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Research paper

Exploring uncertainties regarding unsolicited findings in genetic testing

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ABSTRACT

Objectives: Non-normative uncertainty (uncertainty about empirical facts) and normative uncertainty (uncertainty about moral values or beliefs) regarding unsolicited findings (UFs) might play an important role in clinical genetics. Identifying normative uncertainty is of special interest since it might guide towards novel directions for counseling practice. This study aims to gain insight into the role of non-normative and normative uncertainty regarding UFs, as expressed by counselees and counselors.
Methods: We performed a secondary qualitative analysis of interviews with counselees (n = 20) and counselors (n = 20) who had been confronted with UFs. Following a deductive approach, we used Han et al.'s existing theoretical framework of uncertainty, in which we additionally incorporated normative uncertainty.
Results: Major issues of non-normative uncertainty were practical and personal for counselees, whilst counselors' uncertainty pertained mainly to scientific issues. Normative uncertainty was a major theme throughout the interviews. We encountered the moral conflicts of autonomy vs. beneficence and non-maleficence and of autonomy vs. truthfulness.
Conclusion: Non-normative uncertainty regarding UFs highlights the need to gain more insight in their penetrance and clinical utility. This study suggests moral conflicts are a major source of feelings of uncertainty in clinical genetics.
Practice implications: Exploring counselees' non-normative uncertainties and normative conflicts seems a prerequisite to optimize genetic counseling.

1. Introduction

Genetic testing aims to identify genetic variants underlying a person's health condition, or health risk. Conventional genetic tests entail targeted testing of one or multiple gene(s) of interest. Next Generation Sequencing (NGS) enables analysis of an individual's complete set of 20,000 genes (Whole Exome Sequencing; WES) or DNA (Whole Genome Sequencing; WGS) [1]. NGS has been integrated rapidly into the practice of medicine, replacing targeted genetic tests [2,3].

Genetic variants can explain why some people are more likely to be affected by disease or to develop certain conditions. Knowing one is at risk enables timely diagnosis of the condition or measures to prevent disease.

Although genetic testing holds the promise of increasing knowledge, uncertainty seems to be inherent to clinical genetics due to results with uncertain significance, uncertainty about prognostic indicators and uncertainty about pathogenicity of variants [4,5]. Uncertainty can be thought of as the conscious awareness of being unsure, of having doubt, or of not fully knowing [6]. Within the field of ethics, two main types of uncertainty have been distinguished: 'non-normative' and 'normative' uncertainty. Non-normative uncertainty refers to uncertainty about matters of empirical fact, such as an uncertain significance of a genetic

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variant [7]. Normative uncertainty refers to uncertainty involving a value [8]. It has been defined as the question of "what to do when we don't know what [morally] to do" [7]. Normative uncertainty among practical comparisons (i.e. is action A better than action B?) arises from conflicting values or competing moral beliefs ((i.e. convictions someone holds regarding what is right and what ought to be done) [8,9]. Non-normative and normative uncertainty may be interconnected; for example, the decision which empirical facts to value and how to value them is grounded in implicit norms. Non-normative uncertainty can cause anxiety and might influence decision-making in both patients and physicians [10–12]. Additionally, inadequate management of uncertainty may cause unnecessary concern and distress to patients [10].

Non-normative uncertainties are encompassed in a taxonomy of uncertainty within medicine as proposed by Han *et al.*[13], which distinguishes three different dimensions (i.e. source, issue and locus). The source of uncertainty refers to the cause or the reason for a knowledge gap (i.e. probability, ambiguity and complexity). The issues of uncertainty are the topics to which uncertainty applies (i.e. scientific, personal, practical), and the locus of uncertainty refers to the person in whom the uncertainty resides (e.g. counselee, counselor[1]).

Using Han's taxonomy, previous studies have allowed for a better understanding of non-normative uncertainty in the context of genetic testing in general [14], cancer genetics [15,16], variants of unknown significance [17], prenatal genetics [18,19], and unsolicited findings (UFs) in imaging [20]. They showed that counselees experience uncertainty, mainly regarding practical and personal issues (e.g. 'how does the blood test work?' or 'could my children develop cancer?' [16,17]), whilst counselors expressed more scientific uncertainty during genetic counseling (e.g. 'what is the meaning of the variant that has been found?') [16,20,21].

