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How Many People Have a Huntington's Disease Expansion: A Population-Based Prevalence Study in Northern Scotland

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Abstract
Introduction: Previous work demonstrated a prevalence of 14.6 per 100,000 manifest Huntington's disease (HD) patients and 8.3 per 100,000 identified pre-symptomatic gene expansion carriers (IPGEC) in Northern Scotland. Many of those at high risk of having a huntingtin (*HTT*) gene expansion remain untested with the exact number being unknown. ***Objectives:*** The objective of this study was to estimate how many people in Northern Scotland are at 50% risk of having a *HTT* gene expansion to help with HD clinic service planning and to calculate how many people could access an effective treatment if available. ***Methods:*** Clinical and pedigree records from the North of Scotland Genetic Clinic were examined to estimate numbers of manifest HD patients, IPGEC, and individuals at 50% risk. ***Results:*** The prevalence of those at 50% risk living in Northern Scotland was 45.2 per 100,000 people. Every manifest HD patient in Northern Scotland has 4.4 relatives at 50% risk and every patient with a *HTT* gene expansion has 2.9 relatives at 50% risk. There are up to 415 (46.2 per 100,000) adults who could access an effective treatment if available, but this number is likely to be an underestimate as not all manifesting individuals seek diagnosis. ***Conclusions:*** Despite high predictive testing rates, at least 2.2 adults are living with the *HTT* gene expansion for every one of the 14.5 per 100,000 manifest HD patients in Northern Scotland. Regional variation in rates and ascertainment need to be factored into future service planning, including genetic counselling and testing, management, and treatment delivery.

Introduction

Huntington's disease (HD) is an autosomal-dominant neurodegenerative condition, usually with an adult onset, with as yet no cure [1]. The introduction of direct genetic testing for pathogenic triplet repeat expansions within the gene huntingtin (*HTT*) has led to increasing ascertainment of HD worldwide [2]. Prevalence estimates are increasingly important for service planning, especially with the growing expectation of disease-modifying therapies [3–5]. Genetic testing, genetic counselling, and HD care services are free at the point of care within the NHS in Scotland. These services are funded and organised by 14 territorial health boards [6, 7].

Previously, we demonstrated that the ascertained prevalence of manifest HD patients in the North of Scotland had risen by 45.9% from 1984 to 2020, to 14.6

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per 100,000 people for manifest HD patients, with an additional 8.3 per 100,000 people identified through predictive testing as identified pre-symptomatic gene expansion carriers (IPGEC). Furthermore, we showed that general practice data can underestimate HD prevalence by 2.2 per 100,000 people [8].

However, many individuals with the *HTT* gene expansion remain untested, some at 50% risk and others at lower risk. As we move forward towards the treatment era, estimating the number of individuals that could need disease-modifying therapies is increasingly important to plan local services and to inform future budgeting. Previous studies estimated numbers at risk theoretically and empirically [9–13]. We hypothesised that as more individuals undergo predictive testing, the number of people untested at 50% risk would reduce. We therefore sought to undertake empiric estimation of the number of individuals at 50% risk and therefore to estimate the number of people with a *HTT* gene expansion that might need treatment should an effective one be developed.

Materials and Methods

Patient Inclusion Criteria

Individuals living in the North of Scotland who had a pathogenic *HTT* gene expansion (defined as having 36 or more CAG repeats) on January 1, 2023, were included. First-degree relatives of these individuals (therefore their children and full siblings) were also included. These were separated into three categories: (1) manifest HD patients who were assessed as being symptomatic by a certified assessor; (2) IPGEC who had not yet developed motor signs; and (3) those at 50% risk (aged 0 or older), who were a first-degree relative of someone with a known *HTT* gene expansion, which included both pre-symptomatic and symptomatic patients.

