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Abstract

Purpose: Given the limited therapeutic options for most rare diseases diagnosed through genomic sequencing (GS) and the proportion of patients who remain undiagnosed even after GS, it is important to characterize a broader range of benefits and potential harms of GS from the perspectives of families with diverse sociodemographic characteristics.

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Conflicts of Interest
M.T.W. has ownership interest in Personalis Inc.

Ethics Declaration:
All study procedures were approved by the Stanford University School of Medicine Institutional Review Board. Informed consent was required and obtained from all participants.

Methods: We recruited parents of children enrolled in the Undiagnosed Diseases Network. Parents completed an in-depth interview, and we conducted a comparative content analysis of the data.

Results: Parents (n=30) were demographically diverse, with 43.3% identifying as Hispanic, 33.3% primarily Spanish-speaking, and widely variable household income and education. Parents reported minimal changes in their child's health status following GS but did report a range of other forms of perceived utility, including improvements in their child's healthcare management and access, in their own psychological well-being, and in disease-specific social connections and research opportunities. Parents who received a diagnosis more frequently perceived utility across all domains; however, disutility also was reported by both those with and without a diagnosis. Impacts depended on multiple mediating factors, including parents' underlying expectations and beliefs, family sociodemographic characteristics, individual disease characteristics, and prior healthcare access.

Conclusion: Our study suggests that the perceived utility of GS varies widely among parents and may depend on multiple individual, sociodemographic, and contextual factors that are relevant for pre- and post-GS counseling, for value assessment of GS, and for policymaking related to access to new genomic technologies.

Keywords

Rare Disease; Personal Utility; Perceived Utility; Genome Sequencing; Exome Sequencing; Pediatrics; Health Disparities

Introduction

Rare diseases collectively impact nearly 30 million individuals in the United States, two-thirds of whom are children (National Center for Advancing Translational Sciences, 2021). More than half of all children with rare diseases who undergo standard clinical evaluation and targeted genetic testing (single gene and panel based testing) remain without a genetic diagnosis (Shashi et al., 2014). However, recent advances in genomic sequencing (GS), including exome and genome sequencing, as well as other advanced sequencing technologies (e.g., RNA sequencing), may provide a diagnosis for up to 50 percent of patients who remain undiagnosed even after an extended diagnostic odyssey (Beaulieu et al., 2014; Sawyer et al., 2016; Splinter, Adams, et al., 2018). Given the rare and ultra-rare diagnoses typically provided by these tests, however, there is a need to understand the downstream utility of these tests beyond the diagnosis itself to inform patient care, value assessment, and policymaking related to GS.

Much has been written in recent years about the psychological impacts of receiving results from genetic and genomic testing (e.g., Luksic et al., 2020; Parens & Appelbaum, 2019; Rosell et al., 2016; Werner-Lin et al., 2018), and on the concept of perceived utility in genetics and genomics specifically (e.g., Bunnik et al., 2015; Grosse et al., 2009; Grosse & Rasmussen, 2020; Hayeems et al., 2021; Kohler, Turbitt, & Biesecker, 2017; Kohler, Turbitt, Lewis, et al., 2017; Lupo et al., 2016; Mollison et al., 2020; Roberts et al., 2018; Tutty et al., 2021). Measures of perceived utility (also referred to as "personal" or "patient-

oriented" utility) assess patients' subjective perceptions of both the health- and non-health related impacts of a particular health intervention (Bunnik et al., 2015; Hayeems et al., 2021; Kohler, Turbitt, & Biesecker, 2017). Scholars have increasingly called for a broader consideration of perceived utility, including utility that caregivers and other family members may derive from an individual patient's GS (Hayeems et al., 2021; Pollard et al., 2021; Prosser, 2018; Smith et al., 2021; Wittenberg & Prosser, 2016).

The extant literature suggests a range of elements of perceived utility for parents of children undergoing GS, even when the results do not change their child's health outcomes. Examples include reduced anxiety, absolution of feelings of guilt for having caused their child's disease, information to inform family planning, and the relief of ending the diagnostic odyssey, among others (Hayeems et al., 2021; Mollison et al., 2020; Tutty et al., 2021). Studies that have included the perspectives of parents who received a non-diagnostic result from GS for their child also suggest some perceived utility related to ruling out certain conditions, giving parents confidence that they have done everything they could do to find a diagnosis for their child, and allowing families to pause the diagnostic odyssey and focus primarily on symptom management (Mollison et al., 2020; Rosell et al., 2016). However, the existing literature on this topic is primarily descriptive, providing less insight into the factors that lead to more or less perceived utility – or even disutility in the form of either negative or no impacts – for patients and families (Hayeems et al., 2021).

Perhaps most critically, studies of the perceived utility of GS have primarily been conducted with non-Hispanic White parents and patients with high levels of education (e.g., Mollison et al., 2020; Roberts et al., 2018; Rosell et al., 2016; Tutty et al., 2021; Werner-Lin et al., 2018). Thus, although a growing body of research has explored the dimensions of perceived utility, the extent to which these findings are valid for diverse patients and families remains unclear. Sociodemographic factors including education level, income, immigration status, primary language, and cultural factors, as well as healthcare system factors related to racial bias and access to insurance, all have the potential to impact perceived utility of GS (Canedo et al., 2019; Hall et al., 2015; Peterson et al., 2018), making further research with diverse samples essential. A recent call to action for antiracist research in genetics and genomics stated the need for replicating studies conducted in samples that were not diverse in terms of race, ethnicity, education, or other sociodemographic characteristics (Brothers et al., 2021). As large clinical research efforts, such as the All of Us Research Program, seek to expand the diversity of patients receiving GS, it is critical to understand the perspectives of underrepresented patients and families, who have historically been excluded from genomics research, and who may experience the utility of GS differently (Mapes et al., 2020; Popejoy & Fullerton, 2016).