Within the studies on uncertainty in cancer genetics and prenatal genetics, UFs have been identified as potential source of uncertainty [14,16,19,20]. UFs in genetic testing are variants that are not associated with the condition the genetic test was performed for, but predispose to another health condition and, as such, could be of relevance for the health of the individual and/or of family members [22]. UFs have also been referred to as 'accidental findings', 'co-incidental findings' or 'incidental findings'. When actively looked for, additional findings are referred to as 'secondary findings'.

The *probabilistic* nature of UFs (i.e. when will what be found? what will be uncovered?) has been identified as a source of uncertainty in counselors [14,16,19]. In addition, since information on genetic variants is generally perceived to be complex and not all information on genetic variants is applicable in the context of UFs, *complexity* and *ambiguity* regarding UFs could contribute to uncertainty related to UFs[23,24]. For example, recommendations to undergo screening and/or mastectomy are based on the risks when disease-causing variants in the *BRCA1* gene are found in female relatives of a patient with early-onset breast cancer [25]. However, in families in which breast cancer has not (yet) manifested, the risks of developing breast cancer when harbouring *BRCA1* variants are unclear and the effectiveness of screening and preventive measures is unclear/ambiguous [2,26].

Box 1. Dutch National policy regarding UFs.

Before the implementation of national consensus guidelines regarding UF policy mid-2021, the eight Dutch genetic centers each had a local policy regarding disclosure of UFs.

In June 2021, national consensus guidelines were published considering three important principles. First, valuable information ought to be disclosed, leading to a default of disclosing variants in medically actionable disease genes. The second is the right to know and not to know, which has led to the implementation of an option to opt-in for non-medical actionable diseases and to opt-out of actionable diseases. Although a multidisciplinary meeting is recommended, in the end it is the clinician's responsibility to decide on disclosure.

Adding to these scientific issues of uncertainty, the lack of consensus regarding UF policy has the potential to create practical uncertainty [27–29]. For example, although it has been recommended to disclose so called 'medically actionable findings', this concept has been criticized for its inexactness [30]. An option to 'opt-in' for disclosure of non-actionable diseases and to 'opt-out' to abstain from disclosure of actionable conditions should be considered [31,32]. However, obtaining valid consent and deciding whether to hold back information, will depend on local/national best practice recommendations (Box 1) [33].

The potential of UFs to create uncertainty was implicitly affirmed when interviewing counselees and counselors about their views and experiences regarding UFs [34,35]. On one hand, they expressed uncertainty related to empirical issues (i.e. probability, complexity, ambiguity). On the other hand, they seemed to express uncertainty related to their moral values and beliefs. The latter type of uncertainty is of special interest, since it cannot be eliminated by obtaining empirical evidence; it ought to be 'managed' instead of resolved [36]. Studies on uncertainty in clinical genetics have not explored normative uncertainty [15–19].

Performing WES or WGS increases the probability of uncovering an UF [37]. Reflecting on counselees' and counselors' uncertainties regarding UF could provide a basis for recommendations for future studies and guidance for other counselors facing uncertainty [15,18].

With this study we aim to gain insight into the role of uncertainty in counselors' and counselees' experiences with UFs in genetic testing.

2. Methods

2.1. Study design and setting

We conducted a secondary qualitative data analysis of 40 semi-structured interviews. The interviews were held in the context of two different qualitative interview studies on the impact of UFs in genetic testing: [1] among patients and their relatives to whom an UF was disclosed (from now on referred to as 'counselees') [34] and [2] among clinical geneticists and residents in clinical genetics (hereafter referred to as 'counselors') [35].

These studies are summarized briefly here.

- Study 1: The impact of unsolicited findings in clinical exome sequencing, a qualitative interview study

  This study consisted of 20 interviews with index patients, family members and/or legal guardians (participant characteristics can be found in Supplementary tables A.1 and A.2). Counselees were counseled at the genetics departments of Radboud university medical center (Nijmegen, the Netherlands) or Maastricht University Medical Centre (Maastricht, the Netherlands). By means of convenience sampling, we included counselees in whom an UF was detected predisposing them to either an oncological or a cardiac disease. The interviews were conducted between February and October 2019 by a resident in clinical genetics and by a trained intern under the supervision of a skilled qualitative interviewer.
- Study 2: Views and experiences of clinical geneticists concerning unsolicited findings in next-generation sequencing: "a great technology creating new dilemmas"

In this study, fourteen medical specialists (MS) and six residents (R) in clinical genetics were interviewed (participant characteristics can be found in Supplementary table B). They were asked about their experiences with counseling UFs pre-test and UF disclosure. Participants were recruited through representatives from all eight genetic centres in the Netherlands. We applied convenience sampling to select participants whilst continuously assessing the diversity of our sample with regard to qualification (i.e. MS or R), years of experience, experiences with UFs

[1] we refer to the person who is counseled for genetic testing as 'the counselee' and to the person who counsels the counselee as 'the counselor'

Box 1
Dutch National policy regarding UFs.

