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REVIEW

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# Genetic risk for Huntington Disease and reproductive decision-making: A systematic review

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## Abstract

Huntington Disease (HD) is an incurable autosomal dominant single gene neurodegenerative disorder. Typical onset is between 30 and 40 years and characterised by motor difficulties, cognitive impairment, and behavioural and personality changes. The availability of reproductive testing means that affected and at-risk individuals can make reproductive decisions with genetic risk in mind. We aimed to summarise the literature on reproductive decision-making in the context of HD risk in terms of outcomes and the subjective experiences of at-risk individuals. Five databases were searched. Findings were synthesised using Framework analysis to identify common factors across results of quantitative and qualitative studies. Twenty five studies met inclusion criteria. Framework analysis identified the following key areas: 'The relationship between reproductive intentions and HD genetic risk', 'Views on assistive options', 'Complexity and challenges in reproductive decision-making', 'Actual reproductive outcomes', and 'Other factors influencing reproductive decision-making'. Quality of included studies was mixed. Reproductive decision making in the context of HD risk was found to be a complex and emotionally challenging process. Further research is required into reproductive decision-making and outcomes among those not utilising assistive options, and in developing a model of reproductive decision-making in HD.

**KEYWORDS**
genetic risk, Huntington Disease, inherited condition, reproductive decision making

## 1 | INTRODUCTION

Huntington Disease (HD) is a rare neurodegenerative disorder characterised by motor impairment, behavioural disturbance and psychiatric symptoms, and cognitive impairment.[1] These symptoms are associated with impaired quality of life for symptomatic individuals and carers.[2] The trajectory is progressive and fatal,[3] with increasing care and support needs as the disease progresses.[4] Age of onset is typically between 30 and 40 years,[3,4] with the mean duration of disease being between 17 and 20 years.[1] HD demonstrates well-documented patterns of autosomal dominant genetic inheritance.[5,6] Due to its strong heredity, progressive and debilitating disease trajectory, average onset in mid-life, and characteristic disturbance of mood, cognition and behaviour, HD diagnosis has profound implications for the individual, their family and and current and future children.

Currently there are no interventions that prevent, modify or delay the disease process.[7,8] Therefore, treatment focuses on symptom management with most day-to-day support provided by family carers. The caregiving role in HD is particularly challenging, with management of disinhibition, aggression and emotional lability practically

demanding, and navigating emotional and relationship changes emotionally complex.[9,10]

HD is a single-gene disease with an autosomal dominant pattern of inheritance with the disease-causing variant showing full penetrance. The huntingtin gene which codes for the huntingtin protein contains a short, repeated section of the three nucleotides, cytosine–adenine–guanine (CAG) which contains fewer than 27 repeats in the normal gene. Individuals with 40 or more CAG repeats in this section will develop the disease and is classified as a positive result. Children of a parent with HD have a 50% chance of inheriting the disease-causing variant and are thus considered genetically 'at risk' of HD.[5]

The HD gene was mapped in 1983 and presymptomatic genetic tests (PT) to confirm a diagnosis of HD have been available in the form of family linkage tests since 1986. However, this required having intact families and living affected family members. This type of testing was generally only available through select research centres.[11] Direct testing of the HD gene has been available since since isolation of the gene in 1993 and in 2009 the correlation between the CAG repeat size and age of symptom onset was recognised. Given this long history of genetic testing for HD and it being the first heritable disease for which PT were widely available, robust guidelines for PT in HD have been developed, including pre-test genetic counselling and post-test support following a positive result.[12]

Given HD's high risk of almost 100% penetrance heredity, age of onset, progressive and incurable status, HD genetic risk knowledge has profound implications for affected and at-risk individuals. At-risk individuals are often aware of their own potential disease trajectory, and the risk of inheritance to their children.[3] At-risk individuals have several available reproductive options[13]: (1) natural conception without attempts to mitigate genetic risk; (2) use of prenatal diagnosis (PND)—natural conception, followed by in utero genetic testing, with the option to terminate or continue affected pregnancy; (3) use of pre-implantation genetic diagnosis (PGT)—genetic testing of in in vitro fertilised embryos, followed by implantation of gene-negative results; (4) non-biological routes to parenthood (e.g., sperm or egg donation); and (5) abstinence from parenthood. Clinical reviews of HD identify reproductive decision-making (RDM) as extremely challenging, involving multiple complex decisions regarding reproductive intent, use of assistive technologies and knowledge regarding own genetic status.[3] The PT protocol of HD[12] specifies that support in RDM should focus on providing clear and useful information on options and potential outcomes.

The development of PT and late reproductive assistive options has lead to a small but developing body of research exploring the reproductive intentions and outcomes in the context of HD, as well as attitudes and uptake related to PND and PGT. These range from straightforward reports on reproduction in this cohort over time to exploration of the impact of PT on outcomes, as well as a small number of qualitative studies focused on the experience of reproductive-decision making in the context of HD risk. However, this research has not yet been synthesised to allow for identification of themes and patterns regarding the impact of HD genetic risk on RDM. Therefore, this review aimed to (1) integrate research regarding reproductive intentions, decision-making and outcomes among those at genetic risk for HD; (2) report relevant findings on attitudes towards and uptake of developing assistive technologies available to aid reproduction in HD; and (3) summarise research on the subjective experience of RDM in the context of HD genetic risk.

## 2 | METHODS

### 2.1 | Search strategy

Medline, EMBASE, EMCARE, PsycINFO, AMED, Maternity and Infant Care were searched from 1983 to 4th November 2021. The search strategy involved combining terms from previous reviews related to RDM[14] and HD[7] respectively. Relevant study reference lists were also hand searched and relevant 'grey literature' was included if the results were available, and all inclusion criteria were met. Grey literature was included to counteract publication bias,[15] which can be problematic when published research is relatively sparse.[16]

### 2.2 | Study selection

Study selection was an iterative process following PRISMA guidance.[17] Duplicate study records were identified and removed. Next, studies were screened by title, abstract and then full-text. A second reviewer (CR) screened 10% of studies at each stage to ensure reliability of selection criteria, with an overall agreement rate of 95%.

Studies were included if they met the following criteria: involved individuals at genetic risk of developing HD; *at least one aim* related to RDM; published on or after 1983, the year in which genetic testing for HD became possible[18]; peer-reviewed studies reporting novel quantitative and qualitative research, in addition to relevant 'grey literature' consisting of publicly accessible Masters and Doctoral theses meeting all other inclusion criteria; full text available in English. Studies were excluded if they did not report findings on HD or reported aggregated results with other conditions.

### 2.3 | Data extraction and quality appraisal

The key characteristics of all included studies were extracted. Study quality was assessed using the QualSyst tool,[19] as it allows for the appraisal of both qualitative and quantitative study designs, including cross-sectional and observational designs, and has clear, replicable guidance for quality assessment. Resultant quality ratings are expressed between 0.0 and 1.0, based on several quality assessment criteria. For the purpose of this review, the following quality ranges were used: 'High' quality, 0.80 or higher, 'Good' quality between 0.79 and 0.70, 'Medium' quality between 0.69 and 0.60, and 'Low' quality, 0.60 and lower. Low quality studies were excluded from data synthesis.

