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ORIGINAL ARTICLE

Clinical geneticists' views on and experiences with unsolicited findings in next-generation sequencing: "A great technology creating new dilemmas"

Vyne van der Schoot¹ | Carlijn Damsté² | Helger G. Yntema^{3,4} |
Han G. Brunner^{3,4,5,6,7} | Anke J. M. Oerlemans²

¹Department of Clinical Genetics,
Erasmus Medical Center, Rotterdam, The
Netherlands

²IQ Healthcare, Radboud Institute for
Health Sciences, Radboud University
Medical Center, Nijmegen, The
Netherlands

³Department of Human Genetics,
Radboud University Medical Center,
Nijmegen, The Netherlands

⁴Donders Institute for Brain, Cognition
and Behavior, Radboud University Medical
Center, Nijmegen, The Netherlands

⁵Department of Clinical Genetics,
Maastricht University Medical Center,
Maastricht, The Netherlands

⁶GROW School for Development
and Oncology, Maastricht University
Maastricht, Maastricht, The Netherlands

⁷The MHeNS School for Neuroscience,
University of Maastricht, Maastricht, The
Netherlands

Correspondence

Vyne van der Schoot, Department of
Clinical Genetics, Erasmus Medical Center,
PO Box 2040, 3000 CA Rotterdam, The
Netherlands.

Email: v.vanderschoot@erasmusmc.nl

Abstract

Unsolicited findings (UFs) from diagnostic genetic testing are a subject of debate. The emerging consensus is that some UFs from genetic testing should be disclosed, but recommendations on UF disclosure generally leave room for variation in practice. This study aimed to explore clinical geneticists' views on and experiences with UFs during pretest counseling and UF disclosure. We interviewed 20 certified clinical genetics medical specialists and clinical genetics residents, working in 7 Dutch genetic centers. Participants indicated that discussing the probability of detecting UFs is an integral part of pretest counseling and informed consent. However, they expressed doubts about the degree to which this discussion should occur and about what information they should share with patients. They argued that the contents of their counseling should depend on the individual patient's capacity to understand information. These results endorse the importance of tailored pretest counseling alongside informed consent for optimal genetic consultations. While "medical actionability" is broadly accepted as an important criterion for the disclosure of UFs, participants experienced substantial uncertainty regarding this concept. This study underscores the need for further demarcation of what exactly constitutes medical actionability. Installation of an expert panel to help healthcare professionals decide what variants to disclose will support them when facing the dilemmas presented by UFs.

KEYWORDS

communication, exome sequencing, genetic testing, unsolicited findings

1 | INTRODUCTION

DNA testing with next-generation sequencing (NGS) techniques enables analysis of the entire exome or genome. Over the past decade, NGS has increasingly been incorporated into clinical care (Srivastava et al., 2019). Technological innovation has resulted in an improved diagnostic yield, a reduced time to diagnosis, and lower sequencing

costs, improving patient care overall (Dillon et al., 2018; Sawyer et al., 2016; Xue et al., 2015).

One challenge in implementing NGS for diagnostic genetic testing is that the test can find other (likely) pathogenic variants in disease-causing genes which are unrelated to the clinical question for which the genetic test was initially performed (Berg et al., 2011). Unsolicited findings (UFs) are variants in disease-causing genes that

