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ARTICLE

Parents, their children, whole exome sequencing and unsolicited findings: growing towards the child's future autonomy

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Abstract

In a previous study we found that parents of children with developmental delay (DD) favoured acceptance of unsolicited findings (UFs) for medically actionable conditions in childhood, but that preferences diverged for UFs with no medical actionability, or only in adulthood, and regarding carrier status. Sometimes the child's future autonomy formed a reason for withholding UFs for the present, despite an unfavourable prognosis concerning the child's cognitive capabilities. This might be different for children undergoing whole exome sequencing (WES) for reasons other than DD and who are expected to exert future autonomy. This is the focus of the current study. We conducted nine qualitative, semi-structured interviews with parents of children, ages <1–15, after consenting to WES, but prior to feedback of results, and with three adolescent children. Several parents wished to receive any information that might in whatever way be relevant to the health and well-being of their child, and to a lesser extent wished the inclusion of information about non-actionable disorders and information concerning carrier status of autosomal recessive disorders. Although parents understood the rationale behind the centre's UFs disclosure policy, they also felt that they needed this information in order to be able to exert their parental responsibility and take good care of a child still dependent on them. Parents reason from their notion of parental responsibility but are also inclined to take adolescent children's preferences seriously and acknowledge the child's incipient autonomy as a ground for granting an increasing degree of self-determination on the road to adulthood.

Introduction

Compared with traditional methods, whole exome sequencing (WES) enables rapid mapping of DNA for reaching a diagnosis in cases of suspected, yet unclarified, genetic disorders. WES provides the opportunity to finally achieve a diagnosis [1, 2], however, often does not end a diagnostic odyssey [3]. Moreover, even though WES may reveal a finding, these findings often have no significance for the course of treatment. Apart from diagnostic findings, WES has the potential for generating additional findings, also known as incidental findings, beyond those related to the indication for sequencing [4]. In this paper we have adopted the European Society of Human Genetics' preferred term: unsolicited findings (UFs) [5]. WES's potential for revealing unsolicited findings raises the issue of how UFs should be disclosed/withheld, and under what conditions. Moreover, how should UFs be presented during pre-test counselling so that informed consent is safeguarded [4, 6–8]?

These questions become all the more pressing in cases involving children, for which parents must give proxy

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consent because children are not yet capable of making autonomous decisions [9–11]. WES may not only reveal UFs concerning predispositions for conditions that are clinically relevant and actionable in childhood, but also for conditions with adult-onset that may or may not be actionable, are actionable only at a later stage in the child's adult life, or only relevant in the case of reproductive decisions. A specific moral question regarding the conditions for disclosure concerns whether choices about disclosure of UFs regarding the child belong to the discretionary decisional autonomy of the parents. What may parents decide for children who are expected to become competent? Do they have to safeguard a child's future autonomy by deferring decisions regarding the disclosure of UFs to adulthood, when the child is capable of autonomous decision-making [12, 13]? Currently, parents' preferences regarding the disclosure of UFs have scarcely been studied in real-life situations [2].

In a previous qualitative study [14], we observed that parents of children with a developmental delay (DD) favoured acceptance of UFs for medically actionable conditions in childhood, but that preferences and considerations diverged for UFs with no medical actionability, or which emerged only in adulthood, and regarding carrier status for autosomal recessive disorders. For some parents, the child's future autonomy formed a reason for initially withholding UFs, especially in cases where the prognosis concerning the child's cognitive capabilities was uncertain. A number of studies have shown that parents' attitudes toward disclosure of information generated by WES are generally positive [2, 15–23]. Those attitudes might reflect their feelings of parental responsibility, their experience with handling uncertainties, the need to gain control, or moral obligation towards the child [24].

The aim of this study is to gain insight into the preferences and considerations of parents and adolescents concerning the disclosure of UFs for children in cases where diagnostic WES in trio-analysis was performed for conditions other than DD. The focus of this paper is limited to considerations regarding the handling of UFs pertaining to the child's genome. The results of the study will be used to enrich the frame of reference for professionals involved in genetic counselling in paediatric practice, and to contribute to the debate about the disclosure policy of UFs.

