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ORIGINAL ARTICLE

The disequilibrium of hope: A grounded theory analysis of parents' experiences of receiving a "no primary finding" result from genome sequencing

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Abstract

Genome sequencing (GS) has the potential to reduce the "diagnostic odyssey" that many parents of children with rare undiagnosed conditions experience. While much research has considered the impact of receiving a diagnostic result, research has rarely focused solely on the impact of receiving a "no primary finding" (NPF) result. This study aimed to investigate the experience of parents of children with rare and undiagnosed conditions following an NPF result from GS. Nine parents whose child had an NPF result from GS were recruited through the social media platform of the charity SWAN (Syndromes Without A Name) UK. Semi-structured telephone interviews were conducted, transcribed verbatim, and analyzed using grounded theory. Analysis led to the emergence of two main themes. The first theme "Striving to Solve the Unsolved Puzzle" concerned the experience of striving to end the "diagnostic odyssey." The second theme "Navigating Hope, Lost then Found" plots the trajectory of hope raised by the promise of a new technology, dashed by the NPF, and the eventual return of small and distant hope for the future. Taken together, these themes allowed for a proposed theory: "The Disequilibrium of Hope," which highlights the dynamic and modifiable experience of hope participants experience in their GS journey. These results suggest GS can be an emotional rollercoaster for parents. While hope plays an important role in coping with the day-to-day life of living with a rare disease, careful management of expectations from GS is important during pre-test counseling, and continued follow-up and support are needed beyond result disclosure. An understanding of the disappointment and distress caused by an NPF result is valuable for healthcare professionals in this field to ensure counseling can be tailored. Further research should consider how to support parents after an NPF result.

KEYWORDS
distress, genetic counseling, genome sequencing, hope, lived experience, psychosocial, undiagnosed

1 | INTRODUCTION

Genome sequencing (GS), which has been shown to provide a diagnosis in around 40% of rare pediatric disease cases (Wright et al., 2023), has become part of routine clinical practice for the NHS since 2018, through the newly established NHS Genomic Medicine Service (GMS) (Robinson, 2020). The NHS GMS has followed the "100,000 Genomes Project" (hereon referred to as "100 kGP"), which was a hybrid clinical/research project, conducted between 2015–2018, that explored the introduction of GS into clinical practice in the NHS in England (Barwell et al., 2018; Turnbull et al., 2018). Eligible participants included patients (and their families) who had a likely monogenic rare disease based on phenotype, but for whom a genotype had not been established through traditional genetic testing. Most patients were therefore required to have undergone some genetic testing prior to taking part. The 100 kGP recruited parent–child trios where possible which has been shown to increase the probability of obtaining a diagnosis (Wright et al., 2023). Around a quarter of rare disease patients who took part in the project were children (Lewis, Hammond, et al., 2020). The high number of pediatric patients is unsurprising given that the majority (50%–75%) of rare diseases affect children (European Organisation for Rare Diseases, 2005). As part of the consent process for GS, participants were given an information leaflet explaining whole genome sequencing and asked to sign a consent form (or provide proxy consent in the case of children under 16 years old) which specifies that that sample can be used for "collecting DNA for whole genome sequencing."

Research looking at the experience of parents who receive a genetic diagnosis for their child's condition has highlighted that a diagnosis can lead to clinical benefits such as access to disease-specific treatments, information about the likely trajectory of the condition, and information relating to the recurrence risk (European Organisation for Rare Diseases, 2005; Griffin et al., 2017). Practical and psychological benefits include enabling parents to make contact with other parents through support groups, access to social and educational support, relief from guilt and validation in terms of providing legitimacy for the child's behavior or appearance (Ashtiani et al., 2014; Griffin et al., 2017; Lewis, Sanderson, et al., 2020; Peter et al., 2022). Parents have also been found to experience worry, fear, loss of hope, and frustration at the lack of information available when their child has been diagnosed with a rare disease (Rosell et al., 2016; Wynn et al., 2018).

The experiences and outcomes of parents who go through genomic testing (exome sequencing [ES] or GS) and do *not* receive a result are less well known, although research in this area is growing. For example, it has previously been found that parents who did not get a result from GS in the 100 kGP in England experienced frustration and disappointment, particularly if the initial expectations of receiving a diagnostic result were elevated (Peter et al., 2022). Some parents felt anxious and frightened for the future, including concern for the health of other family members (Peter et al., 2022). Other research looking more broadly at the experience of parenting a child with an undiagnosed condition has indicated that parents experienced stress, worry, and anxiety and that care was often un-coordinated leaving parents frustrated and unsure who to contact with questions or concerns (Aldiss et al., 2021). Parents themselves were found to have many unmet needs including holding back their emotions to protect themselves, and lack of time to prioritize their own wellbeing (Aldiss et al., 2021). In a quantitative survey study by McConkie-Rosell et al., parents of undiagnosed children were found to have high rates of anxiety and depression which were significantly inversely correlated with coping self-efficacy (McConkie-Rosell et al., 2018). Yet parents were also found to be engaged in their child's healthcare and tolerant of uncertainty. Notably, a report produced by Genetic Alliance UK and Birmingham Children's Hospital highlighted how families without a diagnosis fight to be heard initially, preventing timely access to specialist care and support, and that coordinating the various elements of care is a task that can become a huge burden for parents (Genetic Alliance, 2018).

Research is also beginning to emerge around the interpretation of a negative result from genomic testing from the patient perspective. In a study by Skinner et al. whereby the authors conducted an ethnographic observation of return-of-results appointments followed by interviews with patients, the authors found that a negative result from ES was either interpreted as a genetic explanation being unlikely, or, more frequently, likely but not yet revealed (Skinner et al., 2016). The authors also identified that patients were given reassurances about the quality and scope of ES and the potential of the technology to produce a genetic diagnosis in the future. In that sense, clinicians and patients were found to turn what the authors describe as a "nuanced negative" into "nuanced optimism" that either a genetic diagnosis will be found in the future or that the condition is not genetic. These studies serve to highlight the complexity and range of experiences related to receiving a negative result from genomic testing.

