European Journal of Human Genetics (2021) 29:930–939
https://doi.org/10.1038/s41431-021-00834-9

ARTICLE

The impact of unsolicited findings in clinical exome sequencing, a qualitative interview study

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Received: 19 October 2020 / Accepted: 10 February 2021 / Published online: 26 February 2021

Abstract

Unsolicited findings (UFs) in clinical exome sequencing are variants that are unrelated to the initial clinical question the DNA test was performed for, but that may nonetheless be of medical relevance to patients and/or their families. There is limited knowledge about the impact of UFs on patients' lives. In order to characterise patient perceptions of the impact of an UF, we conducted 20 semi-structured face-to-face interviews with patients and/or their relatives to whom an UF predisposing to oncological disease ($n = 10$) or predisposing to a cardiac condition ($n = 10$) had been disclosed. We have identified a psychological, physical and financial aspect of the perceived impact of UF disclosure in exome sequencing. Actionability, understanding, patients' pre-test health and social context were influencing factors, according to our participants. Although most expressed considerable psychological impact initially, all but one participant would choose to undergo genetic testing again, knowing what they know now. These novel findings provide insight in patients' perspectives on the impact of UF disclosure. Our study highlights the value of incorporating patients' perceptions in UF disclosure policy.

Introduction

Comprehensive genetic testing by next generation sequencing techniques (NGS) is becoming standard care in many clinical settings [1]. Sequencing the entire exome or genome allows the detection of unsolicited findings (UFs). These are defined as (likely) pathogenic variants in disease-causing genes which are unrelated to the initial clinical question for which the genetic test was performed but that may nonetheless be of medical value to the patients and/or their family [2]. Although throughout the years various terms (i.e. incidental findings, unexpected findings) have been used to describe these findings, UFs is currently considered to be the most appropriate [3–5].

For more than a decade, discussions worldwide have weighed arguments in favour and against disclosure of UFs [6]. A major argument which has been used in favour of disclosure is that knowledge about genetic predisposition could enable prevention or early detection of the condition to which the UF predisposes, potentially resulting in decreased morbidity and mortality. Potential distress, anxiety, additional costs and overtreatment have been mentioned to weigh against disclosure [6]. It has further been argued that if the perceived negative impact of an UF is greater than its potential clinical utility, the UF should not be disclosed [6, 7]. Berg et al. were the first to publish recommendations for the disclosure of UFs [2]. The American College of Medical Genetics (ACMG) provided recommendations to promote standardised disclosure of additional findings that should be actively looked for, or so called 'secondary findings' (SF) [8]. In contrast, the European Society of Human Genetics (ESHG), as well as the

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41431-021-00834-9.

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Canadian College of Medical Genetics and EuroGentest argued to limit the identification (and disclosure) of UFs, considering their potential negative implications, which would conflict with the medical maxim "first, do no harm" [9–12]. Both professional societies recommend reporting additional variants which are found unintentionally, only if they predispose to serious, but treatable or preventable health issues, considering both the health of patients (and their family members) as well as patient autonomy [8, 13].

In order to evaluate these recommendations, we believe insight into the perceived impact of UFs in clinical care is essential. The impact of SFs has been evaluated by the Clinical Sequencing Exploratory Research Consortium (CSERC) in both the diagnostic and research setting [14, 15]. These studies report that a minority of patients experience a negative impact due to anxiety and/or difficulties in conceptualising the associated risks. To our knowledge, no study to date has evaluated the impact of the disclosure of UFs.

By conducting a semi-structured qualitative interview study among patients and their family members to whom an UF was disclosed, we characterise their perceptions of the impact of UFs in clinical exome sequencing.

Methods

Study design and setting

We used semi-structured interviews to ask participants about the impact of the disclosure of an UF on their lives. We intended to interview index patients (i.e. the persons who initially underwent genetic testing). In case of incompetent or minor index patients, we interviewed family members assigned as their legal guardian in case of incompetent or minor index patients. The Research Ethics Committee Arnhem-Nijmegen (registration number: 2018-4909) and the Research Ethics Committee Maastricht (registration number: 2018-0825) both approved this study.

Participants and recruitment

Between 2013 and 2018, material of 16,482 consecutive index patients was sent to the Genome Diagnostic Laboratory of the Radboud university medical centre for exome sequencing. According to their local policy, which is line with the European recommendations on UF disclosure, UFs were disclosed to 86 patients [16]. These concerned mostly variants predisposing to either oncological or cardiac disease [13, 17] (van der Schoot et al., manuscript in preparation).