The data presented in this paper were collected as part of an in-depth qualitative study of parents' perceptions of the challenges, experiences, and outcomes of their child participating in the Undiagnosed Diseases Network (UDN) in a sample with diverse sociodemographic characteristics. The goals of the analysis reported here were to explore diverse parents' perceived utility and disutility of GS following an extended diagnostic odyssey, and to compare the perceptions of those who did and did not receive a diagnosis in a sample enriched for sociodemographic diversity.

Materials and Methods

Study Setting

We recruited parents of pediatric patients enrolled in the Stanford clinical site of the UDN, a research consortium developed to advance the science of genetic diagnosis of rare diseases through a case-based approach (Gahl et al., 2016; Reuter et al., 2018). Applicants to the UDN are evaluated for acceptance based on multiple criteria, including the presence of an undiagnosed condition despite thorough evaluation by a health care provider, the presence of at least one objective finding, and willingness to consent to, travel for, and participate in the required clinical and genetic workup (Ramoni et al., 2017). The UDN evaluates both pediatric and adult patients, and approximately 60% of participants are under the age of 18. Those accepted undergo a detailed clinical review and multispecialty evaluation, as well as exome and/or genome sequencing (or reanalysis of existing sequencing data) in most cases. Participants typically also receive additional research analyses of sequencing data and follow up testing of genomic variants (e.g., through RNA sequencing) and/or collaborative science for functional assays and animal modeling (Schoch et al., 2021). For example, 16 (39.0%) of 41 patients at the Stanford UDN site who received a genetic diagnosis received additional research testing to confirm the diagnosis (J. N. Kohler, personal communication, August 27, 2021). The UDN study is approved by a central institutional review board at the National Human Genome Research Institute (FWA00000014) and is registered at clinicaltrials.gov (NCT02450851) (Splinter, Hull, et al., 2018).

Recruitment

Following separate review and approval by the Stanford School of Medicine Institutional Review Board (FWA00000935), a clinical site coordinator provided contact information for parents of UDN participants who previously agreed to be contacted for future research. To ensure racial/ethnic diversity, we utilized quota sampling (Bernard, 2005), capping enrollment of non-Hispanic White parents at one-third of our target sample. For the remaining two-thirds of participants, we focused on recruitment of the two largest racial/ethnic minority groups represented at the study site – Asian American and Hispanic. We worked with the clinical site coordinator and bilingual researchers to recruit Spanish-speaking parents, the second most commonly spoken language among participants after English. Study staff contacted potential participants through phone and email. Individuals were eligible to participate if they were the parent or legal guardian of a current UDN participant and spoke either English or Spanish.

Data Collection

Enrolled participants completed a single in-depth, semi-structured interview conducted in either English or Spanish, lasting from 1 to 2 hours. The study team developed the interview guide through literature review on the topic and iterative pre-testing with parents of children with undiagnosed or rare diseases. The final interview guide included questions regarding the participant's background and sociodemographic characteristics, family structure, the diagnostic odyssey, and experiences before, during, and after GS. All interviews were audio-recorded and transcribed verbatim, translated from Spanish to English (when necessary), and de-identified for analysis.

Analysis

We analyzed interview transcripts using Dedoose (*Dedoose*, 2021). Three study team members with expertise in qualitative data analysis (MCH, JLY, HKT) led a comparative content analysis of the data, integrating both inductive and deductive approaches (Miles et al., 2014). The analytic team first iteratively reviewed the transcripts to define deductive codes designed to structure the data by broad content area (e.g., "healthcare experiences," "post-diagnosis," "family"). We then conducted repeated interrater reliability testing until the average pooled Cohen's kappa reached $\kappa>0.8$, indicating excellent agreement (Miles et al., 2014; Vries et al., 2008). We then applied the codebook to all transcripts while simultaneously generating "memos," a technique drawn from grounded theory (Glaser & Strauss, 2009), to catalogue and iteratively identify inductive themes that the team determined to be dominant in the data. Through this process, we also examined the relationships among themes and explored potential mediating factors driving similarities and differences in perceived utility and disutility between parents who did and did not receive a diagnosis for their child, and among parents with varying sociodemographic characteristics, including race/ethnicity, primarily language, education, and income.

Results

Participant Characteristics

Thirty parents of children enrolled in the UDN participated in this study, with only one parent participating per family. Seventeen (56.7%) had a child who was undiagnosed, including three with an emerging or candidate diagnosis that remained unconfirmed at the time of interview. The remaining 13 (43.3%) reported having received a confirmed diagnosis through the UDN. Parents were predominantly female (n=27, 90.0%), but were diverse in terms of income, education, primary language, and race/ethnicity, with the largest proportion of parents identifying as Hispanic (n=13, 43.3%). Ten parents (33.3%) completed their interview in Spanish. Across parent sociodemographic characteristics, those with diagnosed and undiagnosed children were generally balanced with, for example, similar rates of diagnosis among children of non-Hispanic White parent participants as among those of Hispanic parent participants (Table 1).