The overall goal of the NHS GMS is that from 2020, and by 2025, genomic medicine will be embedded in multiple clinical pathways in routine care with GS being available as a first-line test for some rare

What is known about this topic

Genome sequencing (GS) in undiagnosed rare disease currently returns a diagnostic result in approximately 40% of cases; however, many will not get a diagnosis and will receive a "no primary finding" (NPF) result. As GS is a new technology, there is little known of the emotional impacts on parents of receiving an NPF result.

What this study adds to the topic

The evolving role of hope in the parental journey is explored, including hope in its different forms at different stages. A deeper understanding of the impact of an NPF result can inform genetic counseling both prior to and following testing.

and undiagnosed diseases. Given that currently fewer than half of patients receive a diagnosis following GS, further research is needed to gain a more nuanced and complete understanding of the experiences of parents who have not received a diagnosis. The aim of this research was therefore to explore the parental experience of receiving a "no primary finding" (NPF) results following GS.

2 | METHODS

A qualitative research design was employed to understand the experiences of parents of children who had an NPF after GS. During data collection, the concept of "hope" was seen to be running through all interviews, and it was noted that the interviews were particularly rich in depth. Based on early reflections during analysis, it was decided that the most appropriate methodology with which to analyze these data should be an interpretive one, and therefore, Grounded Theory Analysis was employed, rather than a descriptive methodology, which would only allow for broad brushstroke reflections of the data. Using Grounded Theory allowed for not only an experiential assessment of data but also would be technically able to cope with the richness of the data, while having the ability to make sense of the recurring patterns linked to hope running throughout the data collected.

2.1 | Ethics

Ethical approvals were granted by Cardiff University School of Medicine Research Ethics Committee, in September 2020 (SMREC 20/70).

2.2 | Participants

Parents of children who had GS as part of the 100kGP (and who themselves would have had GS as part of trio testing) and received an NPF result were recruited through the patient support group SWAN UK [Syndromes Without A Name] through a social media advert posted in November 2020 and again in January 2021. In the advertisement, potential participants interested in taking part in an interview were invited to make direct contact with the researcher by e-mail. In total, eleven potential participants made contact; however, one declined to be interviewed and one did not respond to further contact; thus, the dataset comprises nine interviews.

2.3 | Procedure

A semi-structured interview schedule was developed [JG, CL] following discussions with co-authors and informed by the literature, in particular previous descriptive work examining the experience of participants taking part in the 100kGP (Peter et al., 2022). Topics of discussion included the following: asking the participant to tell their story of trying to find a diagnosis including their experience of being a participant in the 100 kGP; their experience of receiving an NPF result; the immediate and longer-term impact of the NPF result on their emotional wellbeing; and suggestions for what could have made the experience better.

Between January and April 2021, nine semi-structured interviews (McIntosh & Morse, 2015) were conducted by telephone ($n=8$; Holt, 2010) or Zoom video-conferencing software ($n=1$; Archibald et al., 2019). This style allowed for both flexibility of geographical recruitment and for the interviewer [JG] to follow up with individuals' pertinent points. Interviews lasted between 41 and 84 min (mean length 59 min) and were transcribed verbatim [JG], allowing for accuracy checking and re-familiarization with data. Culturally sensitive pseudonyms were assigned to each participant in-line with contemporary qualitative practices (Heaton, 2022; Saunders et al., 2015).

2.4 | Research paradigm

We situate this study in a post-positivist research paradigm (Levers, 2013). In doing so, we embraced both a critical realist ontology and objectivist epistemology (Annells, 1996), whereby participants' narratives are taken as their lived truths even if those recounted narratives are empirically fallible. Thus, the importance is placed on their lived realities within the socio-politico context, rather than a reliance on one objective truth, and in contrast to the belief that truth is intangible and interview data is a co-constructed artifact. When discussing theoretical perspectives, it is also important to discuss positionality – that being both our position in relation to the data and our collective reflexive judgment when approaching the data. To this end, we report taking a critical, but empathic reflexive judgment, whereby behaviors are accepted as being affected by changing structural conditions and other societal pressures, and that some behaviors are laden with an intrinsic value. With regard to our own position within the data, the authorship team is cross-disciplinary, comprising genetic counselors [JG, BSS], behavioral scientists [CL, MH], and social scientists [SAS, MP], with two authors being recognized experts in qualitative research [CL, SAS]. In particular, the first and senior authors (who conducted the analysis) have significant expertise in genomics, including almost a decade of experience at an organization for patients and families affected by rare genetic conditions [CL] and experience consenting families into the 100,000 Genomes Project as well as genetic counseling training [JG].

2.5 | Data analysis

Data were analyzed using Grounded Theory Analysis (Glaser & Strauss, 1967) which utilizes a highly methodical approach to coding: Open coding; focused coding; development of super-categories; grouping into themes; and generating theory (Silverio et al., 2019).

Coding was iterative and inductive and undertaken by one author [JG], with a subset of 20% being confirmatory coded [CL], and in reflexive consultation with the wider team [SAS, MH, MP, BSS].

Saturation was assessed on two key axes: Data saturation, where no new concepts were emerging from new interviews added to the dataset (Guest et al., 2006); and theoretical saturation, where each of the themes was adequately supported by data representing all or at least most of the dataset (Glaser, 2001). In the present study, full saturation was assessed as being achieved with nine participants.

2.6 | Participant characteristics

All parents were female, the majority self-identified as White British. There was a range in terms of educational attainment, with four having achieved Bachelor's degree or higher. Regarding occupation, three participants were full-time carers. Participant characteristics are summarized in Table 1.

During the interviews, parents described the testing that their children had had prior to being on the 100 kGP. All had had prior genetic testing: four parents specifically mentioning microarray, one parent specifically mentioning her child had been in the Deciphering Developmental Disorders study (Firth & Wright, 2011; a research study in which microarray and/or whole exome sequencing were performed), and one parent specifically mentioned her child had undergone gene panel testing. Four parents described how at varying points in their clinical journey, other clinical diagnoses had been suggested and then rejected. The ages of the undiagnosed children ranged from 5–16 years old. In all cases, the time at which the child's health problems first became evident was when they were less than 1 year old, and in four of the nine cases, the child was less than 1 month old. Therefore, the "diagnostic odyssey" for participants ranged from four to 15 years. In terms of the impact of the condition on the child and the family, nearly all ($n=8$) indicated the child's condition had a significant or "very significant" impact on their child's health, and, similarly, nearly all ($n=8$) indicated the child's condition had a significant or very significant impact on the family.