Using convenience sampling, we recruited participants to whom an UF had been disclosed, predisposing to either oncological or cardiac disease. Eligible index patients had been counselled for DNA testing at the department for clinical genetics at the Radboud university medical centre or at Maastricht University Medical Centre. To ensure a varied sample, we continuously assessed if there was variation in index age (minors, reproductive age), genes, the condition DNA testing was performed for, pathologies the UF was related to and the time since disclosure. Clinical geneticists were contacted to ask patients or their legal guardians for permission to invite participation after which interested potential participants were contacted by a researcher (VS) (Supplementary Fig. 1). Interviews were conducted by a resident in clinical genetics (VS) and a trained intern (SV) under supervision of a skilled qualitative interviewer (AO) at a time and place convenient for the participants. Informed consent was obtained prior to each interview. The interviews were held between February and October 2019 and lasted between 32 and 86 min. We reached data-saturation after 20 interviews.

Topic guide

We designed a topic guide to chronologically address relevant aspects of the impact of an UF (pre-test counselling, disclosure, follow-up and social context), which was refined after the first interviews to better fit our research questions.

Data-analysis

Interviews were audio-recorded, transcribed verbatim, anonymized and subsequently analysed using ATLAS.ti (version 8.2, Scientific Software Development, GmbH, Berlin, Germany). We used thematic content analysis, a qualitative approach focussing on identification of themes and concepts without predetermined hypotheses or theories [18]. The first transcript was analysed by three members of the research team (VS, SV, AO) and all subsequent transcripts were independently analysed by two members (VS, SV). Any discrepancies in the analyses were discussed until consensus was reached. The codes we used emerged from the data and were refined in an iterative process of coding, comparing and refining. They were subsequently grouped into minor categories and major themes by three members of the research team (VS, SV, AO).

Results

We conducted 20 semi-structured face-to-face interviews with index patients and/or their family members about the UF that had been disclosed, predisposing to oncological ($n = 10$) or cardiac disease ($n = 10$). In fourteen interviews,

Table 1 Participants characteristics.

Nr.	Index/ family	Participant age range	IF present in participant	Symptoms of IF in participant	Preventive measures implemented by participant	Moment of disclosure	Indication genetic testing	Main reason genetic testing	Causal variant found	Index incompetent adult or minor
Variants predisposing to oncological disease ($n = 10$)										
1	Index	21–30	Yes	No	Reproductive options Future periodic follow-up and prophylactic surgery	2 years ago	Congenital anomalies	Reproduction	No	No
2	Index	51–60	Yes	No	Periodic follow-up	2 years ago	Vision disorder	Family	No	No
3	Index	61–70	Yes	No	Not indicated (age-related)	1 year ago	Haemostatic disorder	Understanding	No	No
4	Index	31–40	Yes	No	Periodic follow-up	>2 years ago	Vision disorder	Understanding	Yes	No
5	Index Family	41–50 61–70	Yes Yes	No No	Surgical Surgical	1 year ago	Cardiovascular disease	Understanding	No	No
6	Index Family	21–30 51–60	Yes Yes	No No	Periodic follow-up and future prophylactic surgery Prophylactic surgery	1 year ago	Developmental disorder	Understanding	No	Incompetent adult
7	Family	31–40	Yes	No	Prophylactic surgery	1 year ago	Developmental disorder	Understanding	No	Minor
8	Family	41–50	Yes	No	No periodic follow-up as had been recommended by clinician	1 year ago	Neurological disease	Understanding	Yes	Minor
9	Family	41–50	Yes	Yes	Periodic follow-up and prophylactic surgery	1 year ago	Developmental disorder	Understanding	No	Minor
10	Family	21–30	Unknown	No	n.a.	>2 years ago	Haemostatic disorder	Understanding	No	Minor
Variants predisposing to cardiac disease ($n = 10$)										
Nr.	Index/ family	Participant age range	IF present in participant	Symptoms of IF in participant	Preventive measures implemented by participant	Moment of disclosure	Indication genetic testing	Main reason genetic testing	Causal variant found	Index incompetent adult or minor
1	Family	51–60	Yes	No	Periodic follow-up	<1 years ago	Neurological disorder	Understanding	No	Incompetent adult
2	Family	31–40	Yes	No	Life-style and periodic follow-up	<1 year ago	Developmental disorder	Understanding	No	Minor
3	Family	31–40	No	No	n.a.	1 year ago	Neurological disorder	Understanding	No	Minor
4	Family	31–40	Yes	No	One time follow-up	2 years ago	Congenital anomalies	Understanding	No	Minor
5	Family	41–50	Yes	No	No periodic follow-up as had been recommended by clinician	1 year ago	Neurological disorder	Understanding	Yes	Incompetent adult