Types and Quality of Perceived Utility and Disutility

Only one of the 30 parents reported a positive impact on their child's health status or outcomes following GS. However, both parents of children who did and did not receive a diagnosis described other types of perceived utility, including: 1) impacts on their child's healthcare management and access; 2) impacts on the parents' own psychological or emotional well-being; and 3) impacts on social connections and research opportunities related to their child's condition. Within each of these categories, parents reported a range of positive, negative, and mixed impacts, and some reported no meaningful impacts (Table 2). We present examples within each category as described by parents of both diagnosed and undiagnosed children below. We then discuss mediating factors referenced in parents' narratives across the three categories.

Impacts on Child's Healthcare Management and Access—Parents reported a range of both positive and negative impacts on their child's healthcare management and access, including changes to clinical recommendations, insurance reimbursement, communication with healthcare providers, and qualification for therapeutic services. Sample quotes are provided in Table 3.

Diagnosed: Seven of the 13 parents with diagnosed children reported a positive impact on their child's healthcare management and access. For example, the parent of diagnosed child number 10 (D10) described how the diagnosis was key to identifying a critical specialist to monitor her child. In addition, she noted that finding a genetic cause of her child's condition resulted in her child's primary care provider taking her concerns more seriously. D14 was one of two parents who reported a medication change for his child following diagnosis, and he was the only parent in our sample who reported a change in a child's health status.

D27 was the only parent of a diagnosed child to report mixed positive and negative clinical impacts. Though her child's diagnosis did result in additional clinical recommendations, she also reported that her child lost access to therapeutic services because the result shifted her out of the diagnostic category that she had previously used to qualify for services. No parents reported solely negative impacts and the remaining five parents reported no changes in their child's clinical care or healthcare access, despite receiving a diagnosis. For example, D04 described how her child's physicians were aware but rarely mentioned the genetic diagnosis, as it did not seem to matter "in the grand scheme of things."

Undiagnosed: Thirteen parents reported no impacts on their child's healthcare management and access, such as the parent of undiagnosed child number 09 (U09). Two parents noted mixed impacts on their child's healthcare management and access. For example, U29 described how her child's lack of a diagnosis was not as important because she already had a persistent healthcare provider committed to meeting her child's needs. However, her husband also was concerned that the amount of blood taken for the evaluation would harm his child. Though this concern may not be consistent with current medical knowledge, from the parents' perspective, their child's participation in research was not without risk, and also had not yet resulted in a diagnosis.

Even without a diagnosis, two parents did note a positive impact on their child's healthcare management and access based on the UDN evaluation. For example, U13 described how her child was connected to multiple new specialists as part of the diagnostic workup conducted by the UDN. No parents of undiagnosed children reported solely negative impacts on their child's healthcare management or access.

Impacts on Parent Psychological and Emotional Well-being—Parents described a range of positive, negative, mixed, and neutral psychological impacts on their own well-being following return of GS results. Sample quotes are provided in Table 4.

Diagnosed: Four of the 13 parents described solely positive psychological or emotional impacts of GS for themselves. For example, D28 described how she found it easier to show affection for her child, who had significant behavioral problems, once she understood the

underlying cause of his disease, and D22 described the joy she felt when her daughter received a diagnosis, as she was able to see pictures of other children with her daughter's condition and recognize similarities in their morphology. Eight parents described a mix of positive and negative psychological impacts. For example, D27 described relief that her child finally had a diagnosis, but also sadness, requiring time to process the meaning and gravity of the diagnosis itself, and its implications for her child's health. D06 provided the only example of a parent of a diagnosed child who did not feel particularly impacted by the results of GS, for reasons discussed further in the section on mediating factors below. No parents of diagnosed children described an entirely negative psychological or emotional impact following diagnosis.

Undiagnosed: Four parents of undiagnosed children described primarily negative emotional impacts, such as U09, who described how she felt so desperate for a diagnosis that she was prepared to accept even a grave diagnosis in order to have an answer. U12 also described her sadness, which stemmed from her children's decisions not to have their own children because they carried an unidentified genetic disease. Four parents (e.g., U08) described more neutral or minimal reactions when asked how they responded to receiving a non-diagnostic result.

Despite a non-diagnostic result, 3 of the 17 parents did describe positive impacts deriving primarily from their perception of the value of receiving GS in the context of research. For example, U03 described positive psychological impacts because he felt his child was contributing to science and the broader social good through participating in research, and U23 noted how she felt reassured that science would continue to progress. Six parents described mixed psychological impacts related to receiving GS in the context of the research. For example, U20 described how, although she was frustrated, she also was happy because she had found someone who seemed truly interested in finding a diagnosis for her child. Similarly, while U07 was disappointed that her child was not diagnosed, she also was reassured that she could continue to check in with the UDN in the future.

Impacts on Social Connections and Research Opportunities—Parents also described a range of impacts on their social connections and research opportunities related to their child's disease. Sample quotes are provided in Table 5.

Diagnosed: Five of the 13 parents reported positive impacts in this domain. For example, D01 described finding comfort in connecting with parents of children with the same diagnosis and being able to learn about their child's potential trajectory. D10 described how she felt families with the same condition understood her circumstances better than even her close friends. For some, these social connections also led to additional research opportunities. For example, D17 was able to access a disease registry for her child, and D14 leveraged social connections with other families to drive research on his children's ultra-rare disease. Two parents who sought social connection following their child's diagnosis described more mixed impacts, such as D06, who found only a small group of families with children with varying phenotypes. While no parents reported a negative impact in this domain, six parents did report that they had no meaningful social or research connections,

either because they could not find connections (e.g., D04) or because they had not sought them out (e.g., D19).