Before the implementation of national consensus guidelines regarding UF policy mid-2021, the eight Dutch genetic centers each had a local policy regarding disclosure of UFs.

In June 2021, national consensus guidelines were published considering three important principles. First, valuable information ought to be disclosed, leading to a default of disclosing variants in medically actionable disease genes. The second is the right to know and not to know, which has led to the implementation of an option to opt-in for non-medical actionable diseases and to opt-out of actionable diseases. 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
Multidisciplinary team meeting (MDTM)	7/8 default 1/8 upon request	Yes
Attending MDTM	8/8 molecular geneticist, clinical geneticist5/8 ethicist4/8 legal representative3/8 social worker1/8 patient representative	Default molecular geneticist, clinical geneticistConsider ethicist, legal representative, social worker and/or psychologist
Clinician involved in MDTM	4/8	Yes
Opt-in	3/8	Yes
Opt-out	3/8	Yes

and genetic center, thus ensuring a varied sample. Interviews were conducted by a resident in clinical genetics (VS) between June and August 2020.

For both studies, we recruited 20 participants. Data saturation was reached several interviews prior to interviewing all participants. We completed all 20 interviews for both studies to confirm data saturation.

2.2. Theoretical framework and coding

Prior to analysis, we created a theoretical framework incorporating different dimensions of uncertainty. Based on studies by Han and colleagues [13,38,39], we specified the different dimensions of non-normative uncertainty (Supplementary table C). The authors acknowledge that the framework to identify different dimensions of uncertainty is not exhaustive and does not include normative uncertainty [38]. For this study, we have incorporated the dimension of normative uncertainty.

We created a codebook using the elements of this framework, to enable identification of verbal expressions of uncertainties. The analysis was performed deductively; distinct verbal expressions of uncertainty were identified and coded (see Box 2 and Box 3 for an example). Expressions of non-normative uncertainties were coded according to their source (i.e., probability, ambiguity, complexity) and issue (i.e. scientific, practical and personal). Expressions of uncertainty due to conflicting values or competing moral beliefs were coded as "normative uncertainty". We further specified the issues or values to which uncertainty applied.

We used qualitative data analysis software ATLAS.ti (version 8.4.2) to facilitate the analysis. An undergraduate student (EvdM) and a research assistant (IM) independently coded the transcripts under supervision of a senior researcher of medical ethics, experienced in qualitative research (AO). A clinical geneticist experienced in qualitative research (VS) subsequently coded all transcripts. Discrepancies in coding were discussed by AO and VS until consensus was reached. All interviews were double coded, six interviews were triple-coded.

3. Results

We performed a secondary qualitative analysis of 40 interviews with counselees and counselors who had been confronted with UFs (see Table 1 for participants' characteristics). In all interviews, verbal expressions of uncertainty could be identified. Overall, uncertainty was less evident in the interviews with counselees. Most aspects within the framework were addressed in both groups (Supplementary table D), but some were only highlighted by either counselees or counselors. In the following results sections, we discuss each aspect. Representative quotes can be found in Table 2.

3.1. Non-normative uncertainty

In the interviews with both counselees and counselors we could identify expressions of non-normative uncertainty. Complexity and ambiguity were the main sources of uncertainty expressed. Both counselees and counselors perceived information about UFs to be complex, imprecise or unavailable. Probability was identified as a source of uncertainty as well: penetrance of disease genes and the effectivity of preventive measures in the context of UFs were commonly identified as uncertain aspects of UFs.

Whilst counselees and counselors experienced similar sources of uncertainty, the issues to which uncertainty pertained differed between

Box 2
Example of a verbal expression of uncertainty of a counselee (nr. 15), coded as 'probability'

For my own health I didn't have concerns. I did have concerns for [my daughthers] health. What if she would get ill? What if I wouldn't have [the kidney disease] and she would? At least I would be able to donate my kidney to her. But what if both my childres would get ill? I only have one kidney to give….
(source) and 'personal' (issue), specified as 'consequences for family members'.