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are unrelated to the clinical question for testing and that are identified inadvertently (Vears et al., 2017; Vears et al., 2018). UFs are differentiated from secondary findings (SFs), which refer to variants in disease-causing genes that are unrelated to the clinical question for testing, but that are actively sought during the analysis (Kalia et al., 2017; Vears et al., 2017; Vears et al., 2018). UF and SF disclosure is the subject of a worldwide debate (Boycott et al., 2015; Green et al., 2013; Kalia et al., 2017; Vears et al., 2018). The ongoing debate carefully considers the proposed benefits and potential harms of UF and SF disclosure to patients. The American College of Medical Genetics (ACMG) recommends pursuing SFs in over 70 genes predisposing to medically actionable conditions (Miller et al., 2022). In contrast, the European Society of Human Genetics (ESHG) and the Canadian College of Medical Genetics (CCMG) do not recommend SF disclosure and argue for a more cautious approach when it comes to disclosing UFs. They emphasize potential physical and/or emotional harm (Boycott et al., 2015; Vears et al., 2018). They recommend a targeted approach to sequencing, which minimizes the likelihood of detecting UFs. If UFs are uncovered, the ESHG propose limiting disclosure to medically actionable variants. In view of patients' autonomy and their right (not) to know, some centers for medical genetics broaden patients' choices by offering them an "opt-in" (the disclosure of nonactionable diseases) and an "opt-out" (the nondisclosure of actionable conditions; Christenhusz et al., 2013; Saelaert et al., 2019). This policy allows patients to choose between wanting to learn a genetic predisposition for nonactionable diseases (e.g., hereditary ataxia) and not wanting to learn their risk of developing actionable diseases (e.g., breast cancer).

A literature review by Mackley et al. (2017) showed that disclosure of medically actionable SFs is generally supported by both patients and healthcare professionals in genetics. Healthcare professionals argue that the potential health benefits (e.g., preventative measures) of both SFs and UFs outweigh the possible burdens (e.g., the psychological burden of knowing; Christenhusz et al., 2013). Additionally, they aim to foster patients' autonomy by providing them with access to personal health information (Christenhusz et al., 2013).

The emerging consensus is that UFs from diagnostic genetic testing should—to some extent—be disclosed to patients (Berg et al., 2011; Boycott et al., 2015; Vears et al., 2018). This has an impact on multiple aspects of pre- and posttest counseling. First, patients need to be adequately informed about the possible outcomes prior to testing, which will enable them to make an informed decision and give their informed consent. Subsequently, a decision needs to be made whether or not to disclose UFs, taking into account multiple factors (e.g., penetrance, expression, actionability). Finally, the disclosure of information during posttest counseling requires healthcare professionals to disclose information which does not, by definition, concern the main objective of the genetic test.

The number of studies that provide insight into how healthcare professionals experience these aspects of genetic counseling is limited (Downing et al., 2013; Vears et al., 2021). They raise various

What is known about this topic

The implementation of recommendations on UF disclosure generally leaves room for variation in practice. The number of studies that provide insight into how healthcare professionals experience the implications of the emerging consensus that UFs should—to some extent—be disclosed to patients is limited and they raise various questions.

What this paper adds to the topic

This retrospective analysis of certified clinical genetics medical specialists' and clinical genetics residents' views and experiences concerning UFs provides insight into the impact of UFs on genetic care and into the dilemmas UFs present in the clinic.

issues, such as, how and to what extent, to inform patients about the probability of detecting UFs, how to obtain meaningful consent, and which UFs should be disclosed and in what manner (Downing et al., 2013; Vears et al., 2021).

The implementation of recommendations (Berg et al., 2011; Boycott et al., 2015; Vears et al., 2018) on UF disclosure generally leaves room for variation in practice (Box 1). For example, the question of how to define medical actionability has proven to be a difficult matter (Barnes et al., 2020; Berg et al., 2011; Boycott et al., 2015; Gornick et al., 2019). UFs likely require an ad hoc evaluation of medical actionability (Thompson et al., 2018; van der Schoot et al., 2021; Yang et al., 2014). Moreover, it remains unclear who should determine medical actionability of variants. Can the treating healthcare professional decide which variants should be considered medically actionable (and therefore eligible for disclosure)? Or should we set up a (local) committee? And should the treating healthcare professional participate in this committee?

Healthcare professionals' views on and experiences with counseling UFs pretest and UF disclosure might contribute to the evaluation and further delineation of current UF disclosure recommendations (Downing et al., 2013; Mackley et al., 2017; Vears et al., 2020). Our aim with this study was to obtain insight into the experiences of medical specialists and residents in clinical genetics with UF counseling pretest and UF disclosure.

