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RESEARCH ARTICLE

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Understanding what drives genetic study participation: Perspectives of patients, carers, and relatives

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Abstract

Genetic research's growing importance in understanding pulmonary arterial hypertension (PAH) and developing effective treatments prompted the RAPID-PAH study. This study sought feedback from stakeholders who participated in two genomic studies to enhance genetic study delivery and clinical integration. Stakeholders from nine UK PH centres, representing various roles, ages, genders, and mutation statuses, took part in 53 semi-structured interviews and focus groups. Transcripts were thematically coded using inductive analysis. Clustering analysis was conducted to identify patient groups that shared attitudes. In this paper, we focus on patients', carers', and relatives' perspectives. The key interview themes revealed insights into participants' attitudes toward genetic research and testing more generally, expertise and knowledge of the disease itself, motivations and barriers to participating in genetic research, awareness of and interest in consent procedures and the use of personal and genetic data, as well as the process of communicating individual genetic results. Factors influencing genetic research participation included altruistic motives, personal diagnostic experiences, and family-related hopes. Clustering analysis produced distinct clusters based on the presence of barriers and motivators for research participation; however, hardly any patients shared identical sets of attitudes, emphasising the need for personalised approaches to recruitment. Most patients reported poor engagement with study-related materials. Patients who received individual genetic results expressed satisfaction with the process, whereas those who did not were disappointed with the lack of feedback. Reflecting on patient perspectives, we offer recommendations to improve the genetic study delivery process. Enhancing genetic research integration into clinical practice requires tailored engagement, clear communication, and support from healthcare stakeholders.

KEYWORDS

genetic research, informed consent, motivations and barriers to participation, pulmonary arterial hypertension, return of individual genetic results

INTRODUCTION

Genetics has long been integrated into many subspecialties of medicine, spanning from cystic fibrosis to lung cancer. However, genetic research and testing have only recently risen to prominence in understanding the underlying mechanisms of pulmonary arterial hypertension (PAH) and in the development of effective treatments. Two large studies, namely, the National Institute for Health Research BioResource Rare Diseases (NBR) study[1–5] and the Cohort study of idiopathic and heritable PAH (the PAH Cohort study), contributed to this integration.[6–9] The NBR study aimed to apply whole genome sequencing (WGS) and deep phenotyping to uncover genetic causes of a variety of rare diseases, including idiopathic and heritable PAH, as well as pulmonary veno-occlusive disease (PVOD) and pulmonary capillary haemangiomatosis (PCH). The PAH Cohort study was a prospective, observational, and longitudinal study in which participants consented to WGS and other omics investigations. Both studies included adult and paediatric incident and prevalent cases and their relatives, resulting in the largest deeply phenotyped and whole genome sequenced cohort for I/HPAH, PVOD, and PCH. While the NBR study has already returned pertinent individual genetic results to patients who consented, the PAH Cohort study has not.

Understanding participants' knowledge and attitudes toward genetic research is vital for the success of genetic studies and, ultimately, for the integration of genetic insights into clinical practice. To date, there have been limited studies that directly asked individuals with specific diseases about their reasons for participating in genetic research.[10,11] Acknowledging the concerns raised by Goodman around conflating disease and healthy population studies,[12,13] we believe that asking patients who enrol in genetic studies about their reasons for enrollment is the most informative approach. This belief is supported by the work of the Clinical Sequencing Exploratory Research Consortium, which has investigated multiple facets of participation in genomic research, including why patients decline to participate.[14] As the potential for increased use of genomic testing is available throughout the life cycle,[15] participants and the public should be made aware of these options and included in the decision-making process. To enable this, sufficient genomic literacy in counselling, consenting, and returning individual results for research and clinical WGS is required across the healthcare workforce.[16,17]

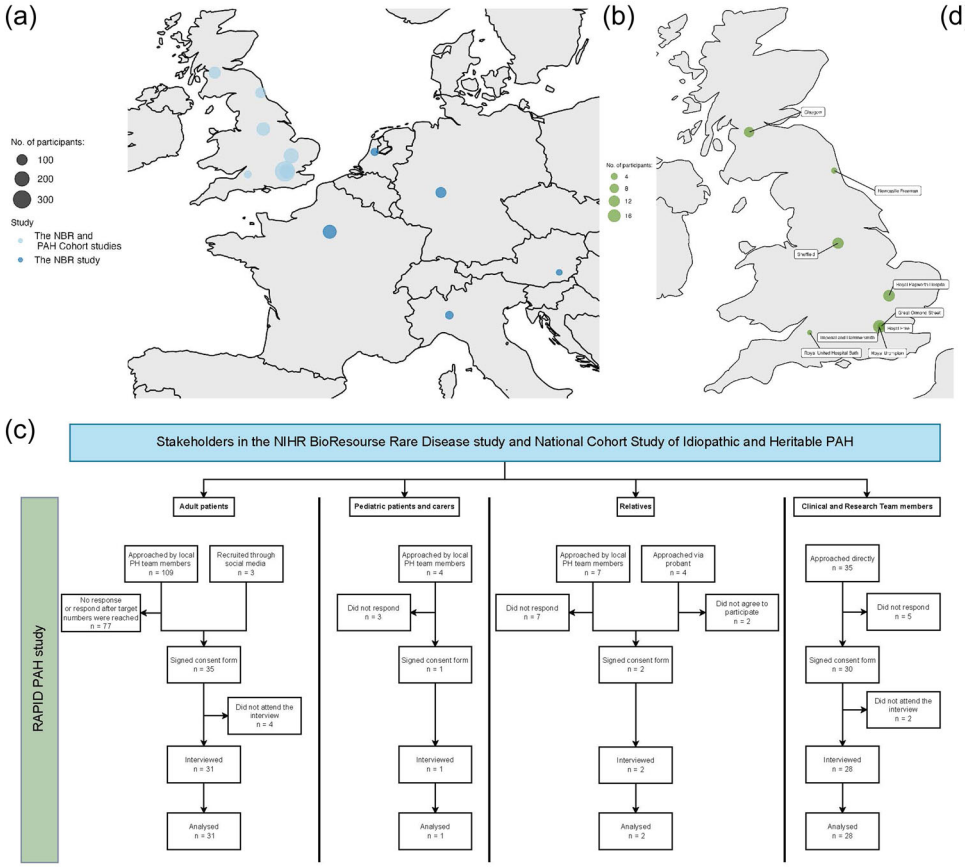
Additionally, genomic testing can challenge traditional models of informed consent. While re-consenting is time-consuming and broad consent may sometimes violate principles of informed consent, a new approach called dynamic consent, an interactive approach to obtaining and managing participant consent throughout the duration of a study, by allowing participants to engage with and control their consent preferences over time through the electronic application, might improve participant engagement and better-informed consent choices[18] and help in tracking their study-related decisions. However, patients' attitudes to the consent process remain largely unexplored in the context of rare diseases. Finally, ongoing progress in genomic technologies and our ability to understand the results impact study designs and counselling approaches.