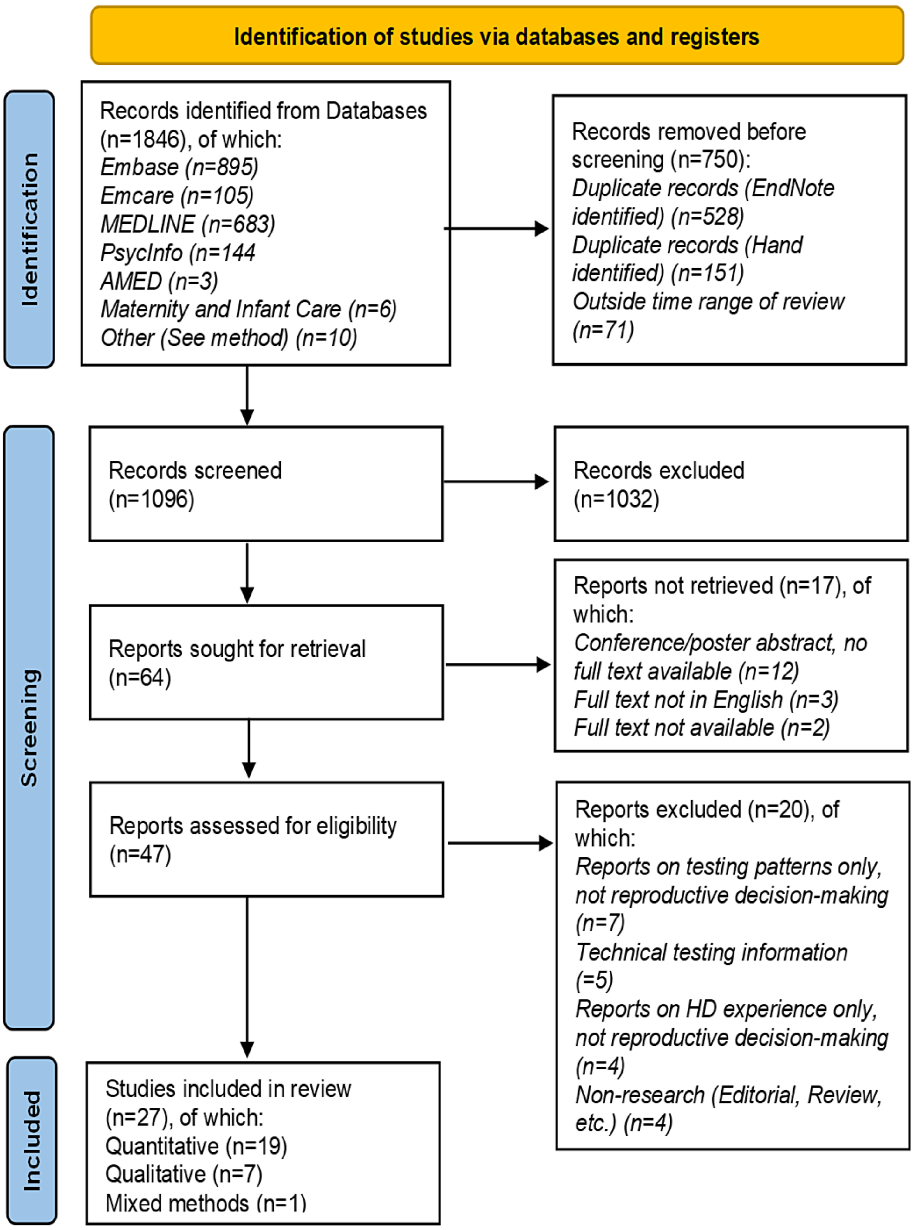


**FIGURE 1** PRISMA flowchart.[17] [Colour figure can be viewed at wileyonlinelibrary.com]

## 2.4 | Data synthesis

Extracted study characteristics and results were reviewed, and given the resultant heterogeneity of study designs, outcome measurement, along with the need to account for both quantitative and qualitative research, a narrative synthesis using a 'Framework Analysis' approach[20] was identified as an appropriate method of data synthesis. This provides a flexible approach in accounting for both qualitative and quantitative data, and a robust iterative process of stepped analysis to ensure relevant data is accounted for both within and between studies. Framework analysis consists of five stages: (1) familiarisation with full text of included studies and relevant extracted data; (2) development of thematic framework based on previous research and patterns identified, reflexively adapted to proceeding analysis; (3) indexing of extracted data to identified framework, using textual codes to connect specific data to different themes; (4) charting of data across all studies to headings from developed thematic framework; and (5) mapping of patterns and associations between the data across studies, and interpretation of the dataset as a whole.

This thematic framework was developed in response to broad areas of reported data, covering both attitudes towards RDM and assistive technologies, actual reproductive outcomes and uptake of assistive technologies. The subjective challenges and complexities of RDM, both practical and emotional were also synthesised. Where possible, themes attempted to synthesise qualitative and quantitative results with equal weight in the development of overarching themes, though certain sub-themes emerge as containing only qualitative or quantitative data. On completion of the initial analysis process, the thematic structure and content was compared to the dataset to ensure representativeness.

**TABLE 1** Study characteristics, aims and summary of the main outcomes of included studies.

| Main author, study year, location | Study aim | Design, participants, comparison (if applicable) | Main outcomes | Quality rating |
|---|---|---|---|---|
| Decruyenaere,[21] Belgium | Comparison of impact of PT on reproductive decision making 12 months post-test, positive result versus negative result. | Cross-sectional comparative survey, descriptive statistics, statistically significant between group differences highlighted.<br>Participants: individuals receiving positive PT result ($n = 22$).<br>Comparison: individuals receiving negative PT result ($n = 31$). | Of 13 individuals intending to have children pre-test who received positive PT result: 30.76% no longer intend, had/having child post-test, 30.76%, undecided 38.46%.<br>Of 17 individuals intending to have children pre-test who received negative PT result: had/having child post-test, 47.06%; intending to have child in future, 29.41%.<br>No reporting of statistical significance of any differences. | 0.67 |
| Decruyenaere,[22] Belgium | Reporting on reproductive decision making among HD gene carriers 5 years post-test, and exploration of factors influencing these decisions. | Mixed methods.<br>Qualitative: retrospective cohort study, descriptive statistics and between-group comparisons with statistically significant results highlighted.<br>Participants: consenting individuals receiving positive PT result in study period ($n = 89$).<br>Qualitative: grounded theory analysis of interview transcripts with consenting individuals receiving positive PT result in study period ($n = 32$). | Quantitative: 46 with reproductive intention, significantly younger and more likely to be childless versus no reproductive intention group.<br>23 participants with at least one pregnancy in the study period; 51 individual pregnancies, 46 utilising PND leading to 23 live births and 23 terminations, 3 utilising PGT resulting in no live births.<br>25 children born to 20 participants—none unaided.<br>No other statistically significant results found.<br>Qualitative: balancing pros of PND/PGT versus distress and discomfort; emotional challenges of approaches (e.g., avoiding attachment); decision complex, multifacted, leading to ambivalence, difficulty balancing responsibility with desire for child. Sense of pressure to utilise new technologies. Eventual choice not to have child as way to stop disease, avoid suffering. | 0.82 |
| Downing,[23] USA | Exploring how responsibility is understood and constructed among HD-risk individuals with regard to reproductive decision making. | Qualitative case study series, grounded theory analysis, only relevant subthemes to reproductive decision making included in this review.<br>Participants: interviews with individuals/families where one partner received positive PT result ($n = 3$). | Forming expectations of responsibility: gendered expectation of caring responsibility towards female children, with some hierarchical age effect also.<br>Growing awareness of responsibility: across all cases, lack of knowledge regarding HD, heritability and impact allowing reproductive outcomes that would otherwise be viewed as less responsible, and for this reason sometimes choosing to maintain ignorance to allow for conception without considering testing.<br>Changing responsibility perceptions: as affected parent deteriorates, role as parent develops, changes in relationship—difficulty of maintaining consistency of decisions across time re genetic testing, and so forth, feeling need to demonstrate responsibility of decision through contrast with other 'irresponsible' actions. | 0.60 |
| | | | | 0.91 |