Undiagnosed: Even without a confirmed diagnosis, two of the 17 parents reported positive impacts on their social connections. U15 described being able to connect with other families in the UDN who were also undiagnosed, while U18 sought connection using a candidate diagnosis (that was not yet confirmed) to connect with other families. No parents of undiagnosed children reported negative impacts in this domain because of GS. More commonly, parents of undiagnosed children reported no impact either because they had already established connections with other families based on their child's symptoms alone (e.g., U16) or because they did not wish to seek social connections based on their child's condition (e.g., U23).

Mediating Factors Shaping Perceived Utility and Disutility

Through their narratives, parents also suggested a number of potential mediating factors that influenced their perceived utility of receiving GS for their child. These included: 1) characteristics of their child's disease or diagnosis; 2) the parent's underlying expectations and beliefs; 3) sociodemographic characteristics of the family; and 4) healthcare access and coordination prior to GS.

Child's Disease Characteristics—First, parents described how the specific characteristics of the child's disease and (for those who received one) diagnosis mediated the perceived utility of GS. For parents whose children did receive a diagnosis, the impacts on their children's healthcare were mediated by the type of diagnosis itself, and whether it was an existing disease versus a newly identified genetic disease. For example, for D14, diagnosis of a known rare disease led immediately to therapy, while D06, whose child was diagnosed with a new disease, experienced no impacts on clinical care for her child (Table 3).

For parents whose children remained undiagnosed after GS, the psychological impacts of this result were mediated by the medical stability of the child. For example, UD25 described feeling desperate for an answer because her child's health was deteriorating, while UD07, whose child was relatively medically stable, experienced a more neutral psychological impact (Table 4). Indeed, U12 explicitly stated that the main factor that has helped her navigate her children being undiagnosed was that, "my kids haven't gotten worse. Otherwise, I think it would be a whole different story."

Disease characteristics also impacted the psychological reactions to diagnosis. For example, for D04, the relief she experienced from the diagnosis was related specifically to the fact that it was caused by a de novo mutation, and therefore would be unlikely to affect her other children (Table 4). On the other hand, the poor prognosis associated with certain diagnoses led to particularly challenging psychological reactions for some (e.g., D14, Table 4).

Further, the specific diagnosis also impacted the extent to which parents were able to connect with others with a known condition. For example, D17, whose child received a diagnosis of a relatively common rare disease, was able to connect with many other parents,

an existing foundation, and ongoing research opportunities, while D04 was not able to connect with anyone with her child's newly identified genetic disease, despite her desire to do so (Table 5).

Parents' Underlying Expectations and Beliefs—Parents' underlying expectations for the outcomes of testing and beliefs about the cause of their child's disease also mediated the psychological impacts of GS. For example, D19 noted that the relief he and his wife felt from receiving a genetic diagnosis stemmed directly from his underlying belief that they had somehow caused their child's illness (Table 4). D17 reported a bittersweet reaction to her child's diagnosis specifically because of her underlying hope for a treatable diagnosis, while D06 reported that her lack of expectations for finding a treatable diagnosis resulted in a less emotional reaction to the results of GS (Table 4). Low expectations also seemed to emotionally protect those who did not receive a diagnosis, such as U08, from what could otherwise have been deep disappointment (Table 4).

Sociodemographic Characteristics of the Family—As summarized in Table 1, the likelihood of diagnosis through GS in our sample does not appear to vary substantially based on sociodemographic characteristics including race/ethnicity, income, education, or primary language. However, parents' narratives do suggest ways in which sociodemographic factors may mediate the downstream utility of GS. Specifically, it is notable that none of the parents in our sample who spoke Spanish as their primary language (n=10) were among the nine parents who described either positive or mixed impacts on their social connections following GS, nor were they among the seven parents who reported that they were already connected to other groups, or those who had attempted to connect and found no relevant groups available (Table 2, Table 5). In addition, the three parents who described identifying research connections specifically related to their child's diagnosis all spoke English as their primary language, reported having a college education or above, and identified as White (n=2), or Asian-American (n=1, Table 5).

Parent narratives also highlighted immigration status as a potential mediator of the perceived utility of GS. As U29 stated, in describing the barriers she faced in caring for her son:

> Since he doesn't have papers, you could say, or insurance, they can't run some test for him or he doesn't qualify to receive certain aid. Or if there's a program that can help him, that can take care of him for me, just the care of him having a person trained for those types of things, well they don't have them.
>
> (Mother, Hispanic)

Though U29 was able to receive GS for her son through the UDN, he may be unable to access additional services, even with a diagnosis, due to his immigration status.

Healthcare Access and Coordination Prior to GS—Existing healthcare access and coordination issues prior to sequencing also mediated the impacts of GS. For example, D05, who previously struggled with insurance reimbursement before GS, reported better access to services after receiving a diagnosis. On the other hand, for D01, receiving a diagnosis through GS did not change her child's healthcare access because her child already had

access to services prior to diagnosis. Further, D27 described how her child actually lost her eligibility for services following GS due to the type of diagnosis she received (Table 3). Her case highlights the ways in which clinical care and coordination both before and after GS can mediate the utility of GS.

This factor also arose for parents of undiagnosed patients. For U29, for example, remaining undiagnosed was not as consequential because she had a dedicated healthcare provider for her child. On the other hand, U02 specifically noted that the challenges she faced in accessing healthcare for her child would persist without a diagnosis (Table 3).