Aims and objectives

The RAPID-PAH study aimed to explore motivations for participation in genetic research among patients, caregivers, and relatives who had previously taken part in genetic studies. More specifically, it investigated participants' experiences with recruitment and consent procedures, attitudes towards genetic testing across life stages, as well as an understanding of genetic results and their impact on family members.

METHODS

A sample of participants from the NBR and PAH Cohort study was selected with a view to include/represent diverse roles, age groups, genders, and individuals with mutations in PAH risk genes (Figure 1a–c). All patients included in the study received a diagnosis of either IPAH or HPAH, with 34% exhibiting mutations in PAH risk genes. One caregiver, specifically the mother of a pediatric patient diagnosed with PAH at the age of one, and whose younger sibling succumbed to PAH in infancy, was not tested due to the absence of known mutations in PAH risk genes in either child. Two relatives participating in the study were identified as healthy carriers, while the third was still contemplating genetic testing. None of the relatives has been diagnosed with PAH (Figure 1d). Patients with pertinent genetic findings identified in the genetic study underwent confirmatory testing in an accredited NHS (National Health Service) genetic laboratory accompanied by genetic counselling. While all research results were reaffirmed, this step was essential to uphold NHS genetic testing standards and offer comprehensive genetic counselling for patients and their families. It also spearheaded the development of new healthcare services



(d)

Clinical and Research Teams N=28	
Role:	
Clinical Trial Coordinator	3 (11%)
Doctor	15 (54%)
Research Assistant	1 (4%)
Research Nurse	4 (14%)
Researcher	3 (11%)
Specialist Nurse	2 (7%)
Centre:	
Great Ormond Street	4 (14%)
Imperial and Hammersmith	6 (21%)
Newcastle Freeman	2 (7%)
NHS Greater Glasgow & Clyde	3 (11%)
Royal Brompton	1 (4%)
Royal Free	1 (4%)
Royal Papworth Hospital	8 (29%)
Royal United Hospital Bath	2 (7%)
Sheffield	1 (4%)
Research involvement: Yes/No	26 (93%)/ 2 (7%)
Patients, realtives, carers N=35	
Role:	
Carer	1 (3%)
Patient	31 (89%)
Relative	3 (9%)
Centre:	
Great Ormond Street	1 (3%)
Imperial and Hammersmith	9 (26%)
Newcastle Freeman	1 (3%)
NHS Greater Glasgow & Clyde	7 (20%)
Royal Free	1 (3%)
Royal Papworth Hospital	5 (14%)
Sheffield, Royal Hallamshire Hosp.	11 (31%)
Age at diagnosis	45 [34;54]
Age current	55 [49;62]
Sex: F/M	27 (77%)/8 (23%)
Mutation: Yes/No/UNK	12 (34%)/22 (63%)/1 (3%)
N. of research studies in 5 yrs	1 [1;3]
Education:	
Higher degree	9 (27%)
Secondary	12 (36%)
Six Form/College	12 (36%)
Income:	
< £12,000	6 (18%)
£12,000 to £50,000	17 (52%)
£51,000 to £150,000	2 (6%)
I prefer not to answer	8 (24%)

FIGURE 1 Depiction of the geographical distribution of participants in (a) the NIHR BioResource Rare Disease study and the National Cohort Study of idiopathic and heritable pulmonary arterial hypertension (PAH), (b) in the RAPID-PAH study. The size of the plotting character represents the participant count, (c) Consort diagram of RAPID PAH, (d) Demographic characteristics of participants.

and pathways, as detailed in the article "Unlocking the Potential of Genetic Research in Pulmonary Arterial Hypertension: Insights from Clinicians, Researchers, and Study Team," currently under revision in Pulmonary Circulation and available in the Supporting Information.

The RAPID PAH study recruitment process covered all PH centres in the United Kingdom and took four distinct approaches, including contacting individuals through local clinical or research teams, referrals from current participants, online recruitment via email, social media platforms, and the Pulmonary Hypertension Association (PHA) webpage. Active recruitment continued for each centre until the target number of participants had been attained (Figure 1c).

The Patient and Public Involvement Team of the UniPHy UK trial network reviewed patient-facing documents for this study. Ethical approval was obtained from the North of Scotland Research Ethics Service (REC: 22/NS/0127). All participants provided written informed consent before enrollment in the study. The interviews and focus groups were conducted by MF, a researcher with qualitative research training, who remained blind to the participant's medical history. Data collection took place between January and August 2023 through telephone or Zoom interviews, lasting between 30 and 60 min. The interviews were recorded and transcribed verbatim while ensuring anonymity and accuracy. Following the principles of Grounded Theory,[19] transcripts were thematically coded to reveal relevant themes and subthemes using inductive analysis. The coding process was conducted independently by the first and second authors using MAXQDA (2022), with regular discussions to establish consensus. Partitioning around medoids clustering was performed in R on Jaccard similarity matrices based on the existence of code. The reporting of the study adheres to the COREQ.[20] and SRQR standards.[21] Names, specific locations, and any other identifying details have been omitted to ensure the confidentiality of the individuals involved (Supplement).

In this paper, we focus on patients', carers', and relatives' perspectives and supplement them with insights from clinicians and researchers into patients' attitudes.