Box 3
. Example of a verbal expression of uncertainty of a counsellor (nr. 13), coded as 'normative uncertainty', in which we identified the values beneficence and autonomy.

I think personally it is hard when a patient asks me 'so nothing has been found? I am so happy with the result!'. It might be something personal, but I always like to inform my patients to the best I can; so they are prepared for what's coming. That would be a struggle, but on the other hand, you would protect them from knowing something they said they did not want to know, which might justify [not telling].'.

Table 1
Participants' characteristics.

Counselees (n = 20)		*n*	Counselors (n = 20)		*n*
Family/index	*Index*	6	Qualification	*medical specialist (MS)*	14
	Family	11		*resident (R)*	6
	Both	3	Years in current qualification	*1–3*	8
Disease category of UF disclosed	*Oncological*	10		*4–9*	5
	Cardiac	10		*>10*	7
Symptoms of UF in participant	*No*	19	Number of UFs disclosed	*0*	3
	Yes	1		*1–2*	12
				3–5	4
				>10	1

both groups. In the subsequent sections, we will discuss these issues (i.e. scientific, practical and personal), for counselees and counselors respectively.

3.1.1. Counselees

Counselees expressed uncertainty regarding several scientific issues. They mentioned being uncertain about when they would develop the condition the UF was associated with. Particularly, the period between the disclosure of the UF and the first time being screened for symptoms of the condition, caused anxiety (see Q1 in Table 2). Some counselees even chose to visit a different hospital, accelerating their first screening. After screening, counselees did not feel uncertain about being affected with the condition anymore. Some did wonder however, whether the screening interval was too long. Following UF disclosure, uncertainty about the UF's impact on their health was caused by a lack of knowledge about the UF and its consequences (Q2). After counseling and follow-up consultations, uncertainty was caused by contradictory, complex or ambiguous information provided by their counselors (Q3). Also, counselees were uncertain about whether the UF could explain parts of their own medical history or the medical history of their family members (Q4).

Moreover, counselees expressed practical uncertainties. For example, they wondered what impact the UF could have on their life insurance, or whether or not the finding would increase their deductible (Q5). They questioned whether the UF would have the same impact on their relatives. These concerns made some counselees wonder if and when family members should get tested.

Some counselees reported uncertainty about the care they had received in the hospital. A few counselees mentioned that the physician they were referred to was not aware of the risks associated with the UF and seemed unaware of the guidelines regarding preventive measures. These counselees questioned whether their genetic counselor had provided this physician with sufficient information (Q6).

The personal issues to which counselees' uncertainty pertained, were how the UF would impact their lives and which financial consequences they were likely to encounter. This made them question their future plans (Q7).

3.1.2. Counselors

Counselors mainly expressed uncertainty related to scientific issues. They mentioned probability as a source of uncertainty, when deciding to offer genetic testing. In pre-test counseling, they questioned whether the odds of finding a causal variant would outweigh the probability of uncovering an UF.

Upon disclosure of an UF, counselors were uncertain whether or not patients would actually develop the condition the UF is associated with. They wondered about the value of a variant when found in a family without medical history regarding the associated condition (Q8). Many counselors reported uncertainty regarding the concept of medical actionability. For example, they wondered whether reproductive options ought to be considered as "actions" (Q9).

Most counselors expressed practical uncertainty regarding counseling UFs prior to testing (Q10). They questioned the extent to which patients can fully grasp the information about UFs during pre-test counseling, for example regarding the potential impact on their relatives. In particular, they thought that opt-in (choosing to have non-medically actionable disease variants disclosed) and opt-out (choosing not to have medically actionable disease variants disclosed) options were complex. They expressed major concerns about the capability of patients to oversee their own choices. Patients' context, such as a language barrier, could affect these concerns (Q11). Those who had experience with counseling UFs pre-test and UF disclosure, generally felt less insecure about counseling UFs. The majority of counselors questioned the feasibility of the policy regarding UFs (Box 1). For example, they wondered how to document test results in patients' medical files when it was decided not to disclose an UF to the patient.

The personal issue to which counselors' uncertainty pertained was their own capability to decide whether or not to disclose an UF. Some recognized feeling more insecure after having experienced UFs outside the strict scope of medically actionable variants (Q12).

