	17.8 (17.3 – 18.4)
12	1:5	14.9 (14.4 – 15.3)
12.3	1:4.2	17.4 (16.9 – 18.0)
12.3	1:5	14.5 (14.0 – 15.0)
13	1:4.2	16.5 (16.0 – 17.0)
13	1:5	13.7 (13.3 – 14.2)

Table 4
Studies of Uptake of Predictive Testing in Huntington's disease

Population	Study Period	Reported HD Prevalence (per 100 000)	Number of Completed Tests	Use of the Tassicker Formula	Reported Uptake (%)	Author
EUROPE						
France	1993-1999	5	409	No	5	Goizet
Greece	1995-2008	5.4	256	No	8.6	Panas
Netherlands	1987-1997	6.5	752	No	24	Maat-K
North-Rhine Westfalia, Germany	1993-2004	10	248	No	-	Bernha
Northern Ireland	1990-2009	10.6	212	Yes	14.4-14.6	Morris
Slovenia	1997-2007	5.16	68	No	44.7	Peterli
United Kingdom	1987-1997	7.5	2722	No	18	Harper
NORTH AMERICA						
Canada	1987-2000	8.4	1061	No	18	Creigh
Montreal, Canada	1994-2008	-	135	No	9.2	Dufras
AUSTRALIA						
Victoria, Australia	1996-2003	8	333	Yes	15.4	Tassick

Table 5

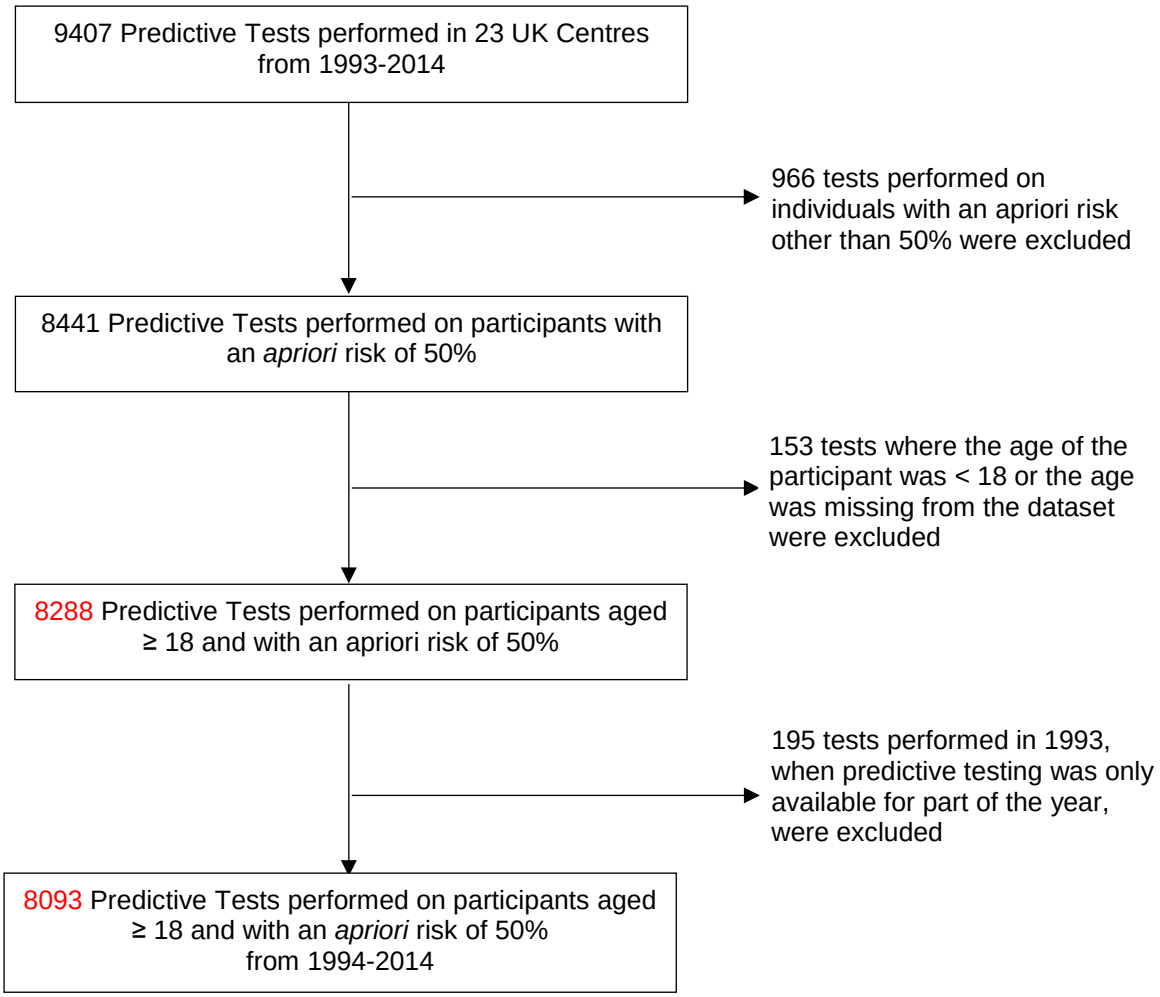
Sources of variation in estimated cumulative uptake of predictive testing in different studies