2 | METHODS

2.1 | Study design and setting

Using semistructured interviews, we asked certified clinical genetics medical specialists (MS) and clinical genetics residents (R) about their experiences regarding UF counseling pretest and UF disclosure. The

Research Ethics Committee Arnhem-Nijmegen (registration number: 2019-6035) gave permission to conduct this study.

2.2 | Participants and recruitment

We asked representatives of all eight Dutch genetic centers, who worked together on national recommendations regarding UF disclosure, to recruit eligible peers to participate in this study. The representatives sent the contact details of potential participants to a member of the research team (VS; resident in clinical genetics), who contacted eligible participants. We considered certified clinical genetics medical specialists or clinical genetics residents eligible for participation when they had prior experience in addressing UFs in pretest counseling. We ensured that the majority of our participants had experience with UF disclosure. All centers disclosed medically actionable UFs in accordance with European standards (Vears et al., 2018; Box 1). Most centers held a multidisciplinary deliberation about variant disclosure at their department, which was attended by clinical geneticists, molecular geneticists, ethicists, social workers, and psychologists (Table 1; Box 1).

We applied convenience sampling to select participants while continuously assessing the diversity of our sample with regard to qualification (i.e., MS or R), years of experience, experiences with UFs and genetic center, thus ensuring a varied sample.

2.3 | Data collection

To explore participants' experiences with counseling UFs (informing and disclosing) and their views on UF disclosure, two senior researchers (VS and AO) designed an interview guide, with help from a clinical geneticist and senior researcher (HB) and a laboratory geneticist and senior researcher (HY). Our research questions formed the starting point for our interview guide. The guide's focus and wording were chosen based on the authors' clinical experience and literature research. To provide structure to the interviews, the questions were ordered to follow the chronology of the counseling and the disclosure process.

We reassessed and slightly modified this guide after the first interviews to better reflect the aim of our study (see the interview guide in the supplemental content for more details).

BOX 1 National policy regarding UFs

Until June 2021, the eight Dutch genetic centers each had a local policy regarding UFs, which was based on recommendations provided by the ESHG. The old policy recommended that these variants (i.e., "secondary findings") should not be actively tested, but when inadvertently found, variants should be considered for disclosure if medically actionable (Vears et al., 2018). Depending on local policy, UFs were reported to either the clinical geneticist or a local expert panel, followed by the decision to disclose the UF to the patient.

In June 2021, national consensus guidelines were published considering three important principles. First, valuable information should be disclosed, leading to a default disclosure of variants in medically actionable disease genes. Second, the principle is the right to know and not to know, which has led to the implementation of an option to opt-in for nonmedical actionable diseases and to opt-out of actionable diseases. Third, in the Netherlands, the clinician ordering the test is legally responsible for all test results. Although a multidisciplinary meeting is recommended, in the end it is the clinician's responsibility to decide on disclosure.

Policy rule	Local policy (n = 8)	National consensus
Expert panel	7/8 default 1/8 upon request	Yes
Attending panel meeting	8/8 molecular geneticist, clinical geneticist 5/8 ethicist 4/8 legal representative 3/8 social worker 1/8 patient representative	Default molecular geneticist, clinical geneticist Consider ethicist, legal representative, social worker, and/or psychologist
Clinician attending panel meeting	4/8	Yes
Opt-in	3/8	Yes
Opt-out	3/8	Yes
Disclosure of SFs	0/8	No

TABLE 1 Participant characteristics

	<i>n</i>
Qualification	
Certified medical specialist (MS)	14
Resident (R)	6
Years of experience (in qualification)	
1–3	8
4–9	5
>10	7
Subspecialty	
DD, MCA	7
Prenatal	3
Other	3
No subspecialty yet	5
Number of UFs disclosed	
0	3
1–2	12
3–5	4
>10	1
Experience with disease category of UF disclosed	
Cardiac and oncological	5
Cardiac	2
Oncological	6
Other	4
No UFs disclosed	3
Department of Human Genetics	
1	5
2	4
3	3
4	3
5	2
6	2
7	1
Multidisciplinary deliberation for variant disclosure at department	
Default	16
Upon request	3
No	1
Direct involvement of healthcare professional in multidisciplinary gathering at department	
Yes	5
No	15
Policy with offering opt-in and opt-out at department	
Yes	7
No	13

Abbreviations: DD, developmental disorders; MCA, multiple congenital anomalies.