Sources of Ascertainment

In our previous study [8], we created a register of HD patients using NHS Grampian Clinical and Laboratory Genetics records. This register was updated for all manifest HD patients and IPGEC living in the North of Scotland on January 1, 2023. Cases were ascertained from five health board areas served by the North of Scotland HD clinic: NHS Grampian, NHS Highland, NHS Orkney, NHS Shetland, and NHS Western Isles, as shown in Figure 1. This clinic is the only HD clinic in the North of Scotland, undertaking genetic counselling, testing, and symptomatic management, and we work directly with family organisation services. All NHS laboratory HD testing in Northern Scotland goes through our clinic, and any testing in the private sector in Northern Scotland is extremely minimal (we are not aware of any at the time of writing). Therefore, the vast majority of manifesting and pre-symptomatic HD patients in the North of Scotland are known to our service. Clinical Genetics records contain a pedigree for each HD family living in the North of Scotland, where self-reported family information is obtained from each patient during their appointment at the Genetic Clinic, as well as before the appointment using pre-clinic questionnaires. Pedigrees have been constructed, with confirmation of diagnosis of affected cases from case notes wherever possible. This records system has been in place since the 1980s, with more recent records electronic to aid linking of nuclear families into extended kindreds. Using the pedigree and questionnaires, we identified those at 50% risk living either within or outside of the North of Scotland. Those at 50% risk were separated into children (those under age 18) and adults (those aged 18 or older).

Statistical Analysis

The prevalence for each category of patient (for the whole of the North of Scotland and per constituent health board) was calculated. Population data were obtained from the published 2021 estimates from National Records for Scotland census data for each local council area [15] which formed part of each health board. The ratio of manifest HD patients to the number at 50% risk (inclusive of those living outside of Northern Scotland identifiable on family history review) was calculated, as well as the ratio of patients with a *HTT* gene expansion (inclusive of manifest HD patients and IPGEC) to the number at 50% risk. An estimate of the number of people who could potentially access an effective treatment for HD if available was also calculated by adding the number of manifest HD patients and IPGEC, to half of those at 50% risk.

Results

Prevalence Data

In the North of Scotland on January 1, 2023, the prevalence of manifest HD patients, IPGEC, and those at 50% risk was 14.5 per 100,000, 7.8 per 100,000, and 45.2 per 100,000 people, respectively. Prevalence per health board in the North of Scotland for each category of patient is shown in Table 1 and Figure 2. Highland has the highest prevalence estimates of the health board areas served in Northern Scotland, with the Islands being the