Discussion

Our findings indicate that even when parents did not perceive health improvements for their children following GS, both parents of diagnosed and undiagnosed children did perceive GS as having utility in terms of positive impacts on parents' psychological well-being, on their child's healthcare management, and through facilitating disease-specific social connections and research opportunities. Some parents did perceive disutility of GS, either as a lack of impacts on themselves or their child across domains or, in a small number of cases, as negative impacts on their own psychological well-being or their child's healthcare access. Overall, parents who received a diagnosis more frequently reported positive impacts across all domains of perceived utility, though impacts for all parents depended on multiple individual and contextual factors, including characteristics of their child's disease, the parent's underlying expectations of GS, the sociodemographic characteristics of the family, and the quality of the child's healthcare access and coordination prior to receiving GS.

Our results reflect and expand on the current literature on the scope of perceived utility of genetics and genomics. Parents in our study who described the psychological impacts of GS referenced categories similar to those captured by Kohler and colleagues' categories of "value of information" and "knowledge of the condition" (Kohler, Turbitt, & Biesecker, 2017; Kohler, Turbitt, Lewis, et al., 2017). However, our domains include not only the value of the information provided, but also the perceived psychological benefits to the parents themselves. Our findings also resonate with aspects of Kohler's "social" domain, but their framework did not include parents' focus on the value of connecting with parents of children with the same condition for information, social support, and further research opportunities, which has been identified in other studies as an important benefit for patients and families managing complex health conditions (Deuitch et al., 2021; Mollison et al., 2020; Roberts et al., 2018).

Further, while Kohler's definition of personal utility explicitly focused only on non-health related elements of perceived utility (Kohler, Turbitt, & Biesecker, 2017), our analysis indicates that healthcare management and access is an important area of perceived utility for parents. A 2021 review of perceived utility by Hayeems and colleagues did include aspects of "healthcare management" as a component of what they refer to as "patient-oriented" utility (Hayeems et al., 2021). However, their definition of this domain is focused on "clinician-directed" activities, and does not include impacts on parents' efforts to manage their child's disease, as described in our findings.

Our study suggests that commonly used definitions of perceived utility may require expansion to ensure that all dimensions of parents' perceived utility and potential disutility are included in measures of the perceived utility of GS, both for those whose children do and do not receive a diagnosis. The inclusion of the psychological and social impacts of GS on the parents themselves has received renewed attention in decision sciences and health economics, as scholars have increasingly recognized "family spillover" as an important component of overall utility to include in value assessments of new genomic technologies (Lavelle et al., 2019; Smith et al., 2021; Wittenberg et al., 2019). However, in order to include such family spillover in value assessment, measures of perceived utility must first capture the full range of potential impacts on families. Our study indicates multiple dimensions of perceived utility that would need to be included in order to capture the full range of benefits of GS for both patients and families.

Our exploration of mediating factors also provides insights for genetic counselors and other clinicians working directly with patients and families. Our findings illustrate the various ways in which characteristics of a child's disease, parent's underlying expectations of GS, sociodemographic characteristics of the family, and the quality of the child's healthcare access and coordination prior to receiving GS may shape a parent's response to the return of GS results, as well as the potential benefits they ultimately derive from these results. Our findings are consistent with a recent study suggesting that pre-test genetic counseling should emphasize the low likelihood of actionable results while recognizing that specific characteristics of a parent and their child may be primary drivers of expectations (Donohue et al., 2021; Roberts et al., 2018). Based on our findings, genetic counselors may wish to focus not only on managing parents' expectations of finding a result, but also the full range of potential prognoses that may be identified, and the low likelihood that treatment will be readily available even if a diagnosis is identified.

A number of parents also struggled with healthcare management and access for their child both before and after receiving GS. Healthcare access, including insurance reimbursement for testing and other services, including medications, is a widely-recognized challenge across the rare disease community (Shire, 2013). Our findings suggest that genetic counselors may wish to assess for challenges with current access in pre-test counseling in order to advise parents and set expectations appropriately. In addition, although only one parent in our sample reported a negative impact on a child's access to care (loss of eligibility for therapeutic services) following diagnosis, this case highlights the need for robust follow-up care for patients and families after GS in order to ensure that a diagnosis does not cause unanticipated harms.

Finally, our results suggest the potential for intersectionality between the challenges related to rare disease and those related to the family's sociodemographic characteristics, which has not been well characterized in the context of GS. Although we found generally equivalent rates of diagnosis across sociodemographic characteristics, in our small sample, our findings suggest that access to diagnosis alone may not ensure equitable access of the potential downstream benefits of GS. For parents of children who face barriers to healthcare access due to challenges such as immigration status, for example, having a diagnosis may not facilitate improved healthcare access and coordination as it could for families without such

challenges. Understanding the ways in which sociodemographic factors may shape the impacts of GS can help to guide both clinical care and policy designed to increase equitable access not only to GS, but also to its range of potential downstream benefits.

Our findings also suggest that parents with limited English proficiency may be less likely to make social and research connections following GS. While this may be by choice in some cases, prior research suggests that rare disease social media groups lack diversity in terms of race/ethnicity and language of communication (Miller et al., 2021). Given that these types of social connections may be one of the core benefits experienced by parents and patients following diagnosis of an ultra-rare disease with no available treatment, we need to consider whether families are able to equitably access all potential benefits from GS. However, further research is needed to disentangle the potential contributors of race/ethnicity, education, immigration status, primary language, and other sociodemographic factors in shaping the potential downstream benefits of GS for diverse patients and families.