Sources of Variation	
Potential overestimation	Inclusion of tests performed on those with apriori risk of 25% in the numerator but not the denominator. [Maat-Kievit *et al*]
	No adjustment for the increasing number of at-risk individuals over the study period [Goizet *et al,* Panas *et al,* Bernhardt *et al*, Harper *et al*, Creighton *et al*, Dufrasne *et al*]
	Expressing uptake as the fraction of tests performed in individuals who engaged in the counselling process rather than the estimated at-risk population [Bernhardt *et al*]
	Expressing uptake as a fraction of tests done in individuals registered being at-risk on HD registries rather than the estimated, total at-risk population. [Maat-Kieivit *et al*]
	Use of the Conneally ratio of symptomatic individuals: 50% at risk individuals as being 1:5 on theoretical grounds which may overestimate the at-risk population when compared to the ratio of 1:4.2 given found empirically. [Creighton *et al*, Panas *et al*]
	Underascertainment of HD cases may underestimate disease prevalence and thereby underestimate the population at 50% risk.
Potential underestimation	Inclusion of individuals under 18 in the at-risk population who generally unable to access predictive testing. Those under 18 may represent 5.6-9% of the 50% at-risk population. [Harper *et al*, Creighton *et al*, Panas *et al*]

FIGURES

Figure 1

Selection of Cases for Analysis of Cumulative Uptake



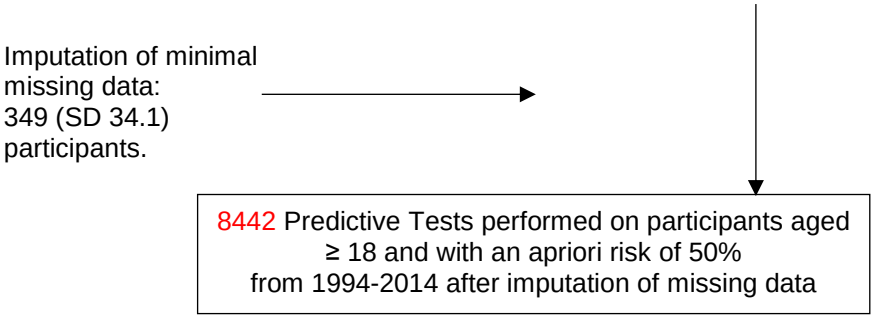
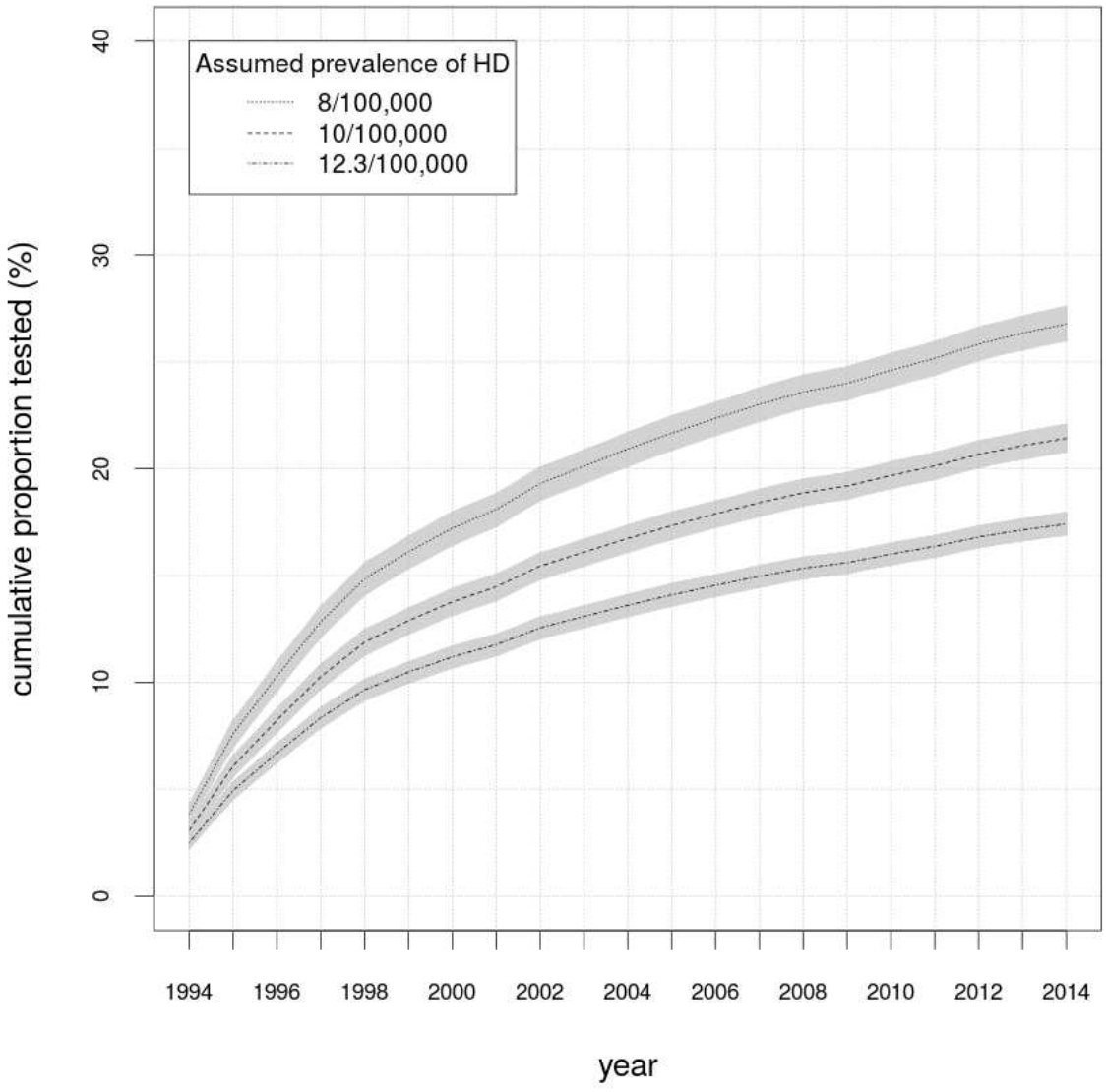


Figure 2

Cumulative Uptake of Predictive Testing for HD in the 50% at-risk population assuming different prevalence estimated for HD in the UK adult population (shaded bars represent 95% confidence intervals).



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