The psychosocial and service delivery impact of genomic testing for inherited retinal dystrophies

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Abstract

Next-generation sequencing (NGS) provides diagnostic information for many rare conditions. The evolution of NGS for panel, exome, and genome testing is set to be the platform for transforming genomic diagnosis in the National Health Service (NHS). Inherited retinal dystrophies (IRDs) are a highly genetically heterogeneous disease group causing progressive visual impairment. IRDs are ideal for an NGS panel approach due to phenotypic overlap and were one of the first diagnostic panels to be developed in the NHS. While diagnostic yield for patients with IRD has improved significantly with NGS, a proportion of patients remain without a diagnosis. The clinical value of NGS testing is well understood; however, the patient experience of panel testing is not well documented. Semi-structured qualitative telephone interviews were conducted with 23 participants with IRD who had undergone NGS testing. Interviews were transcribed verbatim and analysed using interpretative phenomenological analysis. Participants' experiences were interpreted to explore the psychosocial and service delivery impact of this testing technology, inclusive of those who received a pathogenic, negative, carrier status or variant of uncertain significance result. Collectively, three core themes were identified: (1) the journey towards a genomic diagnosis, (2) the impact of NGS testing, (3) service delivery of NGS tests. Disclosure of results had no reported adverse implications. Participants appreciated an open discussion about the potential for an uncertain or unexpected result, prior to testing. They valued pre-test counselling discussions, expert opinions and on-going care from genomic services.

Keywords Variant of uncertain significance · Incidental findings · Genomic testing · Inherited retinal dystrophy · Next-generation sequencing

Introduction

The evolution of next-generation sequencing (NGS) technologies, including panel testing and whole-exome sequencing

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(WES), are rapidly transforming clinical care in the National Health Service (NHS) in the United Kingdom (UK), setting a platform for personalised medicine. The NHS is a publicly funded healthcare system which provides free medical care to all legal residents of the UK. Clinical genetics in the UK is managed regionally and covers populations from one to five million people. The development of whole-genome sequencing (WGS) has significantly improved the clinical management of many conditions (Stavropoulos et al. 2016) which in turn has led to the implementation of the 100,000 Genomes Project in the UK. As technologies improve, there is an increased chance of finding a variant of uncertain significance (VUS) or a carrier status result (Cornelis et al. 2016; Johnston et al. 2012). The management of these results is still widely debated (Berg et al. 2011; Halverson et al. 2016).

As a group of conditions with phenotypic overlap, inherited retinal dystrophies (IRDs) are an ideal candidate for a NGS approach. The IRD-NGS panel was one of the first diagnostic panels to be developed in the NHS. While the diagnostic yield for patients with IRD has significantly

increased with this new technology, a proportion of patients remain without a genomic diagnosis or receive a VUS or carrier status result. However, WGS is expected to improve diagnostic yield by a further 29% (Ellingford et al. 2016). There still is a clear need for specialist services in understanding and thus advising on the role and potential applications of identifying genetic variants in rare disease. This has been clearly documented by Parliament in the recent white paper document (Department of Health and Social Care 2018).

IRDs are a group of hereditary disorders characterised by retinal damage leading to visual impairment (VI). They have variable ages of onset and patterns of inheritance, and they demonstrate high levels of genetic, allelic and phenotypic heterogeneity (Daiger et al. 2014; Koenekoop et al. 2007; Veltel et al. 2008). IRD affects 1 in 2500 individuals in the UK (Berger et al. 2010; Fight for Sight 2014). Currently, there are no widely available treatments outside clinical trials (Fischer et al. 2017). Over 200 genes have been found to cause IRD, yet providing an estimation of disease progression and risk assessment is still difficult for clinicians. Therefore, a high degree of uncertainty remains for the patients.

Many individuals with VI experience a lower quality of life and a need for support (Bittner et al. 2010; Slade 2014). Many access support through a network of family, friends or support groups in order to adapt to their VI (Bong et al. 2010; Massof et al. 2007). An individual may search for the cause of their VI through genomic testing in order to facilitate adjustment (Hayeems et al. 2005), aid decision-making for the future (Combs et al. 2013a) or to improve healthcare outcomes and hope for possible treatment options (Fischer et al. 2017).