**TABLE 1** (Continued)

| Main author, study year, location | Study aim | Design, participants, comparison (if applicable) | Main outcomes | Quality rating |
|---|---|---|---|---|
| Evers-Kiebooms et al.[24] Several European Countries | Reporting pre-test reproductive history and post-test reproductive decision making, uptake of PND, impact of PT result on later reproductive decision making across several European genetic testing centres, 1992–1999. | Retrospective cohort study, descriptive statistics and between-group comparisons with statistically significant results highlighted.<br>Participants: individuals under 45 receiving positive PT result in study period ($n = 181$).<br>Comparison: individuals under 45 receiving negative PT result in study period ($n = 271$). | Approximately 50% of both participants and controls have had a pregnancy pre-test.<br>Post-test, no pregnancy: 85% of carriers and 72% of non-carriers.<br>Post-test, one or more pregnancies: 15% of carriers and 28% of non-carriers.<br>'Family Planning' subgroup: carriers significantly less likely than non-carriers to have post-test pregnancy.<br>Test result significant predictor of subsequent reproductive decision making, especially in 'family planning' subgroup. | |
| Fowler,[25] United States | Exploration of impact of positive PT result number of factors including on reproductive decision making. | Qualitative case study series, grounded theory analysis, only relevant subthemes to reproductive decision making included in this review.<br>Participants: interviews with couples where one partner received positive PT result ($n = 3$). | All couples report impact of test result on family planning, but no unity of themes due to idiosyncrasies of each situation.<br>Couple 1: no pre-test children; female partner continues to want, male partner does not; consideration of adoption.<br>Couple 2: both desire no further children post result, regret pre-test child due to risk, used adoption to expand family.<br>Couple 3: complex picture where dynamics of relationship played main role in having child post-test without PND. | 0.70 |
| Gong,[26] United States | Explore impact of positive HD genetic test on young adult's attitude towards life milestones, challenges faced—including reproductive decision making. | | Qualitative: Thematic and Grounded Theory analysis of interview transcripts Participants: young people who have received a positive PGT result ($n = 14$) 'Get started early' on romantic relationships, family planning post test result ($n = 8$) Worries about disclosure and potential rejection by partners in romantic relationships ($n = 8$) Greater selectivity of potential romantic partners around HD acceptance and understanding of reproductive challenges ($n = 10$) Family planning (female participants): desire to have unaffected child via aided conception ($n = 10$), though concerns about cost of PGD ($n = 5$). Family planning (male participants): unsure, dependent on desire of future female partners, context at time ($n = 2$). | 0.90 |
| Holloway,[27] UK | Reporting characteristics of those seeking PT between 1984 and 1994 in UK, comparison of reproductive decision making between positive and negative result groups. | Cross-sectional comparative survey, descriptive statistics, statistically significant between group differences highlighted.<br>Participants: individuals receiving positive PT result ($n = 22$).<br>Comparison: individuals receiving negative PT result ($n = 27$). | 80 individuals applied for testing—22 positive results, 27 negative results, 6 inconclusive results, 25 withdrawals.<br>Post-test reproductive decision making: 5 negative results intending to have children where did not before, 4 positive results intending not to have children where previously did; 7 sterilised or out of reproductive age. | 0.60 |
| Kessler,[28] United States | Reporting impact of availability of PT for HD on reproductive decision making. | Cross-sectional survey, descriptive statistics, statistically significant between group differences highlighted.<br>Participants: individuals at genetic risk for HD ($n = 69$).<br>Comparison: none. | 67.2% indicate HD has major influence on family planning.<br>78.8% willing to pursue PT when available; significant negative correlations between length of marriage, PT willingness.<br>65% willing to pursue PND when available.<br>Anticipated response to positive PT result: no (further) children, 70.9%, fewer children 13.9%, adoption 6.5%, unsure 6.5%. | 0.70 |

(Continues)

**TABLE 1** (Continued)

| Main author, study year, location | Study aim | Design, participants, comparison (if applicable) | Main outcomes | Quality rating |
|---|---|---|---|---|
| Klitzman,[29] Country Unclear | Exploring the factors influencing reproductive decision making among HD-risk individuals, tested and not. | Qualitative: grounded theory analysis of interview transcripts.<br>Participants: $n = 21$ (8 gene carriers, 4 non-carriers, 9 untested). | Having children: push-pull between responsibility to others (stop disease, care for child) count against having children, at other going with desire for children—even ignorance of HD; pregnancy sometimes divorced from HD, viewed as 'taking a gamble'.<br>Role of others: often decision between people, but conflict between lots of sources (e.g., spouse, family, HCWs, societal pressures)—power in relationships affecting this decision; role of HCWs, especially in optimism re potential cure, or source of judgement.<br>Other options: adoption—mixed, helping someone but also burdening them; PGT—generally positive, though not resolving question of what happens when HD appears; CVS/Abortion—tension of responsibility to look after potential child but not engender suffering, also ambivalence to idea of abortion because of HD, need for things to 'sit right'.<br>Guilt and shame: pouring over current and past reproductive decisions, concerns about future views of, for example, not testing or having children from self and others, responsibility to children complicated.<br>Abstience: sometimes considered, from children and relationships, as way out—also leaving it 'up to God' as relief from complex and heavy decisions. | 0.85 |
| Krukenberg et al.[30] United States | Brief reporting of comparative demographics associated with likelihood to change reproductive decisions in light of HD risk knowledge. | Retrospective cohort study, descriptive statistics and between-group comparisons with statistically significant results highlighted.<br>Participants: $N = 16$, carriers identified at Centre who had at least one child, and had not been aware of risk status when having child. | Factors significantly associated with increased likelihood to reevaluate reproductive decision making in light of HD risk knowledge: not attending church regularly, having less than three children pre-test, and having one's father as HD-affected parent. | 0.58 |
| Leontini[31] Country Unclear | Explore how people at risk of Huntington's Disease discuss their reproductive decision making in terms of risk, and how their conceptualisation agrees or disagrees with broader social narratives about how people with genetic risk of disease should approach reproductive decision making. | Qualitative case study series: method of analysis unclear beyond interview transcripts being analysed 'as narratives'.<br>Participants: individuals currently or previously at genetic risk for HD ($n = 3$). | First case: relatively low uptake of testing among at risk individuals despite potential benefits. Two children post knowledge of risk, without testing—sense of testing 'setting them apart' rather than helping. Change of POV following death of HD affected parent, and seeking own test with positive result—challenge of how to share 50% risk status with children. Retrospective guilt regarding choice not to be tested, concerns about 'selfishness', passive contribution to children's suffering.<br>Second case: had test pre-marriage following death of affected parent, received negative result. Ambivalence as to whether | 0.38 |