TABLE 1 Participant characteristics.

Characteristic	*n* (%)
Age range	
28–37	4 (44%)
38–47	5 (56%)
Gender	
Female	9 (100%)
Ethnicity (self-identified)	
White British	8 (89%)
Black British	1 (11%)
Education	
GCSE[a]	2 (22%)
A level[b]	2 (22%)
NVQ[c]	1 (11%)
Bachelor's degree	3 (33%)
Post-graduate degree	1 (11%)
Occupation	
Full-time carer	3 (33%)
Part-time employed/carer	3 (33%)
Full-time/self-employed	3 (33%)

[a]General Certificate of Secondary Education, taken when students are generally aged 15–16.

[b]Advanced Level Qualifications, usually taken when students are 17–18.

[c]National Vocational Qualification, a work-based qualification that recognizes the skills and knowledge a person needs to do a job.

3 | RESULTS

Analysis resulted in two main themes comprising a total of five super-categories, which centered on the concept of "hope":

Striving to Solve the Unsolved Puzzle

- Striving for a Diagnosis
- Fearful Ambivalence

Navigating Hope, Lost then Found

- Hopes Dashed
- Isolation Revisited
- Hope out of Darkness

Three of our super-categories (Striving for a Diagnosis, Hopes Dashed, and Hope out of Darkness) were supported by data from across all nine interviews. The remaining two super-categories (Fearful Ambivalence and Isolation Revisited) were more pronounced for some parents than others. However, we propose that when taken together, these super-categories had sufficient explanatory power to support the final proposed theory, comprised of two themes. Representative quotations from participants have been used in the following analysis section below, to illustrate these themes.

3.1 | Striving to Solve the Unsolved Puzzle

The themes grouped together under "Striving to Solve the Unsolved Puzzle" encompass the lived experience of having no diagnosis, the motivations underpinning the desire for a diagnosis, and how the offer of GS raises hopes that a diagnosis will be found (Striving for Diagnosis). It also includes the hope participants have for a diagnosis that is balanced against their fear of what the diagnosis will be (Fearful Ambivalence).

3.1.1 | Striving for a Diagnosis

Parents opting for GS pinned their hopes on this new technology finding a genetic cause for their child's condition. There was a sense

that even when participants knew factually that they might not get a diagnosis from GS, having access to a "new technology" encouraged them to feel that diagnosis was possible and that the 100kGP may be their "last hope." The determination and sometimes desperation for a diagnosis were ubiquitous and persistent as illustrated by Marissa below.

> In all honesty, if someone said to me 'we'll cut off your arm and your leg and we'll give you a diagnosis for your son', I'd do it in a heartbeat.
>
> (Marissa)

For Kate, a clinical diagnosis had been suggested. She had become accustomed to it, researched it, and become involved with a support group. When the clinical team decided to explore, with a view to discounting the suggested diagnosis, Kate described the ambivalence and psychosocial impacts that reverberated as though the diagnosis was a lifeline which when removed left her feeling untethered and unsupported.

> When she was four they decided to admit us and do a trial withdrawal of some of the drugs for the [suggested diagnosis] as they still weren't sure what was going on. I can remember being very ambivalent about the admission as I was thinking 'are they going to take away the diagnosis of [suggested diagnosis]?' when we had just met this group of people and I had done quite a bit of research by that point… So when they started saying they don't think she does have [suggested diagnosis] then I felt like we were back out on a, I don't know, like we were losing our raft I suppose.
>
> (Kate)

Motivations to have GS and to strive for a diagnosis included feeling driven to do everything possible to help their child by obtaining more information about the cause of the condition and the prognosis for the future.

> So, I didn't think it [100 kGP] was this all singing all dancing that was going to fix her. I knew that wasn't going to be the case. But as a parent, it came back to that very need for me, that we had done everything we could to find out as much as we could to help her, and if there was some magic charm, snake oil, that we had done everything to do it.
>
> (Kate)

> We went into it [100kGP] feeling like we were in a pioneering project. It felt good. It felt like we were doing everything we could.
>
> (Lucy)

The desire to alleviate feelings of guilt was another strong motivational drive to opt for GS. This included feeling guilty that the condition was caused by something they had done during pregnancy, such as having an alcoholic drink early in the pregnancy, not coming off the contraceptive pill early enough, and/or not taking enough folic acid.

> Should I have done a detox? I'm always thinking something you know?
>
> (Angela)

One mother worried that her child's condition was punishment for having even considered terminating the pregnancy.

> I think what was going through my mind 'was this something I did'? … obviously I felt huge guilt, because… we had conversations about, were we going to continue with the pregnancy.
>
> (Kate)

Guilt was not just an immediate, short-term experience for parents, but one that could endure for many years, even if it did subside to some degree.

> It's hard not to think. Is it something that I did? Is it my fault? I'm eleven years of holding onto that 'is it my fault?'
>
> (Sam)

Parents articulated a belief that having a diagnosis would mitigate these feelings of guilt.

> [Be]cause I'm sure that for a lot of parents, knowing, I think knowing kind of eases that guilt for you
>
> (Angela)

This view that a diagnosis would lessen their feelings of guilt was enhanced by talking with parents who had received a diagnosis for their own child.

> I have spoken to some families who pursued a diagnosis like I've described… And you know what they all said? The sense of relief, as if a massive weight has been lifted off their shoulders. And yeah, I definitely would like some of that…That's what the other mums said to me, that feeling, feeling of relief they could say: 'Thank goodness. It definitely wasn't my fault'.
>
> (Lucy)

Other motivating factors that prompted parents to opt for GS were to provide validation that the child's condition was beyond the mother's control and to potentially enable parents to belong

to a specific support group which could help with coping, even if it did not change clinical management.

