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Title: Patient attitudes towards prenatal diagnostic testing for inherited retinal disease

Running title: Attitudes towards prenatal diagnostic testing for inherited retinal disease

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What's already known about this topic?

- Advances in genetic technology are providing low cost readily accessible genetic testing
- There are potential benefits to genetic testing in inherited retinal disease but its role in prenatal diagnosis is not well understood

What does this study add?

- Patients with inherited retinal disease have mixed views about the use of prenatal genetic testing
- Varied attitudes and uncertainty about the risk and accuracy of test results suggest the need for genetic counselling to support informed decision making

ABSTRACT

Objective: To explore factors that influence decision-making in relation to prenatal diagnostic testing (PDT) for inherited retinal disease (IRD).

Method: Semi-structured interviews were conducted with 50 adults with IRD, selected from a larger sample to provide a diversity of backgrounds and opinions on genetic testing. Interviews were transcribed verbatim and analysed using thematic analysis.

Results: Mostly participants supported PDT, believing that it would provide information to help them prepare for and plan the future care of the child and the potential for early access to emerging therapies. Opposition to PDT stemmed from its use to justify termination of pregnancy, with participants feeling that it was not justified as they retained a good quality of life despite their visual impairment. Participants raised concerns about the risk of PDT and the accuracy of the results. However, most suggested that it should be available as an option for others, but for specific reasons and not as a part of routine care.

Conclusion: The variation in attitudes towards PDT and uncertainty about the risk and accuracy of results suggest that individuals at risk of having a child with IRD should have access to genetic counselling to support decision making.

Keywords: Prenatal diagnosis, Inherited retinal disease, Attitudes, Genetic testing.

INTRODUCTION

Inherited retinal disease (IRD) is a common cause of visual impairment, especially in children and adults of working age. Visual impairment can be caused by loss of central or peripheral retinal function. Macular dystrophies impair function of the central retina and cause loss of visual acuity, with difficulty reading and recognising faces, impaired colour vision and light sensitivity. The most common macular dystrophy is Stargardt disease. Generalised retinal dystrophies impair function of the peripheral retina and cause loss of visual field, with problems navigating independently and seeing objects to the side, and night blindness. The most common disease in this group is retinitis pigmentosa. Inherited retinal diseases can be inherited as dominant, recessive and X-linked conditions and are genetically heterogeneous.

Advances in genetic technology, particularly the development of next-generation sequencing and the introduction of whole-exome sequencing, will allow low cost, rapid and readily accessible genetic testing for rare conditions, such as inherited retinal disease (IRD). Recent studies have demonstrated demand for such testing among adults with IRD.[1-6] A potential benefit would be to allow affected individuals and their relatives to make informed reproductive choices.

Previous studies have documented a wide variation in access to specialist genetic services and genetic testing within the publicly funded National Health Service (NHS) in the United Kingdom, particularly for those with IRD.[7] However, this issue is being addressed with advances in technology and planned changes in NHS service delivery, particularly the introduction of specialised ophthalmology services with greater access to multidisciplinary teams providing a service to those with a range of ocular genetic disorders.[8]

Prenatal diagnostic testing (PDT) would be an option for pregnant women who are at risk of having children with IRD. Prenatal diagnostic testing for retinoblastoma and other IRDs is currently available, for conditions in which the familial mutation is known, in the UK, USA and other countries.[9-11] During genetic counselling, individuals are often given information about PDT, when this is relevant, to help them make an informed decision. Currently requests for PDT are either not common for IRD[11] or value of PDT is not clear. However requests may become more common with greater access to and success of diagnostic testing. In order to plan services for IRD and to provide accurate and relevant information for informed decision making, it is important to understand the attitudes of the target population. This study therefore utilises a qualitative approach to gain insight into the opinions and attitudes of adults with IRD on PDT.