**TABLE 1** (Continued)

| Main author, study year, location | Study aim | Design, participants, comparison (if applicable) | Main outcomes | Quality rating |
|---|---|---|---|---|
| | | | positive result would or should have prevented having children—shared story of discussed sterilisation when he was child to 'stop spread'. Draws attention to eugenic/oppressive nature of this view, and emphasises the legitimacy of any individual choice counter to broader narratives.<br>Third case: changing medical technological landscape attempts to shift issue from moral to technical one—participant stressed choosing not to have children despite options for avoiding risk, as burden of caring for affected parent as challenging as passing on risk. Stresses idea of 'good parent' as healthy, not placing child at risk. | |
| Maat-Kievit et al.[32] The Netherlands | Reporting uptake and outcomes of PND among HD-risk individuals in The Netherlands, 1987–1997. | Retrospective cohort study, statistically significant between group differences highlighted.<br>Participants: individuals at genetic risk of HD seeking PND ($n = 43$).<br>Comparison: individuals at genetic risk of HD seeking PT ($n = 582$). | 2% estimated uptake among HD-risk population under 50; those seeking PND statistically younger, less likely to have children versus those seeking PT.<br>Total tests: 72, negative result 44, positive 17, indeterminate 11.<br>60% seeking PND following PT.<br>35% using PND across more than one pregnancy.<br>No statistically significant differences reported. | 0.60 |
| Markel,[33] United States | Reporting attitudes of HD-risk individuals towards PT and PND. | Cross-sectional survey, descriptive statistics, statistically significant between group differences highlighted.<br>Participants: individuals at genetic risk for HD ($n = 155$).<br>Comparison: none. | 63.2% willing to pursue PT when no treatment available; significant predictors of increased likelihood, earlier age of onset for affected parent, more affected relatives. 86.5% willing to pursue PT if treatment available.<br>66.67% would want children to pursue PT; older respondent age significant predictor of increased likelihood.<br>Anticipated effect of positive PT result: 42.6% deterred from having children (significantly associated with college education, more affected relatives); those who already have children less likely to be deterred.<br>Response to pregnancy post positive PT result: 41.1% complete, 13.5% terminate (significant positive correlation between Catholic faith and continuing).<br>Attitude to PND: would use when available, 49.0%, 33.5% would continued affected pregnancy (all participants significantly more likely to terminate pregnancy post positive PND vs. post positive PT). | 0.89 |
| McCormack,[34] United States | Comparison of reproductive intention and decision-making, and attitudes towards artificial insemination between HD-risk individuals and comparable controls. | Cross-sectional comparative survey, chi-square analysis.<br>Participants: individuals at genetic risk of HD ($n = 91$).<br>Comparison: demographically comparable individuals not at risk ($n = 63$). | At risk males less likely to have and more likely to want children than controls.<br>Younger at risk females less likely to have children than controls. At risk females less likely to want children than controls.<br>Younger at risk males and females less likely to intend to have children post HD risk knowledge than older at risk males and females.<br>No reported statistical significance of differences. | 0.77 |
| | | | | 0.85 |

(Continues)

**TABLE 1** (Continued)

| Main author, study year, location | Study aim | Design, participants, comparison (if applicable) | Main outcomes | Quality rating |
|---|---|---|---|---|
| Quaid,[35] United States | Explore reproductive decision making among three groups: those having children while known carriers, those having children and choosing not to test, and those choosing not to have children due to known carrying. | Qualitative: thematic analysis of interview transcripts.<br>Participants: $N = 51$ (Knew risk, had children = 26, Had children without risk knowledge = 15, No children because of risk = 10). | *Group 1 Themes*: Hoping for cure: optimism regarding treatment and improvement, trusting that it will be worked out ahead of it affecting children; Magical thinking: mix of denial, optimism—theme of 'decision I do not have it', or focusing on other aspects like suitability for parenthood; 'Just another something': acknowledgement of HD as a risk among many.<br>*Group 2 themes*: Too little too late: knowledge of HD coming too late, going back over things to look for clues; Getting it wrong: incorrect info being shared, either through families or professionals, or previously thought correct info being updated too late to resolve situations.<br>*Group 3 themes*: Vigilant witness: deterioration of loved one with HD leaving a lasting impression of not wanting to put others through this; Stopping HD: advice from others or own conviction; Being alone: isolation from others to protect them and you—saving a child from looking after you, or partner, but feeling lonelier as a result. | |
| Richards and Rea,[36] Australia | Reporting and comparison of pre and post PT reproductive decision making. | Retrospective cohort study, descriptive statistics and between-group comparisons with statistically significant results highlighted.<br>All testes at involved centre, between 18 and 45 at time of test result, between 1990 and 2002.<br>Total pre-test $N = 281$ (carriers, $N = 118$; Non-carriers, $N = 163$).<br>Total post-test $N = 231$ (carriers, $N = 109$; Non-carriers, 122). | Pre-test, 132 subject with at least one child; 53% with knowledge of potential HD risk; 2.2% used PND previously. 1.2% used aided methods (adoption, fostering, donation).<br>Post-test, 28% of carriers and 32% of non-carriers became pregnant; no significant differences.<br>6 PNDs undertaken by carriers—4 terminated positive results, 2 negative results carried to term.<br>No other statistically significant differences found. | 0.76 |
| Schoenfeld,[37] United States | Reporting attitudes of HD-risk individuals towards having children. | Cross-sectional survey, descriptive statistics, statistically significant between group differences highlighted.<br>Participants: individuals at genetic risk for HD ($n = 45$).<br>Comparison: none. | At time of study, more than half had a child; significant negative correlation with college education.<br>82% desire to have at least one child.<br>Response to HD-gene positive pregnancy: 60% continue, 16% terminate, 34% unsure; significant negative correlation between having a child and termination, significant positive correlation between college education and termination. | 0.72 |
| Schoenfeld,[38] United States | Reporting impact of availability of presymptomatic genetic testing (PT) for HD on reproductive decision making. | Cross-sectional survey, descriptive statistics, statistically significant between group differences highlighted.<br>Participants: individuals at genetic risk for HD ($n = 55$).<br>Comparison: none. | 73% willing to pursue PT when available.<br>80% intend to have (more) children at time of study.<br>Among those willing to take test, impact of hypothetical positive result on reproductive decision making: 2.5× increase in those reporting would not have further children.<br>No significant between-group differences identified. | 0.72 |
| | | Retrospective cohort study, descriptive statistics. | Characteristics: mean age of 31, 53.9% female, 48% in ongoing relationship, positive PT result 51% untested 42%. | 0.79 |

