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ORIGINAL ARTICLE

Hope, but never expect? Comparing parents' pre- and post-disclosure attitudes toward return of results from diagnostic exome sequencing for their child

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Abstract

Background: Counseling for whole-exome sequencing (WES) could benefit from aligning parents' pre- and post-disclosure attitudes. A few studies have qualitatively compared parents' pre- and post-disclosure attitudes toward receiving WES results for their child in a diagnostic setting. This study explored these attitudes in the context of children with a developmental delay.

Methods: Semi-structured interviews were conducted with parents ($n = 27$) of 16 children undergoing diagnostic WES in trio-analysis, both before and after receiving results.

Results: Three key insights emerged. First, the distinction between hoping and expecting was relevant for shaping parents' experiences with receiving results related to the primary indication. Second, parents of young children whose development of autonomous capacities was uncertain sometimes found themselves in a situation resembling a Catch-22 when confronted with decisions about unsolicited findings (UFs): an important reason for consenting to WES was to gain a better picture of how the child might develop, but in order to make responsible choices about UFs, some ideas of their child's development is needed. Third, default opt-ins and opt-outs helped parents fathom new kinds of considerations for accepting or declining UFs in different categories, thereby aiding decision-making.

Conclusion: Results from this study are relevant for counseling and policy development.

KEYWORDS

children, ethics, genomic sequencing, return of results, unsolicited findings

Nine Knoers and Annelien L. Bredenoord are joint last authors.

1 | INTRODUCTION

Massively parallel sequencing techniques, such as whole-exome and whole-genome sequencing (WES/WGS), that map vast parts of persons' DNA all at once, are increasingly being employed in the clinic to clarify medical conditions with a suspected genetic cause. WES provides between 25% and 50% of clinically tested individuals with a definitive diagnosis (Nurchis et al., 2023). While this is a considerable number, some individuals receive no diagnosis or they receive results that are unclear to interpret—so-called variants of unclear significance (VUSs)—due to limited evidence regarding pathogenicity of the variant. While the levels of evidence can vary and thus the degree of uncertainty regarding a VUS, new scientific insights may allow for a more precise interpretation of whether the variant in question is (likely/unlikely) benign or pathogenic.

In addition to results related to the diagnostic aim, WES/WGS may also give way to unsolicited findings (UFs): variants unrelated to the clinical question for which sequencing was performed, but that may be relevant to the health of the child, parents, and family members due to their (likely) pathogenicity (Berg et al., 2011; Van der Schoot et al., 2022). UFs encompass a broad range of genetic predispositions for developing or being a carrier for health conditions with varying degrees of severity, ages of onset, and medical (in)actionability.

To date, the body of the literature is still limited on how parents and patients react to the results that WES may produce and the specific ways in which they integrate them into their lives and in care for their child. This of course depends on what results or combination of results is found (e.g., no diagnosis with UFs or VUS regarding diagnosis with no UFs). As far as results related to the diagnostic aim are concerned, we know that parents' reasons for consenting to diagnostic WES for their child can vary and that these reasons seem to depend on their attitudes toward prospective results. After return of results, previous studies have shown both positive and negative parental attitudes, depending on which results were disclosed (diagnosis, VUS, negative result related to the diagnostic aim) (Chassagne et al., 2019; Mollison et al., 2020; Skinner et al., 2018; Strande & Berg, 2016; Taber et al., 2015).

As far as UFs are concerned, much of the ethical debate focuses on how return of results ought to be structured and what the conditions are for structuring them. These questions become especially salient when children are involved, since in such cases parents must offer their proxy consent for the child and there can be competing interests involved between the child, parents, and/or family members in what type of information ought to be returned or withheld. An important question in this context pertains to what we should take as a moral starting point: the autonomy of parents to decide for their child, or must we also acknowledge the child's future autonomous decision-making capacities as morally relevant when formulating such policies, and if so, to what extent? (Bredenoord et al., 2013, 2014; Dondorp et al., 2021; Tibben et al., 2021) In order to answer such questions, we need to know what context-related factors and considerations are at play in decisions about (non-)disclosure of UFs in children.

To date, only a limited amount of qualitative empirical studies have investigated how parents' attitudes and/or reasoning toward receiving WES results compare before and after disclosure of results (Liang et al., 2022; Peter et al., 2022; Robinson et al., 2019; Schwartz et al., 2022). Gaining insight into potential congruencies and discrepancies in these attitudes and reasoning that may appear in practice is both relevant for counseling and policy development. Moreover, when contemplating whether fluctuations exist in parents' reasoning, it is also pertinent to consider the whole range of findings that WES may reveal (i.e., both results related to the primary indication (diagnosis, VUS, negative result) as well as various types of UFs), since the same types of considerations can be at play for favoring or declining disclosure of UFs and for receiving a diagnosis, as our previous research has indicated (Cornelis et al., 2016).

In the study described here, we examined and compared parents' attitudes and reasoning before and after disclosure of WES results.

2 | MATERIALS AND METHODS

2.1 | Ethical compliance

The study was approved by the University Medical Center Utrecht's (UMCU) Medical Research Ethics Committee prior to the commencement of research.