Table 1 (continued)

Nr.	Index/ family	Participant age range	IF present in participant	Symptoms of IF in participant	Preventive measures implemented by participant	Moment of disclosure	Indication genetic testing	Main reason genetic testing	Causal variant found	Index incompetent adult or minor
6	Family	51–60	Yes	No	Periodic follow-up	2 years ago	Developmental disorder	Understanding	No	Incompetent adult
7	Family[a]	21–30	Unknown	No	n.a.	<1 year ago	Neurological disorder	Family	No	Incompetent adult
	Family[a]	31–40	Unknown	No	n.a.					
	Family[a]	61–70	Yes	No	Periodic follow-up					
8	Index	18–20	Yes	No	One-time follow-up	2 years ago	Immunodeficiency	Reproduction	Yes	Incompetent adult
	Family	51–60	No	No	n.a.					
9	Index	31–40	Yes	No	Periodic follow-up	>2 years ago	Oncological disease	Understanding	No	No
10	Index	31–40	Yes	No	Periodic follow-up	1 year ago	Haemostatic disorder	Future perspective	No	No

[a]Family other than parents.

we spoke to the family (parents in all but one interview) about the impact of the finding from the perspective of the index and their own experience, since all but two relatives had tested positive for the UF as well. For index patient and participant characteristics see Table 1.

Psychological, physical and financial impact

Describing the impact of UF disclosure, participants mentioned aspects within three different dimensions: the psychological, physical and financial impact. Participants interrelated these themes and described four mediating factors, namely actionability, understanding, pre-test health and social context. Interviews with index cases yielded the same themes as those which emerged from interviews with family members.

The psychological impact was highlighted in all interviews. Both short- and long term impact were addressed frequently. Most participants indicated they were at first overwhelmed and some were even 'shocked' by the news of the UF.

"Actually, hearing the news was a shock; you don't expect it, certainly not at a young age. It was quite intense." (Oncological/Patient)

They acknowledged this initial feeling to fade with developing a better understanding of the meaning of the UF and the consequences for their well-being. Most participants said that, after a while, they would think no more of the UF. One participant said:

"But as soon as you get back to your normal life, and you pick up your daily routines, you quickly forget about it." (Cardiac/Family)

Patients attributed the physical impact to the different invasive (i.e. prophylactic surgery, colonoscopies) and non-invasive (i.e. imaging by CT, X-ray, ultrasound or MRI, ECG) preventive measures, lifestyle changes and reproductive choices.

Participants with an UF predisposing to oncological disease all said they were offered periodic follow-up (i.e. colonoscopies or non-invasive imaging) or prophylactic surgery, depending on their age. They expressed that these measures would enable timely diagnosis or prevent the development of malignancies. Invasive measures were described as to be unpleasant but acceptable considering their purpose.

The majority of participants with an UF predisposing to cardiac disease said they were offered periodic follow-up, according to their age and the condition to which the UF predisposes.

This allowed them to assess their current health status and could make them feel reassured no therapy was needed yet. Some were seen once by a cardiologist who told them no further assessments were indicated.

A few participants with an UF predisposing to cardiac disease talked about lifestyle changes: they reduced their workload in order to reduce their stress level or tried to become fitter by going to the gym.

One participant with an UF predisposing to oncological disease mentioned she had received counselling regarding reproductive consequences, namely timely starting a family and the option to try to prevent the condition in offspring.

Most participants were aware of possible consequences for taking out insurance (NB. In the Netherlands, results of genetic testing can might be requested by the insurance company before approval of the request to take out life insurance over a certain threshold for the insured sum). While none of the participants talked about having experienced actual adverse financial effects, they did mention worrying about future financial plans and indicated having reservations about testing children or informing family members because of this. A father said:

"They're young, they want a mortgage and then it would be like: 'are you under treatment, do you have an illness or anything?' So I told them: 'If I were you I would not get myself tested.'" (Cardiac/Family)

A few participants mentioned contemplating not to undergo preventive assessments because of the costs of these treatments. (NB. In the Netherlands, health insurance covers these costs after patients have paid a deductible).

Actionability

All participants underscored the importance of the actionability of the UF, meaning to what extent preventive measures are available. Most participants said that the availability of preventive measures made them value disclosure. A guardian said:

"But I can say: okay, now I know and they can do something." (Cardiac/Family)

Participants described that learning about interventions provided them with more insight in the actual consequences of the UF for their health. Those who underwent more definitive medical interventions to prevent the development of oncological conditions (i.e. prophylactic surgery), said to feel relieved from their fear of becoming ill. Most participants who underwent (periodic) screening to detect disease early mentioned to feel reassured as well. Some participants with an UF predisposing to cardiac disease indicated that they were aware they could develop the condition in question in the interval between cardiac assessments.