RESULTS

Several key themes emerged from the interview data that shed light on various aspects of participation in genetic research in PAH. These themes reflect participants' understanding of the aims of the genetic studies, attitudes towards genetic research and testing more generally, knowledge of the disease itself, motivations and barriers to participating in genetic research, awareness of and interest in consent procedures and use of personal and genetic data, as well as the process of communicating individual genetic results and their impact on family members and relationships (Supporting Information S1: Table 1). The findings from these interviews not only offer valuable insights into patients' perspectives on genetic study delivery but also allow us to make recommendations for improving this process (Table 1).

Motivations, barriers, and expectations associated with participating in research

Feedback from patients who were interviewed suggest a number of reasons that influence genetic research participation, falling broadly into the following categories: the outward-looking or altruistic desire to contribute to science and improve health outcomes for others; one's personal experience of the protracted diagnostic journey and resulting trust in and gratitude toward PH teams; as well as hopes and concerns for family members and a sense of belonging to a wider community (Figure 2).

Altruism

Consistently, interviewees shared an altruistic perspective, grasping that the research explores uncharted territory and that participants with both known and unknown disease aetiologies can make substantial contributions to our understanding of it. They acknowledged that while the study's outcomes may not offer immediate benefits to them, there exists the potential to benefit future individuals, including family members who could be afflicted by the disease. This sentiment was shared even by those interviewees who were not aware of the genetic causes of their disease. As one interviewee put it,

> *Personally, it doesn't benefit me because I don't think mine is genetic, but I just think any information is good, so if me giving a blood test to somebody goes on and perhaps in a year or 2 years, just taking part in that can help one other person, then that's enough for me. (Patients > DS335)*

There is consensus that science cannot advance without the help of those affected by the disease, and there is an element of civic duty to contribute. As one interviewee put it,

TABLE 1 Lessons learned from the delivery of NIHR BioResource Rare Disease study and National Cohort Study of Idiopathic and Heritable PAH—patients' perspectives.

Top lessons learned
1. Study design
Conduct the study within the framework of routine NHS care.
Choose minimally invasive and nonintrusive procedures.
Whenever possible, ensure that the study is administered by the patient's established clinical team.
Time the study to align with the patient's disease management status.
2. Recruitment and consent:
Ensure patients possess a comprehensive understanding of the research objectives and the implications of their participation.
Mitigate practical barriers, such as travel, time commitments, and financial concerns, to enhance patient engagement.
Acknowledge that patients' willingness to participate can be influenced by factors like prior knowledge, familial dynamics, and lived experiences.
3. Motivations to participate:
Recognise that patients often exhibit a strong desire to contribute to research that may benefit others sharing their condition.
An informed awareness of the potential benefits and limitations of genetic research serves as a motivating factor for patient participation.
Amplify motivation through personalised counselling and transparent communication regarding the study's relevance to their specific condition.
Remove barriers to participation, including financial, time-related, and travel-related obstacles.
4. Return of genetic results:
Prioritise timely communication of genetic results and provide regular updates on the study's progress and its broader impact.
Acknowledge and appreciate patients' contributions to scientific advancement, fostering a sense of involvement and gratitude, even when individual genetic results are not provided.
Recognise patients' desire for information, including negative results, and pertinent incidental findings.