**TABLE 1** (Continued)

| Main author, study year, location | Study aim | Design, participants, comparison (if applicable) | Main outcomes | Quality rating |
|---|---|---|---|---|
| Simpson,[39] Several European Countries | Reporting characteristics of HD-risk individuals seeking PND in several European and PND outcomes. | Participants: individuals at genetic risk of HD seeking PND ($n = 305$). | 57% of PND produced negative results, 43% produced positive result, with 8 positive pregnancies being carried to completion. | |
| Tassicker,[40] Australia | Reporting uptake and outcome of PT, PND, PGT in Australia, 1994–2003. | Mixed methods. Quantitative section, retrospective cohort study, descriptive statistics. Qualitative, considers clinician experience, beyond scope of this review.<br>Participants: individuals seeking PT, PND, PGT during study period ($n$ = unspecified). | 776 positive PT results during study period.<br>63 PND tests undertaken, of which 52% negative, 48% positive.<br>18 PGT cycles undertaken, resulting in 13 unaffected live births. | 0.62 |
| Tibben,[41] The Netherlands | Reporting attitudes towards PT and reproductive decision making 6 months post-test. | Cross-sectional comparative survey, descriptive statistics, statistically significant between group differences highlighted.<br>Participants: individuals receiving positive PT result ($n = 24$) and partners ($n = 17$).<br>Comparison: individuals receiving negative PT result ($n = 27$) and partners ($n = 44$). | All groups less likely to endorse statement 'test result has allowed me to plan for the future of my family' post-test versus pre-test, with largest drop in individuals receiving positive PT result. However, no significant changes or between-group comparisons.<br>20.83% decrease in intention to have children among those receiving positive PT result. No change in willingness to terminate pregnancy to avoid gene transmission.<br>Actual outcomes 18 months post-test: one completed pregnancy without PND, one terminated pregnancy following positive PND, one completed pregnancy following positive PND. | 0.90 |
| Tsang,[42] United States | Explore impact of HD risk on romantic relationships and reproductive decision making. | Cross-sectional comparative survey design: descriptive statistics, statistically significant between group differences highlighted.<br>Participants: individuals at genetic risk for HD and their partners ($n = 202$). | Family planning subsection: Current reproductive intent: 36% currently have children; 38% had no children but intended to; 26% neither had nor want children. Factors influencing reproductive decision making: HD inheritance as very important 79%; Those with children significantly less likely to report this as very influential factor. Awareness of PGD: 88%; willingness to use, 55%. Common reasons: cost 44%, lack of info 29%, time 26%, negative experience, 24%. | 0.90 |
| Van Rij,[43] Several European countries | Reporting characteristics of HD-risk individuals seeking PGD, uptake and outcome of PGD, 1995–2008. | Retrospective cohort study, descriptive statistics and between-group comparisons with statistically significant results highlighted. | 174 individuals undertook 331 PGD cycles (68% direct). Previous reproductive history: at least one previous pregnancy, 39%; at least one at least 0.70.<br>European Countries 20 Participants: individuals at genetic risk for HD seeking PGD during study period ($n = 174$) Comparison: none one previous termination following PND, 21% (significant correlation with seeking direct rather than exclusion testing), at least one living child, 18% (45% of whom born using PND/PGD). Percentage couples having unaffected live birth: 37.4%. Rate PGD uptake versus eligible at-risk population per country: Belgium, 8.5%; Netherlands, 5.8%, France, 3.7. | 0.70 |

(Continues)

**TABLE 1** (Continued)

| Main author, study year, location | Study aim | Design, participants, comparison (if applicable) | Main outcomes | Quality rating |
|---|---|---|---|---|
| Van Rij,[44] The Netherlands | Explore motivations for at-risk couples pursuing exclusion prenatal diagnosis (ePND) or preimplantation genetic diagnosis (ePGT). | Qualitative: IPA analysis of interview transcripts.<br>Participants: individuals with HD-diagnosed parent, and sometimes partner, who have used ePND/ePGT ($N = 17$). | Reasons for exclusion methods: desire not to know own status balanced with desire to avoid having a carrier child—to avoid that child experiencing HD, to avoid a 'double loss' for partner, or to attempt to 'break chain' of HD inheritance.<br>Choice of method: previous unawareness of unavailability of ePGT; issue of natural conception versus IVF; difficulties with idea of termination; non biological methods also considered.<br>Changes in decision: ePND discontinued due to distress at terminations, either to stop or to ePGT; delicate balancing of rights of child, partner and need to avoid suffering; ePGT as 'least bad' option. Desire for outside moral judgement to be removed.<br>Impact of HD: desire to 'live in moment', 'I could be hit by a car tomorrow'; balanced with concerns about future and child's wellbeing.<br>Change of method: majority stick, some change—general sentiment of 'making right choice at the time'. | 0.70 |
| Van Rij, de Koning Gans, Aalfs, et al.[45] The Netherlands | Reporting uptake, outcomes of PND over 10 years among those at HD risk. | Cross-sectional survey, descriptive statistics, statistically significant between group differences highlighted.<br>Participant: HD-risk individuals seeking PND ($n = 126$).<br>Comparison: none. | 126 seeking PND—216 tests undertaken, 214 pregnancies.<br>74% had PT prior to or during PND process (significantly more females than males).<br>Of 216 PND, 53% produced negative result, 4% intermediate allele, 2% withdrew prior to result.<br>Of 91 positive test, 76 terminations, 12 carried to term, 2 miscarriages.<br>126 children born, 86% without HD inheritance.<br>Uptake of PND versus HD-positive population 22%, with young people significantly more likely to opt in. | 0.75 |
| Van Rij, de Koning Gans, van Belzen, et al.[46] The Netherlands | Report uptake and outcomes of PND and PGT for HD risk individuals over 10 year course, looking for statistically significant differences between and within groups. | Cross-sectional survey, descriptive statistics, statistically significant between group differences highlighted.<br>Participant: HD-risk individuals seeking PND and PGT ($n = 162$).<br>Comparison: none. | 162 individuals at least one attempt of one method—108 PND only, 20 PGT only, 25 both.<br>Total attempts—458.<br>PND—47% had at least one termination, 76.5% at least one non-carrier child, 9.1% continued affected pregnancy.<br>PGT—53.5% at least one unaffected child, 48.8% at least one miscarriage, 7% at least one termination.<br>Total children born—183, 92.3% non HD inheritance.<br>Uptake as proportion of HD-positive population, 32%. | 0.90 |
| Wedderburn,[47] Australia | Reporting uptake, outcomes of PND, PGT among HD at risk individuals in Australia during study period. | Cross-sectional survey, descriptive statistics, statistically significant between group differences highlighted.<br>Participant: HD-risk individuals referred for genetic testing ($n = 466$).<br>Comparison: none. | 38 people sought out: 34 PND, 4 PGT.<br>PND: 12 negative pregnancies carried to term, 11 positive pregnancies terminated, 3 positive pregnancies carried to term. 8 withdrew in counselling phase.<br>PGT: no pregnancies occurred. | 0.65 |

# 3 | RESULTS

## 3.1 | Search findings

Initial searches resulted in 1849 studies identified. After duplicates and studies published pre-1983 were removed, 1075 studies were screened by title, leading to removal of an additional 660 records. Abstract screening left 64 papers screened at full text level. 27 met inclusion criteria and underwent quality analysis (see Figure 1 for summary). Study quality findings are in Table 1, 33% were rated as high quality, 37% as good and 22% as medium. 8% ($n = 2$) of studies[30,31] were excluded based on low quality ratings, leaving 25 papers included in analysis.

