Which types of conditions should be included in reproductive genetic carrier screening?: Views of parents of children with a genetic condition

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Abstract

Reproductive genetic carrier screening identifies couples with an increased chance of having children with autosomal and X-linked recessive conditions. Initially only offered for single conditions to people with a high *priori* risk, carrier screening is becoming increasingly offered to individuals/couples in the general population for a wider range of genetic conditions. Despite advances in genomic testing technology and greater availability of carrier screening panels, there is no consensus around which types of conditions to include in carrier screening panels. This study sought to identify which types of conditions parents of children with a genetic condition believe should be included in carrier screening. Participants (n=150) were recruited through Melbourne paediatric hospital outpatient clinics, the Genetic Support Network of Victoria (GSNV) and a databank of children with hearing loss. This study found that the majority of participants support offering carrier screening for: neuromuscular conditions (n=128/134, 95.5%), early fatal neurodegenerative conditions (n=130/141, 92.2%), chronic multi-system disorders (n=124/135, 91.9%), conditions which cause intellectual disability (n=128/139, 92.1%) and treatable metabolic conditions (n=120/138, 87.0%). Views towards the inclusion of non-syndromic hearing loss (n=88/135, 65.2%) and preventable adult-onset conditions (n=75/135, 55.6%) were more mixed. Most participants indicated that they would use reproductive options to avoid having a child with the more clinically severe conditions, but most would not do so for clinically milder conditions. A recurring association was observed between participants' views towards carrier screening and their lived experience of having a child with a genetic condition.

Key Words: *carrier screening; parent view; genetic condition; reproductive; lived experience.*

Introduction

Reproductive genetic carrier screening (referred to as carrier screening hereafter) is the process by which people are screened to determine whether they have an increased chance of having a child with an inherited genetic condition. When two individuals are genetic carriers for the same autosomal recessive (AR) condition they have a one in four chance of having an affected pregnancy (1). If a woman is a genetic carrier for an X-linked recessive (XLR) condition, there is usually a one in four chance of having an affected son (1). Carrier screening can be offered either pre-pregnancy or in early pregnancy to enable utilisation of reproductive options. Previously, carrier screening has been limited to the most common genetic conditions and/or offered to individuals with a high *priori* risk due to family history or ethnic ancestry (2). Notable examples include haemoglobinopathy screening for sickle cell disease and alpha and beta thalassaemia, Tay Sachs disease (TSD) screening in Ashkenazi Jewish populations and cystic fibrosis screening for those with a family history (3);(4).

Rapid developments in genomic technologies have led to the evolution of large carrier screening panels which is referred to as 'expanded carrier screening' (ECS), whereby couples can be tested simultaneously for hundreds of AR and XLR conditions (5). Whilst practice varies widely with respect to carrier screening, a number of countries have policy/position statements supporting the offer of reproductive genetic carrier screening to all people planning a pregnancy or in early pregnancy (6) (7) (8). Despite a shift towards endorsing carrier screening, there is no clear consensus around which types of conditions should be included in carrier screening panels.

Consideration of which conditions to include has raised ethical concerns from both public and professional standpoints. Previous studies have highlighted the complexities associated with determining where to draw the line, specifically regarding the inclusion of conditions with variable presentation, later onset and milder phenotypes (9) (10). Disability rights communities have flagged potential negative impacts, with some believing that offering screening for particular conditions could impose a lesser societal value on those with the condition (11). This reinforces the importance of including families with experience of a genetic condition in discussions about carrier screening.

Lived experience of a particular condition has been shown to underscore attitudes towards screening. Boardman, Young, Warren & Griffiths (2017) found a difference in views towards prenatal screening for SMA depending on which SMA type the individual/family member was affected by or had experience of. A follow-on study demonstrated that individuals without experience of SMA exhibited greater support for preconception carrier screening compared to those with experience of SMA (12) (13). A key element in determining the acceptability of screening for particular conditions is understanding the views of people impacted by the condition. This study sought to ascertain the perceptions of parents of children with a genetic condition as to which types of conditions they believe should be included in carrier screening panels.

Methods

Ethical approval

This research project was approved by the Royal Children's Hospital (RCH) Human Research Ethics Committee (HREC/46825/RCHM-2019).

Study design

A quantitative questionnaire-based study was undertaken to ascertain the views of parents of children with a genetic condition as to which types of conditions they believe should be included in carrier screening panels. An online survey was used as the vehicle for data collection and descriptive statistics were used to present the views of participants. This study is set within a pragmatic framework, which allows the research question to guide the research methods (14) and involves obtaining knowledge to inform practice and decision-making (15).