Interviews were held between June and August 2020. They took place at a time convenient for participants and were conducted by an experienced interviewer (VS). We used Microsoft Teams (version

1.0, Microsoft Corporation) to conduct and record the interviews. We obtained informed consent prior to each interview.

2.4 | Data analysis

Recordings were transcribed verbatim and anonymized. We used ATLAS.ti (version 8.2, Scientific Software Development, GmbH, Berlin, Germany) to conduct a content analysis following an inductive approach. Rather than using a predefined hypothesis or codebook, this approach follows an iterative process in which codes, categories, and themes are constructed from the data. All transcripts were independently coded by a skilled trainee (CD) and VS. Discrepancies in the analyses were discussed (with AO) until consensus was reached. No relevant differences were observed between certified medical specialists and residents, aside from the fact that clinical geneticists had more experience with disclosing UFs than residents had. This made us decide to combine the data of the two groups for the analysis and reporting. We continued interviewing until we reached data saturation (i.e., when no relevant information emerges and codes only show small variations; Given, 2008).

For additional details about the research process, see the COREQ checklist in the supplemental content.

3 | RESULTS

We conducted semistructured interviews with 20 participants from 7 genetic centers. We did not include eight further potential participants, since we reached data saturation prior to their participation. We interviewed 14 certified clinical genetics medical specialists and 6 clinical genetics residents in clinical genetics via teleconference. The interviews lasted between 30 and 76 min. All but three participants had experience with disclosing UFs (see Table 1 for participants' characteristics).

3.1 | Pretest counseling: Informing and obtaining consent

All participants reported addressing UFs during pretest counseling. The majority expressed ambivalence regarding informing patients about UFs. On one hand, they considered informing patients about UFs to be an integral part of their job. Those who were asked, denied feeling burdened in doing so. On the other hand, participants mentioned they refrained from elaborating on the topic. Their aim was not to unnecessarily burden patients with information, knowing that the probability of UFs occurring is low. Also, most participants believed that emphasizing this topic would divert attention from aspects of their counseling they considered to be more relevant (i.e., a potential diagnosis, the probability of finding a causal variant). Finally, participants questioned patients' capacity to fully comprehend information regarding this topic and their ability to oversee the

potential implications. They felt reluctant to elaborate on UFs, as they felt this effort would be in vain.

But I also think it's impossible to give people a full understanding of what it all means. What are the norms and values you associate with that? You know, you will then have to discuss your views on life, and nobody wants to get into that. It's simply not done. (Medical Specialist; MS; no.17)

A low educational level or language barrier increased participants' reluctance to engage patients in this complex discussion. A minority of participants said that the religious views of patients sometimes also complicated pretest counseling. In their experience, patients with a strong religious background have a different outlook on the concept of genetics and DNA, which hampers genetic counseling in general.

Additionally, participants questioned patients' ability to comprehend opt-in and/or opt-out options. A majority of participants who work at centers that offer opt-ins and opt-outs, acknowledged that they adopted a more directive method of counseling.

I think that when it comes to pre-test counseling I ... quite frankly say, 'Hey, if something's actionable, we'll tell you'. Because with the knowledge we have today, you can actually make a difference. But if there's no possible treatment or nothing else we can do, then we won't tell you. And that ... I convey this in a pretty directive way—I think—and people accept this. (MS; no.15)

In contrast, only a minority mentioned that they explicitly emphasize opt-in and opt-out options to encourage patients to freely express their preferences.

It doesn't happen that often, but I really do give people the option [opt-out] because I understand it. I can imagine you'd say okay, I want to know what's causing my heart defect, but I don't want to know if it turns out that I have an increased risk of developing breast cancer, I just don't want to know. (MS; no.13)

In the case of patients leaning toward an opt-in or opt-out, participants said they would further elaborate on the subject. Some consulted their colleagues to ask them for their views on what advice to give.

