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27 years of Pprenatal Ddiagnosis for Huntington disease in the United Kingdom

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Abstract

Purpose:

There is little long-term, population-based data on uptake of prenatal diagnosis for Huntington Disease (HD) a late-onset autosomal dominant neuro-degenerative disorder, and the effect of the availability of preimplantation genetic diagnosis (PGD) on families' decisions about conventional prenatal diagnosis is not known. We report trends in prenatal diagnosis and pre-implantation diagnosis for HD in the United Kingdom since services commenced.

Methods:

Long term UK wide prospective case record-based service evaluation in 23 UK Regional Genetic Centres 1988-2015, and four UK PGD centres 2002-2015.

Results:

From 1988 – 2015, 479 prenatal diagnoses were performed in the UK for HD. An exclusion approach was used in 150 (31%). The annual rate of HD PND has remained around 18 (3.5 / million) over 27 years, despite a steady increase in the use of PGD for HD since 2002.

Conclusions:

Although increasing number of couples are choosing either direct or exclusion PGD to prevent HD in their offspring, both direct and exclusion prenatal diagnosis remain important options in a health system where both PGD and PND are state funded. At risk couples, should be informed of all options available to them, preferably pre-pregnancy.

Introduction

HD is an autosomal dominant neurodegenerative disease characterised by cognitive decline, movement disorder and frequent psychopathology, leading to death over 10 – 25 years. Onset is most often in a person between the ages of 30 and 50 years, but may be earlier or later[1]. Growing-up with an affected parent can present a significant psychological burden for those at risk[2]. Those at risk of HD have a number of reproductive options[3]. Many choose to accept the 50% risk of each child being affected, some choose to remain childless, adopt a child or use gamete donors. The identification by linkage of the HD locus resulted in the additional option of prenatal diagnosis (PND) and termination of affected pregnancies, or increasingly, the possibility of pre-implantation genetic diagnosis (PGD) to select mutation-negative embryos conceived by in-vitro fertilisation (IVF).

Pre-symptomatic predictive testing and prenatal diagnosis (PND) in HD serve as paradigms for testing in other late-onset genetic neurodegenerative disorders, such as familial early-onset Alzheimer Disease. Family based linkage studies have been used to offer PND in the UK since 1988. Direct mutation testing became possible in 1993 with the discovery that a triplet repeat expansion within exon 1 of the gene Huntingtin causes the disease[4]. Fetal DNA samples for PND can be taken using chorionic villus sampling (CVS) from 11 weeks' gestation, and from around 15 weeks by amniocentesis. However, the only therapeutic option for couples who are found to have a fetus at high risk is termination of pregnancy ~~However, couples with a fetus who is at a high risk can only undergo termination of pregnancy if they are to avoid the birth of an affected child.~~ As HD is typically a late onset condition, prenatal testing is not offered for information only ~~because this~~ because it would be tantamount to predictive testing of a child for an adult onset condition~~could result in a predictive testing of a child for an adult onset condition~~. Genetic counselling carefully addresses ~~this~~ these issues

in reproductive decision making. In pre-implantation genetic diagnosis (PGD), couples avoid the need for termination through embryo biopsy and genetic testing of embryos created prior to implantation using in vitro fertilisation[5]. PGD for HD was first reported in 1996[6].