Materials and methods

Participants

At the time of this semi-structured, open-ended, qualitative interview study (October 2016 to July 2017), the University Medical Center Utrecht (UMC) offered WES for diagnostic purposes. Recruitment of families occurred through clinical geneticists at the UMC. Inclusion criteria for parents were that they had undergone pre-test counselling for WES, had given consent for WES for their child (and themselves) before the interview, underwent diagnostic WES in trio-analyses (father–mother–child), and that children did not have a developmental delay—but that they had not yet received results. Participating parents and adolescent children were offered preliminary information about the interview study. One of the authors (C. Cornelis), who conducted the interviews, was not involved in the genetic counselling and testing process. She contacted parents about participation and obtained informed consent prior to the interviews. The children for whom WES was indicated were aged <1–15 years. If parents consented, their adolescent child was also invited to be interviewed. According to Dutch law, adolescents aged 12–16 years need the additional consent of their parents.

In total nine interviews were conducted with seven couples and one single mother; Couple 008 were interviewed individually. Two couples refused participation in this interview study for unknown reasons. Three adolescent children aged 14–15 years participated in the interviews. Table 1 shows the participants and indication for WES. The

Table 1 Diagnostic WES in children who are expected to exert future autonomy.

	Information regarding parent characteristics	Medical problem of the child (age)
Family 001	Mother + Father	Palatoschisis; anorectal malformation, hypospadias (3 yrs)
Family 002	Mother + Father	Possible explanation for congenital urogenital anomaly (vesicoureteral reflux) and possible additional cause for hypodontia (14 yrs)[a]
Family 003	Mother	Multiple congenital abnormalities ECI (5 yrs)
Family 005	Mother + Father	Unexplained episode of cholestasis, clinically compatible with BRIC (liver disease) (15 yrs)[a]
Family 006	Mother + Father	Exocrine pancreatic insufficiency and mild dysmorphic characteristics (13 yrs)
Family 007	Mother + Father	Misunderstood skeletal abnormalities (fractures, arthritis) (10 yrs)
Family 008	Mother + Father	Autism spectrum disorder and retinitis pigmentosa (15 yrs)[a]
Family 010	Mother + Father	Palatoschisis, microretrognathia skeletal dysplasia (1 year)

[a]Adolescent child was also interviewed.

Table 2 University Medical Center Utrecht's return-of-results policy for UFs regarding children, at the time of the interviews.

Outcome categories of UFs	Return policy
Severe, medically actionable[a] conditions in childhood regarding the child	Always
Severe conditions, only medically actionable in adulthood regarding the child	Always
Child's carrier status for severe autosomal recessive conditions	Never
Severe, medically nonactionable conditions regarding the child	Never

UFs unsolicited findings.

[a]University Medical Center Utrecht's standpoint takes the term medically actionable to mean that (preventive) medical treatment or controls are available to reduce the chance of a severe/fatal outcome.

Medically unactionable is taken to mean that no (preventive) medical treatment or controls are available to reduce the chance of a severe/fatal outcome.

children of the parents interviewed presented clinically heterogeneous disorders. Interviews were held at parents' residences.

Genetic counselling

During genetic counselling, participants were informed about the potential risks, benefits and limitations of WES [5, 25]. Participants also received information about the possibility of UFs and the expected frequency of UFs in WES, which was presented as 2% [26]. The centre's return-of-results policy at the time of the interviews (as shown in Table 2) was explained to the parents, and (if applicable) to their child. It was also pointed out that findings may not have significance for the course of treatment of the condition for which WES was offered. Participants were also informed about UFs. A distinction was made between medically actionable or nonactionable UFs, based on the likelihood of whether consequences can be influenced by therapy or prevention [27]. It was explained that UFs are divided into childhood-onset and adult-onset depending at what point a condition reveals itself. Some findings may have reproductive significance.

Methods

Our multidisciplinary research team, including a psychologist, a paediatrician, clinical geneticists, and ethicists devised a semi-structured topic list for the interviews. After a short introduction regarding the aim of the interview, interview questions (see Supplementary materials and methods) focused on parents' reasons for consenting to diagnostic WES, on their preferences with regard to receiving information about the pre-defined categories of UFs that had been explained to them during pre-test counselling, and their views regarding the centre's policy standpoints (i.e., always/never return) for the various categories. If appropriate, the interviewer prompted interviewees to further explore personal considerations favouring acceptance/decline of those categories.