METHODS

Participants for interview were selected from a larger sample of 200 adults, all of whom had completed an earlier, telephone questionnaire.[1] Participants for the questionnaire were recruited via postal invitation sent to patients attending any of five local clinics (response rate 48%), approach at the time of clinic review or through newsletters of relevant, national charitable organisations. Patients aged over 16 years, with a clinical diagnosis of inherited retinal disease but without a significant hearing impairment, were eligible. Selection for the interviews was based on a purposive sampling frame, constructed to provide a sample with a maximal diversity of demographic and baseline characteristics, self-reported knowledge of and support for genetic testing. The following characteristics were included in the sampling

frame: age (across four groups considered to represent different life stages: 16-25y, 26-39y, 40-59y, 60+y), gender, ethnicity, education, severity of visual impairment, parenting status, family history of IRD. Both the telephone questionnaire and the format for the subsequent interviews have been described in detail previously.[1, 12]

Semi-structured, face-to-face interviews were conducted with 50 adults with IRD to explore attitudes to PDT and the factors that influenced their views. All of the 50 participants approached to complete the interview consented to do so. Although the focus of the interviews was on diagnostic genetic testing, questions were also asked about predictive testing and both prenatal and pre-implantation genetic diagnosis. In relation to PDT, participants were asked if they felt that genetic testing should be offered to pregnant couples to see if their unborn child carries a gene for inherited eye disease, why they understood about the process and how they felt that the results should be used. No information on PDT was provided beforehand. Other topics included in the interview were knowledge and understanding of relevant terms (e.g. recessive, dominant, carrier), potential risk and benefit of genetic testing, preferred source of information, sharing information/results among family members, personal experience of genetic testing and willingness to pay for testing. All interviews were recorded and transcribed verbatim. Analysis and coding was performed using a thematic approach.[13, 14]

To ensure consistency, two researchers analysed a number of randomly selected transcripts for the emerging themes independently, coded the data, and compared codes and themes. Any disagreements were resolved by consensus. The researchers continued with the analysis of the remaining interviews and met at regular intervals to agree or refine themes. Analysis was undertaken using a constant comparison and contrastive approach. Looking for negative cases further refined understanding and relationships between and within the themes.

Participants gave written, informed consent before the interviews. The study was approved by the Leeds (East) Research Ethics Committee (10/H1306/90).

RESULTS

Sample

The mean age of participants was 45.7 years (range 18-74). Other demographic and baseline characteristics are presented in Table 1. Participants with a range of clinical diagnoses, including both congenital and acquired disorders, and inheritance patterns were included. Most participants had generalised retinal disease, including 22 with retinitis pigmentosa and two with Leber congenital amaurosis, but 20 had disease limited to the macula including seven with Stargardt disease and four with Best disease.

Attitudes to pre-natal diagnosis are dependent on personal circumstance

Participants often stated that their personal attitudes to PDT may differ from others with IRD because their circumstances were different. For example, some had already had children with no plans for any more and had already made a decision not to have children. For these participants, PDT was less relevant. Others mentioned that support for PDT may also vary according to the number of children already in the family, the parents' enthusiasm to have children or prior problems with conception.

P115: "People have different parental urges and mine isn't very strong. So I think that if you know that yo*u are going to bring somebody into the world with that condition, then just don't bring them in..."*

P60: "I'd probably try again to see if the next one didn't…There wasn't a problem with me getting pregnant but everybody isn't as lucky. Some people can't get pregnant."

Another common opinion was that support for PDT may be dependent on the likelihood of the child being affected, with stronger support for dominant or X-linked disease but with weaker support for recessive disease outside of a consanguineous relationship.

*P08: "…*probably not unless there was a good chance of the child having the *disability…*unless there was like a very strong cha*nce, otherwise… it's not worth it."*

A common belief among participants was that although they may not choose to access PDT themselves, it should be available to others. However, PDT should not be routinely available but limited to specific and unusual circumstances.

P25: "I think it should be there for everybody if they need it… it depends on individual circumstances really *…I wouldn't stop them having the choice."*

P53: "I agree that testing should be offered to the couple… but not done as standard."

<u>Support for pre-natal diagnosis</u>

Many participants were in favour of PDT purely for the information that it would provide, even if this confirmed that the child would probably be affected. Some participants appeared to value that information alone and were unsure about any practical benefits. Others felt that the information would help them to plan their own and their child's future, enabling access to support for those with visual impairment as early as possible.