3.2. Normative uncertainty

We identified expressions of normative uncertainty in the interviews with both groups. Overall, expressions of normative uncertainty were less prevalent in the interviews with counselees.

3.2.1. Counselees

Counselees expressed uncertainty regarding their responsibility towards their family members. They reported being uncertain about whether it was up to them to decide if it would be in someone else's best interest to learn about the possibility of having the genetic variant. One counselee mentioned a negative experience when sharing the information with a relative (Q13).

Several counselees mentioned they found it difficult to decide whether or not to have their children tested. The right not to know and the potential financial impact were reasons not to (Q14), whilst the right to know and the risk for future offspring were mentioned in favour of testing (Q15).

Table 2
Exemplifying quotes.

	counselee	scientific	Q1	*"Having an UF disclosed can cause anxiety. Tension. Uncertainty. Which we did experience. But we took action to deal with this uncertainty." (family; nr. 1)*
non-normative			Q2	*"I went to the hospital for the genetic test results when they told me that I had the BRIP1 gene. My mother and I were both like 'what is that?' We asked ourselves how to deal with it; is it something serious? Is it not serious? Can doctors do anything, can they remove my ovaries or not.?" (index patient; nr. 5)*
			Q3	*"Because of the contradictory information about the genetic variant, I had a conversation with the clinical geneticist again to clarify the information that was given. (…) The clinical geneticist told us something different than what we had heard before." (index patient; nr. 3)*
			Q4	*"I read what is associated with the UF. 'Low immunity', I have a low immunity; I have always had respiratory infections, (…) It made me wonder, is it related to the genetic variant in any way?" (index patient; nr. 17)*
		Practical	Q5	*"I asked this question to the doctor; 'how do I need to report this to the life insurance; am I sick or not sick?' This is a conflict. Until one year ago, I could say 'I am a healthy person'. And now I'm still healthy but I have this worry, this concern." (family; nr. 2)*
			Q6	*"'I wouldn't know what other examinations we would have to do,' the doctor said. Well, I had all the diagnostic records from [academic hospital 1] I had already received these at home and could show them to this doctor. […] what if I hadn't done that? Would I then have been risking my life, as well as my daughter's?" (family; nr. 1)*
		personal	Q7	*"For me it was a disadvantage considering I was planning to buy a house. But as long as they don't know [about the UF]…Can I keep this a secret? Can I keep it out of my papers, this UF?." (family; nr. 16)*
	counselor	Scientific	Q8	*"It is different for conditions that are not fully penetrant. Especially when no one in the family is affected by breast or ovarian cancer or another related condition. Because then one could wonder whether or not this variant affects this family to a lesser extent, with lower associated risks." (R; nr. 1)*
			Q9	*"I think the distinction between actionable and non-actionable is fine. But what is actionable and what is not actionable? Well, if WES*, for example, reveals Huntington's disease, there is nothing you can do to prevent the disease, but you can prevent your children from getting it" (MS; nr. 5)*
		Practical	Q10	*"I find it difficult to disclose such abstract information, especially when comparing it with presymptomatic testing for BRCA2 mutations. These counselees have 45min to discuss whether or not they want to know. What are the pros? What are the cons? And regarding UFs, the same result [as in presymptomatic testing] can be obtained. But the odds are so small, so I do understand spending limited time on discussing UFs" (R; nr. 20)*
			Q11	*"I am concerned that they don't oversee it. That I don't actually obtain informed consent because they just don't speak the language and the translator doesn't understand it either." (MS; nr. 6)*
		Personal	Q12	*"I highly value multidisciplinary meetings. I know that my opinion is only one of many. And maybe I forgot something. Maybe I didn't think of a certain detail. That just might happen…" (MS; nr. 11)*
Normative		Counselee	Q13	*"[The counselee's relative] also feels that I have burdened her with disclosing the UF to her. And of course that's true in a way. I wonder, should I have kept my mouth shut? But I would find that very difficult, since I know something." (family; nr. 7)*
			Q14	*"We have never performed [DNA testing in our daughter]. We immediately wondered if it would be ethically right to have the test performed. The results would be in her medical file and she would always have problems with insurances and mortgages." (family, nr. 4)*
			Q15	*"If my daughter were a carrier and she would have children, she could pass it on. I think she has the right to know that this could happen." (family, nr. 12)*
		Counselor	Q16	*"If the patient in questiondoesn't ask about it, it still doesn't feel right, because you hold back something that was in fact identified. But we think there is no value in disclosing it and no benefit for the patient. But still, especially if patients start asking about UFs, you feel like you're lying." (R; nr. 2)*
			Q17	*"It creates a moral dilemma; having certain information that can be very important for someone's health when that person knowingly opted out of receiving such information. It creates a feeling of being burdened with information about the UF." (MS; nr. 8)*
			Q18	*"Suppose you find a random BRCA mutation and you know that this patient has a sister and three daughters. Then I would have a moral conflict, thinking: 'shouldn't we tell the family about this?' That's the tricky part; when a patient has made a certain choice regarding UF disclosure and you have information that is potentially important for family members. Where does that leave your responsibility?" (MS; nr. 18)*