> I think I've gone past that point now, where I think having a diagnosis will change him in some way... I just think having a diagnosis will help me to deal with it better. Because I'll be able to speak to other parents. I'll be in a group; I can see what's working for them. I think that's how I'm looking at it now.
>
> (Angela)

3.1.2 | Fearful Ambivalence

Hope for a diagnosis was frequently mentioned but was rarely straightforward as the hope for an answer often merged with the fear of what that answer might be. Marissa highlights that while she knows she could "lose" her child, she wants to know anyway so that she can be prepared:

> I think I may be the only one who wants to know, and that's so that I can prepare myself, whereas everyone else...they don't want to know...And I understand, because of his health conditions I could lose him to a seizure. I know I could lose him to an infection. I know this.
>
> (Marissa)

Some people hoped for a diagnosis so that they would have a prognosis, to know what the future holds. However, at the same time there was also a fear that a diagnosis might reveal a condition that was life-limiting. In some cases, parents had differing views around whether they wanted a diagnosis.

> He [partner] was worried about getting a diagnosis that was very bad news and he said he'd rather not have [a diagnosis] than to get a diagnosis when she was maybe nine years old and be told that most children don't live much after nine years old. That was his worst nightmare.
>
> (Lucy)

Feelings reflecting a fearful anticipation were often heightened by a deterioration in the child's condition.

> Now I'm just sitting here thinking what's the next big thing that's going to appear? You just never know. I mean he is now tube-fed. He used to be able to eat, he's now tube-fed.
>
> (Marissa)

Managing this fear of the unknown extended to difficulty in responding to the fears of other family members who were also struggling.

> Because I don't know what other conditions could pop up. His brother is always asking questions, like 'will this happen, will that happen', especially as last year [child's name]'s friend passed away.
>
> (Tessa)

3.2 | Navigating Hope Lost then Found

The themes grouped under the concept of "Navigating Hope Lost then Found" explain the experience of receiving an NPF and focus on the emotions and consequences of the impact of this news. Many participants recalled the descent into disappointment and sadness they experienced on receiving the NPF from 100kGP. Isolation was reported as another powerful initial consequence of receiving the result (Isolation Revisited). However, despite the dashing of hope from the NPF result, over time hope re-emerged and helped parents to go on with day-to-day life. This new type of hope was described as difficult to hold on to, but necessary (Hope Out of the Darkness).

3.2.1 | Hopes Dashed

When parents described their response to receiving the NPF result, it was clear that this was the moment at which all hope they had invested in obtaining a diagnosis from GS was extinguished.

> For me it felt like that was our shining guiding pathway, if anything was going to give us our answer that would be it. At that point there wasn't anything else out there. No one was talking about the whole exome sequencing either, so I kind of felt like it was almost a bit like that is another door shut.
>
> (Kate)

On receipt of an NPF, parents spoke of feeling "defeated," "gutted," "really disappoint[ed]," and "deflated."

> Gutted. Gutted and I knew exactly where I filed it, so I pulled it out earlier today actually, knowing that I was going to speak to you. And read it again and I still felt gutted.
>
> (Natalie)

> At the time that we got the letter, there was nothing else that would find, there was nothing else on offer, so that was it. That was our chance of finding something, so when that came back with no finding that was disappointing and upsetting.
>
> (Sam)

Marissa described feeling broken by the result.

> When I got it [NPF result letter] in my hand, I chucked it. I literally just chucked it across the room. And walked away from it and then my partner picked it up and read it and came out to me, because he knew it would have broke me.
>
> (Marissa)

For at least one participant, the NPF result led to a period of feeling low for some weeks.

> I've gone, 'it's come back with nothing' but it wasn't a surprise, it did affect us, I was quite low for sort of, for the following weeks, because I felt like we were back at square one again.
>
> (Helena)

For some, the timing of receiving the letter heightened the misery of disappointment and increased sadness as the joy of a family holiday time was marred.

> I said, 'please, please don't phone me up out of the blue giving these results, Please don't send me a letter just before Christmas', which is actually what they did. So, I kind of knew it, it arrived, and I knew. I kind of knew it would be a no result sort of thing, but I opened it and I did, I did have a short cry about it was, yeah, I was disappointed.
>
> (Lucy)

Cerys described her extreme frustration as she felt that mistakes had been made by her clinician in their choice of the gene panel applied in the GS. She described the process as having taken both an emotional and physical toll.

> On the emotional and physical side, it's taken quite a bit out of myself particularly. It was all a bit messed up to be honest, I didn't know it would be that frustrating. I think that's why it has taken out so much from me emotionally. Because not knowing why we've got these issues, by not knowing, we don't know what we should be avoiding and what we should be doing...I just want answers and it's just not getting anywhere... So as far as I see it with all that, something that could have been potentially really helpful for us, was actually a waste of time.
>
> (Cerys)

For some, the associated frustration fades over time and in its place was a resignation that a diagnosis, if it ever will be possible, is now a long way off.

> But this one, it was like 'don't get your hopes up' if they come back with anything ... I think they're at the point where they've sort of exhausted everything they can do at the moment. So, there's a small chance that this could show something...very small, and I'm not hopeful that this will come back with anything and after that point I really don't know where we'll go from there. I think we'll just carry on as we are.
>
> (Helena)

3.2.2 | Isolation Revisited

Isolation Revisited reflects how dashed hopes left parents with feelings of isolation. This isolation mirrors the isolation they had felt without a diagnosis prior to undergoing GS. Isolation was also associated with feeling unable to contribute to "normal" parental roles, such as helping at playgroups, feeling isolated from friends who were perceived as having a totally different experience of motherhood and whom they did not' want to burden with their negative experiences. This social isolation was coupled with the lack of support available for parents when their child does not have a diagnosis. The absence of others who could relate to what these parents were going through compounded this sense of isolation. One parent described feeling isolated because she did not want to be judged or pitied by society, and her initial reaction was to hide away and "lock everyone in the house."

> I just wanted to lock everyone, like lock everyone in the house and just not like, not go out because you don't, you know, you just don't want that judgement. You don't want that pity kind of thing.
>
> (Angela)

Parents described how the NPF result intensified their feelings of isolation as there is no one who can relate to their experiences.

> To just get 'no finding', and just be told you know, he's one in a million, it's quite, it's very isolating as well. I have no one that I can share, who can relate to my child.
>
> (Marissa)

Angela described seeking out her own isolation in response to being "really upset"; needing some "time to think": time for herself. We get a sense here of Angela allowing herself this time to feel and absorb the news before gathering herself to face the world outside the bathroom.