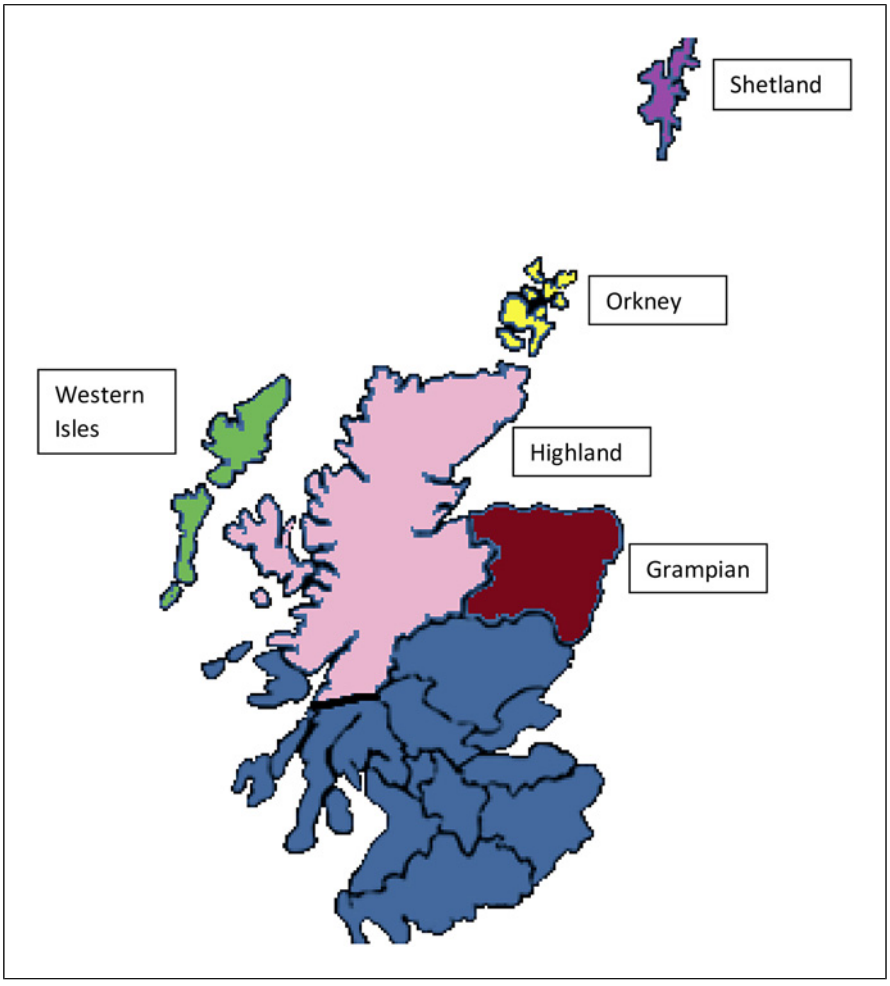

Fig. 1. Map of Scottish health board areas served by the North of Scotland Genetic Clinic where Grampian, Highland, Orkney, Shetland, and the Western Isles are defined. Figure modified from NHS Scotland [14].

Table 1. HD prevalence data for regions in North of Scotland on January 1, 2023, for manifest HD patients, IPGEC, and relatives at 50% risk

Location	Population	Category	Number of individuals (number aged under age 18 in brackets)	Prevalence (per 100,000 people, to 1 dp)
Grampian	586,530	Manifest IPGEC 50% risk	86 46 271 (38)	14.7 7.8 46.2
Highland (excluding Argyll and Bute)	238,060	Manifest IPGEC 50% risk	37 19 110 (26)	15.5 8.0 46.2
Islands (Orkney, Shetland, Western Isles)	72,120	Manifest IPGEC 50% risk	7 <5 24 (7)	9.7 6.9 33.3
Total (North of Scotland)	896,710	Manifest IPGEC 50% risk	130 <70 405 (71)	14.5 7.8 45.2

North of Scotland is inclusive of Grampian, Highland, and the Islands. Those at 50% risk are inclusive of all ages, with the number in brackets defining how many relatives are under age 18.