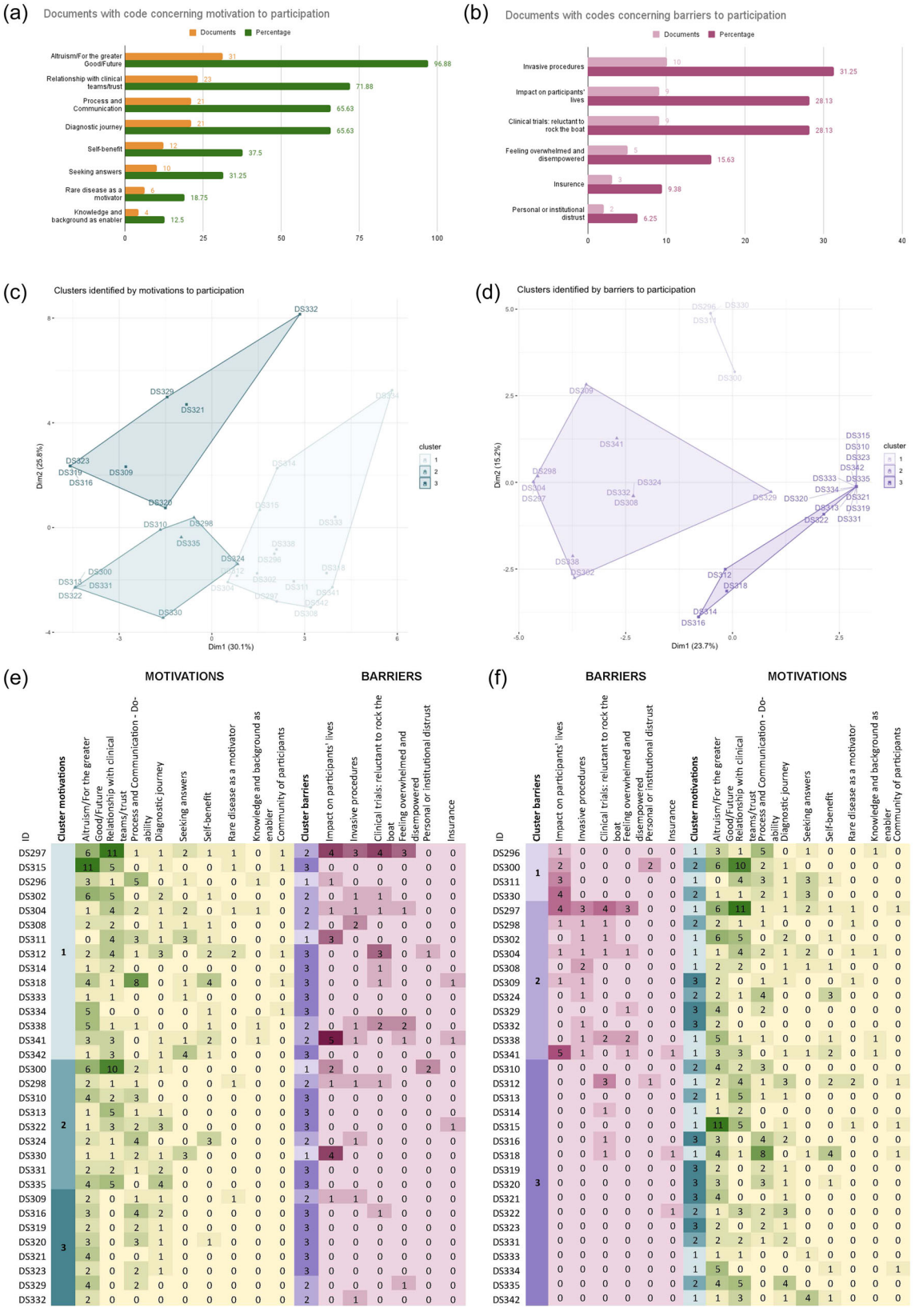


FIGURE 2 Barplots display (a) the rationales behind patient participation and (b) the barriers to patient participation. Partitioning around medoids clustering based on the existence of codes on (c) motivation to participate (d) barriers to participation. Matrix presenting clusters distinguished by the presence of codes related to motivation for participation (e), and participation barriers (f), employing PAM clustering. The "Motivations" and "Barriers" columns display the segment distribution for a specific code among each patient, indicating the count of segments associated with that particular code. PAM, partitioning around medoids.

> *We've all got to do our bit, and if nobody does it, then nothing is learned, and nothing evolves from all the studies that are done, and there are no steps forward and research into the disease is helping people to get over it or to develop something that helps more than what you get at the moment. (Patients > DS316)*

A strong drive to contribute to finding a cure exists among participants who recognise that current treatments primarily alleviate symptoms without reversing the underlying changes caused by the disease. Their motivation stems from a genuine desire to make a meaningful impact and improve outcomes for themselves and others. As one participant put it: *You can't sit on the fence [...] you're either all in or you're all out*, and added,

> *My personal opinion is if it's going to help people 20-30 years down the line from my samples, then I'm all for it because I wouldn't want someone going through what I've been through. (Patients > DS331)*

Some participants cited the desire—often driven by a sense of gratitude at having been correctly diagnosed after what was usually a long and arduous diagnostic journey—to want to give back and be of use to science.

> *I was approached, and as I say, I was so grateful that I'd finally found out what the problem was; not knowing what was wrong with me was actually worse than being given the diagnosis. So I was like, "You guys have done so much for me over the last periods of time; anything I can do for you with regard to trials or research or whatever, I'm more than happy to be a guinea pig. (Patients > DS312)*

This is also reflected by the fact that many of our interviewees have participated in more than one PH-related research study. The desire to contribute and be an active driver for scientific advancement and improved treatment options is particularly pronounced in light of the rarity of the disease.

Personal experience

Personal experience with the disease can significantly influence attitudes towards research and genetic testing. Long diagnostic journeys often foster a desire to contribute to research and raise awareness of this rare disease. *Until it lands on your feet*, one participant summed up, *it really hadn't crossed my mind. And I always use a phrase: you can only play the cards that you're dealt, so once it actually happens to you, then there are decisions that you need to make. (Patients > DS312)*

Some felt that research participation gives them a sense of belonging and purpose and, therefore, allows them to better cope with having a life-altering disease. One participant mentioned having built a small support network of other PH sufferers in the process:

> *The friendship thing is through the trials, I would say, because if you go to the clinic, nobody that's sitting waiting really talks to you, and it's not that kind of place [...] and the trials, there's a bit more, how you doing, how you feeling today, that kind of contact [...] I absolutely know that those three people especially would be there; if I were to message them, they would [understand] what's happening, that sort of thing. [...] It's a support network. (Patients > DS312)*

Involvement in social media platforms further fosters learning about the disease and offers a sense of support and belonging for some, and some interviewees appreciate the fact that, on the PH Facebook group, for example,

> *There are people that are like me that have found out it's genetic* and that the group offers a platform to *talk about everything about PH there [...] not just the genetics bit [but] about treatments and things like that. (Patients > DS331)*

Not all participants share this fondness for social media, and some find patient groups frustrating and negatively impacting their mental health and well-being.

> *I did join the pulmonary hypertension Facebook group, but then I decided to leave Facebook entirely because it was negatively affecting my health. There were a lot of negative people on it, and I prefer to avoid negativity. (Patients > DS315)*

Notwithstanding these sources of information and support, patients identified Consultant Geneticists, PH Physicians, and Specialist Nurses as their primary sources of knowledge regarding the disease. They were quick to add that they are careful to check information gained via these channels with their clinical teams.

Levels of scientific curiosity, genetic knowledge and awareness can differ significantly between patients. Some participants are keen to better comprehend the disease and are curious about its origins.

> *I like answers so I can wrap it up neatly. It's been a life annoyance that I got something that you can't prove how it started. (Patients > DS304)*

Some patients reported taking the initiative to conduct their own research and read scientific journals, although this was only mentioned by a few individuals.

Impact on family members

Participants are keenly aware that their children may, at some point, be affected by the disease. Contributing to the advancement of scientific knowledge is seen as a way to improve their children's chances for disease prevention, early diagnosis, and better treatment options. Speaking for the majority of our interviewees, when asked what motivated her to sign up for the study, one interviewee didn't hesitate to exclaim,

> *Me son! [...] when they said that I'd got the exact same disease as my dad, [...] I'd got a 1-year-old son, and I was determined to do everything I possibly could. (Patients > DS315)*

Being research-active is also a way of being seen by families, in particular children, as being proactive rather than defeatist.

> *If I hadn't done all the research studies, I don't think I would have felt as though I'd done enough. And I'll do more. And I think it's my way of proving that, no, I'm not just sitting on my backside. I want to help. (Patients > DS315)*

Some participants expressed a motivation to validate or challenge their preconceptions regarding their own genetic makeup, with family history playing a significant role in influencing their perspectives.

Depending on genetic findings, participation may impact de-facto nonconsented family members, therefore potentially introducing additional layers of concern and required action, including the decision of whether or not children should be genetically tested or involved in research studies to improve their outlook,

> *I really, really pushed to get my children onto a study of some description so they could have focused tests done periodically that would give them an early warning before they got to the point that I got to. (Patients > DS296)*

Family planning considerations also factor into the motivation for participation, as individuals contemplate the implications of the disease on future generations, ranging from wanting to prevent disease in their children to having to make often difficult decisions about the risks that having biological children may pose both in terms of the health impact of carrying a child and the potential to pass on mutated genes.