> I was really hoping that it would come back with something. I, I was really upset. And took some time

> just for myself when we finished the call… just took some time, to like just, okay, so I go to the [bathroom]. It's my spot where I go sometimes to have my time, and sometimes I have my iPad slipped under the door (laughing). And it's my time to think. And so, I'm like, let me have my moment, and then…'we'll see (deep sigh).
>
> (Angela)

Posts on support group social media celebrating another diagnosis engendered a sense of being "left behind" without a diagnosis. This was mentioned as a factor contributing to deepening feelings of isolation.

> Interviewer: What about [name of support group]? Does that provide a sense of belonging?
>
> "Erm, yeah. Except when people pop up to say they've had results all the time."
>
> (Tessa)

Natalie suggested that the sense of isolation could have been alleviated if the result had been accompanied by a generic leaflet saying how many others also received an NPF result. She suggested that if she had known that the majority of participants in 100kGP had also received an NPF result, she would not have felt so alone.

> Perhaps if it's a negative result or no findings at the moment, perhaps some sort of percentage of how many other people in the study had no findings, just so you know. Regardless of whether you really have a support group for it or not. That you don't feel like you're alone. You know this if there's been, say 40% of people who have been part of it, have had a result and 60% haven't, then you might think 'OK so you know, the majority haven't had. Maybe it's not such a bad thing, but it helped science somewhere in the long run'.
>
> (Natalie)

3.2.3 | Hope out of Darkness

Hope out of Darkness collates the expressions of a transition through resignation and a re-emergence of hope that appears reborn but altered. In this latter guise, it has a purpose, no longer something needing to be kept under control, but as a prop in coping, something to be "held on to."

> Maybe we'll never know. We still have that little bit of hope, but it gets harder and harder. Holding onto that little bit of hope.
>
> (Sam)

However, the very act of "holding on to hope" is described as hard when there is not even a vague notion of what a diagnosis could be nor of the prognosis.

> Just to have that: this is what we know, what it is and whilst we can't say: 'This this, and this will happen. This is what could happen. This is what is likely to happen.' Just for the answers, it's even just, even if they have no answers, just to be able to say this is what it is, because when there's nothing, it's hard, it's hard to hold onto the hope.
>
> (Sam)

Following the NPF result, there was an expression of difficulty in remaining hopeful and some questioned if it was even a good thing to hold on to hope. A need or desire to hold on to what was often described as a "little bit of hope" was expressed by several participants. For Sam holding on to this hope was described as a "fight" but it was necessary to ensure family and friends kept holding on to some hope. Sam describes the act of hoping almost as a responsibility, maybe even a burden, so that others did not give up hope of getting a diagnosis. A diagnosis here was considered as so important that it was prized even above a "bad news" result.

> It would be nice to have: 'This is what it is and this is what could happen' yeah. It would be lovely to have that, even if it's not what we want to hear.
>
> (Sam)

Despite not getting a result from the 100 kGP, some participants commented that they remained hopeful that they would get a diagnosis in the future. Lucy described hope as "a thing that you get in the back of your mind," as if it is ever present and involuntary.

> We were told that we're in the system and you never know something might happen in a year, two, five, ten years' time. So, there's this thing that you get in the back of your mind. We might get a letter out of the blue. In a few years' time, who knows. So that's the same feeling, I guess, as we felt a few years ago.
>
> (Lucy)

For Marissa, the nature of her hopes changed over time. Living without a diagnosis had led to the loss of hope that there could be a transition from a sick to a healthy child. The NPF had further confirmed this, and she described having to alter her imagined futures. The usual parental hopes and dreams for her child are something she described as "not allowed." Hope was described as fading with time because the reality of what her child was able to do (and not do) became more marked and she learnt to accept the situation as it is rather than hope for something different.

> I have no idea what my son's future is. So that's the hardest part, is not knowing what's going to happen to my son. I mean, when he was a baby, it's easier to sit there and think, you know, let's hope, let's wish, you know, this time next year you'll be walking, but as obviously he's got older, I realise that those expectations probably will never happen.
>
> (Marissa)

For some participants, there was a sense of progression through frustration and resignation following the NPF to a hope for a diagnosis to come at some point in the future. These participants highlighted that it remained possible that a diagnosis might arise in the future from re-analysis in the 100 kGP or from other developments within genetics.

> But we're only scratching the surface with what we can actually look at the minute. As we know, science improves, then maybe later in life we will, well, know and have something you can name in Google, but for now he's just a bit of an anomaly.
>
> (Natalie)

These hopes for a diagnosis in the future seemed, for some, to be intertwined with an acceptance of not having a diagnosis and a feeling that hope for a diagnosis could continue despite the NPF result.

> it's a little bit of hope in the background that, that work is going on potentially in the background, um, so a bit of hope there.
>
> (Lucy)

For Angela, who described an overall negative experience of the 100 kGP, the NPF result left her with a conflict of her hopes. She talked about hoping the technology would improve and one day lead to a diagnosis, while also, she told of not letting herself feel hope because it was too painful when let down, a protective measure against future disappointment. She described choosing to focus on the here and now in terms of what her child can achieve and what can bring her happiness. The focus of her hope shifted from getting a diagnosis to hoping for a good life.

> But you do know, generally I'm like let me look at my child, he can hug, he's making eye contact. I literally write, I've got a book where I write all the good things that he does, and you know I look at that, like what is he doing today, you know what he's doing today? And I focus on that, I literally focus on that, and it helps, it does really help.
>
> (Angela)

In this final super-category, we have seen a re-emergence of hope, a very different hope than that expressed earlier in the journey of having GS as part of the 100kGP. This hope is dulled, less tangible, and less immediate than the "ray of hope" that one participant "just ran with" when they were initially offered GS.

> Hope is still there and as time goes on it just gets harder to hold onto it, but it's still there, definitely.
>
> (Sam)

There remains the hope for a diagnosis, now less immediate, as the promise of the 100 kGP has been snatched away, that former "shining" hope dashed.