2.2 | Design

In the Netherlands, where this study was conducted, WES is now routinely used in pediatric disease diagnostics and health insurers cover the costs. Semi-structured interviews were conducted with parents of 16 children undergoing diagnostic whole-exome sequencing (in trio-analysis) for DD. All parents were interviewed at two different timepoints: after consent, but prior to feedback of results (referred to as pre-disclosure interviews) and after receiving results (referred to as post-disclosure interviews). Prior to consenting to WES and inclusion in our study, parents received counseling for WES, which, according to center policy, included being notified of the possible outcomes

of WES related to the primary indication: "diagnosis," "VUS," or "no diagnosis achieved" as well as the possibility of UFs in diverse outcome categories. Table 1 shows the center's policy for returning or withholding UFs that parents consented to at the time of the interviews.

2.3 | Participants and recruitment

Interviews were conducted at parents' residences or at UMCU. None of the children whose parents were included met the Dutch legal criteria for competence, either because of their age and/or level of cognitive development. Inclusion criteria for pre-disclosure interviews were that parents: had received pre-test counseling for WES; consented to WES for their child before the interview; and had not yet received results. Inclusion criteria for post-disclosure interviews were that parents had received the final results from WES during post-test counseling. Table 2 displays participants' characteristics.

Recruitment occurred through clinical geneticists at UMCU. Clinicians provided parents' initial information about the goal of the research and asked whether they would like to be contacted by the research team. CC contacted interested parents regarding participation and obtained their informed consent prior to the pre-disclosure interviews. Parents were asked at the end of pre-disclosure interviews whether they would be interested in participating in a post-disclosure interview. Pre-disclosure interviews were conducted with parents ($n = 34$) of 20 children. Although all parents agreed to be contacted for a post-disclosure interview, four dropped out of our study (one candidate did not respond to phone calls or messages; one child passed away the night before the scheduled interview; one candidate was interested but unable to participate before the end of enrollment; one candidate declined due to emotional impact of diagnosis).

2.4 | Data collection

Center policy regarding results related to the primary indication for sequencing was that parents would receive all diagnostic information that clarified that child's DD and/or the child's congenital abnormalities. In addition, parents also consented to hearing any findings for which further genetic testing was needed in the family in order to clarify the meaning of the finding in relation to the reason for sequencing (i.e., results that could be causative of DD and/or multiple congenital abnormalities). Parents were also informed that VUSs would generally only be returned if there was a reason to believe that the finding could clarify (part of) the child's current condition.

Topic lists for both interviews were created by our multidisciplinary research team, which included a psychologist, a pediatrician, clinical geneticists, and ethicists. Pre-disclosure interviews focused on: parents' reasons for consenting to diagnostic WES (including preferences for VUSs related to a potential diagnosis); projections regarding emotional reactions toward receiving a diagnosis via WES versus receiving no diagnosis via WES. Results from the individual pre-disclosure interviews were used to formulate post-disclosure interview questions. This was done by creating case-specific prompts and tailoring/specifying interview questions for parents' own unique situations (e.g., "Last time we spoke to each other, you said that having a diagnosis might reduce the amount of red tape you have to go through with insurers and other agencies. Could you build on this some more?"). Questions during the post-disclosure interviews focused on: whether there were any changes in perceptions during the waiting period (the period between the pre-disclosure interview and receiving results) toward receiving WES results related to the primary indication; what parents' experiences were with receiving WES results from the moment of post-test counseling up

TABLE 1 UMCU's Department of Genetics return of UFs policy regarding children and parents at the time of the interviews.

Child: UF categories	Policy standpoint	Parents: UF categories	Policy standpoint
Severe conditions medically actionable[a] in childhood	Return	Severe conditions medically actionable[a] in childhood	Not applicable
Severe conditions only medically actionable in adulthood	Recommend returning, but allow opt-out	Severe conditions only medically actionable in adulthood	Recommend returning, but allow opt-out
Severe medically inactionable conditions	Withhold	Severe, medically inactionable conditions	Recommend withholding, but allow opt-in
Carrier-status for severe conditions with X-linked or autosomal recessive inheritance	Withhold	Carrier-status for severe conditions with X-linked or autosomal recessive inheritance	Recommend withholding, but allow opt-in

[a]In center policy at the times of the interviews, "medically actionable" means that there is treatment or prevention (e.g., in the form of controls) to limit the chances of a serious or fatal outcome. For inactionable conditions, such interventions/preventive measures are lacking.

TABLE 2 Participant characteristics.

