THE EPIDEMIOLOGY OF HUNTINGTON DISEASE IN BRITISH COLUMBIA

by

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BSc, The University of British Columbia, 2012

THESIS SUBMITTED IN PARTIAL FUFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

in

The Faculty of Graduate Studies

(Medical Genetics)

THE UNIVERSITY OF BRITISH COLUMBIA
(Vancouver)

September 2012

Abstract

Introduction: Global prevalence estimates for Huntington Disease (HD) vary widely, and those cited for Canada are outdated and not specific to British Columbia (BC). The most recent incidence calculation was performed in BC and includes diagnoses only up to the year 1999. Reports on the population at risk in Canada are based on theories and estimates that do not pertain to any particular population. Despite the presence of an extensive laboratory and clinical research hub in this province, a comprehensive epidemiological study of the prevalence, incidence and population at risk for HD has never been assessed. As such, the specific objectives of this study were to: 1) Calculate the minimum prevalence of HD in BC on April 1, 2012; 2) Calculate the incidence of HD in BC from January 1, 2001- December 31, 2011; and 3) Calculate the minimum population at risk for HD in BC on April 1, 2012.

Methods: A comprehensive province-wide assessment of the HD patient population and the population at risk was conducted using multiple sources of ascertainment including: UBC HD clinic records, hospital and physician records, DNA diagnostic lab reports, the HD research lab at the Centre for Molecular Medicine and Therapeutics (CMMT), nursing homes, The Huntington Society of Canada and HD community members.

Results: The minimum prevalence of HD in BC was estimated at 12.5 - 14.9/100,000 (95% CI: 11.5-16.0) (1/8,697 – 1/6,250), the incidence, 7.2 per million/year (95% CI: 6.5-7.9), and the minimum population at risk: 1/1,064 (95% CI: 1/1,941 - 1/2,107).

Conclusions: The prevalence of HD is nearly twice as high as suggested by a previous Canadian report. This study comprised the most thorough HD patient ascertainment study since the advent of direct mutation testing and may set a precedent for future prevalence studies. Incidence has remained the same since 1999 and BC is only the fourth region in the world to provide a direct estimate of the population at risk for HD.

Preface

Study methods were approved by the Children's and Women's Research Ethics Board (H10-00943). The Cure Huntington's Disease Initiative (CHDI) provided funding for this project (CHDI, 2012).

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Acknowledgements

First, I would like to acknowledge my thesis supervisor, Dr. Michael Hayden, for providing me with the opportunity to reach my potential. Only accepting excellence and nothing less is Dr. Hayden's way and I know that his influence will change the way that I analyze and attempt to solve problems for the rest of my life. I would also like to thank my supervisory committee, Susan Creighton and Jan Friedman for taking the time out of their extraordinarily busy schedules to show me the ropes and critique my research. I would like to mention Alice Hawkins, who has gone above and beyond in ensuring my experience in graduate school has been successful. She has been a mentor to me. Thank you as well to Jennifer Collins, who provided major assistance in setting up the HD database for this project and to Alicia Semaka, for allowing me to work with her as a summer student and for supporting my decision to join the lab as a graduate student. Thank you to the whole HD research lab for providing their expertise and insight whenever asked and for being unconditionally helpful. Finally, thank you to my family, mom, and dad, Ben, Gillian, Sara, Andrew and David. You all inspire me and have been role models for me since day one. I do not know where I would be without you.

Introduction

Background

Huntington Disease

Huntington Disease (HD) is a neurodegenerative disorder characterized by autosomal dominant inheritance. Symptoms include psychiatric disturbances, cognitive decline and neurological abnormalities such as chorea, dystonia and rigidity (Tabrizi et al. 2009). Onset can occur at any time of life but most commonly arises in the mid 40's (Kirkwood, et al. 2001). George Huntington described HD in the 1872 and observed the autosomal dominant inheritance pattern (Huntington G, 1972). In 1987, the linkage test for HD became available. In this test, restriction fragment length polymorphisms (RFLPs) were analyzed in multiple family members in order to obtain results for one individual. Certain RFLPs segregated only with affected family members. Inferences could thus be made on whether the individual in question carried the mutation responsible for HD prior to the gene discovery (Gusella 1987). Linkage analysis was mainly used for pre-symptomatic (predictive) testing, but in some cases, aided in confirmation of diagnoses (S. Creighton, personal communication, 2012). British Columbia was the first place in the world to offer predictive testing for HD using the linkage technique (Fox et al. 1989). In 1993, the specific mutation responsible for HD was identified and the direct mutation test became available. This test was used for both predictive and diagnostic purposes. Direct mutation test results are more accurate than linkage test results and contrary to linkage – requiring the analysis of multiple family members – individuals undergoing the direct mutation test are able to do so independently. It was found that an individual with 36 or more CAG repeats in the HTT gene (4p16.3) will likely become affected with HD in her lifetime (MacMillan et al. 1993). Clinical data have led to the classification of CAG sizes into four specific ranges: fewer than 27 repeats result in a normal phenotype; intermediate alleles (IAs) comprise a range of 27–2 repeats – IAs are below the affected CAG repeat range, but are thought to carry a risk of expansion into the disease range within one generation; 36–39 repeats are

considered abnormal but are associated with reduced penetrance (RP) - age of onset for RP allele-bearing individuals may be either very late or may not occur at all (Quarrell *et al.* 2007); forty CAG repeats or greater - lifespan permitting – invariably give rise to HD. Evidence suggests that the age of symptom onset for HD is inversely correlated to the individual's specific CAG repeat length; an individual with a CAG repeat length in the lower range is likely to develop HD symptoms later in life and vice versa (Langbehn, et al. 2004).

Epidemiology of Huntington Disease

Prevalence is the proportion of a population affected with disease during a defined period of time (Rothman 2002). Prevalence has been the central focus of epidemiological assessments on HD to date (Table 1, Appendix 1a,b). *Incidence* is the rate of new diagnoses and has been studied less than prevalence. The *population at risk* is the proportion of a population that is living during a defined period of time who are likely to become affected with disease in the future (Rothman 2002). The population at risk for HD has been given little attention (Table 1).

The majority of studies on prevalence took place prior to the advent of the linkage or direct mutation test for HD (Appendix 1a), and all prevalence studies in Canada were performed before either type of testing was available (Barbeau et al. 1964, Shokeir, 1975). Global prevalence estimates range from 0.01/100,000 (1/10 million) in South Africa (Hayden et al. 1980), to 46.2/100,000 (1/2,000) on the Island of Mauritius (Hayden et al. 1981). In addition, an extraordinarily high prevalence of 699.2/100,000 (1/143) was reported for the Lake Maracaibo region of Venezuela. This abnormally high prevalence in Venezuela along with those from Mauritius and from the Genoa region of Italy (Appendix 1) have all been attributed to extreme founder effects or insufficient sample population sizes (Young et al. 1986, Roccatagliata et al. 1983). The average global prevalence including Lake Maracaibo is 11.2/100,000 (1/8,929), while that excluding this region is 5.1/100,000 (1/19,608) (Appendix 1). The global prevalence while excluding all three of these disproportionately large estimates is 4.5/100,000 (1/22,000). When

considering only studies performed after the availability of the direct mutation test, the global average is again 5.1/100,000 (1/19,608) (Table 1).

Table 1. Estimates of HD prevalence, incidence and population at risk that took place after the advent of the direct mutation test (post 1993)

Region	Study year	Prevalence (#/100,000) (1/X)	Incidence (#/million/year)	Pop. At 50% risk (#/100,000)	References
Switzerland & Austria	1993-1997	10.0**		-	(Laccone et al. 1999)
Germany	1993-1997	10.0**	-	30.0*	(Laccone et al. 1999)
British Columbia	1993-2000	-	6.9	42.0*	(Almqvist et al. 2001, Creighton et al. 2003)
Australia	1999	8.0	-	33.9	(Tassicker et al. 2009)
Malta	1994	11.8	-	-	(Gassivaro Gallo et al 1999)
Spain	1994-2002	-	4.7	-	(Ramos-Arroyo et al. 2004)
Greece	1995-2008	2.5-5.4	3.3	-	(Panas et al. 2011)
Australia - New South Wales	1996	6.3	-	-	(McCusker et al. 2000)
Japan	1997	0.7	-	-	(Adachi & Nakashima 1999)
Northern Ireland	2001	10.6	-	44.9	(Morrison et al. 2010)
The Netherlands	2002	6.5	-	32.5	(Maat-Kievit et al. 2000)
Croatia	2002	1.0	-	-	(Hecimovic et al. 2002)
Slovenia	2006	5.2	-	-	(Peterlin et al 2008)
Venezuela	2007	0.5	-	-	(Paradisi et al 2008)
Taiwan	2007	0.4	1.0	-	Chen and Lai 2010
Mexico	2008	4.0	-	-	(Alonso et al 2009)
UK	2008	5.9-6.5	6.1	37.5*	(Sackley et al 2011)
England & Wales	2010	12.4	-	-	(Rawlins 2010)
Global average		**5.1**	**5.7**	**34.0**	

* Indirect assessments of the population at risk that have been calculated from estimates of prevalence
** Published estimates not based on exact, but approximate patient and general population numbers

The prevalence of HD appears to vary widely across ethnic populations and geographic regions (Figure 1, Figure 2, & Figure 3 and appendix 1a). A long-standing question is whether these observed fluctuations are due primarily to variation in ascertainment precision or due to true differences in prevalence

(Myrianthopoulos 1966). Evidence suggests that HD prevalence in populations of Asian and African descent is significantly lower than HD prevalence in populations of European descent (Figure 3) and thus HD is thought to have arisen in Northern Europe (Warby et al. 2009). The mean prevalence for all studies performed in populations of European descent is 5.8/100,000 (1/17,241) and for populations of Asian descent it is 0.62/100,000 (1/161,290) (Figure 3). The mean prevalence of all studies performed in populations of African descent is 2.8/100,000 (1/35,714); this is lower than the European average (Figure 3). However, prevalence estimates from African populations range widely, from 0.01-7.0/100,000 and all reports from this region are outdated (Appendix 1). Further work is thus required in order to gain a greater understanding of the true prevalence in these populations. Only two prevalence studies have ever taken place in Canada. The first, conducted in Quebec in 1964, found a prevalence of 3.4/100,000 (1/29,412) (Barbeau et al. 1964) and the second, conducted in Saskatchewan and Manitoba in 1975, estimated a prevalence of 8.4/100,000 (1/11,905) (Shokeir 1975).

Figure 1. Global prevalence averages (#/100,000) by region. The Americas: 4.2, Europe: 5.8, Africa: 2.8, Asia: 0.62 and Australia & New Zealand: 6.8

Appendix 1 provides a full list of individual studies and their corresponding references

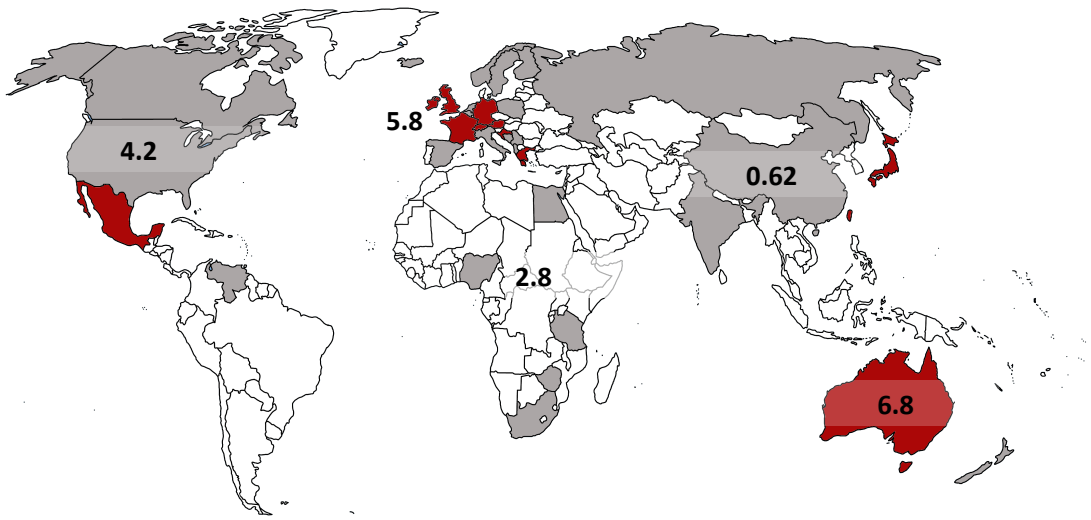


Figure 2. The average of all reports on HD prevalence for each region. Bar colours represent the diagnostic techniques available during the study period

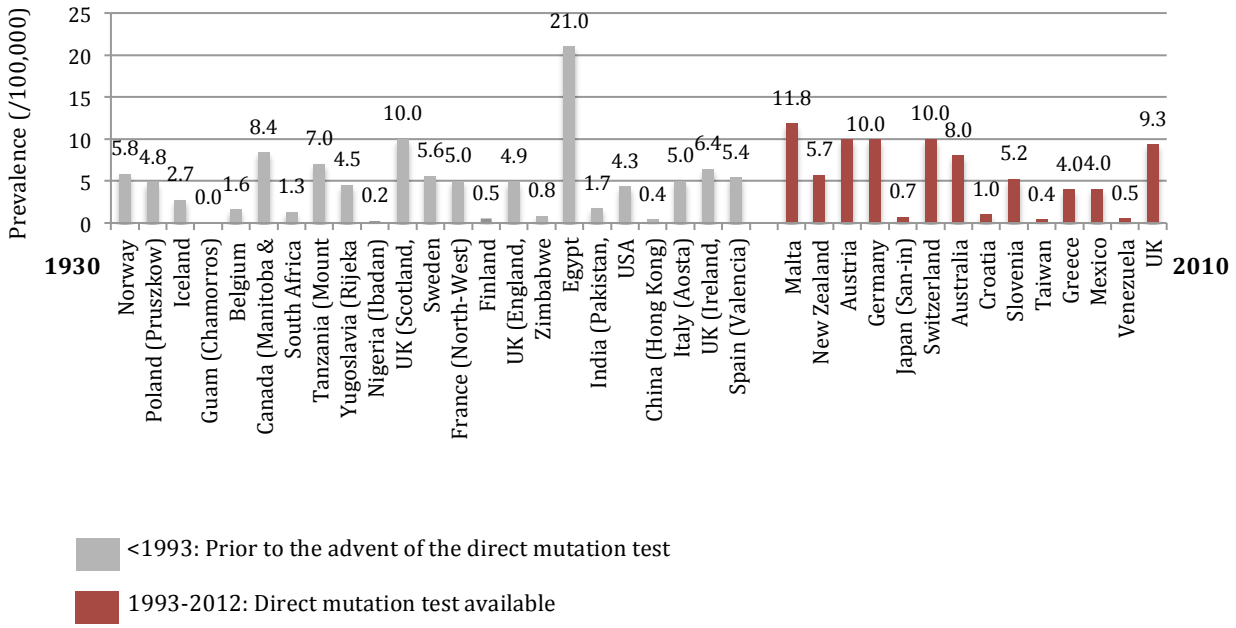
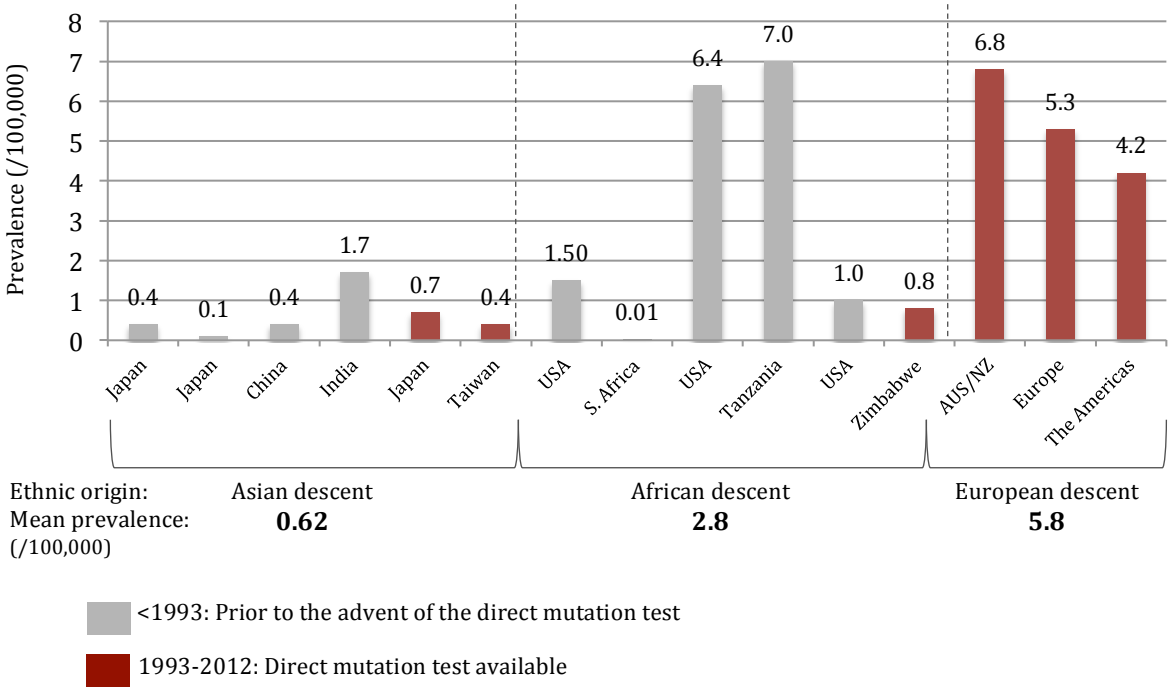


Figure 3. Comparison of HD prevalence averages between populations of Asian, African and European descent.



The incidence of HD ranges globally from 1.0 per million/year in Taiwan (Chen and Lai, 2010) to 6.9 per million/year in British Columbia (Almqvist et al. 2001). To our knowledge, only seven assessments of incidence have taken place worldwide, two of which were performed prior to the advent of the genetic test (Appendix 1b). The availability of the genetic test, in addition to improving diagnostic accuracy, has simplified the ascertainment of new HD cases. The average global incidence of HD, when accounting only for those studies that took place after 1993, is 5.7 per million/year (Table 1).

The population at risk for HD has received little attention (Table 1). With the exception of three studies, estimates of the population at risk have been calculated only from estimates of prevalence. These exceptional studies include one from the Netherlands, one from Victoria, Australia, and one from Northern Ireland, all of which utilized electronic registries to calculate the population at 50% risk directly (Maat-Kievit et al. 2000, Tassicker et al. 2009, Morrison et al. 2011)[1, 2, 3]. For the remaining studies, the population at 50% risk has been calculated by multiplying the prevalence by three or by five depending on the specific study in question (Taylor 1994, Laccone et al. 1999, Maat-Kievit et al. 2000, Harper et al. 2000, Goizet et al. 2002, Creighton et al. 2003). Multiplying the prevalence by five was provoked by Conneally's theory (Conneally, 1984). This theory suggested that each individual has on average five first-degree relatives; thus for every individual affected with HD, there are likely to be five individuals at 50% risk. Only one study has estimated the population at risk by calculating the affected population by three and did not provide an explanation as to why this number was chosen (Laccone et al. 1999). A full review of the population at 25% risk has yet to be studied in a population.

There have been several accounts worldwide of the estimated uptake of predictive testing for HD in Caucasian populations (Taylor 1994, Lacconne et al. 1999, Maat-Kievit et al. 2000, Harper et al. 2000, Goizet et al. 2002, Creighton et al.

[1] The Leiden roster is a database containing information on every individual who attended one of the eight clinical genetic departments in the Netherlands for HD testing and counseling (Maat-Kievit et al. 2000).
[2] The Victoria registry is a database of individuals affected with and at risk for HD. This registry began in 1950 and has been up kept ever since (Tassicker et al. 2009).
[3] The Northern Ireland HD register is a database of individuals affected with and at risk for HD. This register began in 1976 and only contains data up to 2005 due to software incompatibility issues involving the hospital database system (Morrison et al. 2010).

2003, Tassicker et al. 2009, Morrison et al. 2010, Bernhardt et al. 2009). Uptake is defined as the number of individuals who have undergone predictive testing as a proportion of the number of individuals estimated to be at 50% risk in the population and is expressed as a percentage (Tassicker et al. 2009). Reports of uptake range from 3% in Germany, Switzerland and Austria (Lacconne et al. 1999), to 25% in the Netherlands (Maat-Kievit et al. 2000). An uptake of 21% was calculated for British Columbia for the years 1987-2000 (Creighton et al. 2003). As stated above, the population at 50% risk, with the exception of few studies, has been estimated from the assumed prevalence lending a high possibility for inaccuracy in calculating the uptake. In 2009, Tassicker et al. proposed that all previous accounts of uptake were likely overestimated. This report suggested that every previous calculation failed to take into account the study period. During the study period, the population at 50% risk may change, thereby altering uptake results. Tassicker et al. suggested a formula that would account for the study period and showed that by using this formula, when compared to conventional methods, the uptake of predictive testing in Victoria Australia had decreased by nearly half.

Rationale

1. Updated and accurate epidemiological assessments for HD are required:

It is important to acquire accurate epidemiological assessments for HD. Firstly, these assessments allow for the appropriate planning of services and allocation of resources for those populations in need. Furthermore, accurate assessments allow for meaningful comparisons of HD epidemiology to be performed across populations and over time. With a clearer understanding of true differences in HD epidemiology amid discrete populations, efforts towards studying genetic factors that underlie these differences can be more efficiently designed (Warby et al. 2009).

Prevalence: The majority of HD prevalence assessments were performed prior to the advent of direct mutation testing for HD (Appendix 1a). These assessments are outdated and cannot be meaningfully compared to modern studies as the accuracy of diagnostic methods has since improved. However, when comparing studies performed post-1993, after the direct test became available, it is apparent that even these estimates vary widely (Table 1, Figure 2). It is uncertain as to whether the bulk of this variation is due primarily to differences in ascertainment precision or to true differences in prevalence across populations. In order to minimize the possibility of under-ascertainment, as many ascertainment sources as possible should be used. An extensive search for secondary cases (i.e. affected patients found via family survey as opposed to chart review) is also essential (Harper, 1992, Levy and Fenigold, 2000). The majority of the post-1993 assessments of HD prevalence used less than three ascertainment sources, with three being the maximum number of sources used (Peterlin 2009). Furthermore, the most recent study took place in the United Kingdom (UK) in 2010, and, although estimating a prevalence of 12.4/100,000 (1/8,065), nearly double what a previous UK assessment found (Sackley et al. 2011), this study used only one ascertainment source and requires revision to achieve more accurate results (Rawlins 2010). A thorough multi-source ascertainment study is required in order to obtain an updated and accurate estimate of prevalence that is capable of setting a precedent

for future studies and can be compared with confidence to findings from other regions.

Incidence: The most recent incidence calculation for HD was conducted in the UK in 2008 (Sackley, et al. 2011). Only seven estimates of incidence have been performed to date, two of which took place before genetic testing became available (Appendix 1b). One of these incidence studies is from BC and included diagnoses from 1993-1999; all diagnoses from this study were confirmed with diagnostic testing (Almqvist et al. 2001). In order to maintain accuracy in incidence estimates and to observe variation in incidence over time, it is important that these numbers are updated. With 12 additional years of available clinical and genetic data for HD, incidence can be updated in BC at this time.

Population at risk: Worldwide reports on the population at risk for HD are largely based on theories and estimates that do not pertain to any specific population and have been calculated from estimates of prevalence (Table 1). Patients with familial diseases such as HD are often asked to provide information regarding their family structure as a component of their clinical records. These pedigrees, which are necessary for estimating the population at risk, are readily available from Vancouver's HD clinic. Knowledge of the number and geographic distribution of individuals at risk for HD is essential in care and service planning for the HD community. The population at risk should be studied empirically from family pedigrees in order to provide a comparison to those estimates based on the predicted prevalence and the average number of first-degree relatives in a population. Furthermore, the number of first-degree relatives varies significantly between populations (CIA World Factbook 2012), and recent evidence suggests that multiplying the prevalence by a factor of 4.2 – as opposed to the previous notion of 5 – may be more accurate. It is important to update the calculation of predictive testing uptake. Firstly, the equation for calculating uptake has changed since BC's latest estimate (Tassicker et al. 2009, Creighton et al. 2003), and second, empirical evidence regarding the population at 50% risk will become available from this study. As a result, the calculation of uptake can be compared in two ways in BC: from empirical data, and from theoretical data.

2. British Columbia is an appropriate model for this study:

There is ample opportunity for complete ascertainment in British Columbia. One lab is responsible for performing all HD genetic tests for the entire province and one clinic serves as an HD care hub for BC. It is thus likely that every clinical and genetic diagnosis of HD in BC can be ascertained. Further, in 2000, it was shown that BC had provided a larger number of total genetic tests (predictive and diagnostic) for HD, proportional to its population size, than any other province in Canada, however, Quebec and Alberta were not included in this analysis (Creighton et al. 2003). Having been the first province to provide the predictive test, BC's population may have a greater awareness of the test as compared to other provinces. This further emphasizes the high potential for full ascertainment in BC. Further, as BC is a global hub for HD research and care and as there are many opportunities for patients and families to participate in clinical trials and other types of HD research, members of the HD community may be more likely to seek medical attention in this province than in regions offering no such services or opportunities; BC has a specialized HD medical clinic equipped with genetic counsellors, social workers, neurologists, psychiatrists, geneticists and an extensive research team, all with experience in HD-specific challenges. Furthermore, it has been suggested that the accuracy of epidemiological calculations may be improved with a population consisting of 500,000 to 5,000,000 people. Populations smaller than this are thought to be vulnerable to skewing due to large families and populations larger than this, vulnerable to incomplete ascertainment (Harper, 1992, Levy and Feingold, 2000). BC's population is within these suggested limits (British Columbia Statistics, 2012).