Limitations

This study has several limitations. First, our participants' children received GS in the context of research. The research process of the UDN includes detailed multidisciplinary phenotyping along with research analysis of GS and additional follow-up testing (e.g., RNA sequencing). These steps can contribute to both diagnostic yield and the family's perceptions of the experience, the impacts of which are not easily disentangled. Thus, aspects of parents' perceptions of utility in this sample, and particularly those related to UDN participation overall, may differ from those whose children receive GS in a clinical setting. However, given that research will likely continue to play a central role in diagnosis of rare and ultra-rare disease, understanding the utility of receiving GS specifically in a research context remains broadly relevant in this population.

Second, though the diversity of our sample may increase generalizability of our findings, our sample is still small and is lacking representation from many racial and ethnic groups (for example, Black patients and families) who are underrepresented among patients receiving GS both within and outside of the UDN (Popejoy & Fullerton, 2016; Splinter, Adams, et al., 2018). Our sample is also predominantly female and provides only three fathers' perspectives. Third, our findings are based on retrospective accounts from parents whose children received GS in different timeframes. The design of this study was exploratory, and our findings warrant further investigation using prospective methods in other settings in which GS is used for diagnosis of rare diseases in children.

Conclusion

The results of our study indicate that even when parents do not perceive health improvements for their child following GS, both parents of those who do and do not receive a diagnosis may experience impacts on their own psychological well-being, their child's healthcare management, and disease-specific social connections and research opportunities. Parents who received a diagnosis were more likely to report positive impacts across all domains, though impacts on both groups depended on individual and contextual factors,

including characteristics of their child's disease, the parent's underlying expectations and beliefs, the sociodemographic characteristics of the family, and the quality the child's clinical care and coordination prior to receiving GS.

A better understanding of these and other potential factors mediating the impacts of GS may help to inform the genetic counseling process and the follow-up care needed following return of results. These findings also can be used to expand and better interpret patient-reported outcome measures designed to assess patient and parent perspectives on the utility of GS for diagnosis of rare diseases for incorporation in value assessments to inform policymaking. As GS increasingly moves into routine clinical care, it will be essential to incorporate the perspectives of diverse patients and families in research on the range of potential downstream impacts of these new genomic technologies.

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Data Availability:

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Table 1:

Respondent Characteristics by Child's Diagnostic Status

	Diagnosed n (% in row)	Undiagnosed[1] n (% in row)	Total n (% in column)
Gender			
Female	11 (40.7%)	16 (59.3%)	27 (90.0%)
Male	2 (66.7%)	1 (33.3%)	3 (10.0%)
Race/Ethnicity			
Hispanic (any race)	6 (46.2%)	7 (53.8%)	13 (43.3%)
White (non-Hispanic)	5 (45.5%)	6 (54.5%)	11 (36.6%)
Asian-American (non-Hispanic)	1 (25.0%)	3 (75.0%)	4 (13.3%)
More than one race/ethnicity	1 (50.0%)	1 (50.0%)	2 (6.6%)
Household Income			
$50,000 or less	2 (28.6%)	5 (71.4%)	7 (23.3%)
More than $50,000 to $100,000	3 (42.9%)	4 (57.1%)	7 (23.3%)
More than $100,000 to $150,000	5 (55.6%)	4 (44.4%)	9 (30.0%)
Greater than $150,000	3 (42.9%)	4 (57.1%)	7 (23.3%)
Education			
Primary school or less	1 (50.0%)	1 (50.0%)	2 (6.6%)
Some high school	2 (40.0%)	3 (60.0%)	5 (16.7%)
High school degree or GED	1 (25.0%)	3 (75.0%)	4 (13.3%)
Some college or associates degree	2 (66.7%)	1 (33.3%)	3 (10.0%)
College degree	4 (57.1%)	3 (42.9%)	7 (23.3%)
Advanced coursework or degree	3 (33.3%)	6 (66.7%)	9 (30.0%)
Primary Language			
English	8 (40.0%)	12 (60.0%)	20 (66.6%)
Spanish	5 (50.0%)	5 (50.0%)	10 (33.3%)
Number of UDN Children			
One	9 (39.1%)	14 (60.9%)	23 (76.7%)
Two	4 (66.7%)	2 (33.3%)	6 (20.0%)

Am J Med Genet A. Author manuscript; available in PMC 2023 April 01.

	Diagnosed n (% in row)	Undiagnosed[1] n (% in row)	Total n (% in column)
Three	0 (0.0%)	1 (100%)	1 (3.3%)
Total All Parent Participants	13 (43.3%)	17 (56.7%)	**30 (100%)**

[1] Includes three participant with candidate or emerging diagnoses that were not confirmed at the time of interview.

Table 2:

Types and Quality of Perceived Utility and Disutility

	Diagnosed (n=13)	Undiagnosed (n=17)	All (n=30)
Health Status or Outcomes			
Positive	1 (7.7%)	0 (0.0%)	1 (3.3%)
No Impacts	12 (92.3%)	17 (100%)	29 (96.7%)
Healthcare Management and Access			
Positive	7 (53.8%)	2 (11.8%)	9 (30.0%)
Mixed (both positive and negative)	1 (7.7%)	2 (11.8%)	3 (10.0%)
Negative	0	0	0
No Impact	5 (38.5%)	13 (76.5%)	18 (60.0%)
Psychological or Emotional Well-Being			
Positive	4 (30.8%)	3 (17.6%)	7 (23.3%)
Mixed (both positive and negative)	8 (61.5%)	6 (35.3%)	14 (46.7%)
Negative	0	4 (23.5%)	4 (13.3%)
No Impact	1 (7.7%)	4 (23.5%)	5 (16.7%)
Social Connections and Research Opportunities			
Positive	5 (38.5%)	2 (11.8%)	7 (23.3%)
Mixed (both positive and negative)	2 (15.4%)	0	2 (6.7%)
Negative	0	0	0
No Impact	6 (46.1%)	15 (88.2%)	20 (70.0%)
Not attempted	*5*	*9*	*1*
Not available	*1*	*2*	*3*
Already connected	*0*	*4*	*4*