NGS testing is now being standardised throughout the NHS (Combs et al. 2013a; Combs et al. 2013b; Consugar et al. 2015; O'Sullivan et al. 2012; Stone 2007; Wallis et al. 2013) making genomic testing more accessible for patients with IRD (Biesecker 2012; Glöckle et al. 2014; Shanks et al. 2013). When using NGS panels to test for IRD, a number of results may arise (Carss et al. 2017). In this paper, we define a positive result when a pathogenic variant which confirms the genetic aetiology of the IRD has been identified (Richards et al. 2015). A negative result means that no causative variant has been identified to support the clinical diagnosis of IRD. A patient may also receive a carrier status result for a recessive or X-linked form of IRD or one or more VUS result; for the purpose of this paper, we are defining these as incidental findings (IF) (Westerfield et al. 2014). NGS produces such an abundance of information; the discovery of IF is increasing (Gillespie et al. 2014).

As there is a significant chance of finding an IF through NGS testing, it has been debated as to what should be disclosed or withheld and how to counsel these patients (Cornelis et al. 2016). At the time of this research, there was

no consensus on how to manage carrier status or VUS results in either genomics services or in research settings (Abdul-Karim et al. 2013). Since the interviews took place, the ACMG guidelines for variant interpretation have been widely adopted (Green et al. 2013; Richards et al. 2015) and in particular across the UK (Ellard et al. 2017; Raza et al. 2017). The clinical importance of reliable and consistent variant interpretation is well recognised (Wildeman et al. 2008). By ensuring the implications of variants are explicit, this will minimise any errors in diagnosis and thus improve patient management (Crawford et al. 2013; Lubin et al. 2009). Variants are separated into five classes: (1) clearly not pathogenic, (2) unlikely to be pathogenic, (3) VUS, (4) likely to be pathogenic and (5) clearly pathogenic (Richards et al. 2015; Wallis et al. 2013). However, it is often left to the clinician to decipher whether the VUS or carrier status is clinically relevant to the patient or not (Christenhusz et al. 2013a; Christenhusz et al. 2013b).

Research exploring the psychological impact of genomic testing has previously focused on hereditary cancer syndromes (Heshka et al. 2008; Meiser et al. 2002). The majority of individuals undergoing genetic testing for BRCA1/BRCA2 gene variants found the experience positive overall (Meiser et al. 2002). However, it has been shown that having a positive result from genetic testing may increase levels of anxiety and depression (Aatre and Day 2011; Heshka et al. 2008; Meiser et al. 2002). The psychological risk of a positive result from genetic testing has also been highlighted for IRD, where individuals stated that knowing about a future risk of progressive VI can be psychologically difficult (Combs et al. 2013a). Patients' views on IF from genetic testing are becoming more widely explored. However, this has previously been in a research setting (Clift et al. 2015). In a clinical setting, research is on-going as to the impact of results from genomic testing, and considerations about potential results need to be made during the patient's decision-making process (Clift et al. 2015; Cornelis et al. 2016). Research into the impact of all possible results for NGS testing of IRD has not been explored.

This study aimed to define the 'impact' of delivering results from NGS on patients who had received either a positive, negative, carrier status or VUS result from the 105 gene NGS panel testing for IRDs. By examining both the psychosocial and practical impacts, the study aimed to discern patient views in order to advise on the best practice for consent and the disclosure of results in the context of genomic clinical practice (Carss et al. 2017).

Methods

Semi-structured telephone interviews were conducted with 23 participants recruited from the Manchester Centre for Genomic Medicine.

Participants

Patients with IRD and parents of children with IRD were invited to an interview through purposive sampling, after careful review. All participants had received a result from the 105 gene NGS panel testing for IRDs at the Central Manchester Foundation Trust Regional Genomics Service between the year 2012 and 2016 (Metzker 2010). Participants were excluded if they had genetic testing for other conditions, including microarrays, or if they were known to have another potentially genetic disease. These exclusion criteria were to avoid overlap in their reflections on genetic testing. Participants were also excluded if English was not their first language. Individuals with a hearing impairment were excluded due to difficulties conducting telephone interviews. Individuals could not participate in the interviews if they had a learning disability or if they were under 18 years of age. However, their parents were invited to take part in the study on their behalf.