> In the future, you know, I remember being, like he could get to adulthood, and then we still wouldn't know and then, then suddenly, out of the blue, there might have been a match, or something and, and, then you know there it is: There's your diagnosis.
>
> (Natalie)

Hope, although its focus was changed, seemed to be part of the process of coping with an unknown future and a return to an uneasy equilibrium. These experiences are encapsulated by Kate who when receiving an NPF result from the 100 kGP realized she had not made the peace she thought she had and references a hidden, unconscious hope. When stating "it's funny," she indicates that the situation seems strange to her, and she interrogates her own reactions and finds the striving for a diagnosis had never gone away. As such, she was not protected from the dashing of her hope and the disappointment and sadness that took her almost by surprise. "The knowing" that great progress is being made with the introduction of genomics to healthcare, but that through the fault of time, "not quick enough," her child may not benefit, suggests a myriad of emotions continue within the apparent stasis of being "in limbo."

> It's funny, I thought, I thought I'd made peace with the fact that we would never get a diagnosis, but obviously as I felt that sadness and that disappointment, I suppose in the back of my mind there was that hope that we are going to get it. And now it's back to kind of treading in limbo and knowing that they are finding out so much and they are finding out more information so quickly, but not quick enough.
>
> (Kate)

This re-emergent hope, hard as it may be to hold on to, has with it a current of determination and strength to go on.

> I've got to be hopeful. It's made me more determined if anything, 'cos I know there's an answer: I just don't know it.
>
> (Tessa)

3.2.4 | Proposed theory: The disequilibrium of hope

Taken together, the emergent themes described above were interpreted as the theory: "The Disequilibrium of Hope" (Figure 1). This captures the role and nature that hope plays for participants in this study, and the various peaks and troughs participants experience in their journey, firstly investing in hope to "solve the unsolved puzzle" and then having to navigate through lost hope and hope which is found again as they continue their journey.

In the first instance, there is a peak when participants join the 100kGP, with the "hope" of this new GS technology, which is captured by the first theme "Striving for a Diagnosis." This is countered by feelings expressed in the second theme: "Fearful Ambivalence" where participants report their attempts to subdue and keep hope tempered and controlled for fear of what the answer might be. The receipt of an NPF result saw a sharp change of direction in hope – as captured in the theme of "Hopes Dashed," which encompassed profound disappointment, a period of sadness, frustration, and resignation taking the place of hope. Around this time, the fourth theme of "Isolation Revisited" emerged, with many participants reporting the feeling of being alone in this journey once again. However, hope is not entirely lost, and our findings show that it re-emerges in time, as seen with the theme "Hope Out of Darkness." It is important to note, however, in this new guise "hope" is more dulled, less tangible, less immediate, and one which they "put to the back of the mind."

Hope was both central and integral to parents' experiences of having a child with a rare and undiagnosed condition following an NPF result from GS. The nature of hope changed from somewhat naïve, optimistic hope, which metamorphosed as their journeys progressed to a version of hope which was viewed as an unwanted nuisance, tinged with sadness. Hope, therefore, served as a cognitive process which played a part in coping and was drawn upon as a functional emotion when required. There was a notable disequilibrium of hope, whereby not only did hope fluctuate in its magnitude, but also in form. Yet parents retained hope throughout their journeys, often resigning themselves to place hope in the science of the future, ultimately expressing hope as small, difficult, but necessary.

4 | DISCUSSION

While GS has the potential to end the diagnostic odyssey for children who were previously undiagnosed (Wright et al., 2018, 2023), the reality for many parents is that GS fails to provide an answer and they are left disappointed, saddened and frustrated with unmet expectations and no road left to travel on their diagnostic journey (Aldiss et al., 2021; Donohue et al., 2021; Peter et al., 2022). A key contribution of our study is in illuminating the emotional burden that parents take on when undergoing the diagnostic journey and in particular underscores the dynamic and complex role that hope plays. Our proposed theory, "the disequilibrium of hope," summarizes the trajectory of hope – shiny and bright as a mast for parents to pin their hopes on with the "promise" of this new technology, blunted on receipt of an NPF, and then revived in a diminished form, this time as a coping mechanism to support parents to navigate their daily life yet remain positive for the future.