Some couples who use reproductive technologies to avoid having a child affected by HD have undergone predictive testing and know that they carry the HD gene. In such cases, PND is typically performed using "direct" testing of the pregnancy for the HD gene mutation. Those at risk who wish to avoid passing on the gene but do not wish to find out their own HD status, can use an approach termed "exclusion", ~~or~~ "indirect" ~~testing~~or "nondisclosing" testing. ~~–~~ Traditionally DNA markers linked to the HD gene ~~are~~ were used to establish which grandparent contributed the HD gene passed to the fetus from the at-risk parent: the affected grandparent or their spouse. If the fetus had~~s~~ not inherited the gene from the affected grandparent, this excluded~~s~~ the mutated HD gene in the pregnancy or embryo. Exclusion testing, whether applied through PND or PGD, allows the at-risk parent to avoid discovery of their genetic risk. However, this means that parents who do not have the mutated HD gene, may terminate an unaffected pregnancy or discard unaffected embryos that happen to share the affected grandparental haplotype, as there is a 50% chance that this haplotype harbours the mutated gene, and a 50% chance that it harbours the normal copy. In recent years, many services have replaced the use of linked markers in HD prenatal testing with non-disclosure of mutation test results to avoid incorrect results, leading to the term "nondisclosing testing" being used in the US. In the UK, exclusion testing using linked markers has continued in PGD to avoid incorrect results through allele dropout.

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In the UK access to PND is overseen by NHS boards/trusts and professional networks, but access to PGD is regulated by the Human Fertilisation and Embryology Authority (HFEA). Before 1993, prenatal diagnosis for HD was performed using linkage analysis. Both direct and exclusion PND have been available in the UK since 1993, free at the point of care through NHS public funded healthcare. Direct PGD for HD was licensed in the UK from 2002, and exclusion PGD from 2009. NHS funding for direct and exclusion PGD testing for HD is now widely available free of charge to couples at risk across the UK who do not already have a child and fulfil other NHS funding criteria for PGD.

With better awareness of reproductive risks and options within families, and increasing optimism driven by global research efforts in HD treatment and better availability of PGD, we hypothesised that the request rate for PND might be in decline.

Data on HD PND has been systematically retrospectively collected from all 23 regional genetic centres on an annual basis since testing began 27 years ago. Results from the first years 1994-1998 have been reported[7]. Here we describe the trends in PND in the UK since inception of these services, and compare these with available data on UK PGD uptake.

Material and Methods

Study population

Members of the UK predictive testing consortium retrospectively submitted annual anonymous data on prenatal diagnosis uptake from 1987 to 2015, using the same core data format for most of that time.

The number of PGD cycles performed each year for HD in the UK were reported by Guy's Hospital, the Centre for Reproductive and Genetic Health in London, the Western General Hospital in Edinburgh and the CARE Centre in Nottingham.

Ethics

"UK predictive testing for Huntington's disease group annual prenatal testing audit" has been given formal approval by National Health Service (NHS) Grampian (reference 3992) and the Caldicott guardian as a national audit, and therefore did not require additional IRB / ethics approval.

~~Formal ethics approval is not required because this study was a service evaluation using anonymised data.~~

Endpoints

Numbers of cases and the types of test were recorded annually and presented at the annual HD Consortium meetings. Additional data were gathered on age, sex of the at-risk partner, predictive testing status of the at-risk partner, timing of predictive testing with respect to the pregnancy, mode of prenatal diagnosis (direct or exclusion testing), results of prenatal diagnosis and pregnancy outcome. Available PGD data included the number of couples undergoing treatment and the total number of cycles commenced.

Statistical analysis

Analysis of case frequency was performed in all cases. Detailed information was available for 411 PND cases. Data were analysed using IBM SPSS version 23, and the Chi squared test of proportions.

Results

From 1988 to 2015, 479 prenatal studies were performed across 23 UK centres. An indirect (exclusion) approach was used in 144 (31.2%; Figure 1). Testing rates were low before the identification of the gene in 1993, and 1994 saw the highest number of tests requested (37). From 1995 – 2015, the rate of PND has remained modest but steady, with a mean of 18 pregnancies per year being tested.

Detailed case information was available for 411 PND pregnancies. The at-risk parent was female in 51% ~~(Figure 3)~~. Forty-five percent of the at-risk PND parents ~~The majority of at-risk PND parents~~ had undergone pre-symptomatic predictive testing and 3% ~~had undergone pre-symptomatic predictive testing (84%)~~ had undergone diagnostic testing; ~~,~~ only 15.8% of these predictive tests were performed during the pregnancy.