Information regarding parent participants	***n* = 27**	
Ages of parents at time of pre-disclosure interviews	*Number of mothers*	*Number of fathers*
20–29 years old	1	–
30–39 years old	7	5
40–49 years old	8	4
50–59 years old	–	2
Parents' highest level of education	*Number of mothers*	*Number of fathers*
Secondary education	3	2
Post-secondary, vocational education	6	5
Post-secondary, non-academic higher education	5	4
University education	2	–
Information regarding children of participants		
Ages of children at time of pre-disclosure interviews	*Number of children*	
<1 year old	2	
1–2 years old	3	
3–4 years old	1	
5–6 years old	2	
7–8 years old	1	
9–10 years old	4	
11–12 years old	1	
13–17 years old	2	
Gender of child	*Number of children*	
Male	6	
Female	10	
Combination of WES results received per child–parent trio		
WES results related to the primary indication	UFs: Carrier autosomal recessive condition	UFs: Severe, medically actionable condition/outcome
8 diagnoses	2	1
4 VUS	–	1
4 cases in which no diagnosis was achieved	1	–

until the post-disclosure interview; and to what extent, if any, WES results met parents' expectations.

Pre-test interviews were conducted between January 2014 and January 2015. Post-test interviews were conducted between April and December 2015. The range in length of time between pre- and post-test interviews was 6–19 months. Interviews were approximately 1 to 1.5 h in duration.

2.5 | Data analysis

CC conducted the interviews with parents and audio-taped them. A commissioned typist transcribed the interviews. We adopted a thematic approach to analysis (Braun & Clarke, 2006). Interview transcripts were open coded by two authors separately (CC analyzed all transcript with either MvS or IB). These two authors then compared which text fragments were coded and whether there were any discrepancies in the coding. They also interpreted the meaning of the text fragments against the backdrop of both whole interviews held with the couple/parent in question. In this manner, a consensus was reached about appropriate codes. Codes were then grouped into (recurrent) overarching themes using NVivo 10/11 software. During the course of the analysis, the themes were discussed with the rest of the research team and were regrouped if needed in an iterative process.

3 | RESULTS

Table 2 outlines the characteristics of participants included in our study as well as the types of results participants received. We classified WES results related to the primary

indication as either "diagnosis," "VUS," or "no diagnosis achieved." For each of those categories, we also registered the type of UFs that were disclosed to participants.

Results pertaining to receiving WES results for the primary indication are first discussed. Thereafter, we turn to discussing results with receiving UFs.

3.1 | Interview findings related to receiving results pertaining to the primary indication

We identified four main themes in the interview results related to receiving results pertaining to the primary indication for WES.

3.1.1 | Theme 1: Reactions to receiving results related to the primary indication

Parents who received a diagnosis sometimes said that it felt strange or shocking at first to receive a clarification for their child's condition, even though they were eventually relieved. This was even the case in situations in which the child's medical prognosis changed for the better due to receiving genetic diagnosis following WES. As one mother explained "...but then it's just like they rip the ground from underneath your feet. ... Yeah, that's really weird, six years you're telling everyone that he has [an energy metabolism disease] and in the back of your head, you're thinking who knows it's probably going to get worse, and now all of the sudden, everything's completely different." (Resp.005). The time between the pre- and post-disclosure interviews was 12 months for this respondent. Parents also reported mixed feelings about receiving a diagnosis. Feeling relieved was prominent in this constellation of feelings. A diagnosis put an end to the diagnostic odyssey and could answer some questions, for example, about reproductive implications for themselves or other children. Sadness was also reported to varying degrees, caused by acknowledgment of the fact that the child's health and/or cognitive capacities could definitely not improve. As one father explained, "... but I didn't start dancing around the room [after hearing the diagnosis], because of the following. I know it's impossible to change what [my child] has. I asked about it too..." (Resp.020). As one mother explained who did not receive a diagnosis, but did receive a VUS: "At first we thought we really want a diagnosis, but the closer we came to [receiving WES results] the more afraid we became of hearing a bad diagnosis, which meant that receiving no diagnosis would be more positive than receiving a bad diagnosis" (Resp.010). For this respondent, the time between the pre- and post-disclosure interviews was 13 months.

Parents for whom WES results constituted a negative result (neither a diagnosis nor a VUS related to the primary indication) oftentimes reported feeling content that they had done all they could do to find the cause of the child's condition. In one case, a couple expressed disappointment at receiving a negative result due to the fact that had thought that WES would have revealed at least something of relevance in their or their child's DNA. Sometimes, feelings of comfort were reported that certain causes for the child's condition could be ruled out due to the coverage of the gene panel used for intellectual disability. As this mother put it: "it is of course the case that they didn't find anything now [negative result], so they can cross off an enormous number of possibilities [for a possible diagnosis]" (Resp.008).

3.1.2 | Theme 2: Support and emotional acceptance or a lack thereof

Gaining financial and/or emotional support was an important reason for parents to consent to WES. This included support from friends, teachers, other family members, co-workers, insurers, and (financial) aid agencies such as foundations. A portion of parents reported that either receiving a diagnosis or a VUS that formed a strong candidate for a diagnosis was conducive to gaining these forms of support. Having some kind of "label" (even if only a gene number) for their child's condition offered some clarity and/or evidence of its severity, which in turn makes (financial/emotional) support possible. As one mother shared, who received a diagnosis: "... you can stick a label on [the child's health problems], so now you do get [financial/insurance] reimbursement for stuff .... Because if you just don't know... yeah, then the answer is just: 'Yeah, sorry we can't help you'" (Resp.002).