* Whole Exome Sequencing.

3.2.2. Counselors

The majority of *counselors* expressed normative uncertainty. Some were not always sure whether performing a genetic test was the right thing to do when considering the small probability of finding a causative variant versus the odds of uncovering an UF. Counselors indicated that they struggled with the amount of information to give pre-test. They were uncertain whether the value of enabling informed decision-making outweighed the potential negative impact of burdening patients with knowledge about UFs pre-test. Also, they questioned whether the potential benefits of UF disclosure outweighed the burden of knowing to be at risk of developing a certain condition.

With regard to the opt-out option, many counselors stated that if they could not disclose an UF based on an opt-out consent, they would feel like they would have to lie (Q16). Also, some said withholding beneficial information would not feel right (Q17).

Counselors reported uncertainty about what and when they ought to decide for their patients. They were not sure whether a patient's autonomy should outweigh potential benefits of UF disclosure (Q18).

Most counselors expressed normative uncertainty regarding opt-in and -out options. They questioned whether there could be situations in which they ought to overrule a patient's choice, because they doubted their patients' ability to actually oversee the implications of their choice during the pre-test counseling session. Others mentioned the importance of the potential benefits of UF disclosure for family members (Q18).

4. Discussion and conclusion

4.1. Discussion

With this study, we have gained insight into uncertainty associated with UFs in NGS experienced by counselees and counselors. Major issues of uncertainty were practical and personal for counselees, whilst counselors' uncertainty pertained mainly to scientific issues. Normative uncertainty was a major theme throughout the interviews with counselors and, although less evident, present in the interviews with counselees as well.

4.1.1. Non-normative uncertainty

UFs were perceived to be complex and ambiguous, as has been described for genetic information in general [5,14–16,18]. We identified

several issues of non-normative uncertainty which have not been addressed in previous publications on uncertainty in genetic testing [15–19].

4.1.1.1. Counselees. Our results indicate that UFs may reveal a predisposition to medical conditions which raises questions regarding potential financial consequences. The use of genetic test results by life insurance companies has raised various long-standing concerns [40]. Although none of the counselees we interviewed had experienced any actual financial consequences, reflecting general experiences in clinical genetics in the Netherlands [41], the uncertainty experienced by counselees might add to the previously raised ethical, medical and societal concerns.

4.1.1.2. Counselors. First, counselors expressed uncertainty regarding whether the probability of finding a genetic cause underlying a patients' condition would outweigh the probability of receiving an UF. Counselors could benefit from continuous studies on the yield of NGS [42,43] and the probability of uncovering UFs [37]. Second, we identified evident uncertainty regarding the concept of medical actionability. In the context of UFs, the efficacy and the burden of interventions, together with the probability and severity of an adverse health outcome due to the UF, are often unclear, causing UFs to be ambiguous [2,23,24,26]. Counselors used the concept medical actionability in their pre-test counseling to allow patients to opt in for or opt out from hearing certain findings, while simultaneously emphasizing the ambiguity of this concept. The term medical actionability is known for its lack of terminological uniformity and interpersonal variability in interpretation [23,24,30,44,45]. For example, Berg et al. (2011)[46] consider variants to be actionable when carrying a high likelihood of disease (e.g. monogenic, highly penetrant disease) for which medical interventions could significantly reduce morbidity and mortality [24]. Less restricted definitions align with Yang et al. (2014)[47], who consider variants medically actionable when "there are potential therapies or established surveillance protocols available". In yet other studies, healthcare providers acknowledge an even wider interpretation of medical actionability, which includes almost any action that can be taken based on the knowledge of bearing a genetic variant, including reproductive decision-making[31,48]. Counselors could benefit from guidance on how to discuss this ambiguous concept. Some authors have argued that uncertainty ought to be discussed with patients to protect and promote their autonomy, while others have pointed out the potential adverse effects of discussing uncertainty [49–51]. Different strategies to communicate uncertainty have been explored and may optimize counseling depending on the goals of counseling, the topic of uncertainty, the clinical scenario and how uncertainty is appraised by counselees and counselors [50,52]. Instead of trying to bypass uncertainty, counseling might benefit from acknowledging and guiding counselees in appraising and managing the uncertainties regarding UF. This is in line with the Uncertainty Management Theory which posits that uncertainty is appraised for its meaning and that these appraisals influence subsequent behaviors intended to manage uncertainty [53]. Until consensus has been reached about how to decide on actionability, variants with ambiguous actionability (for example, when screening protocols have not proven to enable early detection in order to start treatment) should be disclosed with great caution [54].