Participants mentioned that various factors influence the degree of emphasis on UFs and their directiveness in pretest counseling. Most participants considered the clinical value of exome sequencing to have a major influence. When the likelihood of finding a diagnosis was perceived as substantial, participants indicated they were more likely to counsel patients toward the decision to have exome sequencing performed. They said that, in those cases, they would not emphasize the likelihood of detecting UFs, in order to prevent patients from refraining from genetic testing because of this possible

outcome. Some participants mentioned that addressing UFs during counseling felt "inappropriate" in high-care settings (neonatal or pediatric intensive care units [ICU]) because they felt that families had a limited ability to cope with additional information in times of great mental stress.

I don't think it's right to keep people who're already very concerned about a seriously ill child on the ICU occupied for an hour with the ins and outs of our diagnostics. You shouldn't do that. (MS; no.13)

Conversely, when they questioned the value of the genetic test, participants said they were more inclined to elaborate on UFs and/or to counsel toward refraining from (extended) genetic testing. Either way, they acknowledged that the perceived clinical value of the genetic test increased their directiveness in genetic counseling.

Most participants experienced differences between counseling parents of minors or guardians of intellectually disabled patients and competent index patients. They strongly expressed awareness of children's right not to know and their inability to make an autonomous choice at the present time. They wanted to respect the child's incipient autonomy by preventing parents/legal guardians from making a decision that might adversely impact their child, if such a decision could be postponed until that child could decide for himself or herself.

Participants felt more comfortable counseling toward accepting the probability of UFs when they counseled (guardians of) intellectually disabled patients on UFs, compared to counseling parents of minors without an intellectual disability, since the moment when persons in that first group would be able to make a decision autonomously would never come.

Some said they took a more directive approach toward performing DNA testing and accepted the probability of uncovering an UF more easily.

If there will be a time in the future when people can choose at will, I would be very reluctant to deny them that choice. But if that choice isn't going to be there anyway, it would bother me less. (resident; R; no.20)

Others did not experience differences between counseling minors or intellectually disabled patients regarding UFs.

Most participants emphasized how parents' attitudes affected pretest counseling. They said they provided reassuring information on UFs to parents who felt reluctant to have genetic testing performed because of the possibility of uncovering UFs. Furthermore, participants mentioned they discussed the matter extensively with parents who did not seem to have critically considered the possibility that UFs could be uncovered. Participants felt that parents' urge to find a diagnosis for their children outweighed other implications of genetic testing, such as detecting an UF.

They really wanted to know what was going on, but they were very afraid of any unsolicited findings. In my view that seemed rather unrealistic, which is why I was able to help them with their question. I couldn't take away their fear, but since that fear had increased so dramatically in their minds, I was able to deal with their other question, probably without stumbling over the hurdles they were so afraid of. And that balance needed to be—yes, I probably changed that balance somewhat by providing them with more information, but it only started to tip when a diagnosis was required in school. (R; no.18)

Participants indicated that engaging both parents in the process was important but challenging, especially in the case of parents who were divorced.

3.2 | UF disclosure: Deciding to disclose and posttest counseling

A multidisciplinary decision-making process regarding UF disclosure was generally highly valued. Most participants appreciated sharing each other's expertise in and experience with UFs. The degree to which participants felt involved in the decision-making process varied. Some mentioned that, on rare occasions, they diverged from the advice on UF disclosure that had been given.

Most participants did not attend multidisciplinary meetings when an UF found in their patient was discussed (Table 1). Those who did attend, appreciated doing so. It enabled them to provide information about the patient's context, which could be taken into consideration during decision making.