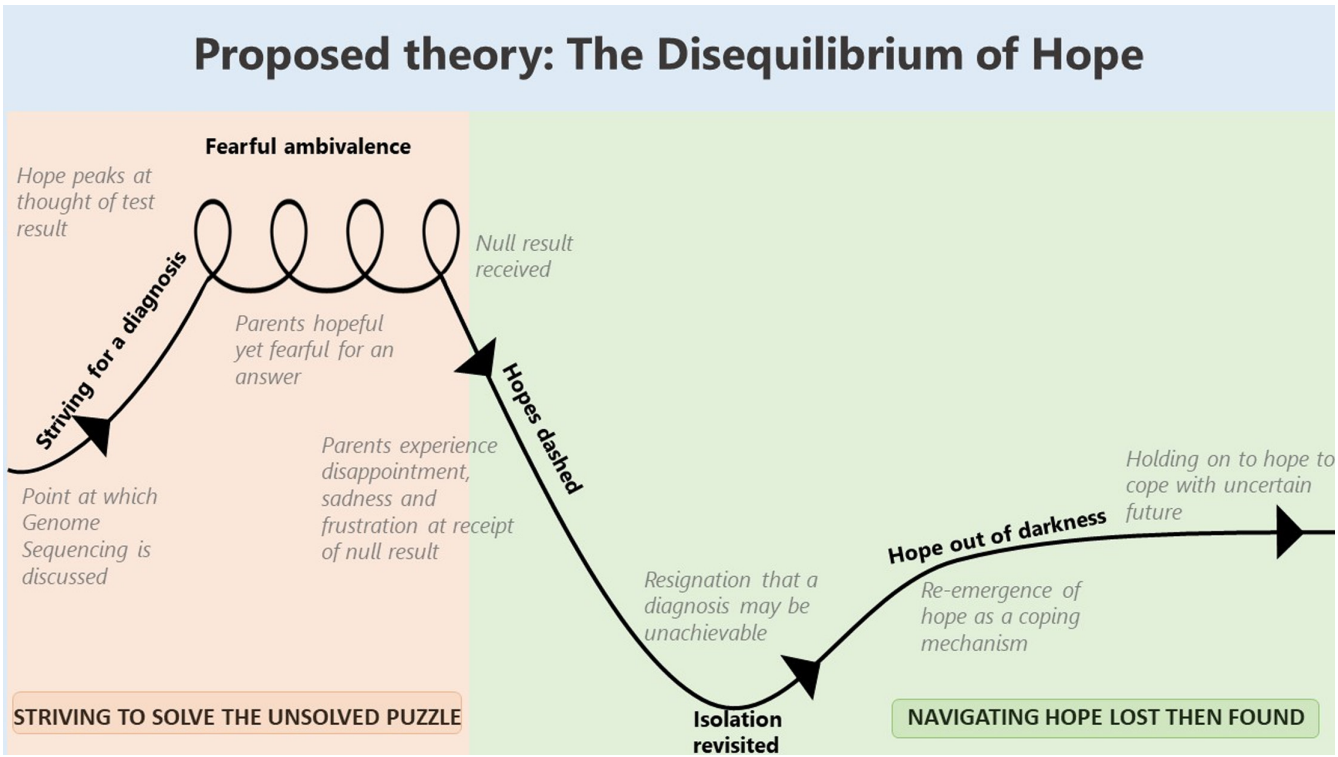

FIGURE 1 Proposed theory: The Disequilibrium of Hope.

Hope has been conceptualized in numerous ways including as a motivational/emotional state, (Lazarus, 1999) a belief (O'Connor, 1996), an inner power (Nekolaichuk et al., 1999), and an expectation (Benzein & Saveman, 1998). However, the consensus across definitions as found in a review of the literature on hope was that it is "dynamic and changeable" p.426 (Schrank et al., 2008) as conceptualized in this study. Schrank and Slade view hope as a primarily future-orientated expectation where attainment will first give meaning, is considered realistic or possible, and depends on personal activity or external characteristics (Schrank et al., 2008). Our findings in this study are concordant with this explanation. In the context of genomic testing for this study: expectation of a diagnosis gave meaning for parents by, for example, alleviating feelings of guilt and confirming that parents "had done everything" they possibly could; it was considered realistic or possible in that parents understood GS to be a new technology which could potentially provide an end to their diagnostic odyssey; and finally, it was dependent on personal activity or external factors in that parents had consented to take part in the 100 kGP and understood there could be a re-analysis of the genome in the future capitalizing on advances in our understanding of genomics.

Hope as a defining experience of parents going through genomic testing has been identified across several studies and at various stages of the testing process, supporting the findings from this study. Peter et al. identified that many parents who chose to have GS had pinned their hopes on finding a genetic cause for their child's condition (Peter et al., 2022). Donohue et al. found that expectations around a diagnosis from GS were deeply rooted in parents' profound hope to end their child's diagnostic odyssey (Donohue et al., 2021). Krabbenborg et al. similarly identified hope as a key driver for undergoing testing with parents hoping for more information about their child's condition and hope that a diagnosis will improve care. These findings echo those we describe in our super-category "Striving for a Diagnosis." On receipt of an NPF result, a mother in a study by McConkie Rosell et al. described being an "optimistic realist" in that she remained "hopeful enough to keep the faith that something is coming" yet "realistic enough to know that you cannot live your life waiting" (McConkie-Rosell et al., 2018). A mother in the Donohue et al. study recounted how her hopes were dashed as she expected "more to be done, or there's more to be found" (Donohue et al., 2021). This range of experiences again echoes those we found in our super-category "Hope out of Darkness."

Although hope has been a key finding in several studies in this area, a unique contribution of our research is that we have been able to describe the trajectory of hope over time and highlight the dynamic way that hope changes and evolves at different stages of the diagnostic journey. Our research reflects a specific situational context, that is the 100 kGP which has received much media attention, in particular highlighting those stories where patients and families affected by rare conditions receive a diagnosis from this "transformational" project (BBC, 2018, 2021). Such media stories are likely to have contributed to raised hopes and expectations amongst parents that a diagnosis would be found. Yet, there may be other critical factors at play that may influence the diagnostic journey and the trajectory of hope as proposed in our theory. These may include, amongst other things, whether parents have realistic expectations around diagnostic yield, the quality of pre- and post-test counseling, and the severity of the condition on the child's health and family functioning. These are areas for further exploration.

Hope has been identified as having an important psychological function in healthcare and recovery processes. Applied psychology research suggests that hope helps to combat demoralization (Frank & Frank, 1991). In their narrative literature review of empirical research on hope and illness, Wiles et al. talk about how hope is a common adaptive response and a coping mechanism in the face of what people may experience as the otherwise intolerable impact of a health crisis (Wiles et al., 2008). They also say that hope adapts over time and can be seen as two ends of a continuum: hope-as-expectation, where people perceive there to be a high probability of a desired outcome, and hope-as-want, where the outcome is a desired one but the perceived likelihood of this occurring is low. Our findings arguably reflect this viewpoint; hope and optimism are far stronger at the start of the parental journey, compared to after receipt of an NPF result when hope shifts to a more diminished form, suggesting that hope is modifiable and experienced in varying degrees. Similarly, Leite et al. in their study looking at narratives about hope for families in the context of pediatric chronic illness describe "waves of family hope," aligning with our concept of hope as dynamic and moving (as in Figure 1) (Leite et al., 2021; Skinner et al., 2018).

The role of the health professional in supporting hope has also been widely discussed in the literature and highlights the tension between health professionals encouraging hope but not raising false hopes (Eliott & Olver, 2002; Wiles et al., 2002). This position is thoughtfully reflected in Dana Knutzen's paper on genetic counseling through hope, where she describes her professional experience of having to "dance the fine line between igniting the flames of unrealistic hope and smothering the flames of what little hope may remain" (Knutzen, 2012). Our parents found it difficult to maintain hope when the child remained undiagnosed but held on to the notion that a diagnosis may be achievable in the future. Skinner et al. found that some parents who received a negative ES result transformed it into a sense that they had done everything they could for their child and, as in our findings, voiced optimism for the potential of ES to lead to a diagnosis in the future with advances in gene-disease associations (Skinner et al., 2018). These findings have important implications for counseling practice whereby clinicians could make a point of highlighting the ongoing developments taking place in genomics to maintain realistic hope and facilitate coping.