Data collection

The interview topic guide was reviewed with members of the patient advisory group (PAG), including representatives from RP Fighting Blindness and Royal National Institute of Blind People (RNIB). PAG involvement in research provides a wider range of discussion topics, enhancing relevance and reliability of qualitative data and improving ethical considerations (Staley 2009). The practice was in keeping within RNIB guidelines; all documents sent to participants were written with font size 14–16 with no underlining, capitals or italics and all formatting was clear and concise (RNIB 2014). Audio version, larger font and braille copies of all documents were available upon request. Participants had the right to withdraw at any time. Telephone interviews were chosen as they have been proven to not only produce high-quality data but also allow participants to feel more relaxed and therefore more likely to discuss sensitive information (Novick 2008). The interviews ranged from 25 to 50 min. All questions were open ended, and all participants were asked the same questions from a defined interview schedule (Supplement 1). The participants were asked to answer all questions where they felt comfortable and able to do so. Ethical approval from the NHS Research Ethics Committee (ref: 12/NW/0197) in concordance with the ethical review requirements set out by the Governance Arrangements for Research Ethics Committees was granted for this study.

Data analysis

Each interview was recorded and transcribed verbatim and analysed using interpretative phenomenological analysis (IPA). This method was chosen due to the lack of research in this area and the small sample size being used (Smith and

Osborn 2003). The IPA method makes each participant's interview critical to the research and requires the researcher to work rigorously to validate their findings (Pope et al. 2000; Pringle et al. 2011). Therefore, IPA produces high-quality results with a small sample size. IPA has also been strongly praised by medical researches as it allows for an understanding of healthcare and illness from the patient's perspective (Biggerstaff and Thompson 2008). Three researchers, including the two first authors, conducted the interviews and performed the initial analysis each for a group of participants, with either positive, negative and IF results to create individual themes for each group. The IF results included participants who had received a carrier status or VUS result. These participants have been grouped together as there is a remaining uncertainty of the implications of the results for the patients (Westerfield et al. 2014). A second analysis was performed by the two first authors, for each interview and across the cohort as whole. This data revealed three main themes across all result types. Thematic saturation was reached in each of the group analyses and across the cohort.

Results

This study had a total ascertainment of 25%. Of the 97 invitations sent, 24 returned the consent form to participate in the study including 21 adults and three parents on behalf of their child with IRD. Non-responders were sent one reminder letter up to 4 weeks after the initial invitation. The recording of one interview failed. The mothers of three individuals with IRD were interviewed because two individuals were under age 18, and one, aged 21, did not have sufficient capacity to consent due to learning disabilities. See Table 1 for full list of patient demographics.

Three main themes encompass the overall data. These were described by participants to be (1) the journey towards a genomic diagnosis, (2) the impact of NGS testing and (3) the service delivery of NGS tests.

Theme 1: The journey towards a genomic diagnosis

The analyses revealed that participants were describing a journey of searching for a genetic diagnosis following their initial acceptance of their VI. The first stage in the journey was described as adapting to loss, both of independence and control. All participants discussed how they have adapted and built skills to help them in their daily lives as their vision progressively deteriorates.

“But it does, it does impact on my life. Urr it doesn't happen just in the dark, it's also when it's really bright, I struggle quite a lot. Even though I, I've got night

Table 1 Participant demographics ($n = 23$)

		Positive result	Negative result	Carrier status/variant of uncertain significance	Total
Gender	Females	4	3	4	11
	Males	1	8	3	12
Clinical diagnosis	Retinitis pigmentosa	4	5	5	14
	Retinal dystrophy (RD)	0	3	0	3
	Syndromic RD	0	1	0	1
	Macular dystrophy	0	2	0	2
	Cone-rod dystrophy	1	0	1	2
	Leber's congenital amaurosis	0	0	1	1
		0	3	0	3
Age	0–18 years	0	3	0	3
	19–38 years	1	2	2	5
	39–59 years	3	4	3	10
	60 years and over	1	2	2	5
Total		5	11	7	

blindness, I squint even when the weather is really really sunny. So I just make sure again that I've got sunglasses in my pocket all the time" ... "Like I say, I've adapted my life around it." - Negative result

As the participants' vision deteriorates, they have an increasing dependence on others which in turn has a ripple effect for their families. There was an emphasis on the importance of support networks.

The majority of participants relied primarily on their partner or a very close family group. It was often close family networks that supported participants when they received their initial clinical diagnosis, which in many cases was poorly delivered and came as a shock to individuals.