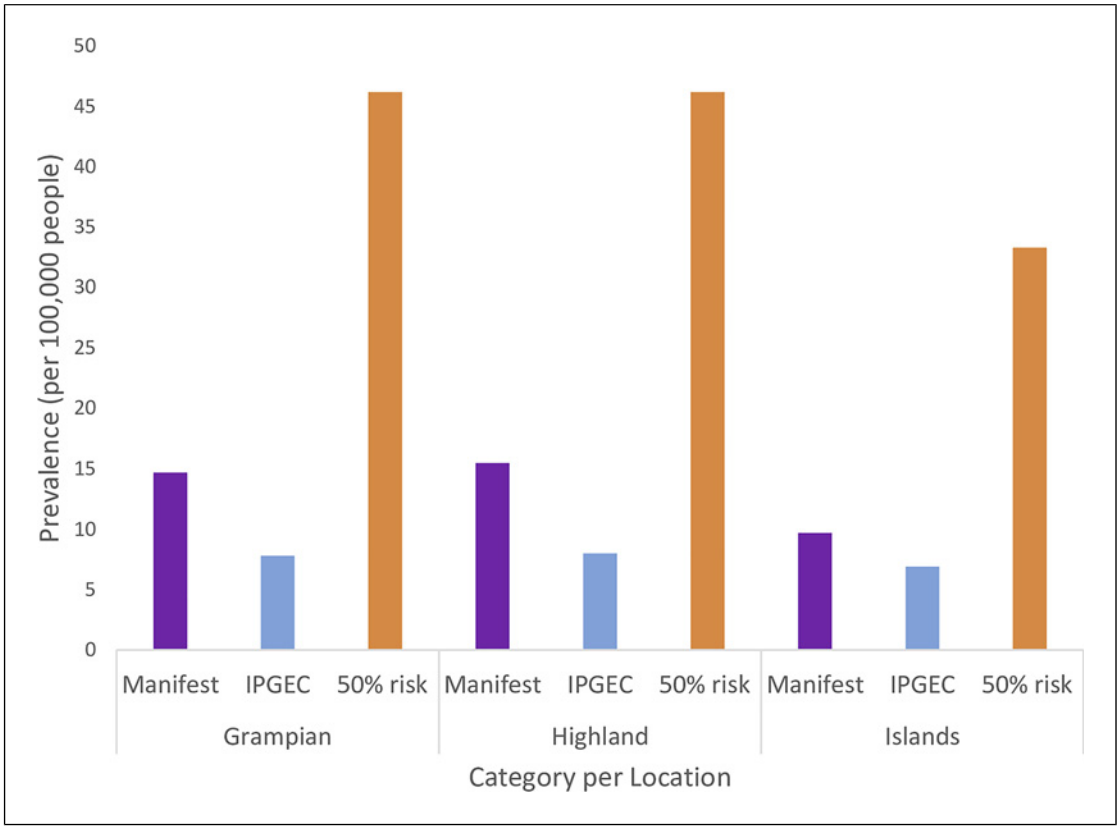

Fig. 2. Prevalence of manifest HD patients, IPGEC, and relatives at 50% risk of HD in the Northern Scottish health boards.

lowest. To protect anonymity and following NHS Scotland guidance, <5 was used where there were less than 5 patients in that category.

Ratio Calculations

The 200 people with a known *HTT* gene expansion (the sum of IPGEC and manifest HD patients) in the North of Scotland collectively had 574 relatives at 50% risk. Of these 574 at risk relatives, 405 reside in Northern Scotland and 167 live outwith the area. On average, each person with a *HTT* gene expansion had 2.9 relatives at 50% risk. Likewise, the average number of relatives at 50% risk (IPGEC and manifest) per manifest case was (574 at risk/130 manifest cases).

Treatment Access Calculations

If an effective treatment for HD was available, there are up to 403 (44.9 per 100,000) people living in the North of Scotland who could access it. However, if you also include half of those living outside of the North of Scotland at 50% risk, this number rises to up to 486 (54.2 per 100,000) people. If only adults are included (those age 18 and over), then this number is 415 (46.2 per 100,000) people.

Discussion

Here, we have empirically calculated for the first time how many people in the North of Scotland are at 50% risk of having a *HTT* gene expansion (45.2 per 100,000 people) and that 46.2 per 100,000 adults in Northern Scotland could access an effective treatment for HD if available. The strengths of the study included using population-based data with clinical record review on a case-by-case basis. Only one HD Clinic is based in Northern Scotland which means that we had access to all the known HD families and records in the region. However, the study was limited by only including those at 50% risk of having a *HTT* gene expansion. There will also be those at 25% risk or less residing in Northern Scotland, which would mean that the true numbers of those who

may need to access our service (and indeed other healthcare services in Northern Scotland) now and in future will likely be significantly higher. There may also be families residing in the North of Scotland who are not known to the HD Clinic. Furthermore, the family information is self-reported which may not be fully accurate or reliable. Ascertained cases outwith the North of Scotland might be biased to underreporting, given the case notes would not be available to the study team as they would be for residents, and there can also be secrecy in families.