Specific objectives

In order to appropriately characterize the epidemiology of HD in BC, this study posed three main objectives:

1. **Calculate minimum prevalence of HD in BC**

   The first objective was to assess the number and approximate geographical location of symptomatic HD patients living in BC on April 1, 2012.

2. **Calculate minimum incidence of HD in BC**

   The second objective was to assess the number of new HD cases diagnosed each year between January 1, 2001, and December 31, 2011, and the positive diagnostic test-rate for HD in BC between 2000 and 2012.

3. **Calculate the minimum population at risk for HD in BC**

   The third objective was to assess the number of people living in BC on April 1, 2012 who were likely to develop HD in the future. There are two levels of risk category, *a priori* risk (i.e. 25% or 50%) and risk categories after accounting for genetic test results. This objective also included an assessment of the number and uptake of the predictive testing for HD in BC between April 1, 2000, and April 1, 2012.

Methodology

Epidemiology: definitions

Epidemiology is defined as the branch of medicine that deals with the incidence, distribution, and possible control of diseases and other factors relating to health in a population (J. Simpson 1989). Prevalence, incidence and population at risk are epidemiological assessments commonly studied for disease. *Prevalence* is a calculation of the total number of people affected with disease in a defined population at a point in time or over a range of time (Rothman 2002); prevalence is often expressed as the number of affected individuals per 100,000 in a population or 1 over X number of people where X indicates the average number of individuals that must be observed in order to detect one affected case. *Incidence* is a calculation of the number of people who are newly affected with a disease over time, the rate of new diagnoses (Rothman 2002); incidence is often expressed as the number of newly affected patients (incident cases) per million individuals per year. The *population at risk* refers to the proportion of a defined population at a specific point in, or range of, time that is likely to become affected with disease (Rothman 2002). Similar to prevalence, the population at risk is often expressed as the number of at-risk individuals per 100,000 in a population or 1 over X number of people. The risk of acquiring a disease depends on the genetics, transmission patterns and other external factors related to the specific disease at hand. For HD, the population at risk has been calculated largely from the prevalence (Taylor 1994, Harper et al. 2000, Goizet et al. 2002, Creighton et al. 2003). In doing so, the ratios of 1:3, 1:5 and more recently 1:4.2 (Tassicker et al. 2009) – number of individuals affected: number of individuals at 50% risk – have largely been used. An explanation of the 1:5 ratio is as follows. In theory, ½ of those at risk will carry the CAG expansion. A third of this ½ will be affected at any given time, leaving two thirds at risk. However, none of the other ½ at risk (who do not carry the mutation) will be affected, leaving all of this remaining ½ at risk. This results in a ratio of (**1**/3)**:**(2/3 + 1 = **5**/3) (Conneally 1984). An explanation was not provided for use of the 1:3 ratio (Laccone et al. 1999). The 4.2 ratio has been observed by two separate populations via empirical

data (Tassicker et al. 2009, Morrison et al. 2011) and thus may provide a more accurate measurement.

Population under review: British Columbia

The defined population in which the patient ascertainment took place is the province of British Columbia, Canada (BC). The population of BC for 2012 as projected by BC Statistics is **4,609,659** (Statistics BC, 2012). The last census took place in 2011, and the actual (non-projected) census population is not yet available. In order to assess the distribution of patients and individuals at risk for HD, the province was divided in two ways. First, BC was divided into "Rural" and 'Urban' regions. For the purposes of this study, cities that are more than two hours away from Vancouver by car were designated to the "Rural" category. Cities two hours or less from Vancouver by car, were designated to the "Urban" category. This definition renders some "Urban" centers – such as Victoria – as being "Rural" areas. Although this may seem counterintuitive, these specific categorizations were chosen in order to mirror the convenience in accessing the HD clinic in Vancouver. Individuals requiring specialized HD care or wishing to take part in HD research are required to commute to Vancouver to do so. As a result, more than two hours by car from these opportunities renders these seemingly larger "Urban" centers as being "Rural" for the purpose of this particular study. The second categorization involved dividing the BC into its constitutive provincial health regions. Provincial health regions are legislated administrative areas defined by the provincial ministries of health. These regions represent geographic areas of responsibility for hospital boards or regional health authorities. BC is made up of five health regions: the Northern region, comrising 7% of BC's total population; Interior health, comprising 17%; Fraser, 36%; Vancouver Coastal, 23% and Vancouver Island, 17% (Statistics Canada 2007, British Columbia Statistics 2010).

Defining an affected patient: Age at onset

Calculating the prevalence and incidence involves counting patients who experience *onset* of HD symptoms at a particular point in time. Therefore, it is

imperative to define what particular factors render a case of *onset*. Before the advent of direct mutation testing, the diagnosis of HD could only be made when characteristic neurological signs and symptoms and a positive family history of HD were present. Psychiatric and cognitive symptoms were often too general to entail a definitive diagnosis on their own (F. O. Walker 2007). Due to the availability of the direct mutation test, cases of onset have been defined in two ways for the purposes of this study. Affected patients are either considered "symptomatic HD positive", or "clinically diagnosed".

Symptomatic HD positive: A patient is considered to be "symptomatic HD positive" if they have received a positive result from the direct mutation test (HTT CAG size ≥36) and there is evidence, from physician notes, a family member, an HD community member or caregiver, that this patient has begun to exhibit neurological symptoms of HD. If no information is available regarding onset of the patient's disease symptoms, and the patient has undergone a Unified Huntington's Disease Rating Scale (UHDRS)[4] assessment, the date on which the patient first received a UHDRS diagnostic confidence score of ≥2 was used to define the date of onset. The UHDRS diagnostic confidence score is a value ranging from 0-4; zero means that no symptoms are present and 4 means that severe symptoms are present. The diagnostic confidence score is an average score taken from 30 specific motor tests (Huntington Study Group 1996). Although a motor score of 4 is used in detecting onset for studies that closely track the progression of specific disease symptoms (Orth and Schwenke, 2011), a minimum motor score of 2 was applied in this study as this score has shown to be sufficient in detecting noticeable motor symptoms in clinical practice (M. Hayden, personal correspondence, 2011).

[4] The Unified Huntington's Disease Rating Scale (UHDRS) is a research tool that was developed in 1996 by the Huntington Study Group (HSG) to provide a uniform assessment of the clinical features and course of HD. The UHDRS has undergone extensive reliability and validity testing and has been used as a major outcome measure by the HSG in controlled clinical trials. The components of the UHDRS are Motor Assessment, cognitive Assessment, behavioral Assessment, independence Scale, functional assessment and Total Functional Capacity (Huntington Study Group 1996).

Clinically diagnosed: A patient is considered to be clinically diagnosed if it is clear that this patient has a positive family history of HD *and* there is evidence (from physician notes, a family member, an HD community member or caregiver) that this patient is exhibiting neurological symptoms of HD. These patients have not undergone the direct mutation test or their results are not available for review. Like the "symptomatic HD positive" patient, if there is no information available regarding onset of the patient's disease symptoms, and the patient has undergone a United Huntington's Disease Rating Scale (UHDRS) assessment, the date on which the patient first received a UHDRS diagnostic confidence score of ≥2 was used to define the date of onset.

Sources of Ascertainment

In order to obtain a comprehensive ascertainment of HD cases in BC, multiple ascertainment sources were used:

1) **The HD clinic at UBC Hospital in Vancouver BC**. The UBC HD clinic has served patients and families affected with or affected by HD since 1983. Multidisciplinary teams including geneticists, neurologists, psychiatrists, a social worker, and a genetic counsellor work together at the clinic (Centre for Huntington Disease 2011). The HD clinic is a major hub for clinical research and medical care; HD patients and families from across the province and from out of province attend this clinic. In addition to symptom management, the HD clinic offers predictive and diagnostic testing and counselling for HD and was the first place in the world to provide the predictive test in 1987 (Fox et al. 1989).
2) **The Medical Genetics department at Victoria General Hospital (VGH).** This department houses specialized professionals who serve the HD community of British Columbia's Islands. VGH Medical Genetics offers genetic counselling and predictive and diagnostic testing for HD but is not involved in the same clinical research as the UBC HD clinic.
3) **The research laboratory at the Centre for Molecular Medicine and Therapeutics (CMMT).** Dr. Michael Hayden's HD research lab at the

CMMT was the sole facility in BC responsible for performing linkage analysis (1987-1993) and direct mutation testing (1993-2001) for HD until 2001.

4) **The DNA diagnostic laboratory at Children and Women's Hospital in Vancouver (C&W).** This lab has been and continues to be the sole facility in BC responsible for performing predictive and diagnostic testing for HD since 2002.
5) **Medical records** from BC General Practitioners, Neurologists and all additional physicians in BC who have sent DNA to the Diagnostic lab.
6) **The Huntington Society of Canada (HSC) and HD genetic counsellors**. The BC resource director for the HSC and HD genetic counsellors were in frequent contact with the primary researcher for the duration of this study. These individuals work directly with HD patients and families in BC and are most familiar with BC's HD community.
7) **Communication with BC's HD Family community.** These individuals are likely to be familiar with other members of BC's HD community who may be affected or at risk and have not yet come to our attention.
8) **Nursing homes in BC.** Please see appendix 3 for a full list of the nursing homes contacted for this study.
9) **Death records**. Statistics Canada maintains a database for all causes of death categorized by International Classification of Disease (ICD) code. Diseases of the basal ganglia are classified under ICD code 333.0, and HD has its own sub category under ICD code 333.4 (Vital Statistics British Columbia, 2009).

Methods of Ascertainment

The first step in ascertaining patients was to perform a detailed chart review at the UBC HD clinic and the VGH Medical Genetics department. A custom electronic database was built on a Microsoft Access platform and pertinent information was extracted from patients' medical charts and entered into the database. Information extracted that was most relevant to calculating prevalence, incidence and

population at risk, included: province of residence, presence or absence of a family history, whether the patient is living or deceased, date of death, age and year of neurological symptom onset, date of UHDRS motor score assessment, upper CAG size, HD and risk status, and the number of family members affected and at risk who were not seen in the clinic (Table 2). Appendix 2 contains a complete list and description of each field included in the HD database.

Table 2. Fields from the HD Access database pertaining to the calculations of prevalence, incidence and population at risk

Field Name	Field Description
Province of residence	
Family History of HD?	• Yes • No • Unknown
Deceased?	Yes or No If yes, date of death
Motor age/year of onset	The age/year at which the patient was first noted to have experienced **neurological symptoms** of HD • Chorea/dystonia • Rigidity • Difficulty with balance Difficulty breathing/swallowing
UHDRS?	Has the patient undergone a UHDRS assessment? United Huntington Disease Rating Scale: Developed by the Huntington Study Group in 1996[i] - Assessment of HD clinical features to track disease progression on a standardized scale
Upper CAG size	Dictates HD test results CAG ≥ 36 is a positive test result
HD Status	• Symptomatic HD + • Clinical Dx • UNKNOWN • Unaffected (spouse/other) • At Risk
At risk (AR) Status	• 50% AR • 25% AR • Unknown AR • Affected • Pre Manifest (100% AR)
Family risk totals	• Total number of individuals in this family at each risk category • BC residents only
Total affected – Not yet in database	• Total number of affected living individuals in this family • Not a clinic patient • BC residents only

The second method of ascertainment was to obtain results from every diagnostic and predictive genetic test that has ever been performed in BC. HD direct mutation test results have been available in BC since 1993 and as a result, nearly 20 years worth of test results were available. A single lab is responsible for performing all of these tests for the entire province. Genetic test reports from the CMMT HD laboratory and the DNA Diagnostic Laboratory at Children and Women's Hospital in

Vancouver (C&W) were reviewed. All HD Genetic tests performed between 1987-2001 were available from a database at the CMMT HD research lab and those performed between 2002-2012 were available from the DNA diagnostic lab at C&W. The diagnostic lab provided hard copy test reports, excluding patient personal information in order to maintain privacy. All tests were separated by Predictive or Diagnostic test and each type of test was separated by year.

Throughout the chart review process, the BC resource director of the Huntington Society of Canada (HSC) provided guidance in confirming and updating information in the database. Patients and family members who were known to be deceased but were not recorded as such in their clinic file were updated, city of residence was updated for patients and family members who had moved locations and family pedigrees were analyzed and updated.

In order to obtain greater coverage of the province and receive information from physician records outside the UBC HD clinic and VGH, short questionnaires were sent to the following physicians: 1) every neurologist practicing in BC, 2) every BC physician who has ever sent DNA to the diagnostic lab or the CMMT research lab for an HD genetic test, and 3) every GP in BC that serves an area that is not covered by either 1) or 2). Physicians were asked if they currently care for any patients affected with neurological symptoms of HD and if so how many. They were also asked to list the number of patients who have undergone the genetic test and those who have not. Furthermore, they were asked if any of their patients had additional affected family members in BC. Most importantly, physicians were asked to mention whether their reported patients had ever been referred to the UBC HD clinic or VGH medical genetics. Patients who had been referred had already been ascertained via chart review and were not counted again. A complete list of the questions included in the physician questionnaires is listed in Appendix 4. To encourage responses, physicians who replied to the questionnaire were entered in a draw to win an iPad2.

In addition to physician questionnaires, surveys were distributed to families in BC's HD community. In 2011, the HSC conducted a 'Family Day' at the CMMT attended by over 100 individuals. An introductory presentation and information

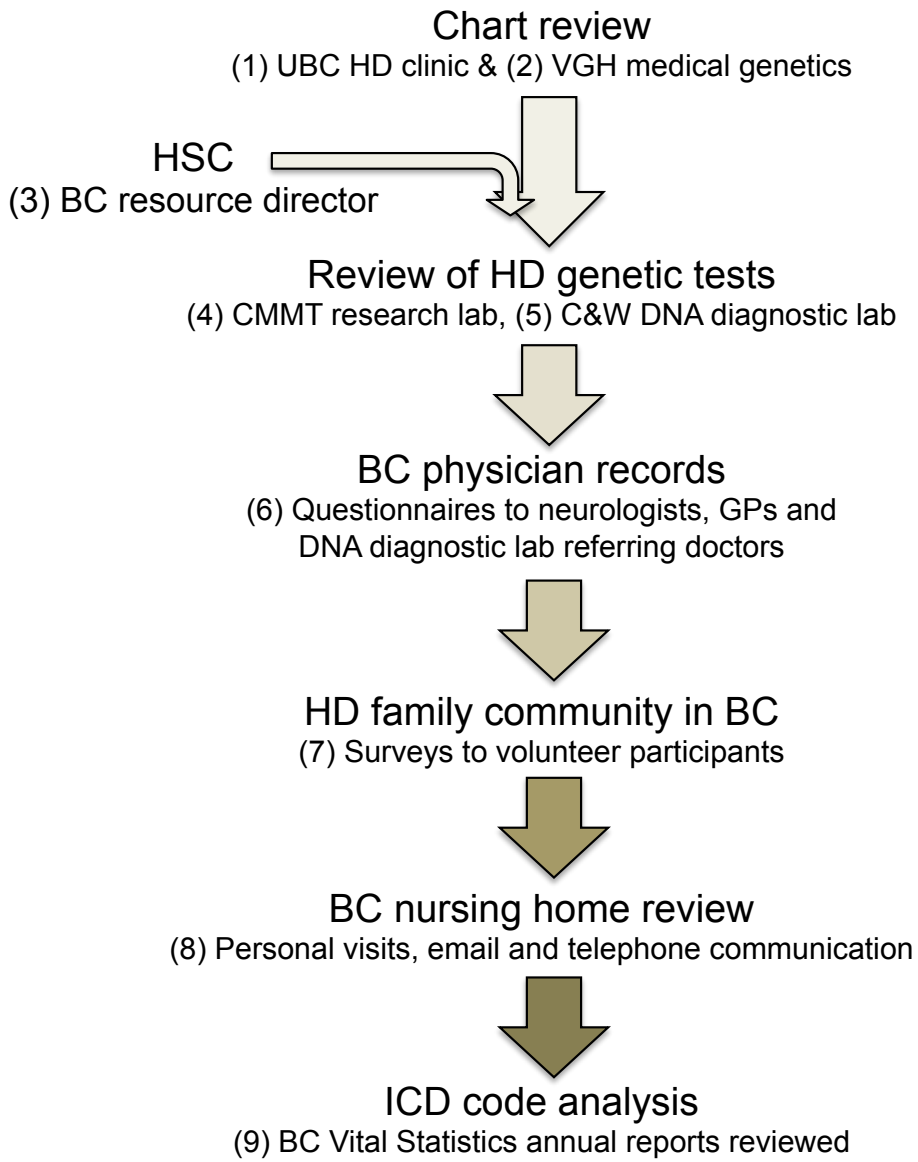
booth describing the present study was set up. Surveys were made available for those members of the HD community who were interested in participating. Surveys asked participants to list the number of living HD patients to their knowledge, who currently exhibit neurological symptoms, in which city, who these patients' GP and/or neurologist is and/or whether they are known to have visited the UBC HD clinic or VGH medical genetics (Appendix 4).

In order to cover the province further and ascertain elderly HD patients who may not have been ascertained from UBC or VGH, long-term nursing homes in BC were contacted. Care managers at these homes were visited, emailed or phoned and asked if they had any HD residents with the diagnosis of HD living in their home and if so, to provide the number of residents. If possible they were asked to provide the name of the resident's referring doctor and/or if the resident had ever been referred to the UBC HD clinic or VGH medical genetics. A total of 49 nursing homes were contacted (Appendix 3). Nursing homes in Vancouver were not contacted as Evergreen hamlets in Surrey is advertised as specializing in HD long-term care (Evergreen Hamlets, 2011) and HD patients in the Vancouver area requiring living assistance are referred to this home (V. Jojin, personal communication, 2011). Nursing homes in Victoria were not contacted either. We found a number of additional (non-clinic) affected patients on family pedigrees from Victoria (Appendix 6). These pedigrees did not include personal information regarding these patients. Questions could thus not be formulated for nursing home staff in order to ensure their potential HD residents were not already counted.

The International Classification of Disease (ICD) code number 333.0, covers systemic atrophies primarily affecting the central nervous system. Huntington's disease has its own sub-category of this code, under the number 333.4 (British Columbia Vital Statistics, 2009). When death occurs, a corresponding ICD code is recorded for each individual in order to account for the cause of death. British Columbia Vital Statistics publishes annual reports describing the causes of death each year under each particular code. In addition, Statistics Canada maintains a database for annual deaths under each larger ICD code category i.e. code 333.0 is available from Stats Can but code 333.4 is not. In order to acquire the number of

individuals recorded under ICD code 333.4 each year, BC Vital Statistics annual reports were reviewed. Annual reports from 2000-2009 are currently available.

Figure 4. Chronology of ascertainment sources



Maximizing accuracy of prevalence numbers: certainty measures and overlap risk scores

Certainty measures

In order to maximize the accuracy of our prevalence estimate, a certainty scale was applied to all patients ascertained from clinic pedigrees. Patients ascertained from pedigrees are affected family members of clinic patients who have never themselves been seen at the UBC HD clinic or VGH medical genetics but are recorded to be living in BC. It is rare that information regarding these patients' city of residence, full name, birthdate or age of symptom onset is included on their pedigree, but where these pieces of information were provided, they were used in an attempt to ensure these individuals do not overlap with patients ascertained from physician and family surveys or nursing homes. Certainty measures were assigned based on certainty scores. Two factors contributed to the resulting certainty score: 1) the likelihood that the patient in question is still alive and 2) the likelihood that the patient in question is affected with HD:

Certainty scores:

1) The likelihood the patient is still alive:

   Score of 0: the pedigree, from which the patient was ascertained, was updated ≥20 years ago (before, or in, 1992)

   Score of 1: the pedigree, from which the patient was ascertained, was updated between 10 and 20 years ago (1993-2001)

   Score of 2: the pedigree, from which the patient was ascertained, was updated ≤10 years ago (before, or in, 2002)

2) The likelihood the patient is affected with HD:

   Score of 0: no genetic test information or clinical information was available regarding the family member(s) (seen in the clinic) of the patient in question

   Score of 1: family member(s) (seen in the clinic) of the patient in question were clinically diagnosed with HD and/or have been referred for predictive testing

Score of 2: at least one family member (seen in the clinic) of the patient in question has tested gene positive for HD.

Defining certainty measures:

"Low": A total score of **0-1**, from the sum of 1) and 2) above
"Medium": A total score of **2**, from the sum of 1) and 2) above
"High": A total score of **≥3**, from the sum of 1) and 2) above

Overlap risk scores & Prevalence ranges

Overlap for the purposes of this study, is defined as the process of ascertaining the same patient from more than one source. Patient medical information is confidential and as such, the identity of patients from all ascertainment sources, with the exception of the HD clinic and VGH medical genetics, was not available for review in this study. The inability to directly crosscheck patients between ascertainment sources causes limitations to the feasibility of the data (Levy and Feingold, 2000). Cases of overlap would cause the same prevalent case to be counted more than once, resulting in an overestimate of minimum prevalence. Assuming overlap when it does not exist would result in failure to count a prevalent case and therefore lead to an underestimate of minimum prevalence.

To maximize the accuracy of our prevalence estimate, a range of prevalence values was calculated – lower, mid and upper prevalence. In order to quantify the chances of overlap, overlap risk scores (ORS) were assigned to each patient ascertained from those sources for which patient information was withheld - nursing homes, physician questionnaires, and family surveys. Each of these patients was initially assigned an ORS of 2, the highest risk of overlap. Further work, described in detail below, was required to lower this score. In surveys, physicians and family members were asked to record whether their patients had or

had not been referred to the UBC HD clinic or VGH medical genetics. Patients who had been referred to one of these locations were automatically removed from all prevalence estimates, as it is likely that these patients have already been ascertained from the chart review. These patients are not included in the overlap risk analysis, as it is likely that these patients are indeed cases of overlap. Patients ascertained from surveys that had never been referred to the UBC HD clinic or VGH medical genetics run the risk of having already been counted from patients ascertained from nursing homes and from clinic pedigrees. Due to privacy concerns, it was not possible to obtain patients' personal information from nursing homes or physician and family survey responders. As a result, additional steps were required in order to minimize the possibility of overlap for each prevalent case (Figure 5).

Defining risk scores

0: An overlap risk score (ORS) of zero suggests there is an extremely low chance that this is a case of overlap i.e. there is an extremely low chance that this patient has already been ascertained from another source. In order to become assigned to a score of 0, secondary information regarding the patient in question must be obtained. For example, the physician or nursing home that reported the patient has been re-contacted and has been asked to provide specific information regarding the patient in question. The information requested depended on that available from the patient's family pedigree. Examples include, number and gender of siblings and/or number and gender of children and first and last name initials of the patient or a family member. If the information provided by the physician or nursing home did not match with our pedigree information, it is as certain as possible that this patient has not yet been accounted for and will be assigned an ORS of 0, and be included in all three of the upper, mid and lower prevalence range calculations.

1: An ORS of 1 means there is evidence to suggest that this patient has not been ascertained from both sources, but obtaining secondary evidence was not possible. For example: there are no clinic patients or known family members living in the same city as the physician who provided the original survey response, but the

physician could not provide any secondary information. Patients with an overlap score of 1 were included in the upper and mid range prevalence estimates but were left out of the lower.

2: An overlap risk score of 2 suggests that it was not possible for any of the steps required to minimize ORS to be taken, as there was no information necessary to complete steps 1 and 2 (see steps to minimize ORS below). The patients in question, however, were not definite cases of overlap, as there was no information available to suggest this patient had definitely been ascertained via chart review. Patients with an ORS of 2 were included in the upper prevalence range only.

