Discussing uncertainty during cancer genetic counseling about multigene panel testing

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General introduction

BACKGROUND

Genetic counseling

In approximately 5% of all cancer patients, cancer is due to an underlying genetic predisposition [1]. One may suspect a genetic predisposition when, for example, multiple relatives develop the same type of cancer or when cancer is diagnosed at an uncommonly young age [1]. When a genetic predisposition is suspected, one may seek or be referred for genetic counseling to find out if one carries a predisposition. Genetic counseling is the process of helping people understand and adapt to medical, psychological and familial implications of genetic contributions to a disease [2]. Both (former) cancer patients and non-affected relatives of cancer patients (hereafter called counselees) can undergo genetic counseling [2]. During genetic counseling, clinical geneticists or genetic counselors interpret family and medical histories, educate counselees about inheritance, testing and prevention, promote informed choices and adaptation to the risk or condition [2]. In the Netherlands, genetic counseling for suspected hereditary cancer is provided at nine hospitals; eight university medical centers and one specialized cancer hospital (i.e., Antoni van Leeuwenhoek hospital) [3]. All healthcare providers working at a clinical genetics department, i.e., clinical geneticists, residents, interns, genetic counselors, physician assistants (-in-training) and psychologists (hereafter called 'counselors') may provide genetic counseling [3].

Genetic counseling entails first a pretest counseling session primarily aimed at gathering information to assess someone's risk of carrying a genetic predisposition, providing information about risks and management possibilities, and making decisions about undergoing genetic testing [4]. When a genetic test is carried out, a second, posttest, counseling session usually takes place involving the disclosure of the test result and the discussion of the implications thereof [5]. In a small number of counselees, a genetic predisposition causing cancer is identified that involves an increased risk to develop cancer [1]. This allows providing management recommendations and testing of relatives for that particular predisposition [6]. However, most commonly, no genetic predisposition related to the type of cancer(s) in the family is found. This can imply either a definitive confirmation of the absence of a pathogenic variant that is known in the family, or the confirmed absence of a pathogenic variant in the genes that are currently tested [6]. Finally, there is the possibility that a variant is identified for which it is unknown whether it increases the likelihood to develop

cancer [6]. These variants are ordered in categories ranging from 'very likely not to be pathogenic' to 'very likely to be pathogenic'. The performance of a genetic test that includes a limited number of genes has a small probability of identifying such a variant.

Next Generation Sequencing

Until recently, genetic tests were performed using Sanger sequencing mainly, to determine whether someone carries a genetic predisposition. This means that individual genes associated with the cancer(s) in the family were sequenced to identify variants [7]. Developments within the genetic field result in a rapid increase in knowledge about disease-associated genes [8]. Consequently, the number of genes for which the association with a particular type of cancer is known, is continuously increasing. Sequencing multiple cancer-related genes can be informative to examine if someone is at higher risk to develop cancer. New genetic technologies based on Next-Generation Sequencing (NGS) enable the massively sequencing of genes related to one or more type(s) of cancer, with the aim to identify genetic predispositions [8, 9]. In clinical practice, NGS techniques are commonly used in the form of multigene panel tests [10]. Panel tests increase the yield of genetic diagnosis within cancer genetics, and vary in the number of genes they comprise [11]. For example, in the Netherlands, currently, a relatively small panel including five informative genes (i.e., BRCA1, BRCA2, CHEK2, ATM and PALB2) is often performed in families in which breast cancer occurs. However, in families in which multiple cancer types occur and who therefore fit multiple cancer syndromes, a family history is absent, or an atypical cancer phenotype exists, panels containing high numbers of genes may be preferred to enhance the probability of providing a diagnosis [10]. Performing a large panel in such families increases the identification of predispositions that are potentially missed with small panels or Sanger sequencing, and allows providing screening recommendations to counselees and/or their relatives when necessary [12-15]. Besides the increased diagnostic yield, panel testing has relatively lower costs per gene and a more rapid turnaround time compared to Sanger sequencing [10, 16]. Nevertheless, despite the advantages of NGS-based multigene panel testing, this technology may surpass its clinical utility as it often includes relatively unknown genes with ill-defined risks and unclear management guidelines, resulting in increased rates of uncertain test results and unsolicited findings [12]. Consequently, multigene panel tests generate an increased level of uncertainty compared to targeted genetic tests [17].