Few previous studies have examined the ratio of symptomatic HD patients to those at risk, with the most recent estimate being from 2011 [9–13]. Conneally [9] calculated this figure to be 1:5 on a theoretical basis. Tassicker et al. [10] found this ratio to be 1:4.2 using empirical evidence from HD services in VIC, Australia. Morrison et al. [11], similarly using empirical evidence in Northern Ireland, found this ratio to be 1:4.4 in 1991 and 1:4.2 in 2001. On the other hand, Harper [12] found, empirically, that for every person with HD, there were around 8 people at high risk in Wales, while Simpson and Johnston [13] previously estimated the Grampian figure to be 1:10. The symptomatic to at risk ratio for the North of Scotland calculated in this study at 1:4.4 is similar to that seen in more recent studies despite high test rates in our region. Indeed, the increase in testing in our region can clearly be demonstrated by the change in the ratio in Grampian from 1 in 10 in 1989 to 1 in 4.4 demonstrated in the current study. The average number of children a woman has in Scotland has fallen from 2.53 in 1971 to 1.70 in 1985 and 1.30 in 2023 [16]. Therefore, nowadays, a person with HD will on average have less relatives at risk than they would have had 40 or 50 years ago. This would help explain this change in ratio for the North of Scotland. Previous estimates of the percentage update of predictive testing have ranged from 3% to 24% [10, 11, 17–20]. Using the calculation from the paper by Tassicker et al. [10], our predictive test uptake estimate is around 24.9% (where there was 297 predictive tests done and D was 1,194), which demonstrates the high testing rates in our region, given 24.9% is higher than previous estimates. We postulate that the ratio calculations would likely be higher in regions with lower testing rates.

HD research is in an exciting phase where a range of potential therapeutic avenues are being explored and clinical trials are underway [3–5]. If, and when, the hopes for effective disease-modifying treatments are realised, up to 403 (44.9 per 100,000) people living in the North of Scotland could access this treatment (that is the sum of manifest HD patients, IPGEC, and half of those at 50% risk). Likely, there are at risk relatives living in Northern Scotland who we are unaware of, as their relative who has a *HTT* gene expansion lives outwith the North of Scotland. We can include half of those at 50% risk who live outside the North of Scotland but have a relative living in the North of Scotland with a *HTT* gene expansion, which would at least cover a proportion of people we are unaware of. Using the figures available, up to 486 (54.2 per 100,000) people could access an effective treatment if we include manifest HD patients, IPGEC, and half of those at 50% risk. Given treatments would usually not be given to children, there would be up to 415 adults who could access an effective treatment (46.2 per 100,000 people).

Our estimates assume migration into Northern Scotland HD Community broadly equals migration out. The most recently available Scottish Government data demonstrated that net migration inward increased substantially in 2021–2022, largely due to international student migration, not migration from within Scotland or the UK [21]. However, the population increase in North of Scotland health boards represent less than 1% of the total population (Grampian 760 per 100,000 people, Highland 451 per 100,000 people, Islands 632 per 100,000 people) and indeed is somewhat less than that seen in the major cities (Greater Glasgow and Clyde 1,357 per 100,000 people, Lothian 1,306 per 100,000 people [21, 22]). Buruma et al. [23] found that men with HD tended to have lower socio-economic status and women with HD tended to marry men with lower socio-economic status. In our experience, social and economic deprivation leads to reduced mobility, but this requires further study. Certainly, many of our HD families have been resident within Northern Scotland for many generations, as evidenced by the founder effect within Northern Scotland [8]. Indeed, 81.5% (163/200) of our manifesting cohort have affected relatives known to our service, and we have documented several six or seven generation kindreds residing in Northern Scotland [24]. Taking all these aspects together, we propose that variation in general population migration trends is having minimal impact on HD numbers overall. However, this aspect needs to remain under review, as different languages and transcultural aspects can compound the complexity of caring for those with this multifaceted long-term condition.

It may be that not everyone with a pathogenic *HTT* gene expansion will require potential disease-modifying treatment. For example, the benefits compared to the risks of a treatment may not be sufficient for those who