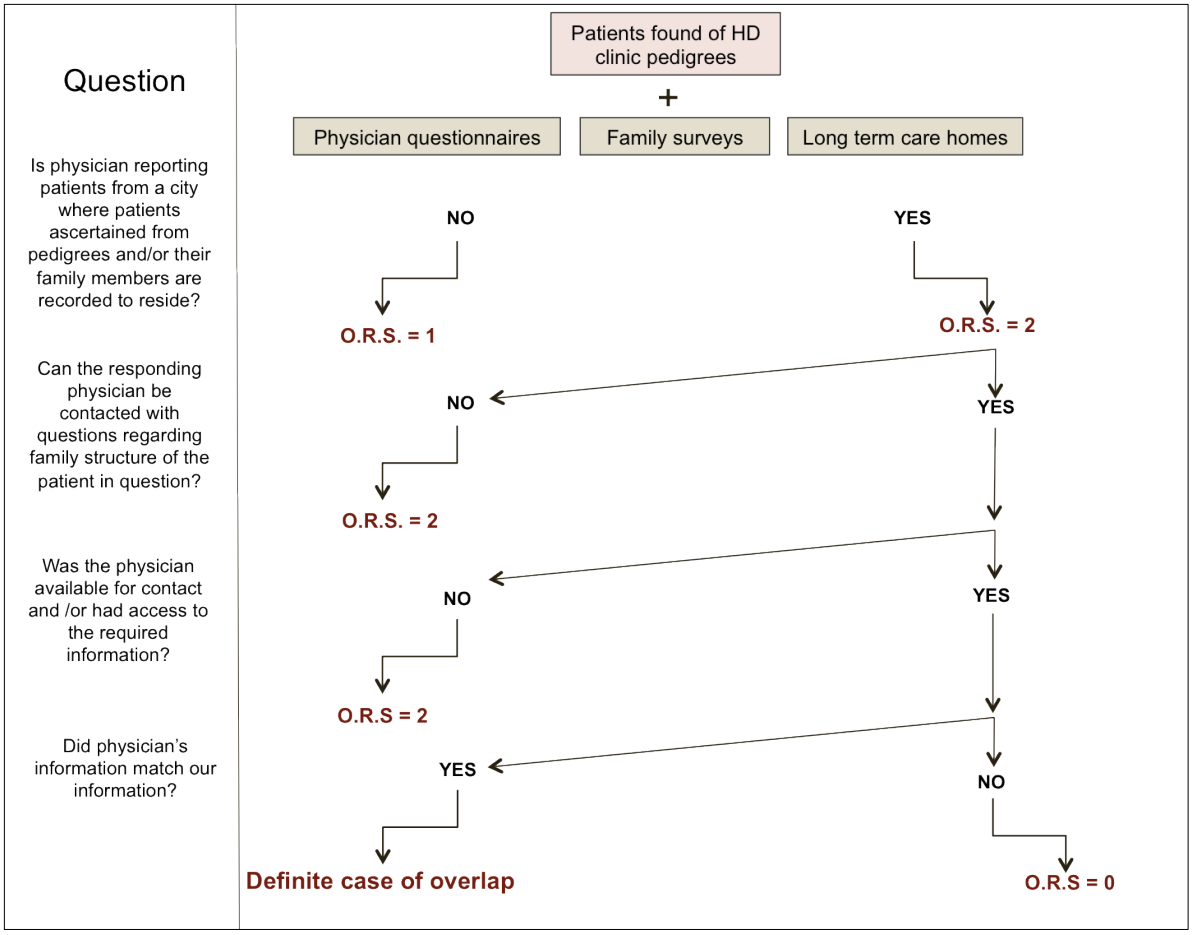
Specific steps to minimize ORS:

Step 1: Check if the responding physician has reported patients from a city where affected patients found on a family pedigree (non-clinic patients) or their family members were recorded to reside. Please note: it is rare that information regarding the city of residence is included on the pedigree; often only the province or country is included. If the city was not available, the city of the closest possible relative was recorded. If the there was in fact a common city between a pedigree and survey response, the number of siblings, number of children and initials of the patient (if available) were recorded. Physicians from these overlapping cities were re-contacted and asked, if possible, to provide these same pieces of information. If the information provided by the physician were to match our information, the patient was removed from all prevalence estimates. It is known with near complete certainty that these patients have already been counted. If answers did not match our information, the patients were bumped up to an ORS of 0. If this information was not available to the physician or the physician was not available for re-contact, the patients remained with an ORS of 2 and were included in the upper range prevalence estimate only (figure 5).

Step 2: Check if the physician who provided the survey response serves any clinic patients from the chart review that are recorded to have affected family members

who were ascertained from their pedigree. If cases like this were to be found, information such as the number of siblings, number of children and initials of the patient (if available) were recorded. These physicians were re-contacted and asked, if possible, to provide this same information. If the information provided by the physician were to match our information, the patients were taken out of all prevalence estimates. It is known with near complete certainty that these patients have already been counted. If their information did not match ours, the patients were to be bumped up to an ORS of 1 (not an ORS of 0, as the city of residence of a family member does not necessarily indicate the city of resident of the patient). If this information was not available to the physician or the physician was not available for re-contact, the patients remained with an ORS of 2 and were included in the upper prevalence range calculation only (figure 5).

Figure 5. Steps taken to minimize overlap risk scores (O.R.S.) for patients ascertained from physician questionnaires, family surveys and nursing homes by ensuring they do not overlap with patients ascertained from clinic pedigrees

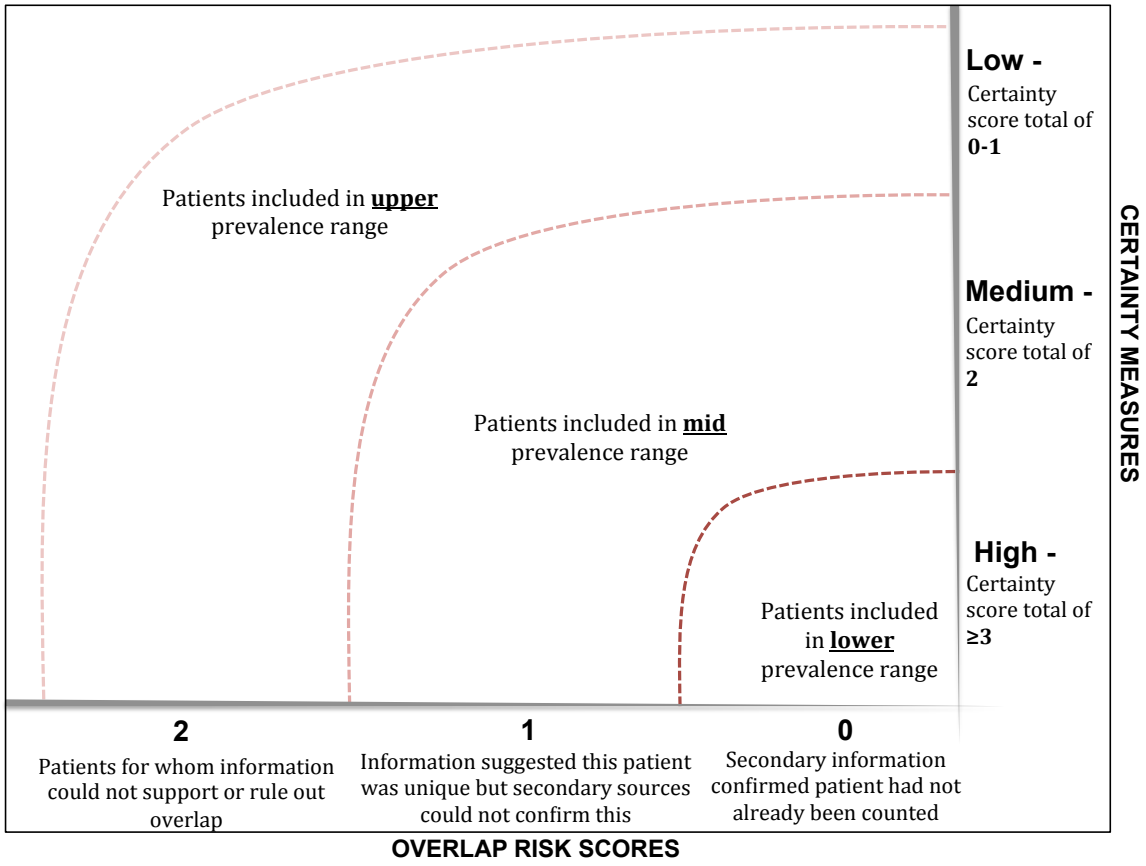


Performing calculations

Minimum prevalence ranges

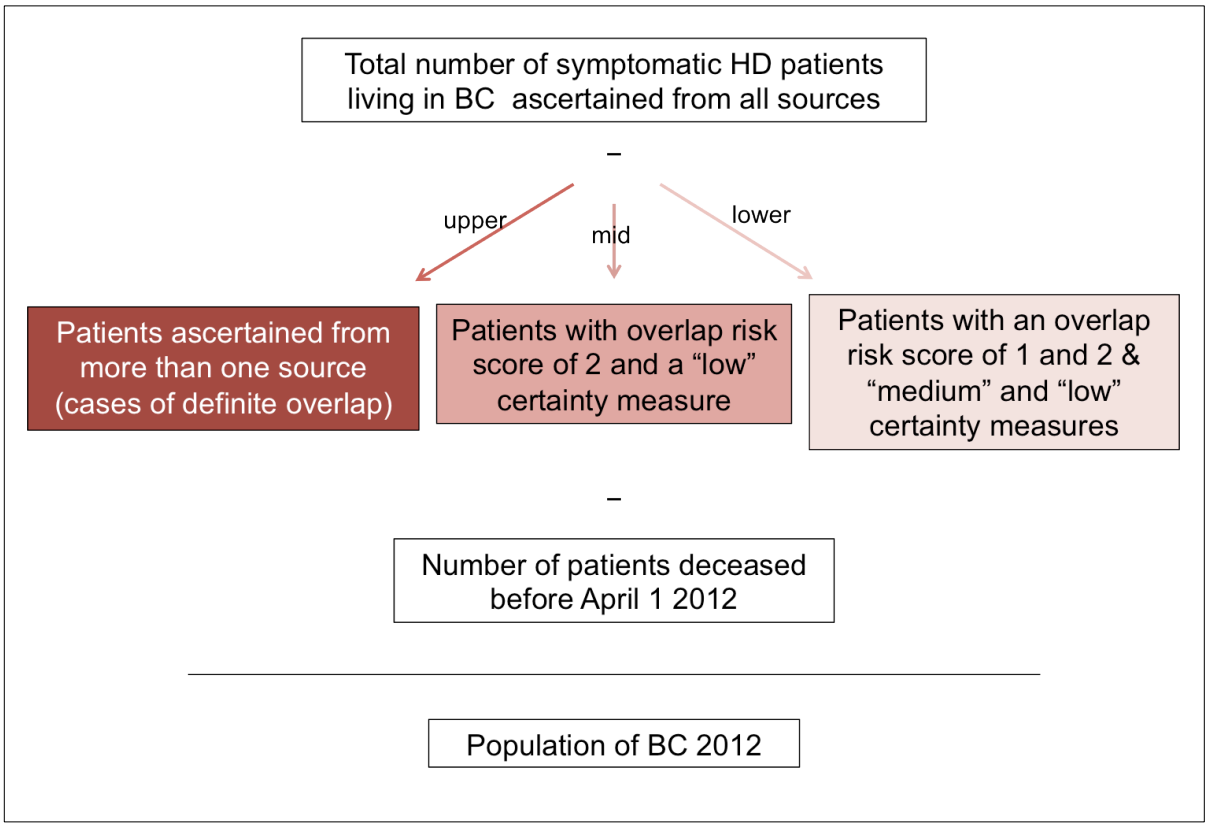
The minimum prevalence estimate was divided into a lower, mid and upper range. The lower prevalence estimate included only patients ascertained from survey responses with overlap risk scores of 0 and patients ascertained from clinic pedigrees with "high" certainty measures. The mid prevalence range included overlap risk scores of 0 and 1 and "high" and "medium" certainty. The upper prevalence range included overlap risk scores of 0, 1 and 2 and "high", "medium" and "low" certainty measures (Figure 6).

Figure 6. Graphical representation of the specific overlap risk scores and certainty measures that make up the upper, mid and lower prevalence ranges



The prevalence was calculated for each range. All prevalence ranges included patients ascertained from the UBC HD clinic and VGH chart review. The upper prevalence range also included patients with "high", "medium" and "low" certainty measures and patients with an ORS of 0, 1 and 2. The only patients subtracted from the high prevalence range were those who were known with full certainty to be cases of overlap (i.e. patients reported by physicians, family surveys or nursing homes to be already referred to the HD clinic or VGH). In addition to these definite cases of overlap, patients with an ORS of 2 and a "low" certainty measure were also subtracted to arrive at the mid prevalence range. The lower prevalence range was the mid range minus patients with an ORS of 1 and those with a "medium" certainty score. The total number of patients for each range was then divided by the population of BC in 2012: 4,609,659 (Figure 7).

Figure 7. Equation for the calculation of upper (red), mid (light red) and lower (light pink) prevalence estimates



Mortality estimates

Specific parameters were applied in order to account for potentially missed mortalities in the patient population. If a patient's year of symptom onset subtracted from the prevalence year (2012) was greater than or equal to 19 *and* there was no information to suggest the patient or their family member (whose chart included the pedigree on which the patient in question is drawn) had been seen in the clinic in ≤5 years, the patient was suspected to be deceased, for the purposes of the lower and mid prevalence estimates. These patients were maintained in the upper prevalence estimate as there was no documentation available to ensure their death. Nineteen years was chosen as this is shown to be the approximate average disease duration for HD (Roos et al. 1993, Foroud et al. 1999).

Prevalence by ethnicity

British Columbia is an ethnically heterogeneous population. While BC is predominantly Caucasian, approximately 25% of the population is of visible minority. Visible minorities include, South Asian (7%), Chinese (10%), Black (0.7%), Filipino (2%), Latin American (0.7%) and Southeast Asian (1%) (Statistics Canada, 2006). The classification of ethnic groups by the European Huntington's disease network (EHDN) registry[5] is slightly different than those presented above by Statistics Canada. Categories by Statistics Canada can however be grouped accordingly in order to fit with and be compared to those from the EHDN registry. For the present review, EHDN registry ethnic classification was followed. These included: Caucasian, African-North, American-Latin, Asian-East, Asian-West, Mixed and Other (EHDN, 2010). Information regarding a patient's ethnicity and country of origin were collected wherever possible during the chart review process of this study (Appendix 2). Ethnicity was also requested from nursing home responders but was not requested in physician questionnaires or family surveys (questions

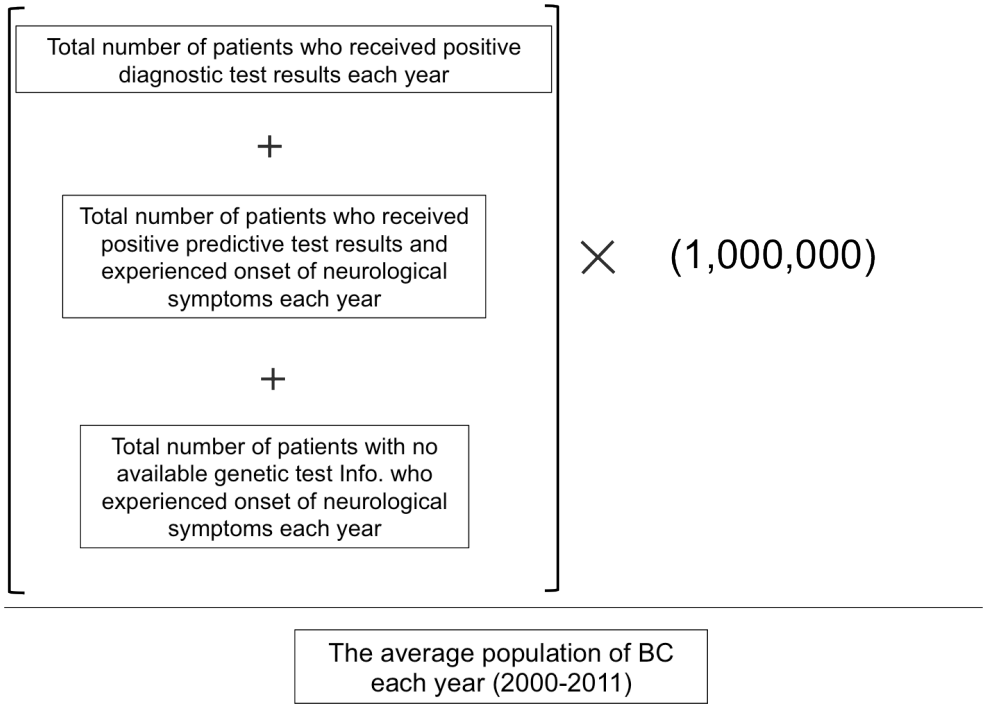
[5] The European Huntington's disease network (EHDN) registry is a multi-center collaboration aiming to obtain clinical and genetic information on a large number of individuals interested in taking part in various HD-associated studies. The registry maintains information on HD patients in Europe and is the largest database for HD patient information in the world (EHDN, 2010).

regarding ethnicity of patients were excluded from these surveys in order to minimize complexity and in turn maximize response rate). The prevalence of HD was estimated within each ethnic group by adding the number of patients ascertained from each ethnic group to the proportion of the 'unknown' ethnic group expected to be composed of the group in question based on empirical ascertainment numbers; this total was then divided by the population of the specific group in question in BC. There are approximately 938,488 East Asian, 647,123 West Asian, 31,108 Latin American, 30,410 North African and 219,604 Canadian Aboriginal individuals estimated to be living in BC in 2012 (Statistics Canada, 2012). These populations were used as the denominators in estimating the ethnic-specific prevalence figures for HD in BC.

Incidence

The incidence of HD in BC was calculated by summing the total number of patients who had either received a positive diagnostic test result and/or had experienced onset of neurological HD symptoms each year between January 1, 2000 and December 31, 2011. This number was divided by the average population of BC for each respective year (BC Stats, 2012) (Figure 8). This calculation was applied to each year separately. Patients included in the incidence calculation who lacked diagnostic test results were either 1) those who had received a positive predictive test result in the past but experienced symptom onset during the study period, 2) those patients who had never undergone the genetic test and were diagnosed clinically, or 3) patients whose test results were not available for review. Additionally, the positive diagnostic test-rate (Creighton et al. 2003), was measured from 2000-2011.

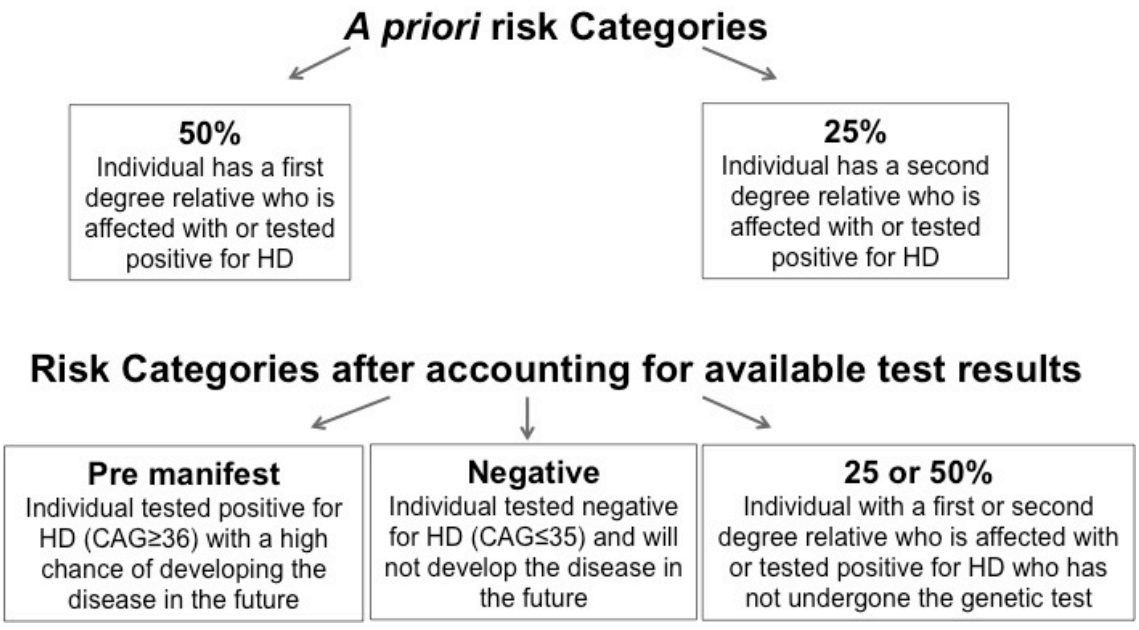
Figure 8. Equation for the calculation of incidence (per million/year). This equation was applied separately for each year reviewed (2000-2011)



The population at risk

The population at risk for HD was divided into two separate analyses. The first involved the calculation of the *a priori* risks. *A priori* risk refers to the risk of disease associated with an individual at birth since, in actuality, an individual's specific risk for HD decreases with age (Harper 1992). *A priori* risk measurements are useful in categorizing risks into two distinct groups: 50%, meaning the individual has a first degree relative who is affected with or has tested positive for HD and 25%, meaning the individual has a second degree relative who is affected with or has tested positive for HD (figure 9a). The second analysis involved risk categories after accounting for those genetic test results available for review: pre-manifest, meaning the individual tested positive for HD and is likely to develop the disease in the future; and Negative, meaning the individual has received a negative genetic test result and will not develop the disease in the future. Individuals who have not undergone the genetic test will remain in one of the *a priori* risk categories (Figure 9b).

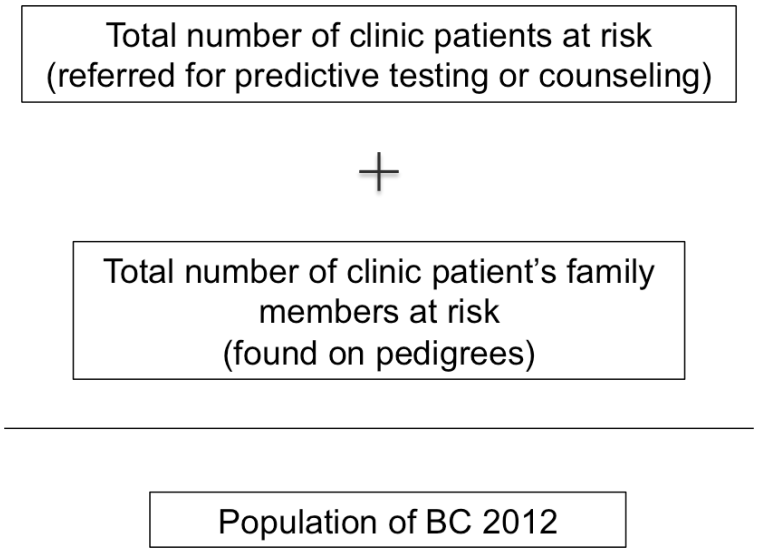
Figure 9. *A priori* risk categories and risk categories after accounting for genetic test results



Each risk category was calculated using the same equation (Figure 10). The total number of clinic patients at risk who were referred to the clinic for predictive testing and counselling was summed with the total number of clinic patients' family members who were ascertained from family pedigrees. This total was divided by the population of BC in 2012, 4,609,659.

In order to determine the geographic distribution of individuals at risk for HD in BC, their city and BC health region[6] of residence was recorded. The health region of residence was however inferred for a large portion of this group. Locations were unknown for those individuals at risk who were ascertained from patient pedigrees. These additional individuals at risk were distributed amongst BC health regions in proportion to the percent of the population living in each region[7].

Figure 10. Equation for the calculation of population at risk. This equation was applied to each risk category separately



[6] Health regions are legislated administrative areas defined by provincial ministries of health. These administrative areas represent geographic areas of responsibility for hospital boards or regional health authorities. British Columbia is made up of five health regions: Northern, Interior, Fraser, Vancouver Coastal and Vancouver Island (Statistics Canada 2007, British Columbia Statistics 2010).

[7] Approximate percentage of British Columbians residing in each health region: Fraser: 36%, Interior: 17%, Northern: 7%, Vancouver Coastal: 23% and Vancouver Island: 17% (British Columbia Statistics, 2010).

Predictive testing

British Columbia was the first place in the world to offer the predictive test for HD (Fox et al. 1989). The linkage test has been available since 1987 and the direct mutation test, since 1993 (Gusella et al. 1987, MacMillan et al. 1993). Predictive testing is generally offered to those at the age of majority (Tassicker et al. 2009). The age of majority in BC is 19 (Statistics Canada, 2012), but eligibility for predictive testing in BC begins at the age of 18 (MacLeod et al. unpublished report). Uptake has generally been defined as the number of individuals who have undergone predictive testing as a proportion of the number of individuals estimated to be at 50% risk in the population (Tassicker et al. 2009). However, in order to account for the study period, and in turn, the possibility of the population at 50% risk changing during this period, a revised equation was used in the present study to calculate uptake (Figure 11).

Figure 11. The equation for calculating uptake as proposed by Tassicker et al. (2009)

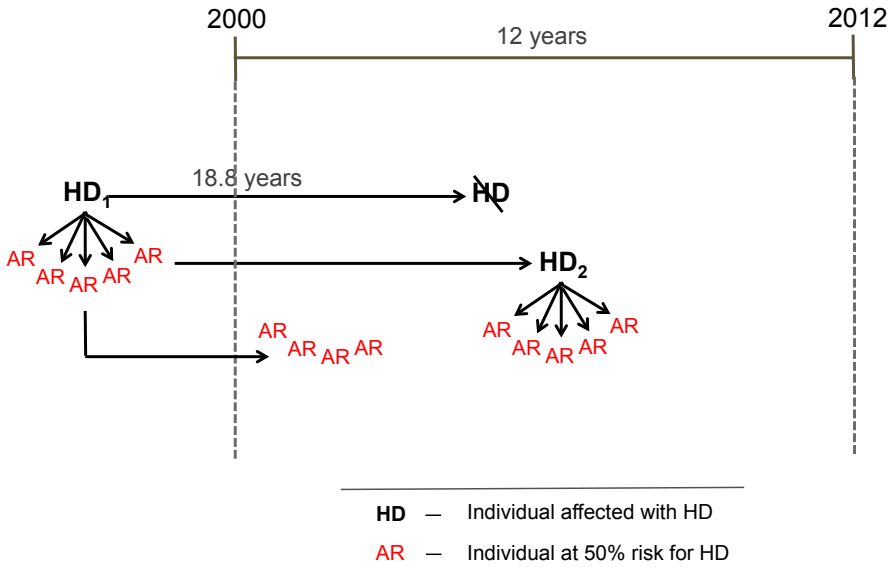
$$\text{Uptake } (\%) = (\text{number of predictive tests in the study period/D}) \times 100.$$

$$\text{D} = P + (P \times \text{study duration in years})/18.8$$

This equation corrects for the previously static denominator that has been used to represent the number of individuals at 50% risk in a population. The revised denominator consists of the number of individuals eligible for predictive testing but only during the course of the study period. This includes the number of 50% risk individuals who were at the age of majority on the day the study began (denoted as 'P'), plus the number of 50% risk individuals who became eligible over the course of the study. In order to estimate this number of additional individuals added to 'P', Tassicker et al. propose multiplying 'P' by the study period and dividing this number by the average disease duration - 18.8 years (Roos et al. 1993, Foroud et al. 1999) (Figure 11). Tassicker et al. reason that an individual affected with HD at the start of

the study and who dies during the study period, will be replaced by a previously 50% risk individual who has since become symptomatic. This newly affected individual will in turn represent a new group of individuals at 50% risk that is proportional to the group that was previously represented by the recently deceased HD patient (Figure12).