Questionnaire development

Drawing from two previous condition taxonomies (a means of categorising conditions based on disease characteristics), (16); (17) (Supplementary Table 1) seven types of conditions which vary in severity and include both treatable conditions and conditions for which no treatments have been proven to improve prognosis were selected for inclusion in the online questionnaire (Table 1). With the exception of hearing loss, the condition descriptions were general and the names of the conditions were not included in the questionnaire. This was to encourage participants to focus on the nature of the condition rather than specific diagnoses.

For each condition type, participants were asked: (i) whether they believe reproductive carrier screening should be offered for this type of condition; (ii) whether they would choose to have reproductive carrier screening for this type of condition and (iii) whether they would use reproductive options (prenatal diagnosis 'PND', pre-implantation genetic diagnosis 'PGD' or donor gametes) to avoid having a child with this type of condition. Questions about religious views, genetic knowledge, reproductive choices and the genetic condition in the respondent's family were also included. The questions relating to religion were taken from the Centrality of Religiosity Scale (CRS-5) (18) (See supplementary material for full questionnaire). The questionnaire was reviewed by several subject matter experts: Genetic Counsellors, Clinical Geneticists, respiratory physicians, senior researchers, epidemiologists, and ethicists.

Recruitment

Participants were included in this study if they were over the age of 18 and have a child with a genetic condition. Potential participants were invited to participate through RCH (Melbourne, Australia) outpatient clinics (neuromuscular, cystic fibrosis and metabolic medicine), the Genetic Support Network of Victoria (GSNV) and the Victorian Childhood Hearing Impairment Longitudinal Databank (VicCHILD). Potential participants from the cystic fibrosis clinic, Members of the GSNV and VicCHILD were emailed the study invitation by their respective coordinators. For clinics in which parent email addresses were not routinely collected (metabolic medicine and

neuromuscular), potential participants were invited to take part in the study by a researcher (LT) in the clinic waiting room. The study details were shared via the GSNVs social media outlets.

Data analysis

Cleaning and analyses of survey data collected via REDCap (19) were performed in STATA version 14 (20). Preliminary descriptive analyses generated frequency data. Categorical data were presented as frequencies and percentages, with comparison of the cohort (type of condition) group for religiosity, genetic knowledge and severity of the condition in the family undertaken using $\chi 2$ (chi-squared) tests. Partially complete questionnaires were included in the data analysis, hence the number of participants that completed each question varies throughout. Due to small numbers of 'no' and 'unsure' responses to questions pertaining to participant views towards carrier screening for each type of condition, these were grouped into one category ("no/unsure") for each question.

An overall severity rating for the genetic condition affecting the participant's child was devised. Three questions were used to ascertain the perceived severity of the participant's child's condition: (i) how would you rate the severity of your child's condition; (ii) does the condition affect your child's day to day life and (iii) does your child's condition affect your daily life. The first question was scored from one to five, the second and third were scored from one to four, with the minimum and maximum scores possible being three and 13, respectively. Scores less than or equal to six were

classified as ‘mild’, scores from seven to 10 were classified as ‘moderate’ and scores greater than or equal to 11 were classified as ‘severe’. Overall scores were checked against the first question to ensure that the final classification reflected the parent’s assessment of the severity of their child’s condition.

The religiosity questions (CRS-5) were scored as per Huber and Huber (2012). This scoring grouped participants as either ‘highly religious’, ‘religious’ or ‘not religious’. A genetic knowledge score was created to summarise the five questions pertaining to genetic knowledge. As there is limited research exploring knowledge related to carrier screening, these questions were modelled on a previous Australian study’s genetic knowledge questions (21). Participants who answered 0 or 1 question correctly were categorised as having ‘low’ genetic knowledge, participants who answered 2-3 questions correctly were categorised as having ‘moderate’ genetic knowledge and participants who answered 4-5 questions correctly were categorised as having ‘high’ genetic knowledge.

Results

One hundred and fifty people completed the questionnaire. Sixty-five individuals were invited to participate in clinic and approximately 1300 individuals were invited to participate via email. The participation rate is unable to be calculated as the number of individuals who were eligible to participate is unknown (some invited individuals would not have had a child with a confirmed genetic condition). Participants were mostly female (n=136/150, 90.7%) and aged 30 to 49 (110/150, 73.3%). The majority

of participants were born in Australia (n=129/150, 86.0%) and Caucasian (n=138/149, 92.6%). Most participants had one child with a genetic condition (n=126/149, 84.6%) (Table 2). The most common conditions were cystic fibrosis (n=53/138, 38.4%), hearing loss (n=28/138, 20.3%) and Duchenne muscular dystrophy (n=9/138, 6.5%) (Table 3).