Uncertainty

The occurrence of uncertainty in itself is not unique as uncertainty has always been integral to healthcare [18]. For example, uncertainty can exist about whether symptoms are related to a certain disease, or to what extent or which treatment is beneficial. Several researchers have tried to grasp the meaning of uncertainty and described factors that contribute to the existence of uncertainty in healthcare [19-24]. For example, Mishel and colleagues described four dimensions from which uncertainty originates, i.e., ambiguity, complexity, deficient information, and unpredictability [20, 21]. Another example is the model of Kasper and colleagues that describes eight categories of uncertainties experienced by cancer patients [24]. Contrary to the model of Mishel and colleagues, this latter model focuses on the topics to which uncertainty relates instead of what causes uncertainty. Based on the variety of uncertainty approaches, Han and colleagues proposed an overarching taxonomy of uncertainty in healthcare including causes of uncertainty and topics to which the uncertainty relates [25]. Although the proposed taxonomy has its limitations, such as a high level of abstraction [17], it provides a good starting point to understand uncertainty in clinical practice, and has been used in conceptual work on uncertainty in genetics and genomics [26, 27]. From the perspective of Han and colleagues, uncertainty is seen as 'the subjective perception of ignorance' -a state of awareness about one's lack of knowledge [25]. They state that uncertainty in healthcare results from three causes: probability, ambiguity, and complexity. Probability refers to the unpredictability of the future and is also described in other literature as risk, aleatory uncertainty, stochastic uncertainty, or first-order uncertainty [25, 28-30]. Ambiguity involves the inadequacy or unreliability of information, and is equivalent to epistemic uncertainty or second-order uncertainty [25, 28, 29]. Finally, complexity refers to aspects of an event that make it difficult to understand, such as multiplicity (e.g., the existence of numerous potential outcomes) [25]. The taxonomy of Han and colleagues also distinguishes three topics to which uncertainty may relate: scientific, practical, and personal [25]. Scientific uncertainty may, for example, involve uncertainty about diagnosis and prognosis. Practical uncertainty pertains to processes and structure of care whereas personal uncertainty relates to psychosocial and existential issues, for example the effects on one's goals in life [25]. For a medical perspective, uncertainty in the genetic field primarily exists in the form of risks as it often involves predicting and preventing diseases, and relates to different topics [31]. For example, information about a genetic predisposition associated with breast cancer

entails risk information about someone's chance to develop breast cancer during their lifetime. These risks imply that no certainty can be provided about whether and when someone will actually develop breast cancer.

In recent years, uncertainty has become more and more substantial in the medical field in general, and in clinical genetics specifically. NGS-based multigene panel testing greatly increases uncertainties as, for example, the likelihood of identifying variants of unknown significance (VUS) is increased (see Table 1) [12, 16, 32]. The meaning and implications of VUS are unclear, e.g., whether risks to develop cancer are increased [10]. In the Netherlands, clinical genetics departments agreed not recommending screening options accordingly, but, if applicable, to test relatives to expand their knowledge about those variants. As a consequence, it may occur that a VUS is eventually reclassified as a pathogenic variant and screening has to be undertaken. Uncertainty about the (re)classification of some variants in the future does therefore always exists [10]. Furthermore, multigene panel tests more often contain new genes as well as both high- and moderate-penetrance genes (i.e. genes with a high and modest degree of cancer risk) [10]. Identifying variants in new, unknown genes may generate uncertainty about the meaning and implications of those variants. In these cases, it is unclear whether screening recommendations should be provided and/or testing of relatives is needed [16]. Knowledge about implications of variants in such genes is needed, but is however difficult to obtain as they are often rare. Variants in moderate-penetrance genes imply clear cancer risks and screening recommendations, however, an increased level of uncertainty exists regarding the development of cancer during lifetime compared to variants in high risk genes, as risks are moderately increased [12]. Also, a multigene panel test may include genes that would not have been chosen to be sequenced based on clinical phenotype or pedigree, but that are somehow related to cancer. These genes may be included to increase the likelihood of determining an explanation for cancer in the family, and as designing panels for each counselee individually is a nonstarter [33]. The identification of variants in these genes, i.e. unsolicited findings, generates uncertainty about whether screening or preventive options are desirable for the counselee, and whether testing or screening of relatives is necessary as this cancer has not occurred before within the family [10]. Interpretations of variants resulting from multigene panel testing in itself may thus be difficult for counselors and laboratories.