Figure 12. A depiction of the theory proposed by Tassicker et al. in support of the proposed equation for calculating uptake of predictive testing. Dotted vertical lines enclose the example study period. An individual affected by HD (HD_1) is replaced in the patient population by a newly affected individual (HD_2), thereby maintaining the prevalence over time. The newly affected individual now represents additional members of the 50% risk population. Theoretically, the number of these additional individuals is equal to the number of 50% risk individuals represented by the previously deceased.



Uptake of predictive testing in BC was determined using two methods; the above methods and the methods used in the previous review of uptake in BC (Creighton et al. 2003). Both methods were applied in order to allow for comparisons in BC over time. Uptake was calculated for the time period of April 1, 2000 to April 1, 2012. This time period was chosen as the previous study of uptake in BC reviewed the period from January 1, 1987 to April 1, 2000. Not every predictive test report was available from the CMMT research lab, the DNA diagnostic lab or the chart review, but the number of tests and the year each test

was performed were available. For this reason, geographic distribution of test participants and regional-uptake could not be determined.

Statistical analyses

Differences in prevalence estimates between populations were analyzed using chi square analyses. Standard error and 95% confidence intervals for prevalence, incidence and at-risk popuation estimates were calculated on the assumption of Poisson distribution (Massey University, 2012).

Results

Patient ascertainment results

Clinic chart review:

A total of 1,914 charts comprising more than 775 families were reviewed at the UBC HD clinic and Victoria General Hospital's (VGH) Medical Genetics department. These charts belong to anyone who has ever been seen in one of these clinics, including patients affected with or at risk for HD and individuals related to or connected with a person affected by HD. Of the approximately 775 family files present in these clinics, 696 (90%) of these files included extensive family pedigrees available for review.

A total of 410 HD patients from UBC and 99 from VGH were suggested to be alive, living in BC and affected with symptoms of HD on the prevalence day, April 1, 2012. An additional 127 HD patients were found on clinic pedigrees and were also suggested to be alive, living and affected with symptoms of HD on prevalence day. Of these 127 potentially additional patients, 98 were assigned a "high" certainty measure, 18 were assigned a "medium" certainty measure and 11 were assigned a "low" certainty measure (Table 5, Appendix 5). Thirteen of the 98 (13%) patients assigned a "high" certainty measure, in addition to having been updated in the past 10 years, included information regarding their city of residence on their pedigree. Ten of these 13 patients were recorded to be living in cities different to those cities from where nursing homes reported patients and different to those cities from where physicians and families provided survey responses. Appendix 5 shows the breakdown of certainty measure assignments.

A total of 452 (89%) affected patients, 360 ascertained from the UBC HD clinic and 92 from VGH medical genetics, had been confirmed as affected with HD via a positive genetic test. The remaining 57 (50 from UBC and 7 from Victoria) were clinically diagnosed based on a positive family history and clinical presentation of the disease (Table 3).

Table 3. Numbers and proportion of HD patients diagnosed with and without a genetic test

Ascertainment source	Number of affected patients with the genetic test	Number of affected patients without the genetic test	Percentage of patients with the genetic test
UBC HD clinic and VGH	452	57	89%
Physician questionnaires	15	17	47%
Total	469	74	86%

Physician questionnaires:

A total of 722 questionnaires were sent to physicians in BC; this included 510 General Practitioners (GPs), 132 neurologists and 80 additional physicians who had sent blood to the HD research lab at the CMMT or the DNA diagnostic lab at C&W for predictive or diagnostic testing. Responses were received from 174 GPs (34%), 42 neurologists (32%) and 27 diagnostic lab-referring physicians (34%). The total number of responses was 243, resulting in an overall response rate of 34% (Table 4). Patients were reported from 19 GPs (46 patients), 23 neurologists (54 patients) and 11 diagnostic lab-referring doctors (13 patients). A total of 113 patients and an additional 48 affected family members were ascertained from these questionnaires (Table 3). Of the 113 patients, 32 had not been referred to the UBC HD clinic or VGH medical genetics and were included in the overlap risk score (ORS) analysis. Of the 48 total HD affected family members, 36 belonged to families of referred patients and it is thus highly likely that these individuals had already been ascertained via clinic pedigrees. These patients were considered to be definite cases of overlap and were not counted. The remaining 12 HD affected family members were included in the ORS analysis.

From physician questionnaires, a total of 81 patients and 36 affected family members (117 patients total) were considered to be cases of definite overlap, as physicians had responded stating these patients had already been referred to UBC or VGH and have thus already been accounted for via chart review. Forty-four of the reported patients (including affected family members of patients) were not referred to the HD clinic or VGH and were therefore assigned ORS scores. Nineteen patients

were assigned an ORS of 2; 4 reported by GPs and 15, by neurologists. The remaining 25 patients were assigned an ORS of 1. The justifications for these ORS assignments are described in detail in Appendix 6. No patients were assigned an ORS of 0; physicians were either not available for re-contact or the information required to rule out overlap was not available to them (Appendix 6). Of the 32 additional patients ascertained from physician surveys, 15 (47%) were recorded to have undergone the genetic test and thus be genetically confirmed to have HD and 17 were diagnosed based on a positive family history and clinical presentation (Table 4).

Table 4. Summary of patients ascertained from physician questionnaires

	Total sent	Number Responded	Total Response Rate	Number of patients	Number of BC resident family members affected with HD	Number of patients not referred to UBC HD clinic or Victoria	Number of affected family members of non-referred patients
GPs	510	174	34%	46	17	16	5
Neurologists	132	42	32%	54	16	15	6
DNA Diagnostic lab referring doctors	80	27	34%	13	15	1	1
Total	722	243	**34%**	113	48	**32**	**12**

HD research lab and DNA diagnostic lab assessment:

Test results were available for 929 patients; 295 were diagnostic and 634 were predictive tests. Of the predictive tests, 107 of the positive results belonged to patients who became symptomatic during the study period.

Family Surveys:

A total of 30 surveys were distributed to interested participants at the 2011 HDC family information day. Six surveys (20%) were returned, and reported a total of 36 HD patients. Only 1 of the 6 survey responders (reporting 1 patient) stated

that this patient had been referred to the UBC HD clinic or VGH. The remaining 5 responders did not provide this information; the 35 reported patients associated with these responses underwent overlap risk analysis. Twenty-nine of these 35 patients were considered to be cases of definite overlap, as they were reported to reside in large metropolitan centers and were thus very likely to have been ascertained via chart review or physician survey. Three patients were assigned an ORS of 2. Two of them reside in Princeton, a city from where no physician survey responses were received and from where no HD clinic families with affected members found on their pedigrees are recorded to live and one resided in Tsawwassen, a city where only one patient had been ascertained via chart review. Three patients were assigned an ORS of 1, as all three of these patients were also reported to be living in Tsawwassen (Table 4, Appendix 6).

Nursing home assessment:

Of the 49 nursing homes contacted, 32 homes (65%) were available for contact and provided the requested information. Four homes (8%) reported HD patient residents living in their location: 1 in Penticton, 2 in Westbank, 1 in Powell River and 14 in Surrey (Appendix 6). All 14 patients from Surrey and the patient from Powell River had already been referred to the HD medical clinic and were removed from the ORS analysis. The patients from Penticton and Westbank were assigned an ORS of 2, as the nursing staff was unable to answer the necessary questions required to minimize overlap (Appendix 6).

Overlap risk score totals:

For affected individuals ascertained from clinic pedigrees, resident cities were used to formulate questions. Questions maintained the privacy of these non-clinic patients and were used to follow-up with physician questionnaire, family survey and nursing home responders in the best possible attempt to rule out overlap. Overlap risk scores for each patient ascertained from physician questionnaires, family surveys and nursing homes are listed in column 8 of Appendix 6 and each particular case of ORS analysis is described in the footnotes

labeled in column 9. No patients were assigned an ORS of 0 (patients ascertained from the chart review were not involved in the ORS analysis). All follow-up questions either confirmed the existence of overlap or could not be answered (Appendix 6). Twenty-eight patients were assigned an ORS of 1. Three were ascertained from family survey responses and 25 from physician questionnaires. Twenty-five patients were assigned an ORS of 2. Three from long-term care homes, 3 from family surveys and 19 from physician questionnaires.

Mortality estimates:

A total of 30 patients were presumed to be deceased for the purposes of the mid and lower prevalence estimates. The difference between the prevalence year (2012) and the year, on which the patients' neurological HD symptoms began, was ≥19 for these 30 patients. Additionally, there was no information in these patients' charts nor in the charts of their family member(s) to suggest these patients are still living.

Prevalence calculations

The upper prevalence estimate included all certainty measures and all ORS's. When added to those patients ascertained from the chart review (509), the total number of patients included was 689, resulting in a prevalence of 14.9/100,000 (1/6,711) (95% CI: 13.8-16.0). The mid prevalence estimate included "high" and "medium" certainty measures and ORS's of 0 and 1 and excluded patients presumed to be deceased (30 patients). The total number of patients included was thus 623, resulting in a prevalence estimate of 13.5/100,000 (1/7,407) (95% CI: 12.4-14.6). The lower estimate included only "high" certainty measures and ORS's of 0 and also excluded patients presumed to be deceased (30), totaling 577 patients, and thus a prevalence estimate of 12.5/100,000 (1/8,000) (95% CI: 11.5-13.5) (Table 5, Figure 13). The minimum prevalence estimate for BC for April 1, 2012 thus ranges from 12.5-14.9/100,000 (95% CI: 11.5-16.0; 1/8,696-1/6,250)

Prevalence – individuals affected with HD

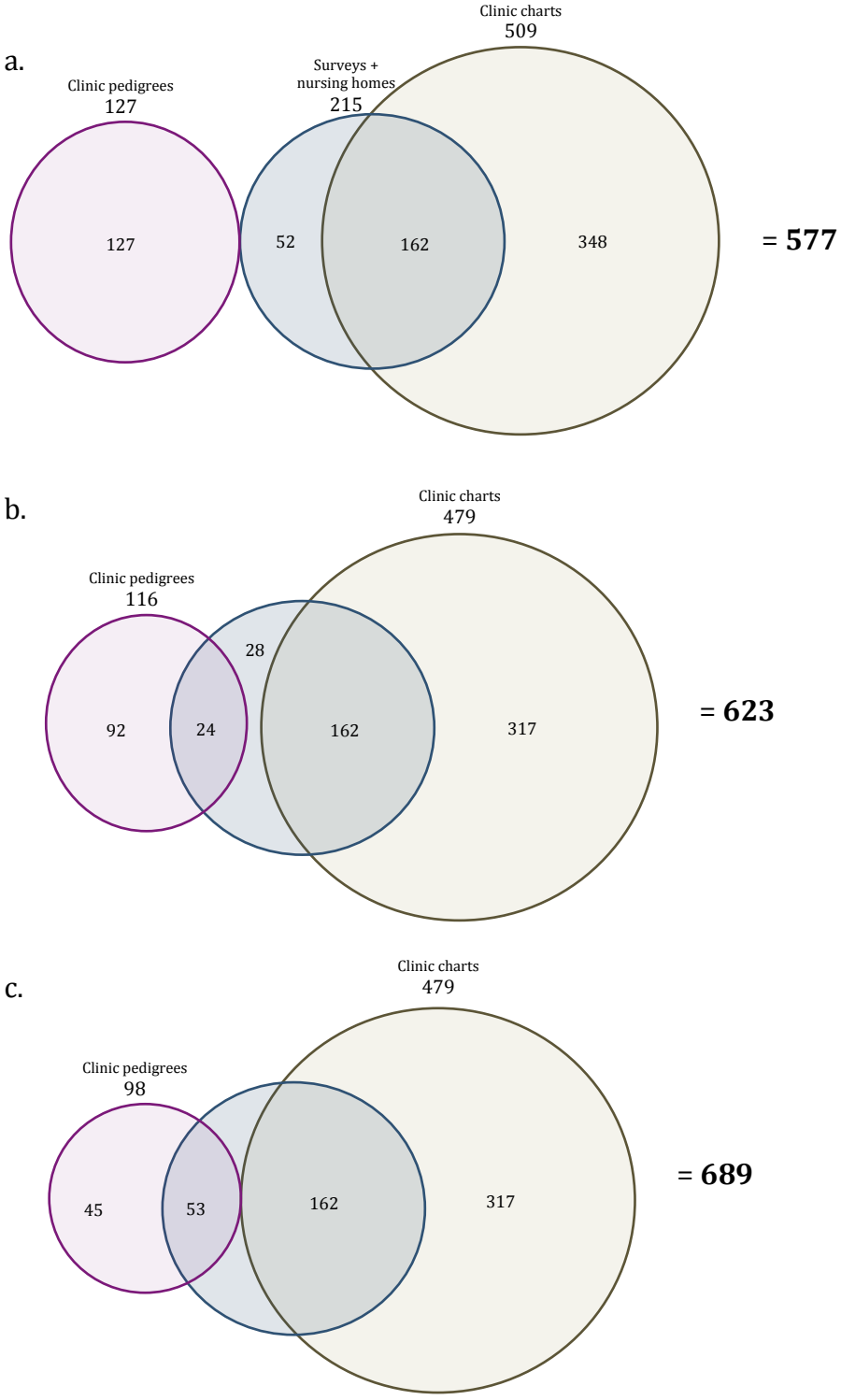
Table 5. The number of patients ascertained from each source under each certainty measure or overlap risk score is shown below. Each of the upper, mid and lower prevalence range calculations is broken down

Ascertainment source	Certainty measure			Definite Overlap	Total
	Low	Medium	High		
HD clinic pedigrees	11	18	98		127
UBC HD clinic	27		383		410
Victoria General Hospital Medical Genetics	3		96		99
Long term care home assessment	3			15	18
Family surveys	3	3		30	36
Physician questionnaires	19	25		117	161
	2	1	0		
	Overlap risk scores				

Prevalence range	Upper	Mid	Lower
Overlap risk scores included	0+1+2	0+1	0
Certainty measures included	High + Medium + Low	High + Medium	High
Total patients	689	623	577
Minimum prevalence (/100,000)	**14.9**	**13.5**	**12.5**
Prevalence (1/X)	1/6,711	1/7,407	1/8,000

Minimum prevalence ranges

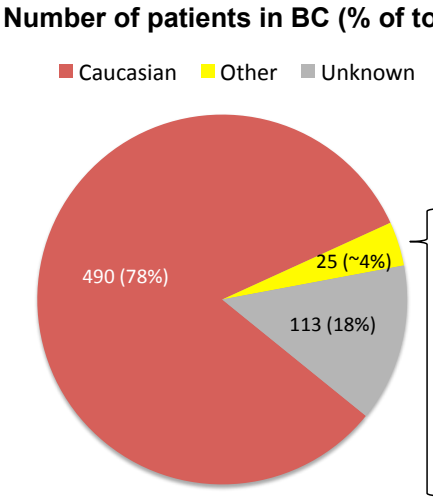
Figure 13. Venn diagrams showing the patient number breakdown for the: a. lower, b. mid and c. upper prevalence range



The ethnic composition of BC's HD patient population

The chart review revealed 490 patients to be Caucasian, one to be African-North, one American-Latin, six Asian-East, 16 Asian-West and one Canadian Aboriginal (the Canadian Aboriginal belongs in the EHDN 'Other' category). In addition, approximately 113 of the patients ascertained were of unknown ethnicity. The total number of patients used in this analysis comprises the average of the three prevalence estimates. After extrapolating the proportion of patients in each ethnic group from the empirical data to include patients from the 'Unknown' category, the total number of Caucasian patients became 597, total North African, 1; Latin American, 1; Canadian Aboriginal, 1; East Asian, 7 and West Asian, 20. Appendix 7 lists the countries of origin and numbers of patients from each country associated with each EHDN ethnic category. Figure 14 shows the proportion of the patient population from each ethnic group and the prevalence estimates for each group with respect to BC's population of the specific group in question.

Figure 14. HD patients in BC separated by ethnicity. The pie chart shows relative proportions of each ethnic group in BC's patient population. Breakdown of the 'Other' category shows the proportion of BC's HD population from each listed ethnic group. Ethnic-specific prevalence estimates are shown in column 4 of the table.

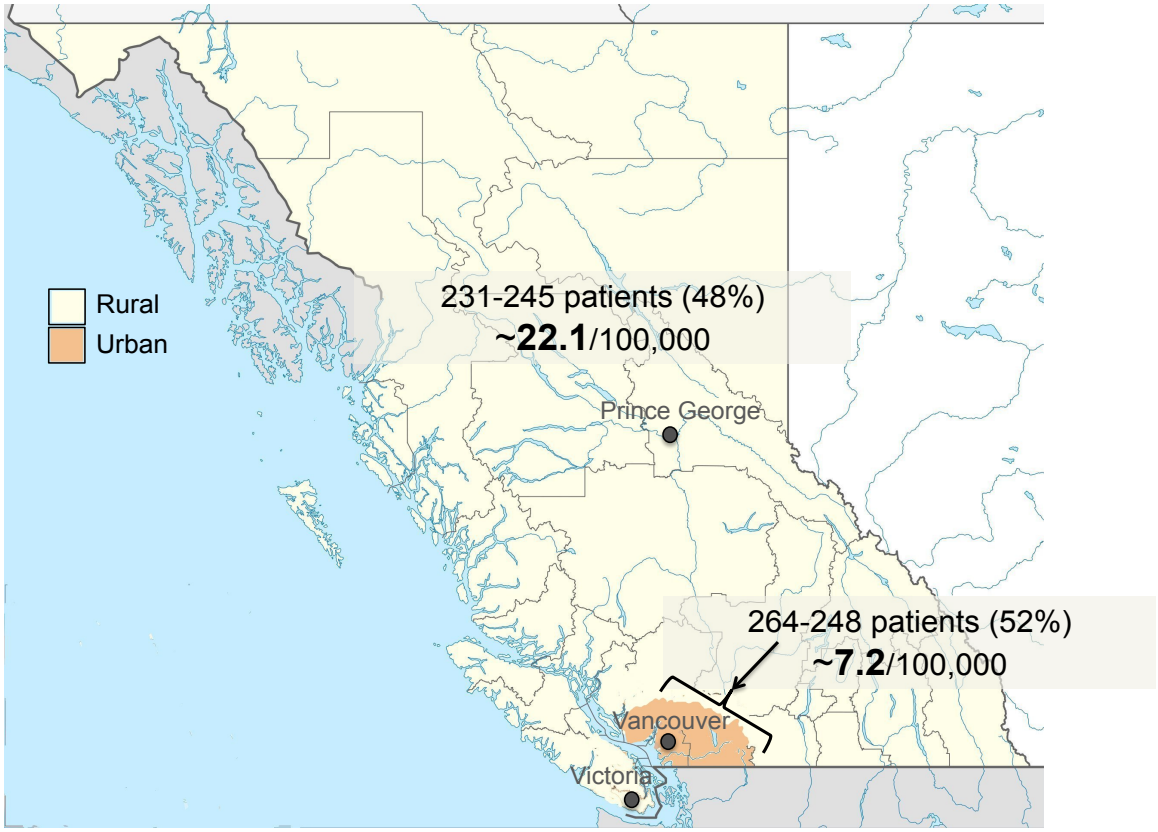


Origin (ethnicity)	# of patients	Percent of patient population	Ethnic-specific prevalence (#/100,000)	Ethnic-specific prevalence (1/X)
Caucasian (countries listed in Appendix 7)	597	95%	**17.2**	1/5,815
Tanzania (African-North)	1	0.2%	**4.14**	1/24,155
Mexico (American-Latin)	1	0.2%	**4.05**	1/24,691
Philippines, Hong Kong (Asian-East)	7	1.2%	**0.78**	1/128,205
Pakistan, Afghanistan, India, Iran, Iraq (Asian-West)	20	3.0%	**3.01**	1/33,222
Aboriginal-Canada (Other)	1	0.2%	**0.57**	1/175,439

Geographic distribution of patients

Patients were ascertained from 96 cities in BC. Appendix 6 shows the number of patients ascertained from each source and from each city. A range of 231-245 (48%) HD patients were found to reside in "Rural" BC – more than two hours from Vancouver by car. This range reflects the lower and upper prevalence estimates respectively. As a result, average prevalence estimate for the "Rural" region was found to be 22.1/100,000 (95% CI: 19.3-24.9; 1/5,181-1/4,016). A total of 248-264 (52%) patients were found to reside in "Urban" BC – within two hours by car from Vancouver. The average prevalence for this region was estimated at 7.2/100,000 (95% CI: 6.4-8.1; 15,625-1/12,346), whereas the upper prevalence was 9.3/100,000. The prevalence is significantly lower in the "Urban" region that the "Rural" region (P<0.0001, t=10.2) (Figure 15). The ratio of "Urban": "Rural" prevalence is 1:3.1.

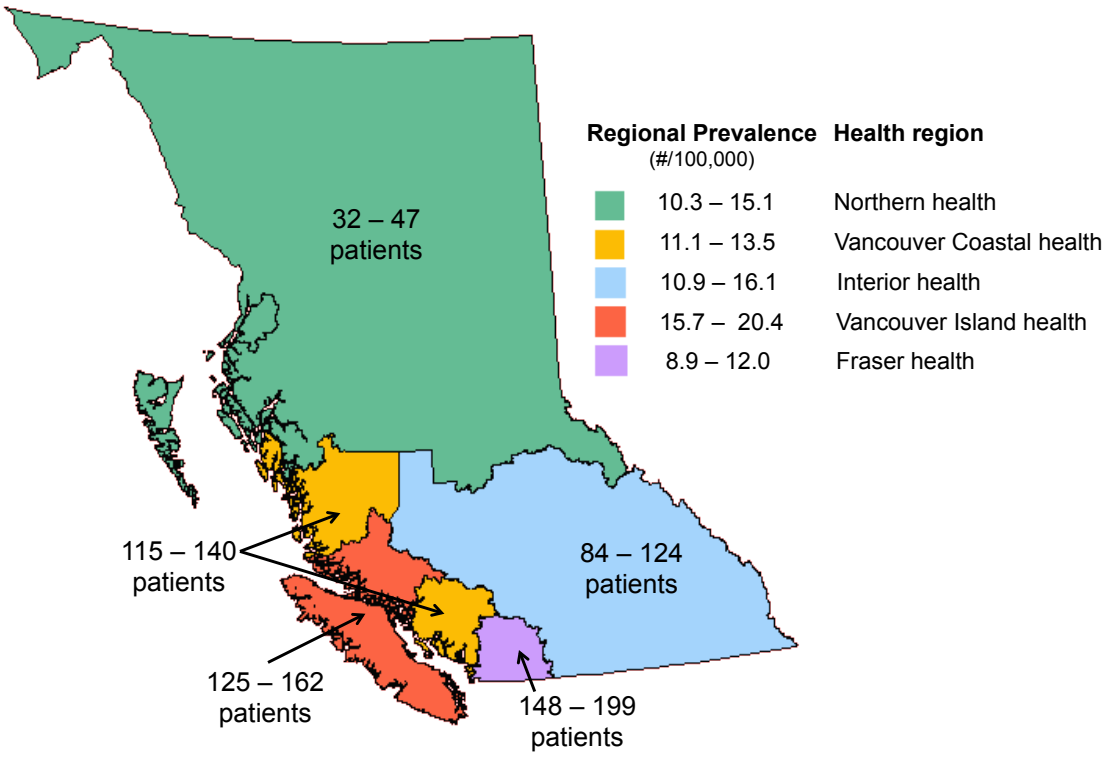
Figure 15. Prevalence of HD separated by "Rural" and "Urban" BC



Rural= more than 2 hours away from Vancouver by car;
Urban= within two hours by car from Vancouver

Figure 16 shows a range of the number of patients living in each provincial health region. The lower range includes patients with an ORS of 0 and a high certainty measure and the upper range includes all patients (ORS of 0, 1 and 2 and high, medium and low certainty measures). The regional prevalence estimates range from 8.9/100,000 (1/11,236), in the Fraser health authority, to 20.4/100,000 (1/4,902) in the Vancouver Island Health Authority however the prevalence estimates in all health regions do not differ significantly from one another (ANOVA, F=1.83, P=0.26) (Figure 16).

Figure 16. The number of patients living in each British Columbian health region based on lower and upper prevalence range. The colour key shows the prevalence (/100,000) for each respective region.



Minimum Incidence

A total of 350 incident cases were counted between 2000-2011. Of these, 235 (67%) were positive diagnostic test recipients, 85 (24%) were positive predictive test recipients who had experienced symptom onset during the study period, and 30 (9%) were patients who had not undergone the genetic test or for whom results were not available but who had experienced symptom onset during the study period (Table 6). The yearly incidence of HD between 2000-2011 ranged from 3.7 per million/ year in 2011 to 9.1 per million/year in 2005. The average incidence was 7.2 per million/year (95% CI: 6.5-7.9) over the twelve-year period (Figure 17, Table 6). The diagnostic test-positive rate ranged from 1.6-4.8 per million/year with an average of 3.3 per million/year over the ten-year period (Table 6).