Several participants with an UF predisposing to cardiac disease questioned the knowledge and experience of the cardiologist to whom they were referred. For example, one participant does not undergo cardiac screening because the cardiologist told him this was not necessary:

"[The doctor] asked me: 'How did you end up here?' I told him that genetic tests showed that there was a gene missing or wrong or I don't know what exactly. And he said: 'That's a load of nonsense. That's still in its infancy, they're just crying wolf.'" (Cardiac/Family)

Some participants said that they felt insecure about their health before being seen for medical interventions. Several participants experienced the time they had to wait for their first workup as unpleasantly long. Multiple participants told us that their follow-up consults had ended. They indicated feeling uncertain about their current health status, not knowing if since their final assessment, they might have developed the condition.

None of the participants who underwent periodic workups had been diagnosed with the condition and no participants had required cardiac therapy or curative surgery.

Understanding

Participants frequently addressed their ability to comprehend the consequences of the UF. They said to feel less occupied by worries once they had developed a better understanding. During the interviews, we heard of multiple factors enabling participants to better understand these consequences: the pre- and post-test counselling; the disclosure; associations with (family) medical history; gathering information and follow-up.

All participants indicated that before consenting to the DNA test, they were informed about the possibility of detecting an UF. Some said they told their counsellors explicitly they wanted to know if a genetic variant related to another condition was found. Most participants mentioned that no genetic testing could have been performed had they not consented to UF disclosure. Participants mentioned the return of the DNA test results took a few months to a year. Most participants told us they had forgotten about the possibility of potential UF disclosure when receiving the DNA test result. They said to be surprised or even distressed. Some talked about how this diminished their ability to absorb further information about the UF. The mother of a patient:

"It's about your baby. It's not something you ever want to hear. At that moment, everything they tell you just goes past you." (Oncological/Family)

Most participants indicated they felt able to understand the information provided. Several participants told us they did not fully comprehend the finding. For example, some mentioned they only truly realised the implications for family members at a later stage. Participants sometimes said that they had been focussing on learning whether exome sequencing revealed a causal variant rather than learning about an UF, especially when hearing about the outcome via a telephone call.

Only one participant said to have had experienced symptoms of the condition the UF was related to at the time of UF disclosure (Oncological/Family).

Several participants with an UF predisposing to a cardiac condition said to be struggling with the answer to the question '*Am I sick or am I healthy?*'. We found some of them conceptualised their health status regarding the UF (affected by the condition the UF predisposes to, not affected, or something in between?) differently, even within the same interview.

Multiple participants immediately related the UF to conditions that were already known to run in the family. A woman to whom an UF predisposing to ovarian cancer was disclosed:

"I know my mom had cervical cancer, and my second cousin had cancer before her. So you can kind of assume that something like that would be running in the family." (Oncological/Patient)

Participants who related the UF to their family's medical history, would conclude that in a way it made sense that the UF was found, even if their clinicians did not confirm that the conditions that ran in the family could be caused by the UF.

Several participants said that they had have tried to learn more about the UF by looking for information online. Others indicated they did not use any other resources than those provided by their clinician, to avoid being informed incorrectly.

Most participants mentioned that they had been contacted by their clinical geneticist after a period of time. The majority of participants who had not heard from their geneticist after the disclosure, expressed being uncertain about the consequences of the UF. A woman with an UF predisposing to heritable breast cancer told us she did not know if this variant could be related to her thrombotic disorder:

"We hoped to find the explanation for my complaints but we did not. Unless…I don't know…Maybe if you have one gene you can get very mild complaints. I don't know. It is not clear to me." (Oncological/Patient)

Overall, most participants indicated feeling that they had developed a comprehension of the nature and implications of the UF. However, when discussing facts such as risks during the interviews, we regularly found their knowledge to be inconsistent with current literature and clinical guidelines, particularly in interviews about UFs predisposing to cardiac disease.