Table 1. Overview of the main uncertainties generated by NGS-based multigene panel testing and their primary causes.

Main uncertainties
• The strength of association with cancer • The extent to which a variant explains the occurrence of cancer in the family • The need for screening recommendations for the counselee • The need to test relatives for that particular variant • The need to provide screening recommendations for (tested and/or non-tested) relatives
Primary causes
The identification of: • Variants of unknown significance (VUS) • Variants in new, unknown genes • Variants in moderate-penetrance genes • Unsolicited findings (in high- and moderate-penetrance genes)

Impact of uncertainty on clinical practice

When discussing a multigene panel test during genetic counseling, communicating uncertainty is inevitable. This is most visible in posttest counseling sessions, as counselors are then required to disclose and discuss uncertain test results with counselees [5]. Counselors are challenged in what to communicate to counselees with regard to such a result, for example whether the identified variant has caused the cancer they have developed and whether screening recommendations are necessary [12]. But not only the communication during posttest counseling is more complicated. Pretest counseling is also influenced by the rise of panel tests in clinical practice [2]. Usually, during pretest counseling, counselees are provided with general information about the sequenced genes as well as potential test results and their management options [34, 35]. As panel tests may include the sequencing of high numbers of genes, potential test results and their associated risks cannot all be discussed (extensively) during pretest counseling [11, 36, 37]. Moreover, panel tests may involve more less-known genes, which complicates informing counselees about their meaning and implications. Therefore, informing counselees about essential elements to allow fully informed consent for genetic testing is less straightforward when discussing a panel test [38]. It is unknown how difficult it is to communicate panel test-related uncertainties and how counselors deal with this in current clinical practice.

Not only counselors but also counselees are faced with uncertainty when discussing a multigene panel test. It might be questioned how beneficial it is for counselees to be informed about uncertainties during genetic counseling. Previous research on the effects of communicating uncertainty in other medical settings has shown mixed findings [39-43]. On the one hand, communicating uncertainty is potentially harmful for counselees as it was shown to overwhelm patients and cause anxiety [40, 41]. Moreover, communicating uncertainty was shown to result in less satisfaction about treatment decisions in cancer patients [39]. On the other hand, discussing uncertainty allows counselees to prepare for potential outcomes and set realistic expectations, which could limit their distress afterwards [11]. Moreover, it enables counselees to make a well-informed decision about whether or not to pursue multigene panel testing, in line with their personal values and preferences [42]. In recent years, patients' rights and desire for information have increased and there has been a rise in patients' involvement in decision making, with an emphasis on respect for patients' autonomy [44, 45]. This is particularly important regarding decisions in which there is no clear best option. From a counselee's perspective there is no *best* option in deciding about panel testing since it may involve both harms (e.g., ending up with a non-actionable test result) and benefits for them (e.g., finding the cause for cancer and providing relatives with the opportunity to be tested) [42]. Therefore, counselees need to be enabled to individually weigh the pros and cons of performing a small (more targeted) vs. large panel. For example, individuals at risk for high distress after testing may choose not to proceed with a large panel as this increases the likelihood to end up with an unclear or non-actionable test result [11]. On the other hand, counselees who are motivated to use every resource to gain knowledge on a possible carriership, may choose for a large panel. Discussing uncertainty may also beneficially affect the relationship between counselors and counselees. Previous research has shown that honesty in information provision positively impacts the patient-provider relationship as it promotes trust and equality [43, 46]. Hence, discussing uncertainty may affect counselees differently. What causes this is currently unexplored.