By contrast, in some cases, parents reported that the information regarding the diagnosis or a VUS did not allow for an increase in understanding from their social environment due to its complexity. Friends and/or family either did not understand why the child's genetic condition could not be cured or found the uncertainty connected to VUSs difficult to comprehend, creating more confusion and disbelief, such as in the case of this mother who received a VUS: "... we got some comments from my partner's colleagues ... 'yeah, can't they just solve it with a pill?' .... My partner was pretty mad about that ..." (Resp. 015).

Besides gaining support, parents oftentimes reported that they wanted to be able to offer support to other parents with children of the same (suspected) rare condition. Exchanging care tips and recognition of daily care struggles and participation in scientific studies were forms of mentioned support. Coming into contact with other

parents via social media (such as Facebook) was also mentioned. At times, however, the balance of receiving and offering support seemed to be skewed, such as in the case of one parent whose child was the oldest known person to have the rare genetic condition in question: "... everyone raced toward me with their questions, because [my child] was 13 [years old] and their children are all 3 or 4 or 2 even, they don't walk, they don't talk, they don't do a lot yet. [My child] didn't start developing until long past 3,5 [years old] – that he could talk and took a few steps. So they all have something like: 'Can he do this? Can he do that?'" (Resp.005).

Parents also frequently discussed the significance of how WES results could allow for emotional acceptance of their child's condition. Whether this reason for consenting to WES produced this effect varied. Some parents who received a definitive diagnosis said that this allowed them to be able to place the blame for the cause of the child's condition on something outside of the scope of their control, thereby alleviating feelings of guilt for the suspicion that they may have somehow caused the child's health problems. Both parents who received VUSs related to the primary indication as well as definitive diagnoses from WES stressed that their insecurities about the severity of the child's condition and their parenting styles and/or abilities as parents – often brought on by comments from their social environment – were softened by receiving this information.

At times, parents also stressed that other factors, besides receiving results from WES, positively contributed to their acceptance process. These contributing factors included: more experience with seeing how other children develop in their social surroundings (especially for first-time parents); psychotherapy for parents; and specialized behavioral coaching that helped families adapt to their child's situation. According to one mother explained who received a VUS and no definitive diagnosis, "... what we can do is adapt to her and then [she] reacts differently. ... [our child] hasn't really changed, but thanks [to family coaching] we've changed in such a way that everything is more manageable. And that makes it possible to explain to our environment what's going on ..., how they can approach it... everything is easier than it was before. But that has nothing whatsoever to do with [results received through WES]..." (Resp.010).

3.1.3 | Theme 3: Answers and ambiguities

Parents sometimes said that a diagnosis did not offer them answers to all the questions they had concerning the etiology of their child's condition. Or, even if a diagnosis clarified a portion of the child's behavioral problems, it did not automatically make clear how those problems could best be addressed. One couple who received a VUS that formed a strong candidate for clarifying the child's DD said that it was important to remain vigilant of not blaming behavioral issues solely on the child's condition (whether or not the VUS turns out to form a definitive diagnosis in the future):: "... that's the danger. That's what I think ... that costs a lot of back-and-forth actually, you shouldn't treat her [-the child-] as a patient, because a child needs an upbringing. She just has her own character, and she's just got quite the temperament compared to [our other child]" (Resp.014). For a number of parents, especially those of young children, a key motivation for consenting to WES was to be able to know how their child might develop cognitively. In some cases, receiving a diagnosis was able to offer some clues about how to answer this question. In other cases, receiving a diagnosis showed that the child would never be able to develop autonomous capacities needed for leading an independent life, "We had the hope that she would make big strides [developmentally] ... on the one hand that hope isn't there anymore after [receiving a diagnosis through WES]. But you adjust to that. You get hope back in other areas. And we're going to make the best of it. But ... it's very clear to us that she has a severe intellectual disability" (Resp.012). Although a diagnosis offered a general frame of the child's development, a few parents also emphasized that they still had questions about what specific skills their child may be able to develop. As one parent elucidates who received a VUS that formed a strong candidate for clarifying the child's DD: "... we asked, because we wanted to know if she could ever talk and walk. .... I shut down completely, because ... they said that it could be the case that [she] can't talk in sentences .... Maybe words, but not sentences." (Resp.015) The fact that these questions remained was viewed as undesirable.

By contrast, other parents of young children experienced having these remaining questions as less problematic and instead emphasized certain positive effects. This included being able to anticipate certain (health) problems associated with the child's condition. Knowing about these risks gave them a sense of control. Receiving a diagnosis was thus seen as a first step in understanding the child's condition, but not the last one: having a diagnosis makes it possible to search for possible ways of dealing with certain problems, but it does not directly solve all of one's problems. Parents who received VUSs that were thought to be the cause of the child's condition had diminished at least some of the uncertainty they had regarding the child's development.