> *If I'd known about I've got this defective gene, and I could pass it on to my child before I had [my daughter], I probably would have put things in place so that I didn't pass it on to [her]. [...] I think anything that we can do to try and prevent horrible diseases, I think we should do it. (Patients > DS331)*

Similarly, relatives who had previously taken part in genetic studies were often motivated by witnessing the disease struggles their family members had endured and saw participation as a way to help their loved ones. One participant expressed this sentiment, saying, *because he is my dad, and I know what it is like with this pulmonary hypertension. (Relatives > DS347)* This first-hand experience often differentiated siblings who lived with or were near their parents and participated from those who were not in close contact with their family.

When considering factors that might deter patient participation in research, concerns such as difficult travel arrangements, time commitments, invasive procedures, privacy and insurance issues, trust-related matters, and varying interests based on disease severity emerged. External factors like the COVID-19 pandemic also played a role. Additionally, many probands acted as gatekeepers for their relatives, and the study's introduction of new NHS genetic testing pathways sometimes hindered relative recruitment as they favoured local options.

Time and financial considerations

Time and financial considerations are concerns for research participants, particularly when additional hospital visits are required. Reluctance to have additional hospital visits applies particularly to those whose everyday life is already burdened by more invasive treatment such as continuous intravenous drug administration, but also those who are well enough to be in employment. Additionally, if the PH centre is far from their place of

residence, the frequency of hospital visits can pose a logistical challenge. Participants with dependents or caregiving responsibilities may struggle to allocate time and attention to the study.

> *If they said, "We want you to travel to [name of the] Hospital every week to give three millilitres of blood, at your own cost and in your own time." I might go, "Oh, you know what? That's just too hard." (Patients > DS300)*

These concerns were even more pronounced in the case of relatives. Similar to probands, they were driven by both altruistic and self-benefit motives. However, they expressed concerns about the time burden and its impact on their daily activities.

> *What would it entail? And that is purely from a time point of view, really, because I am really, really busy, but obviously, health is quite an important thing to stay on top of it. I am more happy to certainly do something, do what I can do. What does entail? Certainly, I am not going to say I am not interested whatsoever, so yeah, there is definitely some interest there because it would be good to know. (Relatives > DS350)*

Burdensome study procedures

Invasive procedures, particularly right heart catheterisation, are cited as the biggest deterrent for some individuals considering participation. *there was another study where they were going to do another right heart catheter, and I'm like, "Been there, done that." That was horrendous! (Patients > DS309)* In addition, interview participants whose disease is well managed are reluctant to participate in studies that would require them to change their medication for fear of their health deteriorating, even in the short term. Similarly, one participant mentioned having been approached to take part in a study that would require him to take the medication he knows to be his personal end-of-the-road treatment and declined participation on the grounds of wanting to "pull out the big guns" prematurely.

Some individuals may feel overwhelmed by their diagnosis and experience a sense of being a full-time patient, making it more challenging to engage in research activities. Clinicians are aware of this and reflect on the skills required to know when and how to approach patients with requests and information.

Probands gatekeeping impact on relatives

Participants in the study themselves acted as barriers to recruiting their relatives due to concerns about the impact of genetic results on family dynamics. They took on various roles, including being information gatekeepers, emotional managers, and observers of symptoms. Watching one's children for the onset of telltale symptoms was a common theme in the patient interviews. Several participants reflected on the strain of constant vigilance, combined with the hope that spotting signs early would be the best path to preventing disease onset.

> *I'm apprehensive all the time I watch him play football, and he puts his hands on his knees, and he's run out of breath, and I think: "Oh." He is football crazy, and this kid...he's playing in an academy and stuff. So it's going to break his heart if we have to say to him: "You're not allowed to do this anymore. (Patients > DS330)*

This vigilance is made more complicated by the knowledge some patients have on the penetrance of the disease.

> *I have no idea what we would do if we discovered a genetic risk for our son. Perhaps we would need to monitor him closely to see if the condition develops. Other than that, he would continue as he is. There's a chance he may not develop it. (Patients > DS330)*

The concern for disease onset in children leads to discussions among many interviewees about whether their children should be tested for their genetic status.

> *"[my son] hasn't been tested. I have told him that he can be tested if he wants to go down that route, but he's not gone that way at the moment. So I have said to him, "If you ever get out of breath for unknown reasons, you might know which way to go." (Patients > DS333)*

Disease severity and research interest

Perhaps one of the most interesting and surprising barriers to research participation is the apparent fluctuation of interest in research participation in line with how well the disease and associated symptoms are managed. If patients find themselves able to cope with their symptoms, the tendency is to want to forget

about their disease and get on with living a 'normal-ish' life.

> *I'm the type I've got the disease, you get on with your life, I don't sit and mope about it and tell every bugger and moan about it all the time I get on with it, you know, but that's me. (Patients > DS319)*

Conversely, when the disease is less well managed, it moves to the forefront of one's life, and the motivation to contribute to research increases.

> *For the last 4 years or so, I can't really forget about it. I've got like a Hickman line, so I have to do my medication every 24 h. I do really well, but I definitely have symptoms that I didn't have before. So it's more at the forefront of my life, and I've just had to deal with it, which I didn't really want to do for eleven years. I was really well, so there wasn't a reason to make a big deal of it, really. But now, yes, it's different. So yes, I do look into things more and more keen to see new research and what's going on, I suppose, that I was before. (Patients > DS338)*

This shift in perspective underscores the importance of considering the dynamic nature of disease experiences when engaging patients in research endeavours. Additionally, it sheds light on the challenges confronted by healthy relatives who may not have a direct vested interest. One patient summarised her son's attitude as follows:

> *I don't think he would [like to be tested] now, not at this moment, because he's 23, having fun and going out and living his best life at the moment, and he wouldn't want to think about it. Maybe at another time, he might, but not at the moment. (Patients > DS297)*

Impact of COVID-19 pandemic on study participation

Lastly, the COVID-19 pandemic posed a number of barriers to study participation, including health impact if PH was compounded by COVID-19, as well as delays in results delivery, testing of family members, and disruption of treatment and hospital appointments.