Potential moderators of the impact of uncertainty

Mixed effects of communicating uncertainty can possibly be explained by variation between counselors in their manner of communicating uncertainty. Previous studies examined the effects of particular manners to discuss uncertainty in different settings [47-50]. Framing uncertainty as something positive or negative was shown to evoke either hope or distress in counselees

[48] and in the general population [50]. Further, patients' satisfaction was particularly negatively affected if no actions to resolve the uncertainty were provided [49]. Moreover, an explicit expression of uncertainty, e.g., 'I don't know', was seen as detrimental to patients' confidence, whereas behaviors that implicitly showed uncertainty, for example consulting a colleague, were seen as beneficial to trust [47].

Another explanation may be the existing differences in counselees' individual characteristics. For example, counselees' educational level may impact how well they are able to understand uncertainty and subsequently act upon it, such as engage in decision making [51]. Also, someone's tolerance for uncertainty is an indication of how one responds (cognitively, emotionally, and behaviorally) to uncertainty and therefore determines how uncertainty is dealt with [52]. Someone who has little tolerance for uncertainty may for example respond with high levels of worry and aversion and may therefore be predominantly negatively affected by uncertainty. Moreover, counselees' information preferences and their motivations to receive genetic counseling may determine whether they are willing to receive uncertain information and how well they are able to deal with it [53].

Another factor that may influence the impact of uncertainty communication, is the extent in which the counselee's own questions and uncertainties are addressed during genetic counseling. Previous research has shown that patients are generally focused on receiving an answer to their own question and may therefore not listen to information other than that relevant to their question [54]. However, whether and to what extent these factors play a role in the effects of communicating uncertainty, and how counselors can use these to optimally convey uncertainty to counselees is currently unexplored.

AIMS

The foregoing has led to the overall aim to obtain evidence on how to discuss uncertainty concerning multigene panel testing during pretest genetic counseling for suspected hereditary cancer, in such a way that counselees feel supported and informed decision making is enhanced. Although risks are a substantive part of the uncertainties in the genetic setting, we deliberatively avoided focusing on risk communication in this dissertation. First, extensive literature on discussing risks during genetic counseling already exists [48, 55-57]. Second, uncertainty resulting from ambiguity and complexity is particularly increased by multigene panel testing [25], but its discussion is relatively unexplored. Third, counselors are likely to be familiar with communicating risk during genetic counseling as it is such a substantive part of genetic information [31, 58].

In this dissertation, the following sub-aims were addressed:

1) To explore whether and how uncertainty is discussed in current cancer genetic counseling in general, and multigene panel testing in particular, and how this discussion is experienced by both parties, i.e., counselors and counselees.
2) To investigate how counselors' discussion of uncertainty impacts cancer genetic counseling in the context of multigene panel testing.
3) To identify how counselors can be supported in optimally discussing uncertainty during genetic counseling.

OUTLINE OF THIS DISSERTATION

This dissertation is structured into three parts that correspond with the abovementioned sub-aims. Each part describes two or three studies each with their own aim. In Figure 1, the structure of this dissertation including the focus of studies within each part is shown.

Part I – The discussion of uncertainty in genetic counseling practice

In the first part of this thesis, we explored current clinical practice regarding