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Direct mutation testing was performed in 62.5% of PND, with the exclusion approach being used in 37.5 %. The vast majority of fetuses at 50% risk underwent a direct mutation test (97%). In contrast, where the fetal prior risk was 25% or less, an exclusion (non-disclosing) approach was used in 58%.

The fetus was found to be affected by HD in 53% of direct PND cases, and 90.2% of these pregnancies underwent termination. The remaining 12 (9.8%) were continued, resulting in the parents being aware that the child would one day develop HD. Only one HD unaffected pregnancy was reported to have been terminated ~~(Figure 4)~~. Of the exclusion tested pregnancies, termination was performed in 87.5% with a high-risk result, and the remaining 9 (12.5%) continued. None of the low risk exclusion pregnancies underwent termination. In these 21 continued affected and high-risk pregnancies, the at risk/ affected parent was

more often the mother (56.3% vs 43.7%), whereas in terminated pregnancies the at-risk parent was more often the father (52.9% vs 47.1%) ~~(Figure 5)~~, however neither of these differences reached statistical significance (two tailed Chi-square, p=0.1616).

From 2002 to 2015, 305 PGD cycles were performed in the UK for HD. The annual number of PGD cycles has increased steadily over time (Figure 2).

Discussion

PND has been available in the UK since 1988. Other than a peak in the year the HD gene was identified, the rate of uptake of PND has remained modest and remarkably similar over more than two decades. The annual number of PGD cycles has steadily increased since UK licensing of the procedure in 2002.

Exclusion testing remains an important option for couples at risk, with around one third of PND in the UK using this method. Intriguingly, available data suggests that exclusion testing is used more often in PGD (personal communication; data not shown as not available for all centres).

Both at risk men and at-risk women choose PND and PGD. Around 15% of parents are symptomatic at the time of reproductive testing.

During our 27-year study period, the UK population grew from 56.93 million to 65.11 million, thus the annual rate of HD PND has fallen from to 0.316 per million to 0.276 per million. The rate of HD PGD cycles was 0.463 per million in 2015. Taking into account the prevalence and incidence of HD[8], we have estimated that the order of magnitude for the uptake of PND or PGD in 2015 was at least 3.0% of at risk births pregnancies (see

supplementary information). Despite the rising uptake of PGD for HD, the vast majority of UK pregnancies at risk of HD continued to remain untested.

Access to PND and PGD funding varies worldwide. In the UK, both PND and PGD for HD is fully publicly funded for couples by the NHS and is generally co-ordinated through Genetic Regional Centres. Although in some areas (e.g. Scotland) PGD access is limited to couples without a child, we propose that our data indicate couples' behaviour in an environment where at least some real choice is available.

As genetic diagnosis of HD is only provided in the UK by the NHS, our data represent a true nationwide picture, in contrast to other countries where a market in private genetic testing limits data access. A small proportion of these UK cases have been reported in a European series[9]. However, only a few studies have reported national experience of PND for HD, with reports from Canada[10], Australia[11] and the Netherlands[12], but these reports did not capture the transition to PGD.

Van Rijj et al.[12] reported a series of 126 Dutch HD prenatal diagnoses. 82% of affected pregnancies in that series resulted in termination, in contrast to 90% in our UK series. They estimated that in the Netherlands 22% of at risk couples used PND when pregnant. An adjunct paper analysing the uptake of PGD found that couples opting for PGD after pregnancy were more likely to have terminated a previous affected pregnancy than those undergoing PND alone (87% vs 55%)[13] .

In the present study, other factors may play a role. In the UK, funding for both PND and PGD is provided by the NHS; although the support for PGD is more limited. NHS funding for PGD is limited to 3 cycles or one successful pregnancy, if couples had an existing

unaffected child together they would often be unable to access PGD on the NHS. There are also restrictions for NHS funding based upon the female partner's age, body mass index, the smoking status, alcohol and illegal drug use of both partners. Funding thus excludes those who had successful PGD/PND previously and also those who have chosen not to have a test and therefore do not know the genetic status of their current child.