Pre-test health

During the interviews, participants often compared the severity of the condition the DNA test was initially performed for, with the perceived severity of the condition the UF predisposes to (e.g. the burden of untreatable epilepsy compared to a predisposition to an actionable cardiomyopathy). Many expressed worries about their own health or, in case of family, about the health of their child. They would qualify the condition the UF predisposes to as being relatively less severe than the initial condition. Also, most participants said that they accepted the possibility of disclosure of an UF and the consequences of an UF for the sake of finding a diagnosis. Family of a patient with a severe neurological disorder told us:

"On the one hand it's a shock, because it's yet another thing to deal with. On the other hand it's an absolute pain to still not have a diagnosis. That is just unacceptable." (Cardiac/Family)

They indicated to be urgently looking for a way to understand and/or find proper treatment for the health condition of the index patient which they said motivated them to undergo genetic testing. All but one participant answered '*yes*' to the question '*would you have chosen to undergo the DNA test, knowing what you know now?'*. The father of a girl with epilepsy and a developmental disorder who had a cardiac UF disclosed, was not sure whether he would have chosen to undergo genetic testing. He questioned whether the clinical utility could outweigh the resulting financial consequences.

Social context

Participants discussed sharing the news of the UF with relatives in order to inform them about their risks and/or hoping to find comfort. They said to feel burdened by having to be the bearer of the bad news, especially when they experienced poor intrafamilial communication, vulnerability of family members or fear of negative consequences for their relationships. Some participants mentioned their clinical geneticist requested them to inform family members and told them whom to inform and how. They said this made them more comfortable when confronting their family.

With few exceptions, participants said that family members' reactions were mostly understanding and calm. They mentioned that when they shared the news with relatives, friends or colleagues to seek comfort, those people generally reacted compassionately.

Discussion

Over the course of 20 in-depth interviews, we encountered a psychological, physical and financial aspect of the perceived impact of UF disclosure in exome sequencing. Actionability, understanding, patients' pre-test health and social context were influencing factors for these three aspects, according to our participants.

Although most expressed considerable psychological impact initially, all but one participant would choose to undergo genetic testing again, knowing what they know now. This finding is in line with previous qualitative studies about UFs across different clinical settings, as well as for SFs in genetic testing [14, 15, 19]. As in our study, the consequences of the UF are generally considered to be more beneficial than adverse, which would argue in favour of UF disclosure [6].

Actionability was a major theme throughout all interviews, similar to studies on the impact of SFs in DNA testing [20, 21]. The majority of the participants valued disclosure as they were offered measures that would enable early detection or prevention. This finding affirms current policy guidelines in which actionability is a prerequisite for UF disclosure [13].

Even though all variants disclosed were deemed 'medically actionable' by an expert panel [17], the experienced effectiveness differed among participants. Generally, preventive measures offered for cardiac disease were perceived to be less effective than those to prevent oncological conditions. In this context, it has been suggested that patients value "more concrete" interventions [22]. Effectivity of preventive measures has been an acknowledged criterion for UF disclosure, but it is subject to personal judgments of genetic professionals [23]. It would be of added value to incorporate patients' perceptions of which interventions are effective and their views on the perceived importance of this criterion.

Only one participant (Oncological/Family) indicated being symptomatic, which reflects the low prevalence of phenotypic expression of UFs [24]. Reduced penetrance of both cardiac as well as oncological variants in the context of UFs/SFs previously has led genomic professionals to question their utility [25–27]. In our study, the value of the UF was mainly attributed to its utility. Potential limited utility of UFs should be embedded in disclosure policy and clinical studies on expression and penetrance of UFs would be of added value [27].

Participants frequently addressed the value of being able to *understand* the finding. They mentioned the relevance of being provided with adequate and timely information through thorough pre- and post-test counselling and follow-up consultations, which has been previously emphasised for delivering bad news in genetic testing and in other medical procedures [22, 28–30]. Understanding allows patients to develop disease conceptualisation, contributing to their empowerment. Feelings of empowerment could suppress the initial negative feelings regarding the UF as has been seen in the context of secondary findings [15].

Some of our participants still expressed uncertainty about gene associated risks. Notably, we regularly found participants' knowledge to be inconsistent with current literature and clinical guidelines (e.g. no genetic testing of first degree relatives was recommended in case of an autosomal dominant predisposition for cardiomyopathy in the index with a known low de novo occurrence [31]).

Whether this was due to a lack of understanding or inadequate counselling, is unclear. We saw the extent to which the finding was understood differed between cardiac and oncological variants. Variants predisposing to cardiac disease make up a substantial portion of UFs (van der Schoot et al., manuscript in preparation) and SFs [32], and – compared to variants predisposing to oncological disease – they are known to display reduced penetrance and phenotypic variability [31, 33]. In our study, neither participants with a cardiac UF, nor their family members were known to have experienced any UF-related symptoms. The complex relationship between genetic variants and the associated phenotypes are a challenge to the genetic counselling process, and potentially limit health care professionals in enabling patients' understanding. Counselling UFs influences patients' behavioural responses [19, 34]. Inadequate information and guidance by health care professionals due to the complexity of UFs could endanger the fulfilment of UFs' actionability. This further emphasizes the need to critically consider if adequate counselling and follow-up can be ensured before UF disclosure [34].