P24: *"For my children's sake, I would like to be aware of it… the more information you have the better."*

P150: *"I would personally go for the test either way, just for our reference, we'd like to know if it was the worst case scenario."*

P184: "If the test was available for myself, then I would have *it…I would not want to terminate the pregnancy…It would just mean that I was better prepared for the child having that condition."*

Some participants were in favour of PDT because they believed that the results could lead to a reduction in the incidence of IRD through termination of pregnancy (TOP). Several believed that support for PDT and TOP would be stronger for earlier onset or more severe diseases. Others hoped that PDT would also reduce the visual burden resulting from IRD by allowing earlier access to support and treatment. Most participants commented that support for PDT would inevitably increase if there was an opportunity to access a novel therapy early that may help to stabilise or improve visual function.

P169: "I think that the parents have a right to choose and if they think that the child is going to have a lot of difficulties, they should have the right to choose to continue or not to continue (the pregnancy). They need to be given the choice.*"*

P13: "No, I wouldn't have it…but my condition is not that severe and I think that if you had a more severe one…it's more your call to decide. If I had the one where you are blind at 15...maybe I wouldn't feel the same"

P07: "For this condition, no...If you're going to have a baby and you know they are going to need help when they're born, that'd be different."

*P111: "Yes if there's something that can be done! If t*here was a treatment or a cure or *'*we can stop it getting any worse*'...*then yes. But *if there's no*thing that can be done, then maybe *not."*

Opposition to pre-natal diagnosis

Many participants stated that their visual impairment had not started early enough, nor was it either sufficiently severe or life-threatening to warrant PDT and TOP. Given that they retained a good quality of life, they were opposed to PDT and TOP. Some participants felt that it may be acceptable for others to proceed to termination but only for severe and early onset visual impairment.

P01: "I just think that's [termination] *generally what people…you know, when they're offered testing for genetic stuff when they're pregnant, that's generally what's in the patient's mind"*

P011: "... So therefore the mother would only want to do it if she wanted the option to abort, I presume.*"*

Many participants assumed that the most frequent outcome of a positive PDT would be termination of an affected pregnancy. As a result, their opposition to PDT was inextricably linked to opposition to terminations. Several participants mentioned personal or religious reasons for opposing termination, hence opposing PDT. Carrier status testing and pre-implantation genetic diagnosis were often reported as preferred alternatives.

*P02: "*I have a Christian faith, so you *know, it's not something that I'm happy with."*

P110: "I think once the child is conceived, that's it. I don't believe in abortion for whatever reason."

P013: "I know I've had quite a decent life till now! I'm still having a good life... it wouldn't stop *me."*

P121: "Now that I'm over the grieving and the bad part of losing my sight…and rebuilt my life and my career…It's not the worst thing that could happen and to deny a child being born because of it, I'm not that sure how I'd feel."

P25: "I think it's quite a cruel decision to have to make when the child has already been made…I think it's better to know…before you make a baby…I would not want testing while it was in the womb. I'd want the tests before I…even plan a child."

*P130: "*If *you know that you are carrying the gene, that's one thing. You can go into an informed position about whether or not…to have children. But to choose to have children and to discard ones that may be faulty…having tested them…that does not seem good to me."*

Several participants realised that if TOP for IRD had been practised in the past they may not have been born. For some, the idea of PDT followed by termination seemed either to suggest eugenics or that the life of an individual with IRD was less valuable than someone without visual impairment. Another view was that parents may experience greater guilt about completing a pregnancy after a positive result than if they had decided not to pursue PDT.

P130: "I wouldn't agree with it. No not *all…*that would…bring in the idea of some kind of eugenics or the fact that you may choose *not to have a child because it…*demonstrates a condition t*hat you're not comfortable with…* To choose to have children and to discard ones

that may be faulty ... it does not seem good to me. It seems *very eugenic in its outlook…trying* to create the perfect child*."*

*P130: "*I may have been disregarded *and I wouldn't have existed…n*or would my brother and sister. Potentially then, you could take it one step further and say *"*well, we will try and eliminate the gene*"*, in which case 50% of my siblings would have been disregarded because *they carried the gene"*

P205: "I probably would feel quite guilty if I were to have passed it on and to have …knowingly done that because, in a way, ignorance is bliss."