"Just over 10 years ago I went to the opticians and unfortunately um I think it was more of a locum optician rather than the one who was normally there, unfortunately he turned around and said, 'oh by the way I think you're going blind'" ... "um which was quite traumatic at the time" - Negative result

A significant milestone on this journey was the potential diagnosis provided by NGS testing. They described not being able to move onto the next stage in the journey without a genetic diagnosis. This next stage included accepting their diagnosis and the potential for treatments.

"I actually think, that would be helpful because as I say, if you've got an answer, you know, it's not just, again it's knowledge, is what you need to move forward. If

you get the knowledge that, yes it's inherited, you know genetically inherited this way, or we still don't know, it's just better even if it's been tried, because that's painful for me, you know, I have to find out." - VUS result

Theme 2: The impact of NGS testing

All participants were highly motivated to have NGS testing for IRD. Major motivating factors in the decision-making process in having NGS testing included personal motivations such as a need to know and a need for closure. When making a decision about having NGS testing, patients described a vested interest in the potential knowledge NGS testing could provide in supporting them to find answers particularly regarding disease progression, aetiology and genetic risk. However, they did seem aware that these questions may not be answered by initial NGS testing, but the results may be important for their families in the future.

"It's different for different people. I see it as a positive thing, that I could get an answer. I haven't so far, but I could get an answer. And you know, knowledge is power, that type of thing, you know if I know it might be difficult to deal with, but at least I'll know." - VUS result

"That's why we sort of said it would be best to have genetic testing done because if the girls in the future years decided that they wanted to have children ... the time they get to that age, there might be more research

and they might be able to tell whether the children would definitely have it or not.” - Positive result

All participants were able to draw both positives and negatives from their testing experience, with positives outweighing the negatives. Perceived disadvantages included waiting, the potential for a syndromic aetiology and receiving an uninformative result. However, there were some thematic differences seen in the perceived impact of results from the three groups.

“Say it was another syndrome and they told you, we want to test for this syndrome but the problems with the syndrome, you know, can have and at some point they might be prone to a life-limiting illness or something, then that would I think be difficult. But would it stop me going ahead with it? I don’t know, I really don’t know.” - Negative result

Those who received a positive diagnostic result felt empowered by the information, especially in regard to educating the next generation. The patients’ children will have the knowledge to make informed decisions about treatments that might be available.

“... now we’ve got that we can tell him that information when he can understand it a bit better and he can make informed decisions himself now.” - Positive result

Participants, who received a VUS or carrier status result, were the most able to draw both positives and negatives from testing. Although disappointed, they hoped that an answer would be found in the future, both selfishly and altruistically.

“I mean the only negative aspect is that obviously they have been unable to find my gene, erm you know. And I think, for me, I was a little bit disappointed, but because I’ve lived with it for so long. I’m relatively, because I lived with it for so long, I didn’t find it too disappointing. But I think maybe for somebody else who was really pinning their hopes on finding the gene, I think could be quite negative for somebody who maybe newly diagnosed or quite down about it.” - Carrier status result

Often participants who received a negative result were left feeling disappointed. The feeling of ongoing uncertainty was more profound in those with negative results. It was important for patients to keep up to date with technology in order to look forward to the next test.

“I suppose I wanted them to find the gene. I was really hoping they would find it really. So that I’d know more about it because, um you know there’s different names for macular dystrophy, you know the Stargardt’s, Best dystrophy, you know there’s different names but I feel I can’t read up about mine because I haven’t got a name. I think I just wanted a name for it really so that I could do... you know it came back negative. That was a real disappointment.” - Negative result

“The fact that every time I’ve been, the team there have always been looking at the next stage and if there’s something else. I’ve never been told, well this is the end of the line, we don’t know what it is, there’s always been something else right, we’re gonna try this, we’re gonna try that. Um so it doesn’t feel like I’ve been left on the shelf waiting for their decision to go.” - Negative result

Finally, participants sought access to treatment or a cure for their IRD, and they saw NGS as a way to gain access to this. All participants hoped that with enough research and unrestricted access to genomic testing, they would be able to find the cause of their IRD in the future before it could affect other people and family members.

“Medical research is advancing all the time. I know they’re doing a lot of stuff at the moment, so the time he’s in his 20s, 30s, there might be stuff there for him”... “We want them to have a good outlook on it and not just think that it’s all doom and gloom because at the end of the day, they’ve for the rest of their life to live as well.” - Positive result

“I had this genetic testing done and hopefully something was going to become of it and I’m still hoping something is going to become of it eventually but erm, it might not be for me, it might be just in time for them, if they come about with it, but I would like to keep carrying on so somebody somewhere will find something for it... I think the research should keep on because one of these days someone’s going to click something is going to be there and it will help not just me but thousands of people.” - Carrier status result

Theme 3: Service delivery of NGS tests

All of the participants described perceiving the NGS panel test as part of the routine practice for an individual with IRD.