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Table 3:

Impacts on Child's Healthcare Management and Access

	Diagnosed	Undiagnosed
Positive Impacts	D10: Had we not gotten the diagnosis and **had she not been referred to Cardiology, we would be dealing with a much more fatal condition…** I feel like the biggest change was the relationship between us and like her general practitioner…. **I felt like they finally took my concerns more ser…like I was no longer that worried first-time mom.** (Mother, White) D14: I'd say that's a good thing to get the diagnosis because we added**, we tweaked their supplement regimen.** We had started a, you know, [mitochondrial] cocktail of sorts…**I would say we did see a difference, you know, that did at least initially seem to help them**…. **maybe it's just a placebo**, maybe it's just like the fact that you're…you have control over this, you think you're doing something. (Father, White) D05: It feels like it [the diagnosis] comes up … definitely with **[California Children's Services]…for getting a wheelchair or whatever… justification stuff.** (Mother, White)	U13: [The UDN] was instrumental in **helping us have a road map, so [they] connected us with several physicians** at [the hospital] so we went and saw all like different specialties. (Mother, Asian)
Mixed Impacts	D27: They told me what tests they had to do with [my children] as follow-up with their doctors. Like, for example, **they asked that they do an ultrasound with [my child] every three months… Because of her diagnosis…she didn't qualify to be in [California Children's Services] anymore. Because it wasn't a cerebral diagnosis** or anything like that, something in the brain. (Mother, Hispanic)	U29: The thing is that we come from a culture where we don't start thinking about how "yes, it is a lot of blood, but your body will replace it immediately" …in [my husband's] mind it was no, **that's not going to come back, now you aren't going to feel well, you're always going to feel ill.** /// Thanks to God **I've had a doctor who is very persistent, very stubborn, you could say. She's done everything possible**. (Mother, Hispanic)
No Impacts	D04: I think even the doctors here…they still keep calling it MS or, like or the general term like neurodegenerative disorder… sometimes they do refer, oh, it's like this certain gene mutation…but it's rare that they even bring it up…Yeah. **I don't think it matters in the grand scheme of things what exactly it is.** (Mother, Hispanic) D06: I'm glad that we found something because it's just…it's frustrating to feel like there's just no reason. Not that it gives us any kind of reason really, **and it doesn't give us a plan of action, and it doesn't give us any change, really, in anything honestly.** (Mother, More than One Race/Ethnicity) D01: E**ven without the [GENE] diagnosis she still would have [Medi-Cal]** …with the other stuff happening with her, you know, the delay and stuff. (Mother, Asian)	U09: I: What information exactly did you receive from the UDN about the results of the test? R: **I received one phone call…That was pretty much it.** (Mother, White) U02: Because I think only diagnosis we have at this point proper is rheumatoid arthritis. **And everything that they have to treat for the same things they had to use that to get approval for the medications.** Those are very expensive medications, biologics, that we have tried for her. **So it has put challenge because we don't have an answer. (Mother, Asian)**

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Table 4:

Impacts on Parent Psychological and Emotional Well-being

	Diagnosed	Undiagnosed
Positive Impacts	D28: I: Knowing that your son has a diagnosis, how has that changed how you see your son? P: **I have more affection with him. I try to take care of him more**. (Mother, Hispanic) D22: Last November **when I finally received her diagnosis…you can't imagine what joy she gives me**. Because I see her… when I saw one of the photographs they have, I saw, imagined "babies" and I can tell you "Look this is my C when she was that age." The hands, the little feet, **there are many similarities that to me another window when I could finally have that information and to give thanks.** (Mother, Hispanic) D19: We had the cry over [it], but the rest was a relief that, you know, **we both wondered did we do something wrong**, you know, especially [my wife], so it was such a burden lifted.(Father, White) D04: I was like super relieved because, again, like **my biggest fear was that our other children like maybe when they were older were going to all of a sudden stop talking or stop walking** or…so like they gave me peace of mind that you know what, our kids are going to be healthy…. I think that was like the biggest because **I thought like what if like our grandchildren are going to be born like this**. (Mother, Hispanic)	U03: We have a team that's really solid and we…like **the whole time we thought about the UDN is like there's a possibility of more information, that's great, but, you know, like it's more for like the documentation and like research** and, you know, maybe helping somebody in the future…I would like to think that our stuff with [our daughter] is going to make it to where, you know, there might be more out there for another kid that has stuff like this. I: Yeah. Definitely. **So in a way, like the helping other people, learning what we can, that really makes you all feel good and feel optimistic?** **R: It really does**. (Father, Hispanic) U23: Either way there will be another opportunity. **Science grows science**…maybe one day they find something for my son…. **For me nothing is useless because I am fighting for my son's illness** and give him at best a better quality of life, for me it's good…for me is not wasting time and it's also not a bad thing. (Mother, Hispanic)
Mixed Impacts	D27: What can I say? It's really difficult. We feel relieved. We feel relieved with D, because for D we said: "Okay, they found something, they found a diagnosis." But it was sad. **We were content hearing the news, on one side, because we had found something, they had found the diagnosis, but we were sad because of the situation**. **And it was a situation that we took days to take in**, the situation, what it was, when the doctor explained it to us. (Mother, Hispanic) D17: **Well, I always had this hope that it was just going to be like something so simple**, and they're going to figure it out, and it's going to be a nutritional deficiency and there's going to be a simple vitamin, you know, [laughter] that he takes daily… **So it was bittersweet because we were happy to know what it is because that provides the opportunity for clinical studies** and obviously getting involved in the organizations that specifically research this gene, but **then at the same time it's like the hope for it just to be something simple was gone**. (Mother, White) D14: You know, **there's sadness because it's like, okay, yeah, you can turn the corner, but again, you've got this thing that's not going to get better. It's not…it's probably not going to stay the same and there's going to be, you know, more challenges that lay ahead base on what we know at this point**, or what we knew at the time, because you know, again, that neurodegenerative condition. (Father, White)	U20: Well, **I was a little frustrated because I expected them to find the answer** to of what they too were thinking…. . Ah what can tell you then, my favorite part was when **I saw that the doctor was sincerely interested.** Yes, that's what I have been pleased with… that they are still working on it. (Mother, Hispanic) U07: I think **we all were sort of bummed** like, eh, you're not getting any additional answers… But you know, we understood that all along and that…**at least, we got a pathway for checking in.** (Mother, White)
Negative Impacts		U09: Honestly as awful as it is to think your kid might have something life-threatening or whatever, **I just wanted an answer. So it was disappointing. I just wanted a name**, so that I could then work [from] there. (Mother, White) U12: What's unfortunate to hear is them say well I don't want to have children. R: So that's **the kind of sad part is they already know like, well, since they know they have, you know, they're carriers for something and then they have something that they don't know what it's called** – there's not a name to what they have…So it's been kind of sad to see that. (Mother, Hispanic) U25: I, to be honest, feel really desp… They haven't given me an answer, a diagnosis…**I feel desperate. [the researchers] should put themselves in the parents' shoes**, that we're desperate for them to find a solution for our children's illnesses. (Mother, Hispanic)
No Impacts	D06: The significance was just kind of, I don't know, I had stopped thinking that we could figure something out for her at that point. **I kind of realized at some point**	U08: Pretty well…I knew going into this **there was slim chance of finding an actual diagnosis.** (Mother, Hispanic)

	Diagnosed	Undiagnosed
	that we were just going to get some letters and numbers and that they probably wouldn't lead to anything that would cure her seizures. (Mother, More than One Race/Ethnicity)	

Table 5:

Impacts on Social Connections and Research Opportunities

	Diagnosed	Undiagnosed
Positive Impact	D01: One of the biggest plus items is finding a group of other families with the same gene and **understanding better like where they're at, where we will be at – or could be at.** (Mother, Asian) D10: I've found quite a bit of support on Facebook, whether it's through groups that are specific for her conditions, or …a [disease category] group, there's a group for [gene mutation]… **I almost feel like they understand us maybe even a little better than our friends do because they're kind of on that side where they've kind of gone through similar things, too**, so we have turned to Facebook quite a bit. (Mother, White) D14: I went ahead and formed a foundation that we're…you know, two years later **we're just like getting off the ground and we hope to have the first meeting of a small group of researchers** that are…that hopefully will help decide on a research agenda to develop treatments for [disease]. (Father, White) D17: **Online through a Facebook group we've become more involved in fundraising and stuff**…. [**the] foundation does have an international registry and so I immediately got him registered** on there since we knew his mutation, and they follow up on any sort of clinical trials and studies and stuff. (Mother, White)	U15: So **the UDN Facebook group, yes, that is one that my husband actually found before…when…I think it was during the application**, it was playing that waiting game when, you know, waiting on that application to be approved or denied. **Kind of wanted to feel out what that process would look like with the UDN.** (Mother, White) U18: There is like a Facebook group with [condition] that's pretty large, although we haven't said she's [condition] because **her genetic test didn't come back 100% positive. It doesn't have to for her to have it, though**. But we connect with them. (Mother, White)
Mixed Impacts	D06: **There's like a Facebook group, and there are like four people on there, you know. But they have such different things going on**. That's the problem. Completely different. Some of them don't even have seizures, you know, like two families have – it looks more like autism…sometimes **I relate so much more to the, you know, just the CP group** – the cerebral palsy group – because I'm like, oh yeah, brain stuff, you know, and G-tubes. (Mother, More than One Race/Ethnicity)	
No Impacts	D04: That would be nice to see if like…because what they told us when we had our testing **there was one case of a gentleman like in Morocco that was 25** – I'd like to know if he's still alive to see like how long my kids are going to live. (Mother, Hispanic) D19: And have you all connected with any other patients who have this diagnosis – the 15, you know, or the other 14, I guess? **R: Yeah, we have not. No, we have not.** (Father, White)	U16: I am on a few Facebook sites. I don't necessarily… I'm not a big poster on those things, but **I have gotten a lot of knowledg**e, and I do know if I was to need…you know, I have had questions – even about the UN and stuff and I've went on there. **I think one of my favorite ones is my hypotonia awareness site because hypotonia seems to be a symptom for a lot of children,** you know, and so I don't know, that's been helpful because it's been a lot of different situations because of the hypotonia. (Mother, White) U23: No, I also don't want to be sent a list of people who have the same illness as my son because **I don't want to look at advanced cases and I don't want to watch how my child will die**. I don't want to look at that, I'd rather stay away from those groups. (Mother, Hispanic)