Interviews were about 60 min in duration, audio-recorded and then transcribed verbatim by a commissioned typist. Each interview transcript was read and re-read using a phenomenological approach (trying to understand what is essentially presented in the interviews), and open-coded by four authors separately (AT, WD, IB and MvS). After extensive group discussions, consensus was reached on the interpretation of relevant topics and themes.

Results

In this section we provide an overview of the following topics: parents' and adolescents' reasons for consenting to WES diagnostics and the decision-making process (shared with the child or not); their preferences and considerations regarding disclosure of four different categories of UFs; and the UMC's return-of-results policy (see Table 2).

Reasons for WES

All parents and the three adolescents interviewed expressed the urgent wish to have an explanation for the health problems of the child or, more explicitly, a diagnosis. Knowledge about potential heredity and the impact on siblings, and on future offspring for the child, was also often mentioned. Certainty about the cause of the health problem was expected to provide more control over one's health and future. Some parents specified that knowing the cause of the disorder might provide more opportunities for medical care and treatment. Some parents expected that an explanation or diagnosis might lessen the child's uncertainty regarding the future/prognosis of their condition.

The parents of the adolescents aged 13–15 had all discussed the WES option with the children and made a joint decision. The parents of the children aged 5 or younger considered their children too young to involve them in the decision-making process but they said that they would certainly have done so if the children were 12 years or older. The parents of the 10-year-old girl did discuss it with her,

but said that their daughter was not interested and left it up to them to make a decision.

Considerations concerning disclosure of UFs UFs and availability of (preventive) medical treatment in childhood/adolescence

All parents and adolescents wished to receive UFs for medically actionable conditions in childhood because of the availability of medical treatment or prevention (controls), stressing that this was in the child's best interest.

One of the children (002) said: 'I just like it when people just tell me what's wrong with me and withhold nothing from me, even if the outcome is far-reaching.' Another child (005) stated: 'I think it's nice to know, because if you know that you have a chance of having a disease, you can take it into account a little, but I also understand that people would rather not know because otherwise you would start living in such a controlled way.' A third child (008) asserted: 'I think keeping things secret is stupid, I want to be able to decide for myself.'

A father (002) noted: 'If someone [the hospital] knows something about one of us, then it must also be known to us.' Apart from one mother, all parents and adolescents were very convinced that in their opinion they had the right to be informed about the finding of genetic variants associated with disorders that occur during childhood, and for which treatment is possible. 'Such a result has an impact on our child's life, and we are responsible for that,' said a mother (007), and she continued: 'The interest of your child is always paramount.' It was also felt that doctors had the obligation to inform parents in order to give them the opportunity to opt for treatment options and adapt their lifestyle. Most parents wished also to be informed in order to prevent feelings of regret or guilt that might arise if they were not given the opportunity to act upon medically actionable test outcomes in a timely manner. One mother was unsure whether she could handle adverse and far-reaching information. Most parents said that they would inform their children about such a result, although the mother of a 3-year-old boy thought one should not burden a child with this kind of threatening information, because that would take away the innocence of youth. She (001) put it as follows: 'I'm afraid that such information would drive him crazy.' One mother (008) said: 'When our daughter became ill, when she was 15, I was above all concerned about the impact this had on her life, while I think if something like this happens when you have a two-year-old child, you are also very concerned about what awaits us as a family in the coming years. If at some point they are in puberty you also grow towards the fact that they become adults. And that they make their own choices.'

UFs and availability of (preventive) medical treatment in adulthood

Although parents understood the rationale behind the restrictions in the centre's UFs disclosure policy, they also felt that they needed this information to be able to exert their parental responsibility and take good care of a child still dependent on them. Both parents and children found it more difficult to make a definitive statement about receiving such information, but found it important to at least have the choice of whether to be informed.

One of the children (002) expressed a clear preference for knowing, because only then can you decide on possible treatment or what you should do to prevent an illness. A second child (003) emphasised the right *not* to know. She thought it would be too burdensome to be informed about something that could only be expressed in adulthood, and preferred only to be informed if the clinical manifestation could be expected in the short term. A third child (008) thought it was important to be offered the choice of being informed. In addition, she said: 'I don't want people to know things about me that I don't know; if they have found something, please tell me.'