Figure 17. Estimates of incidence (/million/year) from 2000-2011. Error bars represent 95% confidence intervals

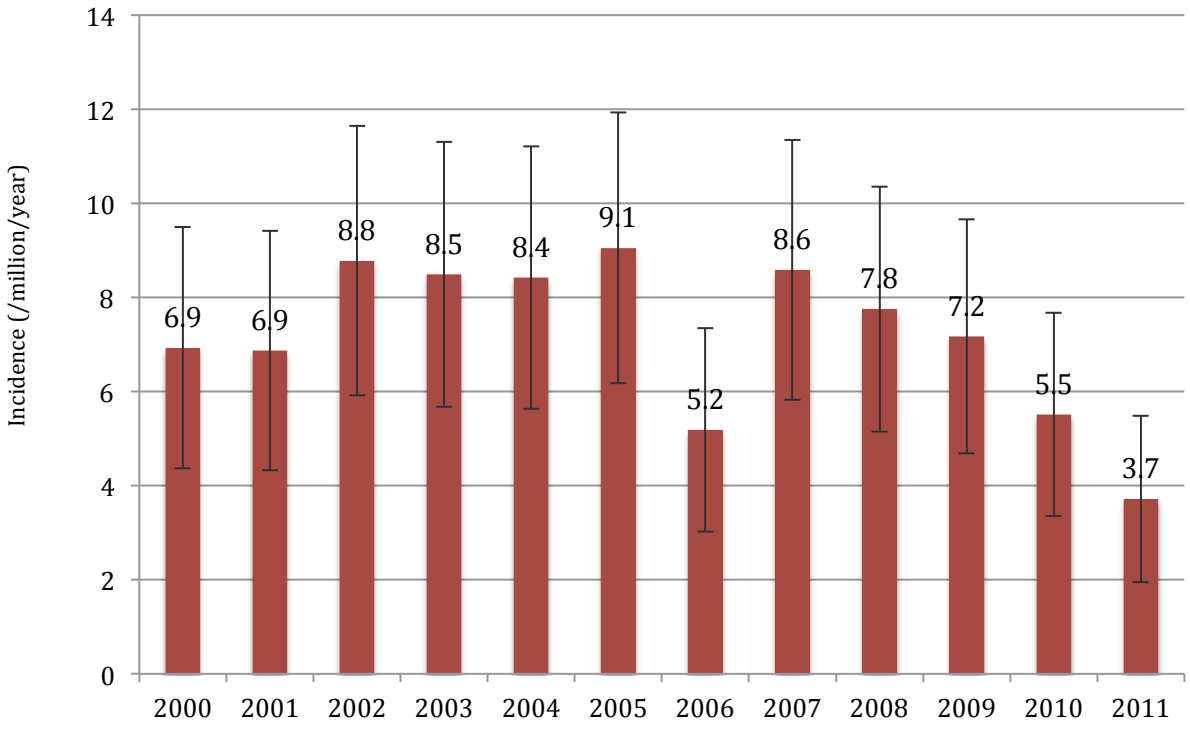


Table 6. Breakdown of the incidence calculation showing the population of BC, the number of cases included from each source, the total number of incident cases and the diagnostic test (DT)-positive rate for each year between 2000-2011

Year	Pop. of BC	# of (+) DT	# of (+) PT and symptom onset (2000-2011)	# with symptom onset – test unavailable	Total # incident cases	Incidence (/million/yr.) (95% CI)	DT positive rate (/million/yr.) (95% CI)
2000	4039200	19	7	2	28	6.9 (4.4-9.5)	3.7 (2.0-5.4)
2001	4,076,264	16	8	4	28	6.9 (4.3-9.4)	2.2 (1.1-3.2)
2002	4,098,178	24	8	4	36	8.8 (5.9-11.7)	4.4 (2.6-6.2)
2003	4,122,396	31	3	1	35	8.5 (5.7-11.3)	3.4 (2.2-4.6)
2004	4,155,170	23	11	1	35	8.4 (5.6-11.2)	4.6 (2.7-6.5)
2005	4,196,788	28	9	1	38	9.1 (6.2-11.9)	4.8 (3.0-6.6)
2006	4,243,580	16	4	2	22	5.2 (3.0-7.4)	2.4 (1.2-3.6)
2007	4,309,632	21	10	6	37	8.6 (5.8-11.4)	3.9 (2.2-5.6)
2008	4,383,860	25	8	1	34	7.8 (5.2-10.4)	2.7 (1.6-3.8)
2009	4,460,292	15	12	5	32	7.2 (4.7-9.7)	1.6 (0.79-2.4)
2010	4,530,960	17	5	3	25	5.5 (3.4-7.7)	2.0 (1.0-3.0)
2011	4,472,600	7	1	9	17	3.7 (1.2-5.5)	1.1 (0.29-1.9)
Total		235	85	30	350		
Mean	4,257,410	20	7	3	32	7.2 (6.5-7.9)	3.1 (1.7-4.5)
%		67%	24%	9%			

ICD codes and mortality rates:

BC Vital Statistics only began to record the annual breakdown for ICD code 333.4 (Huntington's disease) in the year 2000. Prior to 2000, annual reports only considered larger categories, and HD was grouped in with ICD code 333.0. Annual reports were only available up to the year 2009 (British Columbia Vital Statistics Agency 2000-2009). The total number of individuals recorded at death under ICD code 333.4 between 2000-2009 is 124 and the highest number recorded in a single year occurred in 2004 and reported 19 individuals with HD as their cause of death (Table 7). The average mortality rate for HD when taking only ICD codes into account is 2.9 per million/year (95% CI: 1.3-4.5) between 2000-2009 with a range of 1.5-4.6 per million/year (Table 7).

Table 7. Number of patients recorded at death under ICD code 333.0 and 333.4 between 2000 and 2009

Year	Number ICD 333.0 recorded	Mortality rate for CNS atrophies (/million/yr) (95% CI)	Number ICD 333.4 recorded	Mortality rate for HD (/million/yr) (95% CI)
2000	Not available	Not available	10	2.5 (1.0-4.1)
2001	Not available	Not available	12	2.9 (1.3-4.5)
2002	Not available	Not available	7	1.7 (0.4-3.0)
2003	Not available	Not available	6	1.5 (0.3-2.7)
2004	111.3	24.3 (23.0-28.8)	19	4.6 (2.5-6.7)
2005	116.8	25.6 (23.7-30.2)	14	3.3 (1.6-5.0)
2006	133.3	24.8 (21.5-29.0)	15	3.5 (1.7-5.3)
2007	122.6	26.8 (22.1-31.5)	10	2.3 (0.9-3.7)
2008	126.2	27.6 (22.8-32.4)	16	3.6 (1.8-5.4)
2009	Not available	Not available	15	3.4 (1.7-5.1)
Total	**610.2**		**124**	
Average	**122.0**	**25.8**	**12.4**	**2.9 (1.3-4.5)**

Minimum population at risk

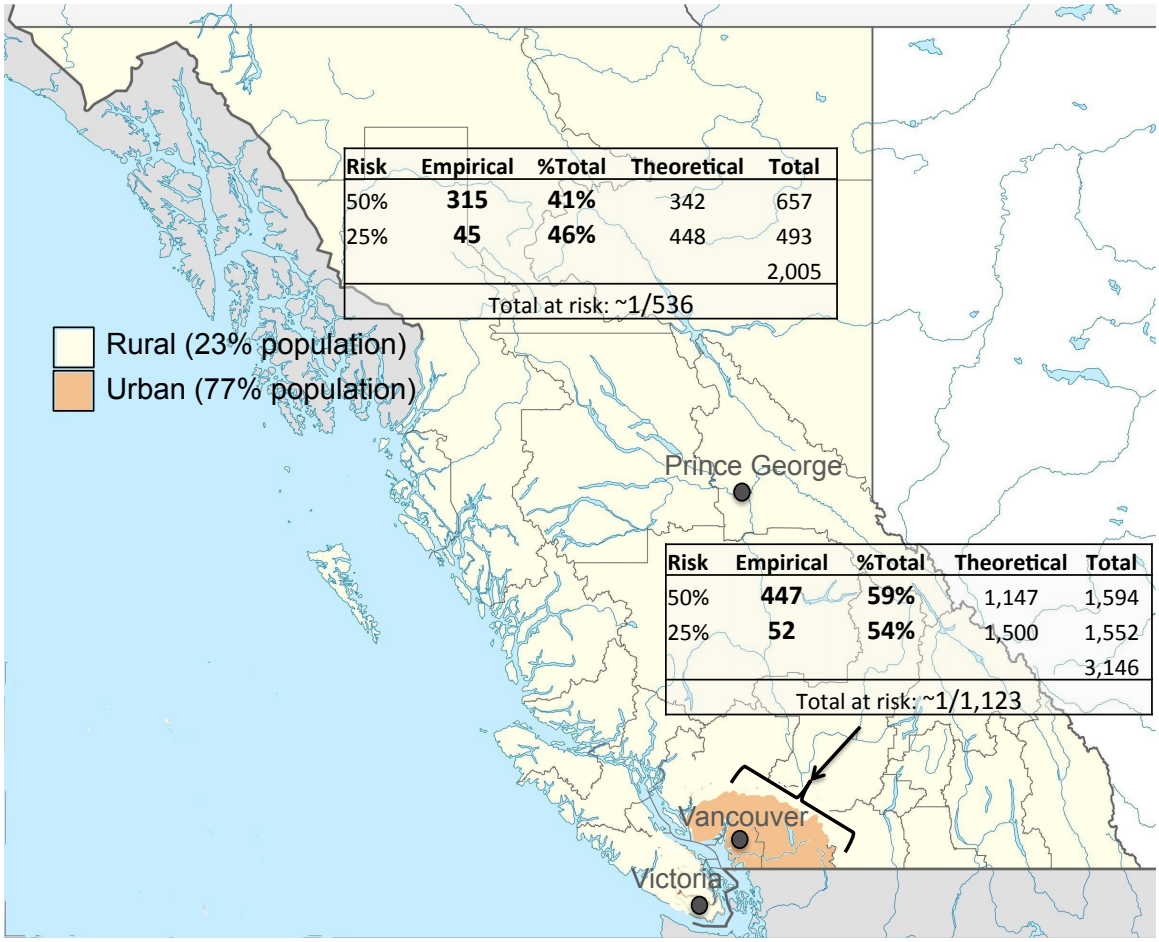
A-priori risk categories: A total of 2,252 patients in BC were found to be at 50% risk for HD, signifying that approximately 49.2/100,000 (1/2,047) of the population are at 50% risk. A total of 2,045 were found to be at 25% risk for HD and therefore approximately 44.7/100,000 (1/2,254) of the population are at 25% risk. Taken together, a total of 4,297 individuals in BC (94.0/100,000 or 1/1,073) are at either 25 or 50% risk for HD. A total of 920 (21%) of these individuals possessed clinic files and the remaining 3,377 (79%) were discovered on family pedigrees but did not themselves possess clinic files (Table 8).

Table 8. Breakdown of the population at risk based on *a priori* risk categories

Risk Category	Seen at Clinic	Discovered on pedigrees	Total	Proportion of population (/100,000)	Proportion of population (1/X)
50%	787	1465	2,252	49.2	1/2,047
25%	133	1912	2,045	44.7	1/2,254
	920	3377	4,297	94.0	1/1,073

Of the 920 individuals at risk ascertained from the chart review, the city of residence was known for 859 of them, 762 at 50% risk and 97 at 25% risk. A total of 315 of those at 50% risk were found to reside in "Rural" BC – in cities that are more than two hours by car from Vancouver; 45 of those at 25% risk were also found to reside in the "Rural" region. The remaining 447 of those at 50% risk were found to reside in "Urban" BC – within two hours by car from Vancouver. The remaining 52 at 25% risk were also found to reside in the "Rural" region. Using the population of "Rural" BC, 1,075,589 (23% of the total population) (British Columbia Statistics, 2012), the remaining number of individuals at risk – 3,438 – was assigned a "Rural" or "Urban" designation. Twenty-three percent of these individuals were assigned to the "Rural" region and 77%, to the "Urban" region. In total, approximately 1/536 appear to be at risk for HD in the "Rural" region, whereas 1/1,123 appear to be at risk in the "Urban" region (Figure 18).

Figure 18. The population at risk for HD separated by "Rural" and "Urban" BC

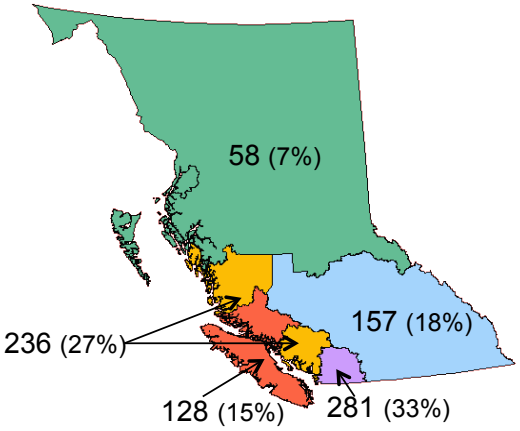


Rural= more than 2 hours away from Vancouver by car;
Urban= within two hours by car from Vancouver

Of the 920 individuals at risk who were seen in the clinic, the charts belonging to 859 of these individuals included information regarding their provincial health region of residence. The remaining 3,438 individuals at risk were distributed among health regions according to the proportion of the general population living in each region (the 859 individuals with known addresses were found to be dispersed in this manner). A total of 58 (7%) individuals at risk were found to reside in the Northern health region, 236 (27%), in Vancouver Coastal health; 157 (18%), in the Interior; 128 (15%) in Vancouver Island health and 281 (33%) in the Fraser health region (Figure 19). The population at risk was found to be roughly 1/1,074 in the Northern health region; 1/1,029 in Vancouver Coastal

health; 1/1,054 in the Interior; 1/1,106 in Vancouver Island health and 1/1,094 in the Fraser health region (Figure 19).

Figure 19. The population at risk for HD in each provincial health region



	Regional population at risk						
	50%		25%		Total	Population at risk (1/X)	Health region
	Empirical	Theoretical	Empirical	Theoretical			
	52	101	6	133	292	1,074	**Northern**
	210	338	26	442	1016	1,029	**Vancouver Coastal**
	139	251	18	328	736	1,054	**Interior**
	109	258	19	338	724	1,106	**Vancouver Island**
	253	541	28	707	1,529	1,094	**Fraser**
Total	**2,252**		**2,045**		**4,297**	**1,073**	

Risk categories after accounting for genetic test results: When taking into account the genetic test results available from the UBC HD clinic and VGH along with the CMMT research lab and the DNA diagnostic lab, a negative/decreased risk and a Pre-manifest risk category are included in the analysis. A total of 344 individuals make up the negative/decreased risk category and 326 make up the pre-manifest category. Of these 326 individuals with positive predictive test results, 36 of them were discovered on pedigrees and did not themselves possess clinic files. These individuals were likely tested in another province or country but currently reside in

BC. Approximately 1/14,141 individuals in BC are thus highly likely to develop HD in the future due to the confirmation of the HD mutation. The remaining 3,627 individuals at risk have not undergone the genetic test; 2,045 remain with a 25% a-*priori* risk and 1,582 with an *a priori* risk of 50% (Table 9).

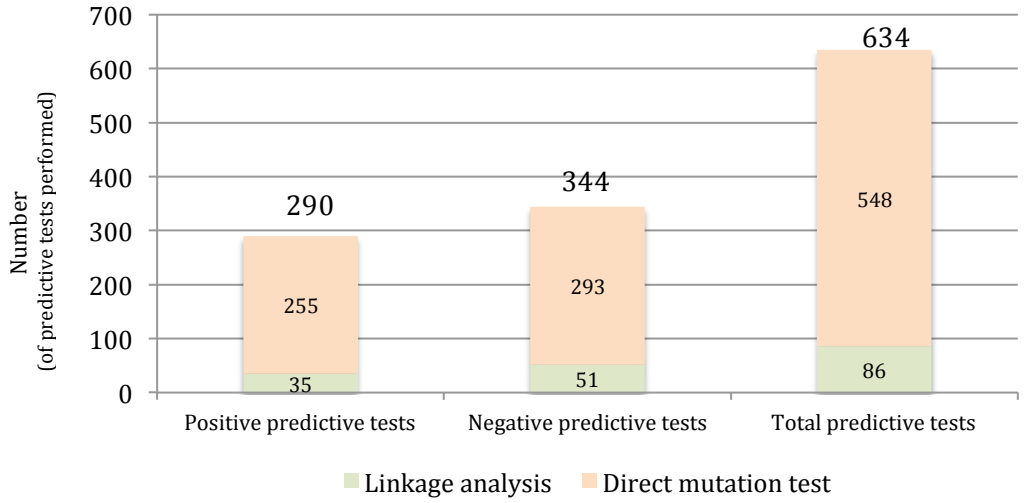
Table 9. Break down of the population at risk based on risk categories after accounting for genetic test results

	Seen at Clinic	Discovered on pedigrees	Total	Proportion of population (/100,000)	Proportion of population (1/X)
Tested					
0% (Direct mutation)	293	0	344	8.6	1/11,574
Negative (Linkage analysis)	51	0			
100%	255	36	326	7.1	1/14,027
Positive (Linkage analysis)	35	0			
Untested					
25%	95	1950	2,045	43.9	1/2,278
50%	323	1259	1,582	38.3	1/2,611
Total			**4297**	**94**	**1/1,073**

Predictive testing

A total of 634 British Columbians have participated in the predictive testing program in BC since 1987; 290 (46%) of which revealed positive and 344 (54%) of which revealed negative results. Of these 634 total tests, 86 (14%) were performed via linkage analysis and 548 (86%) via direct mutation testing (Figure 20).

Figure 20. The number of predictive tests provided in BC between 1987 and April 2012. The bottom section of each bar shows the number of linkage tests and the top portion shows the number of direct mutation tests



Uptake: The uptake of predictive testing was calculated for the 12-year period between April 1, 2000 and April 1, 2012 using two separate methods of estimating the population at 50% risk and two separate methods of calculating the uptake. Using the empirical data from this study to estimate the population at 50% risk, the uptake of predictive testing was calculated at 21% and 13%, using the original formula and then the Tassicker formula respectively (Creighton et al. 2003, Tassicker et al. 2009). The second method of estimating the population at 50% risk was to use theoretical data - multiply the prevalence (13.9/100,000 – an average of all three ranges calculated in the present study) by 4.2. Using this method, the uptake of predictive testing was calculated to be 18% and 11% with respect to the original formula and the formula revised by Tassicker et al. (Table 10).

Table 10. The uptake of predictive testing in BC (2000-2012) using two separate methods for estimating the population at 50% risk and two separate equations for calculating uptake

	# of individuals at 50% risk in the population	Minus population <18 years	D	Uptake (0riginal) D/P	Uptake (Tassicker et al.) D/(P+P*t/18.8)
Empirical (ascertained from BC)	2,252	1,351	280	21%	**13%**
Theoretical (prevalence x4.2)	2,536	1,522	280	18%	**11%**

D= number of predictive tests performed; **P=** number of individuals in the population at 50% risk for HD who are eligible for predictive testing (age 18 or above); **t=**number of years in the study period; **18.8=** average duration of disease (HD symptoms) (Tassicker et al. 2009).

Discussion

Prevalence

The prevalence estimate presented in this study for the province of British Columbia ranges from 12.5-14.9/100,000 (1/8,000- 1/6,711) (mean=13.6/100,000 (1/7,353), 95%CI: 11.9-16.0 (1/8,403-1/6,250). This is the highest reported prevalence in the world since the advent of the direct mutation test in 1993 (Figure 21). When comparing prevalence estimates from studies performed after 1993, only three studies presented comparable findings to those from BC: Malta, Northern Ireland and the UK (Figure 21). The prevalence estimated in the present study is significantly higher than both previous estimates from Canada (χ^2=207.3, p<0.001, df=2) (Figure22). It is also higher than those estimates from Northern Ireland (10.6/100,000, 95% CI: 9.1-12.1, χ^2=9.1, p<0.01, df=1) and the UK (12.4/100,000, 95%CI: 12.1-12.7, χ^2=5.46, p<0.05, df=1) (Morrison et al. 2010, Rawlins, 2010), but is not significantly higher than the estimate from Malta (11.8, 95%CI: 8.3-15.3, χ^2=0.95, p>0.05, df=1) (Gassivaro Gallo et al. 1994). The island of Malta has a relatively small population size and has attributed its abnormally high prevalence to a founder effect associated with Maritime traffic (Gassivaro Gallo, 1994). Ascertainment efforts for the Irish study were limited to a hospital registry (Morrison et al. 2010). The UK prevalence was estimated from only a single ascertainment source, consisting of an HD Association clientele count. Due to the lack of extensive ascertainment efforts and no conformation or follow-up of cases, this study requires repetition with improved methodology to achieve more accurate results (Rawlins 2010).

Figure 21. Prevalence estimate for each region shown over time including updated BC average

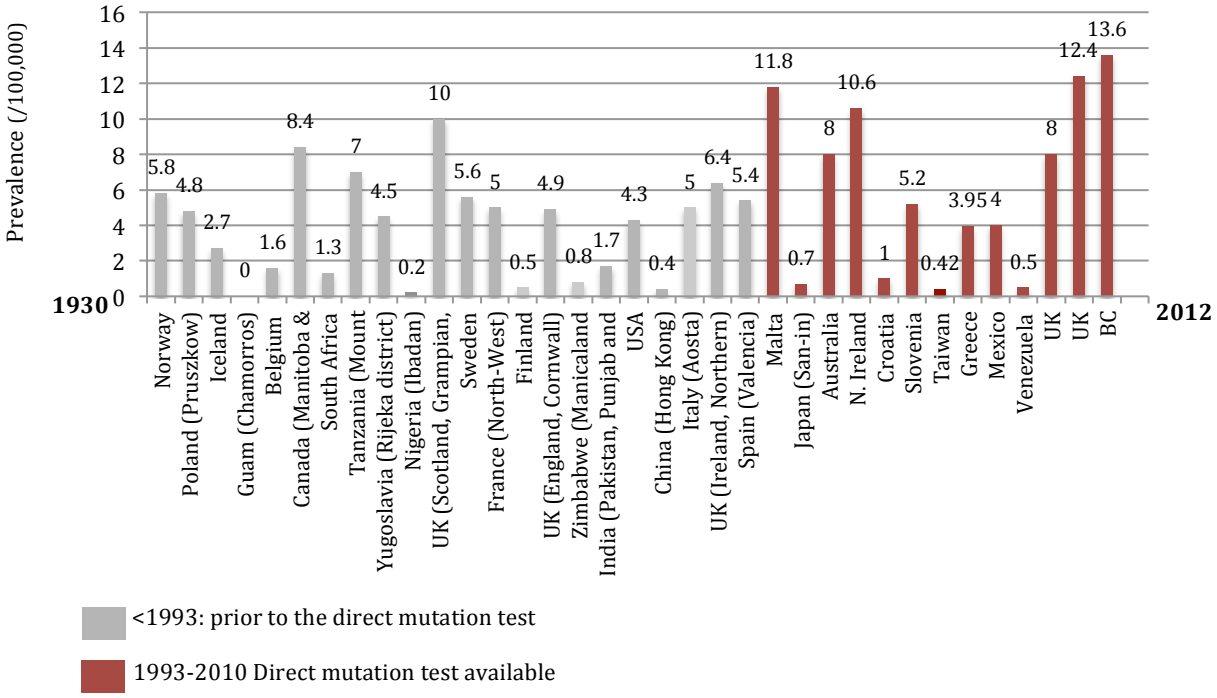
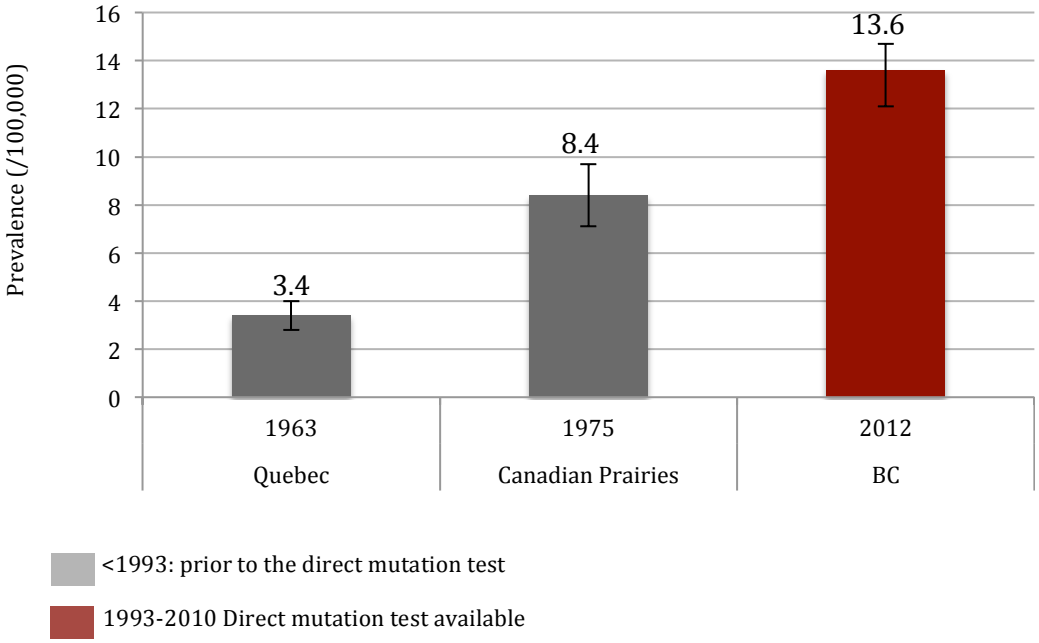


Figure 22. Canadian estimates of HD prevalence over time. Error bars represent 95% confidence intervals



An important question to ponder is whether the increase in prevalence reported here as compared to both global and Canadian studies performed in the past (Figure 21 & 22), is due to an increase in the true prevalence or simply an improvement in ascertainment methodology. Factors that may contribute to a true increase in the prevalence are: 1) the aging of the population and 2) the introduction of new HD mutations. The proportion of the world population over the age of 65 has increased by 10% and the Canadian population aged 45-64 has increased by 10% since the 1980's (StatisticsCanada 2008); these cohorts have likely increased further since the 1960's and 1970's when the bulk of worldwide studies and the most recent Canadian HD prevalence studies were performed. The global life expectancy has increased by 16 years and by 10 years in Canada alone since the 1960's (Figure 23). Taken together, an aging population and the tendency of HD to manifest in mid-life, the proportion of individuals who are experiencing HD symptoms at any given time may have increased. With an increasing life expectancy – a population that is living longer – there is an elevated possibility for late onset HD to manifest before death. Both of these factors may contribute to a true increase in the prevalence. New mutations for HD have been shown to arise at a rate of approximately 10% in the population of HD patients (Falush et al. 2000). New mutations introduced into the population have the potential to further increase the prevalence of HD. Factors that may contribute to a perceived rather than true increase in prevalence are the improved potential for, and rigor in, obtaining complete ascertainment in this study as compared to those conducted in the past. There is ample potential for complete ascertainment in BC. A single lab is responsible for performing all genetic tests for HD for the entire province and specialized professionals at only two facilities - the UBC HD clinic and VGH - provide HD-specific care to patients and families from all around the province associated with this disease. In 2000, it was shown that BC had provided a larger number of total genetic tests (predictive and diagnostic) for HD, proportional to its population size, than any other province in Canada. However, Quebec and Alberta were not included in this analysis (Creighton et al. 2003). Having been the first province to provide the predictive test, BC's population may have a greater awareness of the

test as compared to other provinces, further emphasizing the high potential for full ascertainment in BC. Furthermore, when compared to previous assessments, a greater number of ascertainment sources and a greater variation in ascertainment methods were applied in this study. Multiple methods of communication and nine sources of ascertainment were utilized in the present analysis whereas the number of sources employed in all other worldwide studies conducted after 1993 ranged only from one to three (Table 11). Ten of the 14 studies compared in Table 11 obtained results from genetic testing centers alone with the exception of 2 of these studies, which used both testing centers and clinic and/or hospital records. The remaining studies either used hospital and/or clinic records alone or other methods (Table 11). Only two and five ascertainment sources were employed in the most recent Canadian studies (Barbeau et al. 1964, Shokeir 1975). Although the aging population and new mutations have the potential to contribute to an elevated prevalence, these factors are likely not weighted enough to produce the magnitude of increase observed here. It is likely that this observed increase is primarily due to improved ascertainment methods and represents a prevalence estimate close to the true prevalence of the disease in this population.