Reproductive implications for the parents themselves, their other children, and other family members were also cited as important reasons for consenting to WES. Although receiving a diagnosis or a VUS was viewed as

relevant to reproductive decision-making, some parents said that it also complicated decisions for having another child. Sometimes, mothers and fathers disagreed about the choice of whether to have another child. As one mother explained who received a VUS that formed a strong candidate for clarifying the child's DD: "I don't know if I want a second [child]. On the on hand, I do want it, on the other hand, there's just a lot more that comes along with it now. .... Because my boyfriend says could you decide to terminate the pregnancy if the [child] has something. On the one hand, I say yes, and on the other hand I say no. ... you don't want another child [with the same thing]" (Resp.015).

3.1.4 | Theme 4: Hoping versus expecting

When parents were asked whether receiving results met their expectations, they sometimes made explicit distinctions between "expecting" certain results or "hoping" for certain results. Some parents said that it was a conscious choice to avoid having too many expectations regarding receiving results. According to one father who received a VUS following WES: "It's like buying a lottery ticket, you buy the ticket, you're hoping for the jackpot, but you're not actually expecting to win anything" (Resp.011). During the pre-disclosure interviews, parents sometimes said that they did not expect that a definitive diagnosis would be achieved. Similarly, some parents stated that even if a diagnosis was achieved, it would not be one that would designate curative treatment options or allow for drastic improvement of their child's condition or in caring for their child. Tempering one's expectations was thus used as a coping strategy to guard against having too much hope and disappointment. This especially pertained to parents who had expressed disappointment by the results of previous (non-)genetic diagnostic measures/assays. Parents who guarded against disappointment in this way were deeply satisfied with what a diagnosis had given them, which has already been alluded to under the abovementioned themes. As one mother elucidated who received a diagnosis: "[WES] actually surpassed my expectations. .... Everything I hoped to get, so to speak..." (Resp.005). There was also one case in which a couple expressed disappointment about what WES had brought them, and in doing so also explicitly highlighted the distinction between "expecting" certain results or "hoping" for certain results: "Yeah, we had big expectations, because everything was going to be found. ... We interpreted it that way at least. And that really turned out to be a setback because now we're still searching and hope to get an answer about the symptoms and it just was not there. So that was ... a disappointment, we expected more. But that was due to our own expectations" (Resp.016).

Parents stressed the importance of the clinical geneticists' counseling in maintaining realistic expectations regarding what answers WES results may help them achieve and that it was not even certain that WES would reveal a VUS or a diagnosis. Important qualities during counseling cited by parents where the clinical geneticists' offering of emotional support and perceived commitment to trying to achieve a diagnosis. Some respondents said that their physicians had advised them to focus more on helping the child develop to the best of their ability rather than on finding a genetic diagnosis and that this was viewed as helpful.

3.2 | Interview findings related to receiving UFs

In five of the 16 parent–child trios in which parents were interviewed, an UF was found (see Table 2). It is of note that what some parents considered to be an UF in our study differs from the definition used by clinical geneticists. Clinical geneticists take an UF to be a variant that is (likely) pathogenic, but that is unrelated to the clinical question for which sequencing was performed, and thus of relevance to the health of the child, parents, and other family members (Berg et al., 2011; Van der Schoot et al., 2022). Parents, by contrast, took an UF to mean any finding that eventually turns out not to be causative of the specific form of DD but that is nonetheless of relevance to the child's, their own or other family members' health (with or without multiple congenital abnormalities) that the child has. For example, carrier-status of variants, which cause DD homozygous or compound heterozygous, might be reported to be able to further exclude a second variant on the other allele. When no second variant is found, what is initially thought to be related to the diagnosis, turns out to be indicative of carrier-status for a condition that causes DD but does not clarify the child's condition of which developmental delay is a prominent feature. In such cases, what is initially thought to be related to the diagnostic aim turns out to constitute an UF. We present our results according to what parents viewed as being classified as an UF.

3.2.1 | Theme 1: Reactions to receiving UFs

Only a portion of participants received UFs. These included UFs pertaining to carrier-status for severe autosomal recessive conditions related to DD (but not the child's condition) or for medically actionable conditions.

In general, parents welcomed knowledge of these findings and did not report feeling alarmed. One UF received was for a preventable adverse drug reaction to oncological treatment found in both the child and her father. Parents found this information helpful to know, but did not yet inform the rest of their family. Another finding that parents reported receiving was associated with a variant for colorectal cancer for which preventable screening options exist. Parents treated this finding as receiving an UF – albeit one in which there is a larger amount of uncertainty regarding pathogenicity – in explaining its relevance for them, and therefore, we have decided to treat as such in the presentation of our results. However, from the explanation that parents gave during the interview, this finding should actually be classified as a VUS and not an UF. These parents were pleased to know this result, since their child would not be able to communicate early symptoms of this disease, such as discomfort or pain. Moreover, parents found the unclear nature of the VUS in fact comforting: "if they had said the research shows you have a heightened chance of … developing intestinal cancer, then I would have started worrying, but not now," "… our child can't say my stomach … doesn't feel well," "So I was happy to know about this possibility" (Resp.020).