The *pre-test health* was the third major theme. The urge to find a diagnosis for the index patient was highlighted in all interviews and has previously been noted for genetic testing in general [35]. Participants told us no genetic testing would be performed when they would not consent for UFs. In our centre, targeted panel analysis is offered first, which carries a very low probability of UFs. Thus, a requirement to consent to disclosure of UFs applied only to those in whom genetic testing of the entire exome was performed, as this carries a higher yield of UFs (van der Schoot et al., manuscript in preparation). Over the 2013–2018 period in which our participants were counselled for genetic testing, a specific opt-out option for UFs was not available when analysing the complete exome. This has been a matter of intense debate. An opt-out option will be implemented in national consensus-based guidance for UFs. The majority of our participants stated however, that they needed to consent for IF disclosure to have genetic testing performed, rather than mentioning having had the option to restrict genetic testing to a targeted panel or discussing the possibility of an opt-out.

For them, the imperative to find an explanation for their own or their child's complaints seemed to overrule the impact of the UF. Most participants qualified the impact of the UF as less severe than the impact of the condition genetic testing was performed for, which were generally conditions that were poorly understood and/or for which proper treatment options were lacking. This in contrast to the

medically actionable conditions to which UFs by definition predispose. Although the importance of the context in which genetic testing is performed has been highlighted previously [15, 20], understanding how it can relate to experiencing genetic testing provides a new perspective of embedding contextual factors in counselling for DNA testing.

A minority of the participants addressed the *social context* to be of influence on the impact of UF disclosure. Participants particularly acknowledged not fully grasping implications for family members when consenting to genetic testing. As has been pointed out before, this aspect requires attention before deciding to undergo genetic testing [36]. Overall, implications of sharing the news of the UF with relatives did not appear to differ from what we know from studies about sharing results of genetic testing in general [37].

The *financial impact* was another minor theme. Possible financial consequences were a main reason to have reservations about sharing the news with family. The perceived financial burden showed similarities with what was found in previous studies on presymptomatic genetic testing [38]. At the time of the interview, none of the participants had experienced any actual financial consequences. Of note, the financial impact largely depends on the nature of the health care system.

Overall, participants did not experience a great *physical impact* of preventive measures. This is an important finding, as burdening patients with unnecessary interventions has been put forward as a reason to critically consider disclosure of UFs [6]. Offering more invasive measures (i.e. prophylactic surgery, ICD) should be carefully considered [26, 39].

Strengths and limitations

Our study investigated patient experiences with the impact of an UF following clinical exome sequencing. These results provide valuable insight for both clinical genetics practice as well as policymaking.

Limitations of our study include the risk of bias, given its relatively small sample size and the recruitment which was restricted to one genetic centre and was not limited to index patient inclusion. This study assessed the impact of an UF as perceived and described by index patients or their guardian family members. Recall bias and choice-supportive bias might have impacted participants' descriptions of their experiences. Although the absolute number of participants was relatively small, this sample size is common for qualitative research, considering its labour-intensiveness and the amount of information each interview yields. In addition, since UFs are a relatively rare occurrence, our sample constitutes 22% (20 of 89) of the total number of UFs detected in our hospitals over a 5-year period. We did not address the impact of UFs other than cardiac and oncological variants. However, UFs related to these two disease entities are the most frequent additional findings in exome sequencing [32]. Since participants were recruited from one genetic centre, our results might not be representative of practice in the Netherlands overall. The provided participant characteristics' and access to the local policy guidelines enable readers to assess whether these data are applicable to other genetic centres. We did interview both index patients as well as their family (i.e. parents). However, since most family members had tested positive for the UF as well, we believe their contribution to this study to be valuable. We found that the themes that were brought up by family members generally mirrored those which emerged from interviews with index patients.

Time since disclosure has been less than five years for all of our participants. Only one of our participants had presented with symptoms related to the UF when conducting the interviews, meaning for the others, no prevention or early detection had yet occurred. The extent to which the potential treatability or prevention has been fulfilled might influence participants' appreciation of the actionability. Therefore, long term evaluation would be needed to address this aspect.

The reporting of this study generally follows recent qualitative research standards (ref. COREQ).

Conclusion

In conclusion, patients and their family members express a psychological, physical and financial impact of UF disclosure. Overall, the perceived impact would not keep patients from undergoing genetic testing again, knowing what they know now. To ensure informed consent in pre-test counselling, counsellors should encourage consideration of all potential outcomes of genetic testing, since the desire for a diagnosis potentially lessens the receptiveness for information on UFs. Post-test counselling should enable understanding of the finding, contributing to fulfilling its actionability. The importance of the actionability criterion suggests the need for critical consideration of the perceived effectiveness of interventions and the clinical utility of disclosure of variants in the context of UFs.