There were concerns about the risk to the pregnancy associated with the PDT procedure, inaccurate results, and uncertainty of results as to whether individuals would actually develop visual impairment. One participant believed that there may be a tendency to over protect children identified through PDT as being likely to develop an IRD.

P122: "If the tests are putting mother or baby at risk, I would be against."

*P114: "No, if it puts the baby at risk, no…I mean my first question…*what risk, what are the percentages*?"*

P151: "For me, there is an element of usefulness in knowing whether the child is going to have it…(but) there would be a fine line between having that knowledge so that you know what to look out for and…trying to protect that child from every knock and bump that comes *along…I look at the way my Dad was after I was diagnosed…He tried to infantilise me all over again, trying to protect me from harm."*

P125: "It is not always 100% when they get that test."

Several participants believed that a positive result could be stressful for a couple, particularly if the implications of PDT had not been fully considered beforehand.

*P25: "*If somebody were to say that to me that you could have pre-natal diagnosis and then you *could consider ending a pregnancy if the pregnancy's affected, I would find that really* difficult.*"*

DISCUSSION

This study suggests that adults with IRD have mixed views about PDT. In our original telephone questionnaire study [1] over 90% of participants supported both diagnostic and predictive genetic testing for IRD, whereas fewer than 50% supported pre-implantation genetic diagnosis and PDT. Therefore, this face-to-face interview study aimed to explore the attitudes that lead participants to support or oppose PDT for IRD.

Mostly participants were in favour of PDT for the information that it would provide, but were against the use of PDT if it resulted in a TOP. Participants readily acknowledged that their personal views may differ from those of others and that individual experience and circumstances would often determine levels of support. They were, however, generally in favour of the provision of PDT services for others, if not necessarily for themselves.

Participants who were in favour of PDT often stated that they would want it to provide information about their pregnancy and to help them plan for the future needs of their child. They believed that better understanding would help them make an informed reproductive decision. The information alone appeared to be valuable. Pradhan[3] reported that only three of 35 couples, with a personal or family history of IRD, chose to investigate options for PDT or

pre-implantation genetic diagnosis after a positive, diagnostic genetic test. Similarly, Mezer[15] reported greater support for PDT than for termination of pregnancy.

Several participants felt that support for PDT would be stronger when the risk to the child was higher and for more severe disease. Mezer[15] identified stronger support for PDT and termination of pregnancy among those with more severe visual impairment, although reported that those affected by IRD were less likely to support PDT and termination than those who were unaffected. Many participants were aware that demand would increase if there was the chance of accessing a novel therapy very early in life to stabilise or improve visual function, hence reducing the burden of the disease. Prior studies have suggested that if PDT were available for genetic conditions such as IRD, then demand and uptake would be likely to increase,[16] not necessarily because individuals would want to terminate an affected pregnancy but rather for information only to help them prepare.[17]. In a recent study by Ahmed et. al.,[18] 41% of participants said that they would be willing to have PDT for IRD but only 14% said they would opt for TOP.

Similar to other studies, participants often cited both religious and ethical reasons for opposing PDT.[18, 19] However, this response was based on an assumption that a positive test result from PDT would lead to termination of an affected pregnancy. Although most of the study participants were certified as having sight impairment, they did not perceive that their quality of life was sufficiently poor to justify termination. As in other studies, this suggests that participant decisions to consider PDT and TOP are based on their personal experience or perception of the severity of the condition and involved a reflection on the likely burden of the condition and the stigma for an affected child.[18]

Field Code Changed

Field Code Changed

Although reported support for PDT with termination of an affected pregnancy was low, the actual behaviour of these participants may be different in a real situation.[3, 18]