Participants were asked to discuss what they remembered from their genetic testing appointments. All of the participants who had received a positive result and many of those who received a carrier status or VUS result were able to recall more information regarding their result and demonstrated a good level of understanding around what had been disclosed.

“So basically I’ve been told that there is three defected genes and they think that I’ve probably been given 1 from one side of my family, 2 from the other side, therefore it’s a recessive condition and therefore I carry the three genes and in order for me to pass that on to my family, I would have to have had met somebody who also carried the recessive gene, in order for my children to have it, and when they check my children’s blood, which is what they are doing as we speak now, they expect to find that my son will carry either one of the recessive, or defected genes or two of the defected genes in order to clarify what they already think.” - Carrier status result

Many participants found the genomic services uniquely helpful in providing information and support. Participants also clearly demonstrated benefiting from a multidisciplinary approach and appointments with ‘expert’ clinicians as part of a specialist clinical genomics service.

“[Genetic clinicians] are really calming, and they, you feel like they actually care about, you know, the situation. I’ve had many a doctor that’s just said look, there’s nothing we can do, so you know, go on, get one with it kinda thing. I think [consultant ophthalmologist], although he does say, there’s not anything we can do at the moment. He sort of says it in a nice way, and you know, and actually [Genetic Counsellors] were very, very nice as well, ‘cause my mum got quite upset at one point, erm and you know [a genetic counsellor] was there and, they, they spend hours with you, you know like, usually doctor’s appointments are 10 minutes and you’re out, but we seemed to be there for hours you know... it was like, you know a breath of fresh air really.” - Carrier status result

“There are a few people there from different departments who saw him before he had the blood test. I think that helped because it was someone from the eyes, someone from the genetics and you know people from different departments. That was good because you could clear up some questions.” - Negative result

However, it was also apparent that participants still faced difficulties when dealing with genomic services. Participants relayed that there was sometimes a lack of understanding of patient’s immediate needs and more of a focus on the impact for future generations.

“When [they] spoke to me they were, it was more, it seemed more aimed at my daughter really. [They] seemed to be a lot more interested in how my daughter’s eyes would be in the future and what have you. Erm, it seemed to be more focused on that than finding my faulty gene.” - VUS result

Finally, patients discussed how services for patients with IRD could be extended to meet broader needs. For example, participants want to be kept updated with improvement in care provisions and advancements in research and testing. Patients described being empowered to self-advocate in hope for treatments in the future.

“I’ve had quite a few things happen to me where I’ve had my hopes dashed, so I just don’t I don’t put all my eggs in one basket. So yeah, if that’s how long it takes, then that’s how long it takes. It is going on, and I am being kept updated so, it would be nice to have a few more updates than I do.” - VUS result

“There’s a regular drip feeding of sort of advances, actually positively help people come to terms with it but also manage it because those little, those little wins if you like, you might only get 1 or 2 a year where, ‘Oh such and such did this’, or ‘Such and such did that!’.” - Negative result

Discussion

NGS is the gold standard for diagnostic testing in the NHS. The technology has improved diagnostic yield, decreased time to diagnosis and significantly reduced costs. NGS has paved the way for WGS to be more readily accessible to patients (Department of Health and Social Care 2018). This qualitative study investigated patient views on the psychosocial and service delivery impact of NGS, which has not been extensively explored previously, especially for patients with IRD (Halverson et al. 2016; Willis et al. 2013).

Three clear themes emerged from the data. The first described NGS as a key milestone in the journey to a genomic

diagnosis. This supports previous research which has explored patient's narrative accounts in reaching and understanding their diagnosis (Clift et al. 2015; Combs et al. 2013b). Participants discussed both personal and altruistic motivations for testing. NGS testing gave participants a sense of empowerment about the potential knowledge genomic diagnoses could provide (Halverson et al. 2016; McAllister et al. 2011).

Patients who received a definitive genetic diagnosis for their IRD from NGS testing described a positive experience. Patients benefitted from being able to name their condition as they were able to utilise available support networks. This supported optimism for treatment options in the future and their hope for accessing personalised medicine (Davison et al. 2017).