## 3.2 | Study characteristics

72% (18/25) of included studies were quantitative, 24% (6/25) were qualitative, and 4% (1/25) was mixed-methods. 37% (7/19) of studies with a quantitative element included a comparison group. Studies were conducted in the United States, (40%; 10/25); Continental Europe (37%; 10/25); Australia (12%; 3/25); and the UK (4%; 1/25), with one study leaving location unspecified. Included studies covered the following broad areas, sometimes several per study: factors influencing RDM among people at risk for HD, 28% (7/25); uptake and outcome of PND, 32% (8/25); RDM following PT, 24% (6/25); uptake and outcome of PGT, 20% (5/25); views of at risk individuals on genetic testing and influence on RDM, 24% (6/25) (see Table 1 for full study summary).

## 3.3 | Framework analysis

Framework analysis identified five key areas: (1) The relationship between reproductive intentions and HD genetic risk, (2) Views on assistive options, (3) Complexity and challenges in RDM in the context of HD genetic risk, (4) Actual reproductive outcomes, and (5) Other factors influencing RDM.

### 3.3.1 | The relationship between reproductive intentions and HD genetic risk

*Child desire and future reproductive intentions*

Six studies reported on future reproductive intentions. Three were of 'High' quality—one quantitative,[42] one qualitative[26] and one mixed-methods.[22] Three were 'Good' quality quantitative studies.[34,37,38] Earlier studies reported high levels of future reproductive intention—82% of participants at genetic risk for HD intended to have at least one child, and 78% two or more,[37] and 80% intended to have a further child at time of survey.[38] In comparison, rates of future reproductive intentions in more recent studies ranged between 51.59%[22] and 38%.[42] McCormack et al.[34] identified that at-risk males were more likely to express future reproductive intention than comparable controls, while at-risk females were less likely than control to express the same. Gong et al.'s[26] qualitative study outlined the relationship between genetic risk and reproductive intentions among a sample of affected young people. The majority expressed future child desire, with PGT often considered to avoid potential inheritance. A minority expressed changes to their reproductive intentions explicitly in response to genetic risk, either in the form of a choice not to have children, or decreased emphasis on becoming a parent. Male participants all deferred future reproductive intentions to preferences of female partner.

*Major role of HD knowledge in reproductive decision making*

Five studies explore the major impact of risk knowledge on RDM. Three 'high' quality studies—one quantitative,[42] one qualitative[35] and one mixed-methods[22]—as well as one 'good' quality quantitative study[28] and one 'medium' quality qualitative study.[23] In Quaid et al.[35] knowledge of HD risk of heredity was a major consideration in RDM, overshadowing other issues of parenting suitability and life circumstances. The qualitative findings in Decruyenaere et al.[22] demonstrate the overriding consideration of HD inheritance in RDM, especially among those choosing not to have children, while in Tsang,[42] 78% of at-risk individuals considered HD inheritance a 'very important' factor in RDM. Kessler et al.[28] additionally described the 'enormous' impact of HD inheritance on decisions about having children among 67.2% of participants. Downing[23] found participants equating lack of HD risk knowledge with reduced responsibility for reproductive inheritance, and characterising the point of gaining genetic risk knowledge as a 'turning point' in responsibility to respond to potential risk inheritance going forward.

*Impact of genetic testing on reproductive intentions*

Seven quantitative studies of various quality reported on anticipated and actual impact of positive PT result on reproductive intentions—two 'high' quality,[24,41] three 'good' quality,[33,37,38] and two 'medium' quality.[21,27] In terms of anticipated response to PND, between 33.5%[33] and 60%[37] would complete an affected pregnancy, between 16%[37] and 22.6%[33] would pursue termination, and between 27%[37] and 29.7%[33] were unsure. In terms of anticipated response to positive PT, 42.6% predicted they would be deterred, 16.1% undeterred and 30.3% unsure[33] while Schoenfeld reported a 22% anticipated reduction in future reproductive intention following positive result. In terms of actual impact, Holloway et al.[27] found a 40% decrease in definite future reproductive intentions post-positive result, while Tibben et al.[41] reported a 20.83% reduction in future reproductive intention 18-months post-positive result. Similarly, Decruyenaere et al.[21] found an approximately one-third reduction in reproductive intention among those previously intending to have children as a result of PT result, with one-third remaining undecided and remainder pursuing PND, while Evers-Kiebooms et al.[24] found a small but significant association between receipt of a positive PT result and decreased pregnancy likelihood 12-months post-test, more pronounced among those explicitly pursuing PT with 'family planning' as a motivator.

### 3.3.2 | Views on assistive options

*Views on PT, PND and PGT*

Seven studies reported on views regarding PT, PND and PGT. Two were high quality, one quantitative[42] and one qualitative,[26] three were good quality quantitative studies,[28,33,38] and two were good quality qualitative studies.[25,29] In studies conducted as PT was first becoming available, between 63.2%,[33] 73%[38] and 78%[28] reported willingness to pursue PT when possible, rising to 86.5% in the event of improved treatment options.[33] However, actual uptake rates of PT were lower than suggested by these studies. Prospective PND willingness was between 48%[33] and 65%,[28] with qualitative results highlighting the emotional challenges of potential termination of an affected pregnancy.[29] Similarly, Fowler[25] highlighted the interpersonal difficulties raised by pregnancy termination in PND as the main reason for non-utilisation in one case study. Views of PGT were generally positive, qualitatively characterised as the preferred option for having unaffected children,[26] and the 'least bad' option, specifically contrasted with the emotional challenges of PND.[29] Tsang reported 88% awareness of PGT, and 58% future intention to utilise. Commonly identified negative aspects of PGT were prohibitive cost,[26,42] and previous negative experiences of the process.[42]

*Views and use of other assistive options (adoption, donation)*

Three 'good' quality qualitative studies[25,29,36] reported on views and use of other assistive options. Adoption was viewed in mixed terms, characterised as avoiding HD inheritance and potentially 'helping someone in need' but potentially burdening an unknown child with caring responsibilities.[29] In Fowler,[25] one case study involved adoption viewed as a potential response to positive PT result, while another involved an affected individual adopting two children to avoid HD inheritance. Both cases stressed the emotional complexity of adoption, characterised by strong connection with the adopted child coexisting with loss and sadness regarding loss of potential biological parenthood. In Richards and Rea,[36] no individuals had pursued adoption 12-year post-positive PT result, compared to 1.2% of negative results.

*Response to changing technological options*

Five studies—one 'high' quality mixed methods,[22] two 'good' quality quantitative,[39,43] one 'good' quality qualitative[44] and one 'medium' quality quantitative[32]—responded to changing testing and assistive technology options over time. Decruyenaere et al.[22] highlighted both the positive view of continued developments and the less positive experiences of implicit pressure to engage with new options. Maat-Kievit et al.[32] found that 84% of participants continued to use the option they were familiar with from previous experience. A second area of concern was utilisation of direct PND/PGT (involving parents knowing their own genetic status) versus exclusion PND/PGT (involving parents avoiding knowledge of own risk status)—between 32%[43] and 35%[39] of those seeking PND or PGT opted for exclusion testing. Qualitative results highlighted the choice of exclusion testing as an attempt to balance the strong desire to avoid inheritance to children with the desire to avoid own risk knowledge, so as to avoid stigma, hopelessness or 'life being overshadowed' by HD.