It is possible that the prevalence observed in this study is the closest estimate to the true prevalence performed to date. An issue worth questioning however, is whether there is reason to believe that British Columbia represents an overestimate of prevalence; whether the extensive research and care facilities in this province act as a motivating force, pulling more families to migrate to BC. From the extensive province-wide review that took place during the present study, patients' full history was observed for the 509 chart-reviewed patients. None of the histories reviewed suggested migration of HD families to BC for the purposes of acquiring enhanced care or of seeking opportunities to participate in research. It can thus be assumed at this time that the prevalence of HD in BC presented here is not overestimated due to an abnormally large patient presence in this province. Further work involving a province-wide survey of BC's HD community including questions related to family migration patterns would be required in order to gain a clearer understanding of this notion.

Figure 23. Life expectancy in Canada and worldwide (1960-2011).

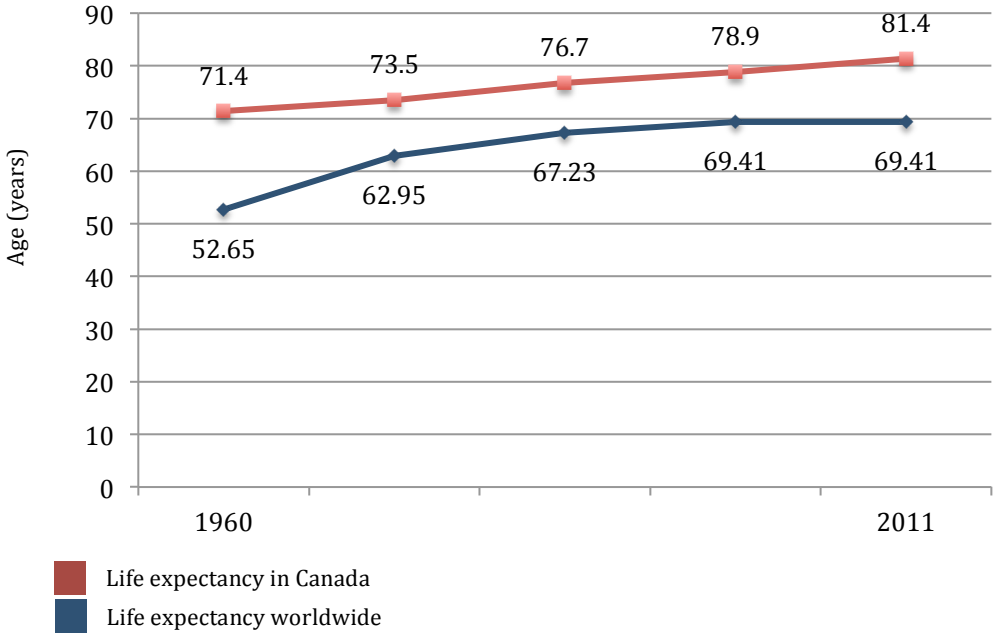


Table 11. Comparison of ascertainment sources employed in studies performed after the advent of the direct mutation test

Study region and year	**Prevalence** (/100,000)	Genetic testing Centre	HD clinic records	Hosp. records	GP & Neurol. records	HD services	ICD codes	Nursing homes	HD families	Pedigree analysis
British Columbia 2012	12.5-14.9	√	√	√	√	√	√	√	√	√
The UK 2010	12.4					√				
The UK 2008	6.2	√								
Mexico 2008	4	√								
Taiwan 2007	0.4						√			
Venezuela 2007	0.5	√								
Slovenia 2006	5.2	√	√	√						
Greece 2002	4	√	√							
Croatia 2002	1	√								
N. Ireland	10.6	√		√						
Japan 1997	0.7	√								
Australia 1996	6.3		√	√						
New Zealand 1996	5.7			√						
Germany 1995	10	√								
Switzerland 1995	10	√								
Malta 1994	11.8	√								

Ethnic-specific prevalence: it is interesting to compare the prevalence of ethnic minorities in BC to the prevalence of these groups as estimated in their countries of origin. In order to calculate the ethnic-specific prevalence, the number of individuals from each ethnic group living in BC was used as the denominator for these calculations. Roughly 20% of British Columbia's population is made up of nationalities fitting into the East-Asian EHDN ethnic category (EHDN 2010, Statistics

Canada 2012). The prevalence of HD in the East Asian population of BC was found to be 0.64/100,000 (1/156,250). As expected, this is much smaller than the prevalence in Caucasians and is similar to, although larger than, the prevalence estimated from studies in this region (0.42/100,000 (1/238,095), Appendix 1b). The West-Asian category showed a prevalence of 3.0/100,000 (1/33,000); this is higher than the prevalence estimated in this region, of 1.7/100,000 (1/58,824) (Appendix 1b). The Latin-American population showed a prevalence of 4.1/100,000 (1/24,390), also higher than that estimated in this region; 2.3/100,000 (1/43,478) (Appendix 1b). The North African prevalence was found to be 4.2/100,000 (1/23,810), also higher than the average estimate from this region of 3.6/100,000 (1/28,000) (Appendix 1b). The only minority without a previous estimate for comparison was the Canadian-Aboriginal group in which a prevalence of 0.60/100,000 (1/167,000) was estimated. The higher prevalence estimates of these ethnic groups in BC as compared to those estimates from their region of origin may reflect cultural differences in adherence to health care. Perhaps it is less common to make public a familial degenerative disease in other cultures than it is here in BC. Further work is required to gain a better understanding of these differences.

Regional prevalence: when observing the prevalence of HD in "Rural" BC as compared to "Urban" BC, it is apparent that the "Rural" prevalence is approximately 3 times higher. This may either be a reflection of under-ascertainment in the "Urban" region as compared to the "Rural" region or it may be an indication that the "Rural" region does in fact have a higher prevalence. In order to maintain legal and ethical obligations, personal information of patients was not available for this study outside of the two clinics from which special consent was granted (UBC HD clinic and VGH). As a result, patients ascertained from other BC physician records were only crosschecked and distinguished via city of residence. Contacting physicians from large metropolitan centers (i.e. Vancouver) was not feasible as there was no way to distinguish patients from one another. For example, a GP, a physician and a psychiatrist may report the same patient and there would be no way to avoid overlap and double counting. Due to this shortfall, only neurologists from these large metropolitan centers were contacted; GPs and other specialists were not. This

may have led to under ascertainment in the "Urban" region. It is, however, expected that the majority of HD patients in the "Urban" region would have been referred to the UBC HD clinic. Thus, if under-ascertainment in the "Urban" region is a factor, it is unlikely that it is extreme enough to cause the abrupt difference in prevalence between the "Urban" and "Rural" regions observed here.

If the higher "Rural" prevalence does in fact reflect a true difference in prevalence between the two regions, there are a number of potential contributory factors. First, it may be that families affected with HD may not be able to afford living within 2 hours from Vancouver. These families may have too large a financial burden associated with caring for those affected and at risk in their family, that "Rural" regions might be the only option that is financially feasible. Another factor may be associated with the lifestyle involved with "Rural" living. In addition, more personal space and less crowd-density may be more suitable for families with HD as compared to urban living. Individuals affected with HD may also feel more comfortable living in a rural environment as the social stigma associated with HD may be more emphasized in urban regions with higher crowd density than in rural regions. In order to explore these factors further, the "Urban"/"Rural" analysis was replicated for patients ascertained from Vancouver Island only. Victoria was designated "Urban" whereas every other island region was designated "Rural". This analysis revealed that approximately half of Vancouver Island's patients reside in Victoria. Since Victoria constitutes only ~12% of Vancouver Island's population, this led to an abrupt difference in prevalence; 82.5/100,000 (1/1,212) for "Urban" Vancouver Island and 9.1/100,000 (1/11,000) for "Rural" Vancouver Island. This information suggests the preference for rural living is likely not a factor contributing to the extreme difference in "Urban" and "Rural" prevalence reported for BC as a whole. The cost of living in Victoria is significantly lower than the cost of living in Vancouver. Perhaps the high cost of living within two hours from Vancouver is a dominant factor leading to the relatively low HD prevalence in this area.

In addition, this abrupt difference may be related in part to the specific definitions of "Urban" and "Rural" applied to this study. Cities designated to the "Rural" category were all cities in BC that are more than two hours away from

Vancouver by car, thus including cities with larger populations, such as Victoria, that are generally defined as "Urban". Findings from this study suggest the vast majority of HD patients are living more than two hours from Vancouver. This may suggest that participation in HD research studies conducted at the UBC clinic is only accessible to a small fraction of the province's patient population. However, it is also possible that this suggests an under-ascertainment of patients in the "Urban" region, as it is expected that the "Urban" and "Rural" proportions should be equal. When the analysis was repeated by placing Victoria in the "Rural" prevalence continued to be nearly 3-times higher although the difference was less extreme.

Despite the extensive efforts put forth in this study to thoroughly search for patients and individuals at risk for HD, there are caveats associated with each ascertainment method.

UBC HD clinic and VGH medical genetics chart review: The chart review portion of the study allowed for a thorough analysis of the medical records belonging to 509 (~80%) patients. However, death records for these patients could not be obtained to ensure every patient was still living on prevalence day. In order to obtain death records, patients' personal health number (PHN) was required for Population Data BC (Population Data BC, 2012). The specific type of consent form used in the UBC HD clinic and VGH medical genetics did not cover the present criteria that are required by Population Data BC to obtain patient's death records. In order to obtain these records, the patient must have signed consent during their lifetime that states their PHN number may be shared for these purposes. The likelihood of linking this database with death records would improve if this database were to be converted from a research database in to a type of disease registry. Further work is required to set this up. Patients who had not been seen in the HD clinic for an extended period of time or who were likely deceased by prevalence day based on their age at onset of HD symptoms, were removed from the patient count. Maximum disease duration of 19 years was applied to this analysis and although this is an average (Foroud et al. 1999, Roos et al. 1993), the absence of information regarding each patient's true disease duration limits data feasibility. Further, the age of symptom onset for 20 (~3%) of the patients ascertained from

the UBC HD clinic and VGH were provided by patient family members. This information was recorded in the physician notes and was initially retrieved from physician interviews with patients' family members. This introduces the possibility in a bias towards either earlier onset, due to hyper-vigilance, or later onset as a result of denial.

Patients and individuals at risk ascertained from clinic pedigrees: Clinic pedigrees are updated as often as possible. The limitation of this data is based on how frequently the proband visits the clinic and how recent their last clinic visit was. Although patients ascertained via this method were assigned certainty measures based on the year their pedigree was last updated, the possibility of patients and family members migrating in and out of province is always apparent. Unfortunately patients and family members could not be contacted for this study, as this could not be approved by the ethics board without prior consent from each individual who we wished to contact.

Patients ascertained from BC physician questionnaires: Physician questionnaires were distributed in June 2011 and all responses were received by September 2011. Patients that were included in the ORS analysis with potential for inclusion in the final patient count were those who physicians had ensured had never been referred to the UBC HD clinic or VGH medical genetics. It is possible, however, that these patients may have been referred to one of these clinics between September 2011 and April 2012. Despite the fact that all possible steps were taken in an attempt to recognize potential cases of overlap in scenarios such as this, the possibility of inaccuracy remains. In addition, in certain cases, patients reported from physician questionnaires that were from unique cities (cities where no clinic patients were recorded to reside), were reported to have been previously referred to the UBC HD clinic or VHG medical genetics. As a result, these patients were considered to be definite cases of overlap and were not included in the ORS analysis nor were they included in the patient count (i.e. Appendix 6, row 1). However, it remains uncertain as to where these patients reside. As the city of residence was used in many cases to minimize overlap, failure to identify where certain patients reside has the potential to be problematic in analyzing overlap in other cities where

these "missing" patients may in actuality, reside. Further, physician surveys were only sent to GPs in areas that were not already served by a neurologist or a DNA diagnostic lab-referring doctor. It was therefore assumed that more than one physician would not report the same patient. It is possible however, that patients have migrated to different areas and/or have seen more than one responding physician and were counted more than once. Lastly, 66% of physicians did not respond to the survey. HD patients may have been missed due to the lack of physician responses.

Patients ascertained from family surveys: The only patients ascertained from this source who were added to the final patient count came from surveys whose responders had knowledge of the patients' physicians and/or whether they were referred to UBC or VGH. Only 2 responders provided this information. Patients included were assigned an ORS based on their, or their family's, city of residence. It is possible that some patients moved to a different city causing the ORS to lack accuracy.

Long-term care homes: In some instances, nursing home staff was unaware of the information required in order to minimize overlap. All patients ascertained under these circumstances were assigned an ORS of 2.

It is possible that, although multiple sources were utilized in this study, we have not achieved full ascertainment of HD patients in BC. If full ascertainment were achieved, no difference between "Urban" and "Rural" prevalence would be expected, as there is no evidence to suggest that HD patients prefer to live in one region in particular. Further, if full ascertainment were achieved, we would expect to see more overlap of the final ascertainment sources (Figure 13), as many HD patient are likely cared for by a number services at once (for example, a neurologist, a GP, a specialized HD clinic and nursing home). This suggests that the prevalence reported in this study may be an underestimate. Achieving full ascertainment would require the surveying of the remaining BC physician population and re-surveying of those physicians (66%) who did not provide responses for this study. It would also require ethical approval for the collection of patient information from all ascertainment sources included in the study (this was limited to two sources –

UBC HD clinic and VGH – for this study). If such approval were obtained, the remaining nursing homes, hospitals and family members could be contacted with more direct questions about their patients in order to avoid overlap.

Incidence

An incidence of 7.2 per million/year was reported in this study; this appears to be a slight increase from that reported in the most recent BC study (Almqvist et al. 2001). It is important, however, to note that Almqvist et al. counted incident cases only if they had been confirmed by a genetic test. Figure 24a shows the yearly incidence of HD in BC since 1987 with the methods used in the present study; incident cases include those diagnosed via clinical symptoms and a positive family history as well as those diagnosed with a genetic test. When comparing the incidence using this method, it becomes apparent that the incidence increased from the first period (1987-1992) to the second period (1993-1999), but then decreased slightly from the second period to the third period (2000-2011) – the present study period (Figure 24a). Figure 24b shows the yearly incidence since 1993 for only those cases with confirmation of diagnosis via genetic test. When comparing incidence with this method, again we see a slight decrease in the average incidence from the first time period (1993-1999) to the second (2000-2011) – the present study period. In general, the incidence has remained fairly constant over time. Incidence for the year 2011 seems very low and when removed, recovers the same incidence as the prior study period. Incidence may be underestimated for the year 2011. The timing involved in having test reports sent from the DNA diagnostic lab to the HD clinic and then scanned into the electronic medical records for review is reliant upon scheduling of a patient's post-testing follow up visit to the clinic. For this reason, the complete list of tests from 2011 may not be available at this time, leading to an underestimate of incidence.

Similar to the prevalence, the incidence of HD also appears to fluctuate across geographic and temporal studies (Figure 25). The two incidence studies, from Italy and the USA, were performed before the direct mutation test became available and both report a lower incidence than those studies performed after.

This may reflect the ability of the direct mutation test to diagnose atypical clinical cases that may have been missed before.

Figure 24a. Estimates of HD incidence in BC since 1987 using clinical and genetic diagnostic criteria. Error bars represent 95% confidence intervals

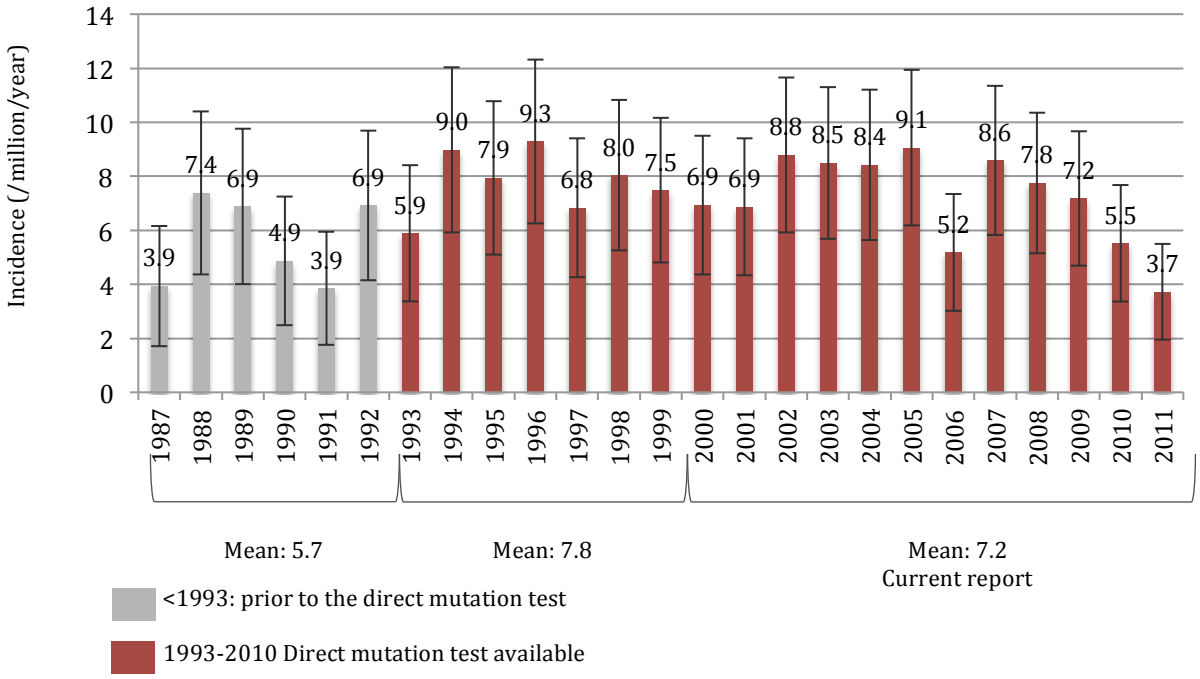


Figure 24b. Estimates of HD incidence in BC since 1993 using genetic diagnostic criteria only. Error bars represent 95% confidence intervals

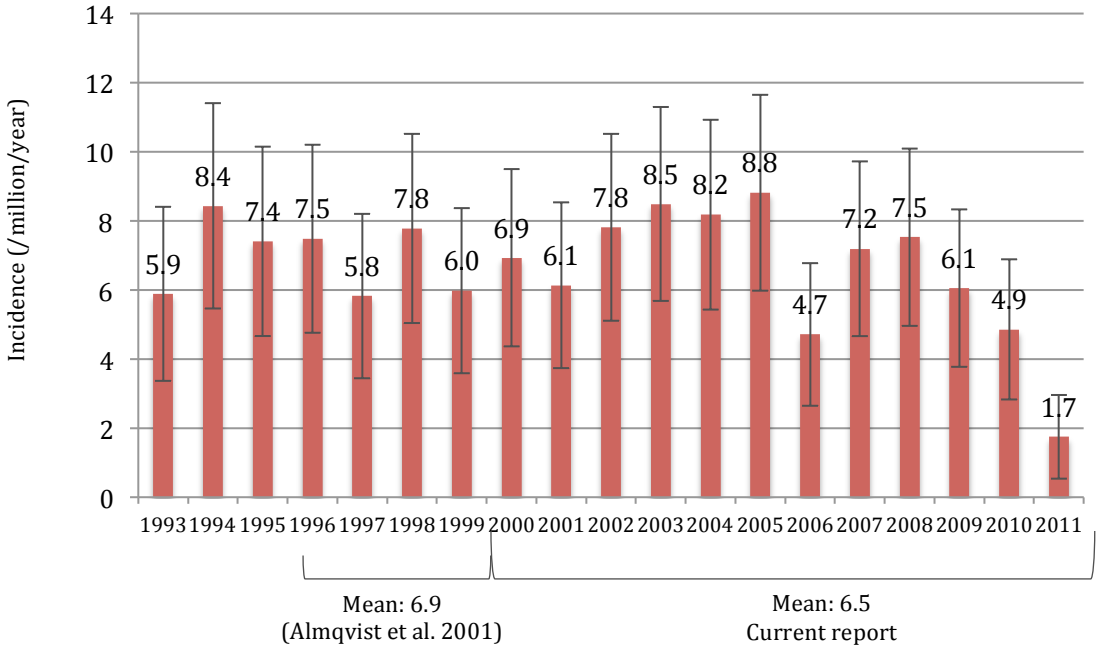
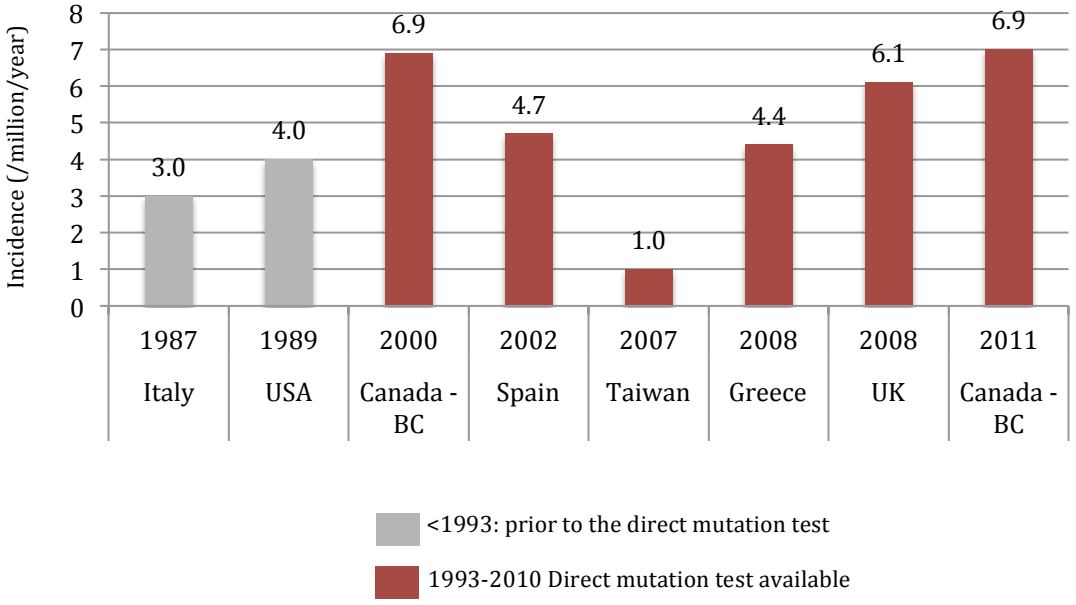


Figure 25. Global estimates of incidence over time and geographic region. For comparative purposes, studies after 1993 include only diagnoses confirmed by genetic test



Sources of error: caveats in the incidence assessment are related to the accuracy of the age of onset information that is recorded in patients' clinical files. Some patients were included in the incidence calculation because they had a positive predictive test and were recorded to have become symptomatic during the study period. Other patients were included who had never undergone the genetic test (or their test results were not available) but who were also recorded to have become symptomatic during the study period. Year and/or age of symptom onset was obtained from physician notes during the chart review and was, at times, expressed as a time frame of several years rather than a specific date. Under such circumstances, the median year was recorded. For this reason, the breakdown of annual incidence may lack accuracy. Additionally, it is apparent that the incidence may me underestimated. In order to be included in the incidence calculation, the date of onset information (or date of positive diagnostic test) must be available. As the date of onset information was not available for 174 of the patients included in the prevalence estimate (patients ascertained from sources outside the HD clinic and VGH), it is possible that at least a portion of these patients experienced first onset in the past 12 years. This would result in the inclusion of these patients to the incidence estimate. For example, if only half of the 174 patients ascertained outside of the clinics experienced first onset in the last 12 years, the incidence from 2000-2011 increases from 7.2 to 8.9 per million/year. If two-thirds of the 174 patients ascertained from outside of the clinics experienced onset in the last 12 years, the incidence then becomes 9.4 per million/year. Due to the privacy of the clinical information belonging to patients outside of UBC and VGH, this date of onset information is not attainable at this time.