Our study stresses the need for follow-up studies on UFs that elucidate the clinical utility and impact of UF disclosure [2,23,24,26].

4.1.2. Non-normative uncertainty

Our results suggest normative uncertainty plays an important role in counselors' and counselees' perspectives on UFs. We saw how non-normative and normative uncertainty were at times interconnected. For example, the question whether the odds of finding a causal variant would outweigh the probability of uncovering an UF, is grounded in implicit norms regarding the desirability of diagnostics when there is a minimal expected yield, and seeking to avoid UFs proportionally.

Even more than non-normative uncertainty – which might be partly reduced or resolved by gaining more knowledge - normative uncertainty needs to be managed [36]. How to manage normative uncertainty is still a topic of debate [36,55]. Cribb describes that "only some of this [normative] uncertainty is deliberately and self-consciously managed through professional ethics, or other overt ethics discourses, but that much is implicitly managed through forms of social organisation and routine practice (i.e. 'moral settlements')" [36]. Exploring the moral settlements counselees and counsellors find themselves in, is needed to identify these settlements' role in navigating counselees' and counselors' normative uncertainty. Insights in their role might provide guidance to counselors and their peers on how to manage normative uncertainty regarding UFs more deliberately.

4.1.2.1. Counselees. Counselees struggled with the idea of deciding for family members whether to have certain information disclosed. This reflects awareness of the right not to know and the desire to respect decisional autonomy and/or to protect others from receiving unwanted and potentially harmful information (non-maleficence), while knowing information could be beneficial (beneficence) [56].

The responsibility counselees feel to inform their family members has been acknowledged in literature [57] and the uncertainty about whether or not to share genetic information with a family is a general issue in clinical genetics [17,58–62]. However, normative uncertainty has only been identified implicitly as a barrier to inform relatives [63]. Existing recommendations regarding informing relatives at risk are practically focused and do not address normative uncertainty [64]. Counselors could identify the moral conflicts that may underlie counselees' uncertainty about informing their relatives. This could facilitate explicit discussion of such moral conflicts and enhance counselors' ability to provide guidance to counselees in appraising and managing their uncertainty[53]. Very few studies have surveyed patients and their family members about the ethical dilemmas they have faced [55,65]. These authors have noticed that although ethics consultations are sought by clinicians, these consultations do no originate from patients' requests [55]. They recommended to more closely involve ethics consultants to better guide patients who face ethical dilemmas [55,66].

Based on our findings, we would recommend a thorough follow-up of counselees to whom an UF is disclosed, bearing the counselees' potential uncertainties in mind. In particular, counselors need to explicitly address counselees' insecurities regarding the financial impact and informing and/or testing family members. When counselors identify uncertainty in their counselees, they could consider to engage ethics consultations as a supportive resource.

4.1.2.1. Counselors. Counselors expressed normative uncertainty regarding the amount of information they should provide prior to testing. In the context of UFs, the emphasis on enabling decisional autonomy lies in obtaining informed consent during pre-test counseling [56,67]. Informed consent refers to the permission granted in full knowledge of the possible consequences and is treated as the core of medical ethics [68]. It has been acknowledged that the techniques that are currently used in clinical genetics create a situation in which a patient can become overwhelmed by the complexity and volume of the information given [68]. Counselors' struggle with pre-test counseling reflects the moral conflict of autonomy vs. non-maleficence.