the discussion of uncertainties during pretest genetic counseling for suspected hereditary cancer, and the experiences of counselors and counselees in light of decision making about testing. **Chapter 2** describes an explorative, observational study in which we assessed the range of verbal expressions of uncertainty by counselors and counselees. To this end, we audio recorded initial genetic consultations between counselors and counselees seeking genetic counseling for suspected hereditary cancer, regardless of the genetic test that was being discussed. Next, we sought more insight into the discussion of and experiences with uncertainties related to multigene panel testing. First, in **Chapter 3**, we performed individual and group interviews with counselees and counselors to understand their experiences with uncertainties regarding multigene panel testing. We asked them about their experiences with uncertainties, and their views on discussing uncertainty and making decisions about multigene panel testing. Then, in the observational study described in **Chapter 4**, we gained insight into clinical practice regarding discussing and deciding under uncertainty related to multigene panel testing for hereditary cancer. Therefore, we examined i) *which* uncertainties regarding multigene panel testing are currently discussed by counselors, and *how*, ii) how counselors respond to counselees' expressions of uncertainty, and iii) the extent to which counselees are involved in decision making about multigene panel testing. To this end, counselors performed a pretest genetic consultation with a simulated patient to enable standardization and allow comparison of communication between counselors.

Part II - The impact of discussing uncertainty

In the second part of this thesis, we focused on gaining insight into the impact of discussing uncertainty during genetic counseling. **Chapter 5** involves a systematic literature overview of the effects of discussing uncertain test results during cancer genetic counseling, on counselees' cognitive, affective and behavioral outcomes. In **Chapter 6**, we conducted an experimental video-vignette study to investigate the effects of different manners to discuss uncertainty related to multigene panel testing. For this purpose, we developed videos of a pretest genetic consultation varying in the communication of and responses to uncertainty which were viewed by former counselees. The video-vignettes design provides an ethical alternative for altering physicians' communication in clinical practice and its validity has been previously demonstrated [59].

Part III - Promoting skills to discuss uncertainty

In the third part of this thesis, we concentrated on how to promote communication skills of genetic and non-genetic healthcare professionals in discussing uncertainty during genetic counseling. To this end, we performed two consecutive literature studies. The first was performed to gain insight into the communication skills training programs that currently exist for health care professionals to discuss genetic information, and is described in **Chapter 7**. This review provided information on whether and how such training programs can promote (genetic) healthcare professionals' skills in providing genetic counseling. The second literature study, described in **Chapter 8**, was performed to review current recommendations for all types of physicians on how to communicate uncertainty to patients. These literature studies were used to inform the development of a training intervention for counselors in discussing uncertainty during cancer genetic counseling of which the development is described in **Chapter 9**. This chapter is not intended for publication but provides insight into the training that is developed based on the research presented in this dissertation.

A complete summary of all study findings is provided in Chapter 10. Furthermore, we discuss our findings in light of existing literature, elaborate on their implications and provide directions for future research.

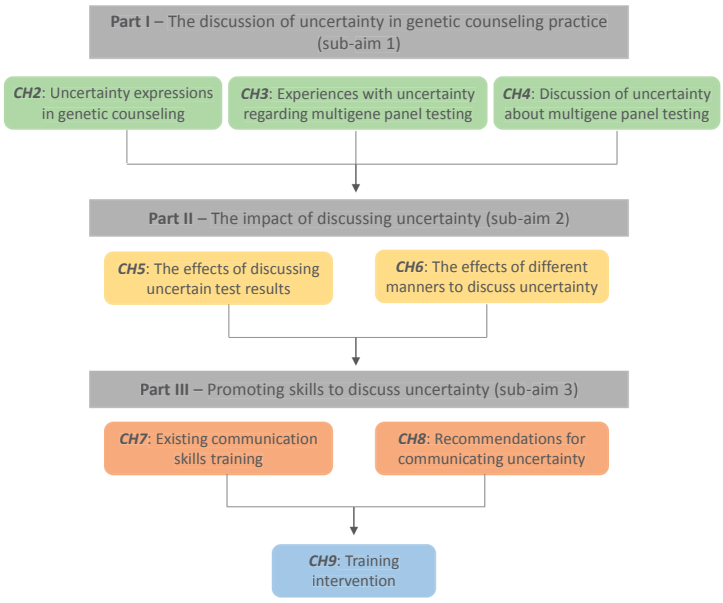

Figure 1. Structure of this dissertation including the focus of each study.
Note: CH means Chapter and corresponds with the chapters in this dissertation.

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