Participants' reproductive choices following their child's diagnosis

Most participants (n=113/144, 78.5%) reported being told that they had an increased chance of having another child with the same condition. Of these participants, 50.0% (n=55/110) reported their reproductive plans changed after receiving their child's diagnosis. The most common change in reproductive plans was choosing not to have more children (Figure 1.1). Twenty-four (16.7%, N=144) participants indicated they did not have an increased chance of having another child with the same condition. Seven (30.4%, N=23) of these participants reported their reproductive plans changed after receiving their child's diagnosis (Figure 1.2). Seven (4.9%, N=144) participants were unsure if they had been told they had an increased chance of having another child with the same condition.

Six participants (4.2%, N=142) indicated they or their partner have had a termination of pregnancy for the genetic condition affecting their child - (cystic fibrosis-4, beta-thalassaemia-1, Pendred syndrome-1). All participants who reported having had a pregnancy termination perceived their child's condition as moderate (data not shown).

Participants' views towards carrier screening for seven types of conditions

For the scenarios presented, over 90% of participants supported offering screening for neuromuscular conditions (n=128/134, 95.5%), early fatal neurodegenerative conditions (n=130/141, 92.2%), chronic multi-system disorders (n=124/135, 91.9%) and conditions which cause intellectual disability (n=128/139, 92.1%). While the majority of participants also supported, to a lesser extent, inclusion of treatable metabolic conditions (n=120/138, 87.0%) and non-syndromic hearing loss (n=88/135, 65.2%), views toward the inclusion of preventable adult-onset conditions (n=75/135, 55.6%) were more mixed. The majority of participants indicated they would choose to undergo carrier screening for each of these types of conditions (Figure 2). For the scenarios presented, most participants indicated they would use reproductive options (PND, PGD or donor gametes) to avoid having a child with an early fatal neurodegenerative condition (n=113/139, 81.3%), a neuromuscular condition (n=108/135, 80.0%), a chronic multi-system disorder (n=100/134, 74.6%), a condition which causes intellectual disability (n=97/138, 70.3%) and a treatable metabolic condition (n=85/138, 61.6%), while approximately one third of participants said they would use reproductive options to avoid having a child with a preventable adult-onset condition (n=49/134, 36.6%) and non-syndromic hearing loss (n=44/135, 32.6%) (Figure 2). Almost half of the participants would choose to undergo carrier screening (n=62/131, 47.3%) for, and supported inclusion of, all seven types of conditions (n=64/137, 46.7%), but only 27.0% (n=34/126) of participants indicated they would use reproductive options to avoid having a child with all of the seven types of conditions.

We looked to see if there was a difference in views towards carrier screening between parents whose child had a condition which was consistent with one of the condition descriptions presented in the questionnaire and all other parents. Although no strong evidence of a difference was identified, the data suggests that a larger proportion of parents of children with hearing loss believe that non-syndromic hearing loss should be included in carrier screening, when compared to parents of children with other genetic conditions (n=26/134; n=61/134 78.8%; 60.4%, respectively, p=0.055).

Factors which may influence views towards carrier screening

Religiosity

The majority of participants reported they were 'not religious' (n=73/131, 55.7%), 38.2% (n=50/131) were 'religious' and 6.1% (n=8/131) were 'highly religious'. Of those who identified with a religion (n=56/137, 40.9%), Catholicism was most common (n=18/51, 35.3%). There was no strong evidence of a difference between participants with respect to religiosity and views towards carrier screening (See supplementary tables 2.1 – 2.3).

Genetic knowledge

Seventy-two participants were found to have a high level of genetic knowledge (N=135, 53.3%), fifty (37.0%) had a moderate level of genetic knowledge and thirteen (9.6%) had a low level of genetic knowledge. No evidence of a difference was observed

between participants with respect to genetic knowledge and views towards carrier screening (See supplementary tables 3.1 – 3.3).

Participants' perceived severity of their child's condition

Participants were asked to rate the severity of their child's condition and indicate the level of impact it has on their child's life and on their own life. Seventy-six participants viewed their child's condition as 'moderate' (N=143, 53.2%), twenty-nine (20.3%) viewed their child's condition as 'mild' and thirty-eight (26.6%) viewed their child's condition as 'severe' (Table 3). For all seven types of conditions presented, a smaller proportion of participants who viewed their child's condition as severe thought that the condition should be included in carrier screening when compared to participants who viewed their child's condition as moderate or mild (see supplementary table 4.1). The largest difference was observed between participant groups with respect to non-syndromic hearing loss, with 76.9% (n=20) of the mild participant group, 72.0% (n=54) of the moderate group and 41.2% (n=14) of the severe group supporting its inclusion in carrier screening (p=0.003).