4.1 | Implications for counseling practice

Managing expectations and preparing parents for the range of possible outcomes at the time of offering GS is key. The process of consent for GS is the point at which the consenting clinician can explore

with parents their expectations for the outcomes of testing and provides an opportunity for an exploration of parents' hopes around a diagnosis. Tailored information-giving around diagnostic yield may be helpful in setting realistic expectations. Discussion could explore the importance of hope during the testing process including the potential for parents to feel loss of hope if a diagnosis is not found. Informing relatives about the "rollercoaster of emotions" they may experience throughout their GS journey (as reported by other parents going through a similar process) including how what they are hoping for may change over time may be a useful counseling practice. GCs could explore what parents are hoping for through undergoing the testing process as a way of ascertaining whether their hopes align with the chances of a genetic cause being found through the testing. This could also present an opportunity to explore with parents what outcomes they fear. This process could enable parents to develop a set of resources ready to draw upon in the event of an NPF result that could help them to manage their disappointment if it arises.

Consideration of the role hope plays at the time of returning results is also important. If parents receive an NPF result, for some, it may be a time of letting go of old hopes and taking up new ones – a process referred to as "hope refinement" (Larsen et al., 2005). One way of articulating this with parents may be to ask them a question such as: "In light of this new information we now have, what are you hoping for now?". It should be emphasized that genetics is a fast-moving field and that we are learning more each day about the role and function of various genes and the pathological effect. Therefore, it could be said that there is no such thing as "false hope" in the context of reaching a diagnosis. The role of hope as a coping mechanism should be considered. It may be helpful to include ways of promoting hope that focusses on healthcare (e.g. access to research, continued medical support despite not having a diagnosis), practical support (e.g. respite services, school support, support groups), and psychological wellbeing (e.g. ways of managing stress, psychological support, spirituality-based resources, etc.). Our findings also suggest that sharing NPF results with an explanation of how common an NPF type of outcome is may help parents to feel less isolated. Highlighting what *is* known about the child's condition, even without a diagnosis, is also likely to be beneficial and support parental coping, as is having a named point of contact within the genetics department as well as regular clinic appointments to monitor progress. The topic of reanalysis should also be addressed (including when this might occur). Signposting to external resources and patient organizations that may be helpful for parents in coping with an NPF, such as the support group SWAN UK. This could include alerting families to a recently developed e-book which was co-designed with and designed to support patients and families to understand their genomic test results, including those receiving a NPF result (Handra et al., 2022).

5 | STRENGTHS AND LIMITATIONS

A key strength of our study is that it included a relatively homogenous sample, that is, all participants had had prior genetic or genomic testing before their participation into the 100 kGP, all had been on a "diagnostic odyssey" for a number of years (from four to 15 years), and all but one indicated that their child's condition had a significant/very significant impact on their child's life. This adds to the strength of our suggested theory for this particular population group. Our participants were recruited through a patient organization, and their children had in most cases a condition that was considered "very significant." All had had previous experience of genetic or genomic testing. Other parents receiving a NPF result in other social contexts may have different experiences. Our suggested theory therefore needs to be tested amongst a more diverse sample of parents. Additionally, the population represented within this study was largely, though not exclusively, white British. Therefore, the participants are not representative of the wider population of patients affected by a rare undiagnosed condition. Participants from other backgrounds may have different experiences or views regarding receipt of an NPF from WGS. This study was also limited to including the perspectives of only mothers and the findings may therefore not be applicable to other parents. While the number of participants, nine, is small, each interview provided rich, in-depth data, and while we feel that we did reach thematic saturation, the small sample size is a potential limitation of the study. Further qualitative research may wish to consider different methodologies which may be more appropriate for asking different empirical questions of this and similar populations (Wainstein et al., 2023).

6 | CONCLUSION

This study has shown the dynamic nature, complexity, and importance of hope throughout the process of GS. In this study, we have followed the trajectory and changing nature of hope ignited by a new technology and dampened through an NPF result. Our findings have implications for how genetic healthcare professionals discuss GS with parents and families, both at pre-test counseling and results disclosure. Further research should test our suggested theory in other testing settings and/or social contexts (including with parents who have had no prior genetic/genomic testing before GS, with parents recruited directly through the NHS, and with parents whose child's condition is not considered to have such a significant impact). Future research could also consider families' experiences of hope across a broader timeframe, from when medical investigations begin to following receipt of an NPF including the longer-term implications of the NPF result. Research could also focus on fathers as well as participants from a wider range of ethnic backgrounds who may have differing experiences. Research to identify further ways of supporting parents who receive an NPF would also be useful.

AUTHOR CONTRIBUTIONS

Conceptualization: JG, CL. Methodology: JG, SAS, C L. Validation: JG, SAS, MH, MP, BS-S, CL. Formal Analysis: JG, CL. Investigation: JG. Data Curation: JG. Writing – Original Draft: JG. Writing – Review

& Editing: SAS, MH, MP, BS-S, CL. Visualization: JG, SAS, MH, MP, BS-S, CL. Supervision: CL, SAS. Project Administration: JG. Authors JG and CL confirm that they had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All of the authors gave final approval of this version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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CONFLICT OF INTEREST STATEMENT

Author Jana Gurasashvili declares she has no conflict of interest. Author Sergio A Silverio declares he has no conflict of interest. Author Melissa Hill declares she has no conflict of interest. Author Michelle Peter declares she has no conflict of interest. Author Bethany Stafford-Smith declares she has no conflict of interest. Author Celine Lewis declares she has no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are part of a common dataset. The datasets are not publicly available due to the sensitive nature of the interviews; however, they are available upon reasonable request from the corresponding author.

ETHICS STATEMENTS

Human Studies and Informed Consent: This study was approved by the Cardiff University School of Medicine Research Ethics Committee (September 2020; ref:- SMREC 20/70). All procedures followed were in accordance with the ethical standards of the British Psychological Society's Codes of Ethics and Conduct. Informed consent was obtained from all participants for being included in the study. All participants consented to their data being published as part of this study's analysis.

Animal Studies: No non-human animal studies were carried out by the authors for this article.

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