Insights from thematic cluster analysis

In addition to the thematic interview analysis, cluster analysis provided valuable insights into the barriers and motivators for research participation among patients. Specifically, Figure 2e,f highlight a group of individuals who identified the impact on their daily lives as the sole barrier to participation. Interestingly, despite this barrier, they expressed multiple reasons that motivated them to consider research involvement, demonstrating a strong understanding of the research processes. Similarly, misconceptions about the impact of research results on insurance and the use of untrustworthy channels to approach patients were often reported as barriers to participation. Reluctance towards invasive procedures drove Cluster: barriers-2, comprising exclusively female patients (Supporting Information S1: Table 2). This reluctance was related to the pain in the sensitive neck area where the procedure is performed and concerns about the scars it might leave. It is crucial to address these factors to boost participant numbers effectively. Finally, while patients can be clustered based on the presence of enablers and barriers to participation, it was observed that hardly any patients shared identical motivations and barriers (Supporting Information S1: Table 3), emphasising the need for personalised approaches to recruitment.

Consent procedures, sample, and data use

The NBR and PAH Cohort studies were integrated within the NHS, with the NBR study benefiting from expertise and funding as part of a broader initiative. However, despite consistent resources and training in consent and genetic counselling provided to all participating centres, disparities in local service infrastructure and access to genetic services emerged. These disparities led to variations between centres in terms of patient and relative recruitment.

Recruitment

Effective recruitment strategies are pivotal to the success of any clinical research study. Both of these studies were relatively straightforward to enrol participants in, thanks to their nonintrusive nature. Participants found them to be an "easy sell," as they only required the donation of additional blood samples during routine appointments, which was perceived as minimal effort. The research components seamlessly integrated into routine clinic

visits, with only verbal re-consent needed during each study visit, a practice that patients highly appreciated.

> *I get bloods taken anyway, so it's not any bother to have it done, I don't object to anything like that, you know, they're taking blood out of my arm anyway, so they might as well have some for research. (Patients > DS316)*

For a significant number of patient interviewees, the NBR and/or PAH Cohort studies were not their first exposure to research participation. Some patients had been involved in multiple studies, occasionally leading to confusion as they struggled to differentiate them in terms of timing and location. Furthermore, some patients did not recall initially signing up for the genetic study but distinctly remembered being approached for genetic counselling before undergoing National Health Service (NHS) confirmatory genetic testing, which speaks to the impact of the time lag between recruitment to the study and return of the individual genetic results. Others recollected spending time with research teams to understand the study and going through the Participant Information Sheets (PIS) and informed consent forms (ICF).

In summarising the various attitudes toward research among patients, one participant highlighted the presence of three distinct cohorts.

> *I suppose you've got three cohorts, haven't you? You've got the yes, I want to get on with it, and they might be younger; you have a cohort that, as soon as these questions pile up, their immediate thing is, "I don't like the sound of this. I don't understand it. So, I'm going to say no." And they might be difficult to get on board if something seems complicated. I don't, as I say, don't mind going to the effort of understanding whatever it is, extra paper-work, and it takes a little longer, I don't mind. (Patients > DS322)*

By acknowledging these differences and tailoring approaches to cater to each patient's individual needs and concerns, we can create a more personalised approach that not only ensures that all patients have the opportunity to engage with research but also contributes to the success and impact of studies in a way that resonates with every participant.

Another common thread that emerged from our interviews with patients was the close relationship patients tend to have with their clinical teams—not least a result of an often arduous diagnostic journey and a sense of relief and gratitude at finally receiving the appropriate care.

The level of trust patients have in their healthcare professionals, as well as the perceived relevance of the research they offer, play a significant role in their decision to engage in the study. This allowed clinicians and researchers to leverage the trust built in the clinical setting to enhance research delivery by way of facilitating patients' "buy-in."

> *I have a great relationship with people at [my hospital], and we can have a laugh and a joke together. There's warmth. If there is no warmth and you're treated as if you're just a guinea pig, you're less likely to participate in a trial. (Patients > DS297)*

> *They're approachable. If they weren't approachable, I don't think you'd actually be, like you say, comfortable in doing it if you didn't feel as though you could approach anyone in the team. That goes for all of the team at [my hospital]. I've never had a problem with any of them. (Patients > DS302)*

A surprising number of interviewees said that they did not find it necessary to read the small print on ICF; wanting to be helpful and trusting their clinical team seemed sufficient reassurance for participation.

> *I didn't even read it, I just signed it. I wasn't bothered. I just wanted to help, I wanted to do it. I didn't care what you did with my results or who you shared them with. I wasn't bothered about anything like that. I just wanted to help, and that's all I want to do. (Patients > DS315)*

Patients may pay less attention to the consent details due to the fact that they expressed high trust in clinical teams in conducting studies ethically and they were aware of stringent research and ethics review processes. This trust extended to the storage and use of blood samples that were given, and thus, for genetic and biobank-based research, patients were satisfied with signing broad and forward-looking consent. They trusted that the samples would be used ethically and in line with the study's purpose.

> *I always figure once you've got it, you usually use them in the best way possible. I don't suppose we're giving blood, and it's just sitting on a shelf or sitting in a fridge somewhere,*

and you are actually doing something. I just think you must be using it for something good. (Patients > DS329)

Conversely, some individuals had reservations about participating in a study that was not endorsed or conducted by a reputable institution or not associated with their PH centre.

If it's a hospital in the middle of nowhere, no one's ever heard of, I'd probably think twice about letting you take my blood. But when it's [my hospital], not a problem. (Patients > DS300)

While some patients showed little interest in the fate of their samples, stating that they *don't know a lot about what happens to the samples once they've taken them* and adding that they are not saying that they *don't care* but rather that they *don't mind (Patients > DS300)* others displayed curiosity about their usage. Intriguingly, those who expressed a desire to learn more about the samples and their impact seldom sought feedback from their clinical or research team.

Privacy and insurance issues

Privacy concerns and the need to protect personal information were also mentioned as factors influencing participation decisions.