In addition, some feel that the option of PGD in the UK is restricted by the geographical location of the few centres that are licenced to offer NHS funded PGD. Therefore, PGD is not freely available to all couples at risk. In the Netherlands, exclusion – also known as 'non-disclosure' - PGD is banned by law, so that those who wish to use this approach must travel to a different country such as Belgium. In contrast, the majority of UK PGD uses exclusion.

There is no European registry of prenatal diagnosis for genetic disorders, but the European Society of Human Reproduction (ESHRE) maintains a PGD registry. The latest report from 2010 found that, of 1574 cycles performed for monogenic disorders, 158 (10%) were for HD. Across the ESHRE dataset, the pregnancy rate for PGD was 22%, with 2 of 10 couples undergoing embryo transfer achieving a pregnancy[14]. HD has become the most common indication for monogenic PGD in the UK, with pregnancy rates are 34% per cycle, with a live birth rate of 23% for fresh embryo transfer and 18% for frozen from 1999-2012[15]. The latest data available from HFEA reported a 25.6% live birth per initiated cycle for 2013[16].

In choosing between PND and PGD couples balance personal, ethical, cultural and health issues. Many couples consider the concept of PGD as more attractive than PND when planning a future pregnancy, as it avoids termination of affected pregnancies and the procedure-associated loss of a normal pregnancy. However, the risks and stresses of PGD

also bring their own burdens, coupled with a lower chance of a successful pregnancy outcome[17] and the extra risks such as hyperstimulation syndrome, surgical egg collection and obstetrical complications. In contrast, the main risk associated to prenatal diagnosis, amniocentesis or chorionic villi sampling, is around a 1% pregnancy loss risk.

Patterns of CVS and amniocentesis usage are changing rapidly with the advent of non-invasive prenatal testing (NIPT) for screening Down syndrome and other aneuploidies and non-invasive prenatal diagnosis (NIPD) for some de novo paternal monogenic disorders using fetal free DNA. A case of NIPD for HD was recently reported[18]. Although Van den Oever[18] demonstrated the proof of principle that free fetal DNA can be used for the diagnosis of HD, the intrinsic technical challenges of sequencing for a triplet repeat disorder means that this technique is not available in the UK and the majority of European countries. A linkage-based approach may be preferred, as often used in PGD for HD and other monogenic disorders. Funding for NIPD in the UK is currently limited.

Further studies of the social and health economic consequences of PND and PGD are required to understand the full effect of these reproductive technologies for the burden of disease in families affected by HD. Our data suggest that a long-term policy of making reproductive technologies available on a population basis free at the point of care has led to a small reduction in HD births in the UK, but the principal motivation for service provision has to remain the wish to support patients and families in facing and coping with this disease. Families with HD require support to face the challenges of this disease and to lead lives, as individuals and families, that are as full and rewarding as can be achieved.

The cost of PND is around £210 plus clinic costs and of PGD is around £12,000 (compared with an IVF cycle costs of around £7,500). These costs are easily outweighed by the

lifetime medical and social care costs of HD that are averted by decisions to avoid having an affected child. The UK health care funding model offers couples the opportunity to choose between PND and PGD, and thus we propose that our results reflect couples' wishes for testing when largely unencumbered by financial considerations.

Although testing rates have been captured reliably through the course of the study, detailed data for 12% of cases is missing due to the challenges of data collection in a nationwide study over three decades and without specific funding. Only minimal and anonymous data were collected, to maintain participation, but PND rates may be slightly under reported. PGD data were obtained directly from all UK centres currently offering PGD. The number of PGD cycles are not equivalent to PND rates as they do not always result in a clinical pregnancy or live birth. The likely level of under ascertainment does not alter our conclusions.