### 3.3.3 | Complexity and challenges in RDM

*Balancing desire for a child with responsibility*

Five studies report experiences of difficulty balancing child desire with concerns regarding impact of HD inheritance—one 'high' quality mixed-methods,[22] three 'good' quality qualitative[25,29,44] and one 'medium' quality qualitative.[23] Five year post-PT, participants struggled to reconcile their desire for biological children with the responsibility to the child to avoid risk inheritance and future caring burden.[22] Klitzman et al.[29] outlined a similar 'push-pull' dynamic between these two concerns, characterised by rumination and uncertainty.[22,29] Some participants expressed a wish to return to a state of pre-risk knowledge 'ignorance', to avoid contending with challenges of managing responsibility.[23,29] This desire to achieve a balance of 'fairness' is highlighted in Downing[23] where each case study involved challenges in establishing the 'responsible' reproductive choice, desire to maintain consistency of approach across pregnancies, and attempts to establish responsibility by demonstrating aptitude for parenthood. Similarly, in Fowler,[25] one case study outlined the challenge of accepting responsibility to avoid inheritance by not having children with the deep sense of loss and sadness this evoked. Where exclusion methods were considered, any reservations about terminating healthy embryos was counterbalanced by the desire for children, protecting them against HD and a strong individual desire to avoid their own risk knowledge.[44]

*Risk acceptance and optimism*

Five qualitative studies explore acceptance of genetic risk in pursuit of strong reproductive intentions—one was 'high' quality,[35] three were 'good'[25,29,44] and one 'medium'.[23] Across studies, participants viewed risk of HD inheritance as one risk among many, often referenced against potential, unavoidable disasters (e.g., 'could be hit by a bus tomorrow'). Overall risk was characterised as fundamentally unavoidable, and the value of pursuing strongly held reproductive intentions emphasised.[29,35,44] A process of 'positive denial' was sometimes utilised, where participants 'decide' no inheritance has occurred, or treatments will be developed, as way of managing concerns.[25,35] Other emphasised parenting suitability characterising 'good parenting' holistically.[23]

*Guilt, regret and rumination on past decisions*

Four qualitative studies—one 'high' quality,[35] two 'good' quality[25,29] and one 'medium' quality[23]—explore rumination, guilt and regret regarding reproductive decisions. These included worries regarding the acceptability of decision to others, to future selves, and to children as they became aware of HD genetic risk later in life.[29] This was particularly challenging for those who became parents prior to risk knowledge and described looking for potential 'signs' of illness they might have missed[35] or a desire to 'start over, make different decisions'.[25] Some participants, previously 'at peace' with their reproductive decisions, begin to stressfully re-evaluate these in the light of the emerging HD symptomology of affected relatives, sometimes leading to regret.[23]

*Role in relationships with others*

Four qualitative studies—two 'high' quality[26,35] and two 'good' quality[25,29]—comment on the role of interpersonal relationships in RDM. The risk of developing HD and resultant RDM is influenced by the information received through healthcare professionals.[29,35] The healthcare professionals are relied upon to share this important information and when this did not occur, it was viewed as extremely harmful.[35] As well as being an important source of clinical information, these relationships could also serve as a source of implicit judgement of reproductive choices.[29] RDM is seen as inherently interpersonal, requiring negotiation with partners,[25,26,29] with RDM sometimes viewed as entirely dependent on the relationship, and not considered outside of this context.[26] Conflicting opinions, with a partner[25] or through multiple strong, differing opinions with a family[29,35] are challenging to navigate, and cause stress in the RDM process. Navigating complex relational dynamics sometimes became the prime factor in RDM, limiting options utilised and overshadowing issues of inheritance.[25]

### 3.3.4 | Actual reproductive outcomes

Ten studies report on actual reproductive outcomes among this population. Three were 'high' quality—one mixed-methods[22] and two quantitative.[41,46] Four were 'good' quality quantitative studies.[36,39,43,45] Three were 'medium' quality quantitative studies.[32,40,47] Tibben et al.[41] reported on reproductive outcomes 6-months post PT among the first Dutch testing cohort, with one unaffected pregnancy, one HD-carrier pregnancy carried to term and one carrier pregnancy terminated. Between 1993 and 1998, across several European sites, 184 pregnancies occurred, of which 123 utilised PND and eight were carried to term following a positive PND result. Between 1995 and 2008, 37.4% of individuals using PGT had at least one unaffected child. Between 1998 and 2008, among Dutch individuals seeking PND/PGT, 183 children were born, 92.3% with HD inheritance precluded.[45,46] Among the cohort of Decruyenaere et al.[22] ($n = 46$), 25 unaffected births occurred during the study period, 23 used PND and two used PGT.

Several studies reported the numbers of PND and PGT undertaken. Across the studies reviewed, 63 instances of PND and 18 instances of PGT were reported in Australia between 1994 and 2010.[36,40,47] At least 776 positive PT results were reported in same period.[40] In the Netherlands, 43 individuals sought PND between 1987 and 1997, with 60% following a positive PT result, and with 35% utilising PND across multiple pregnancies.[32] Between 1998 and 2008, 126 individuals in the Netherlands sought PND across 216 tests,[43] while 162 used PND (66.67%), PGT (17.90%) or both (15.43%).[46] In this sample, 47% of those using PND had one termination and 76.5% had one unaffected child, 77.8% of those using PGT had one unsuccessful cycle, and 44.4% had one unaffected child. Across several European sites between 1993 and 1998, 305 individuals sought PND, with 51% following a positive PT result,[39] while between 1995 and 1998, 174 individuals in the Netherlands, Belgium and France had at least one PGT cycle.[43]

Several studies reported the estimated proportional uptake of PND and PGT. Early estimated uptake of PND in the Netherlands during the study period was 2%.[32] Later Dutch estimates for uptake increased to 22% for solely PND,[45] 5.8% for solely[43] and 32% for both.[46] In Belgium estimated update of PGT was 8.5%, while in France it was 3.7%. In Australia, 776 positive PT results across the study period led to 63 PND and 18 PGT instances but did not report the proportional uptake.[40] Subsequent research estimated an uptake rate of 8.15% for both PND and PGT at one Australian site.[47]

### 3.3.5 | Other factors influencing RDM

Eight studies reported on demographic factors influencing RDM in this group. Three were 'high quality'—one quantitative,[42] one qualitative[26] and one mixed-methods[22]—and four 'good' quality quantitative studies[28,33,34,37] as well as one 'medium' quality quantitative study.[32] Age was associated with both an increased[22] and decreased[34] likelihood of maintaining reproductive intentions post-positive PT result, as well as increased likelihood to pursue PND over PGT.[32] Current parenthood was associated with a decreased likelihood of deterrence from future children by positive PT result,[33] decreased importance placed on HD inheritance as factor in RDM,[42] and decreased PND engagement.[33] However, Decruyenaere et al.[22] conversely found that those without children were significantly less likely to change reproductive intention following positive PT result. Being female was associated with both lower future reproductive intentions[34] and more definitive future reproductive intentions compared to male participants.[26] Several other factors influenced RDM including: higher educational attainment which was associated with being deterred from parenthood by positive PT, as well as decreased likelihood to have children at time of study and increased likelihood of terminating an affected pregnancy[37]; greater familial experience of HD having more affected relatives was significantly associated with increased likelihood of pursuing PT[33]; Catholic faith was associated with a significantly less likelihood of terminating an affected pregnancy[33]; and length of marriage was negatively associated with likelihood to pursue PT.[28]

## 4 | DISCUSSION

This review is to our knowledge the first to integrate research findings regarding RDM in the context of HD genetic risk. Five key themes were identified: '*The relationship between reproductive intentions and HD genetic risk*', '*Views on assistive options*', '*Complexity and challenges in reproductive decision-making*', '*Actual reproductive outcomes*' and '*Other factors influencing reproductive decision-making*'.