Uncertainty regarding informed consent has led to discussions that tend to focus on the content of the information provided [68–70]. However, information transactions depend on various counselee- and counselor-specific factors (e.g. information can be seen as context- and norm-dependent) [70]. Since patients' internalisation of information depends on more than information that has been provided, it has been argued to focus on the quality of information transactions rather than on

their content [70]. This approach fits the much older view on genetic counseling, according to which decision-making capacity is maximally enhanced by means of a dialogue [71]. In order to enable counselors to engage in this dialogue when counseling UFs pre-test, Manson and O'Neill propose substantive changes on institutional and governmental levels (i.e. they propose to stop adhering to "ever more exacting informed consent forms" and suggest regulators should judge medical performance by the quality of communication that is achieved) [70].

Widely adopted policies regarding the return of unsolicited findings recommend disclosing actionable findings [27–29], while offering the option to refrain from receiving these results, which shows an effort to balance beneficence, non-maleficence and patients' autonomy. Our data show counselors' struggle with the conflict of non-maleficence vs. autonomy, which has been described before in the context of UF disclosure [56], suggesting ambivalence in applying guidelines in the reality of clinical practice [72]. Interestingly, qualitative research showed that although most counselees expressed considerable psychological impact initially, almost all would in hindsight choose to undergo genetic testing again [34,73]. This suggests that presumed potential harm ought not to be a reason to refrain from UF disclosure. However, no non-actionable disease genes were disclosed to these counselees. Also, the potential harm of unnecessarily exposing patients to preventive measures ought to be considered as well.

Normative uncertainty was most frequently expressed when discussing opt-in and opt-out options. Counselors thought that withholding potential beneficial information or disclosing burdening genetic test results would create tension with the intention to respect patient autonomy and to being truthful.

Regarding UF disclosure, we have previously recommended to have a multidisciplinary team meeting (MDTM) to guide decisions on UF disclosure [35]. This multidisciplinary approach relieves the counselor of bearing the sole responsibility in potential moral conflicts and enables counselors to reflect on their struggle. This struggle includes decisions on disclosure of potentially unwanted and harmful information and counselors' potential feeling of being untruthful to their patients.

4.1.3. Strengths and limitations

Our study had several strengths and limitations. For some counselees, the interview took place several years after the UF had been disclosed which could be of influence on how they reflected on uncertainty (recall bias). For this study, we conducted a secondary analysis of interviews that did not specifically address the topic of uncertainty. When the interviewee expressed uncertainty, the interviewer did not necessarily ask in-depth follow-up questions. This might have negatively impacted data quality, since expressions of uncertainty were not always explored in depth. For instance, we did not try to make participants differentiate between complexity and ambiguity as sources of uncertainty. However, we feel this differentiation did not affect the value of our findings regarding these sources of uncertainty.

Strengths of this study include the systematic analysis according to a theoretical framework, which allowed comparison of uncertainty between counselees and counselors. We performed double and on occasion triple coding of the same content, improving richness of interpretation. The COREQ checklists of both studies in the supplementary material provides additional details about the research process [74] (Supplementary table E and F).

4.2. Conclusion

Normative and non-normative uncertainty regarding UFs are evident in counselees and counselors who are confronted with UFs. They will benefit from gaining more insight in the prevalence, nature and impact of UFs through further qualitative and quantitative studies on UFs. This study suggests a major role for moral conflicts as a source of uncertainty in clinical genetics in general.

4.3. Practice implications

In order to obtain valid informed consent, counselors should focus more on engaging in a dialogue pre-test, rather than on the content of information transactions. During post-test counseling, counselors need to explicitly address counselees' insecurities regarding the financial impact and informing and/or testing family members and could consider to engage ethics consultations as a supportive resource. Counseling might benefit from acknowledging and guiding counselees in appraising and managing the uncertainties regarding UF. Multidisciplinary team meetings to guide decisions on UF disclosure, ethics consultations or moral case deliberations allow counselors to reflect on the uncertainties they face.

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. Consent was obtained prior to the interviews. 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.

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CRediT authorship contribution statement

Vyne van der Schoot: Conceptualization, Methodology, Analysis, Writing – original draft. **Eline van der Meer**: Conceptualization, Analysis, Writing – original draft. **Marij Hillen**: Writing – review & editing. **Helger Yntema:** Writing – review & editing. **Han Brunner**: Writing – review & editing. **Anke Oerlemans:** Conceptualization, Methodology, Analysis, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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