Yet, one parent (007) said: 'I'm afraid that after being informed I wouldn't be able to think of anything else anymore.' To which his partner said: 'I would think OK, you might have the predisposition for it, but it doesn't mean you actually get it.' Other parents thought that after disclosure of such a finding, you could no longer live a carefree life, or as one parent (008) said: 'Maybe you will get scared to just live a full life.' Parents believed it was important to be able to decide *when* the children should be informed, although they also felt uncertain about when they should tell their children. Sometimes parents were afraid that they might keep postponing informing their child about such results, because there is never a right time to disclose them. However, if children requested these results themselves, they would not further postpone providing information. As one couple (007) expressed it: 'It might be difficult finding a balance between burdening the child and being honest and providing information.'

UFs and carrier status of a child and the right to know

In contrast to the initial policy of the UMC, the majority of parents and children thought that information about carrier status of autosomal recessive disorders should in principle be made available. Important considerations concerned future reproductive desires and decisions, and the possible implications of carrier-status information for other children and adult relatives.

The adolescents thought it important to be able to decide on whether or not to know results themselves, especially in view of reproductive decisions. One girl (005) said: 'Look, the moment you are told that you are a carrier of a disease and you have the chance that your baby will get sick, you can still decide to refrain from having children, because I don't want my children to get sick.' It should be noted that, obviously, the implications of being a carrier of an autosomal recessive condition is often not well understood; some respondents seemed to have failed to understand that one needs to inherit the mutant allele from both parents to develop the disorder.

One couple felt that if the child's carrier status was something inherited from the parents, it was information about themselves, and that they had a right to know (002). Another parent said that she would not want to find out afterwards that there had previously been something to be known with possible far-reaching impact for all involved (003).

UFs and lack of (preventive) medical treatment

The majority of the participants supported the policy of the UMC of not informing them about disorders for which there is no medical treatment or prevention. They felt such information would mainly be experienced as a burden, and that it made no sense to know.

One of the adolescents (002) said: 'Something like that would keep haunting me.' Another (005) noted: 'If it is really important for some people to know, well it's their choice, but I really don't have to.' The third adolescent (008) said: 'I think it's good that they don't say that, because you should not panic if it is not necessary or not relevant.'

Four couples thought that here, too, at least a choice should be offered. A father (006) and mother (007) cited the example of Alzheimer's disease and thought that early knowledge about having the predisposition could be important for the partner and other people in order to be able to recognise the problems that the disease entails. However, they also realised that you can unduly scare relatives with such information. For UFs for medical conditions without treatment or preventive options, some parents cited the possible future availability of (preventive) medical treatment as warranting disclosure at present. One father (005) thought it was important to know because 'you can then prepare, plan a vacation with everyone I love, say goodbye well, and leave the family behind well'. Another (008) said: 'I don't think the predisposition for Alzheimer's is an enrichment of my life, the only advantage is that when the first symptoms appear, you can think of what you want to do with the rest of your life sooner.' 'The biggest stumbling point for me is the loss of my light-heartedness in life.' One parent mentioned the practical objections relating to a life insurance policy or a disability insurance policy (008).

Discussion

Like others, this study shows the need of parents and adolescent children to know the cause and course of their child's, or their own, medical problems [8]. Although a diagnosis might be the end of the 'diagnostic odyssey' [3], the 'medical odyssey' will continue. We have also observed participants' ambivalence, that is their mixed feelings or contradictory ideas about how UFs should be returned, as has also been reported in previous studies [3, 8, 18, 20, 28–33]. Moreover, the preferences of parents and adolescents partly differ from both the UMC's initial policy and health care professionals' preferences, as has been shown by others [31, 34–37]. Parents expect a possible WES diagnosis to help them cope better with the child's condition, but also with their own fears, their expectations and hopes, and future perspectives of the child and entire family.

UFs and availability of (preventive) medical treatment

In general, most adults and adolescents accepted the possibility of discovering UFs and expressed their preference for receiving UFs concerning medically actionable conditions in childhood and carrier status. They had more mixed feelings and contradictory ideas about adult-onset medically actionable conditions, because information might be distressing and treatment options available only in the future. Several participants expressed their preference not to exclude the option of disclosure, and stressed that they wished to decide for themselves. In the case of carrier status for autosomal recessive disorders, participants emphasised the importance of the information with regard to parents' and children's reproductive decision-making, and its relevance to other children and relatives. After all, such information could be important for considering reproductive options. Although some studies have reported that participants encountered difficulties in understanding WES research, such as the heredity issues and their implications for other family members [8, 23], the participants in our study gave no reason to doubt the accuracy of their knowledge, with the exception of the implications of being a carrier of an autosomal recessive condition.