ICD codes and mortality rate: the number recorded deaths caused by HD (ICD code 333.4) are included in this study. Although this information does provide a rough estimate of the HD-specific mortality rate, there are many caveats associated with this assessment. Firstly, although the lives of HD patients are shortened as a result of the disease, the direct cause of death is often associated with some other ailment such as pneumonia (Heemskerk and Roos, 2010). These ailments may be

recorded instead of HD, resulting in an underestimate of the HD-specific mortality rate.

Population at risk

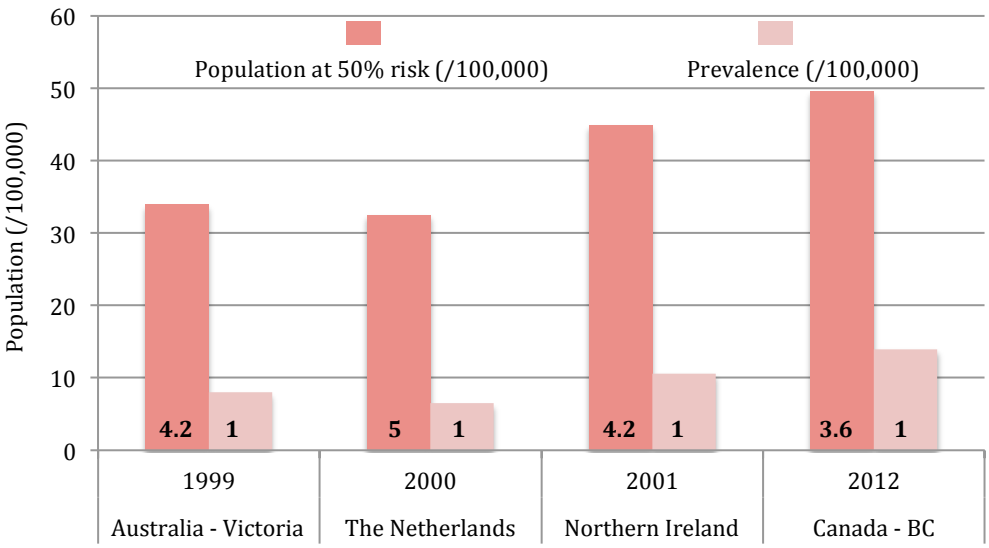
It is important to note that the population at risk for HD calculated in this study only includes the *a priori* risks and the risks after accounting for genetic test results. These classifications are useful as they allow for four distinct risk categories; 0% (negative predictive test), 25%, 50% and 100% (positive predictive test). These classifications do however lack accuracy, as an individual's specific risk for HD is dependent on his age (Harper and Newcombe, 1992). In other words, in many cases, an individual's risk for developing the disease decreases for every additional year that the individual is alive and symptom free. Clinical and demographic information was only available for a small portion of the population at risk ascertained in this study. As a result, the age-specific risk estimates could not be acquired.

Three assessments of the population at 50% risk for HD provide comparisons for the findings obtained in the present study. One study was conducted in the Netherlands (Maat-Kievit et al. 2000) one in Victoria, Australia (Tassicker et al. 2009) and the last, in Northern Ireland (Morrison et al. 2011). All other assessments of the population at risk, to our knowledge, have been calculated from estimates of prevalence (Taylor 1994, Laccone et al. 1999, Maat-Kievit et al. 2000, Harper et al. 2000, Goizet et al. 2002, Creighton et al. 2003). The Dutch, Australian and Irish studies along with the present study from BC, have all calculated the prevalence and the population at risk directly from the specific population at hand. When comparing the prevalence in proportion to population at risk between these studies, it is apparent that the Dutch study has the largest population at 50% risk relative to prevalence, with the population at 50% risk being five times the estimated prevalence (Figure 21). The Australian and Irish studies follow with a population at 50% risk that is 4.2 times the prevalence (Figure 26). The present study from BC appears to have the lowest population at 50% risk relative to prevalence – only 3.6 times the prevalence (Figure 26). The relative

population at 50% risk from the Dutch study is keeping with Conneally's theory of 1:5 affected: at 50% risk ratio (Conneally, 1984). The Australian and Irish studies are lower than would be expected by this theory but are equal to each other and may represent a more appropriate ratio, than the commonly used 1:5, for future reviews. The relative population at risk in BC is the lowest of the four. This seemingly low BC estimate may be due to one of two potential factors: an overestimate of prevalence or an underestimate of the population at risk. In this study, a high degree of rigor was applied to the ascertainment of affected patients that were included in the prevalence estimate. Multiple methods of ascertainment including follow-up on secondary cases were involved in the ascertainment process. All patients who were included had been diagnosed by a physician and the majority of these patients were confirmed by a genetic test (Table 2). Conversely, fewer avenues were available in the ascertainment of individuals at risk. Individuals at risk were either active patients at the UBC HD clinic or VGH who were referred for predictive testing and/or counselling or they were individuals included on the pedigrees of active clinic patients. The clinic counselling team and the HSC resource director were able to provide some information for the updating of family pedigrees. However, no further steps could be taken to follow up with families for further update. Approximately 3,500 (65%) of those at risk individuals that were included in the final estimate were ascertained from family pedigrees and were not active clinic patients. Unlike those affected patients ascertained from pedigrees, these individuals at risk were not assigned certainty measures. Assigning certainty measures to at risk individuals would not improve the accuracy of the data, as there was no concern for overlap; individuals at risk were only ascertained from one source – the chart review. A substantial portion of the pedigrees included in the at-risk calculation may be outdated and may not include the children that were born since the proband's most recent clinic visit. In addition, approximately 10% of the family files at the HD clinic did not include pedigrees or lists of family members. This may be related to the independence of the direct mutation test; test participants are no longer reliant upon the medical history of their family members as they were during linkage analysis. As a result, first or second-degree family

members of these patients lacking pedigrees who live in BC would have been missed, contributing further to an underestimate of the population at risk.

Figure 26. The ratio of population at 50% risk to the prevalence of HD in 4 different populations



The population at risk for HD in BC appears to be approximately double in the "Rural" region as compared to the "Urban" region. Similar to the distribution of the affected patient population, this difference may either be a reflection of under-ascertainment in the "Urban" region as compared to the "Rural" region or it may be an indication that the "Rural" region does in fact have a larger population at risk for HD. It is unlikely that this difference is the result of an under ascertainment in the "Urban" region. At risk individuals were not ascertained from sources outside of the HD clinic and VGH and as pedigrees were only available from the UBC HD clinic, the ascertainment of at risk individuals in the "Urban" region is likely more thorough than that from other BC regions. When the "Urban" and "Rural" population at risk analysis was reproduced for Vancouver Island (Victoria designated as "Urban" and any other Island region, "Rural"), results similar to those regarding prevalence were revealed. The population at (50 and 25%) risk in Victoria (using empirical data only) was 89.0/100,000 (1/1,123) and that outside Victoria was 8.5/100,000 (1/12,000). The tendency for the population at risk to live outside of Vancouver by

over two hours may be related to the financial pressure associated with being part of an HD family and thus the inability to afford living in this financially pressing Greater Vancouver region.

The difference may, in part, be due to the fact that "Rural", for the purposes of this study, was defined as any location in BC that is more than two hours from Vancouver by car. Therefore populous "Urban" centers, such as Victoria, are included in the "Rural" category, adding a relatively large number to the pool of individuals at risk. Despite this definition, it is apparent that the majority of individuals at risk in this province are living more than two hours from Vancouver, and in turn, more than two hours from the HD clinic. Therefore, individuals at risk wishing to participate in predictive testing are required to travel long distances in order to do so. This information supports the requirement in this province, for more equitable access to predictive testing. A telehealth[8] program in BC is currently in its development phase (Alice Hawkins, unpublished). This program aims to provide access to predictive testing for this large proportion of the population at risk that is out of the Vancouver "Urban" region.

The geographic distribution of individuals at risk among BC health regions seems to show an even dispersion in proportion to the population living in each region. Although this suggests that there is no specific regional 'HD hotspot' in BC, surveying those at risk ascertained from pedigrees (n=3,377) and those for whom an address was not available (n=61), is required in order to gain a more accurate assessment of the true distribution. Despite this uncertainty, this study provides the first ever estimate of the distribution of the population at risk for HD in BC. This assessment may aid in region-specific care planning and resource allocation for those in need of HD services.

Predictive testing

In addition to the 634 individuals who have undergone predictive testing in BC, 36 individuals were found to have received a positive predictive test result from

[8] Telehealth uses videoconferencing and supporting technologies to put patients in touch with health professionals across distances. It is especially useful in remote areas where patients have to travel long distances to meet health professionals (Ministry of Health 2012).

outside of BC; this information was available from family pedigrees. The existence of these additional 36 tests raises the possibility that there are other unknown individuals who had predictive testing but did not reveal their results to their families. It is thus likely that total number of predictive tests ascertained in BC during this study reflects an underestimate of the total number of individuals living in BC who have received predictive test results.

A different equation for calculating the uptake of predictive testing was used in the present study than was applied in the most recent account of uptake in BC (Creighton et al. 2003). As a result, in order to conduct a meaningful comparison of these two studies and in turn understand trends in uptake over time in this province, uptake was re-calculated for each study period using both the original equation and the revised equation. Additionally, three methods of calculating the population at 50% risk were applied to both equations (Table 12). It appears that the uptake of predictive testing has declined in BC since 2000. Using all methods of calculating the population at risk and both equations for uptake, all 2000-2012 values remain lower than those from 1987-2000. This decline in uptake may be related to the greater enthusiasm surrounding predictive testing during its beginning stages and potentially higher hopes of the development of a treatment during these first ten years of predictive test availability. From Table 12, it can be noted that the uptake results differ considerably between equations. This supports the notion that a standard method must be adopted when considering the uptake of predictive testing in a population. Without a standardized method, uptake cannot be meaningfully compared between populations and over time. Secondly, the uptake results differ considerably when different methods are used to estimate the population at 50% risk. As most studies incorporate an estimate of the 50% risk population by multiplying the prevalence by 4.2 (Tassicker et al. 2009, Morrison et al. 2011) or by 5 (Conneally 1984, Creighton et al. 2003), it is important that an accurate estimate of prevalence is available. Underestimates of prevalence render overestimates of predictive testing uptake. It is therefore important that populations wishing to assess the predictive testing uptake using theoretical

methods of estimating the population at 50% risk first ensure that a thorough patient ascertainment study has been conducted in their population.

Table 12. Comparing the uptake of predictive testing in BC over two study periods. Three separate methods of calculating the population at risk are applied while two separate methods of calculating the uptake are applied.

Study period	Pop. At 50% risk	P	D	UPTAKE Method 1 D/P	UPTAKE Method 2 D/P+(P*t/18.8)
	Method 1: Theoretical (prevalence of 8.4/100,000)				
1987-2000	1268	672	354	53%	**32%**
2000-2012	1626	976	280	29%	**18%**
	Method 2: Theoretical (prevalence of 13.9/100,000)				
1987-2000	1980	1049.4	354	34%	**20%**
2000-2012	2536	1522	280	18%	**11%**
	Method 3: Empirical data				
1987-2000	1758	932	354	38%	**23%**
2000-2012	2252	1351	280	21%	**13%**

D= number of predictive tests performed; **P=** number of individuals in the population at 50% risk for HD who are eligible for predictive testing (age 18 or above); **t=**number of years in the study period; **18.8=** average duration of disease (HD symptoms) (Tassicker et al. 2009).

Direct and immediate implications

This study comprises the first assessment of the epidemiology of Huntington Disease (HD) in British Columbia (BC). Generation of HD services in BC has occurred, thus far, without data regarding the prevalence, incidence, population at risk and geographical distribution of HD in BC. Without these figures, it has been difficult to produce a compelling argument to justify the allocation of public resources to aid in supporting these services. Moreover, epidemiological estimates extrapolated from other regions have provided underestimates (Creighton et al. 2003). This study provides the baseline numbers that are essential for an accurate assessment of the true service and care requirements for HD in this province.

Through our physician surveys, we have identified specific regions in this province where patients are numerous. Information obtained regarding the number of patients cared for by each responding physician represents minimum numbers that may be useful for targeting new programs. For example, one general practitioner from Port Alice indicated that he cares for ten HD patients, none of who have been referred to the HD clinic or VGH. No neurologist works in or near to Port Alice, indicating this GP may be the sole care provider for these patients. This GP may be suitable as a key player in a potential pilot project to act as a "remote representative" for HD in BC. As resources are scarce and public funding involvement absent in in this province, recognizing professionals who are already involved with the disease as remote representatives, may be an appropriate first step towards strengthening the HD resource infrastructure in this province. Further, with a population of only 821 (BC Stats, 2011), up to 1/82 people in Port Alice may suffer from HD – this is clearly the highest HD frequency observed in BC.

If we extrapolate from the epidemiological estimates obtained for BC, this study suggests that countrywide, there may be up to 4,700 (95% CI: 4,586-4,862) patients affected with HD and 17,000 individuals at 50% risk presently living in Canada, and approximately 250 new cases may be diagnosed this year. Further, this study implies that in the United States, there may up to 42,000 (95% CI: 42,225-42,945)

individuals affected with HD and 153,000 individuals at 50% risk presently living in the States, and approximately 2,252 new cases may be diagnosed this year.

It is clear from this study that HD has a higher frequency than previously recognized. This has implications not only for service delivery, but also for drug development. It is important to share these findings with the pharmaceutical industry, as investment in therapeutic development for HD, in addition to providing benefit to the patients, will provide benefit to companies. The argument that HD is infrequent is laid to rest.

Conclusion

This study comprised the most modern and comprehensive assessment of HD epidemiology to date. A minimum prevalence ranging from 12.5-14.9/100,000 (1/8,000-1/6,711) (95% CI: 11.5-16.0 [1/8,696-1/6,250]) was estimated for the general population and approximately 17.20/100,000 (1/5,814) (95% CI: 17.19-17.20) for Caucasians. This is the highest prevalence estimate to be reported since the advent of the direct mutation test in 1993 and is more than twice as high as that reported by the most recent Canadian assessment (Shokeir, 1975). The incidence observed in this study was between 6.9-7.2 per million/year (95% CI: 4.4-7.9) between the years 2000 and 2011 and is very close to the incidence estimated in BC for 1996-1999 – 6.9 per million/year (Almqvist et al. 2001). The population at risk was found to be 94.0/100,000 or 1/1,073. This study was the first to estimate both the population at 50% *a priori* risk and the population at 25% *a priori* risk and was only the fourth study to calculate the population at risk empirically from the specific community at hand (Maat-Kievit et al. 2000, Tassicker et al. 2009, Morrison et al. 2011).

This study utilized a significantly greater number of ascertainment sources than did previous reports on HD epidemiology and thus may comprise the most confident results to date. It is also the first study to provide information regarding ethnicity of HD patients. For these reasons, this study may set a precedent for future work and may be compared with confidence to future findings in order to gain a greater understanding of the true epidemiology of HD across geographic regions, between ethnicities and over time.

Future direction

When ascertaining symptomatic patients, only *minimum* prevalence can be estimated as individuals affected with HD may not seek medical attention or the study group may fail to obtain the medical records for every patient. These limitations become more apparent with a shorter study period. The frequency of intermediate allele (IA), reduced penetrance (RP) and full penetrance (FP) alleles in the general population should be assessed. This information is important for an understanding of the true prevalence, the true heterozygousity frequency (Harper, 1991) and for predicting future patterns of HD prevalence in the population. A large random sample population would be required for this analysis such as blood spot cards[9] from local hospitals or random DNA samples from unrelated studies of the general population.

Additionally, an investigation of the HD mutation frequency in residents of nursing homes would provide further information regarding the disease prevalence. Dementia is widespread in Canada; 8% of those over 65 and 35% of those over 85 years of age suffer from dementia (Long term care Canada 2011). This prevalence is expected to increase significantly more due to the aging of the baby boom cohort (Statistics Canada, 2011). Although commonly characterized as having a distinct phenotype (Walker, 2007), symptoms can vary quite dramatically between cases of HD (personal correspondence). Very late onset HD may exist in the form of a dementia-like phenotype without chorea, leading to the possibility of missed cases. An assessment of the HD mutation frequency in the elderly population would allow for the opportunity to detect potential dementia-like cases of HD. This would in turn, further increase the estimated prevalence.

An assessment of the mean CAG size of control chromosomes across populations of varying prevalence is required. Warby et al. (2011) suggest that the difference in prevalence observed between ethnicities is attributable in part to

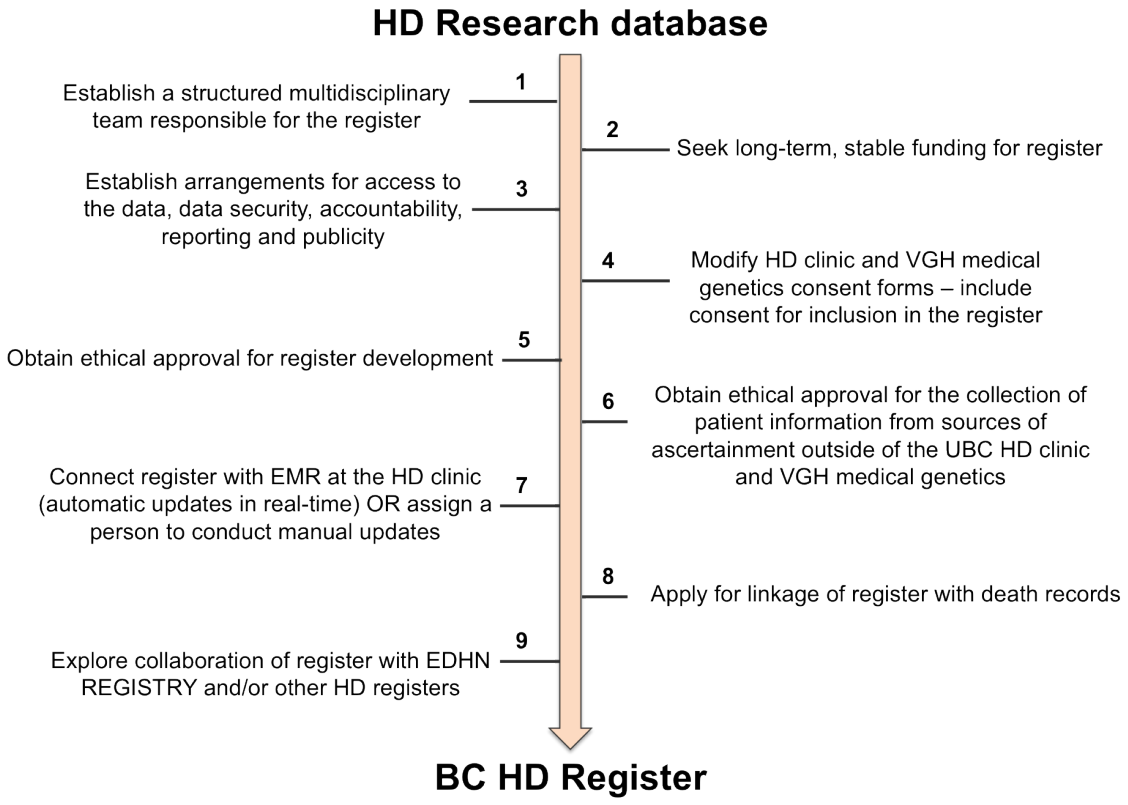
[9] Blood spot cards are cards that contain small blood samples for every newborn baby in hospitals as a part of the newborn screening program. Newborn Screening can identify babies who may have one of a number of treatable disorders.

specific haplotypes. Falush (2009) suggested the cross-ethnic differences in prevalence observed might be explained by the variation in CAG size in each population's control (non CAG expanded) chromosome pool. With data from the present study, BC is now a population possessing confident prevalence findings and haplotype data as well as data regarding CAG size of control chromosomes. BC is therefore a well-suited population in which to conduct in an analysis of the above-mentioned hypotheses.

Finally, an extensive database has been created for the purposes of this study, containing a vast array of clinical and demographic information for individuals in BC who have been seen at the UBC HD clinic or VGH medical genetics. In order to maximize the potential of this database, it is crucial that it be maintained and improved. The long-term goal is to convert this database into a provincial HD register. A number of steps are required to ensure success of this process (Newton and Garner, 2002) (Figure 27). 1) A structured, multidisciplinary team responsible for the register must be established. The UBC HD clinic already composes the framework for this team; a multidisciplinary team with specialty in HD provides care to patients and individuals at risk in the clinic. The addition of a register manager would largely complete this team. 2) Long-term, stable funding must be pursued and 3) arrangements must be made regarding access to the data, data security, accountability, reporting and publicity. 4) It might be necessary (depending on the privacy laws in place at the time) to modify accordingly, the HD clinic and VGH medical genetics consent forms to include consent for participation in the register (this will depend largely on the decisions made in number 3). 5) Ethics approval must be obtained for development of the register. 6) Since the register would ideally include information of every HD patient in the province, ethical approval must be acquired for the addition of clinical and demographic information to the register from patients who were ascertained for this project from sources outside of the HD clinic and VHG (nursing homes, neurologist and GP records, family surveys). For register data to be updated, it may be beneficial to link the register with the electronic medical records (EMR) at the HD clinic. This would allow for the potential of new patient information to be automatically added to the

database. As only specific information will be required for transfer from EMR to the register, specialized programming software may be required for this step. The alternative to this would involve an individual responsible for data-upkeep. 8) In order to ensure every individual is living and in turn the register is constantly up to date, the register should be linked to death records. An application to British Population Data BC must be made in order to request linkage to death records (Population Data BC 2012). 9) Finally, as the database has been designed to mirror fields collected for the European Huntington's disease network (EHDN) registry, the BC register may be well suited for collaborating with this registry for the potential to begin an international register for Huntington Disease.