This study revealed that participants who received an IF result of carrier status or VUS result drew positives from their testing experience and continued to hold faith that advancing technologies would eventually provide them with an answer. Patients described their primary aim of NGS panel testing for IRD is to identify the genetic cause for their IRD, and carrier status or VUS results gave them hope for a diagnostic genomic result in the future. Although the testing was non-informative, participants felt that their motivations had been validated. Therefore, patients perceive benefit from being informed of non-actionable results (Clift et al. 2015; Cornelis et al. 2016). Patients did not report any adverse effects of non-actionable results. This is reassuring as genomic testing through NGS becomes more commonplace in the NHS which often reveals multiple carrier status or VUS results. The study supports previous findings which showed that patients react well to uncertain information, for example, when receiving VUS results from microarrays (Bernhardt et al. 2013; Halverson et al. 2016; Reiff et al. 2012).

Participants who did not receive a diagnostic result from the NGS panel felt demotivated and let down by the testing. However, through contact with specialist genomics centres, participants felt encouraged to continue with NGS tests, for example, through research projects like the 100,000 Genome Project (Marx 2015). This demonstrates the clinical importance of continuing contact with families, particularly those who have not received a genetic diagnosis.

Participants discussed their expectations for an ideal service delivery for NGS testing for IRD. Participants emphasised the importance of genomic services throughout the testing process as supported by previous research (Clift et al. 2015; Combs et al. 2013a; Facio et al. 2014). This included pre-test counselling, which allowed participants to understand the testing procedure and possible results (Hayeems et al. 2001), as well as post-test counselling. There is an essential need for good communication of results including IF results, disease progression, genetic aetiology, inheritance patterns and current research (Clift et al. 2015; Halverson et al. 2016; Moore and Burton 2008). This research supports the

claim that there is a need for more widely available specialist care across mainstream medical services (Davison et al. 2017; Department of Health and Social Care 2018).

As with any thematic analysis, this work is limited by the small sample size as well as geographical constraints of the sample population. Broader demographic information on the economic and ethnic backgrounds of the participants was not formally collated. A bias may be present in this cohort as the participants who enrolled in this research were self-selecting. Those who enrolled explained they were very keen on discovering the genetic aetiology of their IRD. Those who chose not to take part may not perceive a genetic diagnosis as pertinent, may or may not have had a positive experience of NGS testing or were not as well adapted to their results. Finally, there were restrictions to the accessibility of this research for some potential participants, for example, those who rely solely on audio formatted information, those who do not use English as their first language or those who have limited social support.

Research recommendations

This research is an initial step in understanding patients with IRD experiences of NGS panel testing through qualitative work. It could be expanded by including participants from different geographical, cultural or ethnic backgrounds. Although this work has not identified any conflicting opinions on the impact of NGS for IRD between parents with a child with IRD and adult probands, it would also be helpful to understand the potential differing impacts for the two groups. This research has the potential to be replicated in other clinical specialties such as cardiology or as mainstreaming develops in ophthalmology clinics. This research could be further extended to examine the impact of whole-exome and whole-genome sequencing, or focus in more detail on the impact and implications of carrier or VUS results within WGS.

Practice implications

This research has demonstrated the value of genomic counselling in both pre-test and results appointments. For pre-test counselling, participants benefited from 'warning shots' around carrier or VUS results and the possibility of negative results. This improved their understanding when their results were disclosed and managed their expectations. This research has shown the disclosure of carrier status and VUS results to be beneficial to patients in keeping with Clift et al. (2015). Participants prefer face-to-face appointments with specialist clinicians to aid understanding and to avoid misinterpretation of their results. Following receiving their results, all of the patients in this cohort expressed a need for receiving regular updates on current research and treatment opportunities.

Conclusion

There is no doubt that patients go through a journey when looking for a genetic cause of their IRD. NGS panel testing is now a key milestone in the journey to diagnosis for IRD patients and across rare disease. Overall participants viewed the impact or risk of NGS testing as low. The implications of VUS or carrier results did not add more anxiety or perceived risk to this testing. For many, the process was considered as a positive step in understanding their condition, even for those who received a negative or IF result, as they were able to access genomics research studies. Participants valued the support and information provided from the ‘expert’ genetic clinicians, but requested an increased level of ongoing care and contact, preferably through local services.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human studies and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients before being included in the study.

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