In conclusion, this is the longest running study reporting national rates of prenatal and pre-implantation diagnosis for a neurogenetic disorder. Prenatal diagnosis, by both direct and exclusion test methods, is as popular in the UK now as a generation ago. The rate of pre-implantation genetic diagnosis for HD is rising, with many couples seeking exclusion testing. Thus, compared with 20 years ago, more at-risk couples seek to avoid giving birth to children that will later develop HD. Couples including one partner at risk of HD should be offered non-directive information about the reproductive options, pre-pregnancy advice and access to both direct and exclusion PND and PGD.

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Disclosures

All authors declare no conflict of interest.

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Figures Legends

Figure 1. Number of prenatal diagnosis cases for HD in UK, in the period of the study (1988-2015). Red bars refer to direct testing and blue bars to exclusion testing.

Figure 2. Comparison of prenatal diagnosis (PND) vs preimplantation genetic diagnosis (PGD) since 2002. Red line refers to PND direct testing, blue line exclusion testing, black line the total~~, and dotted line the trend during the period~~. Green line displays the number of PGD-in vitro fertilisation cycles.

~~Figure 3. Type of testing in the affected parent. Yellow shows patients with pre-symptomatic testing, green symptomatic (diagnostic) and blue not tested.~~

~~Figure 4. Follow-up of pregnancies with prenatal diagnosis. Top. Indirect testing. Bottom. Direct testing. Blue bar shows number of terminated pregnancies and green continued pregnancies.~~

~~Figure 5. Results of follow-up of pregnancies with prenatal diagnosis according the sex of the parent at risk. Blue bar shows number of terminated pregnancies and green continued pregnancies.~~

Disclosures

All authors declare no conflict of interest.

Figure1

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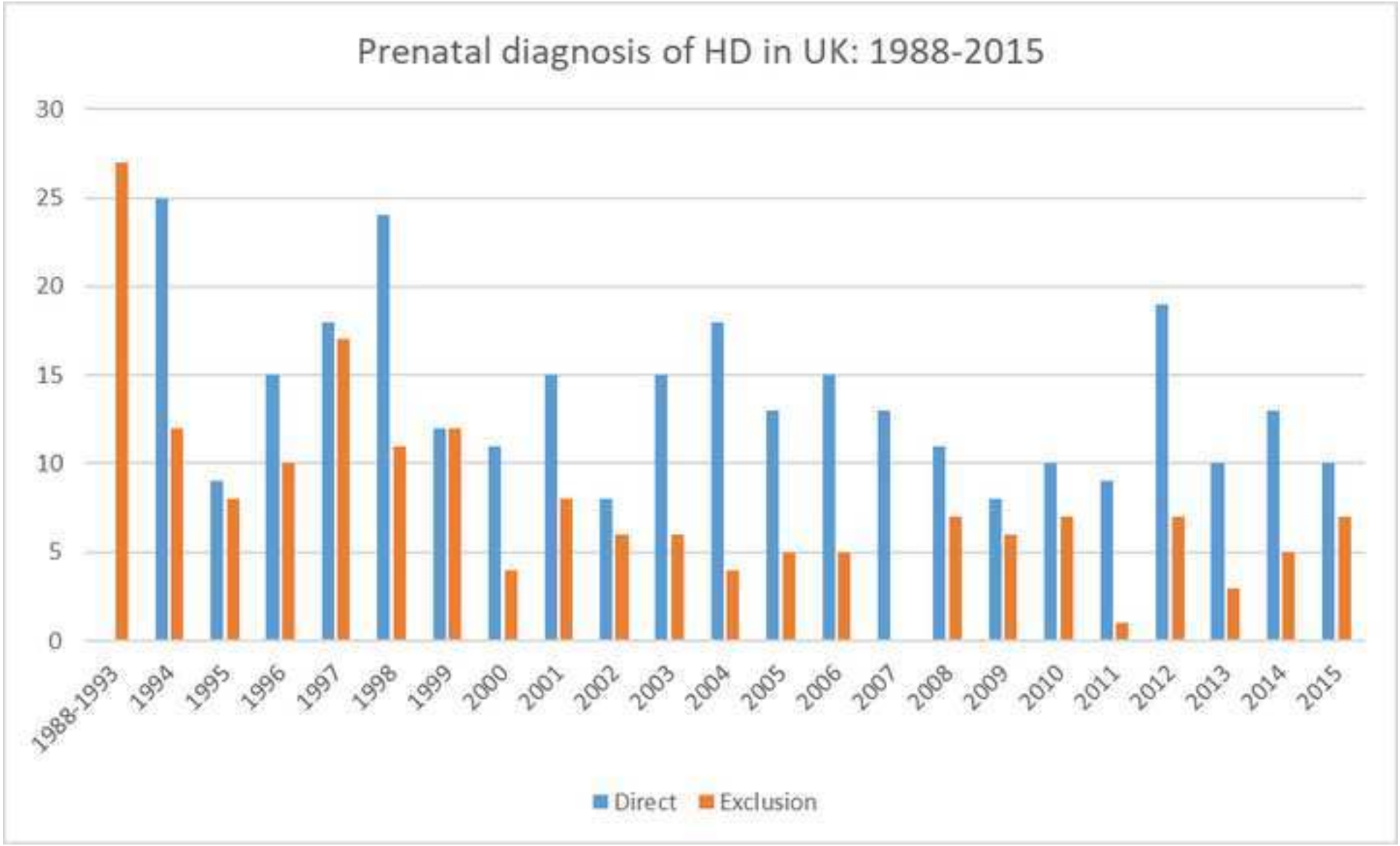