Figure 27. Steps to be taken to convert the HD research database into a register for HD in BC



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Appendix 1a

Worldwide reports on the prevalence of HD from 1940-2010

POPULATION	DATE OF SURVEY	PREVALENCE (#/100,000)	REFERENCE
Australia (New South Wales)	1996	6.3	(McCusker et al 2000)
Australia (Queensland)	1976	5.8	(Wallace & Parker 1979)
Australia (Queensland)	1969	6.3	(Wallace & Parker 1973)
Australia (Tasmania)	1990	12.1	(Pridmore 1990)
Australia (Victoria)	1963	4.6	(Brothers 1964)
Austria	1993-1997	10	(Laccone et al 1999)
Belgium	1970	1.6	(Husquinet 1973)
Canada (Quebec)	1963	3.4	(Barbeau et al. 1964)
Canada (Manitoba & Saskatchewan)	1975	8.4	(Shokeir 1975)
China (Hong Kong)	1984-1991	0.4	(Leung et al 1992)
China (Hong Kong)	1984-1991	0.4	(Chang et al 1994)
Croatia	2002	1	(Hecimovic et al 2002)
Egypt (Assiut)	1988-1990	21	(Kandil et al 1994)
Finland	1986	0.5	(Palo et al 1987)
France (North-West)		5	(Petit & Salomez 1985)
Germany (Kassel)	1950	2.6	(Al-Jader et al 2001)
Germany (Rhineland)	1933	3.2	(Al-Jader et al 2001)
Germany (West, without Berlin & Saarland)	1950	2.2	(Al-Jader et al 2001)
Germany (West, without Berlin & Saarland)	1939	2.2	(Al-Jader et al 2001)
Germany	1993-1997	10	(Laccone et al 1999)
Greece	2004	3.95	(Panas et al. 2011)
Guam (Chamorros)	1967	0	(Chen et al 1968)
Iceland	1963	2.7	(Gudmundsson 1969)
India (Pakistan, Punjab and Gujerat)	1990	1.7	(Shiwach & Lindenbaum 1990)
Italy (Aosta)	1982-1991	5	(Al-Jader et al 2001)
Italy (Emilia & Parma)	1980	4.8	(Al-Jader et al 2001)
Italy (Ferrara province)	1987	1.9	(Govoni et al 1988)
Italy (Florence)	1970-1979	4.1	(Groppi et al 1986)
Italy (Frogiuone)	1981	2.6	(Frontali et al 1990)
Italy (Genoa Region)	1930-1977	28	(Roccatagliata et al 1979)
Italy (Genoa-Savona)	1973	4.5	(Roccatagliata & Albano 1976)
Italy (Latima)	1981	3	(Frontali et al 1990)
Italy (Lazio)	1981	2.6	(Frontali et al 1990)
Italy (Puglia)	1980	2.9	(Al-Jader et al 2001)
Italy (Rieti)	1981	5.6	(Frontali et al 1990)
Italy (Rome)	1981	2.5	(Frontali et al 1990)
Italy (Tuscany)	1978	2.3	(Al-Jader et al 2001)
Italy (Viterbo)	1981	1.5	(Frontali et al 1990)
Japan (Aichi)	1959	0.4	(Kishimoto et al 1957)
Japan (Ibaraki)	1982	0.1	(Kanazawa et al 1990)
Japan (San-in)	1993	0.7	(Nakashima et al 1996)
Japan (San-in)	1997	0.7	(Adachi & Nakashima 1999)
Malta	1994	11.8	(Gassivaro Gallo et al 1999)
Malta		7.8	(Al-Jader et al 2001)
Mauritius (European descent)	1977	46.2	(Hayden et al 1981)
Mexico	2008	4	(Alonso et al 2009)

New Zealand	1996	5.7	(Harper 1996)
Nigeria (Ibadan)	1984	0.2	(Aiyesimoju et al 1984)
Norway	1930	6.9	(Saugstad & Odegård 1986)
Norway	1940	6.7	(Saugstad & Odegård 1986)
Norway	1950	5.8	(Saugstad & Odegård 1986)
Poland (Pruszkow)	1960	4.8	(Al-Jader et al 2001)
Russia (6 populations in Central Asia)		1.3	(Kirilenko et al 2004)
Russia (Volgograd and Volzhsky)		0.6	(Kirilenko et al 2004)
Russia (Vladimir Oblast)		1.9	(Kirilenko et al 2004)
Slovenia	2006	5.2	(Peterlin et al 2008)
South Africa	1979	0.6	(Hayden et al 1982)
South Africa	1979	0.01	(Hayden et al 1980)
South Africa (Cape Coloured, mixed race)	1976	3.5	(Hayden & Beighton 1977)
South Africa (Mixed race)	1979	0.9	(Hayden & Beighton 1977)
South Africa (White and Coloured population)	1979	2.2	(Hayden et al 1980)
South Africa (Whites Afrikaans)	1979	0.4	(Hayden & Beighton 1977)
Spain (Salamanca)		8.4	(Ruiz et al 1985)
Spain (Cadiz province)	1968	1.3	(Calcedo Ordóez 1970)
Spain (Valencia)	1987-1992	5.4	(Burguera et al 1997)
Sweden	1965	4.7	(Mattsson 1974)
Sweden	1985	5.6	(Al-Jader et al 2001)
Switzerland	1993-1997	10	(Laccone et al 1999)
Taiwan	2007	0.42	(Chen et al. 2010)
Tanzania (Mount Kilimanjaro, Bantu)	1980	7	(Scrimgeour 1981)
UK (England, Carlisle)	1961	2.8	(Brewis et al 1966)
UK (England, Cornwall)	1950	5.6	(Bickford & Ellison 1953)
UK (England, Cornwall)	1987	4.9	(Harper 1996)
UK (England, Devon)	1987	4.6	(Harper 1996)
UK (England, East Anglia)	1971	9.19	(Caro 1977)
UK (England, Essex)	1965	2.5	(Heathfield 1967)
UK (England, Leeds)	1966	4.2	(Al-Jader et al 2001)
UK (England, Northamptonshire)	1967-1968	6.3	(Oliver 1970)
UK (England, Northamptonshire)	1960	7.2	(Reid 1960)
UK (England, Northamptonshire)	1954-1955	6.5	(Pleydell 1955)
UK (England, Oxford region)	1985	5.7	(Shiwach 1994)
UK (England, Somerset)	1965	5.5	(Al-Jader et al 2001)
UK (England, Wessex)	1987	3.7	(Harper 1996)
UK (Indian subcontinent immigrants)	1990	1.7	(Shiwach & Lindenbaum 1990)
UK (Ireland, Northern)	1991	6.4	(Morrison et al 1995)
UK (Ireland, Northern, County Donegal)	1991	1.6	(Morrison & Nevin 1993)
UK (Scotland, Grampian, north-east)	1984	10	(Simpson & Johnston 1989)
UK (Scotland, South-East)	1967	7.2	(Cameron & Venters 1967)
UK (Scotland, West)	1960	5.2	(Bolt 1970)
UK (Wales, North)	1981	5.5	(Quarrell et al 1988)
UK (Wales, South & Glamorgan)	1988	8.4	(MacMillan & Harper 1991)
UK (Wales)	1994	6.2	(James et al 1994)
UK (Wales, South)	1981	8.9	(Quarrell et al 1988)
UK (Wales, South)	1971	7.6	(Walker et al 1981)
UK (Wales, South)	1971	7.6	(Harper et al 1979)
UK	2008	6.25	(Sackley et al 2011)
UK	2010	12.4	(Rawlins, 2010)

USA & Australia (Whites)		5	(Al-Jader et al 2001)
USA (African Americans)	1940	1.5	(Reed & Chandler 1958)
USA (Maryland)	1980	5.2	(Folstein et al 1987)
USA (Maryland, African Americans)	1980	6.4	(Folstein et al 1987)
USA (Michigan)	1940	4.1	(Reed & Chandler 1958)
USA (Minnesota)	1955	5.4	(Pearson et al 1955)
USA (Minnesota, Olmsted county)	1990	2	(Kokmen et al 1994)
USA (Minnesota, Olmsted county)	1960	6	(Kokmen et al 1994)
USA (Minnesota, Rochester)	1955	6.7	(Kurland 1958)
USA (New York)	1973	3.5	(Al-Jader et al 2001)
USA (South Carolina)	1980	1	(Wright et al 1981)
USA (South Carolina, White)	1980	4.8	(Wright et al 1981)
Venezuela		0.5	(Paradisi et al 2008)
Venezuela (Lake Maracaibo)	1973	699.2	(Avila-Giron 1973)
Yugoslavia (Rijeka district)	1981	4.5	(Sepci et al 1989)
Zimbabwe (Manicaland region, Shona)	1988-1989	0.8	(Scrimgeour & Pfumojena 1992)
Global Average (including Lake Maracaibo)	**1930-2010**	**11.4**	
Global Average (excluding Lake Maracaibo)	**1930-2010**	**5.1**	

Appendix 1b

Worldwide reports on HD prevalence, incidence and population at risk by region

REGION	YEAR OF REPORT	PREVALENCE (#/100,000)	INCIDENCE (#/million/year)	POP AT-RISK (#/100,000)	REFERENCE
The Americas					
Canada					
Quebec	1963	3.4	-		Barbeau et al. 1964
Prairies (Saskatchewan & Manitoba	1975	8.4	-		Shokeir 1975
British Columbia	1993-2000	-	6.9	42.0	Almqvist et al. 2001, Creighton et al. 2003
Regional average		5.9	6.9	42.0	
United States					
Michigan	1940	1.5 4.1	-		Reed and Chandler, 1958
Maryland	1980	6.4 5.2	-		Folstein et al. 1987
Minnesota	1950-1989	2.0	2.0-4.0		Folstein et al. 1987
South Carolina	1980	1.0 4.8	-		Wright et al. 1980
New York	1973	3.5	-		Al-Jader et al. 2001
Regional average		3.6	3.0		
Mexico					
Mexico	2008	4.0	-		Alonso et al. 2009
Venezuela					
Venezuela	2007	0.5	-		Paradisi et al. 2008
Lake Maracaibo	1973	699	-		Avila-Giron, 1973
Europe					
The United Kingdom					
Carlisle	1961	2.8	-		Brewis et al. 1966
Cornwall	1950 1987	5.6 4.9	-		Bickford and Ellison, 1953, Harper 1996
Devon	1987	4.6	-		Harper 1996
East Anglia	1971	9.2	-		Caro 1977
Essex	1965	2.5	-		Heathfield, 1967
Leeds	1966	4.2	-		Al-Jader et al. 2001
Northamptonshire	1967-1968	6.3	-		Oliver 1970
Oxford	1985	5.7	-		Shiwach 1994
Wessex	1987	3.7	-		Harper 1996
Somerset	1965	5.5	-		Al-Jader et al. 2001
Northern Ireland	1991	6.4	-		Morrison et al. 1995
County Donegal -	1991	1.6	-		Morrison and Nevin 1993

Ireland					
Northern Ireland	2001	10.6	-	44.9	Morrison et al. 2010
Grampian	1984	10.0	-		Simpson and Johnston, 1989
South East Scotland	1967	7.2	-		Cameron and Venters, 1967
West Scotland	1960	5.2	-		Bolt, 1970
Northern Wales	1981	5.5	-		Quarell et al. 1988
South & Glamorgan	1988 1994	8.4 6.2	-		Macmillan and Harper, 1991, James et al. 1994
South Wales	1981	8.9	-		Quarell et al. 1988
South Wales	1971	7.6	-		Walker et al. 1981
UK	2008	5.9-6.5	4.4-7.8	37.5	Sackley et al. 2011
England & Wales	2010	12.4	-		Rawlins 2010
Regional average		6.3	6.1	41.2	
Non-UK countries					
Belgium	1970	1.6			Husquinet, 1973
Croatia	2002	1.0			Hecimovic et al. 2002
France	1985	5.0		25.0	Petit and Salmonez, 1985, Goizet et al. 2002
Germany	1993-1997	10.0		30.0	Laccone et al. 1999
Greece	1995-2008	2.5-5.4	2.2-4.4		Panas et al. 2011
Italy	1981	5.6			Frontali et al. 1990
Italy (Ferrara)	1871-1987	0.36-3.1	2.0		Giovani et al. 1988
Malta	1994	11.8			Gasivaro-Gallo 1990
Netherlands	2002	6.5		32.5	Maat-Kievit et al. 2000
Norway	1950	5.8			Saugstad and Odegard 1986
Poland	1960	4.8			Al-Jader et al. 2001
Russia	2004	1.9			Kirilenko et al. 2004
Slovenia	2006	5.2			Peterlin et al. 2008
Spain	1985	8.4			Ruiz et al. 1985
Spain	1994-2002		4.7		Ramos-Arroyo et al. 2004
Sweden	1985	5.6			Al-Jader et al. 2001
Switzerland	1993-1997	10.0			Laccone et al. 1999
Iceland	1963	2.7			Gudmundsson 1969
Regional average		5.4	3.4	29.2	
Africa					
Egypt	1988-1990	21.0	-		Kandil et al. 1994
Zimbabwe	1988-1989	0.8	-		Scrimgeour and Pfumojena 1992
Tanzania	1980	7.0	-		Scrimgeour 1981

South Africa	1979	2.2 0.9 0.4 0.01	-		Hayden and Beighton 1977, Hayden et al. 1980
Regional average		1.7			
Asia					
Taiwan	2007	0.42	1.0		Chen and Lai 2007
China (Hong Kong)	1984-1991	0.4 0.4	-		Leung et al. 1992
India	1990	1.7	-		Shiwach and Lindenbaum 1992
Japan	1997	0.7 0.7	-		Adachi and Nakashima 1999
Guam (Chamorros)	1967	0.0	-		Chen et al. 1968
Regional average		0.5	1.0	Not calculated	
Australia & New Zealand					
Australia	1994			27.5	Taylor 1994
New South Wales	1996	6.3	-		McCusker et al. 2000
Queensland	1976	5.8	-		Wallace and Parker 1979
Tasmania	1990	12.1	-		Pridmore 1990
Victoria	1963	4.6	-		Brothers 1964
New Zealand	1996	5.7	-		Harper 1996
Regional average		6.8	Not calculated	27.5	

Rows highlighted in pink comprise studies performed after the advent of the direct mutation test. Numbers in light grey were not included in the regional average due to methodological inaccuracies.

Appendix 2

A list of each field included in the HD database and a description of each

Field Name	Field Description
HD Clinic Data Table	
Personal Information	
Unique ID #	A number unique to each individual entered in the database
Gender	
Origin	Country of origin
Ethnicity	Field options following the EHDN guidelines[10]
Date of Birth	
Date of Death	
Cause of Death	What was the direct physiological cause of death
Deceased?	Yes or No
Demographic Information	
BC Health Authority Region of residency	• Vancouver Coastal • Fraser • Vancouver Island • Northern • Interior
City, Province and Postal Code of residence	
"Urban" or "Rural" residence	Rural= more than two hours from Vancouver by car Urban= within two hours from Vancouver by car
Referring physician	Name of the physician who referred the patient to VGH Medical genetics or Vancouver's Centre for HD
Referring physician city	City of referring physician's practice
Initial Clinic Location Information	
HD Clinic	Reason for initial clinic visit: • HD Medical clinic • Referred for PT • PT + HD Medical Clinic • Other
PT/DT?	If the patient has undergone an HD test, was it a predictive test or a diagnostic test?
Family History of HD?	• Yes • No • Unknown
Genetic Test Information	
Date of genetic test report	From the DNA Diagnostic lab
Results reported to patient?	• Yes • No • Unknown
Upper CAG size	Dictates HD test results CAG ≥ 36 is a positive test result
Disease Status Information	
Risk Status	• 50% AR • 25% AR • Unknown AR • Affected

[10] The European Huntington's disease network (EHDN) registry is a multi-center collaboration aiming to obtain clinical and genetic information on a large number of individuals interested in taking part in various HD-associated studies. The registry maintains information on HD patients in Europe and is the largest database for HD patient information in the world (EHDN, 2010).

	• Pre Manifest (100% AR)
HD Status	• Symptomatic HD + • Clinical Dx • UNKNOWN • Unaffected (spouse/other) • At Risk
Disease Onset Information	
Motor age/year of onset	The age/year at which the patient was first noted to have experienced **neurological symptoms** of HD • Chorea/dystonia • Rigidity • Difficulty with balance • Difficulty breathing/swallowing
Age at Diagnosis	The age/year at which the patient was diagnosed by a physician as having HD
Age at onset source	• Family provided information • Referral letter • MD notes
UHDRS?	Has the patient undergone a UHDRS assessment? United Huntington Disease Rating Scale: Developed by the Huntington Study Group in 1996[ii] - Assessment of HD clinical features to track disease progression on a standardized scale
First UHDRS Item 17 > 2	• Item 17 = diagnostic confidence score • Sum of a number of neurological symptom assessments • 0=no symptoms • 4=severe symptoms
UHDRS Motor Score	This particular patient's diagnostic confidence score (0-4)
Most recent UHDRS	Date of most recent UHDRS patient's assessment
Additional Information	
Comments regarding HD	• Any additional information regarding the patient's HD status/ diagnosis • For example if no genetic test info available but chart mentions patient was tested in another province/country
Additional comments	• Additional comments • For example patient is a phenocopy • Any information of interest that does not fit into a database field
Family Risk Table	
Clinic pedigree number	• HD clinic family number • Members of the same family share this common number
Family risk totals	• Total number of individuals in this family at each risk category • BC residents only
Total affected – Not yet in database	• Total number of affected living individuals in this family • Not a clinic patient • BC residents only

Appendix 3

List of each long-term care home contacted in BC

	Nursing home	City
1	Cormorant Island Health Centre	Alert Bay
2	Lakes District Hospital and Health Centre	Burns Lake
3	Sunshine Lodge	Campbell River
4	McKim Cottage	Castlegar
5	Talarico Place	Castlegar
6	Burquitlam Lions Care Centre	Chemainus
7	Dr. F.W. Greene Memorial Home	Cranbrook
8	Hillcrest Extended Care Unit	Creston
9	Swan Valley Lodge	Creston
10	Fort Nelson Health Unit	Fort Nelson
11	North Peace Care Centre	Fort St. John
12	North Peace Care Centre	Fort St. John
13	Hardy View Lodge Intermediate Care	Grand Forks
14	Sunshine Manor Extended Care Unit	Grand Forks
15	Granisle Community Health Centre	Granisle
16	Hudson's Hope Health Centre	Hudson's Hope
17	Cottonwoods Extended Care Centre	Kelowna
18	David Lloyd-Jones Home	Kelowna
19	Lake Country Manor -Pleasant Meadows Lodge	Lake Country
20	Mackenzie and District Hospital and Health Centre	Mackenzie
21	McBride and District Hospital	McBride
22	Pleasant View Care Home	Mission
23	Mountain Lakes	Nelson
24	Country Squire Retirement Villa	Osoyoos
25	Arrowsmith Lodge	Parksville
26	Penticton ECU	Penticton
27	Tsawaayuus (Rainbow Gardens)	Port Alberni
28	Westhaven	Port Alberni
29	Peace River Haven	Pouce Coupe
30	Pouce Coupe Care Home	Pouce Coupe
31	Evergreen Extended Care	Powell River
32	Olive Devaud Residence	Powell River
33	Acropolis Manor	Prince Rupert
34	Prince Rupert Community Health	Prince Rupert
35	Ridgewood Lodge	Princeton
36	Eagle Park Health Care Facility	Qualicum Beach
37	The Gardens at Qualicum Beach	Qualicum Beach
38	Moberly Park Manor	Revelstoke
39	Hilltop House	Squamish
40	Kelly Care Centre	Summerland
41	Evergreen Hamlets	Surrey
42	Rosewood	Trail
43	Harbour House	Trail
44	Tumbler Ridge Community Health Centre	Tumbler Ridge
45	Gateby Intermediate Care Facility	Vernon
46	Noric House	Vernon
47	Heritage Square	Vernon
48	Brookhaven Extended Care Centre	Westbank
49	Westside Care Centre	Westbank

Appendix 4

Physician survey content

Question number	Question
1a	Do you currently care for any patients who are affected with the clinical symptoms of Huntington Disease? Y/N
1b	If yes, how many HD patients in total are under your care or supervision?
1c	How many of these patients have been genetically confirmed to carry the HD mutation (≥36 CAG repeats in the HTT gene)?
1d	How many have been diagnosed with HD solely via clinical presentation and family history (without a genetic test)?
2a	To the best of your knowledge, do any of these patients have living family members residing in BC who are currently affected with the clinical symptoms of HD?
2b	If yes, to the best of your knowledge, how many affected relatives?
3	If any of your HD patients and or/their family members live out of province, please provide the number of patients both in BC and out of province
4a	In order to avoid double counting the patients ascertained for this study, it is important to know whether your patients have also been referred to the Huntington Disease Medical Clinic at UBC Hospital or the Medical Genetics department at Victoria General Hospital
4b	To the best of your knowledge, please provide the number of patients who have been referred to the UBC Huntington Disease medical clinic or Victoria General Hospital Medical Genetics and those who have not.

Family survey content

Number of living symptomatic* HD patients	City of residence	Province of residence	Referring GP or neurologist**	OR have visited the UBC HD clinic or Victoria General Hospital Medical genetics dept.(Y/N)

Appendix 5

The breakdown of certainty measures showing the number of pedigrees last updated on each particular year and the corresponding certainty measure

Year pedigree last updated	Number of patients ascertained from pedigrees
Unknown	18
1995	1
1996	2
1997	2
1998	3
1999	5
2000	4
2001	4
2002	3
2003	15
2004	7
2005	5
2006	3
2007	8
2008	6
2009	3
2010	8
2011	26
2012	2
	127

Appendix 6

City	Chart review (UBC/VGH)	Family Pedigree/ patient file	Physician responses (patients)	Physician responses (Family members with HD)	Family Surveys	Long-term care homes	Overlap risk scores	Overlap risk score justification
100 Mile House			2					
Abbotsford	16	7						
Aiyansh			4					
Aldergrove	2		1					
Agassiz	1		1					
Armstrong	5		2 | 1	1			1, 1	A
Ashcroft			1					
Bella Coola			4					
Berriere			1					
Blind Bay	1							
Burnaby	18	4						
Burns Lake	1	4	2					
Campbell River	5	1						
Castlegar	2							
Chase	1		1					
Chemainus	2							
Chilliwack	11	1, 4						
Christina Lake			1					
Clearwater			2					
Cobble Hill	1		2					
Comox	2	1						
Coquitlam	4							
Courtenay	3							
Cranbrook		1						
Crawford Bay			1					
Creston	1							
Cumberland	1		1					
Dease Lake			1					
Delta	5	3						
Dawson Creek	2							
Duncan	4	2	1	1			2, 2	
Elkford			3					
Enderby			3					
Fort St. James			1					
Fort St. John	3							
Ferni	2	1	4	2			2, 2, 2, 1, 1, 1	B
Fort Nelson		2						
Fraser Lake	1	1	1				2	C
Fruitvale			3					
Gabriola			3					
Garabaldi Highlands								
Gibsons	1		6					
Goldon			8					
Gold River			1					
Hazleton			2					
Hope	2	1	6					
Houston			1					
Invermere			1 | 1				1	D
Kaleden			1					
Kamloops	13	1	3	2			2, 2, 2, 2, 2	E
Kaslo			3					
Kelowna	16	8						
Keremeos			1					
Kimberley			7 | 1	2			1, 1, 1	F
Kitamat		1	1					

City	Chart review (UBC/VGH)	Family Pedigree/ patient file	Physician responses (patients)	Physician responses (Family members with HD)	Family Surveys	Long-term care homes	Overlap risk scores	Overlap risk score justification
Koksilah			1	1			1, 1	G
Lac la Hache	1							
Ladysmith	3		6					
Lake Cowichan	1		2					
Langford	1							
Langley	8	2						
Lantzville	2							
Lazo	1							
Lillooet			2					
Logan lake	1							
Lumby			3					
Lytton	1							
Mackenzie	2	4						
Madeira Park			1					
Malahat	1							
Maple Ridge	8							
Mara	1							
Masons Landing			1					
Masset			2					
Mayne			1					
McBride	1							
Meritt			3					
Mill Bay	1	1						
Mission	6							
Nakusp			2					
Nanaimo	13	2	5				2, 2, 2, 2, 2	H
Nanoose Bay	1	1						
Naramata			1					
Nelson	1							
New Denver		1	4					
New Westminster	8	1						
North Vancouver	15	1						
Parksville	2	1						
Pemberton			3					
Pender Island			1					
Penticton	8					1	2	I
Port Alberni	5	3						
Port Alice			2 10				1 (x10)	J
Port Coquitlam	9	2						
Port Hardy	1							
Port Moody	4	2						
Powell River	5	4	1	1		1	1, 1, 2	K
Prince George	14							
Prince Rupert	1	1	2					
Princeton	1				2		2, 2	L
Pritchard	1							
Quadra Island	1							
Qualicum Beach	1	1						
Quathiaski Cove			1					
Queen Charlotte			1					
Quesnel	3							
Richmond	10							
Rossland			6					
Salmon Arm	2							
Saltspring Island	3	4						
Sayward			1					
Sechelt			8					
Shawnigan Lake	2	6						

City	Chart review (UBC/VGH)	Family Pedigree/ patient file	Physician responses (patients)	Physician responses (Family members with HD)	Family Surveys	Long-term care homes	Overlap risk scores	Overlap risk score justification
Slocan Park			1					
Smithers			5					
Sooke	2							
Southbank	1							
Sparwood	2		3					
Squamish	2							
Stewart			1					
Summerland	3							
Surrey	42	11	2			14	2, 2	M
Terrace	4							
Trail	3	2						
Tsawwassen	1				4		1, 1, 1, 2	N
Ucluelet			2					
Unknown	8	4						
Valemount			1					
Vancouver	76	15, 1						
Vanderhoof			2 | 1				1	O
Vernon	7							
Victoria	67	10, 3	1	2			2, 2, 2	P
Watson Lake	1							
West Vancouver	6							
Westbank	3					2	2, 2	Q
Whistler			8					
Whiterock	1							
Williams Lake	5	1	6 | 1	1			2,2	R
Winfield	1		4					

Note:
Cells shaded in grey contain numbers of patients who are cases of definite overlap and have not been included in the ORS assessment or the prevalence estimates.
Numbers coloured orange in column 2 are those 11 out of 127 non-clinic patients found on family pedigrees whose pedigree included city of residence information for the patient in question. For the remaining 116 patients, first-degree family members' resident cities were recorded.

Overlap risk score justifications:

A. None of our families in this Armstrong have an affected family member ascertained from pedigree
B. Three were given an overlap risk score of 1 because there are only 3 total Ferni patients from the chart review and 3 were given an overlap risk score of 2 because there is no information in the file to confirm with the physician (non-clinic patient was ascertained from referral letter)
C. Physician could not be reached to answer pertinent questions
D. No patients from other sources are recorded to live in Invermere
E. Multiple families with non-clinic patient affected members on their pedigree live in Kamloops. There is far too long a list to re-contact physicians with questions.
F. Patients from Kimberley were not ascertained from any other sources
G. Patients from Koksilah were not ascertained from any other sources
H. Physician did not have access to the information required to minimize overlap
I. Nursing home staff were not able to provide information on whether this patient has been to the UBC HD clinic or VGH nor did they have information regarding the patient's family members

J. These patients have no known family members and no patients or families ascertained from other sources live in Port Alice
K. No families from the chart review have non-clinic patient affected members in Powell River.
L. Cannot re-contact family survey responders
M. Multiple families with affected non-clinic patient family members live in Surrey
N. The one clinic family from Tsawwassen does not have affected non-clinic patient family member, and only has 1 patient from Tsawwassen is recorded as affected. Family survey responders cannot be re-contacted
O. Only family in Vanderhoof has no affected not in database members and saw a different doctor.
P. Multiple families with non-clinic patient affected members on their pedigree live in Victoria. There is far too long a list to re-contact physicians with questions.
Q. Nursing home staff were not able to provide the pertinent information to minimize overlap
R. Physicians were not available to answer the pertinent questions

Appendix 7

Ethnicity	Country of orgin	Number of patients
Caucasian	Acadian/Cajun	3
	Austria	4
	Belgium	1
	Great Britain	154
	Hungary	1
	Iceland	1
	Ireland	30
	Canada	11
	Denmark	5
	Poland	5
	Norway	13
	The Netherlands	16
	Latvia	1
	Italy	5
	Israel	1
	Germany	26
	France	6
	Finland	1
	Russia	17
	South Africa	2
	Sweden	11
	Ukraine	8
	Slovania	2
	Unknown	166
African-North	Tanzania	1
American-Latin	Mexico	1
Asian-East	Philippines	2
	Hong Kong	1
	Unknown	1
Asian-West	Pakistan	3
	Afghanistan	1
	India	8
	Iran	1
	Iraq	1
	Unknown	2
Other	Ontario Aboriginal	1