3.2.2 | Theme 2: Catch-22s in current center's policy

Some parents highlighted the uncertainty about whether their young child could go on to develop autonomous decision-making capacities or whether they would always remain responsible for making (medical) decisions for their child. As one mother of a young daughter explains who received a VUS following WES explains: "if she's mentally able to … make those kinds of decisions, then her own choice is the most important factor. But as long as she can't, then we need to make those decisions for her, and that's still not clear" (Resp.001). This uncertainty about the child's future development complicated decision-making for UFs and gave rise to a situation resembling a Catch-22: An important reason for consenting to WES was to gain a better picture of how the child might develop. Yet, in order to be able to receive a diagnosis and possibly be able to develop this picture, center policy required parents to make choices about UFs before WES could commence. But in order to make responsible choices, some idea of their child's developmental potential is needed, since parents were unsure whether their child would be able to make decisions about whether or not they would want to know about an UF. As one mother of a young child who received a diagnosis illuminates when reflecting back on their choices regarding UFs discussed during the first interview: "you wonder what her own choice would be. But if you look at how she is now [in terms of cognitive development], then she's not going to be decisionally competent at the age of 18 either. But that only comes with time, and we didn't know that yet [when we first consented to WES]" (Resp.018). This parent did not receive any UFs.

3.2.3 | Theme 3: Choices and the role of defaults (opt-ins and opt-outs) in decision-making

Parents stated that they valued having at least some choices over which UFs to receive or decline. Some believed if a policy were to offer no choices, this would be unacceptable, since such a policy would be unable to accommodate their own unique situations in which a child has a DD. But choice over UFs was also valued because of its importance for decision-making: simply having choices over the various types of UFs necessitates critical reflection on the possible negative and positive consequences of (not) receiving UFs for one's own situation. Moreover, parents found default policy options (disclose, but allow an opt-out, 'withhold, but allow an opt-in') in the center's current policy for UFs were also seen as conducive to decision-making. Parents explained that "the experts" probably had good reasons for choosing those particular defaults, and this led parents to fathom new kinds of considerations for accepting and/or declining UFs. As one mother explained: "… if it's written down that way [with an opt-in or opt-out], it's much easier than when it's a very open question, because then you think: 'I have no idea'," "And why would you not choose that? Well, for example, in that situation … because of this and that. And then the abstractness of the question becomes much more concrete. And I found it, indeed, helpful that they indicate that [with an opt-in or opt-out] …. I think that's good because otherwise, if it's formulated too objectively, then it's way too much… then you're swimming, and can't grip onto anything" (Resp.010).

4 | DISCUSSION

Our study highlights that (anticipating) disclosure of diagnostic WES results can evoke ambivalent emotional reactions in parents, such as sadness mixed with relief when a diagnosis is achieved. Some of these mixed reactions can fluctuate over time, such as first feeling shock at receiving

a diagnosis, but then eventually feeling relieved to have one, even in cases where the diagnosis that was revealed with WES had a more favorable prognosis. Parents welcomed receiving a genetic diagnosis and viewed receiving it as advantageous, which is consistent with results from other qualitative studies' regarding parents' post-test experiences with receiving results (Chassagne et al., 2019; Krabbenborg et al., 2016; Werner-Lin et al., 2018).

Support and emotional acceptance were important reasons for consenting to WES. Parents who were informed about a diagnosis or VUS that could explain their child's condition often experienced improved support and emotional acceptance (from others) by "having a label," being able to place blame for the child's condition on something beyond their own doing (relief from guilt), and through seeking out specialized educational opportunities or care for their child – all themes that have emerged elsewhere (Chassagne et al., 2019; Krabbenborg et al., 2016; Peter et al., 2022; Timmermans & Stivers, 2018) Furthermore, these types of findings are consistent with the idea that receiving genomic results is of "personal utility" to parents, children, and their families that extends beyond clinical utility (Bunnik et al., 2015). According to Kohler et al., who conducted a systematic review into what tangible elements personal utility could potentially consist in, having evidence-based knowledge of the different facets of personal utility can aid counselors in helping parents/patients make well-informed decisions that are consistent with their own values and needs (Kohler et al., 2017).

However, even in cases where WES results do offer at least some personal utility to parents, many questions they had remain unanswered or the answers were ambiguous. Even if it is clear that a child might never be able to make autonomous decisions, it is still unclear what specific (mental) capacities they could possibly develop. Sometimes, parents are presented with new questions, or existing questions became more salient for them, for example, questions regarding reproductive matters. The fact that such ambiguities remain or new questions emerge indicates that parents may sometimes have expectations that need tempering as authors of other studies have also suggested (Donohue et al., 2021; Krabbenborg et al., 2016; Mackley et al., 2017; Roberts et al., 2018; Werner-Lin et al., 2018).

Furthermore, we found it noteworthy that disappointment was not especially prevalent among the participants in our study and that most of the parents in our study were ultimately satisfied with consenting to WES, regardless of the type of result they had received related to the primary indication (diagnosis, VUS, and negative result). In only one case did parents explicitly state that they were disappointed with receiving a negative result. The reasoning they offered for this was that they had had high expectations that a diagnosis, or at least a VUS, would be achieved with WES. The finding that disappointment occurs, or even increases, when persons have heightened or unrealistic expectations about the type of result they will receive, is consistent with insights of other empirical studies and points to acknowledging expectation management as part of the informed consent process (Bos & Bunnik, 2022; Donohue et al., 2021; Eichinger et al., 2023; Peter et al., 2022; Wynn et al., 2018). However, our results show that this observation should be built upon further, since parents who adopted a hopeful stance about what WES might offer them reported being ultimately more satisfied with the whole sequencing experience than the couple in our study who expected a certain outcome or answers from WES and thus reported being disappointed.