will not develop manifestations until very elderly. We have focussed here upon diagnosed manifest prevalence in today's clinical practice. Increasing numbers of cases with 40 or more CAG repeats are coming to our attention in old age, as families and their clinicians see the benefit of diagnosis, and as geriatricians become more aware of the condition. Kay et al. [25] studied anonymized population-based cohorts including individuals from Northern Scotland. They reported that 1 in 2,500 people in Western populations have a fully penetrant expansion (40 or more CAG repeats) and 1 in 400 people have a *HTT* expansion [25–27]. Based on these data, we would expect 356 people in the North of Scotland to have a fully penetrant *HTT* allele and 1,885 to have a reduced penetrance allele (36–39 CAG repeats) (total 2,241). In our cohort, of 200 manifest HD cases, only 11 have reduced penetrant *HTT* alleles (5.6% of the cohort), with 189 having fully penetrant *HTT* alleles. Taking into account IPGEC and the estimated numbers of those not yet manifesting from our 50% risk estimates, we know of 391 with fully penetrant alleles, which is more than the 356 people estimated using the Kay et al. [25] data, suggesting that our ascertainment of manifest cases is indeed high. In contrast, we have only identified 0.6% of individuals in the North of Scotland with a reduced penetrant *HTT* allele. We speculate that the majority of these individuals will not manifest HD, or if they do, will do so with minimal symptoms, and likely need not be included in our estimates for those who may benefit from disease-modifying therapies. However, these data do suggest that reduced penetrance alleles are considerably less penetrant than estimates from testing in high penetrance, symptomatic settings suggest. Although many of these individuals will not become symptomatic, it is plausible that manifest prevalence in this group is under-ascertained due to mild or atypical symptoms.

As expected, the prevalence estimates for the North of Scotland have remained relatively unchanged over the last 3 years, but there has been a slight decrease in both manifest HD and IPGEC prevalence for the North of Scotland. This may be linked to the COVID-19 pandemic, which began in 2020 when prevalence was last locally estimated. Scottish healthcare services were challenged by the pandemic, and there were a large number of excess deaths in Scotland in the year of our prevalence estimate [28].

Guttman et al. [29] proposed that 114 HD patients could access an intrathecal medication per clinic per year. This is only 27.5% of the 415 adults who would likely need treatment in Northern Scotland. They estimated that 2 days of both a neurologist's and nurse's time in a suitable clinic facility would be required per week to implement this treatment, which current resources in Canada cannot support [29]. The situation is more challenging in Scotland where there are fewer specialist physicians and there is a shortage of trained staff. Whether or not disease-modifying treatments will ultimately require intrathecal administration, the monetary and societal burden of HD is substantial, as evidenced by the costs of long-term supportive care [30]. It is likely new models of service and/or funding will be needed to realise the benefits of effective treatment in Northern Scotland and elsewhere. The figures calculated in the present study therefore have substantial relevance for the future service planning of HD care in the North of Scotland and beyond.

Future work could include calculating those at 25% risk and less of having a *HTT* gene expansion, as this would give even more accurate figures of those who could access an effective disease-modifying treatment in future if available and for the future service planning of the HD Clinic in the North of Scotland. Moreover, future research could also include examining the impact of socio-economic status and other factors on migration in HD families in Northern Scotland, and how the net migration rate for individuals with an *HTT* gene expansion compares to other regions within Scotland and the wider UK.

In conclusion, despite high rates of pre-symptomatic testing and smaller family size, there are still a large number of people at 50% risk as yet untested (at least 2.2 adults are living with the *HTT* gene expansion for every one of the 14.5 per 100,000 manifest HD patient in Northern Scotland). Regional variation in rates and ascertainment will need to be factored into future service planning, including: genetic counselling and testing, management, and treatment delivery.

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Statement of Ethics

The project was registered as an audit with NHS Grampian. Permission for this project to be conducted as an audit was given by the NHS Grampian Quality Improvement and Assurance Team (Project ID 5820).

Conflict of Interest Statement

H.C. is employed by NHS Grampian. Z.M. is employed by University of Aberdeen and NHS Grampian. Non-personal financial interests for Z.M. include Novartis and Roche – application for Scottish newborn screening pilot for SMA; Akcea and AstraZeneca – payments to department for tests in unrelated area; Akcea and AstraZeneca – acted as expert advisor, giving a talk about a condition that there is a treatment; AstraZeneca – spoke at sponsored meeting on breast cancer with fee given to department; PTC therapeutics – university were paid for time delivering an educational session. Personal non-financial interests for Z.M. include being on advisory boards for Novartis, Roche, AstraZeneca, and Janssen – with money being paid to department. Other interests for Z.M. include attended educational meetings in UK sponsored by MSD, Sanofi, Amgen, Novartis, Roche, and AstraZeneca and attended visit of Norwegian newborn screening laboratory organised by Novartis.