Discussion

Perceptions of the types of conditions to include in carrier screening panels

This study is the first to examine the views of parents of children with a genetic condition towards carrier screening for different types of genetic conditions. Participants exhibited the most support for the inclusion of the more clinically severe types of conditions in carrier screening panels, those being early fatal

neurodegenerative conditions, neuromuscular conditions, chronic multi-system disorders and conditions which cause intellectual disability. Previous studies have highlighted the complexities associated with carrier screening and cautioned against the inclusion of milder conditions (9); (7), however, the participants in this current study appear to challenge the idea that only severe childhood-onset conditions should be included in carrier screening. A large proportion of participants believe that preventable adult-onset conditions and non-syndromic hearing loss should be included in carrier screening. This could be explained by previous research which suggests that individuals with experiential knowledge are likely to perceive carrier screening as more relevant than those without a lived experience of a genetic condition (22).

Our study found that participants with experience of cystic fibrosis were highly supportive of the inclusion of chronic multi-system disorders in carrier screening. Similarly, participants with experience of hearing loss were the most supportive of the inclusion of non-syndromic hearing loss in carrier screening. Previous studies have also demonstrated that individuals with experience of a particular genetic condition are often highly supportive of the inclusion of that condition in carrier screening (23); (12). Fifty-five percent of participants supported the inclusion of the preventable adult-onset condition in carrier screening; this condition was modelled on haemochromatosis, although, no one with lived experience of haemochromatosis was included in this study. It would be useful to compare the views of participant's in this study to the views of individuals with haemochromatosis, as their lived experience would differ to that of a parent of child with a genetic condition.

Types of conditions for which participants would choose to have screening

The proportion of participants who would choose to have screening for each of the seven types of conditions was reflective of the proportion of participants who believe that each condition should be included in carrier screening. Two recent studies examined the views of the general population towards carrier screening and found the majority of participants would choose to have screening for adult onset or mild conditions (24); (25), analogous to the majority of the participants in our study. The Western Australian study found that over 80% of participants would undergo screening for moderate and severe conditions (24), whereas, a study conducted in the Netherlands found that only 34% of participants would have screening for serious, early-onset conditions (26). Interestingly, 23% of participants in the Netherlands study reported 'not wanting to be bothered' by knowing they were an 'at-risk' couple. The difference in views between participant's in this current study and that of the Netherlands study is likely to be linked to participants' experience of having a child with a genetic condition.

Types of conditions for which participants would use reproductive options to avoid having an affected child

This study found that most participants would use reproductive options (PND, PGD, donor gametes) for conditions perceived as more severe, as conditions become milder fewer participants indicated they would access reproductive options to avoid having an affected child. A recent US study of couples with an increased chance of having a child with a genetic condition pre-pregnancy, found that the majority of participants

intended to pursue actions to reduce the chance of an affected pregnancy; 91% for profound conditions, 77% for severe conditions and 65% for moderate conditions (27). Although the categories do not directly align with those in the current study, similarities exist between the two participant groups, with the majority of participants considering the use of reproductive options for the more severe types of conditions.

Notably, this current study found that 32.1% of participants would use reproductive options to avoid having a child with non-syndromic hearing loss. In contrast, a previous Australian study looking at potential future uses of non-invasive prenatal testing (NIPT), found that only 5.2% of participants would terminate a pregnancy for deafness (28). This difference could be explained by the fact that participants in this current study could consider PGD and donor gametes as reproductive options in addition to termination of pregnancy (TOP), whereas the only reproductive option considered in the previous Australian study was TOP. Another possible explanation is that almost all participants in the previous study had no family history of a genetic condition.

Factors which may influence views towards carrier screening

This study identified differences between participants with respect to the severity of their child's condition and their views towards carrier screening. Participants who viewed their child's condition as severe were less likely to support the inclusion of non-syndromic hearing loss and conditions which cause intellectual disability in carrier screening. A UK study examining the views of individuals with experience of bleeding

disorders (haemophilia A and B) found that participants generally had similar views towards carrier screening, irrespective of the perceived severity of their condition/the condition in their family (29). Other studies have found that there is a complex association between lived experience (severity of a condition) and views towards carrier screening and prenatal testing for that condition (30); (12). The difference in participants' views between our study and other studies could be understood by the fact that the participants in the current study were asked about a range of conditions, whereas, previous studies asked participants only about the condition in their family.