In light of the above, a novel key finding from our study is that distinction between *hoping for* rather than *expecting certain results or answers* is important to be aware of, since it can help shape parents' experiences with receiving WES results. Incorporating this distinction into counseling could serve as a could serve as a mitigating factor to shape expectations. This could be done simply by asking parents what questions they are hoping to get answers to and consequently assessing whether a diagnosis can give them those answers, and if so to what extent. A simple reminder that hopes are inherently different from expectations may help protect against overly optimistic assumptions and disappointment. This finding can be added to insights generated on expectation management found elsewhere that have stressed the need to mitigate against false hopes and unrealistic expectations through various strategies, such as encouraging parents to take some extra time to reflect on their choices in more detail before actually obtaining written consent for sequencing (Bos & Bunnik, 2022; Eichinger et al., 2023; Gore et al., 2019; Wynn et al., 2018).

There were only five UFs identified among our study sample. That means our study was limited in capturing the full range of possible reactions to UFs. Parents in our study reported that they did not feel alarmed by receiving the UF in question and in fact welcomed knowledge of it. Hence, we did not encounter parents reporting negative psychological impact with receiving UFs. The fact that we did not encounter such negative reactions toward UFs is consistent with findings collected elsewhere as well as the convictions underlying some policy statements that expected harm from disclosure of certain UFs is minimal (Botkin et al., 2015; Cheung et al., 2022; Directors ABo, 2015; Green et al., 2013; Hart et al., 2019; Kalia et al., 2017; van El et al., 2013; Vears et al., 2021).

One finding, however, did stand out: the couple who received a VUS for colorectal cancer in their child that

they took to be an UF, viewed the uncertainty about whether or not their child could develop the condition as positive rather than negative. These parents imagined this knowledge would make them more attuned to early signs of cancer and thus able mitigate risks. This finding is remarkable since there is some tendency in medicine and genetics to view uncertain results as being categorically harmful (Newson et al., 2016), even though the findings from other studies have also shown that parents state experiencing some kind of form of personal or clinical utility from uncertain results (Donohue et al., 2021; Mollison et al., 2020; Robinson et al., 2019).

However, at the same time, the definitional confusion of these parents also raises the question if they had an adequate understanding of the information and/or whether the explanation they received during counseling was adequate. A possible clarification for the fact that this VUS was disclosed to parents is that our study was conducted when WES was first being introduced into clinical practice in the Netherlands and counselors still had to become accustomed with using WES in a diagnostic setting. Since then, national guidelines have been formulated in the Netherlands (in 2021) in which class 4 or 5 variants may be disclosed under certain conditions. In rare cases, a class 3 variant may be disclosed: "For example, if a diagnostic, validated functional test is available that offers clarity as to whether the variant is disease-causing. Sometimes additional material is needed to this end (for example, urine, plasma) [translated from Dutch]" (https://www.vkgn.org/files/OnderbouwingConsensus-basedleidraadmeldennevenbevindingen.pdf).

Aside from the fact that this type of result would at present not be disclosed, the fact that parents experienced it as something positive raises a further question: how can counselors, in general, present results with some levels of uncertainty to parents and/or patients so that it is empowering. Newson et al. have also pointed to the need to develop a so-called "ethics of uncertainty" that can incorporate positive aspects next to negative ones (Newson et al., 2016).

Our study also underlines that having choices, supplemented by default opt-ins and opt-outs, necessitates critical reflection on the possible negative and positive consequences of (not) receiving UFs for parents' own situations. In this way, defaults served as a type of decisional aid for parents in making choices about UFs. The utilization of defaults in return of UFs policies is not new (Berg et al., 2011; Bredenoord et al., 2011; Directors ABo, 2015; Kalia et al., 2017; Knoppers et al., 2015; Van der Schoot et al., 2022). To date, it has been heavily debated in policy contexts whether parents and/or patients should be offered choices about what UFs to receive or whether they should be required to consent to hearing certain UFs (or "secondary findings", in contexts where opportunistic screening is offered) (Botkin et al., 2015; Directors ABo, 2015; Green et al., 2013; van El et al., 2013). In a study by Vears et al. that examined the consent forms of different centers across the globe, it was found that there was considerable practice variation regarding offering persons choices pertaining to UFs (Vears et al., 2018). Moreover, it appears that the use of default options in the policies that were included in their study had a different intended role than the one parents attributed to them in our study. Defaults in those studies were intended to inform what information would be disclosed if there was a mistake on the consent form or there were intricacies associated with laboratories reporting certain information to clinicians that must further assess the patient. The authors also emphasize that it was unclear from these consent forms what other information is being offered during counseling to accentuate information on the form or whether other informational material exists, such as brochures.