'*Relationship between reproductive intentions and HD genetic risk*' highlights an important interplay between pre-existing child desire

and RDM. Risk knowledge plays a major role in RDM across multiple studies. Given HD's risk of inheritance and quality of life impact,[48] this is understandable, and is similar to other heritable conditions.,[49,50] Positive anticipated and actual PGT results appear to reduce future reproductive intentions. However, the proportion of people who were deterred by an actual positive PGT result was smaller than the proportion of people who predicted they would be deterred by a hypothetical positive PGT result. This suggests other factors involved, such as strength of reproductive intention or contextual factors at time of testing (e.g., relationship status, life stage). Anticipated termination of affected pregnancy following PND was considered challenging given emotional impact of termination,[13] and may offer insight into the relatively low uptake of this option.

'*Views on assistive options*' outlines attitudes towards available risk-mitigation options. Despite early positive attitudes towards PT and high anticipated uptake, actual uptake of PT remains low.[51] Though barriers to testing access, and desire to avoid stigma or hopelessness are potential factors,[51] lack of available treatment options[33] may also be relevant. Mixed views on PND are associated with potential need to terminate an otherwise viable pregnancy, with PGT characterised favourably by comparison, though with noted cost barriers to use. Thus, PGT emerges as the 'least-lose' reproductive option.[52] Adoption emerged as a complex option with ethical concerns about future caring burden, and emotional desire for a biological child. These findings are similar to research into other heritable conditions, where adoption is viewed as the final option.[50] A complex relationship with changing technologies emerges, with positive (e.g., PGT) and negative elements (pressure to engage with newly available options), suggesting that reproductive decisions in HD are only conditionally 'made', reflexive to changing contexts.

'*Complexity and challenges in RDM*', outlines the subjective difficulties and acceptance of outcomes after the fact. Several studies highlighted the attempt to balance child desire with inheritance-related responsibility. Some participants aggregated inheritance risk with other potential risks[52] to reduce decisional complexity. Conversely, RDM can also be characterised by guilt and rumination on past and current decisions, suggesting that reproductive decisions are regularly returned to and re-evaluated over time and changing contexts. The complexity and distress of risk knowledge is contrasted with a sense of eased responsibility prior to knowledge acquisition. The interpersonal element of the decisional process are also highlighted, involving partners, healthcare professionals and wider family, eliciting multiple, often contradictory opinions, something mirrored in other heritable conditions[50] and is important to acknowledge as a major factor in RDM, sometimes overshadowing risk knowledge.

'*Actual reproductive outcomes*' summarised research on births and utilisation of assistive options among the target population. A general trend towards avoidance of HD inheritance where PND or PGT is pursued emerges, with a minority of HD-inheriting pregnancies continued by choice. It should be noted that these studies only reported outcomes among a self-selecting sub-population, and are therefore not necessarily representative of the broader at-risk population. Uptake of PGT, and to a lesser extent PND, appears to be increasing in the population over time from 1993 when PGT first became available, but remains low as percentage of the eligible population, similar to PT.[51] Findings suggest that awareness of PGT is not total among the eligible population, and cost issues limit utilisation. However, risk knowledge may be associated with reduced perceived responsibility.

'*Other factors influencing RDM*', outlines demographic and experiential influences on RDM, and important indicators of the inherently contextual and reflexive nature of RDM. Sex has contradictory findings, with both females[26] and males[33] reported to be more likely to express reproductive intentions, though lack of significance reporting and overall lower study quality in Markel et al.[33] should influence relative weighting to these findings. Similarly with age, Decruyenaere et al.[22] found that younger participants were more likely to maintain reproductive intentions following positive PT result, while McCormack et al.[34] reported the opposite. Given Decruyenaere et al.'s[22] higher quality and more recent data collection, they may be more representative of current cultural attitudes. Previous parents are less likely to consider risk inheritance as important, and less likely to utilise assistive options. It may be the case that, having successfully navigated parenthood they have broader ideas of what has been and therefore will be influential on parenting. Those with increased experience of HD within their family are more hesitant regarding risk inheritance,[13] and Catholics were significantly more hesitant to pursue termination of an affected pregnancy.[33] Educational levels are associated with a range of views related to affected pregnancies, mirroring a general trend towards greater acceptance of termination as an option generally associated with greater educational attainment.[53]

## 4.1 | Clinical implications

This review highlights the complex, challenging process of RDM in HD as well as the importance of timely and ongoing access to genetic counselling in order to facilitate person-centred information giving and decision making. It reinforces the need to consider the context of the RDM; age, sex and family history of the at-risk individual and the importance of including partners in discussion. Advances in genetic technologies have introduced new options for at-risk individuals (e.g., NIPT) with limited uptake in line with limited uptake of PST. Clinically, the ongoing nature of RDM, where decisions are returned to and re-evaluated across the lifespan, suggests the importance of facilitating access to genetic counselling reflexively to need across time, rather than discretely during testing process and assistive option utilisation only. There is an important role for patient support organisations to play in reaching the whole at-risk population with good quality information regarding RDM and encouraging early referral for genetic counselling. There is also a need to educate primary care physicians that a referral for genetic counselling does not require the individual to have PST but allows the opportunity for discussion with a professional with knowledge of HD. Lastly, the emotional complexity of these processes suggest genetic counselling services require the capacity to provide space for emotional processing, and time given to consider implications of decisions, rather than focussing solely information provision.

### 4.2 | Limitations

Existing literature focusses on the minority of individuals who engage with genetic counselling and therefore suffers from selection bias and may not reflect the views of the total at-risk population. Future research could focus on establishing reasons for lack of uptake of assistive options among the eligible population and how it might be facilitated, as well as exploration of RDM and outcomes among those who do not utilise these options.

In addition, there is a lack of an overarching psychological model of RDM in HD, despite both a rich body of qualitative research findings exploring its complexities, and the development of similar models in heritable physical conditions.[54] Given that HD is the longest tested for and most researched heritable neurogenerative disorder, and that on which the approach to others is often based, the lack of explanatory model of this key issues is an area for future consideration.

## AUTHOR CONTRIBUTIONS

**Neil Fahy**: initial conceptualisation; investigation; formal analysis; writing – original draft. **Charlotte Rice**: investigation; writing – review and editing. **Nayana Lahiri**: writing – review and editing. **Joshua Stott**: supervision; writing – review and editing. **Roopal Desai**: writing – review and editing.

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## CONFLICT OF INTEREST STATEMENT

The authors have no competing interests.

## PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/cge.14345.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

## ETHICS STATEMENT

No ethical approval was required as this is a review of the literature.

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