I think the information they can get from rare diseases is enormous in the long run, as long as it's not used against the population for insurance reasons and to put people at a disadvantage. But I can't control that either. (Patients > DS341)

However, these were less pronounced than perhaps anticipated, in particular when taking into account the high level of trust patients have in their clinical teams and the NHS. Likewise, only a scant number of concerns were raised about how donated blood samples and other information were stored and used, including the involvement of commercial companies for potential drug trials and development or genetic treatment options, both of which were welcomed and hoped for by participants.

Well, yes, I don't have a problem with that; no, I really don't because, at the end of the day, they've told me it costs billions to get a new drug to market. Somebody has to pay for that somewhere, don't they? I'm not daft. I know that... yes, I don't have a problem with any of that, to be honest, I really don't. (Patients > DS297)

Similarly, patients were of the opinion that re-consent would be desired only if the research scope changed. Equally, most adult patients were willing to share their samples internationally, but some parents of paediatric patients were reported to have expressed reservations. Patients generally accepted the use of their samples by commercial companies for advancing PAH research to the effect that NHS-based activity depends on the financial power of commercial partners to advance treatment. Some participants raised privacy concerns and motivations of such companies but felt that anything being communicated directly through their clinical team would automatically be trustworthy. Should they ever be approached directly for research by a commercial company, they said they would seek advice from their PH centre before participating in research conducted by an unrecognised institution or a commercial company.

If a private company approached me and said, "Hi, we're doing something related to PH," my immediate reaction would be to contact [my hospital] and inquire if they know it. If they do, then it wouldn't be a concern. However, if they say they have no knowledge of it, that would raise a different level of concern. Therefore, it is important for information to come through people whom I know and trust. (Patients > DS312)

The relative lack of engagement with consent material should, however, not be confused with a lack of interest or engagement with the potential risks and benefits of the research, which the majority of patients were keen to discuss with their clinical teams. Patients distinguished between different types of research, perceiving genetic and biobank-based studies as lower-risk and less burdensome compared to clinical trials. Patients unanimously expressed willingness to participate in future genetic studies, including recall by genotype studies, either as cases or controls. Additionally, all patients expressed their consent for their blood samples to be used for research purposes after their death. Furthermore, the majority of patients indicated their willingness to donate other tissues for research in the event of lung transplantation or death and most added that they carried an organ donation card and would happily give their body to research.

When I go, they can take whatever they want, and my family are aware of that. I carry a

donor card in my wallet, yes. I'm not going to need it any more; if it's useful for someone else, they can have what they wish. (Patients > DS312)

Some participants added a caveat regarding their family's needs and wishes but usually added that they had had conversations about end-of-life and organ donation with their spouses and children.

Whilst most participants commented on the volume of ICF and PIS, the extent to which participants engaged with this information is shaped by education and socioeconomic factors as well as personality traits such as levels of scientific curiosity and confidence. Most patients did not see a need for electronic ICF.

The NHS, as a tax-funded healthcare system, offers free care at the point of entry. Patients incur no out-of-pocket expenses for genetic testing, and a positive result does not affect tax deductions or healthcare coverage. However, patients' insurance-related concerns predominantly focused on private options, including private health insurance, travel insurance, and life insurance, especially in light of positive genetic findings. Concerns about travel health insurance while on experimental drugs have been cited as reasons for nonparticipation in clinical trials. Additionally, some individuals have identified indirect costs, such as lost earnings, as barriers to their involvement in research.

Insurance-related concerns also emerged during discussions regarding the recruitment of relatives for genetic studies. Patients, regardless of their mutation status, already have the disease. However, healthy relatives might encounter risk selection procedures from their insurers, especially in the private insurance sector. For instance, one patient shared, *My sister and her husband live in the States; they would never have their genetics tested because all their health insurance was based on not knowing. (Patients > DS341).*

These findings emphasise the intricate relationship between the healthcare model and the willingness to engage in genetic research or testing, shedding light on the far-reaching consequences of insurer risk selection practices.

Return of individual genetic results

Pertinent research genetic findings have been fed back to local clinical/research teams who relayed them to patients who consented to receive their results back. The patients were then referred to Clinical Genetics services for confirmatory NHS testing and counselling.

The understanding of this process varied among participants and was partly influenced by their mutation status. Those who had mutations and underwent NHS counselling tended to have a better grasp of the study, whereas those who tested negative and never received results or counselling had lower awareness.

It's important to note that both studies provided patients with the option to receive individual genetic results related to their condition. Incidental findings, genetic variants associated with known medical conditions or increased susceptibility to diseases other than PAH, and variants of unknown significance were not provided. Patients consented to their samples to be used beyond their lifetime and shared internationally and with industry to advance PAH research.

Overall, patients expressed satisfaction with the process of receiving and comprehending the results. They demonstrated a good understanding of the implications of genetic diagnosis, including the mode of inheritance and the inherent uncertainty associated with incomplete penetrance. However, some instances of confusion still emerged. For instance, a few patients found themselves perplexed by the differing technologies employed in research and NHS contexts, such as Whole Genome Sequencing (WGS) versus gene panels. Additionally, some patients were surprised that the research results did not align with the Direct-to-Consumer (DTC) genetic tests they had previously undergone. These observations highlight the ongoing need for continuous patient and public education regarding the benefits, limitations, and appropriate applications of various genetic techniques while managing patient expectations effectively.

One patient praised the in-depth conversations she had with the Clinical Geneticist about her positive test result but expressed disappointment that the topic was not brought up during her visits with the PH team, indicative of the potential negative impact of disconnect in care and communication between different healthcare providers.

Some patients mentioned disappointment with the long waiting period, while those who did not have a detected mutation expressed frustration at not receiving negative results.

I have not had any correspondence from anybody, be it the research team or [my hospital] or my GP or anybody to say, as an idiopathic pulmonary hypertension patient, whether I've got a genetic thing going on for me and my family. So, I've had no correspondence. All I know is I've been giving blood till

you contacted me but there has been no correspondence. (Patients > DS318)

Several participants were frustrated with the lack of feedback on study findings, which they felt was at odds with their motivation to participate in the first place. Even if they would have been happy with minimal scientific feedback, they would have liked to know if their contribution made a difference, a point which would usefully be reflected in the design of any future studies.