Unlike other studies, we did not find a significant evidence of a difference with respect to religiosity or genetics knowledge in terms of attitudes about carrier screening. Two Dutch studies which looked at the views of the general public towards carrier screening found that people who identified as religious were less likely to participate in carrier screening (31); (32). Nijmeijer et al. (2019) found that religious participants were less likely to believe that offering carrier screening was ethically acceptable (31). Although these populations differ to that of the current study, in that participants in the Dutch studies did not have experience of a genetic condition, it could be inferred that religiosity influences views towards carrier screening because some reproductive options may not align with commonly held religious beliefs. Although this current study did not identify any differences between participants with respect to genetic knowledge and views towards carrier screening, an Australian study found that genetic knowledge underscored attitudes towards undergoing carrier screening (24). Participants who had 'good' genetics knowledge were seven times

more likely to intend to undergo carrier screening, while participants with 'high' levels of genetic knowledge were only four times more likely to intend to undergo carrier screening (24). This suggests that individuals with higher levels of genetic knowledge could have a greater awareness of the broader implications of genetic testing. Level of genetic knowledge was tested more extensively in the other Australian study, with 21 questions, whereas, our study used only five genetic knowledge questions, which may account for the difference between the two participant groups

Limitations

This study saw an overrepresentation of females of Caucasian background, which is possibly a reflection of the recruitment strategy and mode of data collection. Participation was limited to individuals who speak English and many invited participants were mothers accompanying their child to a hospital appointment. Additionally, when emails were used for recruitment, mothers were more often listed as the contact person. Individuals with lower literacy and/or technical skills may have been less likely to participate due the survey being administered online.

This study captured participants with experience of a wide range of genetic conditions, with 38 different conditions represented. However, there were no participants whose child had a preventable adult-onset condition, in particular haemochromatosis. Some participant groups were small (for example parents of children with neuromuscular conditions), meaning that there is a limit to the generalisability of these results to other individuals with experience of similar genetic conditions. No cardiac conditions

or cancer syndromes were included amongst those surveyed. It would be useful to ask adults with these types of conditions their views towards carrier screening.

Conclusion

This study sought the views of parents of children with a genetic condition as to which types of conditions they believe should be included in carrier screening. It found that while the majority of participants support the inclusion of all seven types of conditions, as conditions become clinically milder, support for their inclusion decreased. Fewer participants indicated they would use reproductive options to avoid having a child with each of the types of conditions presented, however, this number increased as the severity of the condition increased. This suggests that the severity of the condition under consideration is a key factor in determining whether or not it should be included in carrier screening and in decision-making associated with carrier screening. There was a recurring association between participants' views towards carrier screening and their lived experience of having a child with a genetic condition. This exemplifies the importance and value of including the views of those impacted by genetic conditions in discussions about carrier screening.

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Conflict of interest and funding

The authors declare no conflict of interest. No financial assistance was received in support of the study.

Figure Legends

Figure 1.1: Changes in reproductive plans of participants who recall being informed of an increased chance of having another child with the same condition

Figure 1.2: Changes in reproductive plans of participants who do not recall being informed of an increased chance of having another child with the same condition

Figure 2: Participant's views towards reproductive carrier screening for seven types of conditions

Table Legends

Table 1: Types of conditions included in the questionnaire

Table 2: Demographics

Table 3: Conditions reported by participants as affecting their child, with their assessment of severity

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Supplementary material

Supplementary table 1: A summary table of two condition taxonomies (a means of classifying conditions based on disease characteristics) (Korngiebel et al., 2016 & Lazarin et al., 2014).

Supplementary tables 2.1-2.3: These tables present the data from the Chi^2 analyses of views towards reproductive carrier screening for each type of condition and participants' religiosity. This was used to determine whether there was a difference in views between participants who identified as religious/highly religious and those who identified as not religious.

Supplementary tables 3.1-3.1: These tables present the data from the Chi^2 analyses of views towards reproductive carrier screening for each type of condition and participants' genetic knowledge. This was used to determine whether there was a difference in views between participants with low, moderate and high genetic knowledge.

Supplementary tables 4.1-4.3: These tables present the data from the Chi^2 analyses of views towards reproductive carrier screening for each type of condition and participants' perceived severity of their child's condition. Used to determine whether there was a difference in views between participants who viewed their child's condition as mild, moderate and severe.

Questionnaire: The full questionnaire that participants completed.