A majority of participants who did not attend mentioned they expected to feel uncomfortable attending the meetings. They anticipated a potential conflict of duties if they were to be involved. These participants imagined finding it difficult having to withhold information that might be clinically relevant. This feeling was articulated by a minority of participants who had attended a meeting during which an UF in their patient was discussed. An opt-out by the patient was thought to complicate this position further. When imagining this situation, one medical specialist said:

I also find it quite hard when I'm aware that a patient doesn't want to know about any unsolicited findings, not even actionable ones, and a BRCA2 mutation has been found and I know that she should get screened. I find that a very difficult position. I'd rather not know. (MS; no. 5)

The concept of medical actionability was mentioned as one of the most, and for some the most, important factor(s) for consideration when deciding whether or not to disclose an UF. Most participants used this concept in their pretest counseling to indicate what a patient

could expect if an UF would be uncovered. However, they found it difficult to apply the term when actually confronted with an UF.

Some participants described situations in which the UF was considered medically actionable by multidisciplinary review, while they themselves perceived this differently (i.e., a variant in COL3A1, predisposing to cardiovascular Ehlers-Danlos syndrome).

I found that very difficult in this case and the committee did agree on considering this a treatable condition. But I still think it is, well, there are also plenty of aneurysms that you cannot treat or that rupture between checkups. [...] So then, how treatable is it really? (R; no.2)

Some participants indicated that these posttest experiences affected their perception of the definition of "medically actionable." It made them realize how ambiguous medical actionability could be; something they did not address in their pretest counseling. Overall, participants expressed a need for a national policy on UF disclosure, including a clear definition of medical actionability.

Other factors mentioned for consideration when deciding on UF disclosure were the severity of adverse health outcomes, the physical impact of screening, and the psychological impact of knowledge of the UF. A minority mentioned taking into consideration potential consequences for patients' families (i.e., potential health benefits and/or the psychosocial impact).

Uncertainty about the expression, penetrance, and age of onset of the disease was said to complicate the weighing of the above-mentioned factors when considering UF disclosure. Participants particularly questioned the clinical relevance of UFs in the absence of phenotypic expression in their patient or in the patient's family.

Conversely, participants frequently gave examples of conditions about which they had no doubts when considering disclosure. These mainly concerned variants predisposing to inherited breast and ovarian cancer.

I found it relatively easy because it concerned a gene [ATM] for which guidelines are in place. You can provide your patient with clear advice regarding preventive measures. That makes it easier. (MS; no.4)

Participants described that they disclose UFs with great care. They emphasized the potential psychological impact on patients caused by receiving this information. The disclosure of UFs with potentially disputable benefits was considered harmful to patients.

Practice has shown that there are cases where things turn out to be more complicated. In these cases, a healthcare provider like myself would be inclined to, you know, report this, just to be on the safe side as it were, and so that something might be done with it, potentially. But I seriously wonder whether that would actually help these people. (R; no.9)

Participants' perspectives on UFs changed after having disclosed an UF. The majority of clinical geneticists were less concerned about potential UFs. In their experience, patients to whom they had disclosed an UF eventually appreciated the fact that this knowledge had been shared. This experience was shared by the more experienced residents.

Participants mentioned they appreciated receiving information about the follow-up of their patients. Some said they hoped to learn from these cases, while others felt personally involved. A minority stressed that providing aftercare was essential. They felt responsible for burdening patients with a UF disclosure and offered psychosocial support.

Overall, participants outsourced the clinical work-up (i.e., family testing, clinical follow-up) by referring patients to an expert regarding the condition toward which the UF is predisposed (a geneticist or another medical specialist). They said they did not feel up to the task of providing the required care. Generally, they expressed having great confidence in their colleagues.

4 | DISCUSSION

NGS techniques are now widely implemented in genetic testing, but the potential of these techniques to uncover UFs has an impact on the practice of genetic counseling. To our knowledge, this is the first study focused on healthcare professionals' views and posttest experiences with UFs. Our findings provide unique insight into how medical specialists and residents in clinical genetics experience UFs in clinical care.

4.1 | Pretest counseling: Informing and obtaining consent

Our results show that experienced geneticists and residents currently agree that discussing the potential of detecting UFs is an integral part of providing diagnostic exome sequencing. Yet, they often chose not to elaborate on the subject during pretest counseling. They questioned the ability of patients to understand the meaning and consequences of UFs, especially when opt-in and opt-out options are offered. Irrespective of the perceived level of understanding, they tended to simplify the information and adopt a more directive approach. This was particularly evident in situations where they felt that a long and complex discussion was beyond the coping ability of the patient (e.g., parents of a child at the NICU), and/or when they presumed that testing would yield major health benefits for the patient.