A study by Hewison et al.[16] looked at attitudes about prenatal testing and TOP for 30 different conditions in 420 women (198 Pakistani and 222 European white) in UK. Similar to this study, they found variation in views of women where they were in favour of PND but had less favour able attitude towards TOP, except for some sever conditions, e.g. anencephaly, trisomy 13 or 18, quadriplegia, Duchene muscularly dystrophy. There were also considerable individual variation in responses with regard to prenatal diagnosis and TOP. Therefore, health-care providers should not assume attitudes towards PDT but to see patients as individuals who may have different views and needs. In particular, effort should be made to dispel misconceptions about the relationship between PDT and TOP, with individuals reassured of their autonomy in decision making. Equally, it is important to be aware that the concept of quality of life may have different meanings for different people and quality of life can also change for the same person over the course of a disease.[15, 20]

Despite published evidence that the risks of both amniocentesis and CVS are low (1-3%),[21] some participants had concerns about the procedural risks of PDT. Several expressed concerns about the accuracy of results and worried that individuals may make a wrong decision and terminate an unaffected pregnancy. Participants also highlighted that the decision to opt for PDT may lead to psychological distress, particularly if they were not adequately prepared for positive results. They believed that individuals may feel guilty if they decide to carry on with the pregnancy following a positive result, compared with those who decided against the idea of undergoing a PDT test. At the same time, participants showed their willingness to receive more information about the implications, both in terms of inheritance pattern and prognosis of their condition to make informed choices. It is therefore pivotal that individuals have access to genetic counselling services, where they can receive accurate, balanced and unbiased information and support to make informed reproductive decisions.[12, 22]

Prior studies have demonstrated that the information needs of those with IRD appear to be unmet.[12, 23] Healthcare professionals, both ophthalmologists and those involved in clinical genetics services, and national charities can play key roles in addressing the needs of adults with IRD and their families. Verbal, face-to-face, communication should be supplemented by additional material, accessible to those with visual impairment. Such information can facilitate informed decisions among adults with IRD and also dissemination of accurate information within the family. Lack of information disseminated within families can result in poor understanding of genetic risk and low uptake of available genetics services.[24, 25]

The findings of this study are limited by the relatively small sample size, the United Kingdom focus and the fact that most participants were actively engaged with healthcare professionals or national charities. However, participants were chosen from a larger cohort of 200 adults and the purposive sampling frame ensured that they reflected not only a diversity of self-reported levels of understanding but also a varied demographic background. In addition, most of the study participants had already completed their family or taken a decision not to have a family. As a result, a qualitative study with younger adults with IRD, who are still planning their family, may provide different views. Further research (quantitative and qualitative) is also needed with young adult from diverse population with regards to their views on new genomic development , where there is a more possibility of identification of novel IRD mutations and also their views on the advent of non-invasive prenatal testing for IRD.

CONCLUSION

Participants had mixed views about PDT for IRD. PDT can provide valuable information, enabling participants to prepare for having an affected child and to access novel interventions earlier. However, concerns were raised around the potential use of a positive result to justify

termination of an affected pregnancy. Despite this, most participants were generally in favour of the availability of PDT for others, if not for themselves. Like many genetic conditions, PDT is available for IRD where a mutation has been identified in the family. The request for PDT for IRD may not be common as there may be differences in opinion among individuals with regard to motivation for such service, e.g. whether PDT is requested for early diagnosis or to terminate an affected pregnancy. The demand of PDT may increase with better diagnostic tools and increased knowledge among individuals. Also, with the advent of non-invasive prenatal testing for single gene disorders such as IRD, the demand is more likely to increase as there would be advantage of early and safe testing with no risk of procedural miscarriage, as highlighted in this study. The variation in attitudes towards PDT and uncertainty about the risk and accuracy of results suggest that individuals at risk of having a child with IRD should have access to genetic counselling to support decision making. The provision of non-judgemental, accurate and balanced information to individuals with IRD may facilitate informed reproductive decisions that are inclusive of PDT discussions.

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Table 1. Baseline characteristics of study participants

Characteristic		**N**
Sex	Male	25
	Female	25
Ethnicity	White British	39
	British Asian or Other	11
Highest educational level	To GCSE or O-level (aged 16)	13
	To College or beyond	37
Sight impairment certification status	Sight impaired	12
	Severely sight impaired	29
	Not certified	9
Parenting status	Have or plan to have children	38
	No plans to have children	12
Other affected family members	Yes	29
	No	21