UFs and lack of (preventive) medical treatment

Participants were more ambivalent about adult-onset medically non-actionable conditions and, though they

appreciated the institutional policy of non-disclosure, they felt that they should be allowed to decide for themselves. In addition, participants often emphasised the usefulness of knowledge not rooted in (preventive) medical treatment, because of possible future availability of medical treatment options for currently untreatable conditions.

Interestingly, in contrast to results from our previous study [14] regarding parental considerations for or against receiving UFs for their child undergoing WES for a developmental delay, parents in this study mainly emphasized their responsibility for the well-being of their children, and rarely explicitly discussed the child's future autonomy —understood in terms of postponing the decision to disclose UFs for an adult-onset condition or carrier status until the child reached adulthood. We speculate that this difference between the two studies is due to two contextual factors. Firstly, in the current study, the three adolescent children who were interviewed actively participated along with their parents in the decision-making process regarding WES and the return of results. In our previous study, none of the children was able to participate in the decision-making process, due to their developmental delay. The parents of these children with DD may have been more conscious of whether their child would be able to acquire a certain degree of autonomy in the future, while this was self-evident to the parents in the present study. Hence, the whole question about whether or not the child could make choices itself was brought to the fore. Secondly, the policy context in which our previous study was conducted and the policy context of this study differ from one another, due to a modification in the UMC's policy when the two sets of interviews were conducted [14]. According to the policy at the time of the interviews in our previous study, parents were able to choose whether or not to receive UFs for their child for severe conditions only medically actionable in adulthood, with the default being an 'opt-out'; whereas in this study, the centre's policy required these types of UFs always to be disclosed. It is possible that offering choices over which types of UFs to receive or withhold might have influenced respondents' answers.

The adolescent child and UFs

Among the adolescents interviewed, there was already a strong awareness of being able to choose and make decisions, and an explicit desire to be taken seriously. They were also sensitive to parents or professionals withholding information; they did not want anything to be kept secret for them. In the case of actionable conditions, the adolescents appreciated the benefits of early interventions, but they also recognised the potential burden of knowledge. In any case, they felt it was important to be able to decide for themselves regarding UFs for treatable conditions. Regarding UFs for conditions without treatment options, adolescents agreed with the policy of not communicating such UFs, because this type of information may cause mental distress—yet they were of the opinion that the possibility should be kept open for the individual who would like to have this knowledge, for whatever reason. However, they did not express any thoughts about their parents, who might be hesitant and/or reluctant about accepting/foregoing such results, and their considerations for doing so, or about the impact of results on siblings. After all, parents can be expected to consider the interests of both the child in question and those of other children, as well as of themselves. The developmental tasks of adolescents, i.e., taking responsibility, re-evaluating the norms and values of their parents, and the challenge of increasing independence, become very explicit with regard to decisions on genetic testing and issues related to illness and health [38]. But there may be a limit to whether an adolescent child is already able to comprehend the implications of far-reaching decisions, both for him- or herself and for others.

The parents of the (future) competent child and UFs

The parents in this study have indicated that on the one hand they involve the child in making decisions, but on the other they also feel responsible for the child's well-being. Parents are challenged to decide and act in the best interests of the child [33]. They wish their child to have a carefree childhood and express their intention to inform their child about UFs when the time is right. An important issue for parents is when to tell their children what has been discovered. However, they notice that there is never a right time to do this, and that they might be tempted to postpone telling the 'bad news'. Most parents indeed seem consistently to reason from their view on parental responsibility in the present, which may inhibit their explicit thoughts about future autonomous choices of their child. Parents feel responsible and must therefore find a balance between what is good for the child in question and what is good for the other members of the family system. The genetic counsellor might encourage parents to explore whether their motives or interests are purely child-centred or purely parent-centred. Child-centred motives concern protection, carefree youth, self-esteem, stigma, social relationships, and (near) future autonomy. Parent-centred motives concern the perceived need to feel empowered to control all information that may be relevant for fulfilling one's parental responsibility, but also their hesitation and reluctance to tell such news because of feelings of guilt, shame, or an inability to respond to the child's emotions. Results from this study show that parents do realise that far-reaching knowledge about their child and family, whether disclosed to the children or not, can result in a veil being draped over the family, a shadow that will

always be there, which may make them hesitant in favouring the disclosure of UFs. Furthermore, parents may, possibly wrongly, believe that their child cannot fully grasp the far-reaching and long-term implications of test results, and consequently fail to take the child's autonomy/decisional capacity in the (near) future into account. As a result, they may consider the decision regarding UFs to fall within their responsibility as parents.