These results suggest that providing information for the purpose of enabling deliberate decision making and obtaining informed consent is complex, potentially restricting the autonomy of patients (Saelaert et al., 2019). This raises questions about the desirability and feasibility of providing the same information to all patients in the context of informed consent, as is usually assumed when

guidelines are formulated. Experts have argued that instead of providing every patient with standardized information on UFs, clinicians should offer personalized information regarding UFs (Biesecker et al., 2019), balancing comprehensiveness and comprehensibility (Vears et al., 2021). With this in mind, several alternatives to a fully informed consent have been explored (Bunnik et al., 2013; Samuel et al., 2017; Sheehan, 2011). These alternatives conclude that at least, patients should be informed about the probability of uncovering UFs. Clinicians ought to provide extended information on UFs based on the patient's wish to receive and ability to process more information, which will partly depend on patients' clinical context (Bos & Bunnik, 2022).

Our study reflects that genetic counseling may require varying degrees of a directive approach when a genetic counselor's primary goal is to support a patient's decision making (Biesecker et al., 2019; Vears et al., 2020). Instead of focusing on the transfer of information, genetic counseling should be thought of as a dialogue (Resta et al., 2006; Vears et al., 2021; White, 1998), aimed at enabling patients to make decisions consistent with their goals, values, and beliefs. This dialogue approach allows counselors to consider the patient's urge to find a genetic diagnosis while guiding patients toward a tailored choice for genetic testing. Exploring patients' values pretest enables an assessment of actionability based on counselees' perceptions of what would be valuable information to them. Only through personalization of pretest counseling, opt-in and opt-out options might increase patients' autonomy.

4.2 | UF disclosure: Deciding to disclose and posttest counseling

Participants struggled with the concept of medical actionability and recognized that the concept lacks a uniform definition and interpretation (Gornick et al., 2019; Moret et al., 2017; Ormondroyd et al., 2018; Weck, 2018). Through direct experience with an UF with unclear or limited actionability, such as a predisposition for a less penetrant vessel disease with dubious screening options, participants became aware that the concept of medical actionability was less clear-cut than what they had presented to patients during pretest counseling.

Participants highly valued the installation of an expert panel to help participants decide on actionability. Also, they tremendously appreciated the opportunity to consult peers about providing follow-up for UFs.

Our results underline that, while the concept of "medical actionability" is broadly accepted as an important criterion for feedback of UFs, clinical geneticists experience considerable uncertainty in the actual application of this concept in clinical practice. Based on these findings, we believe that a further debate among healthcare professionals about what exactly constitutes medical actionability is urgently needed in addition to research on how the patients themselves perceive actionability. Pending such information, a possible way forward would be to ask patients how they appreciate medical

actionability during the consent process and, based on this conceptualization, withhold or disclose UFs.

Our study strongly endorses the value of an expert panel to relieve clinicians of bearing the sole burden of responsibility for what would and what would not be relevant to patients based on what was discussed during pretest counseling. Participants valued the expertise of other clinical geneticists, molecular geneticists, ethicists and social workers, and/or psychologists. It may be worthwhile to involve clinicians and laboratory staff with expertise in the condition and variant to provide insight into the consequences of the finding and the pathogenicity of the variant. Their involvement might be of special value when no consensus on actionability has been reached. We believe that the patient's clinician should also take part in panel meetings to leverage the knowledge gained during the consent process with the patient. Additionally, as UFs are still relatively rare and experience with UFs is generally sparse, the expertise of such panels will be useful for future consultations and follow-up care on UFs. Nevertheless, empirical studies on UFs (Mackley et al., 2017) and studies on the clinical relevance of UFs are urgently required (Ormondroyd et al., 2018; Weck, 2018).