Viewing defaults as decisional aids, as parents in our study do, affords them a more robust role – one that could in fact be relevant for ensuring informed consent. This idea has also been discussed elsewhere. For example, in the context of decisions in intensive care units, some authors have argued that when defaults are used as decisional aids persons must actively be made aware of the fact that they can choose counter to the default, for example, during discussions with healthcare providers and through additional informational material (Hart & Halpern, 2014). In this way, the default serves as a starting point in helping them fathom other types of considerations they may not have considered and contributes to well-informed decision-making. We suggest that the moral argumentation behind the default option(s) in the center's policy is explained to parents can relate it to their own unique situation with their child and accordingly make their own well-informed choice(s) about whether to accept/decline UFs in various categories. Even in situations where centers require consenting to having certain UFs returned, this can make parents more attuned to the fact that the possibility of UFs with potentially life-changing effects is present. This should also be weighed against the relative importance of obtaining a genetic diagnosis for the child and their care-takers. As WES/WGS becomes more widespread in different medical contexts and at different points in the diagnostic process (e.g., NICU, prenatally), a possible avenue for further research is to investigate how offering choices to accept and/or decline (certain types of) UFs influences patients' satisfaction with results that are reported back to them. Does choice, in other words, influence satisfaction? As Planting et al. stress in the first study ever to assess participants' experiences

of rapid exome sequencing in cases of major ultrasound abnormalities, even though the majority of participants opted to receive UFs, this decision was not one that "was always easy or self-evident" and some parents reported feeling overwhelmed about making such decisions regarding UFs not too long after being informed about the fetal abnormality (Plantinga et al., 2021).

A second novel key insight from our study is that the policy configuration for return of UFs at the time of the interviews can lead to a Catch-22 situation in cases of DD in diagnostic contexts where UFs are not actively sought for. An important reason for parents to consent to WES is to gain more insight into whether their child can develop autonomous capacities. But, in order to make responsible choices regarding UFs for adult-onset conditions and carrier-status, some idea of their child's developmental potential is needed. Yet, sometimes it is uncertain whether a child could develop the autonomous capacities needed for making decisions regarding UFs later on in life. This causes a decisional conundrum. In our view, this makes decision-making unnecessarily complex. Furthermore, research should focus on ways in which a return of results policy can limit these types of decisional impasses. This may seem to suggest that parents should simply not be given choices for UFs with adult-onset and the choice ought to be made to withhold or return these kinds of UFs in all types of situations. However, we believe this route to be too simplistic, since it ignores the intricacies inherently present in conducting WES in trio-analyses, where it is not possible to withhold an inherited UF in the child, but disclose it to parents, since the finding in the child is always the inducement to revealing that finding in the parents DNA. Moreover, any inherited UFs are not only relevant for the parents and child undergoing sequencing but also the wider family. Each of these persons may have differing interests that are not necessarily congruent with one another when assessing disclosure. Furthermore, research should investigate ethically evaluating these possible interests.

This study has several limitations that have also been discussed at length in a previous article (Cornelis et al., 2016). We did not include parents: who declined WES after pre-test counseling; from important minority groups in the Netherlands, such as persons from Turkish/Moroccan descent; or whose child does not have a DD. Including such cases may offer new types of reasoning/considerations that are relevant for policy development (Cornelis et al., 2016). A further limitation is that we were bound to a certain number of respondents due to the study's design: participants must have participated in the pre-disclosure interview in order to participate in the post-disclosure interview. A consequence of this is that our investigation only included a limited number of parents who received UFs pertaining to themselves or their child, even though a larger dataset may give insight into new types of experiences associated with receiving UFs.

5 | CONCLUSION

Pre-test counseling for diagnostic WES in children with DD should focus on exploring parents' hopes and expectations for certain types of results. Furthermore, avenues for research ought to inquire whether a staged approach to consent can limit catch-22 situations and whether, and if so how, the level of (un)certainty regarding a child's development of autonomous capacities could justify developing different disclosure guidelines for UFs. Furthermore, our results indicate a role for default opt-ins and opt-outs in decision-making and a line for further inquiry could include studying what role such prompts could have in improving persons' informed consent.

AUTHOR CONTRIBUTIONS

The authors confirm contribution to the study as follows: study conception and design: Candice Cornelis, Aad Tibben, Eva Brilstra, Ineke Bolt, Marieke van Summeren, Nine Knoers; data collection: Candice Cornelis; analysis and interpretation of results: Candice Cornelis, Ineke Bolt, Marieke van Summeren; draft manuscript preparation: Candice Cornelis, Aad Tibben, Eva Brilstra, Ineke Bolt, Marieke van Summeren, Nine Knoers, Annelien L. Bredenoord. All authors reviewed the results and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from M. J. H. van Summeren. The data are not publicly available due to legal restrictions.

ETHICS STATEMENT

The research received a waiver of approval from the ethics review board of University Medical Center Utrecht as it did not fall under the Dutch Medical Research with Human Subjects Law. All participants in the study gave

written informed consent prior to participation in the study.

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