I never heard anything about it afterwards. It's frustrating because you say yes, and then you never hear anything about it afterwards. I just don't know what the study ever evolved into and if it was of any use or not really. (Patients > DS304)

Whilst some participants do acknowledge that too much "scientific information [could] be overwhelming", they felt that "general information maybe would've been nice." (Patients > DS323)

Like probands, relatives expressed satisfaction with how they were informed about positive results and felt well-supported by family members and healthcare professionals. Those with some background knowledge in biology found the topic fascinating and unanimously agreed that knowing the risk is preferable to living in uncertainty.

My family members got tested as well; their results came back negative, while mine came back positive. It was kind of like they were reassuring me. I thought, it's not cool, but it's like I have this mutated gene that some people don't have, so that's kind of fascinating. At that time, I was doing my A-levels, and it was quite captivating. The person who informed me about the result said if I needed more information, I could call them. (Relatives > DS346)

DISCUSSION

Although clinical genetics have found their way into different aspects of respiratory medicine over the years, their utilisation in the realm of pulmonary hypertension is relatively recent.[22] The introduction of new diagnostic tools, continually evolving technologies, and the rapidly expanding body of knowledge can pose challenges that may seem overwhelming for both patients and clinicians. Advancements in medicine, including those emerging from research studies, are crucial for improving clinical practice. Therefore, it is essential to understand how the delivery of research studies impacts the integration of new findings into clinical practice.

Our study sheds light on patients' perspectives on genetic study delivery and provides recommendations for improving the process.

First and foremost, patients are overwhelmingly keen to contribute to research; however, engagement with the study materials and understanding of information about the research, its objectives, and the potentially far-reaching consequences might, at times, be lacking. This can be blamed on broad consent, lengthy study materials and long research cycles. In a survey conducted by Lopienski[23] involving different completed trials, individuals who dropped out of a trial prematurely were twice as prone to expressing that understanding the ICF was challenging in comparison to those who saw the trial through to completion. It is, therefore, paramount to ensure that patient-facing materials are clear and engaging and that patients are aware of the benefits and limitations of research and have basic disease literacy that would allow them to contextualise their own experience. There is a growing body of evidence that AI tools could assist in creating more empathetic language in ICF and related materials, enhancing patient confidence and maintaining readability.[24]

Second, our study and others[25] showed trust in healthcare providers can have a significant impact on patient recruitment and retention.

From the patient's perspective, the accessibility of the study is an important driver for participation. Studies have shown that the financial impact of some trials can adversely affect patient adherence and retention[26]; addressing practical barriers such as travel, time commitments, and financial concerns, as well as remote participation, especially for patients with significant treatment burdens, may significantly increase participation and patient satisfaction. Similarly, less invasive study procedures or those that align with existing healthcare routines can reduce the burden on participants. It has been shown before that personalised counselling procedures are more effective than a teaching-based approach.[27] Likewise, recruitment procedures should consider the disease management status, recognising that interest in participation may fluctuate with symptom severity as well as patient prior knowledge, familial dynamics and lived experience. Resulting from this is the need to recognise the impact of genetic findings on family dynamics and provide resources and support for participants making decisions about involving family members in research.

Finally, the effective communication of research results to participants requires better consideration. Two types of feedback can be distinguished: return of genetic results or updates on the progress and impact of the study and acknowledging participants' contributions to scientific advancement, even if they did not receive individual genetic results. Closing the research cycle by providing meaningful feedback not only fosters trust and goodwill among participants but also plays a pivotal role in research delivery. It ensures that participants feel valued and connected to the ongoing research efforts, ultimately contributing to the study's continued success and engagement.

To summarise, to enhance genetic research participation and its integration into clinical practice, several key recommendations emerge. Researchers should adapt engagement strategies to account for the dynamic nature of disease experiences and prioritise clear, empathetic communication with participants at all stages of the research cycle. Healthcare providers play a vital role in facilitating research and should receive training to effectively communicate the benefits of genetic studies and testing, considering varying levels of scientific knowledge among patients. Funding should be allocated to support initiatives aimed at removing practical barriers to participation. Simultaneously, policymakers should enhance privacy regulations to safeguard participants' information and uphold public trust. Additionally, there should be a strong emphasis on the implementation of nondiscrimination policies within the insurance sector to shield individuals from unwarranted consequences based on their genetic information. Furthermore, future studies should delve into the impact of genetic research on family members and formulate strategies to offer support in such instances.

Strengths

This is the first comprehensive qualitative study that examines the attitudes towards genetic research in PAH among patients, their carers and relatives who have participated in genetic study. Through in-depth interviews, it uncovers the motivations driving stakeholders' participation and conducts a thorough analysis of their perspectives on various aspects of study delivery. Additionally, it formulates valuable lessons learned that can be applied to similar research endeavours as well as inform changes to clinical practice. By employing a substantial sample size for qualitative research, the study ensures that a comprehensive and diverse range of perspectives and attitudes are captured, resulting in a well-rounded overview.

Limitations

While our intention was to recruit participants with prior genetic research experience, we acknowledge potential bias due to the high mortality rate among PAH patients. We primarily captured “super-survivors.” This potential bias could result in an overrepresentation of individuals with milder disease, those who have shown exceptional responses to existing therapies or benefited from participation in clinical trials, deepening their trust in both research and their clinical teams.

CONCLUSIONS

Enhancing genetic research participation and its integration into clinical practice requires adapting engagement strategies, clear and empathetic communication, and support from healthcare providers, policymakers, and researchers. By addressing practical barriers and ensuring transparency, we can advance genetic research while maintaining patient trust and promoting improved patient outcomes. Further research should explore the impact of genetic research on families, contributing to a more comprehensive understanding of this evolving field.

AUTHOR CONTRIBUTIONS

Emilia M. Swietlik conceived the project, analysed the data, and wrote the manuscript. Michaela Fay conducted the interviews and focus groups, analysed the data and cowrote the manuscript. Nicholas W. Morrell supervised the project.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Access to anonymised interview transcripts can be granted upon request, subject to ethical clearance. Please contact Emilia M Swietlik at e.swietlik@nhs.net to discuss access and ethical considerations.

ETHICS STATEMENT

Our study was approved by the North of Scotland Research Ethics Service (REC reference: 22/NS/0127). All patients provided written informed consent before enrollment in the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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