4.3 | Strengths and limitations

Limitations of our study include the risk of selection bias as a result of using a convenience sampling strategy and its relatively small sample size. Participants were asked to take part on a voluntary basis, which might have caused an unintentional selection of clinical geneticists with affinity for the topic. Even though our study is small, the sample size was nevertheless sufficient to reach data saturation. All participants were recruited from Dutch genetic centers, which might have limited generalizability of our results for settings beyond the Netherlands. To enable readers to assess whether our data are applicable to their practice, we have provided participants' characteristics (Table 1).

Strengths of our study include its in-depth approach, diverse sample, and double- and, on occasion, triple coding of the same content, which improved interpretation and decreased subjectivity. We safeguarded internal validity by assessing interpretations during interviews. The COREQ checklist in the Supporting Information provides details about the research process.

4.4 | Practice implications

Our findings have several implications for counseling UFs pretest and UF disclosure policy. Clinical geneticists were uncertain about how to inform patients and about what information to disclose pretest. Instead of focusing on obtaining a fully informed consent, the emphasis of pretest counseling should be on exploring patients' values and beliefs. With this in mind, seeking consent for tests with the potential for UFs requires a certain level of competency. Consequently, counseling UFs pretest might imply specific training

needs. Participants struggled with the concept of medical actionability as well. Our results suggest that a multidisciplinary panel with expertise in UFs may be installed to support clinicians in their decision-making process.

4.5 | Research recommendations

Participants expressed uncertainty throughout the interviews. Uncertainty in clinical genetics has been studied previously (Hammond et al., 2021; Lewis et al., 2021; Makhnoon et al., 2019; Medendorp et al., 2019; Reyes et al., 2021). This has led to recommendations for future studies and guidance for counselors who face uncertainty (Hammond et al., 2021; Reyes et al., 2021). Gaining more insight into the role of uncertainty regarding UFs could be of added value to recommendations regarding counseling UFs pretest and UF disclosure.

5 | CONCLUSION

Medical specialists and residents in clinical genetics agreed that discussing the probability of uncovering UFs in genetic testing as an integral part of pretest counseling for diagnostic exome sequencing. They had doubts about the extent to which patients need to be informed and about what information they should disclose. They argued that the content of their counseling should depend on the individual patient's capacity to understand information. These results point to tailored pretest counseling aimed at optimizing genetic consultations. Furthermore, medical specialists' and residents' uncertainty regarding the concept of "medical actionability" underscores the need for further clarification of this concept. The installation of an expert panel to help decide what variants to disclose will support healthcare professionals who face the dilemmas presented by UFs.

AUTHOR CONTRIBUTIONS

Vyne van der Schoot: Conceptualization; data curation; formal analysis; writing – original draft. **Carlijn Damsté:** Formal analysis; writing – original draft. **Helger IJntema:** Writing – review and editing. **Han Brunner:** Writing – review and editing. **Anke Oerlemans:** Conceptualization; data curation; formal analysis; writing – original draft; writing – review and editing. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work will be appropriately investigated and resolved.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT

The authors elected not to share data (i.e., interview transcripts), as anonymity would not be preserved.

INFORMED CONSENT

All appropriate steps were taken to obtain informed consent from all human subjects who participated in the research reported in the manuscript, submitted for review and possible publication. Verbal consent was obtained prior to the interviews. Since we could not perform the interviews physically, participants were provided with a digital version of the informed consent form, requesting them to return the signed document to the research team after the interview. All potential participants were given full disclosure of the content of this study. They were given the opportunity to ask questions about participation and were, at any time before, during, and after the interviews, given the opportunity to withdraw from participation.

Participants' anonymity was preserved and all identifying information was excluded from the manuscript.

ANIMAL STUDIES

No nonhuman animal studies were carried out by the authors for this article.

ORCID

Helger G. Yntema  <https://orcid.org/0000-0002-3877-6328>

Han G. Brunner  <https://orcid.org/0000-0001-9274-8865>

Anke J. M. Oerlemans  <https://orcid.org/0000-0003-1791-1620>

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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