Acknowledgements We would like to thank all participants for sharing their experiences and thoughts. Also, we thank the clinicians who contacted their patients to ask for participation in this study. Finally, we express our gratitude for the work of the local expert committee on unsolicited findings in genetic testing.

Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

References

1. Srivastava S, Love-Nichols JA, Dies KA, Ledbetter DH, Martin CL, Chung WK, et al. Meta-analysis and multidisciplinary consensus statement: exome sequencing is a first-tier clinical diagnostic test for individuals with neurodevelopmental disorders. Genet Med. 2019;21:2413–21.
2. Berg JS, Khoury MJ, Evans JP. Deploying whole genome sequencing in clinical practice and public health: meeting the challenge one bin at a time. Genet Med. 2011;13:499–504.
3. Christenhusz GM, Devriendt K, Dierickx K. Secondary variants-in defense of a more fitting term in the incidental findings debate. Eur J Hum Genet. 2013;21:1331–4.
4. Tan N, Amendola LM, O'Daniel JM, Burt A, Horike-Pyne MJ, Boshe L, et al. Is "incidental finding" the best term?: a study of patients' preferences. Genet Med. 2017;19:176–81.
5. van El CG, Cornel MC, Borry P, Hastings RJ, Fellmann F, Hodgson SV, et al. Whole-genome sequencing in health care. Recommendations of the European Society of Human Genetics. Eur J Hum Genet. 2013;21:S1–5.
6. Christenhusz GM, Devriendt K, Dierickx K. To tell or not to tell? A systematic review of ethical reflections on incidental findings arising in genetics contexts. Eur J Hum Genet. 2013;21:248–55.
7. Ali-Khan SE, Daar AS, Shuman C, Ray PN, Scherer SW. Whole genome scanning: resolving clinical diagnosis and management amidst complex data. Pediatr Res. 2009;66:357–63.
8. Kalia SS, Adelman K, Bale SJ, Chung WK, Eng C, Evans JP, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017;19:249–55.
9. Matthijs G, Souche E, Alders M, Corveleyn A, Eck S, Feenstra I, et al. Guidelines for diagnostic next-generation sequencing. Eur J Hum Genet. 2016;24:1515.
10. Dondorp WJ, de Wert GM. The 'thousand-dollar genome': an ethical exploration. Eur J Hum Genet. 2013;21:S6–26.
11. Parker LS. The future of incidental findings: should they be viewed as benefits? J Law Med Ethics. 2008;36:341–51. 213
12. de Wert G, Dondorp W, Clarke A, Dequeker EMC, Cordier C, Deans Z, et al. Opportunistic genomic screening. Recommendations of the European Society of Human Genetics. Eur J Hum Genet. 2020. Epub ahead of print.
13. Vears DF, Senecal K, Clarke AJ, Jackson L, Laberge AM, Lovrecic L, et al. Points to consider for laboratories reporting results from diagnostic genomic sequencing. Eur J Hum Genet. 2018;26:36–43.
14. Wynn J, Lewis K, Amendola LM, Bernhardt BA, Biswas S, Joshi M, et al. Clinical providers' experiences with returning results from genomic sequencing: an interview study. BMC Med Genom. 2018;11:45.
15. Hart MR, Biesecker BB, Blout CL, Christensen KD, Amendola LM, Bergstrom KL, et al. Secondary findings from clinical genomic sequencing: prevalence, patient perspectives, family history assessment, and health-care costs from a multisite study. Genet Med. 2019;21:1100–10.
16. Radboudumc. Policy document on 'Disclosing incidentalfindings in a diagnostic setting' by the division Genome Diagnostics of the Department of Human Genetics, Radboudumc. 2018.
17. center Rum. Policy on discloure of incidental findings in genetic diagnostic practice. Nijmegen: Committee of Incidental Findings; 2020.
18. Braun VaC V. Using thematic analysis in psychology. Qualitative Res Psychol. 2006;3:77–101.
19. Freiman MR, Clark JA, Slatore CG, Gould MK, Woloshin S, Schwartz LM, et al. Patients' knowledge, beliefs, and distress associated with detection and evaluation of incidental pulmonary nodules for cancer: results from a multicenter survey. J Thorac Oncol. 2016;11:700–8.
20. Wynn J, Martinez J, Bulafka J, Duong J, Zhang Y, Chiuzan C, et al. Impact of receiving secondary results from genomic research: a 12-month longitudinal study. J Genet Couns. 2018;27:709–22.