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Author Contributions

H.C.: execution of project and writing the manuscript. Z.M.: project design and editing manuscript.

Data Availability Statement

The data that support the findings of this project are not publicly available due to this their containing information that could compromise the privacy of patients.

References

1 Rawlins MD, Wexler NS, Wexler AR, Tabrizi SJ, Douglas I, Evans SJW, et al. The prevalence of huntington's disease. Neuroepidemiology. 2016;46(2):144–53. https://doi.org/10.1159/000443738
2 Vicente E, Ruiz de Sabando A, Garcia F, Gaston I, Ardanaz E, Ramos-Arroyo MA. Validation of diagnostic codes and epidemiologic trends of Huntington disease: a population-based study in Navarre, Spain. Orphanet J Rare Dis. 2021;16(1):77. https://doi.org/10.1186/s13023-021-01699-3
3 Estevez-Fraga C, Tabrizi SJ, Wild EJ. Huntington's disease clinical trials corner: November 2022. J Huntingtons Dis. 2022;11(4):351–67. https://doi.org/10.3233/JHD-229006
4 Pan L, Feigin A. Huntington's disease: new frontiers in therapeutics. Curr Neurol Neurosci Rep. 2021;21(3):10. https://doi.org/10.1007/s11910-021-01093-3
5 Kim A, Lalonde K, Truesdell A, Gomes Welter P, Brocardo PS, Rosenstock TR, et al. New avenues for the treatment of Huntington's disease. Int J Mol Sci. 2021;22(16):8363. https://doi.org/10.3390/ijms22168363
6 NHS Scotland. NHS Scotland health boards; 2019. Available from: https://www.nhs.scot/ (Accessed 10 23, 2024).
7 Scottish Government. Charter of patient rights and responsibilities - revised: June 2022; 2022. Available from: https://www.gov.scot/publications/charter-patient-rights-responsibilities-revised-june-2022/pages/2/ (Accessed 10 23, 2024).
8 Kounidas G, Cruickshank H, Kastora S, Sihlabela S, Miedzybrodzka Z. The known burden of Huntington disease in the North of Scotland: prevalence of manifest and identified pre-symptomatic gene expansion carriers in the molecular era. J Neurol. 2021;268(11):4170–7. https://doi.org/10.1007/s00415-021-10505-w
9 Conneally PM. Huntington disease: genetics and epidemiology. Am J Hum Genet. 1984;36(3):506–26.
10 Tassicker RJ, Teltscher B, Trembath MK, Collins V, Sheffield LJ, Chiu E, et al. Problems assessing uptake of Huntington disease predictive testing and a proposed solution. Eur J Hum Genet. 2009;17(1):66–70. https://doi.org/10.1038/ejhg.2008.142
11 Morrison PJ, Harding-Lester S, Bradley A. Uptake of Huntington disease predictive testing in a complete population. Clin Genet. 2011;80(3):281–6. https://doi.org/10.1111/j.1399-0004.2010.01538.x
12 Harper PS. The prevention of Huntington's chorea. The Milroy lecture 1985. J R Coll Physicians Lond. 1986;20(1):7–14.
13 Simpson SA, Johnston AW. The prevalence and patterns of care of huntington's chorea in grampian. Br J Psychiatry. 1989;155(6):799–804. https://doi.org/10.1192/bjp.155.6.799
14 NHS Scotland. Map of Scotland health regions; 2024. Available from: https://www.scot.nhs.uk/mos4/ (Accessed 08 27, 2024).
15 National Records of Scotland [NRS]. Mid-2021 population estimates by council area in Scotland; 2022. Available from: https://www.nrscotland.gov.uk/statistics-and-data/statistics/stats-at-a-glance/council-area-profiles (Accessed 01 04, 2023).
16 National Records of Scotland [NRS]. List of Data Tables - Table 3.04 Birth rate, gross and net reproduction rates and general and total fertility rates, Scotland, 1971 to 2023; 2023. Available from: https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/vital-events/general-publications/vital-events-reference-tables/2023/list-of-data-tables#section3 (Accessed 10 25, 2024).
17 Baig SS, Strong M, Rosser E, Taverner NV, Glew R, Miedzybrodzka Z, et al. 22 years of predictive testing for Huntington's disease: the experience of the UK Huntington's Prediction Consortium. Eur J Hum Genet. 2016;24(10):1515–402. https://doi.org/10.1038/ejhg.2016.81
18 Futter MJ, Heckmann JM, Greenberg LJ. Predictive testing for Huntington disease in a developing country. Clin Genet. 2009;75(1):92–7. https://doi.org/10.1111/j.1399-0004.2008.01044.x
19 Maat-Kievit A, Vegter-van der Vlis M, Zoeteweij M, Losekoot M, van Haeringen A, Roos R. Paradox of a better test for Huntington's disease. J Neurol Neurosurg Psychiatry. 2000;69(5):579–83. https://doi.org/10.1136/jnnp.69.5.579
20 Laccone F, Engel U, Holinski-Feder E, Weigell-Weber M, Marczinek K, Nolte D, et al. DNA analysis of Huntington's disease: five years of experience in Germany, Austria, and Switzerland. Neurology. 1999;53(4):801–6. https://doi.org/10.1212/wnl.53.4.801
21 National Records of Scotland [NRS]. Migration; 2024. Available from: https://www.nrscotland.gov.uk/statistics-and-data/statistics/statistics-by-theme/migration (Accessed 10 25, 2024).
22 National Records of Scotland [NRS]. Mid-2022 population estimates Scotland; 2024. Available from: https://www.nrscotland.gov.uk/mid-year-population-estimates/mid-2022 (Accessed 25 10, 2024).
23 Buruma OJS, Van der Kamp W, Barendswaard EC, Roos RAC, Kromhout D, Van der Velde EA. Which factors influence age at onset and rate of progression in Huntington's disease? J Neurol Sci. 1987;80(2–3):299–306. https://doi.org/10.1016/0022-510x(87)90164-x
24 Simpson S, Davidson MJ, Barron LH. Huntington's disease in Grampian region: correlation of the CAG repeat number and the age of onset of the disease. J Med Genet. 1993;30(12):1014–7. https://doi.org/10.1136/jmg.30.12.1014