Interestingly, in this study, parents and their adolescent children jointly discussed WES and the issues of UFs. Parents took it for granted that the children were involved in the decision-making process respecting the (increasing) autonomy. While parents and adolescents agreed on their need for information, the parents showed awareness of a broader scope of the impact of results, such as the impact on other stakeholders. This can result in a tension between the interests of parents and those of adolescent children, which should be recognised and addressed in genetic counselling.

As far as treatable conditions are concerned, parents in this study believed that they, as well as the adolescent child, have the obvious right to be informed, also when it comes to being identified as a carrier of an autosomal recessive condition. Although they understood that professionals feel a responsibility when it comes to non-actionable conditions, parents still argued for an opt-in, that is, the right to be informed without restrictions. Parents regarded themselves as more competent than professionals in judging what is best for their child. However, in the era of patient-centred medicine, an ideal of shared decision-making has emerged that advocates that healthcare professionals and patients (or their representatives) exchange information and views, and jointly reach a decision [39, 40]. We consider the implications of this ideal in the context of decision-making about WES-findings in a separate paper [41].

Limitations

This study concerned a small group. However, the group was not self-selected on the basis simply of people who had accepted WES: two couples refused participation in this interview study for unknown reasons. A further limitation is that it remains an open question whether parents and adolescents sufficiently understood the information provided in the counselling sessions, especially with regard to the relevance and impact of autosomal recessive conditions, which seemed in some cases to be misunderstood, and the risk for siblings and relatives overestimated.

The purpose of the interviews was to gain more insight into parental considerations around UFs. One of these considerations could be that parents prefer not to know certain—late-onset—UFs, with a view to the future autonomy of the child. Although we deduced parental considerations regarding the future autonomy from the rest of the discourse, we suggest that in a future study this issue should be explicitly asked about and explored.

Respondents in this study were Caucasian. Given the relevance of culture-related family dynamics, similar studies need to be conducted with families from other ethnic backgrounds.

Conclusion

In this exploratory study of the preferences and considerations of parents of children undergoing WES for reasons other than developmental delay, we have observed a strongly shared view that any information that might in whatever way be relevant to the health and well-being of their child in the course of its further life, should be available to them to enable them to exercise their parental responsibility. Although parents appreciated the restrictions imposed by the policy of the institution, they also felt that information about non-actionable disorders, and information concerning carrier status of autosomal recessive disorders and later-onset conditions, should be an option in case parents felt they needed the information in order to care for their child and to protect their child's best interests. Our observations suggest that genetic counselling requires both flexibility of the results-return process and options for the categories of results to be returned. We have seen in this study how parents include their adolescent children in WES decision-making. We found them inclined to take adolescents seriously and acknowledge their incipient autonomy by granting them a certain degree of self-determination. They seem to take into account that the adolescent is a stakeholder in the process of their medical condition. However, parents of pre-adolescent children did not explicitly refer to the child's future autonomy as a reason for not wanting to be informed about UFs about medically actionable conditions with a later-onset, or about medically unactionable conditions.

A pitfall in a centre's policy might be that emphasis is put on (the transfer of) information at the expense of psychological characteristics and features of family-systems, and of the counselling process [24]. Transfer of genomic information must take into account the personal values and needs of all involved. Respect of the future autonomy of the child is seen as a prima facie argument in medical professional guidelines and ethical literature about the disclosure of UFs in paediatric WES [42]. Counselling should entail the patient-tailored elaboration of what needs to be told: when, to whom, why, and how. The findings of this study show the urgency of the ethical question as to whether and how the consideration of the future autonomy of the child should be taken seriously in genetic counselling (should

counsellors address this aspect during counselling?), and the disclosure policy of clinical centres (should all UFs be disclosed to parents?).

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Compliance with ethical standards

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

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