21. Haukkala A, Kujala E, Alha P, Salomaa V, Koskinen S, Swan H, et al. The return of unexpected research results in a biobank study and referral to health care for heritable long QT syndrome. Public Health Genom. 2013;16:241–50.
22. Oliveri S, Ferrari F, Manfrinati A, Pravettoni G. A systematic review of the psychological implications of genetic testing: a comparative analysis among cardiovascular, neurodegenerative and cancer diseases. Front Genet. 2018;9:624.
23. Lazaro-Munoz G, Conley JM, Davis AM, Prince AE, Cadigan RJ. Which results to return: subjective judgments in selecting medically actionable genes. Genet Test Mol Biomark. 2017;21:184–94.
24. Vassy JL, Christensen KD, Schonman EF, Blout CL, Robinson JO, Krier JB, et al. The impact of whole-genome sequencing on the primary care and outcomes of healthy adult patients: a pilot randomized trial. Ann Intern Med. 2017;167:159–69.
25. Loveday C, Josephs K, Chubb D, Gunning A, Izatt L, Tischkowitz M, et al. p.Val804Met, the most frequent pathogenic mutation in RET, confers a very low lifetime risk of medullary thyroid cancer. J Clin Endocrinol Metab. 2018;103:4275–82.
26. Turnbull C, Loveday C, Izatt L, Ellard S. Response to Letter to the Editor: "p.Val804Met, the most frequent pathogenic mutation in RET, confers a very low lifetime risk of medullary thyroid cancer". J Clin Endocrinol Metab 2018;103:3518–9.
27. Ormondroyd E, Mackley MP, Blair E, Craft J, Knight JC, Taylor JC, et al. "Not pathogenic until proven otherwise": perspectives of UK clinical genomics professionals toward secondary findings in context of a Genomic Medicine Multidisciplinary Team and the 100,000 Genomes Project. Genet Med. 2018;20:320–8.
28. Munoz Sastre MT, Sorum PC, Mullet E. Breaking bad news: the patient's viewpoint. Health Commun. 2011;26:649–55.
29. Jagadeesh H, Bernstein M. Patients' anxiety around incidental brain tumors: a qualitative study. Acta Neurochir. 2014;156:375–81.
30. Broadstock M, Michie S, Marteau T. Psychological consequences of predictive genetic testing: a systematic review. Eur J Hum Genet. 2000;8:731–8.
31. Hershberger RE, Givertz MM, Ho CY, Judge DP, Kantor PF, McBride KL, et al. Genetic evaluation of cardiomyopathy: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med. 2018;20:899–909.
32. Haer-Wigman L, van der Schoot V, Feenstra I, Vulto-van Silfhout AT, Gilissen C, Brunner HG, et al. 1 in 38 individuals at risk of a dominant medically actionable disease. Eur J Hum Genet. 2019;27:325–30.
33. Haggerty CM, James CA, Calkins H, Tichnell C, Leader JB, Hartzel DN, et al. Electronic health record phenotype in subjects with genetic variants associated with arrhythmogenic right ventricular cardiomyopathy: a study of 30,716 subjects with exome sequencing. Genet Med. 2017;19:1245–52.
34. Leung LY, Han PKJ, Lundquist C, Weinstein G, Thaler DE, Kent DM. Patients' responses to incidentally discovered silent brain infarcts - a qualitative study. J Patient Rep. Outcomes. 2019;3:23.
35. Lewis C, Sanderson S, Hill M, Patch C, Searle B, Hunter A, et al. Parents' motivations, concerns and understanding of genome sequencing: a qualitative interview study. Eur J Hum Genet. 2020;28:874–84.
36. Hill M, Hammond J, Lewis C, Mellis R, Clement E, Chitty LS. Delivering genome sequencing for rapid genetic diagnosis in

critically ill children: parent and professional views, experiences and challenges. Eur J Hum Genet. 2020;28:1529–40.
37. Daly MB, Montgomery S, Bingler R, Ruth K. Communicating genetic test results within the family: Is it lost in translation? A survey of relatives in the randomized six-step study. Fam Cancer. 2016;15:697–706.
38. Hadley DW, Jenkins J, Dimond E, Nakahara K, Grogan L, Liewehr DJ, et al. Genetic counseling and testing in families with hereditary nonpolyposis colorectal cancer. Arch Intern Med. 2003;163:573–82.
39. Katz AE, Nussbaum RL, Solomon BD, Rehm HL, Williams MS, Biesecker LG. Management of secondary genomic findings. Am J Hum Genet. 2020;107:3–14.