25 Kay C, Collins JA, Miedzybrodzka Z, Madore SJ, Gordon ES, Gerry N, et al. Huntington disease reduced penetrance alleles occur at high frequency in the general population. Neurology. 2016;87(3):282–8. https://doi.org/10.1212/WNL.0000000000002858
26 Gardiner SL, Boogaard MW, Trompet S, de Mutsert R, Rosendaal FR, Gussekloo J, et al. Prevalence of carriers of intermediate and pathological polyglutamine disease–associated alleles among large population-based cohorts. JAMA Neurol. 2019;76(6):650–6. https://doi.org/10.1001/jamaneurol.2019.0423
27 Sundblom J, Niemela V, Ghazarian M, Strand A, Bergdahl IA, Jansson J, et al. High frequency of intermediary alleles in the HTT gene in Northern Sweden - the Swedish Huntingtin Alleles and Phenotype (SHAPE) study. Sci Rep. 2020;10(1):9853. https://doi.org/10.1038/s41598-020-66643-0
28 Islam N, Shkolnikov VM, Acosta RJ, Klimkin I, Kawachi I, Irizarry RA, et al. Excess deaths associated with covid-19 pandemic in 2020: age and sex disaggregated time series analysis in 29 high income countries. BMJ. 2021;373:n1137. https://doi.org/10.1136/bmj.n1137
29 Guttman M, Pedrazzoli M, Ponomareva M, Pelletier M, Townson L, Mukelabai K, et al. The impact of upcoming treatments in Huntington's disease: resource capacity limitations and access to care implications. J Huntingtons Dis. 2021;10(2):303–11. https://doi.org/10.3233/JHD-200462
30 Jones C, Busse M, Quinn L, Dawes H, Drew C, Kelson M, et al. The societal cost of Huntington's disease: are we underestimating the burden? Eur J Neurol. 2016;23(10):1588–90. https://doi.org/10.1111/ene.13107