Figure2

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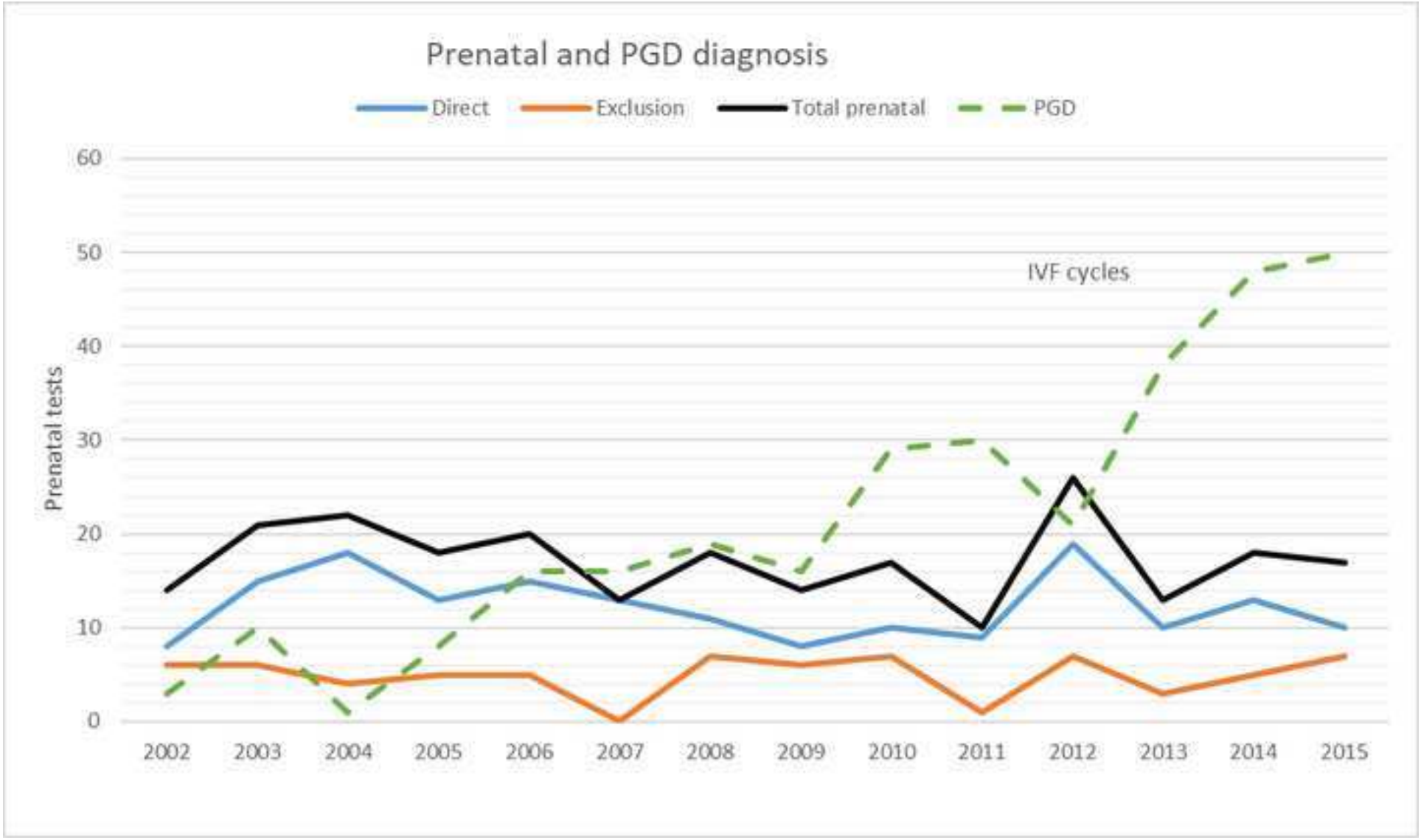

Supplementary Information

Estimation of PND/PGD uptake in 2015.

The estimate of the percentage of HD at risk births undergoing prenatal diagnosis or PGD was estimated based upon:

1) The denominator: number of 12-week pregnancies at 50% risk:

The UK population in 2015 = 65,110,000

Assuming a prevalence of 10 / 100,000 gives 6511 cases

Assuming a disease duration of 18.8 years gives an incidence of 346.3 per year in the UK

A distribution for the age of onset was assumed as reported in Harper & Newcombe 1992. Standard life tables were used to estimate that there would need to be 365.3 births per year to maintain this incidence. Using a pregnancy loss rate of 4 % at 12 weeks (Avalos et al 2012) it would require 380.5 twelve week embryos, and therefore 761.1 embryos were at 50% risk.

2) The numerator for the prenatal tests:

The number of direct tests is 10. The number of exclusion tests is 7, but half of these would have been unnecessary if the parents had all been tested - so we have 3.5 tests of pregnancies at 50% risk. So, the annual total number of prenatal tests is 13.5.

3) The numerator for the PGD tests:

The numerator for direct PGD tests is 36 / 80 (based on Guy's PGD data collected for this study) x 52 PGD tests = 23.4 tests.

The numerator for the exclusion PGD tests is 44 / 80 x 52 PGD tests = 28.6 tests (which means that 28.6 / 2 = 14.3 tests were for pregnancies at 50% risk).

The annual total number of PGD tests at 50% risk was 23.4 +14.3 =37.7

Only 25% of PGD cycles result in a pregnancy (Sharpe et al., 2017) so the number of live births following HD-PGD testing is 9.4.

Overall, the testing proportion is thus around (13.5 +9.4) / 761.1 = 3.0%.

We cannot assume that all those undertaking a pregnancy were aware of their risk. There are no estimates for this but, if half of those undertaking a pregnancy were aware of their risk, the uptake would be 6.8%. If estimates of those aware of their risk were closer to 25%

or 75% then the uptake would be of the order of magnitude of 13.6% and 4.5% respectively.

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